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Congestive Heart Failure Symposium

Texas Heart Institute
Houston, Texas
18 April 2007

Overview

This symposium will focus on advanced treatment options for patients with end-stage congestive heart failure (CHF). The faculty will discuss stem cell research, new medical treatments, mechanical circulatory support, heart transplantation, and other surgical therapies. Both program sessions will conclude with a panel discussion, and audience members will be invited to participate in a question-and-answer session.

The target audience for this continuing medical education activity includes cardiologists, cardiovascular surgeons, and clinical researchers with an interest in CHF.

Learning Objectives

At the conclusion of the symposium, participants will be able to—

- Describe the current management and treatment of CHF.
- Understand the potential of stem cell research for treating heart failure.
- Discuss the latest medical options available for CHF patients.
- Assess the need for mechanical circulatory support of the failing heart.
- Comprehend the principles of continuous-flow assist devices.
- Explain the role of transplantation in this group of patients.
- Review other surgical therapies for treating CHF.

Accreditation

The Texas Heart Institute is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians.

The Texas Heart Institute designates this educational activity for a maximum of 5 *AMA PRA Category 1 Credits™*. Physicians should claim credit commensurate only with the extent of their participation in the activity.

Program

7:30 AM	Registration & Continental Breakfast
Session I	
8:30	Welcome
	Overview of Stem Cell Research for Heart Failure: Where Are We Now? *James T. Willerson, MD*
8:55	Remodeling and New Medical Therapy for Heart Failure *Douglas L. Mann, MD*
9:20	Can Devices Improve Cardiac Function? *Marvin Konstam, MD*
9:45	Mechanical Support Devices for the Cardiologist: Beyond the Balloon Pump *Biswajit Kar, MD*
10:10	The Role of Transplant Now and in the Future *Guillermo Torre-Amione, MD, PhD*
10:35	The Future of Care for the Heart Failure Patient *Reynolds Delgado III, MD*
11:00	Panel Discussion: Q & A Session with Audience
11:30	Break for Lunch and Visit Exhibits
Session II	
1:00 PM	Welcome and Historical Overview *Denton A. Cooley, MD*
1:10	Medical and Surgical Therapies for Heart Failure *Rebecca Bogaev, MD*
1:30	Present Status of Chronic Mechanical Support *Branislav Radovancevic, MD*
1:50	Axial Flow Devices: Continuous Flow Issues *O.H. Frazier, MD*
2:10	Acute Heart Failure Beyond Cardiology Support Bridge-to-Bridge: When Is It Not Enough? *Igor Gregoric, MD*
2:30	Panel Discussion: Q & A Session with Audience
3:00	Adjourn

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TEXAS HEART INSTITUTE JOURNAL
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Editorial

The "Father of Modern Interventional Pediatric Cardiology" Retires

After an illustrious career of more than 48 years in pediatrics, Dr. Charles E. Mullins retired at the end of December, 2006. Charles was born in 1932 in Washington, DC, graduated cum laude in 1954 from Princeton University, and received his MD degree "with Distinction" in 1958 from the George Washington University School of Medicine, Washington, DC. I have known Charles since 1959, when he was a resident in pediatrics at Walter Reed General Hospital. At that time, his interest in cardiology was already evident and he was encouraged to seek a cardiology residency at Walter Reed. Although the program there was in adult cardiology, most of the patients encountered in the catheterization laboratory and at open-heart surgery were infants and children with congenital heart defects. It is interesting to note that Charles began his pediatric cardiology career on an adult cardiology service, and in an "adult" catheterization laboratory. Forty-one years later, he performed his last cardiac catheterization and transcatheter interventional procedure in late December 2006 in the St. Luke's Episcopal Hospital Adult Catheterization Laboratory, closing a patent foramen ovale in an adult. This is not surprising, because he has worked well with adult cardiologists throughout his career.

Charles's Army career encompassed, in addition to his cardiology residency, a cardiovascular research fellowship, a tour as a pediatric cardiology consultant for United States forces in Europe, and, last, service as Assistant Chief of Cardiology, Pediatric Section, Walter Reed General Hospital. In 1963, he received the U.S. Army Commendation Medal for outstanding service as the Army's 1st pediatric cardiologist and for establishing the specialty of pediatric cardiology in the U.S. Army. To this was added, in 1968, the award of an Oak Leaf Cluster for outstanding service as the pediatric cardiology consultant in Europe and for his continued development of pediatric cardiology in the U.S. Army. He separated from the service in 1969, at the rank of Lieutenant Colonel.

Upon leaving the Army, Charles was recruited by Dr. Dan McNamara to the pediatric cardiology section of Baylor College of Medicine at Texas Children's Hospital, a move that I strongly encouraged. Dr. Mullins's fame resides in his development of procedures and devices in the cath lab, his development of interventional transcatheter techniques in the management of congenital defects, and his consummate dedication to teaching. He has trained over 150 pediatric cardiology fellows and has been an invited speaker at over 200 national and international conferences. The "hands-on" teaching of new techniques to physicians in catheterization laboratories in over 150 different institutions, in the United States and abroad, has brought him worldwide recognition.

The American College of Cardiology awarded Dr. Mullins the Gifted Teacher Award in 1989, and in 2000 the Department of Pediatrics, Baylor College of Medicine, bestowed upon him the Arnold J. Rudolph Career Teaching Award. In 2003, the cardiac catheterization laboratories at the Texas Children's Hospital were formally dedicated as "The Charles E. Mullins, MD, Cardiac Catheterization Laboratories." He was awarded the Founders' Award in 2004 by the American Academy of Pediatrics, section of cardiology and cardiac surgery.

Dr. Mullins has been a pioneer in advancing catheterization from a diagnostic procedure, in which correction was left to the surgeon, to the current state of the art, in which many congenital heart defects are treated through interventional transcatheter techniques. These procedures have replaced cardiac surgery in many instances and

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have delayed surgery in many others. His innovative work has led to the development of new and improved techniques and devices for diagnosing and treating children and adults who have congenital heart defects. "He is the father of modern interventional pediatric cardiology," said Dr. Ziyad M. Hijazi, University of Chicago Professor of Pediatrics and Cardiology and Secretary of the Society for Cardiac Angiography and Interventions.[1]

In pursuing these activities, Charles has served as the principal investigator on 8 multicenter clinical investigation protocols, written over 200 publications in peer-reviewed journals, published 2 books—*Congenital Heart Disease: A Diagrammatic Atlas*[2] and *Cardiac Catheterization in Congenital Heart Disease*[3]—and contributed more than 20 chapters to various other texts.

Those Texas boots that are his trademark will be missed at Texas Children's Hospital and will be hard to fill. Dr. Ralph Feigin, Chief of Pediatrics at Texas Children's Hospital, with whom Dr. Mullins has worked for 30 years, said that "Mullins's real *legacy* is the thousands of children who have benefited and who will benefit from the catheterization techniques he developed." In the words of one of his long-term patients, "even when he is not here, he'll be here."[1] His patients admire him not only for his skill and acumen, but for his gentle manner and fatherly approach. They appreciate his reassuring touch and his habit of spending time with each and every one of them.

Charles will be greatly missed at the Texas Children's Hospital, at St. Luke's Episcopal Hospital, and at the Texas Heart Institute. We all congratulate him on his achievements, his dedication to teaching, and his innumerable contributions to pediatric and interventional cardiology. We congratulate his loving and supportive family—his wife, Arlene, and his children and grandchildren—who have supported him on his remarkable career path, and who will now be appreciative of his full attention.

Robert J. Hall, MD,
Director Emeritus of Cardiology Education,
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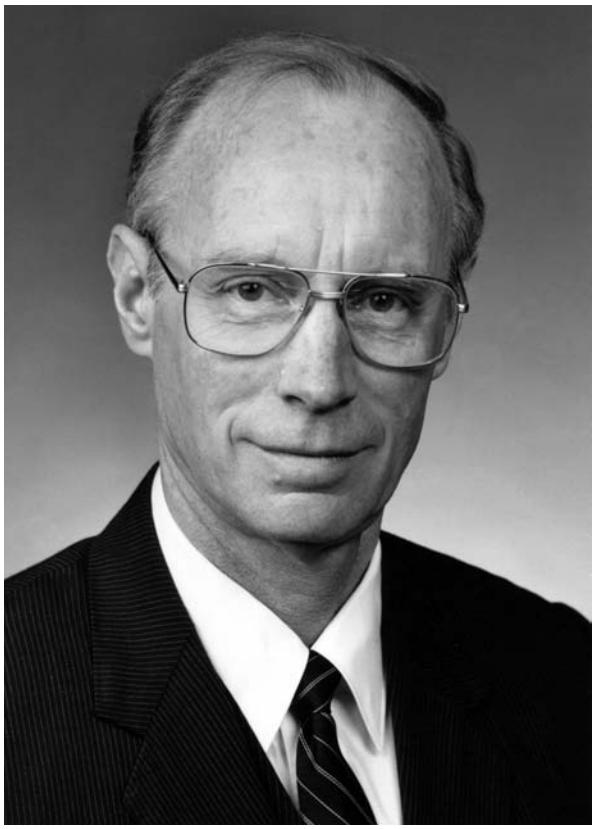

Charles E. Mullins, MD

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Guest Editorial

These Are the Days

The Internship Revisited

All things are changed, and we change with them.

— Lothair I, Holy Roman Emperor, circa 840 AD

Herbert L. Fred, MD, MACP

These are the days when interns have reason to gripe. Unless they demonstrate unflagging commitment and indisputable integrity, they risk being fired—sometimes on the spot and without warning. They have no formal contracts.

Their responsibilities are daunting and their schedule grueling. They work every day and every other night. While on duty, they rarely find time to sleep. And when off duty, they must remain in the hospital until all of their patients are in stable condition and all studies planned for the next day have been ordered. Consequently, on their post-call days, interns typically leave the hospital about 8 PM, and sometimes not until midnight.

Ward rounds on the inpatients begin sharply at 7 AM, 7 days a week. In attendance are the ward resident, the 2 interns, and the chief nurse. Medical students do not participate. These rounds are sacred, generally last 2 hours, and only a bona fide emergency can interrupt them. The intern on the case briefly examines the patient while the resident examines the patient's chart. Results of tests and procedures done the previous day are discussed, and, with input from the chief nurse, the resident and intern make decisions regarding additional testing or consultation, medication changes, discharge considerations, and other "housekeeping" matters. Similar rounds often take place around 6 PM that same evening.

Aided at times by medical students and the resident, interns perform and interpret all admission and follow-up blood counts, peripheral blood smears, urinalyses, stool guaiac tests, and electrocardiograms. Additionally, they start and maintain all intravenous therapy; draw all blood cultures; stain and examine microscopically all pleural, pericardial, peritoneal, spinal, and joint fluids; apply skin tests; and search for ova and parasites in stool specimens. The intern on call also draws the early morning blood samples from about 20 to 30 patients—the team's average number of patients at any given time. That job—undertaken with frustratingly blunt, nondisposable needles and ill-fitting, easily broken glass syringes—must begin by 5 AM or earlier to be completed before work rounds begin. Interns also fill out the requisition slips for all laboratory tests and procedures and are responsible not only for recording the results in the patients' charts, but also for reciting the results on command.

By carrying out these seemingly menial tasks—called "scut work" in housestaff lingo—interns begin to realize the importance of accountability. They learn firsthand the subtle factors that can influence test results. They learn to appreciate other members of the healthcare team who ordinarily do such work—nurses, laboratory personnel, phlebotomists, and ward clerks. And most important, perhaps, the scut work repeatedly brings interns into physical contact with their patients, strengthening the doctor–patient bond.

Interns make daily trips to the main hospital laboratory, radiology department, microbiology unit, and other areas to obtain test results, review x-ray studies with a staff radiologist, check on the growth of various cultures, etc. This important routine requires a lot of physical effort, but it ensures timely and uninterrupted patient care.

In addition to the workload already described, interns must squeeze in time for daily chart rounds. During this ritual, the intern and resident scrutinize each inpa-

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tient record for missing data, illegible notes, disorganized inserts, and other common deficiencies. "A sloppy chart indicates a sloppy doctor," the department chairman says. Not surprisingly, therefore, defective patient records provoke his wrath.

Interns occasionally are discussants at weekly Grand Rounds. This assignment compels them to spend long hours in the medical library searching the stacks for pertinent articles on their topic. In the process, they learn what it takes to research a subject thoroughly, how to read with discrimination, how to critically evaluate what they read, and how to give a formal presentation before a discerning audience.

They also prepare vigorously for teaching rounds, which take place at 10 AM, 4 times a week—3 with an attending physician, and 1 with the chairman. The attendings and chairman serve as consultants who simply offer opinions and make recommendations. Responsibility for managing the patient—particularly all decision-making and order-writing—rests solely with the intern and resident on the case. These teaching sessions last 1½ to 2 hours and focus on 1 patient, who is presented, examined, and discussed in detail. Interns must make certain beforehand that the patient is in bed, properly gowned, and willing to have the teaching physician come by. Interns are also expected to bring pertinent literature to the conference room and to have on hand all of the patient's past and current medical records; a microscope with which to look at relevant urine sediments, blood smears, and tissue sections; and an x-ray view box for display of relevant radiographs. The case presentation must be clear, well-organized, and free of ramblings and redundancies. Anything less is unacceptable and will earn harsh reprimands. After the case presentation, the group goes to the patient's bedside, where the attending or chairman takes over. Observing these master clinicians in action is the best part of the internship.

Once a week, the interns work a half-day in the outpatient clinic. This activity always takes place in the afternoons so that it doesn't interfere with the work rounds and teaching conferences held in the mornings. On the other afternoons of the week, the interns are busy performing work-ups of new patients, tending to patients previously admitted, and completing other assignments and duties.

These are the days when a constant bed shortage limits admissions to the very young, the very old, and the very sick. Because no Intensive or Coronary Care Units exist, interns cannot transfer their severely ill patients to a specified area for close monitoring. Instead, they must monitor the patients themselves, using the only monitors available—their own eyes, ears, nose, hands, and brain. This situation forces interns to observe their patients carefully and repeatedly, often for long periods of time. They must also attend every operation on their patients and every autopsy performed on any patient from the medical teaching service. From these various routines, interns gain competence and confidence in their clinical skills, learn the pathophysiology and natural history of disease, and understand when to treat and why.

The highlight of the workday actually occurs at night—midnight to be exact. That's when many of the house officers on duty throughout the hospital meet in the hospital cafeteria for a free meal. Although the food isn't great, the camaraderie is. Furthermore, this respite is just what it takes to recharge the interns' batteries.

These are the days when the internship ingrains discipline, stimulates a taste for continual self-education, and promotes mutual respect among all hospital personnel. Indeed, these are the days when good patient care and the education of the intern are all that matter.

What days are these? The days 53 years ago when I was a medical intern in the main teaching hospital of a state university.

Since that time, the medical internship has changed significantly, bearing almost no resemblance to the one I did. Given the ever-increasing emphasis on sophisticated technology, the shrinking of government funding for medical services, and the devastating impact of managed care,[1] clinical teaching has suffered a serious blow. In addition, medical schools are so strapped for money these days that they force the clinical faculty to spend more and more time caring for paying patients and less and less time caring for medical students and house officers.

Even more disturbing to me as a medical educator is the mandate that was promulgated in 2003 by the Accreditation Council for Graduate Medical Education (ACGME), imposing work-hour limits across all training programs, regardless of specialty.[2] Acting to promote patient safety, the ACGME sided with the widely held—but still disputed—notion that sleep deprivation and physical fatigue in physicians lead to harmful medical errors.[3-22] As a result, interns now take call every 4th, 5th, or 6th night (but only on required rotations; the other rotations are call free). Moreover, they must leave the hospital by 1 PM on their post-call days, are not allowed to average more than 80 hours of work per week, and typically take 1 day a week off.

Thus, from its roots as a patient-centered, education-oriented year of learning, the medical internship has evolved into a laboratory-centered, algorithm-oriented, technology-driven, computer-dependent, Internet-based, "treat first, diagnose later" training program. Consequently, we are exchanging sleep-deprived healers for a cadre of wide-awake technicians[23] who cannot take an adequate medical history, cannot perform a reliable physical examination, cannot critically assess information they gather, cannot create a sound management plan, have little reasoning power, and communicate poorly.[24]

Is this what patients want? Is this what patients need? Is this what patients deserve? I think not. I also think

that unless medical education undergoes substantial reform, things will only get worse.

Meanwhile, we need to find a balance between policies of the past (which emphasized compassion, empathy, and *high-touch,* direct patient care) and policies of the present (which place a premium on *high-tech* machines and gadgets).[25] But whatever the future brings, we must always view medicine as a calling, not a business, and hold fast to the patient-oriented traditions that have sustained our profession throughout its history.

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Editorial Commentary

Cardiovascular Disease in Africa

Worldwide concern about the human immunodeficiency virus (HIV) pandemic in Africa is justified, but it should not overshadow the need for treatment of other diseases. Infectious diseases such as malaria, tuberculosis, and even polio continue to pose major health risks for the 10% of the world's population who live in Africa. Cardiovascular disease is a growing threat to health in Africa, accounting for 9.2% of deaths in 2001, principally due to hypertension, stroke, cardiomyopathy, and rheumatic valve disease.[1,2] Cardiovascular disease has a higher mortality rate in developing countries and affects younger people and women disproportionately. Peripartum cardiomyopathy is a major cause of heart failure in Africa. In some parts of Nigeria, heart failure in women is reported to occur after childbirth as often as once in every 100 births.[3] Although ischemic heart disease is relatively uncommon in Africa, rheumatic valvular disease remains a commonly encountered cause of disability and death, and pericardial disease may be the first manifestation of HIV infection in its early stages. Aneurysms can also be associated with HIV. Worldwide surveys have found that congenital heart disease may occur in 12 to 15 of 1,000 live births and that it is often associated with high infant mortality rates.[4]

Meeting the healthcare needs of Africans is an enormous challenge. The World Health Organization (WHO) lists sub-Saharan Africa as one of the geographic areas least served by healthcare providers (doctors, nurses, and midwives).[5] Socioeconomic barriers to cardiovascular care in Africa have included inadequate financing, lack of education of health workers, and poor laboratory support. Besides, poverty, political instability, and corruption exist in many parts of Africa today.

The Texas Heart® Institute was established in 1962 to foster excellence in cardiovascular care through education, research, and patient care. Over the past 45 years, the Texas Heart Institute has trained physicians and surgeons from all regions of the world (Fig. 1). In the current issue of the *Texas Heart Institute Journal*, Dr. John Eze, a recent graduate of our fellowship program, reports on the history and challenges encountered in establishing a program for cardiac surgery in Nigeria.[6] Specifically, Dr. Eze relates the clinical experience of the cardiothoracic program in Enugu, Nigeria. More broadly, he talks candidly about the economic and social obstacles to health care in the country at large.

Located in West Africa, Nigeria is slightly larger than twice the size of California and has a population of over 130 million people, or approximately 1 of every 6 Africans. That's the largest population in Africa; but 66% of the population falls below the poverty line of $1 in income per day. In fact, Nigeria is among the 20 poorest countries in the world, despite being the world's 5th-largest oil producer. Life expectancy is around 50 years. The prevalence of HIV was 5% in 2003, with 3.3 million people infected. In 2005, AIDS caused an estimated 220,000 deaths in Nigeria and left 930,000 orphans. Ten percent of HIV infections were attributed to blood transfusions.

Despite the complex challenges posed by disease in the African continent, there is hope for improvement of health care. Polio remains endemic in some countries in Africa, and northern Nigeria reports the largest number of active cases in the world. To eradicate polio, the WHO in 2004 began the mass immunization of 63 million children in 10 countries in west and central Africa. Studies in Nigeria have suggested that effective treatment of hypertension could avert 2 out of 5 deaths caused by that disorder, a reduction over 10 times that now observed in the United States.[7] International health organizations, in cooperation with governments in Africa, have attracted funding for the screening and treatment of diseases, including hypertension and HIV infections.

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Fig. 1 *Countries of origin of Texas Heart Institute trainees in cardiology and cardiovascular surgery.*

It is hoped that one day the people of Africa will be able to receive appropriate cardiovascular care in their own countries. We are indebted to Drs. Eze and Ezemba for bringing this important topic to our attention. We invite them to report their experience with cardiovascular care in Nigeria over the next 5 years. We trust that improvements will be forthcoming, and we applaud these physicians for their dedication and commitment to the health care and well-being of their fellow citizens.

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Guest Editorial

Open-Heart Surgery in Nigeria

Indications and Challenges

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Ndubueze Ezemba, MD

From the early 1940s through the 1950s, it was a popular belief throughout the world that cardiac diseases were rare among Nigerians. However, the establishment of the cardiac registry in 1964 in Ibadan revealed all types of cardiac diseases, including those requiring surgical intervention.[1] Virtually all who were affected died without help, except for those who traveled to Europe or America for treatment.

Now, the situation is different because of new cardiac centers in Nigeria. At the University of Nigeria Teaching Hospital (UNTH) in Enugu, the first open-heart surgery in Nigeria was performed on 1 February 1974.[2] The team of surgeons included M. Yacoub, F.A. Udekwu, D.C. Nwafor, C.H. Anyanwu, and others. By the year 2000, a total of 102 such operations had been carried out at the center by different Nigerian teams, with Professor Martin Aghaji's team being in the forefront (Fig. 1). The patients ranged in age from 2.5 years to 63 years. Forty-six (45%) patients were aged between 11 and 20 years (Fig. 2).

Cases of mitral valve disease, at 40 (39.2%) in number, topped the list of the pathological processes. These included mitral stenosis, mitral regurgitation, and combined lesions. The high incidence of mitral valve disease has been attributed to the aftereffects of rheumatic heart disease in the region.[3] Mitral valve disease was followed in frequency of observation by 16 (15.7%) cases of ventricular septal defect (VSD), 13 of tetralogy of Fallot (12.7%), and 12 of atrial septal defect (11.8%). There were 7 cases of ascending aorta–aortic arch aneurysm. Other lesions included ventricular aneurysm and total anomalous pulmonary venous connection. These 102 patients are of course far fewer than the World Health Organization's estimated figure for Nigeria, with its population of 126 million.

Our center at Enugu was for a long while the only center in Nigeria that was doing open-heart surgery. The patients treated were the young, those who could afford the fees, and those whose cases could be handled by our center. The average age of our patients was 20 years. Many were in their youth, because experience has shown that the outcome of open-heart surgery is better among young people. Nigeria lacks facilities to combat the comorbid conditions that are prevalent among elderly patients.

By 2003, when Dr. William Novick's International Children's Heart Foundation paid a working visit to Enugu, the Kanu Heart Foundation, which had invited the team, had a registry of 2,555 heart disease patients who needed open-heart surgery. These were drawn from the KHF registry, UNTH, and other hospitals. Of the 72 patients evaluated during that visit, more than 50 required open-heart surgery, but only 9 had the surgery.

What is needed is political will on the part of the policymakers to act in providing adequate human and material resources in the Enugu center and in the 2 new centers in Lagos and Ibadan. All of these centers are government owned. It is of course more cost-effective to treat Nigerians in these centers than anywhere else in the world.

In Nigeria, the challenges facing the cardiac surgery team are many. A look at Figure 1 shows no definite pattern in the number of patients per year. Ups and downs in patient population have characterized activity at the Enugu center, and the same is true for the other centers. Among the reasons for this state of affairs is the unavailability of high technology. All the equipment is imported from other countries, as are virtually all of the required drugs and prosthetic devices. These things must be paid for in United States dollars; and because of the current severe devaluation of

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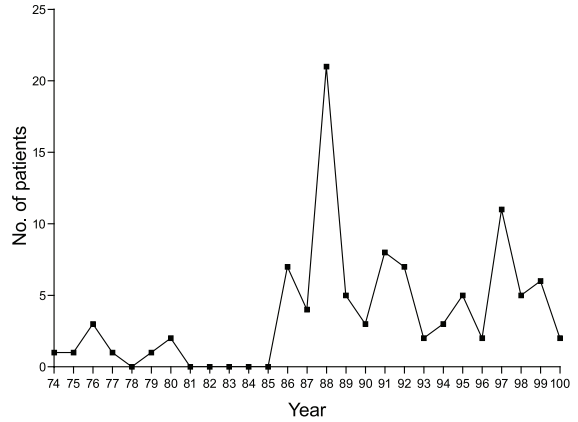

Fig. 1 *Fluctuations, from 1974 through 2000, in numbers of open-heart-surgery patients treated throughout Nigeria.*

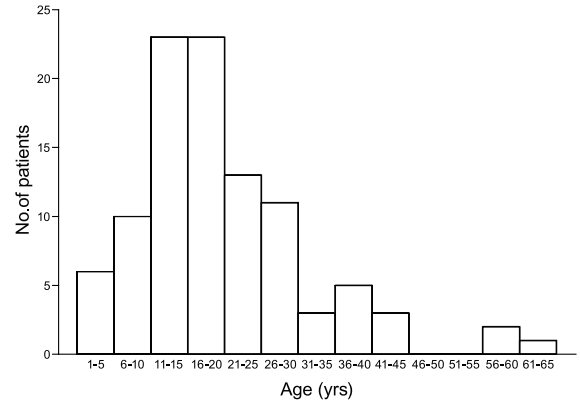

Fig. 2 *Histogram showing the number of patients per age-group during the 1974-2000 period.*

the Nigerian naira, many of these items are lacking. Therefore, the cardiac team has to improvise.

As a result of the heavy financial outlay for surgical treatment, cardiac patients must pay more, on average, than do other patients in the hospital. Many of these patients and their relatives cannot afford the bill. Moreover, there is no health-insurance scheme for this kind of treatment. (There was no health insurance at all until 2004, and even now cardiac surgery is not covered.) We have a situation wherein the government of the day has succeeded in providing some infrastructure, but most patients cannot benefit from what is available. Because all 3 centers that perform open-heart surgery in Nigeria are government owned, there is some small subsidy for patients' bills. When compared with the costs of treatment abroad, the cost of treating patients at home is still far lower.[4]

A total hospital bill for open-heart surgery without a prosthesis typically costs $4,800; with a prosthesis, it costs $5,600. An overnight stay in the intensive care unit is about $85, while a gram of the Rocephin antibiotic agent for injection is $20. Payment sources generally are: household, 62.5%; employer, 20.5%; government, 9%; and donors, 8%. The minimum wage in Nigeria is between $44 and $62 per month. The per capita income estimate in 2004 was $1,050. Nigeria's gross domestic product for that year was $64.1 billion, but with the estimated 126 million people, this amounts to $493 per capita.

Poor medical and surgical training and skills leave room for trial and error. Every member of the team is expected to be proficient, but there is a need for further training, workshops, seminars, recertification, and continuing education. Unfortunately, the "brain-drain syndrome" has adversely affected the growth of cardiac surgery in Nigeria. The surgical management of heart disease is labor intensive, but there is little incentive to stay in Nigeria. Something urgent must be done to reverse the situation. This is where a leader with vision is needed.

Political instability in the country and frequent widespread violence combine to limit the number of foreign agencies that participate in the surgical management of heart disease in Nigeria. Some of these charities have personnel and equipment. Some foreign physicians want experience in treating types of heart disease that are no longer common in their countries. However, even charitable organizations cannot take their safety for granted. Furthermore, political decisions that affect the treatment of heart disease vary with each political leader, and these leaders change very often. Their successors do not maintain continuity. Some emphasize primary health care to the detriment of the treatment of heart disease.

It is well known that our hospital and other health institutions have been experiencing inter-professional conflicts. It was a topic at the health summit in Abuja in 1995.[5] These conflicts rob patients of the united attention that is necessary to achieve greater levels of success. There is a need to improve human relationships among staff, because the patient should be our rallying point.

Another problem is that fraudulent contractors and their collaborators often supply us with outdated and nonfunctional equipment. The end user is seldom involved in the purchase of such items. Moreover, much of the equipment is now computer-based, and computer illiteracy and poor handling lead to frequent breakdowns. If we could use the information technology that is now available, retrieval of information would be easier, and planning and management would become more comfortable.

Much more basic challenges are the lack of regular water and electric power supply, nonpayment of salary when due, stagnation of staff services, and lack of knowledge about modern information technology on the part of personnel who carry out patient services.

Apart from open-heart surgery, other cardiothoracic procedures are carried out at UNTH. In a retrospective analysis of inpatient admission records from 2000 through 2004, all cardiothoracic cases (704) were documented. Chest-wall disorders constituted most of the cases (28.68%), and chest trauma from traffic accidents accounted for the majority of these (Table I). Pyothorax that required decortication was high on the list of pleural collections. Third were esophageal disorders such as corrosive stricture, achalasia, and cancer of the esophagus.

TABLE I. Distribution of Cardiothoracic Lesions Treated 2000 through 2004

Lesion	Men	Women	Children	Total (%)
Chest-wall disorders	164	40	–	204 (29)
Pleural space collections	91	35	17	143 (20.3)
Lung tissue diseases	52	12	3	67 (9.5)
Esophageal disorders	59	7	31	97 (13.8)
Pericardial diseases	28	13	7	48 (6.8)
Acquired heart diseases	15	6	9	30 (4.3)
Congenital heart diseases	10	–	42	52 (7.4)
Vascular disorders	43	7	–	50 (7.1)
Mediastinal diseases	5	1	1	7 (1)
Diaphragmatic diseases	2	–	4	6 (0.9)
Total	469	121	114	704

Despite all of this, we believe that Nigeria has what it takes to attain self-sufficiency in the treatment of heart diseases that require open-heart surgery. What is needed is the normalization of these irregularities and the good management of resources. The recently introduced health-insurance scheme may help.

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Laboratory Investigation

Systemic Infections Cause Exaggerated Local Inflammation in Atherosclerotic Coronary Arteries

Clues to the Triggering Effect of Acute Infections on Acute Coronary Syndromes

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Key words: *Arteriosclerosis/complications; cardiovascular diseases/diagnosis/prevention & control; coronary arteriosclerosis/pathology; coronary disease/pathology; inflammation/complications/etiology/pathology; coronary vessels/pathology; myocardial infarction/etiology/pathology; retrospective studies; risk assessment; sepsis/complications*

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Systemic infections can trigger heart attacks. We conducted an autopsy study to investigate the pathologic effect of systemic infections on coronary artery inflammation.

We studied 14 atherosclerotic patients diagnosed with an acute systemic infection. Our control group (n=13) had atherosclerosis without infection. The groups were similar in luminal stenosis and age. Coronary artery sections were stained with H&E and markers for macrophages (CD68), T cells (CD3), and dendritic cells (S100).

On pathologic examination, 5 infected patients had acute myocardial infarction with thrombosis. Macrophage density in plaques and in periadventitial fat was higher in the infected group (NS). The infected patients' adventitia had significantly more macrophages (1,577 ± 1,872 vs 265 ± 185 per mm^2; P=0.047). The macrophage density, similar in the control group's adventitia and plaque, was significantly greater in the infected group's adventitia than in the plaque. The adventitia and periadventitial fat of the infected group had more T cells than did samples from the control group (48.4 ± 45.0 vs 14.1 ± 6.3 per mm^2; P=0.002). The groups exhibited similar plaque T-cell density. The infected patients' plaques, but not the adventitia and periadventitial fat, had more dendritic cells than did the controls' (3.2 ± 2.5 vs 0.3 ± 0.5 per mm^2; P=0.022).

To our knowledge, this is the 1st report to establish a connection between acute systemic infections and significant increases in inflammatory cells in the atherosclerotic coronary arteries of human beings.This offers a new therapeutic target for preventing heart attacks in high-risk patients. ***(Tex Heart Inst J 2007;34:11-8)***

Inflammation plays a major part in the initiation and progression of atherosclerosis and in the development of its acute clinical manifestations.[1,2] Acute infections, with their consequent inflammation, may affect atherosclerotic disease. This relationship was first proposed by William Osler at the beginning of the 20th century.

The following infectious agents have been linked to atherosclerosis: cytomegalovirus, *Chlamydia pneumoniae*, herpes simplex viruses 1 and 2, *Helicobacter pylori*, *Mycoplasma pneumoniae*, *Porphyromonas gingivalis*, enterovirus, and, more recently, the influenza virus.[3-5] A series of acute and chronic infections, occurring alone or in combination, may lead to the development and progression of atherosclerosis. By rapidly increasing inflammation in the coronary arteries, acute infections may trigger destabilization and possible rupture of vulnerable plaques.[6] Given the central role of inflammation in atherosclerosis, we investigated whether a wide range of systemic infections might exacerbate local inflammation in coronary arteries.

Materials and Methods

Study Population

We reviewed the pathology files of a large teaching hospital from 1991 through 2002. The study protocols and procedures were approved by the institutional review boards, and approvals from the treating physicians were obtained before the medical records were released. After excluding patients who might have had an inadequate or altered inflammatory response to infections (for example, persons with human immunodeficiency virus or cancer, or those who were on a regimen involving im-

munosuppressive or corticosteroid drugs), we identified 14 patients who had clinical and pathologic evidence of coronary artery disease (atherosclerosis) at autopsy and an acute systemic infection within 2 weeks of death. The study group comprised 11 men and 3 women, aged 64 ± 14 yr. This group was compared with 13 control patients (8 men and 5 women; mean age, 65 ± 11 yr) who had died with coronary artery disease but without infection. There were no significant differences between the groups in age (P=0.82) or sex (P=0.41). Table I lists the acute infectious agents in the study group.

Sepsis was defined as the presence of systemic infection as determined by the treating physician or from laboratory data. Twelve study-group patients had upper or lower respiratory infections; 2 had urinary tract infections. Most of the control patients had died abruptly due to pulmonary embolism (2 cases), postoperative decompensation or complications (3), aortic aneurysm (3), acute myocardial infarction (AMI) (1), aortic dissection and AMI (1), asthma (1), airway obstruction (1), and acute respiratory distress syndrome (1).

Histopathologic Examination

The coronary arteries obtained at autopsy were formalin-fixed, paraffin-embedded, and cut into 4-µm-thick serial sections. One to 4 sections per patient (mean, 1.2 sections) were immunohistochemically stained with all 3 of these antibodies: the macrophage marker CD68 (all markers were from DAKO; Carpenteria, Calif), the CD3 marker for T cells, and the S100 protein for dendritic cells. Quantitative morphometric evaluation (blinded) was performed by 2 separate observers who used the Olympus MicroSuite Software™ B3SV on an Olympus BX61 microscope (Olympus America Inc.; Center Valley, Pa). Cell counts were performed in the intimal plaque, adventitia, and periadventitial fat at ×200 magnification for the entire circumference of each coronary artery. The results were presented as the number of cells per mm^2.

Histologic Definitions

The plaque area was defined as the area inside the internal elastic lamina (IEL). The adventitia was defined as the region extending from the external elastic lamina to the beginning of the periadventitial fat. The periadventitial fat was considered to extend from the adventitia to 250 µm beyond. Macrophage density was the number of macrophages per mm^2. Stenosis denoted the (IEL area – lumen area)/IEL area, expressed as a percentage. We quantified all the slides that were available.

Statistical Tests

Results are expressed as mean ± standard deviation. Because of the small sample size and nonnormal distribution of the data, we used the Mann-Whitney U test and the Wilcoxon signed rank test to study the significance of our findings. An α level of 0.05 was considered the threshold for statistical significance. The Fisher exact test was used to evaluate categorical variables, such as the sex of the patients. The software used for statistical analysis was the Statistical Package for the Social Sciences, version 9 (SPSS Inc.; Chicago, Ill).

Results

The 2 groups had similar percentages of luminal stenosis (67% ± 14% vs 55% ± 25%; P=0.23). Subocclusive luminal thrombi were seen in 4 infected patients,

TABLE I. Acute Infections in the Study Group

Sex	Age (yr)	Infectious Agent(s)	Duration of Infection
M	80	*Pseudomonas aeruginosa*	~1 wk
M	58	*Streptococcus pneumoniae*	~2 wk
M	40	*Bacillus cereus*	10 days
M	69	*P. aeruginosa*	~1 wk
M	43	*Staphylococcus aureus*	>2 wk
M	58	Beta-hemolytic streptococcus, *Candida albicans*	>1 wk
F	50	Herpes virus, viridans streptococcus	<2 wk
F	58	*S. aureus, Klebsiella pneumoniae*	>2 wk
M	81	Polymicrobial sepsis	2 wk
M	78	*Legionella pneumophila*	~2 wk
M	69	*P. aeruginosa, C. albicans, Citrobacter freundii, Staphylococcus epidermidis,* methicillin-resistant *S. aureus*	~6 wk
M	70	*P. aeruginosa*	5 wk
M	60	*S. aureus*	<1 wk
F	81	*P. aeruginosa, Acinetobacter calcoaceticus*	~2 wk

and a small luminal thrombus was present in a 5th; all 5 had histologic evidence of AMI. Only 1 organized thrombus was seen in the control group. Of the 5 infected patients who had AMI on pathologic examination, only 2 had been diagnosed clinically to have AMI.

In the plaques, the macrophage density showed a nonsignificant trend toward higher levels in the patients with a systemic infection (582 ± 774 vs 281 ± 321 per mm^2; P=0.41) (Table II). However, in the adventitia of the infected patients, there was a significantly greater number of macrophages than in the adventitia of the control patients (1,577 ± 1,872 vs 265 ± 185 per mm^2; P=0.047) (Figs. 1 and 2).

The macrophage density in the periadventitial fat showed a nonsignificant trend toward higher levels in the infected patients (776 ± 821 vs 212 ± 219 per mm^2; P=0.085). In the control patients, the macrophage density was similar in the adventitia and the plaque (281 ± 321 vs 265 ± 185 per mm^2; P=0.85); however, in the infected patients, the density was significantly higher in the adventitia than in the plaque (1,577 ± 1,872 vs 582 ± 774 per mm^2; P=0.047).

Significantly more T cells were observed in the adventitia and periadventitial fat of the infected patients than in the control patients (48.4 ± 45.0 vs 14.1 ± 6.3 per mm^2; P=0.002). In the intima, the number of T cells did not differ significantly (infected, 14.0 ± 13.2 per mm^2; control, 14.3 ± 20.5 per mm^2; P=0.49).

Similarly, the dendritic cell counts were not significantly different in the adventitia and periadventitial fat (infected, 34.1 ± 53.7 per mm^2; control, 21.8 ± 15.3 per mm^2; P=0.87). On the other hand, significantly more dendritic cells were seen in the plaque of the infected patients (3.2 ± 2.5 per mm^2; control, 0.3 ± 0.5 per mm^2; P=0.022) (Table II; Figs. 3 and 4).

In summary, we found a significantly higher number of macrophages in the coronary adventitia of the infected patients than of the control patients, who were atherosclerotic without infection. The macrophage density tended to be higher in the plaque and periadventitial fat of the infected patients, but this difference was not significant. The infected patients also had more T cells in their adventitia and periadventitial fat, and more dendritic cells in their intima and media. The higher number of inflammatory cells was associated with an increase in the incidence of myocardial infarctions and luminal thrombosis. Interestingly, the percentage of stenosis was not significantly different between the 2 groups.

Discussion

To our knowledge, this is the 1st report to establish a connection between acute systemic infections and significant increases in inflammatory cells—known to play a major role in AMI—in the atherosclerotic coronary arteries of human beings. This discovery suggests a mechanism for the triggering of AMIs after acute infections, and it offers a new therapeutic target for the prevention of heart attacks.

How Might Acute Infections Trigger Acute Myocardial Infarction?

Over several decades, scattered clinical reports have noted that up to one third of myocardial infarctions are preceded by an upper respiratory infection.[6-12] The occurrence of AMI undergoes seasonal variation, having its highest incidence in the winter months, when the incidence of upper respiratory infections is also highest.[13-15] Influenza epidemics have been associated with a significant increase in overall cardiovascular deaths,[16] a spike usually attributed to deaths of patients with known heart failure. In 2000, we described an association between influenza vaccination and a reduced incidence of winter myocardial infarctions,[6,17] a finding later confirmed by

TABLE II. Densities of Inflammatory Cells in the Plaque and Adventitia

Cell Type/Location	Infected Group*	Control Group*	P Value**
Macrophages/plaque	582 ± 774	281 ± 321	0.41
Macrophages/adventitia	1,577 ± 1,872	265 ± 185	0.047***
Macrophages/periadventitial fat	776 ± 821	212 ± 219	0.085
T cells/adventitia and periadventitial fat	48.4 ± 45.0	14.1 ± 6.3	0.002***
T cells/plaque	14.0 ± 13.2	14.3 ± 20.5	0.49
Dendritic cells/ adventitia and periadventitial fat	34.1 ± 53.7	21.8 ± 15.3	0.87
Dendritic cells/plaque	3.2 ± 2.5	0.3 ± 0.5	0.022***

*Cell density = number of cells per mm^2
**Determined by the Mann-Whitney U test
***Statistically significant

others.[18-21] In addition, a study of 75 patients who had severe acute respiratory syndrome (SARS) found that 2 out of 5 deaths were due to AMI[22]—an occurrence still overlooked by many.

Infectious agents have several potential effects on the pathophysiology of atherosclerosis and its clinical complications.[5,23] Whereas most suspected infectious agents initiate or aggravate a chronic vascular or systemic inflammatory process, acute systemic infections may, instead, destabilize existing vulnerable plaques. For example, we have shown that inoculating atherosclerotic, apolipoprotein-E–deficient mice with the influenza A virus leads to a marked increase in inflammation and thrombosis in murine atherosclerotic plaques but not in normal regions of the aorta.[24] Pro-atherosclerotic changes in mice have also been reported after acute infection with cytomegalovirus and *P. gingivalis*.[25]

Systemic infections can exert acute and chronic influence on vascular walls. The effects are either direct (through seeding of the microbe in the vascular wall) or indirect (through release of inflammatory cytokines and other systemic effects) (Fig. 5).[5,6,26,27]

Adventitial Inflammation in Atherosclerosis

Evidence increasingly suggests an important role of adventitia in the inflammation that is present in atherosclerotic plaques. In 2004, we reported that human atherosclerotic coronary plaques with large lipid cores have a significantly greater number of macrophages in their periadventitial fat than do fibrocalcific and non-atherosclerotic arterial segments, which suggests the involvement of adventitial inflammatory cells in plaque vulnerability.[28] Our previous findings suggested that the adventitia and periadventitial fat may function as a unit.[28] The lack of a functional border between the adventitia and the periadventitial fat has been noted by others after balloon angioplasty.[29]

Dendritic Cells and Atherosclerosis

An immune reaction against certain antigens may play an important role in the development of atherosclerosis.[30,31] Dendritic cells—antigen-presenting cells that have important functions in immune responses—have been observed in atherosclerotic plaques. In advanced atherosclerotic lesions, clusters of dendritic cells have

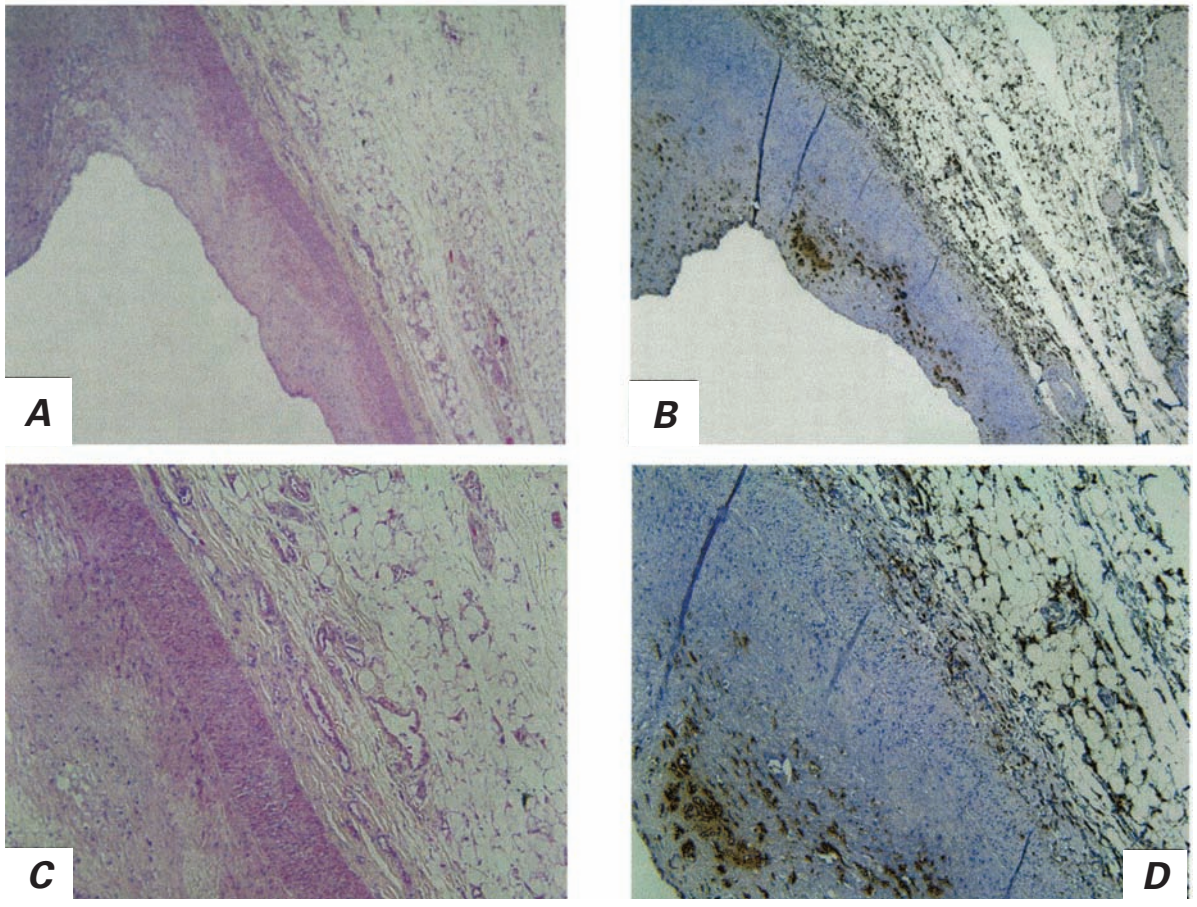

Fig. 1 *Section of coronary artery from an infected patient.* ***A****) Low-power view (H&E, orig. ×4).* ***B****) CD68 staining shows a substantial presence of macrophages that heavily infiltrate the plaque, adventitia, and periadventitial fat, mostly sparing the media.* ***C****,* ***D****) Increased magnification (×10) of the respective stained sections.*

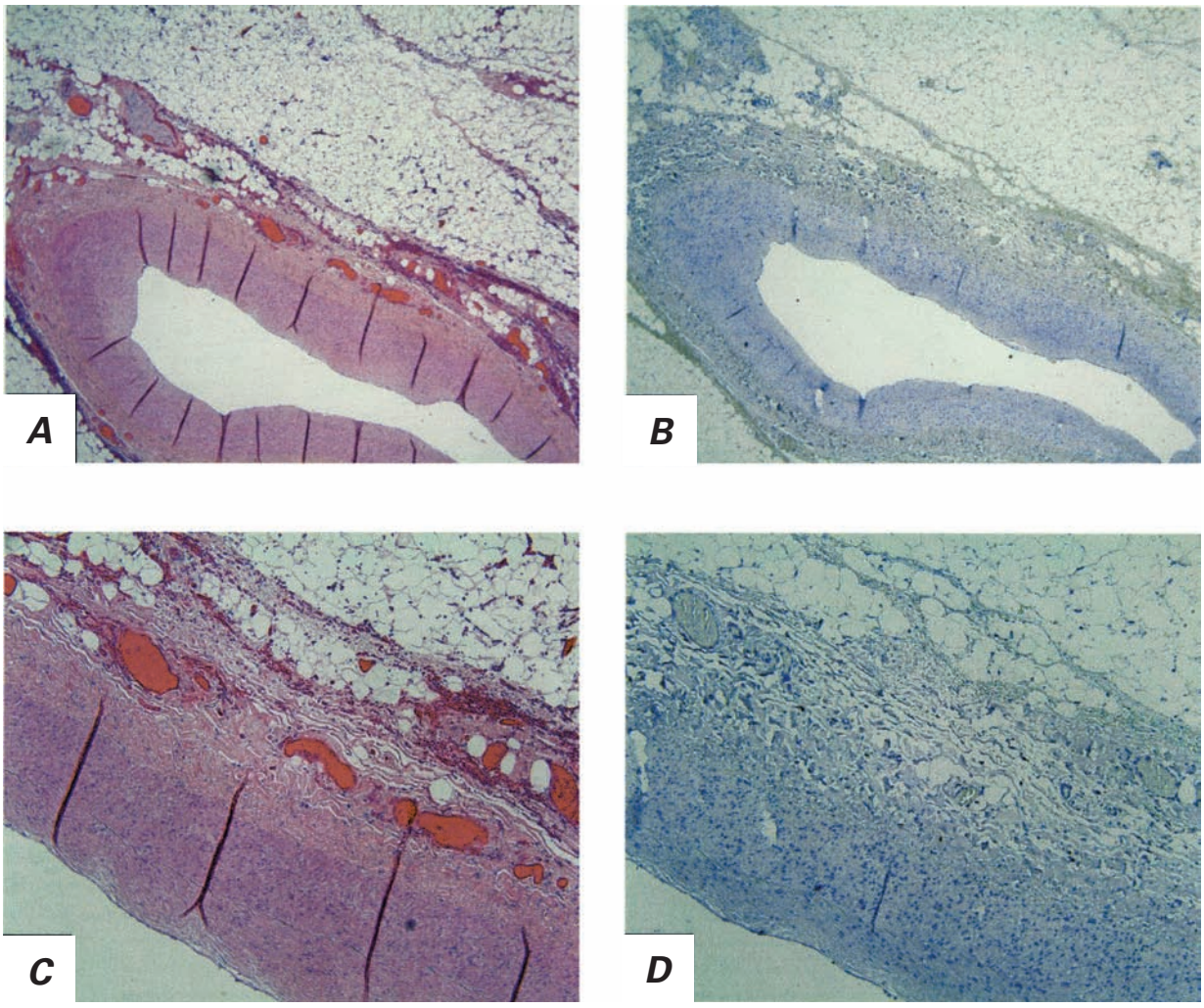

Fig. 2 *Section of coronary artery from a control patient.* ***A****) Low-power view (H&E, orig. ×4).* ***B****) CD68 staining shows an absence of macrophages in comparison with the Figure 1 images of the infected patient's artery.* ***C****,* ***D****) Increased magnification (orig. ×10) of the respective stained sections.*

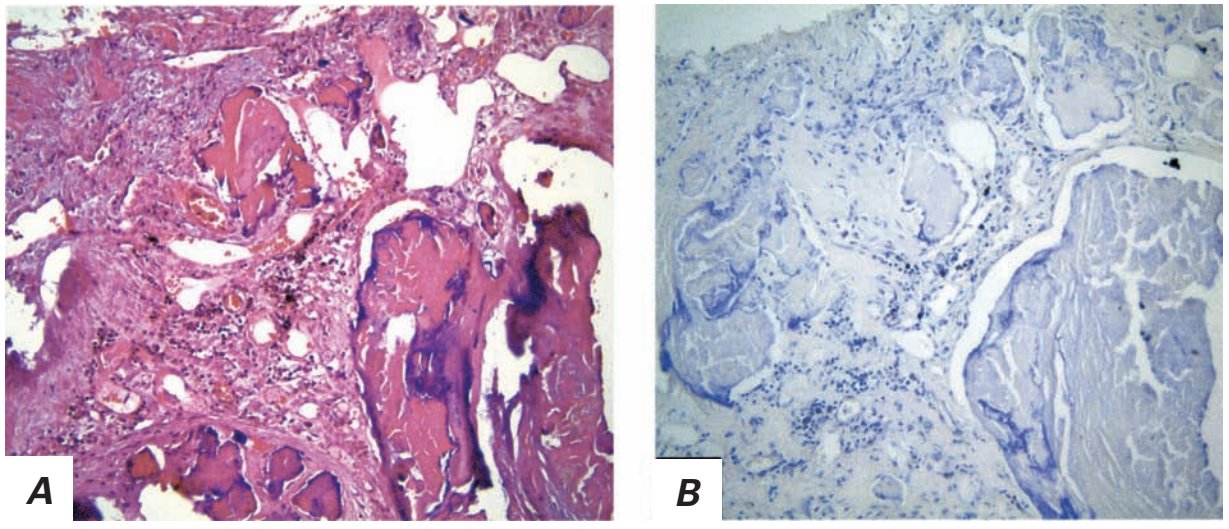

Fig. 3 *Section of coronary artery from an infected patient.* ***A****) Calcified plaque with substantial neovascularization (H&E, orig. ×20).* ***B****) S100-positive dendritic cells are seen mainly around neovascularization (CD68, orig. ×20).*

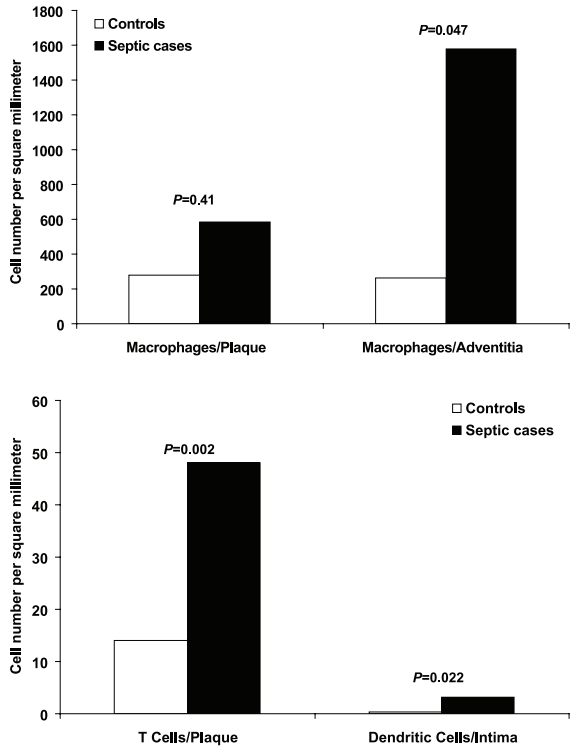

Fig. 4 *Higher numbers of macrophages (upper graph) and dendritic cells and T cells (lower graph) were observed in different layers of the atherosclerotic coronary lesions of infected patients versus control patients.*

been described as part of the inflammatory infiltrates that resemble mucosa-associated lymphoid tissue, where they intermingle closely with B lymphocytes.[32] Dendritic cells also interact closely with CD4 helper and CD8 cytotoxic cells.[33] In our study, dendritic cells were more numerous in the plaques of the infected group than in those of the control group. We infer that acute systemic infections, by increasing the number of dendritic cells, may enhance the immunologic reactions in the plaques and exacerbate the atherosclerotic process. Further studies are needed to evaluate this hypothesis.

Limitations

Although our study's low sample size might have decreased our power to detect some of the associations at an α level of 0.05, our main findings were statistically significant. At a higher sample size, our significant results would still be valid, and the observed trends—which are already biologically relevant—might also reach levels of significance.

Unfortunately, our autopsy study, by its very nature, limited the number of cases that could be studied. The small sample size did not enable us to differentiate between pathologic responses to different infections, such as gram-negative versus gram-positive infections and those at different loci. Nevertheless, given the long list of infectious agents linked to atherosclerosis and the central role of inflammation as a common final pathway for these agents' effects, we conclude that most acute systemic infections have similar nonspecific, injurious effects on the coronary arteries. In fact, the burden of infection itself may increase the risk of AMI.[4] More severe infections, such as influenza and SARS, may have a more profound effect on atherosclerotic disease and could warrant separate studies.[6]

Recent reports have suggested that statins can decrease morbidity and mortality rates in atherosclerotic patients who have sepsis.[34,35] Most of our patients had died in the early 1990s, when statin use was very low. In fact, of the patients in our study, only 1 had received lovastatin. Future studies should seek to determine whether statin use can decrease the recruitment of inflammatory cells to the coronary arteries. Statins may be especially useful in lowering the morbidity and mortality rates among people with and without atherosclerotic disease during a future influenza pandemic. In the event of such a disaster, we foresee a large rise in cardiovascular deaths because of the triggering effect of influenza on AMI.[36,37]

Implications

If further studies confirm that sepsis promotes the infiltration or survival of inflammatory cells in atherosclerotic arteries, many questions meriting further investigation will be suggested: Why are T cells and dendritic cells drawn to plaque, and macrophages to the adventitia? Is this also seen in atherosclerotic carotid arteries and the aorta? Are some microbes more likely than others to increase plaque inflammation? Does increased plaque inflammation increase the risk of rupture, erosion, or thrombosis? Does adventitial inflammation accelerate the progression of aneurysms? Are some arteries themselves infected? If so, is the inflammatory response beneficial or harmful? Although our study falls short of proving a causal relationship between the preceding systemic infection and the coronary inflammation observed at autopsy, our findings are supported by the growing body of evidence concerning the pivotal role of inflammatory cells in coronary events,[38] and these findings deserve further evaluation.

We noted 5 cases of AMI in the infected group, compared with only 1 old myocardial infarction in the control group. However, only 2 of these 5 AMIs had been detected clinically before the patients died—raising the possibility that, in patients with a systemic infection, AMI may easily be missed despite the increased chance of plaque destabilization. Our report highlights the need for clinicians to consider possible myocardial infarction when caring for septic patients.

Inflammatory mediators are central to the pathogenesis of septic shock and multiorgan failure, because sepsis results from an exaggerated systemic inflamma-

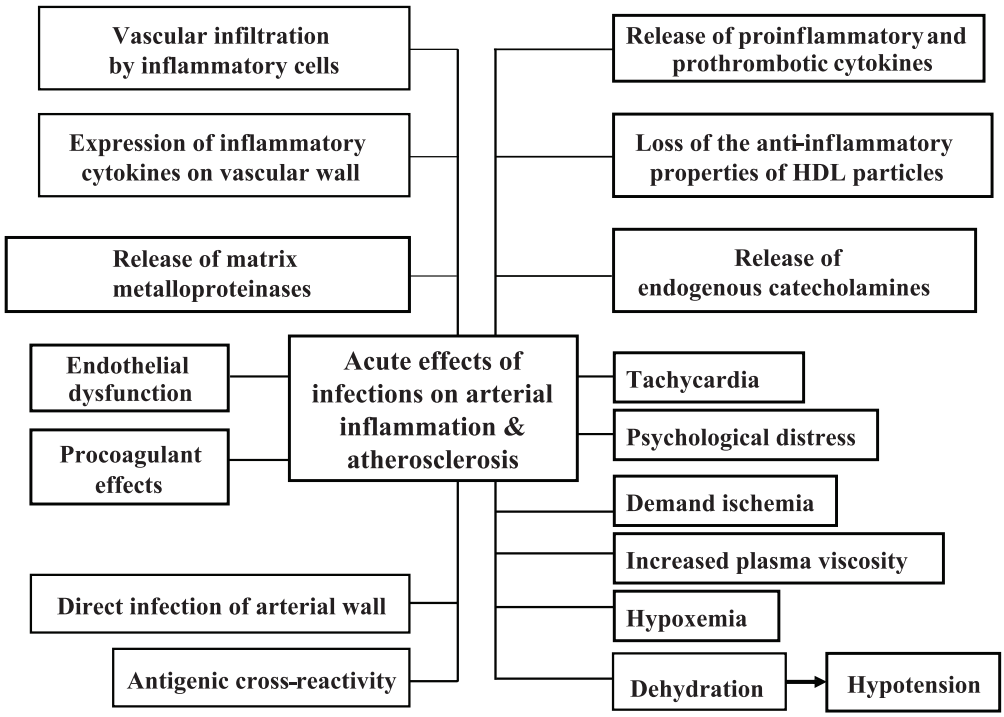

Fig. 5 *Various mechanisms by which acute infections may affect atherosclerotic plaques.*

tory host response induced by infectious organisms.[39] Clearly, the use of anti-inflammatory drugs and statins should be evaluated in patients who have coronary artery disease. These drugs may attenuate the dangerous effects of acute infections on atherosclerotic plaques. The severity of sepsis may be decreased by the administration of statin therapy before the onset of an acute bacterial infection.[40]

Aggressive anti-inflammatory treatment may be indicated for patients who develop an acute infection anywhere in the body. Our findings may also help explain why the risk of myocardial infarction is increased after surgical interventions (which may be associated with bacteremia), and why—if tooth-brushing leads to bacteremia—patients with periodontal disease have an increased rate of coronary and cerebral events.[41]

Therapeutic and prophylactic implications for clinicians and patients include oral hygiene; hand-washing; avoidance of infected persons; vaccinations (for example, for influenza, *Streptococcus pneumoniae*, and *Haemophilus influenzae*); new indications for antimicrobial, anti-inflammatory, and antithrombotic medications; and closer monitoring of at-risk patients.

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Surgical Techniques

Management of Air Embolism during HeartMate® XVE Exchange

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Air embolism is a rare and usually fatal complication of major cardiac surgery. We present a case in which a 45-year-old man supported by a HeartMate® XVE left ventricular assist device required a pump exchange due to failure of the device motor. During pump dissection, a massive amount of air entered the systemic circulation. Urgent cannulation for cardiopulmonary bypass was performed, and cardiopulmonary bypass was initiated, followed by profound hypothermia, circulatory arrest, retrograde cerebral perfusion, retrograde coronary sinus perfusion, and then barbiturate coma and steroid therapy. The HeartMate XVE left ventricular assist device was removed, and a HeartMate II was implanted. After 5 days, the patient awoke with left hemiparesis, which nearly resolved with aggressive physical therapy. Forty-four days after the pump exchange operation, the patient was discharged from the hospital with only mild left hemiparesis.

Exposure of the left ventricular assist device or its external components requires careful monitoring, because air can enter the pump—particularly in a hypovolemic patient. Rapid response after massive air entry into the left ventricular assist device system, as in our patient, can result in a successful outcome. ***(Tex Heart Inst J 2007;34:19-22)***

Key words: *Cardiopulmonary bypass; device removal; embolism, air/etiology/complications/therapy; heart assist devices/adverse effects; hemiparesis; hypothermia, induced; intraoperative complications; methylprednisolone succinate; thiopental*

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As the use of left ventricular assist devices (LVADs) increases, more device-related problems associated with long-term implantation may be expected. With the longer periods of LVAD support and increased frequency of pump failure and device infection, the requirement for device exchange is also increasing.[1,2] Although LVAD replacement methods for pulsatile pumps are improving, complications associated with this procedure remain.[3,4] Air embolism, which is caused by the presence of intracardiac or intradevice air at pump activation, is a highly unusual but possible complication of LVAD exchange.[5] Massive arterial air embolism during cardiac surgery is a rare complication that requires prompt action before substantial cerebral damage occurs. When this complication has occurred as a result of cardiopulmonary bypass (CPB), patients have been successfully treated with hypothermia and hyperbaric oxygen.[6,7] Although there is keen awareness of the potential for air embolism during LVAD implantation, few reports of this potentially catastrophic event appear in the medical literature.[8,9]

We present a case in which a patient experienced massive air embolism before replacement of an LVAD upon unroofing of the outflow conduit. The original device, the HeartMate® vented electric (XVE) LVAD (Thoratec Corporation; Pleasanton, Calif), was being replaced with a HeartMate II axial-flow LVAD (Thoratec). We discuss the possible causes of the embolism, describe steps to prevent such an occurrence during LVAD exchange, and suggest treatment strategies if embolism occurs.

Case Report

A 45-year-old man with a diagnosis of congestive heart failure and progressive end-organ dysfunction underwent implantation of a HeartMate XVE LVAD. After 28 months of support, a critical alarm by the LVAD controller indicated a temporary low flow or pump-off condition. At that time, an excessive amount of metallic dust from the vent filter was noted, and analysis of the dust showed an imminent threat of mechanical failure. The patient was promptly admitted to the hospital, and the LVAD stopped functioning during the patient's transport to his room. The LVAD was actuated pneumatically with a hand pump until it could be connected to a HeartMate pneumatic drive console. The patient remained hemodynamically stable, and an LVAD exchange procedure was performed the next day.

Surgical Technique

The HeartMate XVE was exchanged for the newer HeartMate II LVAD.[10] One provision of the HeartMate II protocol allows for enrollment of patients who have been supported by the HeartMate XVE LVAD and who have also experienced a failure of the system. In our patient, the left subcostal incision was performed first, which allowed easy exposure of the HeartMate XVE LVAD. After the LVAD housing was dissected, we dissected toward the outflow graft; the inflow at the apex had not yet been dissected. During dissection of the scar tissue around the outflow conduit, we discovered a blood leak around the screw ring connector that secures the outflow valve conduit to the LVAD (Fig. 1). Native cardiac function began to deteriorate rapidly, and transesophageal echocardiography (TEE) showed that the left ventricle (LV) and the aorta were filled with air. The XVE LVAD was turned off immediately. The patient was urgently cannulated through previously exposed femoral vessels. He was placed in the Trendelenburg position, and CPB was initiated immediately. Cooling of the patient to profound hypothermia was begun. Median sternotomy was performed, the heart was dissected free from adhesions, and the apex was exposed. The heart fibrillated when the body temperature reached approximately 28 °C. A retrograde cannula was placed into the coronary sinus for retrograde cold (4 °C) blood perfusion. The superior vena cava was cannulated with a 32F venous cannula connected to the cold-blood perfusion catheter. When the core body temperature reached 18 °C, CPB was stopped, and retrograde cerebral perfusion was initiated. The apex was dissected, and the ligatures securing the LVAD in the sewing ring were removed. The outflow graft was then freed, clamped, and divided.

The old LVAD driveline was divided at the entry site in the abdominal wall, and the pump was removed. The LV was explored through the apical sewing ring and was found to be free of clot. The LV cavity was filled with carbon dioxide gas, and the new HeartMate II inflow cannula was placed into the LV through the existing apical sewing ring. The inflow cannula was secured in the usual fashion. The aortic root was continuously de-aired through a vent needle and through the remaining outflow graft from the XVE pump.

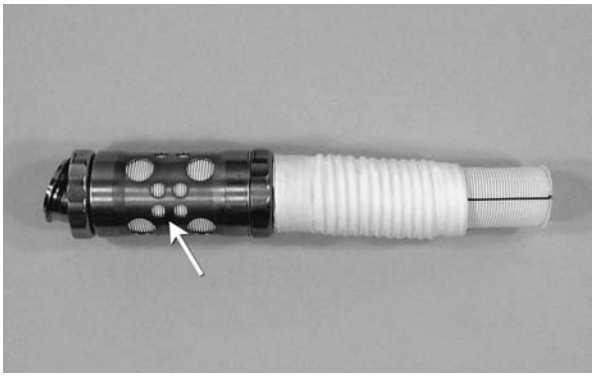

Fig. 1 *After dissection and exposure of the outflow conduit of the HeartMate XVE LVAD, a blood leak was observed at the connection of the conduit to the blood pump (arrow).*

Cerebral perfusion was then stopped, and CPB was reinstituted after approximately 20 min of circulatory arrest. Venting of the aorta was continued, and the patient was warmed to 30 °C. Then warm retrograde blood flow into the coronary sinus was started, and, at a core body temperature of 32 °C, the heart was defibrillated. Warming was completed at 36.5 °C. During this period, inotropic support was restarted. The HeartMate II was de-aired through a Penrose drain placed on the outflow elbow of the LVAD, while blood from the LV was allowed to flow through the pump. The HeartMate II outflow graft was sewn end-to-end to the previous HeartMate XVE graft during de-airing of the LVAD.

When the LV, left atrium, pulmonary artery, and aortic root were free of air, the new outflow graft was filled by retrograde blood flow from the aorta and then clamped. The Penrose drain was removed quickly from the HeartMate II, and the screw-ring connector from the graft to the HeartMate II outflow conduit was secured. De-airing from the aorta was continued, and the LVAD was started at 6,000 rpm. Weaning of the patient from CPB was begun, the outflow graft clamp was removed, cardiac chambers were checked for air on TEE, and the HeartMate II pump speed was slowly increased to 9,000 rpm. At that point, CPB was stopped. The vents from the aorta and the coronary perfusion catheter were removed after de-airing was completed. Hemostasis was achieved and decannulation was performed. Then the patient's chest was closed, and he was transferred to the intensive care unit.

Barbiturate coma was induced intraoperatively, with a loading dose of 1 mg/kg of thiopental sodium, and was then maintained with a continuous infusion rate of 0.5 mg/kg per min over the next 48 hr. An isoelectric electroencephalogram was achieved after the loading dose was administered. The patient's head was packed in ice to lower the cerebral temperature and metabolic rate. Methylprednisolone sodium succinate (1 g) was also given intraoperatively and was continued for 10 days at a dose of 0.5 g per day. Three days after the barbiturate coma was discontinued, the patient was awake and responsive. He initially suffered left-side hemiparesis that resolved with only left-upper-extremity residual muscle weakness, and he was discharged from the hospital 44 days after pump exchange. Despite left-arm weakness, the patient functioned adequately and tolerated his HeartMate II system without difficulty. Three months after the LVAD exchange, a donor heart was located, and he underwent successful transplantation.

Discussion

Cerebral air embolism in patients being supported by an LVAD can be catastrophic. The capacity of the HeartMate XVE blood pump is 83 mL per stroke, but the amount of blood that fills the pump is dependent on LV volume. Because the diaphragm within the pump recoils to its full-fill point, a vacuum can occur when there is insufficient LV volume. While open to the atmosphere, if the pump does not fill completely, air will be drawn into the pump and outflow conduit. The amount of air may be fairly small; nonetheless, at a pump rate of 50 beats/min or greater, the total amount of air pumped into the systemic circulation can increase very quickly if the problem is not detected immediately.

In our patient, we believe that the air began to enter the pump through a connector screw ring defect, just after the tissue surrounding the outflow conduit was dissected free. Then the air was pumped into the coronary as well as systemic circulation, depressing the cardiac function with a marked decrease in LV filling. The decreased filling of the pump allowed more air to enter. In just a few minutes, a large amount of air had been pumped into the systemic circulation and was eventually detected by TEE.

Extreme caution is mandatory whenever the chest is opened and an LVAD is in place. It is very important to use continuous TEE for monitoring during reopening of the chest in an LVAD-supported patient. The LVAD pump rate should be slowed to the lowest output that the patient will tolerate. The lower pump rates will allow more complete filling of the pump with higher stroke volumes and less risk of air entry. The left heart volume must be maintained at an adequate level to ensure that the LVAD pump fills fully. Use of inotropic and vasoactive medications may be necessary.

For our patient, the point of air entry into the LVAD was at the connection between the outflow valve conduit and the pump (Fig. 1). Blood escaped from this point during LVAD systole; however, during LVAD diastole, air entered the LVAD. The defect was of consequence only after the tissue surrounding this portion of the device was dissected free. Unroofing the leaking connector exposed the interior of the pump to the atmosphere. The porcine xenograft valve in the outflow conduit is located at the midpoint (Fig. 2). Below the valve, there is a potential for negative pressure and air entry into the blood chamber of the pump. Above the valve, air entry is much less likely because the pressure is always positive, as in the aorta. A deformed Teflon O-ring in the connector near the LVAD housing caused the leak.

Although the use of retrograde cerebral perfusion to decrease the effects of cerebral air embolism is not common, it is an established technique for cerebral protection in aortic surgery during circulatory arrest.[11-13] Hypothermic cerebral perfusion can potentially protect the brain from severe damage after an initial insult by lowering the metabolic rate of the brain during ischemia.[14-16] Retrograde hypothermic cerebral perfusion was implemented in our patient to expel any air from the cerebral circulation and to provide local cooling of the brain to minimize damage. Use of this technique during a procedure in which air has entered the arterial circulation through an LVAD has not been reported previously. A low cerebral metabolic rate was maintained by means of barbiturate coma, and aggressive steroid therapy was given in order to minimize inflammatory responses and edema. These measures have been effective in minimizing cerebral effects of brain injury.[17-21]

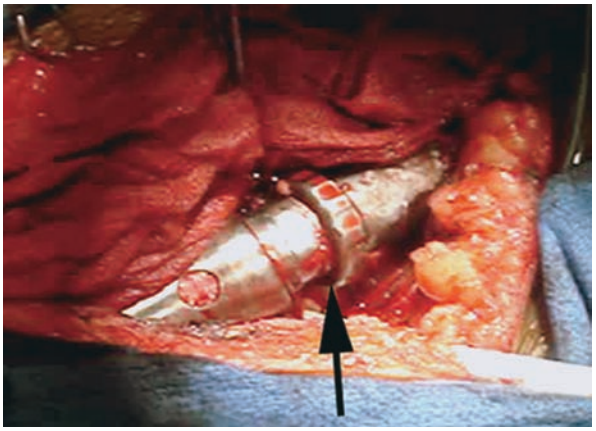

Fig. 2 *The HeartMate XVE outflow conduit shows the position of the valve (arrow). Below the valve, there is a potential for the highest negative pressure; however, above the valve, the pressure is at least as high as the aortic pressure.*

In summary, recognizing air embolism immediately during an LVAD implantation or exchange procedure is crucial. Any bleeding from a long-implanted device that is being exchanged should be a cause for alarm. Continuous monitoring with TEE during high-risk periods of an LVAD exchange is also extremely important. At any sign of air in the aorta, left atrium, or LV, the LVAD must be stopped immediately and urgent CPB initiated. In our patient, prompt cooling, circulatory arrest with retrograde cerebral perfusion, and retrograde coronary sinus perfusion helped minimize the damage to the brain and myocardium caused by air embolization. In addition, barbiturate coma and steroids implemented during device exchange appeared to help in our patient's management and survival. His recovery continues.

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Surgical Technique

Body Perfusion in Surgery of the Aortic Arch

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We propose a new cannulation and perfusion technique for aortic arch surgery, in order to achieve continuous antegrade total-body perfusion under moderate hypothermia.

The heart and the aortic arch are exposed through a median sternotomy. Cardiopulmonary bypass is established from the right atrium to the right axillary artery. At 26 °C of body temperature, the supra-aortic vessels are clamped, the ascending aorta and the aortic arch are incised, and a cuffed endotracheal cannula, connected to an arterial line geared by a separate roller pump, is inserted into the descending thoracic aorta. Perfusion is started in the distal body, while the brain is perfused through the right axillary artery. Once the aortic arch has been replaced with a Dacron graft and the supra-aortic vessels have been reimplanted on the graft, the arterial line in the descending thoracic aorta is clamped and removed. The supra-aortic vessel clamps are removed, the proximal part of the Dacron graft is clamped, and systemic cardiopulmonary bypass is resumed via the right axillary artery.

From January 2002 through December 2005, this technique was used in 12 consecutive patients on an emergency basis, due to acute aortic dissection that required total arch replacement. Within the first 30 postoperative days, 1 patient (8.3%) died, and no patient had permanent neurologic deficits.

This simple technique ensures a full-flow antegrade total-body perfusion during all phases of the surgical procedure, thereby eliminating ischemia–reperfusion syndrome and yielding excellent clinical results. ***(Tex Heart Inst J 2007;34:23-9)***

Key words: *Aortic aneurysm, thoracic/surgery; aneurysm, dissecting/surgery; aortic arch; blood flow velocity; blood vessel prosthesis implantation; brain ischemia/prevention & control; cardiopulmonary bypass/methods; cerebral protection; hypothermia, induced/adverse effects; ischemia/reperfusion; perfusion/methods*

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In aortic arch surgery, especially in the setting of acute aortic dissection, several perfusion and cannulation techniques developed in recent years have focused attention on the organ most sensitive to ischemia: the brain. However, a high incidence of complications involving other organs and tissues, and the considerable morbidity and mortality rates that ensue, have been reported in the worldwide literature regardless of the surgical strategies adopted.

While conscious of the importance of affording the best protection to the central nervous system, we turned our attention also to the protection of the rest of the body, in order to ensure enough time to perform safe and unhurried surgery of the aortic arch.

To date, hypothermia, either alone or in association with different methods of selective brain perfusion, has been used to ensure periods of circulatory arrest. Yet circulatory arrest, quite aside from the deleterious side effects of profound hypothermia, exposes all organs and tissues to ischemia–reperfusion injuries.

The surgical technique that we propose ensures continuous, total-body antegrade perfusion, central cannulation, and full-flow cardiopulmonary bypass (CPB) under moderate systemic hypothermia.

Preoperative Observations

From January 2002 through December 2005, 12 consecutive patients were operated upon by the same surgeon (GN) by means of this technique. The study was approved by our hospital's ethics committee, and all patients gave their informed consent to take part. All patients underwent surgery on an emergency basis due to Stanford type A acute aortic dissection. In 11 patients, the intimal tear, starting in the ascending aorta, involved the aortic arch; in 1 patient, the tear was in the proximal descending thoracic aorta. Nine patients were men; the ages of the 12 patients ranged from 58 to 78 years (mean age, 66 yr). In all patients, the diagnosis was made in the referring hospital by transthoracic echocardiography, and, in 9 patients, the diagnosis was confirmed by computed tomographic scanning.

On arrival in our emergency room, all patients underwent transesophageal echocardiography to locate the entry point and to determine the extent of the aortic dissection. Because most of the patients were operated upon at night, on an emergency basis, Doppler ultrasonography was unavailable for study of the extracranial vessels; and in no patient was preoperative cardiac catheterization or coronary arteriography performed, due to their unstable clinical condition. In 11 patients, we observed moderate-to-severe aortic valve insufficiency due to aortic valve cusp prolapse. Ten patients had a history of arterial hypertension, 3 had diabetes mellitus, and 8 were current tobacco smokers. The interval from initial symptoms to surgery varied from 6 to 21 hr (mean, 9 hr). On admission to the hospital, 3 patients were taken immediately to the operating room because of cardiogenic shock due to cardiac tamponade. For the other patients, the elapsed time from hospital admission to surgery varied from 1 to 3 hr.

Surgical Technique

Induction of anesthesia was obtained with low doses of propofol, fentanyl, midazolam, and pancuronium (0.1 mg/kg of body weight). Thirty mg/kg of methylprednisolone was administered as a bolus. Propofol and remifentanyl were used for maintenance of anesthesia. The alpha-stat method was used for blood-gas management. Both radial arteries were cannulated to monitor arterial blood pressure. With the patient placed in the standard supine position, the right axillary artery was exposed through a linear subclavicular incision. A median sternotomy incision was used in all cases to expose the heart, the ascending aorta, the aortic arch, and the arch vessels.

After the intravenous administration of heparin, an 8-mm polytetrafluoroethylene graft (W.L. Gore & Associates, Inc.; Flagstaff, Ariz) was anastomosed end-to-side to the right axillary artery and cannulated with a 21F femoral artery cannula. The right atrium was cannulated with a standard 36F 2-stage cannula for venous drainage.

Two arterial lines (lines 1 and 2), geared by separate single-head roller pumps (Stöckert Instrumente GmbH; Freiburg, Germany), were set. A Y connector was inserted on arterial line 1. The 1st line (line 1a) was used for systemic perfusion through the right axillary artery; the 2nd line (line 1b) was clamped. Arterial line 2 was connected to the side branch of the right axillary artery cannula and clamped. In case of a need to perfuse the left carotid artery (1 instance, in our series), a Y-connector cardioplegia set (Edwards Lifesciences; Irvine, Calif) was inserted on arterial line 2. One branch was connected to the right axillary arterial perfusion cannula, and the other branch was connected to a 12F retrograde cardioplegia catheter (Edwards Lifesciences) for left carotid artery perfusion. The arterial lines were all made from PVC Medy 6H (Sorin Biomedica Cardio S.p.A.; Via Crescentino, Italy) and were the following sizes: lines 1, 1a, and 1b, 3/8 in × 3/32 in; and line 2, 1/4 in × 3/32 in (Fig. 1).

Right atrium-to-right axillary CPB was instituted, a left ventricular vent was placed through the right superior pulmonary vein, and the patient was cooled. At a nasopharyngeal temperature of 26 °C, the supra-aortic vessels were clamped. No ice bags were placed around the patient's head, and no other forms of cerebral protection were used. Arterial line 1a was clamped and axillary artery perfusion was started through arterial line 2. Myocardial protection was achieved by retrograde administration of cold crystalloid cardioplegic solution (St. Thomas's Hospital No. 1), delivered every 30 min in the coronary sinus: the 1st dose was 10 mL/kg of body weight; the subsequent doses were 5 mL/kg of body weight, with an infusion pressure not above 40 mmHg. Antegrade administration of the cardioplegic solution was avoided to prevent any additional lesions of the coronary ostia, which were often involved in the dis-

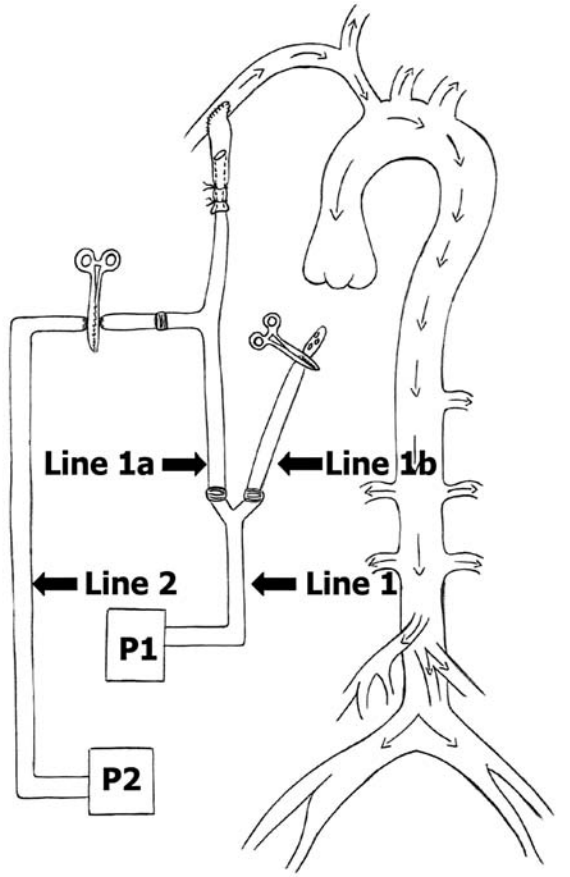

Fig. 1 *Two arterial lines (lines 1 and 2), geared by separate roller pumps (P1 and P2), are set. A Y connector is inserted in arterial line 1: line 1a is used for systemic perfusion through the right axillary artery, while line 1b is clamped. Arterial line 2 is connected to the side branch of the right axillary artery cannula and is clamped. The right atrium is cannulated for venous drainage. Right atrium-to-right axillary artery antegrade cardiopulmonary bypass is started.*

secting process. Pericardial cooling was achieved with ice-cold saline solution. After removal of the ascending aorta and the aortic arch, we chose a collagen-coated InterGard™ tubular graft (InterVascular; Montvale, NJ) of adequate size to replace the aortic arch. In this series of patients, no branched grafts were used to reimplant the supra-aortic vessels. In no instance was an elephant trunk procedure performed. The true lumen of the descending thoracic aorta was cannulated with an endotracheal cannula of 8 mm internal diameter, which was passed through the InterGard tubular graft and connected with arterial line 1b. The endotracheal cannula was tightly cuffed with saline solution to the descending thoracic aorta, and antegrade thoracic perfusion was started (Fig. 2). The opening of the aortic arch and the insertion of the endotracheal cannula into the descending thoracic aorta required a period of circulatory arrest in the distal body that ranged from 3 to 5 min, while the brain was perfused through the right axillary artery without interruption. Once the distal anastomosis of the vascular graft with the proximal descending thoracic aorta was complete and the supra-aortic arterial vessels were reimplanted on the graft, arterial line 1b was clamped and removed. The supra-aortic arterial clamps were removed, arterial line 2 was clamped, and total-body antegrade perfusion was resumed through arterial line 1a (Fig. 3).

During the rewarming phase, the proximal anastomosis of the vascular prosthesis to the ascending aorta was completed. In all cases, the aortic valve showed no disease. In 11 patients, the valve was resuspended to the aortic wall because of aortic valve cusp prolapse.

During CPB, the nasopharyngeal temperature was kept at 26 °C, and the perfusion flow rate was maintained at a constant 50 $mL \cdot min^{-1} \cdot kg^{-1}$. When the supra-aortic vessels were clamped, the flow rate into the axillary artery varied from 10 to 15 $mL \cdot min^{-1} \cdot kg^{-1}$, in order to obtain a right radial artery pressure of 50 to 60 mmHg; and the remainder of the perfusate was administered into the descending thoracic aorta at a flow rate that varied from 35 to 40 $mL \cdot min^{-1} \cdot kg^{-1}$, in order to obtain a total antegrade body perfusion at full flow during the entire surgical procedure.

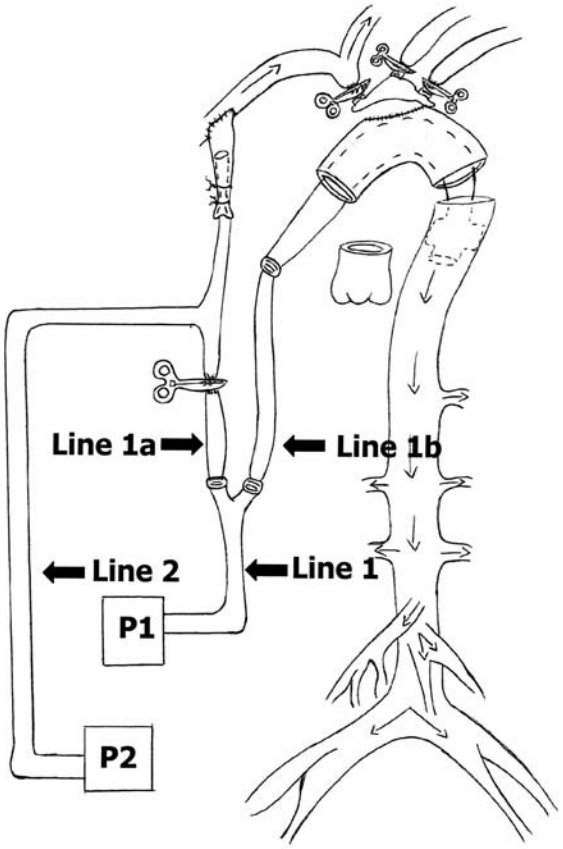

Fig. 2 *At 26 °C of body temperature, the supra-aortic vessels are clamped. Arterial line 1a is clamped, and axillary artery perfusion is started through arterial line 2. Cold crystalloid cardioplegic solution (St. Thomas' No. 1) is used to protect the heart. The ascending aorta and the aortic arch distal to the left subclavian artery are removed. The descending thoracic aorta is then cannulated with an endotracheal cannula (internal diameter, 8 mm) that is connected to arterial line 1b. The orotracheal cannula is cuffed, and antegrade thoracic perfusion is started.*

Postoperative Management

All patients were brought to the intensive care unit on mechanical ventilation. Inotropic agents were used when the cardiac index was less than 3.0 $L \cdot min^{-1} \cdot m^{-2}$, despite volume-loading to ensure pulmonary capillary wedge pressure of between 12 and 15 mmHg. Ten patients needed inotropic support for periods ranging from 2 to 6 days (mean, 4 ± 1 days). Sedation was carried out with continuous infusions of propofol and remifentanyl. Patients were allowed to awaken when stable cardiocirculatory conditions were reached on continuous positive airway pressure ventilation, with low doses of inotropic support, chest drainage <100 mL/hr, and urine output ≥1 mL/kg per hr, and when the patients were warm and cooperative.

Monitoring the Function of Organs

To evaluate the effects of total antegrade CPB on the renal and hepatic function of each patient, we compared preoperative values of blood urea nitrogen (BUN), serum creatinine, aspartate transaminase (AST), and alanine transaminase (ALT) with the same values obtained on the 4th postoperative day. Hourly urine output was also noted for the first 48 hr postoperatively. Pulmonary function was evaluated by monitoring length of intubation time, incidence of pulmonary infection, and presence or absence of acute respiratory distress syndrome (ARDS). Chest radiography was performed approximately 1 hr after admission to the intensive care unit, and then once a day. A radiologist who was blinded to the study scored

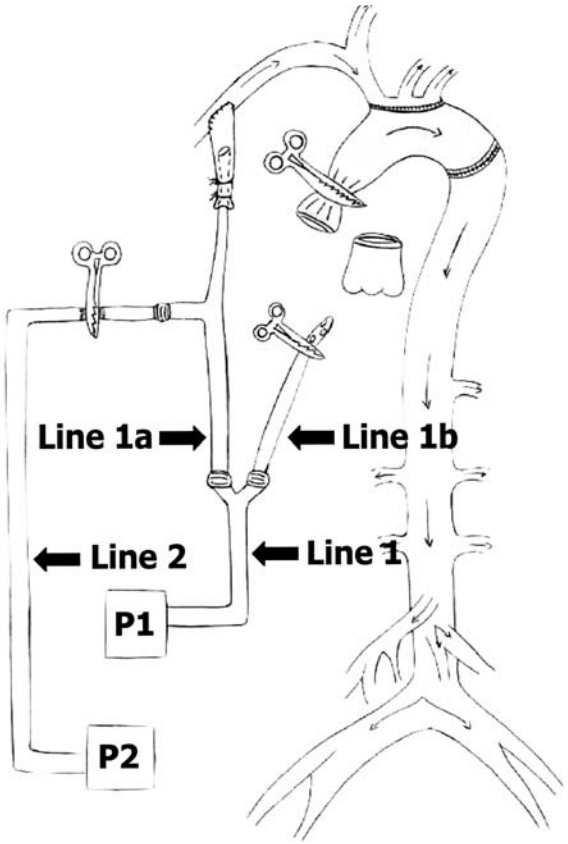

Fig. 3 *The aortic arch is replaced with a Dacron, collagen-impregnated tubular graft. Once the distal anastomosis is complete and the supra-aortic arterial vessels are implanted on the graft, arterial line 1b is clamped and removed. The supra-aortic artery clamps are removed, arterial line 2 is clamped, and total-body antegrade perfusion is resumed through arterial line 1a.*

chest radiography in accordance with the Lung Injury Score proposed by Murray and colleagues,[1] ranging from 0 (no infiltrate) to 4 (extensive alveolar consolidation).

Postoperatively, daily neurologic examinations were performed by a neurologist. A set of 3 neurocognitive tests was conducted by the same psychologist the day before the patients' discharge from the hospital: Raven's standard progressive matrices test, the Stroop task test, and the Rey auditory verbal learning test, to evaluate, respectively, the function of the right cerebral hemisphere and the parietal lobe, the dominant frontal lobe, and the limbic system.

During the first 6 months after discharge from the hospital, all of the surviving patients underwent follow-up transesophageal echocardiography or computed tomographic scanning.

Statistical Analysis

Data were expressed as mean ± standard deviation. The paired Student's *t*-test was used for comparisons of pre- and postoperative variable values. A P value <0.05 was considered statistically significant.

Results

The mean total CPB time was 188 ± 46 min (range, 110–235 min); the mean myocardial ischemia time was 113 ± 29 min (range, 63–138 min); and the mean supra-aortic vessel cross-clamp time was 60 ± 21 min (range, 33–97 min).

The only death in 30 days was that of 1 patient (8.3%), who died on the 2nd postoperative day, of low-cardiac-output syndrome. The mean hospital stay of the survivors was 12 ± 3 days. No permanent neurologic deficits were observed. One patient experienced a temporary neurologic deficit. Cognitive functions were preserved in all cases. Postoperatively, no cases of pulmonary insufficiency, infection, or ARDS were observed. The Lung Injury Score ranged from 0 to 2 (mean, 1.1), and the median intubation time was 13 hr (range, 6–9 hr). Hourly urine output was ≥1 mL/kg in all patients during their intensive care unit stay. The preoperative mean ± SD BUN and serum creatinine levels were 38.7 ± 9.5 and 0.85 ± 0.17 mg/dL, respectively. Postoperative levels of those same values were 56.7 ± 10.9 and 1.11 ± 0.35 mg/dL; differences were statistically significant only for the BUN values (Table I). Postoperative AST, ALT, and LDH values all increased without reaching statistical significance (Table I). The total mean blood loss from drainage was 900 ± 175 mL.

During the first 6 months of follow-up, we observed no additional intimal tears at the level of the insertion of the distal perfusion cannula into the proximal descending aorta.

Discussion

In aortic arch surgery, selection of the arterial cannulation site for CPB is of crucial importance. Our analysis of the literature showed that permanent neurologic damage results most often from strokes due to emboli or malperfusion and is not dependent upon the method of cerebral protection used during surgery.[2,3,6-9] The femoral artery has long been the preferred site of arterial cannulation. It is easy and fast to access, and it ensures a safe backup while the chest is opened in hemodynamically unstable patients. Major complications of femoral artery cannulation result from reversing the blood flow, which can cause embolic showers to the brain, the kidneys, and other organs. At the beginning of perfusion, when the body is warm, the effects of emboli are particularly dangerous.[2] Moreover, acute aortic dissection can redirect the blood flow into the false lumen through a distal re-entry site,[3] thereby causing malperfusion of various organs. Antegrade perfusion during CPB offers the opportunity to reduce the incidence of these possible complications.

At present, the right axillary artery seems to be the preferred site for arterial cannulation in aortic arch sur-

TABLE I. Pre- and Postoperative Measurements of Renal and Hepatic Function

Variable	Preoperative	Postoperative	*P* Value
Urea (mg/dL)	38.7 ± 9.5	56.7 ± 10.9	<0.001
Creatinine (mg/dL)	0.85 ± 0.17	1.11 ± 0.35	0.135
Aspartate transaminase (U/L)	37.2 ± 20.9	64.7 ± 52.13	0.216
Alanine transaminase (U/L)	33.5 ± 29.7	42.5 ± 24.5	0.577
Lactate dehydrogenase (U/L)	437.5 ± 112	668.8 ± 214	0.035

gery.[4,5] This artery is rarely involved in the dissection,[4,5] is rarely affected by atherosclerotic plaques, and is of adequate size to carry full-flow CPB in patients who have a large body-surface area. The brain is perfused with blood flow that has not passed through the often-atherosclerotic ascending aorta or arch. Cannulation of the right axillary artery ensures continuous antegrade cerebral perfusion, avoids manipulation of the supra-aortic vessels (which are often atherosclerotic or dissected), leaves a free operative field, and eliminates the need to change the cannulation site when the arch is replaced. The right axillary artery can be cannulated directly or by interposing a vascular graft. We prefer interposition because it affords the possibility of monitoring right radial artery pressure.

Unilateral selective cerebral perfusion has been criticized due to the risk of cerebral hyperperfusion or of inadequate perfusion of the contralateral hemisphere. On the basis of experimental data, Tanaka and colleagues[11] recommended a minimum mean carotid arterial pressure of 39.8 ± 6.2 mmHg at a flow rate of 50% of the physiologic level for safe, unilateral, selective cerebral perfusion at moderate hypothermia (25 °C). These conclusions have been confirmed by several clinical reports.[7,12,13] Using Tanaka's studies as a guide, we conducted selective unilateral cerebral perfusion at a flow rate of 10 to 15 $mL \cdot min^{-1} \cdot kg^{-1}$ in order to obtain a right radial artery mean pressure of 50 to 60 mmHg. We think that these higher values of mean arterial pressure in the right radial artery have to be reached because of the distal hyperperfusion provoked by axillary artery cannulation via the graft interposition technique. However, in no instance did the distal hyperperfusion provoke an evident clinical sequel in the right arms of our patients. In our series, cerebral hyperperfusion was avoided; we controlled hypertension by lowering the flow rate or by unclamping the origin of the left subclavian artery if the returning blood did not disturb the operative field. Postoperatively, no high-resistance complications such as hemorrhagic strokes were observed in our patients. The efficacy of contralateral hemispheric perfusion through the circle of Willis in this series of patients was evaluated intraoperatively, at the initiation of unilateral cerebral perfusion via the right axillary artery, by observing the amount of blood that returned from the left carotid artery before clamping it. The amount of blood that flowed down from the left carotid artery was judged satisfactory in 11 patients; in 1 patient, we selectively cannulated this artery to counter the risk of left-hemisphere hypoperfusion. Preoperative evaluation of the circle of Willis or more sophisticated monitoring of contralateral hemispheric perfusion during surgery could be used in elective surgical cases.

To ensure a bloodless operative field during surgery on the aortic arch, deep hypothermic circulatory arrest (DHCA) has been used alone or in association with various methods of retrograde or antegrade cerebral perfusion. Although DHCA is the simplest surgical technique, several disadvantages are related to it: suboptimal cerebral protection is reported after only 25 min of DHCA,[6] with decreased survival after 60 min.[7] Other authors have found that DHCA is an independent risk factor for cerebral injuries.[9]

Better results have been reported with antegrade cerebral perfusion conducted in association with periods of hypothermic circulatory arrest[2,3,9] at systemic temperatures of up to 25 °C.[10,14,16] The rationale for raising the body temperature during periods of circulatory arrest is to reduce the risks of coagulopathy and pulmonary insufficiency and to shorten the time of CPB. But maintaining circulatory arrest at moderate systemic hypothermia raises 2 questions: Can the spinal cord tolerate the prolonged periods of ischemia? What happens to the rest of the body when CPB is resumed? It is well known that normothermic CPB in itself can trigger a systemic inflammatory response syndrome that ends in diffuse endothelial cell injury and parenchymal dysfunction. Ischemia–reperfusion is a potent stimulator of endothelial-cell apoptosis and can induce multisystem organ dysfunction. Cooper and associates[15] showed experimentally that endothelial cells malfunction in large-caliber pulmonary veins and renal arteries in pigs undergoing DHCA, which causes renal insufficiency and ARDS. These data are confirmed in the clinical setting by the high incidence of pulmonary, renal, and mesenteric insufficiency reported in the literature in patients who undergo periods of circulatory arrest.[17-19] In 2003, Allen and coworkers[20] proposed avoiding the

"all-body reperfusion syndrome" by modifying the composition of the reperfusate.

The goal of our cannulation-and-perfusion technique is to reduce at minimum the period of circulatory arrest, while providing a dry operative field at the level of the aortic arch. Cannulation of the right axillary artery and the descending thoracic aorta provides total antegrade body perfusion at full flow in mild hypothermia during the entire surgical procedure. Perfusing the brain at a temperature well above 20 °C at a pressure of 50 to 70 mmHg preserves the autoregulation mechanism of cerebral blood flow.[21,22] In the present series of patients, the mean time of unilateral cerebral perfusion was always longer than 30 min; of particular importance, 1 patient reached 97 min without postoperative signs of cerebral hyperperfusion (edema) or hypoperfusion (stroke). Should right axillary artery cannulation not be sufficient to ensure satisfactory contralateral cerebral perfusion, as shown by scanty intraoperative blood flow from the unclamped left common carotid artery, the latter artery can easily be cannulated from inside the opened aorta. In such cases, we think that mild systemic hypothermia can be safely used.

Once the true lumen of the descending thoracic aorta has been cannulated with a cuffed cannula, full-flow antegrade perfusion of the thoracoabdominal organs, as happens in the usual CPB, is guaranteed. In our series of patients, pulmonary function was preserved in all cases, as shown by the short postoperative intubation times, the absence of episodes of pulmonary insufficiency or infection, and the good Lung Injury Scores upon serial chest radiography. Probably, these results are due to continuous perfusion of the lungs through the bronchial collateral circulation. The postoperative renal and hepatic functional tests showed values higher than the preoperative ones, but only the increase in BUN values reached statistical significance. Moreover, increases in these values are normally observed in patients who undergo CPB for routine cardiac surgical procedures.[23,24]

Conclusion

The aim of this technique is to avoid any period of circulatory arrest during aortic arch surgery, especially in the setting of acute aortic dissection. Ensuring antegrade perfusion at full flow for the entire body minimizes the systemic inflammatory syndrome and eliminates the ischemia–reperfusion syndrome. The presence of a cuffed perfusion cannula in the proximal descending aorta does not affect the execution of the distal anastomosis. Because the cuff of the endotracheal cannula is under low pressure and has a large area, inflation of the cuff to eliminate blood backflow does not provoke further trauma to the freshly dissected aorta and ensures a completely dry operative field.

The major limitations of this study are the small series of patients and the absence of comparative studies of other perfusion techniques, but the excellent clinical results so far obtained appear to confirm the validity of our technique. We believe that use of this perfusion technique will enable safe increases in the systemic temperature to 28 to 30 °C during CPB.

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Surgical Technique

Modified Inferior Vena Caval Anastomosis

to Reduce Tricuspid Valve Regurgitation after Heart Transplantation

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Postoperative tricuspid valve regurgitation is moderate to severe in 15% to 20% of heart transplant recipients despite use of the bicaval surgical technique. We hypothesized that the regurgitation might be partly due to increased tension on the donor right atrium.

To study the right atrial distortion, we modified the standard bicaval anastomosis. Our technique involves augmenting the donor right atrial anterior wall with a flap of the recipient's right atrium, which is left attached in continuity with the anterior aspect of the inferior vena cava along 65% of its circumference.

We measured tricuspid regurgitation, right atrial area, and right atrioventricular diameter in 7 consecutive patients who underwent orthotopic heart transplantation with the modified anastomosis. Tricuspid regurgitation was graded as follows: 1 = trace, <10%; 2 = mild, 10%–24%; 3 = moderate, 25%–50%; and 4 = severe, >50%.

All patients were weaned from inotropic support within 1 week after transplantation with excellent ventricular function, no heart block, and 100% survival at 30 days. The median follow-up time was 173 days (44–358 days). Other median measurements included tricuspid valve regurgitation jet area, 0.30 cm^2 (0–1.90 cm^2); right atrial area, 15.90 cm^2 (14.47–18.00 cm^2); atrioventricular diameter, 2.70 cm (2.63–3.09 cm); and tricuspid regurgitation, 1.67% (0–12.42%). Mild regurgitation occurred in 1 recipient; in all others, it was trace.

The modified inferior vena caval anastomosis is simple and safe. It eliminates moderate and severe tricuspid valve regurgitation without routine annuloplasty after orthotopic heart transplantation via the bicaval technique. ***(Tex Heart Inst J 2007;34:30-5)***

Key words: *Anastomosis, surgical/methods; bicaval anastomosis; echocardiography methods; heart atria/surgery; heart transplantation/adverse effects/pathology/methods/physiology; humans; tricuspid valve/surgery; tricuspid valve insufficiency/prevention & control; vena cava, inferior/surgery*

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Tricuspid valve regurgitation (TR) is recognized as a concern after orthotopic heart transplantation (OHT). Shown to correlate with the development of right-sided heart failure, TR has a negative influence on outcome.[1,2] Although TR can be treated medically, more severe cases frequently require surgical intervention.[3] Surgical techniques such as bicaval anastomosis or tricuspid valve annuloplasty at the time of OHT have been shown to minimize the incidence of TR.[4-7]

The technique described herein has been developed as a result of several intraoperative observations. Enlargement of the recipient's native failing heart increases all dimensions of the pericardial space, including the distance between the superior and inferior venae cavae. The traditional left atrial anastomosis affixes the posterior aspect of the right atrium (RA), which potentially limits the reach of the donor inferior vena cava (IVC) to the recipient's (Fig. 1A). This limitation can result in stress on the right-sided chambers of the donor heart. The resultant stretch on the anterior wall of the right atrium may cause tension on the tricuspid valve annulus (Fig. 1B), leading to valve incompetence. Such strain is easily corrected in the superior vena caval anastomosis, but not necessarily in that of the IVC. We hypothesized that relieving this tension could minimize distortion of the tricuspid valve, thereby reducing regurgitation. Herein, we review the results in patients who underwent our modified IVC anastomosis, which attempts to avoid RA and tricuspid valve distortion.

Patients and Methods

The lead author (DM) has been using this modified IVC anastomosis since 1997.

This retrospective review includes 7 consecutive recipients at Thomas Jefferson University Hospital during the first 13 months of its heart transplantation program (November 2004–November 2005). Institutional Review Board approval to review

the records was obtained. Only the records of routine studies were analyzed for the purposes of this study.

Patients' Demographics

All OHT recipients were men. Their median age at the time of transplantation was 57 years (range, 26–62 yr).

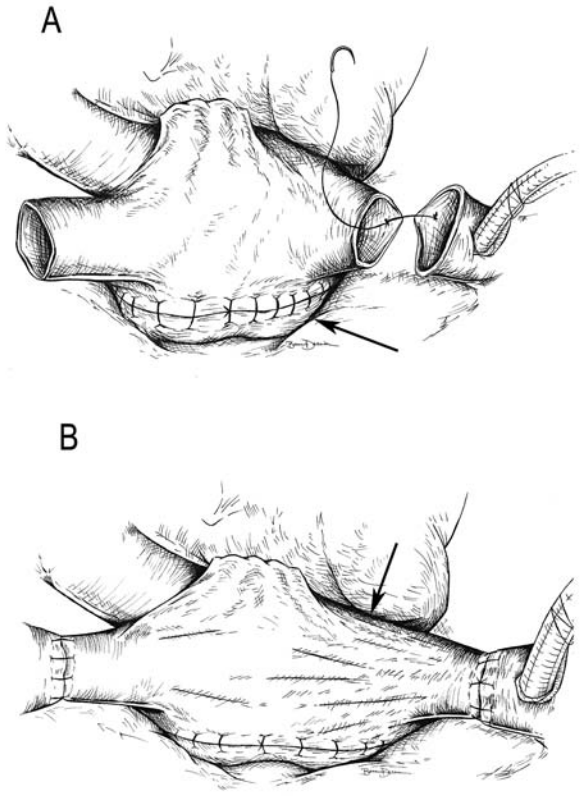

Fig. 1 *Right atrial tension in the traditional bicaval anastomosis.* ***A****) The left atrial anastomosis affixes the posterior aspect of the right atrial septum (arrow).* ***B****) Potential distortion of the donor right atrium due to increased distances in the recipient pericardium results in tension on the tricuspid valve annulus (arrow).*

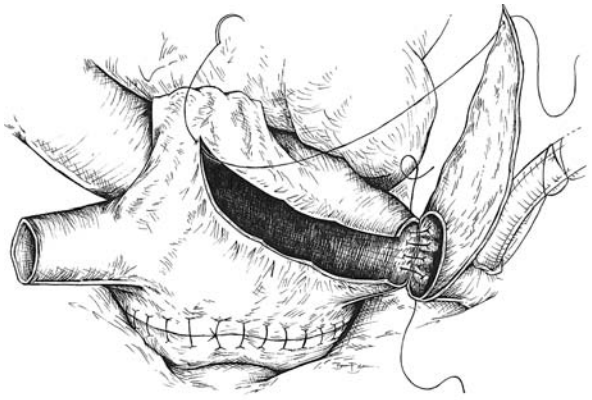

Fig. 2 *Modified inferior vena caval anastomosis. A flap of the recipient's right atrium, left attached to the native inferior vena cava, is used to augment the donor right atrium. The flap is then closed by extending the continuous suture line.*

The indications for transplantation were dilated cardiomyopathy (3 patients), ischemic cardiomyopathy (3), and valvular cardiomyopathy (1). The characteristics of the recipients and donors are summarized in Table I.

Organ Preservation, Surgical Technique, and Postoperative Care

Donor hearts were preserved, transported, and transplanted as described by Marelli and colleagues.[8] The donor hearts were pretreated with thyroid hormone. Then, University of Wisconsin solution (a total of 10–12 cc per kg of the donor's weight) was infused into each heart at a pressure of 80 mmHg, until arrest occurred. After arrest, infusion was maintained for 8 min at 50 mmHg. For transport, the donor hearts were immersed in University of Wisconsin solution and packed in ice at 4 °C. When the hearts reached their destination, cold Plasma-Lyte® A solution (Baxter Healthcare Corporation; Deerfield, Ill) was infused into the left ventricles to aid in topical cooling and the removal of air during implantation. Reperfusion was performed with leukocyte-depleted, aspartate-glutamate–enriched Buckberg cardioplegic solution for 3 min at 150 to 225 cc/min. Before the aortic clamps were released, the cardioplegic solution was followed with leukocyte-depleted warm blood for 10 min at a flow rate similar to that used during reperfusion.

The standard bicaval surgical technique was modified as follows: the IVC anastomosis was modified by the attachment of a triangular flap of the recipient's RA tissue to the anterior aspect of the native IVC remnant. The length of the attached edge of the flap was at least 65% of the circumference of the recipient's native IVC. Following the line of a conventional RA incision, we incised the donor RA from the corresponding point on the IVC anteriorly toward the RA appendage, away from the sinoatrial node. The flap was then incorporated into the continuous suture line to augment the donor RA (Fig. 2).

After transplantation, all patients were placed on inotropic support for at least 48 hours. They received standard triple immunosuppression (cyclosporine, mycophenolic acid, and prednisone) and prophylactic antibiotics per standard protocol. All patients underwent routine right heart catheterization and biopsy weekly for the first 4 to 6 postoperative weeks.

Study Design and Echocardiographic Follow-Up

A single experienced practitioner performed the echocardiography at least 30 days after transplantation. Short and long axes in 2-dimensional mode, M-mode, and color-flow Doppler echocardiography were used to calculate jet area, RA area, and right atrioventricular annulus diameter. The tricuspid regurgitation percentage (TR%) was calculated as (jet area/RA area) × 100. The TR% was graded as <10% = trace (grade 1), 10%

TABLE I. Recipient and Donor Characteristics

Patient		Diagnosis	Age (yr)	Height (cm)	Weight (kg)	LVEDD (cm)	BSA (m^2)	LVEDD/BSA
1	Recipient	ICM	62	178	113	7.5	2.3	3.3
	Donor		20	180	100		2.2	
2	Recipient	ICM	54	173	77	7.0	1.9	3.7
	Donor		37	185	76		2.0	
3	Recipient	VCM	57	163	54	6.1	1.6	3.8
	Donor		19	157	52		1.5	
4	Recipient	DCM	57	173	86	8.2	2.0	4.1
	Donor		31	170	60		1.7	
5	Recipient	DCM	45	180	74	9.3	1.9	4.9
	Donor		21	152	68		1.6	
6	Recipient	DCM	26	191	75	7.1	2.0	3.5
	Donor		44	180	82		2.0	
7	Recipient	ICM	60	188	115	6.7	2.4	2.8
	Donor		21	168	75		1.8	
Median	Recipient		57	178	77	7.1	2.0	3.7
	Donor		21	170	75		1.8	

BSA = body surface area; DCM = dilated cardiomyopathy; ICM = ischemic cardiomyopathy; LVEDD = left ventricular end-diastolic dimension; VCM = valvular cardiomyopathy

to 24% = mild (grade 2), 25% to 50% = moderate (grade 3), and >50% = severe (grade 4).[9] All studies were interpreted by a single observer (DZ). Echocardiographic measurements were done in triplicate at each time point.

Statistical Analysis

The surgical team's usual technique formed the basis of this observational study. The outcomes were compared with those of previously published reports. This comparison is justified by the similarity between the patients presented herein and those studied previously (Table II). Patient populations were compared using Student's *t*-test. Univariate linear regression analysis was performed by means of STATA statistical software, release 6.0 (StataCorp LP; College Station, Tex) to determine possible correlations between degree of TR and recipients' height, weight, and body surface area (BSA); the corresponding donor–recipient ratios; tricuspid valve annulus diameter; donors' age; ischemia time; and recipients' left ventricular end-diastolic dimension indices. A P value of ≤ 0.05 was considered significant. The BSA values were calculated by use of the Dubois equation.[10]

Results

The 30-day survival rate was 100%. There was no incidence of heart block. One patient died on postoperative day 51 of sepsis after small-bowel resection for a previously undiagnosed bleeding stromal tumor. No episodes of hemodynamically significant rejection occurred. Overall, no statistically significant preoperative demographic or clinical difference was observed between the patients described in previous studies[5] and those presented herein (Table II).

The last follow-up transthoracic echocardiograms of the 7 consecutive recipients who underwent the modified bicaval OHT during the enrollment period were reviewed (Table III). The median follow-up time at echocardiographic observation was 173 days (range, 44–358 days). The median TR% was 1.67% (range, 0–12.42%). One recipient had mild TR; all others had trace TR. The median TR grade was 1, indicating trace TR. Four of the recipients were analyzed at 2 time points after transplantation. Two of these patients presented with trace TR at both examinations, and the other 2 improved from mild to trace TR. Except for the patient who died at 51 days, all recipients had trace regurgitation of less than 6% (Table III) at the end of the follow-up period.

The median number of biopsies was 12 (range, 1–17). No correlation was found between the number of biopsies and TR. To determine whether a recipient and donor size-mismatch could explain the progression of TR, single linear regression was used to examine the relationship between TR and pertinent donor–recipient ratios. The median donor–recipient height ratios were 0.94 (range, 0.84–1.07) and weight ratios were 0.92 (range, 0.65–1.08). The median BSA ratio was 0.96

TABLE II. Characteristics of Patients Enrolled in Present Study Compared with Those Reported by Jeevanandam and Associates[5]

	Present Study	Jeevanandam and Associates[5]	
	Modified Bicaval (n=7)	**Standard OHT** (n=30)	**Bicaval OHT with Tricuspid Valve Annuloplasty** (n=30)
Recipients			
Age (yr)	51.6 ± 12.6	53.1 ± 12.2	51.1 ± 11.7
Height (cm)	179.9 ± 7.1	169.2 ± 12.7 *	172.2 ± 10.7
Weight (kg)	85 ± 22	80 ± 12.7	79.5 ± 18.7
Diagnosis % (n)			
Ischemic	43 (3)	43 (13)	43 (13)
Idiopathic	43 (3)	57 (17)	53 (16)
Other	14 (1)	0 (0)	3 (3)
UNOS status % (n)			
I	100 (7)	90 (27)	87 (26)
II		10 (3)	13 (4)
Donors			
Age (yr)	27.6 ± 10	26 ± 13.1	26.9 ± 13.6
Height (cm)	170.3 ± 12.4	161 ± 35.9	167.5 ± 16.2
Weight (kg)	73.3 ± 15.6	65 ± 19.5	67.5 ± 19.5
Donor–recipient weight ratio	0.9 ± 1.6	0.80 ± 0.2	0.80 ± 0.2
Organ ischemia time (min)	254 ± 69.8	208 ± 83.7	198 ± 74.2

*Patients who underwent standard orthotopic heart transplantation in the Jeevanandam study were slightly, but significantly, shorter in height than those in our study (P=0.04). No other statistically significant differences regarding recipients or donors were observed.

OHT = orthotopic heart transplantation; UNOS = United Network for Organ Sharing

TABLE III. Tricuspid Valve Regurgitation

Patient	Jet Area (cm^2)	RA Area (cm^2)	TR%	TR Grade	TV Annulus Diameter (cm)
1	0.30	18.0	1.67	1	2.7
2	0.80	15.0	5.33	1	2.6
3	1.90	15.3	12.42	2	2.7
4	0.03	15.9	0.19	1	2.6
5	0.80	14.5	5.52	1	3.1
6	0.27	17.4	1.72	1	3.0
7	0	16.9	0	1	3.0
Median	0.30	15.9	1.7	1	2.7

RA = right atrial; TR% = percentage of tricuspid regurgitation, defined as the percent-ratio of jet area-to-right atrial area; TV = tricuspid valve

(range, 0.77–1.18). No significant correlations were found between TR% and recipient height, weight, or left ventricular end-diastolic dimension; donor–recipient weight, BSA, or height ratios; tricuspid valve annulus diameter; donor age; or ischemia time. Linear regression analysis showed that the TR% was possibly related to the annulus size/recipient weight index with a regression coefficient of 3.28 (95% confidence interval; range, 0.69–6.85; P=0.026; R^2=0.55).

Table IV compares the results of this technique with those of other published techniques. In the present study, recipients did not exhibit any moderate or severe TR.

Discussion

Development of TR after OHT is associated with morbidity and death. Even mild intraoperative TR (≥ grade 2) decreases long-term survival after OHT.[1]

TABLE IV. Comparison of the Incidence of Tricuspid Regurgitation among Various Studies Using Different Heart Transplantation Techniques

Study	Technique	Trace TR	Mild TR	Moderate-to-Severe TR
Aziz T, et al.[4]	Standard		72%*	28%
	Bicaval		93%*	7%
Jeevanandam V, et al.[5]	Bicaval	66%	27%	7%
	Bicaval with tricuspid valve annuloplasty	100%	0	0
Present study	Modified bicaval	85%	15%	0

*Trace and mild TR were combined.

TR = tricuspid regurgitation

Long-term moderate-to-severe TR leads to right-sided heart failure and potential kidney and liver failure.[2,11] Determining the origin of TR after OHT is complex. Proposed mechanisms include atrial dysfunction, asynchronous contraction of the donor and recipient RA remnants, and distortion of the RA geometry.[12,13] The bicaval anastomosis ameliorates TR by decreasing the RA distortion that can occur with the standard biatrial technique. The bicaval technique reduces the incidence of moderate-to-severe TR after OHT from 35% to 17% of patients.[4] Some studies have shown a possible link between the number of endomyocardial biopsies and the development of TR, leading some researchers to suggest limiting the number of endomyocardial biopsies, if possible.[14,15]

Recently, prophylactic tricuspid valve annuloplasty has been used to decrease TR in both the standard biatrial and the bicaval anastomosis.[5,16] In a 1-year follow-up of tricuspid valve annuloplasty after bicaval OHT, all patients had ≤ grade 1 TR.[5,16] Although those results are promising, annuloplasty adds to the complexity of the operation. Prophylactic annuloplasty introduces these risks: addition of a foreign body, which increases the possibility of infection; additional manipulation at the time of OHT; and possible iatrogenic injury to the atrioventricular node. Ideally, such hazards could be avoided by applying annuloplasty selectively. There is no accepted way to reliably make this prediction at present.

Our modified IVC anastomosis has been used extensively by author Daniel Marelli since 1997, but it was not formally studied until now. The modified procedure avoids possible stretching of the donor RA during OHT when the donor and recipient superior vena cava and IVC are joined; such stretching can occur with the standard bicaval technique. Augmentation of the implanted RA with a patch of recipient RA restores a tension-free geometry to the right-sided atrioventricular junction of the donor heart in an often-dilated pericardial space. The donor RA is allowed to relax toward the atrioventricular groove that marks the location of the tricuspid valve, enabling improved RA function and decreased TR. Because the incision is made toward the right atrial appendage, away from the sinoatrial node, none of our patients required permanent pacing. In addition, the donor RA incision can facilitate access to the tricuspid valve if annuloplasty is needed to complement the modified IVC anastomosis.

Dandel and associates[17] described an augmentation similar to ours, for use with the standard biatrial cuff anastomosis; their technique reduced the incidence of moderate or severe TR to 12.7%, compared with the previously published 35% after use of the biatrial technique. Our procedure results in significantly less TR than does the standard bicaval anastomosis for OHT, which has a low, but not absent, 17% incidence of moderate or severe TR (Table IV).[4] None of our patients had moderate or severe TR, and 85% of our patients had only trace TR, indicating that our technique compares favorably with annuloplasty in limiting post-transplantation TR. Mild TR was observed in the recipient with the shortest follow-up time, and he also had valvular cardiomyopathy. One can speculate that such recipients have a tendency toward higher or reactive pulmonary vascular resistance and would therefore benefit from selective use of annuloplasty. Of note, 2 recipients showed improvement from mild to trace TR over time.

We predict that our results will remain consistent when our technique is applied to larger numbers of patients. The patients enrolled in our study had baseline characteristics similar to those in studies with larger sample sizes. Although the small numbers in our study did not permit definitive prediction of TR, the patients presented herein had a narrow range of tricuspid annulus size (between 26 and 30 mm). There was a possible correlation found between TR% and the annulus–

recipient weight index. Additional prospective studies with larger numbers of patients will better reveal whether there is a consistent way to predict TR after bicaval anastomosis, which could suggest an endpoint by which to measure tricuspid valve distortion among the various right atrial connection techniques.

Acknowledgment

We would like to thank Brandice Durkan for drawing the figures presented herein.

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Clinical Investigation

Percutaneous Ventricular Assist during Aortic Valvuloplasty

Potential Application to the Deployment of Aortic Stent-Valves

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We evaluated the short-term safety and efficacy of using the TandemHeart® percutaneous ventricular assist device in high-risk patients undergoing aortic valvuloplasty procedures.

Aortic valvuloplasty was performed in 4 patients who had no ventricular assist device support and in 7 patients who used the TandemHeart for hemodynamic support. The age range was 65 to 94 years (mean, 83 ± 11 yr). The mean ejection fraction was 0.30 ± 0.14. A transseptal antegrade approach to the aortic valve was used in 8 patients and a retrograde approach in the remaining 3.

With the TandemHeart, all procedures were technically successful: each patient survived at least 1 month after the procedure. The mean total balloon inflation time was 37 ± 10 sec. The aortic valve area was 0.6 ± 0.1 cm² before the procedure and 0.9 ± 0.2 cm² afterwards (P=0.006). Without TandemHeart support, 1 patient died of cardiac arrest during the procedure. The mean total balloon inflation time was 11 ± 3 sec. Aortic valve area was 0.6 ± 0 cm² before the procedure and 1.1 ± 0.3 cm² afterwards (P=0.3). No patient developed aortic regurgitation.

We conclude that use of the TandemHeart for hemodynamic support during high-risk aortic valvuloplasty is associated with favorable intraprocedural and short-term outcomes. With the TandemHeart in place, balloon placement was precise, and inflation was maintained for up to 45 sec without balloon displacement. These attributes are essential during stent-valve placement, are achieved without rapid ventricular pacing, and may reduce the risk of global ischemia and death. ***(Tex Heart Inst J 2007;34:36-40)***

Key words: *Aged; aged, 80 and over; aortic valve stenosis/therapy; balloon dilatation; calcinosis; heart-assist devices; heart catheterization; hemodynamic processes*

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Aortic valve replacement is the treatment of choice for severe aortic stenosis.[1] However, the surgical procedure has an operative mortality rate that ranges from 10% to 50% when performed in high-risk patients with comorbid conditions such as left ventricular failure, concomitant coronary artery disease with prior bypass surgery, chronic obstructive pulmonary disease, small body surface area, and advanced age.[2] In such cases, percutaneous aortic balloon valvuloplasty (PABV) has been used as an alternative or as a bridge to surgical valve replacement.[3] To decrease risks in this procedure, a number of circulatory support techniques have been used, including intra-aortic balloon counterpulsation[4,5] and percutaneous cardiopulmonary support.[6] The TandemHeart®[7,8] (CardiacAssist, Inc.; Pittsburgh, Pa) is a left ventricular assist device (LVAD) that can be placed percutaneously to provide short-term cardiac support for high-risk patients who are undergoing cardiac procedures. We performed this study in order to evaluate the short-term safety and efficacy of using the TandemHeart in high-risk patients who undergo aortic valvuloplasty procedures.

Patients and Methods

Patient Population

From May 2003 through August 2005, 11 patients (age, 83 ± 11 yr; range, 62–94 yr; 6 men [55%]) with symptomatic valvular aortic stenosis underwent PABV procedures at our institution (Table I). All patients had previously been evaluated by both a cardiologist and a cardiothoracic surgeon and had been found to be unsuitable candidates for valve replacement surgery. The valvuloplasty was performed in

TABLE I. Patient Characteristics (n=11)

	Variable
Age at valvuloplasty (yr)	83 ± 11
Male	6 (55%)
Coronary artery disease	4 (36%)
With TandemHeart	7 (63%)
Baseline ejection fraction	0.31 ± 0.14
Baseline aortic valve area (cm^2)	0.62 ± 0.12
Baseline transaortic valve gradient (mmHg)	58.3 ± 17.8

Data are expressed as number, percent, or mean ± SD.

4 patients without any LVAD support, and 7 patients were treated using the TandemHeart for increased hemodynamic stability. The decision to use the TandemHeart device depended on its availability and not on any patient characteristics. Transthoracic and transesophageal echocardiography in each patient showed a severely calcified aortic valve, with a mean valve area of 0.62 ± 0.12 cm^2.

Valvuloplasty Procedure

Percutaneous aortic balloon valvuloplasty was performed after informed consent was obtained. Conscious sedation was used in 5 patients, and general anesthesia was used in the other 6. Venous access from the right femoral vein was attained with a 6F sheath, and subsequently the access site was dilated in a stepwise fashion until a 14F sheath was placed. The left atrium was reached by means of an 8F Mullins sheath (Cook Medical Inc.; Bloomington, Ind) from the right femoral vein, using standard transseptal puncture techniques. Intracardiac echocardiography was used to guide the transseptal puncture in 5 cases. Heparin was administered to maintain the activated whole blood clotting time (ACT) between 250 and 300 sec.

Subsequently, a 7F Berman end-holed catheter (Arrow International; Reading, Pa) was advanced—using balloon flotation together with a 0.038-inch hydrophilic or Wholey guidewire (Mallinckrodt, Inc.; Hazelwood, Mo)—through the Mullins sheath into the left atrium, then into the left ventricle and past the left ventricular outflow tract, and then across the aortic valve into the aortic arch. At this point, the guidewire was removed and replaced with a 0.032-inch stiff exchange-length 260-cm wire. This was passed through the Berman catheter into the abdominal aorta. The 0.032-inch wire was snared in the distal abdominal aorta and secured by means of a 15-mm microsnare catheter. The snare was secured to the wire and left inside a 60-cm left femoral artery sheath, providing support to advance an Inoue balloon catheter (Toray Marketing & Sales, Inc.; Houston, Tex) from the right femoral vein through the atria and left ventricle, and then across the aortic valve. The balloon was inflated across the aortic valve to a diameter of 22 to 26 mm. The Inoue balloon could not be advanced antegrade in 3 of the 11 patients; the procedure was tried by the retrograde approach in those cases. In 2 patients, the Inoue balloon could not be advanced even retrograde, so a Medi-tech balloon (Boston Scientific; Natick, Mass) was passed in a retrograde fashion. In all, we used the Inoue balloon in 9 procedures (1 retrograde approach and 8 antegrade approaches) and the Medi-tech balloon in 2 procedures (both via retrograde approaches).

Implantation of TandemHeart

The technique for insertion of the TandemHeart has been described previously.[7,8] Briefly, a 21F catheter is placed in the left atrium to withdraw oxygenated blood and to decompress the left ventricle. The blood is circulated via a centrifugal pump, and it re-enters the arterial system at a rate of up to 4 L/min, through a 15F or 17F cannula placed in the femoral artery.

Statistical Analysis

Normally distributed data are presented as mean ± standard deviation. Serial comparisons between baseline and follow-up were determined by the paired Student's *t* test. Comparisons between the 2 groups were determined by the unpaired Student's *t* test. A χ^2 or a Fisher's exact test was used to find significant differences between categorical variables. The level of significance was set at $P < 0.05$. For statistical evaluation, SPSS software, version 11.5 (SPSS Inc.; Chicago, Ill) was used.

Results

Of the 11 patients with symptomatic valvular aortic stenosis who underwent a PABV procedure, all were deemed high-risk surgical candidates due to advanced age and comorbidities; their mean ejection fraction was 0.30 ± 0.14). Of the 4 patients who underwent valvuloplasty without LVAD support, 1 died during the procedure, and another died the next day. All 7 patients who had TandemHeart assistance survived for at least 1 month after the procedure.

With TandemHeart Assistance

Aortic valvuloplasty with TandemHeart assistance was performed in 7 patients (4 of them men) who had a mean age of 79 ± 12 yr) (Table II). The average output of the TandemHeart device was 3.0 ± 0.7 L/min. The antegrade approach to the aortic valve was used in 4 patients, and the retrograde approach was used in the remaining 3 patients. The Inoue balloon was used in 5 of the procedures, and a Medi-tech balloon was used

TABLE II. Comparison of Clinical and Hemodynamic Characteristics with or without TandemHeart

Variable		TandemHeart **Yes** (n=7)	TandemHeart **No** (n=4)	***P* Value**
Age at valvuloplasty (yr)		79 ± 12	89 ± 6	0.2
Male		4 (57)	2 (50)	1
Antegrade approach (%)		4 (57)	4 (100)	0.2
Coronary disease (%)		2 (29)	2 (50)	0.6
Balloon diameter (mm)		23.6 ± 4.0	24.3 ± 1.3	0.8
Number of balloon inflations		2.3 ± 0.8	2.8 ± 1.5	0.5
Total inflation time (sec)		37.1 ± 9.5	11.3 ± 2.5	0.001
Baseline ejection fraction		0.24 ± 0.09	0.47 ± 0.10	0.005
Baseline aortic valve area (cm^2)		0.59 ± 0.11	0.68 ± 0.14	0.3
Baseline transaortic valve gradient (mmHg)		61.5 ± 20.9	52.8 ± 11.1	0.5
Procedure time (min)		336 ± 111	183 ± 41	0.011
Fluoroscopy time (min)		52 ± 20	32 ± 10	0.1
Results before and after the procedure				
Ejection fraction	before	0.24 ± 0.09	—	
	after	0.27 ± 0.08 (*P*=0.28)	—	
Aortic valve area (cm^2)	before	0.59 ± 0.11	0.60 ± 0.00	
	after	0.88 ± 0.22 (*P*=0.006)	1.06 ± 0.34 (*P*=0.3)	
Aortic valve gradient (mmHg)	before	61.5 ± 20.9	53.3 ± 13.6	
	after	44.6 ± 15.1 (*P*=0.02)	27.7 ± 14.2 (*P* <0.0001)	

Data are expressed as number, percent, or mean ± SD.

in 2. Two of the patients had coexistent coronary artery disease and required coronary stenting in addition to the valvuloplasty: 1 patient underwent concurrent carotid artery stenting, and the other underwent concurrent iliac artery stenting. All of the procedures were technically successful, because each patient survived at least 1 month after the procedure. The long-term benefit was variable and depended on the baseline ejection fraction and on the patient's comorbid conditions. On echocardiography, aortic valve function improved: the aortic valve area increased from 0.59 ± 0.11 cm^2 to 0.88 ± 0.22 cm^2 (*P*=0.006), and the transvalvular gradient decreased from 61.5 ± 20.9 mmHg to 44.6 ± 15.1 mmHg (*P*=0.02). No patient developed aortic regurgitation or had significant hemolysis. One patient had major bleeding and required blood transfusion (5 units). The mean duration of the procedures, including concomitant coronary artery stenting, was 336 ± 111 min, and the mean fluoroscopy time was 52 ± 20 min. Patients were connected to the TandemHeart for a mean duration of 40 ± 86 hr (range, 1.5–216 hr). Most (6 of 7) had the TandemHeart only temporarily; it was removed in the catheterization laboratory or shortly after the procedure. Surgical repair of the TandemHeart insertion site was required in 4 of 7 patients.

Without TandemHeart Assistance

Four patients (mean age, 89 ± 6 yr) underwent valvuloplasties without LVAD support (Table II). The Inoue balloon, advanced antegrade in all cases, was inflated an average of 2.8 ± 1.5 times, to an average diameter of 24.3 ± 1.3 mm. The average maximum inflation time was 4.5 ± 1.0 sec/inflation, and the average total inflation time was 11.3 ± 2.5 sec. The average ejection fraction was 0.47 ± 0.10. Two of the patients had coexistent coronary artery disease that required coronary artery stenting, and 1 patient presented with an acute myocardial infarction. One patient died of cardiac arrest during the procedure. It is believed that the wire compressed the anterior leaflet of the mitral valve, causing mitral regurgitation, which in turn produced systemic hypotension and pulmonary edema. Another patient had a technically successful procedure but died the following day. Before the procedure, this patient had presented with cardiogenic shock that had required hemodynamic support with multiple vasopressors. The cause of death was brady/asystolic cardiac arrest.

Aortic valve function improved, as evaluated by post-procedure echocardiography: the transvalvular gradient decreased from 53.3 ± 13.6 mmHg to 27.7 ± 14.2 mmHg, and the aortic valve area increased from 0.60 ± 0 cm^2 to 1.06 ± 0.34 cm^2. No patient sustained aortic regurgitation or significant hemolysis. The mean duration of the procedures was 183 ± 41 min, and the mean fluoroscopy time was 32 ± 10 min.

Discussion

This was a small series of PABV performed in very ill patients—nonsurgical candidates with critical aortic stenosis. It has been shown that PABV usually reduces transaortic valve gradients, increases calculated aortic valve areas, and improves left ventricular ejection fractions.[9-11] However, short- and intermediate-term follow-up data indicate that these cardiac hemodynamic variables can revert to their pre-valvuloplasty baseline levels as early as 2 hours after the procedure.[12] These observations demonstrate that balloon valvuloplasty in calcific aortic valve stenosis is a palliative procedure. The results of these aortic balloon dilations, by either the antegrade or the retrograde approach, do not provide dramatic improvements. Nevertheless, the procedure did provide some temporary relief in most of our patients, reduced instances of congestive heart failure, and improved their functional status for a few months. In 2 of the patients who received the TandemHeart device, PABV served as a successful bridge to surgical valve replacement.

The elective use of the TandemHeart for circulatory support during these high-risk balloon valvuloplasty procedures preserved hemodynamic stability in our patients, regardless of the intrinsic cardiac function, and enabled precise placement of the valvuloplasty balloon. In addition, balloon expansion was maintained continuously for up to 45 sec without forward flow across the aortic valve and without balloon displacement. These attributes of precise positioning and adequate time for inflation without ejection of the balloon are essential during stent-valve placement. The development by Cribier and associates[13] of percutaneous implantable prosthetic aortic valves could, in the near future, offer an alternative to patients in similar clinical conditions and perhaps improve the long-term prognoses. Ideally, patients with critical, inoperable aortic stenosis might be treated with nonsurgical implantation of a prosthetic aortic valve, and PABV might be used as a bridge to this procedure in selected patients. To prevent stent-valve displacement during balloon inflation, it has been recommended that operators decrease aortic blood flow during device delivery by means of rapid cardiac pacing (200–220 beats/min) of the right ventricle. In place of this rapid pacing, use of the TandemHeart can support the circulation and unload the left ventricle during deployment of a stent-valve, thereby reducing the risk of global ischemia and death in this high-risk patient group. Moreover, some of the other techniques for percutaneous placement of prosthetic aortic valves, now under development,[14] may be facilitated by percutaneous LVAD hemodynamic support, because they too will require precise placement.

These observations are presented in the hope of providing a methodological concept to improve the safety and accuracy of percutaneous aortic valve placement. In the initial group of 20 high-risk patients with critical aortic stenosis who received the Cribier-Edwards percutaneous valve (Edwards Lifesciences; Irvine, Calif),[15,16] the mortality rate was approximately 20%. There are several explanations of why this initial mortality rate was so high, but possible reasons include the premorbid condition of the patients, the need to rapidly pace the right ventricle to temporarily decrease cardiac output so that the balloon will stay in place during the crucial seconds of stent-valve deployment, and the development of significant paravalvular aortic regurgitation. For at least 1 of these patients, rapid right ventricular pacing induced ventricular fibrillation. In addition, use of the antegrade approach can place pressure on the anterior mitral valve leaflet, drawing it anteriorly toward the left ventricular outflow tract, thereby producing mitral regurgitation. This hemodynamic stress—poorly tolerated by the hypertrophied, poorly compliant left ventricle—can result in global left ventricular ischemia with release of intracellular calcium, producing a "stone heart" similar to that which sometimes occurs during surgical repair of aortic stenosis. Subsequent reports of this procedure have demonstrated a decrease in mortality associated with a greater use of the retrograde approach and better selection of cases with referral of patients who have severely calcified aortas to a percutaneous apical left ventricular approach.

Our series of percutaneous aortic balloon valvuloplasties in critically ill patients suggests that percutaneous heart valve deployment could be performed more safely and precisely in selected patients with use of the TandemHeart percutaneous LVAD.

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Clinical Investigation

Acute Massive Pulmonary Embolism with Cardiopulmonary Resuscitation

Management and Results

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Patients who experience hemodynamic collapse after acute massive pulmonary embolism have a poor prognosis. Herein, we report our results with 8 patients and discuss a surgical strategy that can improve perioperative survival.

From August 1994 through May 2005, 8 consecutive patients (6 women, 2 men; age range, 27–68 yr) were urgently referred to our unit after experiencing hemodynamic collapse. All required cardiopulmonary resuscitation. Seven patients underwent pulmonary embolectomy. One patient was successfully treated with thrombolytic therapy alone under continuous monitoring by the surgical team.

There were 2 intraoperative deaths (30-day mortality rate, 28.5%). One survivor required a right ventricular assist device. Follow-up of the patients ranged from 8 months to 8 years. One patient died 8 months after the pulmonary embolectomy from long-term complications of cerebral damage that had occurred during preoperative resuscitation.

We conclude that prompt surgical management improves the early survival rates of patients who require cardiopulmonary resuscitation subsequent to massive pulmonary embolism. ***(Tex Heart Inst J 2007;34:41-6)***

Key words: *Anticoagulants; cardiopulmonary bypass; cardiopulmonary resuscitation; echocardiography, transthoracic; hemodynamic processes; pulmonary artery/surgery; pulmonary embolism/complications/diagnosis/drug therapy/mortality/surgery; risk factors; thrombolytic therapy/contraindications; treatment outcome; ventricular dysfunction, right*

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Massive pulmonary embolism (PE) is a life-threatening condition. For clinical purposes, massive PE is defined as pulmonary embolism with either hemodynamic collapse or an occlusion of the pulmonary artery that exceeds 50% of its cross-sectional area.[1-5] The overall mortality rate associated with massive PE remains at approximately 30%.[6-8] If cardiopulmonary resuscitation (CPR) is required, mortality rates increase dramatically. Even in the modern era, operative deaths of patients with massive PE who require CPR may approach 75%.[9] An overall mortality rate reported in the world literature is 57% for patients who require CPR, compared with 12% for those who do not.[6,9-17] Herein, we present a retrospective review of the treatment and outcomes of 8 of our patients who required CPR consequent to hemodynamic collapse after massive PE.

Patients and Methods

Patients

From August 1994 through May 2005, 8 consecutive patients with suspected massive PE were referred to our cardiothoracic surgical unit after they had experienced hemodynamic collapse that required CPR. We retrospectively analyzed the patients' demographics, risk factors, methods of diagnosis, operative procedures, and postoperative morbidity and mortality rates (Table I).

The average age of the patients was 45 years (range, 27–68 yr). Six patients (75%) were women. Five patients had no definitive diagnosis of massive PE before surgery, and the decision to operate on them was made on the basis of characteristic clinical scenarios. Seven of the 8 patients underwent emergency pulmonary embolectomy; one was successfully treated with thrombolytic therapy alone.

Surgical Technique

Heparin was administered to all patients during CPR upon arrival at the operating room. The heart was exposed through a median sternotomy. Mild hypothermia (32

TABLE I. Characteristics and Outcomes of Patients with Acute Massive Pulmonary Embolism

Pt. No.	Sex/Age (yr)	Risk Factors	Imaging	Thrombolytic Therapy	CPB (min)	Survival	Follow-Up
1	F/33	Cesarean section	None	No	78	Yes	Died at 8 mo
2	M/27	DVT, testicular cancer	IVC ultrasonography	No	75	Yes	Well at 8 yr
3	F/52	DVT, HRT	None	No	87	Yes	Well at 8 yr
4	M/68	None	V/Q scan	No	74	No	NA
5	F/36	DVT	V/Q scan, TTE, PA angiography	No	70	Yes	Well at 7 yr
6	F/66	Open reduction and internal fixation	TTE	No	66	No	NA
7	F/43	Hepatic hydatid cyst removal	TTE	No	50	Yes	Well at 8 mo
8	F/34	Open reduction and internal fixation	Computed tomography	Yes	NA	Yes	Well at 8 mo

CPB = cardiopulmonary bypass; DVT = deep venous thrombosis; F = female; HRT = hormone replacement therapy; IVC = inferior vena cava; M = male; NA = not applicable; PA = pulmonary artery; TTE = transthoracic echocardiography; V/Q = ventilation–perfusion

°C) was used. The ascending aorta and the right atrial appendage were cannulated for the institution of cardiopulmonary bypass (CPB). Subsequently, during total CPB, bicaval cannulation was achieved. A longitudinal incision made in the main pulmonary artery was extended into the left and right pulmonary arteries. The aorta was not cross-clamped in any patient during the procedure.

Desjardins forceps and Fogarty catheters (Edwards Lifesciences; Irvine, Calif) were used for clot removal. If the emboli extended into peripheral pulmonary arteries, a thoracoscope was also used, and CPB flow was reduced in order to better see the clots and remove them completely. The interventional radiologists placed an inferior vena caval (IVC) filter in all of the surviving patients within 24 hours of surgery.

Timing of Resuscitation

Five patients presented at our emergency department with ongoing CPR having been administered en route by paramedics; the other 3 patients experienced in-hospital cardiac arrest.

Patient 4 (Table I) was admitted with acute shortness of breath and palpitations. After ventilation–perfusion (V/Q) scanning, he was given heparin for anticoagulation. However, on the next day, he began to bleed from the upper gastrointestinal tract, so the heparin was discontinued. On the following day, he developed severe hypoxia that led to cardiac arrest; he was resuscitated and was referred for cardiothoracic surgery. He was urgently brought to the operating room with ongoing CPR. During surgery, multiple bilateral clots were found in his peripheral pulmonary arteries. The patient could not be weaned from CPB, and he died.

Patient 5 was transferred to our hospital with suspected pulmonary embolism. A V/Q scan showed a marked reduction of perfusion to the middle and lower lobes of the right lung, and to the lingula and lower lobe of the left lung. An IVC filter was placed. Heparin and warfarin were administered. Despite these measures, the patient's hypoxia worsened on day 4 of her hospital stay. A 2nd V/Q scan showed persistence of the previously noted defects and their extension into both upper lobes. The patient was taken to surgery and developed cardiac arrest on the operating table, requiring CPR. We removed the clots from her right pulmonary artery and left lobar branches, and she recovered.

A hepatic hydatid cyst was ruptured during its removal from Patient 7. This resulted in a complicated postoperative course with prolonged immobilization. On postoperative day 8, she developed severe hypoxia and hemodynamic collapse that required CPR. After endotracheal intubation and resuscitation, transthoracic echocardiography (TTE) showed severe right ventricular (RV) dilatation, and the patient underwent emergency thromboembolectomy. She survived.

Morbidity and Death

Patients 4 and 6 had no clots in their main, left, or right pulmonary arteries, but they had multiple clots in their peripheral arteries. Both patients died in the operating room of persistent hypoxia and severe RV failure upon discontinuation of CPB. Therefore, the operative death rate was 28.6% (2/7).

Patient 1 was discharged from the hospital. Unfortunately, she had severe hypoxic cerebral damage, and she died 8 months later.

Patient 2, who had a large thrombus in his main pulmonary artery (Fig. 1), developed severe RV failure. He required postoperative RV support with a Bio-Medicus® pump (Medtronic, Inc.; Minneapolis, Minn) and de-

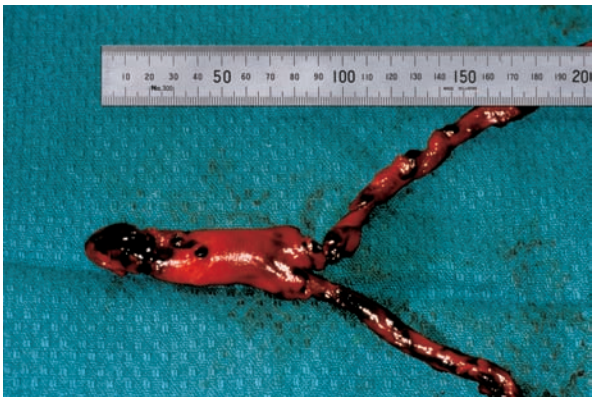

Fig. 1 *Patient 2. A thrombus in the shape of the inferior vena caval bifurcation was retrieved from the pulmonary artery.*

layed sternal closure. On postoperative day 2, he was weaned from the pump and his chest was closed.

The overall postoperative hospital stay ranged from 8 to 77 days (mean, 24 days; median, 11 days).

Follow-Up

The follow-up periods of the 6 survivors ranged from 8 months to 8 years (mean, 50 mo), with 1 death (patient 1) at 8 months. All 6 patients were prescribed warfarin as an anticoagulant postoperatively for 6 months, and an IVC filter was placed in all. As of January 2007, all 5 surviving patients remained asymptomatic and were doing well.

Discussion

Three of our patients had severe RV dysfunction during the attempt to wean them from CPB support. In 1 patient, a very large thrombus (Fig. 1) was removed from the central pulmonary arteries. Despite severe RV dysfunction, his oxygenation improved considerably. Therefore, we believed that most of the obstruction was removed and that the RV failure was reversible. This patient was successfully supported with a RV assist device. In contrast, 2 other patients had no thrombi in their central pulmonary arteries, but they had multiple thrombi in the peripheral arteries, rendering complete surgical thrombectomy impossible. Furthermore, persistent severe hypoxia after weaning from CPB made successful recovery unlikely for these patients even if RV assist devices had been used. Both patients died in the operating room. Our operative mortality rate of 28.6% compares favorably with the previously reported mortality rates of patients with massive PE who required preoperative CPR.[9] Very prompt transfer to the operating room and institution of CPB may explain our comparatively good results.

Five patients survived surgery. Unfortunately, one sustained hypoxic brain injury—despite witnessed cardiac arrest and in-hospital CPR—possibly from preoperative resuscitation that was inadequate because of complete pulmonary artery obstruction. Cardiac arrest occurred while the patient was recovering from a cesarean section in an obstetrics unit. Although this patient was transferred to a rehabilitation ward after discharge from the hospital, she never recovered normal neurocognitive function, and she died of pneumonia 8 months later.

Finally, 1 patient (Patient 8) was managed conservatively. She had experienced hemodynamic collapse at home while recuperating from orthopedic surgery, and she underwent CPR initially performed by a family member and then by paramedics en route to the hospital. She had recovered completely by the time she arrived at the hospital. A computed tomographic scan showed a large thrombus in the left pulmonary artery (Fig. 2A). We suspect that this thrombus was dislodged from the main pulmonary artery into the left pulmonary artery during CPR. This occurrence enabled unobstructed blood flow into the right lung, with consequent restoration of normal oxygen saturation and normal hemodynamics. The patient was admitted to the cardiothoracic surgical ward and was given reteplase. Two days later, a computed tomographic scan confirmed complete lysis of the thrombus (Fig. 2B). An IVC filter was placed, and the patient received warfarin as an anticoagulant.

Pulmonary embolism is an important cause of morbidity and death worldwide.[18-20] Furthermore, the risk of death is dramatically higher in those patients who require CPR because of massive PE. Cardiac arrest increases mortality rates after massive PE by 3 to 7 times.[21] This trend is well documented in the surgical literature.[9,22] For instance, in a 2005 report of 11 patients who underwent pulmonary embolectomy for acute massive PE, the mortality rate in those who received preoperative CPR was 75% (3 of 4 patients). In contrast, all of the patients who did not require preoperative CPR survived the operation. Imaging was performed on all patients before surgery.[9]

Similarly, Leacche and colleagues[22] reported an overall operative mortality rate of only 6% in their series of 47 patients with massive PE. However, in 6 (11%) of their patients who required CPR before surgery, operative death was substantially higher. Two of the 6 patients (33%) died during surgery.

About two thirds of patients with fatal PE develop cardiac arrest within 1 to 2 hours after the clinical presentation.[1,23] Therefore, rapid attendance by cardiothoracic surgeons appears to be crucial to successful outcomes. In our study, the definitive diagnosis of PE was not established in 5 of the 8 patients (62.5%) (patients 1, 2, 3, 6, and 7).

It should be emphasized that massive PE is a clinical diagnosis. A combination of jugular venous distention, low oxygen saturation, recent surgery with a period of immobilization, and clear bilateral lung sounds with

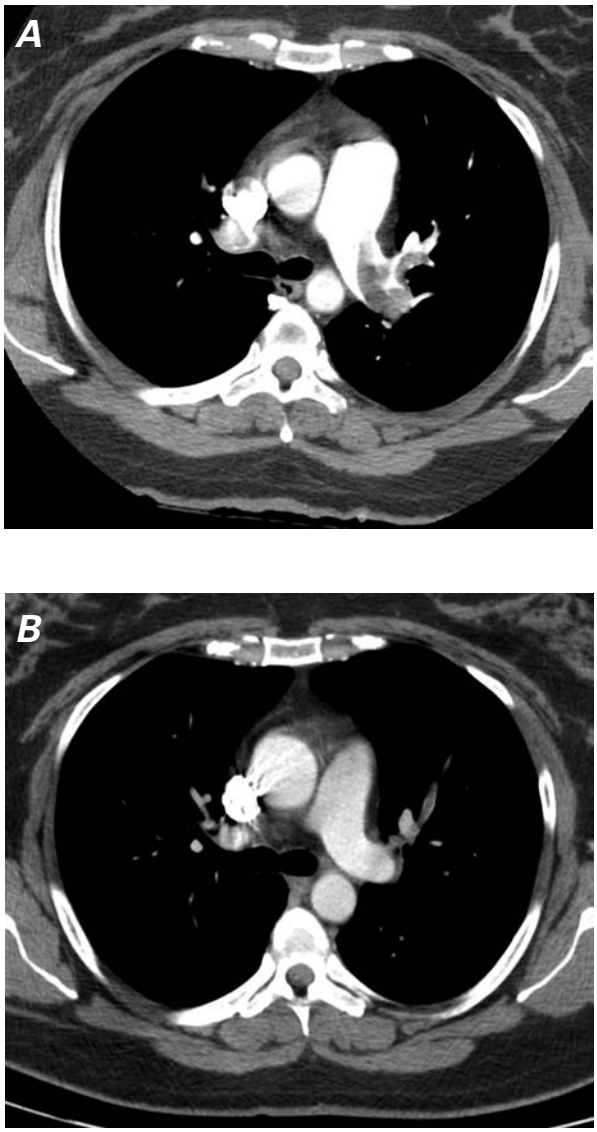

Fig. 2 *Patient 8. Computed tomographic scans of the chest show a massive pulmonary embolus* ***A****) before thrombolysis and* ***B****) after the resolution of the thrombus.*

no pneumothoraces makes massive PE the most likely differential diagnosis. If a patient's condition permits, we perform further evaluation; however, hemodynamic collapse with ongoing CPR makes further imaging impractical or impossible. Therefore, a high index of suspicion combined with rapid deterioration necessitates emergency surgery.

Three of our 5 patients had undergone recent surgery with a period of immobilization, and TTE performed on 2 of these 3 showed severe RV dilatation with ventricular septal deviation, an underfilled left ventricle, and no pericardial effusion. The 2 other patients were being treated for deep venous thrombosis; one of them (Patient 2) also had testicular cancer and a large IVC thrombus diagnosed by ultrasonography. Although transesophageal echocardiography (TEE) can be very helpful as a diagnostic tool in stable patients, none of our patients was sufficiently stable immediately after CPR for placement of a TEE probe. Sudden deterioration followed by cardiac arrest strongly suggested massive PE. In each of these cases, the decision to operate was made very early during the event, which we believe partially explains the better outcomes in our patients. It is known that attempts to stabilize a critically ill patient who has massive PE are often frustrating, and the patient's condition deteriorates during this time. Prompt surgical intervention with CPB can be life-saving.

On rare occasions, massive PE may be misdiagnosed despite a very typical clinical presentation. For instance, we recently encountered a patient with a very typical clinical picture of massive PE 2 weeks postpartum. Ongoing CPR and persistently low oxygen saturation despite massive inotropic support made further evaluation impossible. Her hemodynamic instability was life-threatening; therefore, she was taken to the operating room as a last resort, with a presumed diagnosis of massive PE. No embolism was found, and the patient died. The autopsy showed no cause of death. It is possible that she had acute viral myocarditis superimposed on postpartum heart failure with sudden and dramatic hemodynamic collapse.

Acute dilatation of the RV with accompanying ischemia leads to RV dysfunction. Right ventricular dilatation and hypokinesia are associated with higher death rates and an increased risk of recurrent PE.[24] Prompt institution of CPB is crucial—it provides immediate circulatory support and enables surgeons to use the best method for removing mechanical obstructions from the pulmonary arteries. We prefer sternotomy with aortic and right atrial cannulation for the following reasons. Foremost, patients with massive PE may have residual IVC, iliac, or femoral venous clots, which make femoral venous cannulation difficult and venous return through a small cannula ineffective. Second, midline sternotomy provides very fast access, which speeds the establishment of CPB. We believe that this approach is faster than cannulation of the femoral vessels in obese patients. Five of our patients were obese. Femoral cannulation in those patients would have necessitated placement of a small femoral venous cannula that inevitably would have impeded venous return. Third, we learned from treating the very 1st patient in our series that standard closed-chest CPR can be ineffective in a patient with massive PE, despite cardiac arrest witnessed in the hospital and immediate, uninterrupted CPR delivered by a qualified team. A very large embolus completely occluded this patient's pulmonary artery, making closed-chest CPR ineffective. In addition, we believe that avoiding global myocardial ischemia and maintaining good myocardial perfusion throughout the procedure is important for a successful outcome.

Conclusion

Massive pulmonary embolism is a difficult clinical entity to treat, because even standard CPR is highly unlikely to be successful in the case of mechanical obstruction to blood flow with severe hypoxia. Prompt surgical management can save some of the patients who require CPR after massive PE and associated hemodynamic collapse.

The absence of thromboemboli within the main pulmonary artery in combination with the presence of multiple peripheral thrombi is a bad prognostic sign. On rare occasions, a selected patient with this condition can be treated conservatively with thrombolytic therapy. We highly recommend, however, that the thrombolysis be given in the cardiothoracic surgical unit under the continuous monitoring of a qualified team, in case the need for emergency surgery arises.

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Editorial Commentary

This report of 6 successful results of pulmonary embolectomy reveals the evolving aggressive surgical treatment of a highly fatal vascular complication and disease. Emergency treatment using cardiopulmonary bypass has replaced the early techniques suggested by Trendelenburg a century ago. Few patients survived those heroic efforts.

In 1961, we reported the 1st use of cardiopulmonary bypass for acute massive pulmonary embolism.[1] Since then, surgical treatment of this disease has improved greatly. Often, the emboli have migrated out of the main pulmonary artery and have lodged peripherally. Opening both pleural spaces permits manual compression of both lungs to dislodge the emboli. The authors used a thoracoscope to ensure the completeness of the removal.

Thrombolytic agents are currently used in less desperate situations, but treatment should be monitored

constantly and abandoned if circulatory collapse threatens. Diagnosis of pulmonary embolism is enhanced by noninvasive ultrasonography and other techniques, but awareness of physical findings is still essential.

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Clinical Investigation

Surgical Treatment of Post-Infarction Left Ventricular Pseudoaneurysm

A Two-Decade Experience

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Herein, we present a retrospective analysis of our experience with acquired pseudoaneurysms of the left ventricle over a 20-year period.

From February 1985 through September 2004, 14 patients underwent operation for left ventricular pseudoaneurysm in our clinic. All pseudoaneurysms (12 chronic, 2 acute) were caused by myocardial infarction. The mean interval between myocardial infarction and diagnosis of pseudoaneurysm was 7 months (range, 1–11 mo). The pseudoaneurysm was located in the inferior or posterolateral wall in 11 of 14 patients (78.6%). In all patients, the pseudoaneurysm was resected and the ventricular wall defect was closed with direct suture (6 patients) or a patch (8 patients). Most patients had 3-vessel coronary artery disease. Coronary artery bypass grafting was performed in all patients.

Five patients died (postoperative mortality rate, 35.7%) after repair of a pseudoaneurysm (post-infarction, 2 patients; chronic, 3 patients). Two patients died during follow-up (median, 42 mo), due to cancer in 1 patient and sudden death in the other.

Although repair of left ventricular pseudoaneurysm is still a surgical challenge, it can be performed with acceptable results in most patients. Surgical repair is warranted particularly in cases of large or expanding pseudoaneurysms because of the propensity for fatal rupture. ***(Tex Heart Inst J 2007;34:47-51)***

Key words: *Aneurysm, false/surgery; coronary artery bypass; heart rupture, post-infarction/therapy; heart ventricles; myocardial infarction/complications; retrospective studies; ventricular dysfunction, left*

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Pseudoaneurysm of the left ventricle, which in fact is a contained rupture, is rare, because in most instances ventricular free-wall rupture leads to fatal pericardial tamponade. Rupture of the free wall of the left ventricle is a catastrophic complication of myocardial infarction, occurring in approximately 4% of patients with infarcts and in about 23% of those experiencing fatal infarcts.[1,2] However, pseudoaneurysms develop when cardiac rupture is contained by pericardial adhesions. Myocardial infarction is the most common cause of false aneurysms of the left ventricle, followed by cardiac surgery, trauma, and infection.[3-9] Because such aneurysms have a strong tendency to rupture, this disorder may lead to death if it is left surgically untreated. In particular, asymptomatic pseudoaneurysms that occur a few days after acute myocardial infarction or surgery are extremely unstable and tend to rupture. Although the natural history of the acquired left ventricular pseudoaneurysm is not known perfectly, it is clear that large pseudoaneurysms rupture more easily than the small and chronic ones. On the other hand, the risk of surgery on chronic lesions is still very high, as can be seen in the few case series that have been reported. The literature has concentrated on case reports and collections of case reports. Until the present, only a few surgical series have been reported; these studies are shown in Table I.[10-15] The purpose of this article is to present a retrospective analysis of our surgical experience with post-infarction pseudoaneurysms of the left ventricle over a 20-year period.

Patients and Methods

During the period from February 1985 through September 2004, a total of 14 patients underwent operation for pseudoaneurysm of the left ventricle at Kosuyolu Heart and Research Hospital in Istanbul. There were 9 men and 5 women, with mean age of 61.9 ± 6.7 years (range, 52–75 yr). All of the pseudoaneurysms were discovered after transmural myocardial infarction. The diameters of the pseudoaneurysms were calculated by using transthoracic echocardiography in 8 patients, con-

trast left ventriculography in 4 patients (Fig. 1), and intraoperative direct viewing in 2 patients (Fig. 2). The mean maximum diameter of the pseudoaneurysms was 4.7 ± 0.48 cm. They were categorized as acute when discovered within 2 weeks of myocardial infarction and as chronic (Fig. 2) when discovered more than 2 weeks after the event. The mean interval between myocardial infarction and diagnosis was 7.0 ± 3.05 months (range, 1–11 mo). Two acute pseudoaneurysms were discovered incidentally by echocardiographic examination while patients were in the hospital for acute myocardial infarction. Chronic lesions were discovered in another 12 patients during investigations of symptoms such as cardiac failure, stable angina pectoris, or arrhythmia at least 3 months after myocardial infarction, as determined by the patients' histories. The mean left ventricular ejection fraction of the series as a whole was 0.38 ± 0.95. Clinical features of the patients and the surgical techniques are presented in Table II.

During this time period, we also treated 3 patients with post-infarction myocardial free-wall rupture; all had a hemopericardium with impaired hemodynamics. These patients were not included in this study.

All patients underwent preoperative coronary angiography: 10 patients had 3-vessel disease, and 4 had 2-vessel disease. Cardiopulmonary bypass was used in repairing the defect in all patients. Cardioplegic arrest was accomplished by intermittent antegrade administration of crystalloid solution (1985–1993) or by continuous retrograde administration of tepid (30 °C) blood cardioplegic solution (1993–2004).

Complete dissection of the heart was performed after cross-clamping the aorta, in an effort to avoid systemic embolization. The techniques that were used to obliterate the necks of the pseudoaneurysms were as follows: in 6 patients with chronic pseudoaneurysm, the defect was closed directly with sutures reinforced by Teflon felt; in the remaining 8 patients, a circular patch technique was used. In 7 of the 8, a patch of woven polyethylene terephthalate (Dacron) was used to close the defect externally. In 1 patient with an acute pseudoaneurysm, the defect was covered only with a patch of autologous pericardium, because the myocardium was friable. Three patients had mild mitral valve regurgitation, but none received repair or replacement of the valve. Concomitant coronary artery bypasses were performed for significant stenoses in all patients (mean number of distal anastomoses, 2.6). Contact was established with all surviving patients in the autumn of 2004, either by telephone (4 patients) or by examina-

TABLE I. Previously Reported Surgical Series of Left Ventricular Pseudoaneurysm

Author	Total Patients (n)	Mortality Rate (%)	Reference
Komeda M, David TE	12	25	J Thorac Cardiovasc Surg 1993[10]
Mackenzie JW, Lemole GM	14	21.4	Tex Heart Inst J 1994[11]
Csapo K, et al.	6	50*	Clin Cardiol 1997[12]
Yeo TC, et al.	42	7	Ann Intern Med 1998[13]
Frances C, et al.	107	23	J Am Coll Cardiol 1998[14]
Prêtre R, et al.	10	30	Ann Thorac Surg 2000[15]

*Mortality rate at 2 years

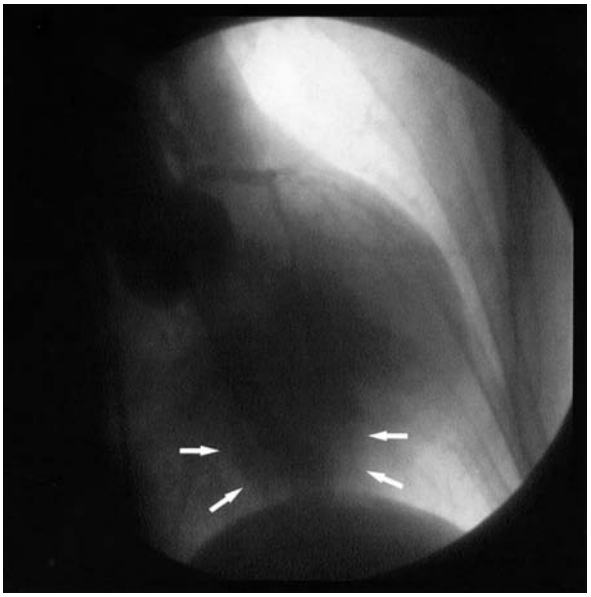

Fig. 1 *Preoperative left ventriculography of patient 9 shows a chronic post-infarction pseudoaneurysm (arrows) of the left ventricle.*

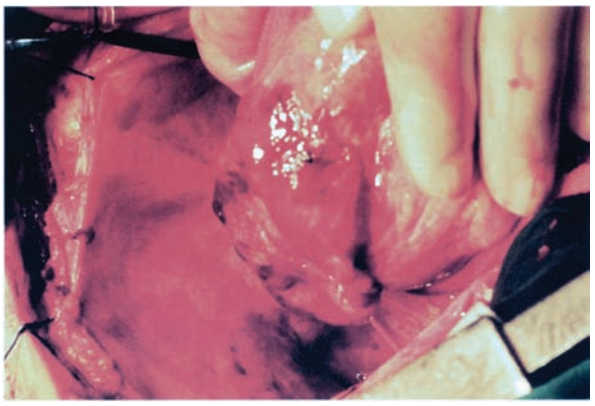

Fig. 2 *Intraoperative appearance of the pseudoaneurysm at the basal part of the left ventricle of patient 14.*

tion in our clinic (3 patients). Follow-up for the entire series ranged from 2 to 108 months (median, 42 mo).

Results

Clinical data are summarized in Table II. In all patients, resection of the pseudoaneurysm and closure of the ventricular wall defect was performed without any sequela, such as embolus, bleeding, or mechanical complication. Five patients died in the immediate postoperative period: 2 after repair of an acute pseudoaneurysm and 3 after repair of a chronic pseudoaneurysm. Three of the 5 patients died of progressive multiple organ failure; the remaining 2 died suddenly in the regular ward, due in 1 instance to sepsis. Overall, the postoperative mortality rate was 35.7%. Two additional deaths occurred after hospital discharge. One patient died suddenly 2 years after the operation, and the other died of cancer 3 years after surgery.

Discussion

It has been established that ventricular rupture occurs in stages and progresses from endocardium to pericardium. Only a few patients survive, and then it is by virtue of an adherent thrombus or pericardial adhesions. Adhesions may be present at the time of infarction or may develop de novo during the rupture. Pseudoaneurysms have been reported to originate usually at the posterior basal and rarely at the apical segment of the left ventricle after occlusion of the right coronary or left anterior descending artery.[11,16]

However, opinions differ as to the most common site of the left ventricular rupture. David suggests that a lateral wall infarction is more likely to rupture than is an anterior or inferior infarction, but anterior infarctions are much more frequent than lateral infarctions—so the anterior wall is the most common site.[17]

Pathologically, pseudoaneurysms of the left ventricle are characterized by a small, narrow-necked channel that connects the ventricle with a larger aneurysmal sac, which contains blood and thrombus and is lined by fibrous pericardial tissue with no myocardial elements.[18] A post-infarction true aneurysm, in contrast, is caused by scar formation that results in thinning of the myocardium. It has been suggested that a posterior location is indicative of pseudoaneurysm rather than true aneurysm. Most true left ventricular aneurysms occur anteriorly, consequent to occlusion of the left anterior descending artery. Extensive infarction in the posterior region involves the posterior papillary muscle, which usually results in severe mitral regurgitation and death; these patients never go on to develop true aneurysm. Another possible explanation for the greater prevalence

TABLE II. Clinical Characteristics, Surgical Techniques, and Outcomes in Patients with Left Ventricular Pseudoaneurysm

Pt. No.	Age/ Sex	Presentation	Location	Timing	Closure Technique	Operative Outcome	Last Seen
1	58/M	CHF	Inferior	Chronic	Direct	Death, unknown	—
2	62/M	Arrhythmia	Inferior	Chronic	Direct	Survivor	9 yr
3	59/F	CHF	Anterior	Acute	Patch	Death, MOF	—
4	68/M	SAP	Inferior	Chronic	Patch	Survivor	Cancer, 3 yr
5	56/M	SAP	Inferior	Chronic	Direct	Survivor	8 yr
6	75/F	CHF	Inferior	Acute	Patch	Death, MOF	—
7	52/M	SAP	Anterior	Chronic	Direct	Survivor	6 yr
8	73/M	CHF	Inferior	Chronic	Direct	Death, sepsis	—
9	65/F	SAP	Inferior	Chronic	Direct	Survivor	5 yr
10	53/M	CHF	Lateral	Chronic	Patch	Survivor	4 yr
11	63/M	SAP	Inferior	Chronic	Patch	Survivor	Sudden death, 2 yr
12	58/M	SAP	Anterior	Chronic	Patch	Survivor	3 yr
13	62/F	CHF	Inferior	Chronic	Patch	Death, MOF	—
14	63/F	SAP	Inferior	Chronic	Patch	Survivor	2 mo

CHF = congestive heart failure; F = female; M = male; MOF = multiple organ failure; SAP = stable angina pectoris

of posterior pseudoaneurysm is that ruptures of the anterior wall cannot be tolerated, as they rarely are compressed by adherent pericardium.

Left ventricular pseudoaneurysms are often asymptomatic and are discovered incidentally upon investigation of some other condition, most commonly angina pectoris or congestive heart failure. Routine echocardiography may detect pseudoaneurysm in an asymptomatic patient who is recovering from acute myocardial infarction. Diagnosis can be made preoperatively by several imaging techniques, including computed tomography, echocardiography, and magnetic resonance imaging; however, contrast ventriculography and coronary angiography seem to be necessary in evaluating the location and anatomy of the aneurysm and the state of the coronary arteries. Although the distinction of pseudoaneurysm from a true aneurysm can be difficult, the presence of a narrow neck on either color-flow Doppler echocardiography or ventriculography is strongly suggestive of pseudoaneurysm. In addition, characteristic features of the left ventricular pseudoaneurysm are a narrow neck at the site of rupture with an abrupt transition from normal myocardium to aneurysm—the diameter of the neck is 50% smaller than the maximum diameter of the aneurysm itself.[19]

Because of its rarity, the natural history of pseudoaneurysm of the left ventricle is not well established.[17] The condition is believed to have a poor prognosis because of a high probability of rupture[20]; however, in some patients the diagnosis is made many years after myocardial infarction.[10,21] Congestive heart failure is the most common presentation, followed by angina, ventricular arrhythmias, and embolization.[10,22] When the diagnosis is established, surgical correction is usually mandatory. Timing of the surgery depends on the age of the myocardial infarction. Surgery is urgently recommended when a pseudoaneurysm is discovered within the first 2 to 3 months after myocardial infarction, because onset of rupture is unpredictable.[21] However, when diagnosis is made years after myocardial infarction, the urgency and even the need for operation is determined by symptoms rather than by risk of rupture.[17] In 10% to 20% of cases, chronic pseudoaneurysms are discovered incidentally.[14] The outcome of patients with this condition who are treated conservatively has been assumed to be poor, with a mortality rate of around 50% at 2 years in 1 series.[12] However, in a study by Moreno and colleagues,[23] 9 of 10 patients with left ventricular pseudoaneurysm treated conservatively had a cumulative survival rate of 88.9% and 74.1% at 1 and 4 years, respectively; indeed, the probability of being free of cardiac death was 88.9% at both 1 and 4 years. Because of the uncertainties surrounding the natural history of the lesions, and the relative safety of surgical repair in this subgroup, the decision to operate should prevail over conservative management in cases of large or expanding pseudoaneurysms. Embolization of thrombotic material, induced by stagnant blood flow, has also been reported with large pseudoaneurysms.[13,14] Although asymptomatic small pseudoaneurysms have a more stable course,[7,14] regular echocardiographic or magnetic resonance evaluations should be performed to detect any increase in size.

The surgical treatment of left ventricular post-infarction pseudoaneurysms raises few problems. If thrombotic material within the pseudoaneurysm has been detected by echocardiography, dissection of the heart should initially be limited to the anterior surface, to enable placement of cannulas and institution of cardiopulmonary bypass. The left ventricle should be dissected free from the pericardium after the aorta has been cross-clamped. Dissection of the heart should be done gently because of the danger of systemic embolization if the pseudoaneurysm has thrombotic material. The neck of the pseudoaneurysm can be closed directly in chronic cases because of its fibrotic edges. In acute cases, closure of the freshly necrotic myocardium with synthetic or pericardial patches is effective. When the defect is large or located near the base of the heart, a patch may be preferable to avoid excessive traction on the myocardium. Concomitant myocardial revascularization and correction of associated mitral valve insufficiency should complement ventricular repair.[10]

Postsurgical pseudoaneurysms can occur after replacement of the mitral valve or consequent to technical failure of a previous ventriculotomy.[3-7] The sequela occurs in 0.02% to 2.0% of mitral valve replacements.[7,14] Predisposing factors include resection of the posterior leaflet, overzealous decalcification of the annulus, insertion of an oversized prosthesis, and "redo" mitral valve replacement. In regard to technical failure of a ventriculotomy, pseudoaneurysm can occur due to tearing of a suture in friable myocardium or to myocarditis after infection of foreign material such as Teflon felt.[2,4] Although rupture has been documented in the literature,[24-26] the risk of rupture seems less dramatic for chronic pseudoaneurysms. In a review by Frances and colleagues,[14] of 31 patients with chronic left ventricular pseudoaneurysm, 16 were alive at a median time of 156 weeks.

The overall early mortality rate for the post-infarction pseudoaneurysm was 23% in Frances' review[14]; in Komeda's series with 12 patients, it was 25%[10]; in Prêtre's study,[15] it was 30%; and in ours, it was 35.7%. In our experience, death was not associated with technical difficulties, but mainly with poor left ventricular function. The repair of postsurgical pseudoaneurysms is more challenging because it is by nature a redo operation.

In conclusion, this study revealed that surgical repair of pseudoaneurysm was associated with an acceptable surgical mortality rate, that cardiac rupture did not occur

in surgically treated patients, and that late death was related primarily to the underlying disease or to cardiac dysfunction.

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Clinical Investigation

Effects of Carvedilol on Plasma Levels of Pro-Inflammatory Cytokines

in Patients with Ischemic and Nonischemic Dilated Cardiomyopathy

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We prospectively investigated the effects of adding carvedilol to the standard treatment of ischemic and nonischemic dilated cardiomyopathy (DCM), by measuring the plasma levels of pro-inflammatory cytokines. Sixty patients with DCM (35 ischemic and 25 non-ischemic) were divided into 2 subgroups: patients on standard therapy alone (digoxin, angiotensin-converting enzyme inhibitors, and diuretics) and patients on standard therapy plus carvedilol. Study participants' serum levels of tumor necrosis factor-α (TNF-α), interleukin-2 (IL-2), and interleukin-6 (IL-6) were measured at the beginning and again at the end of the study. Left ventricular ejection fraction and left ventricular diastolic function were evaluated by means of radionuclide ventriculography.

In ischemic patients on carvedilol, levels of IL-6 and TNF-α dropped significantly (P=0.028 and P=0.034, respectively). In ischemic patients on standard treatment, plasma IL-2 levels were elevated after treatment (P=0.047). No significant differences occurred in IL-6 levels, while TNF-α levels were elevated (P=0.008). In nonischemic patients on carvedilol, IL-6 and TNF-α levels dropped significantly (P=0.018 and P=0.004, respectively). The left ventricular ejection fraction increased significantly (P=0.006). In nonischemic patients on standard treatment, no significant change occurred in any value. Carvedilol suppressed the plasma levels of TNF-α and IL-6 in both ischemic and nonischemic patients. The carvedilol effect was more pronounced in patients with nonischemic dilated cardiomyopathy than in those with ischemic disease. ***(Tex Heart Inst J 2007;34:52-9)***

Key words: *Biological markers/blood; cardiomyopathy, dilated; carbazoles/therapeutic use; carvedilol; cytokines/blood; heart failure, congestive; interleukin-2; interleukin-6; tumor necrosis factor-alpha; ventricular function, left/drug effects*

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Chronic heart failure is a progressive syndrome that is characterized by heart dysfunctions and increases in neurohormonal activity. During the past half century, as various physiopathologic mechanisms have been proposed for chronic heart failure, subsequent changes have occurred in its treatment. Prolonged activation of the sympathetic system is one of the proposed mechanisms.

Pro-inflammatory cytokines have been shown to contribute, by various mechanisms, to the alteration of cardiovascular functions such as left ventricular (LV) remodeling, contractile dysfunctions, and reduction of the myocardial β-adrenergic receptors.[1] In heart failure (HF) patients, plasma levels of pro-inflammatory cytokines are higher and are positively correlated with the mortality rate.[2] Pro-inflammatory cytokines are influential pleotropic endogenic peptides, which are produced by several cell types. Tumor necrosis factor-α (TNF-α), interleukin-2 (IL-2), and interleukin-6 (IL-6) are classified as pro-inflammatory cytokines.[3]

β-blockers, which were thought to be contraindicated for LV dysfunction, are now the 1st step in HF treatment. It has been shown that the addition of β-blockers—with or without angiotensin-converting enzyme (ACE) inhibitors, diuretics, and digoxin—to standard HF treatment reduced the mortality rate. This useful effect of β-blockers is thought to be due to their suppression of the sympathetic nervous system.[4,5]

Carvedilol is a nonselective β-blocker (β_1/β_2 rate, 7.3) with α-blocking, vasodilatory, and antioxidant effects.[6] Recent reports have indicated that carvedilol use in dilated cardiomyopathy (DCM) patients reduced the severity of the ventricular dysfunction, increased the LV ejection fraction (EF), and consequently reduced the morbidity and mortality rates.[6] It is not well known whether the useful effect of carvedilol includes the suppression of pro-inflammatory cytokines in addition to the suppression of the increased sympathetic activity. There are no data concerning the

effect of carvedilol when it is added to standard therapy in patients with ischemic DCM and nonischemic DCM. In this study, we aimed to investigate the effects of carvedilol on LV functions and on the levels of proinflammatory cytokines in patients with ischemic and nonischemic DCM.

Patients and Methods

In this prospective study, 60 patients with ischemic or nonischemic DCM were treated in our department of cardiology as either inpatients or outpatients from February 2001 through November 2001. After approval of the study by our hospital's ethics committee, we obtained signed consent from all patients. Baseline characteristics of the study population at randomization are shown in Table I. There were no significant baseline differences between the groups. Entry criteria for this study included age between 30 and 70 years, an EF of 0.40 or lower, and symptomatic HF as a consequence of ischemic or nonischemic DCM. Exclusion criteria were chronic obstructive pulmonary disease, significant valvular heart disease, thyrotoxicosis, hypothyroidism, chronic kidney and liver diseases, malignancy, anemia (hemoglobin, <9 g/dL), systolic blood pressure lower than 90 mmHg, heart rate lower than 50 beats/min, and 1st- or 2nd-level heart block. Patients on antiarrhythmic drugs or β-blockers, with a permanent pacemaker, and with psychiatric problems were also excluded from the study. The ischemic DCM (n=35) and nonischemic DCM (n=25) groups were each divided into 2 subgroups: ischemic DCM on standard HF treatment (n=20), ischemic DCM on standard HF treatment plus carvedilol (n=15), nonischemic DCM on standard HF treatment (n=10), and nonischemic DCM on standard HF treatment plus carvedilol (n=15). For all patients, we recorded age; sex; presence of coronary artery disease, hypertension, diabetes mellitus, and hyperlipidemia; history of smoking; drugs in use now or in the past; New York Heart Association (NYHA) functional class; blood pressure; and heart rate. A standard HF treatment protocol was applied to all patients in the ischemic and nonischemic DCM groups. Carvedilol at an initial oral dose of 3.125 mg daily was added to the

TABLE I. Baseline Characteristics of the Study Population

	Ischemic Dilated Myocardiopathy Baseline			Nonischemic Dilated Myocardiopathy Baseline		
	Carvedilol (n=15)	**Standard** (n=20)	***P* Value**	**Carvedilol** (n=15)	**Standard** (n=10)	***P* Value**
Age (yr)	60.5 ± 9.7	61.3 ± 8.8	0.821	58.3 ± 12.1	50.4 ± 14.5	0.155
Sex, % male	14 / 1	19 / 1	0.681	10 / 5	8 / 2	0.659
Hypertension	7	7	0.727	5	2	0.659
Diabetes mellitus	3	9	0.237	2	1	1.000
Tobacco use	5	10	0.522	4	2	1.000
Systolic blood pressure (mmHg)	122 ± 16	121 ± 19	0.804	121 ± 16	122 ± 15	0.837
Diastolic blood pressure (mmHg)	78 ± 9	75 ± 11	0.314	77 ± 10	77 ± 12	0.849
Heart rate (beats/min)	82 ± 9	80 ± 11	0.723	80 ± 7	81 ± 8	0.844
NYHA functional class						
I	0	0	1.000	0	0	0.442
II	6	8		5	5	
III	9	12		10	5	
IL-2 (U/mL)	718.3 ± 412.2	734.0 ± 319.1	0.610	991.7 ± 119.3	664.1 ± 241.3	0.807
IL-6 (pg/mL)	10.9 ± 7.7	12.5 ± 9.5	0.780	12.6 ± 14.3	10.0 ± 8.1	1.000
TNF-α (pg/mL)	10.5 ± 4.0	9.8 ± 6.6	0.753	12.3 ± 5.4	9.0 ± 5.0	0.149
Left ventricular ejection fraction	0.22 ± 0.09	0.25 ± 0.09	0.374	0.22 ± 0.08	0.28 ± 0.10	0.141
Time to reach peak filling rate (ms)	161.2 ± 113.9	160.3 ± 88.5	0.978	124.5 ± 86.1	167.3 ± 54.3	0.178
Time to reach peak emptying rate (ms)	113.0 ± 97.9	94.3 ± 60.1	0.490	119.0 ± 77.0	88.7 ± 54.9	0.295
1/3 maximum filling fraction(s)	0.5 ± 0.2	0.5 ± 0.3	0.980	0.4 ± 0.2	0.3 ± 0.1	0.062

IL-2 = interleukin-2; IL-6 = interleukin-6; NYHA = New York Heart Association; TNF-α = tumor necrosis factor-alpha

standard treatment in the subgroups of ischemic and nonischemic DCM patients who were assigned to receive carvedilol.

All patients (on carvedilol or not) were checked in our polyclinics every 2 weeks. The carvedilol dosage (in patients so assigned) could be doubled every 2 weeks, if the dosage was tolerated by the patients. Carvedilol treatment was monitored for the study period of 4 months. Functional class was considered to have improved if the patient's functional status increased by one or more grades of the NYHA classification. It was considered to have deteriorated if the functional class decreased by one or more grades, or if the patient died. Because all deaths were due to progression of HF, all patients who died were classified in NYHA functional class IV at the final follow-up.

Tumor Necrosis Factor-α, Interleukin-2, and Interleukin-6 Levels

To measure TNF-α, IL-2, and IL-6 concentrations, 15 mL of blood was drawn from an antecubital vein and collected into prechilled evacuated tubes containing ethylenediaminetetraacetic acid. Plasma was separated by centrifugation at 2,500 rpm for 12 minutes within 15 minutes of collection. Samples were stored at –70 °C. Measurements of TNF-α, IL-2, and IL-6 were performed in undiluted plasma with a commercially available, enzyme-linked agent for immunoassay (Immulite, Diagnostic Products Corporation; Los Angeles, Calif). Three of these measurements were then averaged to obtain the plasma level. Determinations of TNF-α, IL-2, and IL-6 plasma levels were performed at baseline and then repeated 4 months after the random assignment of patients to groups and subgroups.

Radionuclide Study

We used a multiple-gated equilibrium cardiac-blood-pool scintigraphic technique (Siemens; Erlangen, Germany) to measure LVEF. Imaging was performed in the left anterior oblique projection, which provided the best septal separation of the ventricles with a 0° to 10° caudal tilt. Calculations of LV performance were made as described elsewhere, by means of the automatic edge-detection algorithm for the determination of LV borders.[7] All studies were interpreted by a single observer blinded to the treatment assigned. We calculated the LVEF, the maximum emptying and filling velocities, the time to reach these velocities, the one-third maximum filling fraction, and the regional wall EF rates. Radionuclide studies were performed at baseline and then repeated 4 months after the randomization of patients.

Statistical Analysis

Continuous data were shown as mean ± SD. The suitability of continuous variables with the normal distribution was examined in the 1st study using the Kolmogorov-Smirnov test. The independent-sample *t* test and the paired-sample test were used in the analysis of the changes that were suitable with the normal distribution. The Mann-Whitney U and Wilcoxon tests were used to analyze changes that were not suitable with the normal distribution, and the χ^2 or Fisher's exact test was used in analyzing categoric data. Data were analyzed using Minitab (Minitab Inc.; State College, Pa). Significance was assumed at a 2-tailed value of $P < 0.05$.

Results

None of the 60 patients required discontinuation of the study medication. All patients during the study period received digoxin, 0.25 mg daily; furosemide, 80 mg daily; and enalapril, 10 mg twice daily. Coronary angiography showed normal coronary arteries in nonischemic DCM and abnormal coronary arteries in ischemic DCM patients. Of the ischemic DCM patients who received carvedilol, 1 patient died, and 1 patient developed permanent atrioventricular fibrillation (AF) during the study. Of the ischemic DCM patients who received standard treatment, on the other hand, 7 patients died and 3 developed permanent AF. A patient in the nonischemic DCM-with-standard-treatment group quit attending regular follow-up sessions, and permanent AF developed in 3 patients. Upon exclusion of the patients who either died or developed permanent AF, the study was completed in 13 ischemic DCM patients on carvedilol, 10 ischemic DCM patients on standard treatment, 15 nonischemic DCM patients on carvedilol, and 6 nonischemic DCM patients on standard treatment.

The results of all the subgroups at baseline and at the end of the study are presented in Table II. Carvedilol was received at an average dose of 28.3 ± 10.0 mg daily by the ischemic DCM patients. In ischemic DCM patients on carvedilol treatment, systolic blood pressure, diastolic blood pressure, and heart rate were found to be suppressed at the end of the study ($P=0.004$, $P=0.010$, and $P=0.001$, respectively). Before carvedilol use, 6 patients were in NYHA functional class II and 7 patients were in class III; at the end of the study, 8 patients were in functional class I and 5 patients were in class II ($P=0.226$). The initial LVEF (0.22 ± 0.08) improved to 0.27 ± 0.10, which, however, was not significant ($P=0.117$). Similarly, there were no significant changes in LV diastolic functions. Although no significant changes occurred in IL-2 level, both IL-6 and TNF-α levels fell significantly (9.7 ± 7.2 vs 5.1 ± 0.4 pg/mL, $P=0.028$; and 10.5 ± 4.0 vs 6.0 ± 4.9 pg/mL, $P=0.034$, respectively).

In ischemic DCM patients on standard treatment, no significant changes occurred in systolic and diastol-

ic blood pressures, heart rate, and functional capacity at the end of the study. The plasma IL-2 level (688.0 ± 141.2 U/mL) was elevated to 771.4 ± 172.4 U/mL (P=0.047). Although no significant changes occurred in the IL-6 level, the TNF-α level (9.8 ± 8.4 pg/mL) was elevated to 13.0 ± 8.7 pg/mL (P=0.008). No significant changes occurred in the LVEF, the time to reach peak filling velocity, the time to reach peak emptying rate, and the 1/3 filling fraction. The comparisons of measurements obtained before and after carvedilol treatment in ischemic DCM patients are presented in Table II.

In the nonischemic DCM group, there were no significant differences between the standard-treatment and carvedilol subgroups in regard to age, sex, hypertension, diabetes mellitus, cigarette use, systolic and diastolic blood pressures, heart rate, pro-inflammatory cytokine levels, and LV systolic and diastolic functions as evaluated by means of radionuclide ventriculography (Table I). The nonischemic DCM patients were given carvedilol at an average dose of 28.4 ± 12.9 mg. The systolic blood pressure, diastolic pressure, and heart rate were found to be suppressed in nonischemic DCM patients on carvedilol treatment (P=0.003, P=0.012, and P=0.001, respectively). At the beginning of the study, of the 15 nonischemic DCM patients, 10 were in NYHA functional class III and 5 were in class II; at the end of the study, 1 was in class III, 5 were in class II, and 9 were in class I. Although no changes occurred in IL-2 level, levels of IL-6 and TNF-α dropped significantly (from 12.6 ± 14.3 pg/mL to 5.9 ± 2.6 pg/mL, P=0.018; and from 12.3 ± 5.4 pg/mL to 5.7 ± 3.0 pg/mL, P=0.004, respectively). The LVEF rate improved from 0.22 ± 0.08 to 0.29 ± 0.13 (P=0.006), but no changes occurred in numbers indicative of diastolic function. The comparisons of results obtained before and after carvedilol treatment in nonischemic DCM patients are presented in Table II.

In nonischemic DCM patients on standard treatment, no significant changes occurred in hemodynamic results, pro-inflammatory cytokine levels, and radionuclide ventriculography measurements at the end of the study (Table II). The changes in cytokine levels before and after treatment with carvedilol in ischemic and nonischemic DCM patients are shown in Figures 1–4.

During the course of the study, no patient in the nonischemic DCM groups died; however, 8 patients died in the ischemic DCM groups (P=0.016). Atrioventricular fibrillation developed in 4 ischemic DCM patients and in 3 nonischemic DCM patients (P=0.625). Of the 8 deaths that occurred among ischemic DCM patients, 7 were in the standard-treatment group and 1 was in the carvedilol group. All deaths were due to the progression of HF. In the group of ischemic DCM patients on standard treatment, the incidence of death was higher than it was among ischemic DCM patients on carvedilol treatment, but this difference was not statistically significant (P=0.101).

Discussion

Carvedilol improves the functional capacity of HF patients by increasing the LVEF and cardiac output and by decreasing the heart rate and pulmonary capillary wedge pressure.[6] Metra and coworkers[8] reported in a clinical study of 40 patients who had NYHA class II to IV HF that the addition of carvedilol to the standard HF treatment (ACE inhibitors, diuretics, and digoxin) improved the effort capacity of patients and decreased the severity of HF.[8] In our study, before carvedilol use by 13 ischemic DCM patients, 6 were in NYHA functional class II and 7 were in class III. After 4 months of carvedilol treatment, 8 patients were in class I and 5 were in class II (P=0.266). Of the 15 nonischemic DCM patients on carvedilol, 5 were in class II and 10 were in class III before carvedilol use. After 4 months of carvedilol treatment, functional capacity significantly improved: 5 patients were in class I, 9 patients were in class II, and 1 patient was in class III (P=0.025). In both ischemic and nonischemic DCM patients on standard treatment, no significant changes were observed in functional capacity. The probable reason for the less pronounced effects of carvedilol on ischemic DCM patients is that necrotic areas, which have no function as β-adrenergic receptors, are relatively larger in ischemic DCM patients than in nonischemic DCM patients.

Olsen and coworkers[9] reported in a clinical study of 60 DCM patients (ischemic and nonischemic) who were given carvedilol twice daily—at a starting dose of 3.125 mg with gradual increases up to 25 to 50 mg during 4 months of treatment—that the LVEF and stroke volume index were significantly increased and that pulmonary capillary wedge pressure was reduced, with decreases in the severity of HF. Similarly, in our study, the LVEF was found to be significantly increased in nonischemic DCM patients (P=0.006). The LVEF in ischemic DCM patients also improved, but not significantly so (P=0.117). In ischemic and nonischemic DCM patients on standard HF treatment, no changes occurred in the LVEF.

Plasma levels of TNF-α, IL-1, IL-2, IL-6, and IL-10 are elevated in chronic HF patients. Levine and colleagues[10] evaluated the plasma TNF-α levels in patients with NYHA class III and IV HF. In that study, plasma TNF-α levels of 33 HF patients and 33 healthy age-paired individuals were measured. The TNF-α level of the HF patients (115 ± 25 U/mL) was significantly higher (P <0.001) than that of healthy individuals (9 ± 3 U/mL). Moreover, the TNF-α level was much higher in patients with the most severe HF. A search of the Left Ventricular Dysfunction Studies database revealed

TABLE II. Results at Baseline and at 4 Months for the Patients Who Completed the Study Period

	Ischemic Cardiomyopathy						Nonischemic Cardiomyopathy					
	Carvedilol			Standard			Carvedilol			Standard		
	Baseline (n=13)	**4 Months** (n=13)	***P* Value**	**Baseline** (n=10)	**4 Months** (n=10)	***P* Value**	**Baseline** (n=15)	**4 Months** (n=15)	***P* Value**	**Baseline** (n=6)	**4 Months** (n=6)	***P* Value**
Systolic blood pressure (mmHg)	125 ± 15	115 ± 15	0.004	127 ± 19	121 ± 16	0.217	121 ± 16	108 ± 9	0.003	125 ± 16	132 ± 12	0.394
Diastolic blood pressure (mmHg)	79 ± 9	72 ± 8	0.010	80 ± 11	75 ± 9	0.059	77 ± 10	69 ± 7	0.012	78 ± 12	80 ± 0	0.705
Heart rate (beats/min)	82 ± 9	65 ± 3	0.001	78 ± 13	77 ± 10	1.000	80 ± 7	65 ± 4	0.001	80 ± 4	77 ± 10	0.462
NYHA functional class												
I	0	8	0.266	0	0	0.62	0	5	0.025	0	0	0.858
II	6	5	7	9	5	9	4	6				
III	7	0	3	1	10	1	2	0				
IL-2 (U/mL)	707.9 ± 438.9	720.4 ± 446.8	0.807	688.0 ± 141.2	771.4 ± 172.4	0.047	991.7 ± 1193.3	791.1 ± 722.4	0.307	720.1 ± 281.4	695.5 ± 198.7	0.600
IL-6 (pg/mL)	9.7 ± 7.2	5.1 ± 0.4	0.028	11.1 ± 8.9	10.7 ± 7.3	0.463	12.6 ± 14.3	5.9 ± 2.6	0.018	6.9 ± 8.4	5.5 ± 7.2	0.655
TNF-α (pg/mL)	10.5 ± 4.0	6.0 ± 4.9	0.034	9.8 ± 8.4	13.0 ± 8.7	0.008	12.3 ± 5.4	5.7 ± 3.0	0.004	8.3 ± 4.7	9.6 ± 5.1	0.273
Left ventricular ejection fraction	0.22 ± 0.08	0.27 ± 0.10	0.117	0.28 ± 0.10	0.28 ± 0.12	0.927	0.22 ± 0.08	0.29 ± 0.13	0.006	0.31 ± 0.11	0.30 ± 0.08	0.762
Time to reach peak filling rate (ms)	160.7 ± 118.1	141.6 ± 95.0	0.605	174.8 ± 117.1	137.1 ± 49.6	0.358	124.5 ± 86.1	140.7 ± 79.8	0.563	166.8 ± 71.8	119.1 ± 55.7	0.081
Time to reach peak emptying rate (ms)	122.1 ± 101.9	132.2 ± 55.8	0.805	84.2 ± 50.3	104.3 ± 49.0	0.056	119.0 ± 77.0	135.2 ± 92.9	0.664	72.0 ± 58.1	96.5 ± 45.0	0.371
1/3 maximum filling fraction (s)	0.5 ± 0.2	0.4 ± 0.2	0.058	0.5 ± 0.3	0.6 ± 0.3	0.674	0.6 ± 0.3	0.5 ± 0.3	0.371	0.4 ± 0.1	0.4 ± 0.3	0.616

IL-2 = interleukin-2; IL-6 = interleukin-6; NYHA = New York Heart Association; TNF-α = tumor necrosis factor-alpha

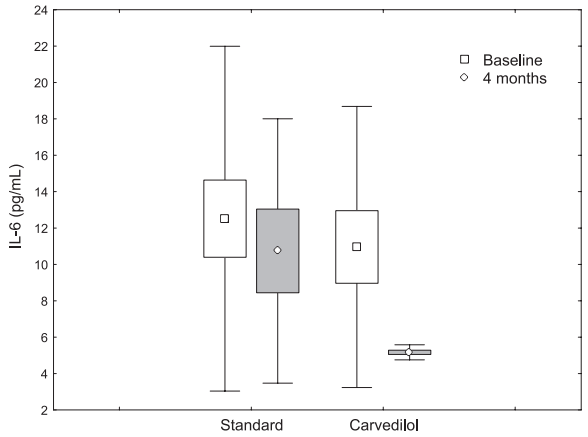

Fig. 1 *The changes in interleukin-6 (IL-6) levels before and after treatment with carvedilol, in ischemic dilated cardiomyopathy patients.*

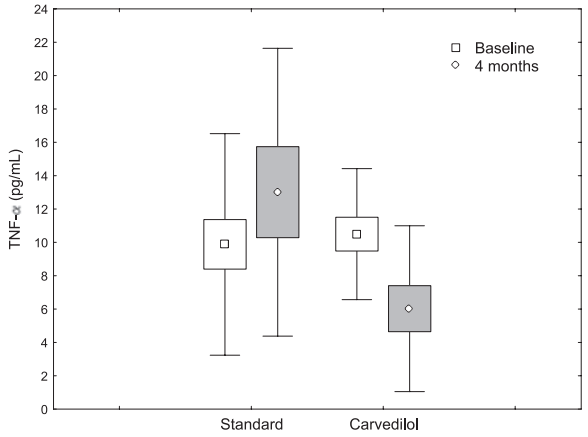

Fig. 2 *The changes in tumor necrosis factor-α (TNF-α) levels before and after treatment with carvedilol, in ischemic dilated cardiomyopathy patients.*

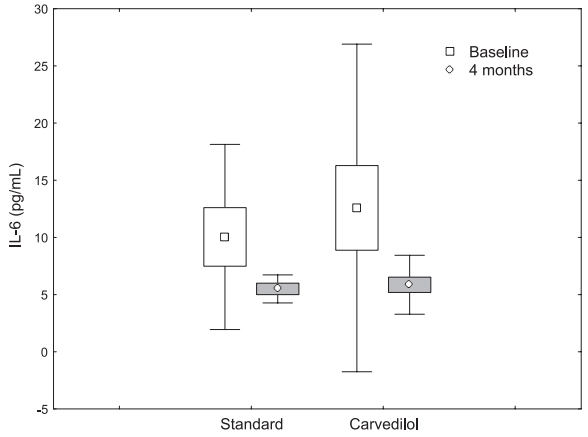

Fig. 3 *The changes in interleukin-6 (IL-6) levels before and after treatment with carvedilol, in nonischemic dilated cardiomyopathy patients.*

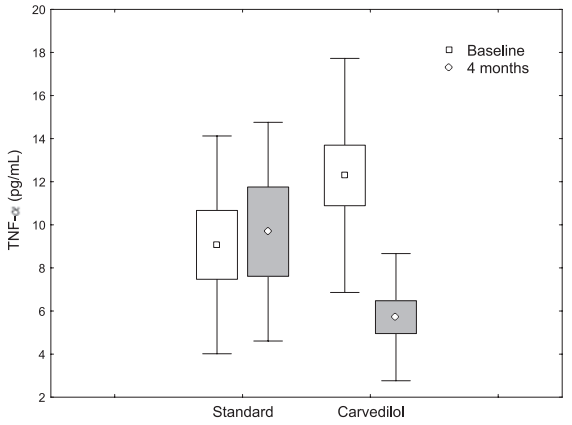

Fig. 4 *The changes in tumor necrosis factor-α (TNF-α) levels before and after treatment with carvedilol, in nonischemic dilated cardiomyopathy patients.*

that TNF-α levels in HF patients with NYHA class I, II, and III HF were 1.95 ± 0.54 pg/mL, 2.60 ± 0.48 pg/mL, and 6.4 ± 1.9 pg/mL, respectively, or 0.75 ± 0.05 pg/mL higher than those of age-paired healthy individuals.[11] The IL-6 levels in patients with NYHA class I, II, and III HF were 3.3 ± 0.5 pg/mL, 6.2 ± 0.48 pg/mL, and 5.2 ± 0.9 pg/mL, respectively, or 1.8 ± 0.5 pg/mL higher than those of age-paired healthy individuals. Cytokine levels were found to be lower in 14 patients with idiopathic DCM who were being treated with a mechanical device implanted on the LV.[12] When cytokine analyses were done 24 hours before implantation, 11 of the 14 patients (79%) had elevated levels of IL-6, 10 (71%) had elevated levels of IL-8, and 2 (14%) had elevated levels of TNF-α. Thirty days after the mechanical-aid implantation, the LVEF was improved and there were decreases in IL-6 and IL-8 levels; however, no significant changes occurred in TNF-α levels. Matsumura and associates[13] reported that the addition of carvedilol to the standard treatment of 9 patients with idiopathic DCM (in NYHA class II) caused a significant drop in IL-6 level, while TNF-α level was not affected. Othsuka and colleagues[14] showed that serum levels of IL-10, TNF-α, and sTNF-R2 significantly decreased during β-blocker therapy.

Our study included enough larger numbers of ischemic and nonischemic DCM patients that the addition of carvedilol to standard HF treatment significantly lowered the plasma levels of IL-6 and TNF-α in both of our ischemic and nonischemic groups.

In a study conducted by Sliwa and associates[15] on 28 patients, 14 patients received a 400-mg daily or twice-daily dose of pentoxifylline, a xanthine derivative, while the other 14 received a placebo. After a follow-up period of 6 months, the TNF-α level was suppressed and functional capacity and LVEF were improved in the pentoxifylline group. In another study, Skudicky

and coworkers[16] used ACE inhibitors, digoxin, and carvedilol for at least 3 months in treating 39 patients with idiopathic DCM and LVEF lower than 0.40. One group (n=20) was given pentoxifylline and the other group (n=19) was given a placebo. At the end of 6 months, the LV end-systolic diameter was decreased in the pentoxifylline group and the LVEF was increased, while the LV end-diastolic diameter was not changed. The TNF-α level was not significantly (P >0.05) changed, either; the initial TNF-α level, 2.5 ± 1.8 pg/mL, dropped slightly to 2.3 ± 1.8 pg/mL. We could find no study that demonstrated definitively the effects of carvedilol on the suppression of cytokines in patients with ischemic or nonischemic DCM; however, we can make inferences from related studies. In Sliwa's study,[15] pentoxifylline improved LV functions and suppressed cytokine levels in DCM patients; however, in Skudicky's study,[16] with a similar experimental design, pentoxifylline did not affect cytokine levels. In this latter study, patients had been receiving carvedilol longer than 3 months before pentoxifylline use. Therefore, carvedilol might already have suppressed the cytokine levels, before pentoxifylline administration. We designed our study to determine whether the useful effects of carvedilol are also related to the suppression of cytokines in patients with ischemic DCM, versus nonischemic DCM. Subsequently, we found that TNF-α and IL-6 levels declined significantly (P=0.001) in both groups after 4 months of carvedilol treatment. Moreover, in patients with ischemic DCM who were on standard treatment, plasma TNF-α and IL-2 levels were significantly elevated (P=0.008 and P=0.047, respectively).

Bristow and colleagues[17] administered 6.25 to 25 mg of carvedilol to their DCM patients, who were followed up for 6 months. Of 49 patients with ischemic DCM on standard treatment, 9 died, whereas 7 patients died among 133 with ischemic DCM in the carvedilol group (P=0.003). Of 38 patients with nonischemic DCM on standard treatment, 4 died, while 5 of 128 patients with nonischemic DCM on carvedilol died (P=0.11). In our study, all of the deaths (8 patients) occurred in the ischemic DCM groups (P=0.016). No patient died in the nonischemic DCM groups. Of the 8 deaths, only 1 patient (7%) was in the carvedilol group and 7 patients (35%) were in the standard-treatment group. Thus, the mortality rate was lower in the carvedilol group, but not significantly so (P=0.101). The reason for our not observing a significant difference in the mortality rate might be the low number of patients in our study or the short period of study.

Krum and associates[18] showed that the severity of ventricular tachycardia and ventricular fibrillation were remarkably reduced in HF patients who received carvedilol. Regardless of whether they had AF or sinus rhythm, DCM patients on carvedilol showed improvements in LV functions and in functional capacity.[19] However, we have found no report that carvedilol prevents the development of AF in DCM patients who are in sinus rhythm. In our study, AF developed in 4 ischemic and 3 nonischemic DCM patients (P=0.625). In ischemic DCM patients on carvedilol, AF developed in just 1 patient (7%); in ischemic DCM patients on standard treatment, AF developed in 3 patients (15%). However, the incidence of AF was not statistically different between the 2 groups (P=0.619). A major limitation of this study was the small number of patients.

Conclusion

Carvedilol suppresses the plasma levels of TNF-α and IL-6 in both ischemic and nonischemic DCM patients. It also improves the functional capacity and the LVEF significantly in nonischemic DCM patients and insignificantly in ischemic DCM patients. Overall, carvedilol seems to be more useful in nonischemic DCM patients than in ischemic DCM patients. In our study, carvedilol appeared to reduce the mortality rate in ischemic DCM patients, but by an insignificant amount. Our results need to be confirmed in a larger series of patients.

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Review

Iliac Vein Stenting for Chronic Venous Insufficiency

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Chronic venous insufficiency has devastating sequelae in terms of patients' lifestyles and negative economic impact on society. Traditional surgical procedures have yielded variable patency results, and follow-up has not always been reported. This review summarizes the current applications, patency rates, stent selection, and complications of balloon angioplasty and stenting in the treatment of chronic venous outflow obstruction in the lower extremity. We conclude that endovenous stenting is the current method of choice in the treatment of chronic venous obstruction. ***(Tex Heart Inst J 2007;34:60-6)***

Key words: *Angioplasty, balloon; catheterization, peripheral; deep vein thrombosis; iliac vein compression syndrome; leg/blood supply; May-Thurner syndrome; peripheral vascular diseases/diagnosis/therapy; stents; venous insufficiency, chronic*

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Traditional therapy for acute lower-extremity deep venous thrombosis (DVT) has been directed toward limiting the progression of existing clots and preventing pulmonary embolism (PE) and recurrent thrombosis. Up to 90% of patients with a history of iliofemoral DVT develop significant symptoms of the post-thrombotic syndrome, which consist of swelling, pain, ulceration, and venous claudication of the lower extremities. Up to 15% of patients develop stasis ulcers, despite adequate treatment of the acute event with anticoagulation.[1,2] The underlying pathophysiology is ambulatory venous hypertension that develops as a result of persistent venous obstruction and incompetent venous valves. The long-term clinical and hemodynamic consequences of chronic iliofemoral venous thrombosis have been well documented. It has been reported that nearly half (44%) of patients with a previous episode of iliofemoral DVT developed symptoms of venous claudication despite treatment of the acute event with standard anticoagulation.[3]

The rationale for early, active clot removal in patients with acute DVT is therefore 2-fold: elimination of acute and long-term venous obstruction, and preservation of venous valve function. Acute DVT may be treated with pharmacologic or mechanical clot-removal methods, combined with correction of any underlying or residual obstructive lesions. This report reviews the current methods for treating chronic venous insufficiency that results from iliofemoral DVT, with emphasis on the emerging use of endovascular techniques.

Current Treatment Methods for DVT

Historically, intravenously administered unfractionated heparin, followed by oral warfarin, was the treatment of choice for acute DVT. Randomized clinical trials have elucidated effective alternative anticoagulant regimens.[4-7] As a result of clinical studies, the subcutaneous administration of low-molecular-weight heparin has become the standard of care for patients with acute DVT.[8] Although available anticoagulants prevent thrombus propagation, PE, and recurrent venous thrombosis, they do not dissolve the occluding thrombus or reduce venous outflow obstruction. Furthermore, the inflammatory process may be unaffected by anticoagulants.[9] Due to these limitations, alternative therapies that focus on clot removal and preservation of valvular competence have emerged. These alternative treatment methods include open surgical thrombectomy, thrombolytic therapy, percutaneous mechanical thrombectomy, and balloon angioplasty and stenting. This review will focus on the current status of this last endovascular approach in the treatment of chronic obstruction of venous outflow to the lower extremity.

Before the development of venous balloon dilation and stenting, obstructions of the venous circulation were corrected by surgical bypass reconstruction. Iliac vein obstruction was usually managed by a Palma femorofemoral bypass or a unilateral bypass between the femoral vein distal to the obstruction and the contralateral iliac

vein or inferior vena cava (IVC).[10] These major surgical procedures usually necessitate lifelong anticoagulation and a temporary or continuous adjunctive arteriovenous fistula to keep the bypass patent. Due to the magnitude of the intervention, only patients with the most severe post-thrombotic syndrome were selected. Although reports on the crossover-bypass technique claim durable symptomatic relief,[11,12] most studies lack consistent follow-up with venography.

Endovascular treatment is much less invasive, for it requires only percutaneous access with a 16G needle, followed by a 6F or 7F sheath. Upon completion of the procedure, hemostasis is achieved by manual compression. This approach has a high technical success rate, with minimal complications. The procedure can be performed as a 1-day (or less) admission, with the patients' return to prior activity levels immediately after discharge.[13] Furthermore, an endovascular approach is advantageous for several reasons: diagnostic venography enables direct evaluation of the degree of venous obstruction and collateralization; catheter-directed thrombolysis can clear a large acute thrombus burden, thus preserving valve function; angioplasty and stent placement can disrupt obstructive intravenous synechiae and webs (spurs); and the integrity of the compressed iliac vein can be restored without apparent long-term damage.

Iliac Vein Compression Syndrome

In some patients with DVT, there is underlying venous disease. Left common iliac vein stenosis frequently occurs where the vein crosses beneath the right common iliac artery. Chronic, repetitive compression at this site causes fibrosis of the vein, with synechiae and spurs that result in stenosis or even occlusion of the lumen. This condition, which is becoming increasingly recognized, is called iliac vein compression syndrome, or May-Thurner syndrome.[14]

Iliac vein compression syndrome may present in 3 distinct clinical patterns. Patients may present with sudden leg swelling and pain associated with iliofemoral venous thrombosis, with the anatomic defect discovered after the clot has been removed by thrombolysis or surgical thrombectomy. This acute presentation is found most commonly in women in the 3rd or 4th decades of life. Iliac vein compression may also be discovered in patients with chronic leg complaints that are suggestive of chronic venous insufficiency, including stasis ulceration, in the absence of acute thrombosis. In these patients, a short-segment stenosis or occlusion of the proximal left common iliac vein is discovered. Last, patients may present—months or years after a known episode of iliofemoral DVT—with extensive occlusion of the left common and external iliac veins, in which instance venous drainage of the leg occurs mainly via collateral vessels that arise from the common femoral vein. Patients with mild degrees of iliac vein compression may manifest some leg swelling, left-leg varicosities, and valvular incompetence in both superficial and deep systems. We are increasingly interrogating the iliac system when treating patients with severe left-leg varicosities, in order to look for iliac vein compression. There are insufficient clinical data, however, to currently recommend this for routine clinical practice.

One must maintain a high index of suspicion to recognize iliac vein compression. With the widespread use of venography in patients who are undergoing percutaneous procedures, it is now possible to identify a culprit lesion in some patients. Once identified, these lesions can usually be treated with percutaneous venoplasty and stenting.[15-17] Endoluminal reconstruction of the compressed iliac vein by means of a stent is a simpler and perhaps more elegant solution than surgery, especially for application to a young and otherwise healthy patient.

Bypass Procedures. The indications for surgical treatment of iliac vein compression (May-Thurner syndrome) are a mean resting pressure difference of >2 mmHg between the right and left common femoral veins; or a variation in pullback pressures from the IVC to the external iliac vein; or venous claudication with a 3-fold increase, upon exercise, in the venous pressure of the affected limb, compared with that of the healthy limb.[15,18-20] Multiple surgical treatment options have been advocated. These include vein-patch angioplasty with excision of intraluminal bands; division of the right common iliac artery and relocation behind the left common iliac vein or vena cava; and contralateral saphenous vein graft bypass to the ipsilateral common femoral vein with creation of a temporary arteriovenous fistula (Palma's crossover).[18]

Unfortunately, there are no randomized comparative trials, and it is difficult to compare 1 technique with another. The reported patency rates of bypass procedures are variable, and follow-up has been inconsistent. Overall, the reported long-term success rate, defined primarily as patency of the left common iliac vein or venous bypass, ranges from 40% to 88%.[11,12] The necessity for long-term anticoagulation makes surgery even less attractive to patients. Recently, combined surgical and endovascular management of iliofemoral DVT has been described. Mickley and associates[19] reported their experience with surgical thrombectomy in 77 patients with acute iliofemoral DVT. Among the 61 patients with left iliofemoral DVT, venography suggested the presence of a spur in 30 patients. Twenty-two of these 30 patients were treated by thrombectomy alone, followed by anticoagulation; 16 of the 22 had acute rethrombosis despite adequate anticoagulation. The remaining 8 of the 30 patients underwent placement of an endovascular stent after thrombectomy. Only 1 of these patients had acute rethrombosis, which was attributed to a malpositioned stent.

Iliac Vein Obstruction and Occlusion

The treatment of outflow obstruction has been hampered by difficulty in identifying hemodynamically significant obstruction,[20,21] a problem that was compounded by the sole availability of invasive surgical techniques.[10] Several authors[13,17,22-24] have reported the results of endovascular management, including balloon angioplasty and stent placement, to recanalize obstructed iliac vein segments. Most series include a preponderance of left-sided interventions, presumably representing cases of iliac vein compression; and stents are placed in nearly all patients, due to the elastic recoil typical of venous lesions.

Raju and colleagues[23] have reported their experience with recanalization of the iliac vein in 38 limbs. In 28 of 38 limbs, the stent was extended below the groin crease into the common femoral vein segment. Large-caliber (14 or 16 mm for the iliac vein), flexible, self-expanding stents were used. Stents were routinely extended for a short distance into the IVC to forestall development of iliocaval stenosis. The median length of the recanalized segment was 22 cm, and multiple stents (median, n=3) were necessary in most patients. Actuarial primary, primary-assisted, and secondary patency rates of stents at 24 months were 49%, 62%, and 76%, respectively. There was a significant symptomatic improvement in the stented group, with minimal morbidity.[23] In another review, the same group[25] reported excellent results with iliac vein interventions, including stents placed in 455 limbs with chronic, nonmalignant obstruction (stenosis or occlusion). At 3 years, primary patency was 75%, primary-assisted patency was 92%, and secondary patency was 93%. Nonthrombotic limbs had better primary patency than thrombotic limbs (89% vs 65%, respectively).

These studies illustrate that, although surgical strategies exist, iliocaval occlusion can more often than not be successfully recanalized by angioplasty and stenting. Patients who experience venous claudication due to chronic isolated iliac vein occlusion often experience immediate relief after such recanalization.

Balloon Angioplasty and Stenting for May-Thurner Syndrome

Patel and colleagues[16] reported on their endovascular treatment of acute extensive iliofemoral deep venous thrombosis due to May-Thurner syndrome. During a 1-year period, 10 symptomatic women were referred for treatment. After ascending venography, an infusion catheter system was placed, and urokinase was infused locally into the thrombus burden. After nearly complete (≥95%) clot dissolution or lytic stagnation, the residual narrowing of the left common iliac vein was treated by means of angioplasty or placement of a Wallstent® endoprosthesis (Boston Scientific, Inc.; Natick, Mass). Initial clinical success was 100%, with complete resolution of symptoms in all patients. During a mean follow-up of 15.2 months, all but 1 patient were asymptomatic. That patient, who was hypercoagulable and was receiving chemotherapy for metastatic adenocarcinoma, had recurrent, symptomatic, acute DVT 1 month after therapy. She responded to repeated lysis. Patel and associates[16] concluded that underlying left common iliac vein lesions invariably need to undergo stent placement.

In another study, Binkert and coworkers[26] reported the use of self-expanding stents in 8 patients who had been diagnosed with iliofemoral DVT and pelvic venous spur. The mean follow-up period was 32 months. The primary patency rate was 100%, with immediate symptomatic relief in all patients. O'Sullivan and coworkers[27] reported a retrospective analysis of 39 patients who had venous outflow obstruction resulting from May-Thurner syndrome. Nineteen of these patients presented with acute DVT, and the remaining 20 presented with chronic symptoms. In the acute DVT group, all patients were treated with catheter-directed thrombolysis, followed by angioplasty and stent placement. In the chronic DVT group, patients were treated with angioplasty and stenting alone (n=8) or in combination with thrombolysis (n=12). Thirty-five of the 39 patients received stents. Patients were then followed up with duplex ultrasonography and a quality-of-life evaluation. Initial technical success was achieved in 87%, patency at 1 year in >90%, and symptomatic relief in 85%.[27] Collectively, these data support the use of endovascular therapy for chronic venous outflow obstruction.

Imaging for Iliac Vein Obstruction

Visualization of the iliac veins in the pelvis can be difficult due to overlying pelvic organs and bowel gas. In addition, Doppler waveforms in the common femoral veins can display normal spontaneous flow and respiratory variation due to large collateral vessels around the site of proximal obstruction. Hurst and associates[22] reported false-negative scans in 5 of 18 patients with iliac vein obstruction. In the setting of unilateral lower-extremity pain and edema, especially after a normal lower-extremity venous duplex scan, direct imaging of the pelvic veins should be considered. Magnetic resonance venography has proved helpful as an alternative to conventional contrast venography.[28,29] Others have used computed tomographic angiography[30] as an alternative to reveal iliac vein stenosis due to compression.

At this time, there is no gold standard for the selection of patients who need treatment for iliac outflow obstruction. Venographic evidence of collateral vessels certainly strengthens the case for intervention, but significant lesions can be present without collateralization. Intravascular ultrasound (IVUS) investigation is highly accurate and should probably be used more liberally, especially in patients in whom there is clinical suspi-

cion of outflow obstruction, with symptoms of pain and swelling and a history of DVT.[25] Trabeculation and axial collateral vessels show up well on the IVUS image, and accurate measurements of venous diameter for stent sizing is also provided. The IVUS accurately displays postdilation flaps or venous wall irregularities and confirms that the stent has completely conformed to the venous wall.

Stent Selection

The mid-term patency of stents in the iliocaval venous system has been considerably higher than that of self-expanding stents in other medium-sized veins, such as the subclavian vein.[31] The possible reasons for this include the relatively immobile nature of pelvic placement, compared with stent placement in the freely mobile subclavian vein, in addition to the absence of adjacent bony structures, such as the clavicle or the 1st rib, which might compress a stent. We acknowledge that the inguinal ligament is a relatively firm, immobile structure, yet extending stents below this level did not affect patency, as we have said above. Perhaps this is because during hip flexion, the point of maximum flexion of the femoral vein is several centimeters inferior to the inguinal ligament.

As we have gained more experience in treating iliac vein compression, we have switched from balloon-expandable stents to the more flexible self-expanding stents.[30] Self-expanding stents have the advantages of longer lengths, large diameters, flexibility at the groin, and less susceptibility to permanent deformation by the pulsatile artery and the inguinal ligament. Hartung and coworkers[32] have described treating left common iliac vein lesions with readily available stents that are 16 mm in diameter and at least 60 mm long. When the self-expanding stent is used, the initial deployment can occur in the IVC, and the entire device can then be pulled caudally so that the cephalad (caval) end of the stent is flush with the iliocaval junction. Therefore, a recommendation that the stent be placed well into the IVC when obstruction occurs close to the iliocaval junction, as in May-Thurner syndrome, appears to be safe.[27]

The use of infrainguinal venous stents is currently controversial. Although it may seem important to keep the stented area to a minimum, stent implantation should extend to cover all identified stenoses, leaving no residual lesion if possible. Because the Wallstent is flexible, it is considered safe to cross the inguinal ligament. However, given the relatively poor patency of infrainguinal stents compared with suprainguinal stents,[27,33] they should be reserved for patients who have severe, extensive disease with very poor outflow.

The Procedure

The procedure is usually performed in the operating room or angiography suite with the patient under local anesthesia and intravenous sedation. Ultrasound-guided cannulation of the common femoral or popliteal vein is performed, followed by insertion of a 6-mm Pinnacle sheath (Terumo Medical Corporation; Somerset, NJ). Antegrade venography is performed to determine the degree, length, and site of obstruction, and the presence of collateral vessels. Once the area of concern has been traversed with a guidewire (Terumo Medical Corporation), we routinely cross the stenosis or occlusion with a stainless-steel, titanium-alloy, self-expanding stent, 10 to 16 mm × 9 cm (Wallstent, Boston Scientific/Meditech). Upon completion, a venogram is mandatory. If significant stenosis remains, postdilation with a 12- to 20-mm × 4- to 6-cm balloon (Meditech XXL, Boston Scientific/Meditech) is carried out (Fig. 1). Finally, the sheath is removed and light pressure is applied. Table I lists the supplies that are required to perform balloon angioplasty and stenting.

Clinical Outcomes after Endovascular Venous Interventions

The most extensive experience has been reported by Raju and colleagues,[34] who described their results after the treatment of 304 limbs with symptomatic chronic venous insufficiency. Their actuarial primary and secondary stent patency rates at 24 months were 71% and 90%, respectively. The median degree of swelling and pain was significantly reduced: the pain level recorded on a visual analogue scale from 0 to 10 declined from a median level of 4 to 0 (P <0.001). Complete pain relief was achieved in 71% of patients, up from 17% before stenting. Stasis dermatitis or ulceration was present in 69 of 304 limbs. The cumulative recurrence-free ulcer healing rate was 62% at 24 months. Quality of life was also significantly improved.[34]

Hartung's group[32] reported similar mid-term results of endovascular treatment of symptomatic, chronic, nonmalignant, iliocaval venous occlusive disease. A high technical success rate was achieved. Thrombotic occlusion occurred in 5% of patients (2/44), with cumulative primary and secondary patency rates of 73% and 90%, respectively, at 36 months; and an in-stent restenosis (reduction of luminal diameter by >50%) rate of 13% was observed. Respectively, the median Venous Clinical Severity and Venous Disability scores were 8.5 (range, 4–18) and 2 (range, 2–3) before surgery, and 2 (range, 0–9) and 0 (range, 0–2) at the end of the follow-up period.[32] These remarkable clinical results, together with improved quality of life, make adoption of this method even more appealing.

In patients with venous valvular reflux, the timing of repair procedures is open to discussion. Raju and Hardy[35] showed that surgical correction of the reflux by, for example, valve repair or subfascial endoscopic interruption (ablation of the perforated vein) can be performed with excellent results despite the presence

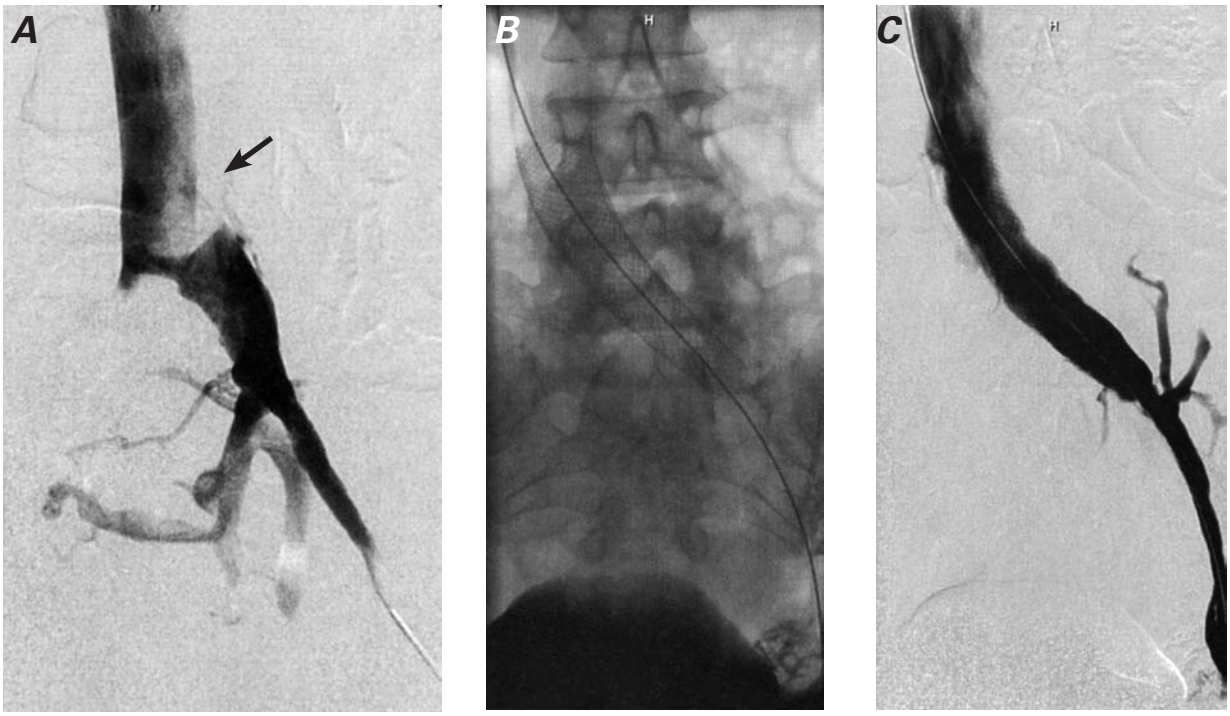

Fig. 1 *A 42-year-old woman had recurrent episodes of deep venous thrombosis in the left lower extremity.* ***A****) An antegrade common femoral vein approach was used, and an ascending venogram showed narrowing of the left common iliac vein (arrow), along with venous collateral vessels consistent with May-Thurner syndrome.* ***B****) Two 20- × 55-mm self-expanding stents were placed.* ***C****) A completion venogram showed the position of the stent in the inferior vena cava and satisfactory venographic resolution of the left common iliac lesion.*

TABLE I. A Practical List of Supplies for the Performance of Balloon Angioplasty and Stenting in the Treatment of Chronic Venous Outflow Obstruction to the Lower Extremity

Micropuncture entry kit (0.014-in platform)
0.035-in entry wire
Straight or angled floppy J-wire
6F–10F short sheath (a larger-diameter sheath may be required, depending upon the diameter of the chosen stent)
High-pressure tubing for power injection
Contrast agent for venography
5F exchange catheter
14–22 × 55–90-mm nitinol self-expanding stent vs Wallstent®
12–20 × 4–6-cm balloon with an insufflation device

of outflow obstruction. However, the relief of pain and swelling after endovascular treatment of venous stenosis has been so obvious that patients may experience more symptomatic resolution when stenting is performed before reflux procedures. The lack of improvement in reflux after stenting suggests that reflux control will be required later in many of these patients, especially those with advanced venous insufficiency. If Raju and Hardy's preliminary results[35] are sustained for a long-term period, stent placement for the correction of iliac vein stenoses will be a useful adjunct in the management of chronic venous insufficiency with resultant valvular incompetence.

Potential Complications of Venous Stenting Procedures

In most series, venous stenting carries no risk of death, pulmonary embolism, or major bleeding. Acute iliac vein rethrombosis (<24 hr) that required reintervention was observed by O'Sullivan and coworkers in 2 of 39 patients.[27] The procedural success rate has been exceptional.[13,16,27,32] In 2000, Neglen and Raju[13] reviewed their experience in treating 102 limbs of patients who had probable iliac vein obstruction. The early (<30-day) complication rate was low (10%). One patient developed retroperitoneal bleeding from a high cannulation site and was treated conservatively with blood transfusion. Another sustained an arterial injury during cannulation, which required open repair with an interposition graft. These injuries were subsequently minimized with the use of ultrasound-guided venous puncture. In another patient, the guidewire was caught in the stent, which was pulled to the femoral vein and then successfully removed through a groin incision. One patient developed postoperative swelling of un-

known cause; the stent was patent on venography, and the swelling subsided within weeks. Thrombosis of the stented area was encountered in 5 limbs (6%), all within 3 weeks of the surgery in patients with post-thrombotic disease.

Overall, balloon angioplasty and stenting is safe and effective, and the complication rate is likely to decrease as technology evolves and our experience increases.

Conclusion

Endovascular treatment is a minimally invasive approach to venous lesions that has a high technical success rate and an acceptable complication profile. Balloon dilation and stenting is a safe and effective treatment for chronic benign obstruction of the iliac vein. Hemodynamically significant venous lesions should always be stented, and the stent should be inserted well into the IVC when an iliocaval junction stenosis is treated. There is currently no acceptable standard for evaluating patients for endovascular therapy. Although mid-term results are good, only longer follow-up will determine whether the hyperplasia observed in the stented area will progress to late recurrent venous obstruction and whether early symptomatic improvement is maintained. The procedure can be performed during a 23-hour hospital stay, followed by immediate return to regular activity after the patient's discharge. Balloon dilation and stenting appear to be superior to conventional surgical treatment and should be considered the 1st line of therapy for many patients suffering from chronic iliocaval venous obstruction.

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Review

Inherited Arrhythmic Disorders

Long QT and Brugada Syndromes

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Inherited arrhythmic disorders comprise a group of syndromes with unique genetic abnormalities and presentations but with very similar clinical outcomes and complications, the most terrifying of which are life-threatening arrhythmias and sudden cardiac death. Advances in molecular biology have enabled us to define and pinpoint many such disorders, which were previously labeled as idiopathic, to specific genes on various chromosomes. The current trend in the management of these potentially deadly disorders is to use pharmacotherapy (antiarrhythmic agents) and defibrillators for the prevention of sudden death; however, targeted therapy at a molecular level appears to be the path of the future. Herein, we review long QT and Brugada syndromes and focus on the genetics, pathophysiology, and clinical manifestations of these inherited arrhythmogenic disorders that affect patients with structurally normal hearts. ***(Tex Heart Inst J 2007;34:67-75)***

Key words: *Action potentials/genetics; arrhythmia/etiology/genetics/pathophysiology; Brugada syndrome/complications/genetics/pathophysiology; death, sudden, cardiac/etiology; electrocardiography; ion transport; long QT syndrome/complications/genetics/pathophysiology; potassium channels; sodium channels; ST-segment elevation; syncope*

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Long QT syndrome and Brugada syndrome are inherited arrhythmic disorders—part of a larger group of syndromes with unique genetic abnormalities and presentations but with very similar clinical outcomes and complications, including life-threatening arrhythmias and sudden cardiac death (SCD). Advances in molecular biology have enabled us to define and pinpoint many such disorders, which were previously labeled as idiopathic, to specific genes on various chromosomes. Beyond today's pharmacologic and defibrillator therapies, treatments of the future may be targeted at the molecular level. Herein, we review long QT and Brugada syndromes, both of which affect patients with structurally normal hearts. We discuss the genetics, pathophysiology, and clinical manifestations of these inherited arrhythmogenic disorders.

Long QT Syndrome

Long QT syndrome (LQTS) is an inherited disorder characterized by a predisposition to the development of life-threatening ventricular tachyarrhythmias and prolongation of the QT interval on the electrocardiogram (ECG). The QT interval on the surface ECG is measured from the beginning of the QRS complex to the end of the T wave and represents the duration of activation and recovery of the ventricular myocardium. The corrected QT interval for heart rate (QTc) is considered to be less than 0.44 sec. Intervals longer than this increase the risk of ventricular arrhythmias exponentially (Fig. 1).

It is currently estimated that one in every 7,000 to 10,000 people in the United States is affected by LQTS.[1] It is worth noting, however, that at least 10% to 15% of those who carry the LQTS gene have a normal QTc duration and remain asymptomatic.

Pathophysiology

To understand the pathogenesis of LQTS, a review of the basic cardiac physiology is warranted. In the heart, electrical signals originate in the sinoatrial node and travel through a network of fibers before triggering action potentials (APs) in the cardiac myocytes. The QRS complex observed on the surface ECG is a representation of the sum of the APs generated in individual myocardial cells (atrial and ventricular tissue, excluding the sinoatrial and atrioventricular nodes).[2]

The cardiac AP, illustrated in Figure 2, is the AP of a ventricular myocyte. Phase 4 is referred to as the resting membrane potential and describes the membrane potential when the myocyte is not being stimulated. This resting potential is deter-

mined by the selective permeability of the membrane to various ions: in particular, potassium ions. Phase 0 (the rapid depolarization phase) of the AP is due to the opening of the fast sodium channels, which causes the rapid influx of positively charged sodium ions into the myocytes. Phase 1 occurs as a result of the closure of the fast sodium channels. Phases 0 and 1 together correspond to the R and S waves on the surface ECG. Phase 2, otherwise known as the plateau phase, corresponds to the ST segment of the ECG and is a result of a balance between inward movement of calcium ions (I_{Ca}) and outward movement of potassium ions. Phase 3, the repolarization phase, is determined by the efflux of positively charged potassium ions from the cells and corresponds to the T wave on the ECG. This order of ion channel activation gives rise to the overall electrical current generated in the heart.[2]

Theoretically, if we were to block potassium ions from moving out of the myocytes, the AP would be prolonged (Fig. 3A). Conversely, if we could block the entrance of sodium ions into the myocytes, we would decrease the velocity of the AP conduction, in addition to prolonging the QRS duration (Fig. 3B).[2]

In essence, the QT prolongation described above is caused by an overload of myocardial cells with positively charged ions during ventricular repolarization. If the AP is sufficiently prolonged, calcium channels that normally close toward the end of the AP now have time to reopen again and generate a 2nd excitation wave before the AP is complete. The correlation seen with AP and QT prolongation is shown in Figure 4.[2]

A 2nd excitation phase (called early after-depolarization) is generated by individual cells in the myocardium that have automaticity potential. This new wave of excitation does not follow the sequence normally initiated in the sinoatrial node. The overall result is a loss of synchronization and the development of arrhythmias such as torsades de pointes.[3]

The mechanisms underlying the formation of arrhythmias are slightly different in the various subtypes of LQTS. However, almost all of these mechanisms are the result of an imbalance between the repolarization currents and the reactivation of the depolarization currents (Fig. 5).

Genetic studies conducted in families with LQTS have linked this disorder to gene mutations affecting cardiac ion channels—specifically the sodium and potassium channels. Because of this finding, LQTS was once referred to as a channelopathy. Thus far, 6 chromosomal loci and 5 specific genes have been identified on chromosomes 11, 3, 4, 7, and 21.[4] Depending on the type of ion channel involved, the LQTS can be categorized into separate types: Types LQT1 through LQT3 and LQT5 to LQT6 encode cardiac ion channel subunits. According to the pattern of inheritance and certain clinical characteristics, the LQTS types

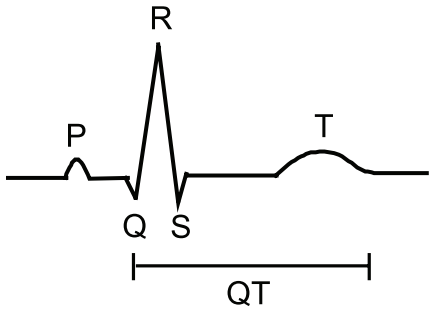

Fig. 1 *QT interval.*

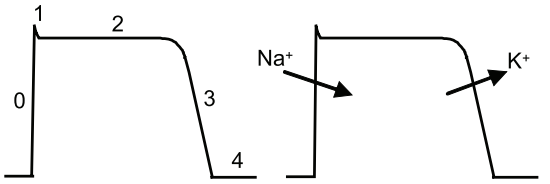

Fig. 2 *Normal phases of the cardiac action potential and the contributions of the sodium (Na^+) and potassium (K^+) ion transfers in the action potential.*

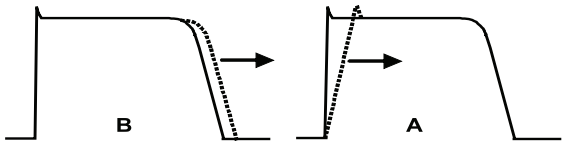

Fig. 3 *Changes in the slope and duration of the cardiac action potential caused by sodium and potassium channelopathies.*

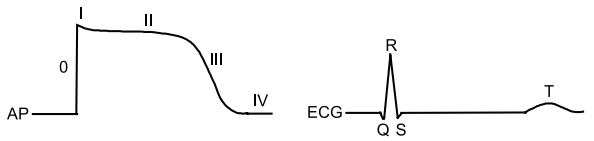

Fig. 4 *Action potential (AP) prolongation and its correlation with the surface electrocardiogram (ECG).*

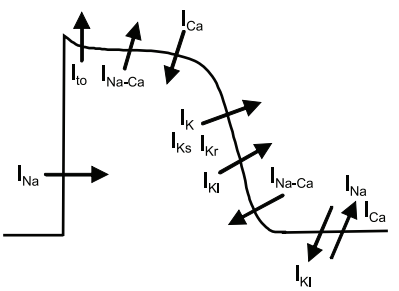

Fig. 5 *Ionic shifts in a ventricular cell.*

TABLE I. Inherited Arrhythmic Disorders[5]

Disease	Inheritance	Chromosome Locus	Gene	Ion Channel
LQT3	AD	3p21–p23	SCN5A	Sodium
LQT4	AD	4q25–q27	ANKB	Ankyrin
LQT2	AD	7q35–q36	KCNE2	Potassium
LQT1	AD	11p15.5	KCNQ1	Potassium
LQT5	AD	21q22.1–p22.2	KCNE1	Potassium
LQT6	AD	21q22.1–p22.2	KCNE2	Potassium
Brugada	AD	3p21–p23	SCN5A	Sodium
JLN1	AR	11p15.5	KCNQ1	Potassium
JLN2	AR	21q22.1–p22.2	KCNE1	Potassium

AD = autosomal dominant; AR = autosomal recessive; JLN = Jervell and Lange-Nielsen syndrome

(From Priori S, Napolitano C, Schwartz P. Genetics of cardiac arrhythmia; Table 28-1. In: Zipes DP, Libby P, Bonow RO, Braunwald E, editors. Braunwald's heart disease: a textbook of cardiovascular medicine. Vol I. 7th ed. Philadephia: Elsevier Saunders; 2005. p. 690.[5] Adapted with permission from Elsevier.)

have been further sub-typed as the Romano-Ward, the Brugada, and the Jervell and Lang-Nielsen (JLN) syndromes.[4] The JLN syndrome has been associated with congenital deafness, in addition to QT prolongation and ventricular arrhythmias.[4] Details regarding these inherited arrhythmic disorders are presented in Table I.[5]

By convention, the 1st letter of the gene's name denotes the ion species involved (K for potassium, S for sodium, Ca for calcium, and CN for channel).

Disorders Involving the Potassium Ion Channel. Types LQT1 and LQT2, caused by potassium channel gene mutations KCNQ1 and KCNE2, respectively, account for the most prevalent genetic forms of LQTS.[4] Approximately 87% of these genotyped patients have a mutation on 1 of these 2 genes.[4,6] The KCNQ1 gene normally codes for the α-subunit of the "slow" component of the delayed rectifier potassium channel, I_{Ks}, which contributes to the repolarization of the cardiac AP (phase 3). Therefore, we can say that a "loss of function" mutation in the KCNQ1 gene results in a decreased potassium efflux through I_{Ks} channels and causes a delay in the repolarization of the overall AP.[7,8] Similarly, mutations in KCNE2, which normally encode the α-subunit of the rapid component of the delayed rectifier potassium channel, I_{Kr}, lead to the LQT2 syndrome. Like I_{Ks}, I_{Kr} contributes to the repolarization phase of the AP, which results in less potassium efflux during the repolarization phase and causes prolongation of the QT interval.[4,8] The LQT5 type is caused by mutations in KCNE1 (the β-subunit of I_{Ks}), and LQT6 is caused by mutations in KCNE2 (the β-subunit of I_{Kr}). Type LQT5 is an uncommon variant of LQTS and accounts for approximately 2% to 3% of all genotyped patients; LQT6 appears to be the rarest form of the disease.[4]

Other diseases involving potassium channel mutations include the JLN syndromes 1 and 2, which account for less than 1% of the overall cases of LQTS.[4] Of note, the risk of cardiac events (syncope, cardiac arrest, and SCD) is higher in patients who have JLN1 and JLN2 than in those who have LQT1 through LQT6. In addition, patients with LQT1 and LQT2 tend to have a higher risk of cardiac events than do those with LQT3. Furthermore, among patients treated with β-blockers, there is a higher rate of cardiac events observed with the LQT2 and LQT3 genotypes.[9]

Disorders Involving the Sodium Ion Channel. The LQT3 and Brugada syndomes are both caused by the SCN5A gene mutation, which encodes the α-subunit of the cardiac sodium channel.[10] It is believed that sodium channel mutations lead to LQTS by inducing an increase in the sodium inward current (I_{Na}), which causes prolongation of the AP and hence of the QT interval. The prevalence of LQT3 is estimated to be 10% to 15% of the overall LQTS genotypes.[11] Whereas patients who have LQT3 experience most of their cardiac events at rest or during sleep, those with LQT1 and LQT2 have cardiac events during physical or emotional stress.[12] Furthermore, death during a cardiac event is substantially more frequent in patients with LQT3 than in those with LQT1 and LQT2. It has been suggested that the inconsistency observed in the LQT3 phenotype may be a result of variable cell surface expression of proteins.[13] The SCN5A mutations are "gain of function" mutations, which means that they prevent channels from switching off during the plateau phase of the AP, resulting in an increased influx of sodium ions and a prolongation of the plateau and the QT interval.[14]

Clinical Features of Patients with Long QT Syndrome

Patients who have LQTS are usually diagnosed after a cardiac event has already taken place. Syncope and seizures are the most typical clinical manifestations; cardiac arrest and SCD have also been frequently reported. The severity of these manifestations ranges from mild to severe and appears to be highly variable, mostly depending on the degree of QT prolongation.[15] A family history of sudden cardiac arrest at a young age or unexplained death suggests the presence of this syndrome.[4] Neuronal hearing deficit may provide a clue in the diagnosis of JLN. In addition, syndactyly has been described in some patients who have idiopathic LQT1.[16,17] Physical examination may be an aid in excluding other causes of syncope, such as hypertrophic cardiomyopathy, valvular heart disease, and neurological disorders. Electrocardiographic findings other than prolonged repolarization (long QT interval) include ab-

normal T-wave morphologies and torsades de pointes. The sex of the individual does not appear to affect the severity of clinical manifestations associated with LQT1, but a higher risk of complications has been described for females who have LQT2 and LQT3 and for males who have the Brugada syndrome.[18,19] There seems to be an association between the LQT genotypes and the triggers of arrhythmia. Patients with LQT1 primarily have exercise-related arrhythmic events. Events related to swimming may be specific to LQT1 (those that occur either immediately after diving into water or during recreational or competitive swimming activities).[20,21] Events triggered by auditory stimuli, such as an alarm clock or telephone ringing, are most typically seen in individuals with LQT2.[21] Acute arousal events (such as exercise, emotion, or noise) are much more likely to be triggers in patients with LQT1 and LQT2 than LQT3.[4,20,22] Those with LQT3 are at highest risk of events when at rest or asleep (see the section on Brugada syndrome); the risk is low during sleep for those with LQT1 and accounts for only 3% of events.[22]

Management of Patients with Long QT Syndrome

As noted previously, there appears to be a close link between the onset of cardiac events and increased sympathetic activity in patients with LQTS. As a result, the initial pharmacological approach to the treatment of congenital LQTS is the use of β-blockers to interrupt this sympathetic input to the myocardium.[23] β-Blockers are used in both symptomatic and asymptomatic patients with LQTS.[24] It is thought that these medications can shorten the QT interval by decreasing activation from the left stellate ganglion and decreasing the incidence of torsades de pointes.[25] Furthermore, studies have shown that β-blockers can decrease the incidence of syncope and SCD in patients with LQTS.[24,25] A hypothetical concern, however, is that by decreasing the sinus rate, β-blockers could prolong repolarization and possibly predispose patients to torsades de pointes. In 1 animal study, β-blockade prevented the induction of torsades de pointes in dogs with LQT1 and LQT2, but facilitated its induction in those with LQT3.[26] For patients with LQT3, the calcium channel blocker verapamil may be effective in preventing torsades de pointes by shortening the endocardial mean APs and by suppressing the early after-depolarization phase.[27] Left cardiac sympathetic denervation may be considered if a patient is unresponsive or intolerant to β-blockers.[23] Placement of a permanent pacemaker may be indicated in patients with LQTS who have bradycardia-dependent tachyarrhythmias or atrioventricular block. Prophylactic placement of an implantable cardioverter defibrillator (ICD) is recommended for patients with LQTS who have survived an episode of cardiac arrest. Of note, early intervention with an ICD has been shown to be cost-effective in young patients with inherited cardiac arrhythmias.[28]

The Brugada Syndrome

As an inherited abnormality of the cardiac sodium channel, Brugada syndrome has been of clinical interest since it was first described in 1992.[29] During the 1980s, the Centers for Disease Control and Prevention had reported cases of sudden death in young immigrants from Southeast Asia, described as Sudden Unexplained Death Syndrome (SUDS).[30,31] Research has now shown that Brugada syndrome and SUDS are phenotypically, genetically, and functionally the same disorder. The occurrence of SCD in normal hearts, without ischemia or obvious electrolyte imbalances, is rare.[32] Aside from the SCD that occurs in patients with Brugada syndrome, most SCD is attributable to LQTS, pre-excitation syndrome, or commotio cordis. Of patients diagnosed clinically with Brugada syndrome, only 18% to 30% have the SCN5A gene mutation.[33-35] As previously noted, this gene encodes the α-subunit of the sodium ion channel and is the only gene that has been linked to Brugada syndrome to date. When SCN5A is present, the resultant nonfunctional protein leads to altered protein trafficking and eventually to the development of cardiac arrhythmias.[36] Brugada syndrome is transmitted within families in an autosomal dominant fashion with variable penetrance, which means that such patients usually have a parent with this condition. Given the nature of this syndrome, there has been extensive debate on the advantages and disadvantages of implementing a mass screening protocol for newborns and infants in order to prevent SCD at a later age.[37]

Pathogenesis, Diagnosis, and Clinical Manifestations

At a molecular level, the SCN5A gene mutation seen in Brugada syndrome leads to the failure of expression of the sodium channel, its increased inactivation, and a prolonged recovery time before its reactivation.[34] It is believed that, through various mechanisms, the end result of this gene mutation is the development of the life-threatening arrhythmias encountered in Brugada syndrome. It is important to note that Brugada syndrome is essentially an "electrical" disease that causes abnormal electrophysiologic activity in the right ventricular epicardium.[38,39]

The ventricular myocardial tissue is composed of 3 layers—the epicardium, the endocardium, and the mid-myocardium (M cells)—each with unique electrophysiologic properties.[40] In general, the epicardium has the shortest AP duration (Fig. 6) and the highest concentration of transient outward (I_{to}) current.[41] The M cells have the longest AP duration and the lowest concentration of I_{to} current.[41] The endocardium, on the

other hand, has intermediate AP duration and I_{to} concentration. A decrease in the AP duration is observed when the I_{Ca} currents are overwhelmed by I_{to} currents, which leads to a significant shortening of phase 2 of the AP. This phenomenon occurs in some myocytes in the epicardial tissue; the others maintain normal AP durations.[41,42] This difference in electrical properties, observed in myocytes within the same epicardial tissue, creates a heterogenous population of cells with different AP durations and, subsequently, different refractory periods. Cells with shorter refractory periods have the potential to be re-excited by cells in the surrounding tissue that have normal AP duration.[41,42] This phenomenon, referred to as phase-2 re-entry, is believed to be the cause of the ventricular arrhythmias in patients who have Brugada syndrome.[41,42] These mechanisms have been elegantly described by Antzelevitch and coworkers,[41,42] and recent optical mapping studies have further supported them.[43]

The Brugada ECG pattern (described below) is seen much more frequently in men than in women,[44] and studies suggest that most of the affected individuals are Asian.[45] The most common triggers of death in Brugada syndrome are sleep, fever (malaria in endemic regions), and antiarrhythmic drugs for supraventricular tachycardia or atrial fibrillation. Other triggers of arrhythmia and possibly SCD in Brugada patients are the use of β-blockers,[24] the combination of glucose and insulin,[46] the use of tricyclic antidepressants,[47] alcohol and cocaine use, and electrolyte imbalances such as hypokalemia, hyperkalemia, and hypercalcemia.[48] Unlike LQTS, exercise has not been shown to play a key role in triggering arrhythmias in Brugada patients.[49] Sympathetic and parasympathetic states, as well as their imbalances, can alter ion channel activity in patients with LQT and Brugada syndromes and lead to the development of arrhythmias.[50,51] Although SCD is often the initial clinical presentation of patients with Brugada syndrome (up to ~30%), several risk factors that place patients at a higher risk of SCD have been identified. These factors include frequent premature ventricular beats that morphologically resemble the beats that initiate ventricular fibrillation,[52] a history of SCD, and unexplained syncope.[53] Patients with a higher risk of SCD may benefit from elective electrophysiologic testing and often meet the criteria for ICD placement. Asymptomatic patients without the risk factors, on the other hand, have a much lower lifetime risk of severe arrhythmias and SCD.[39] Although patients with Brugada syndrome tend to present with symptoms in the middle or later decades of life (mean age at death, 45 years), several malignant forms have been described with much earlier (and deadly) manifestations.[39]

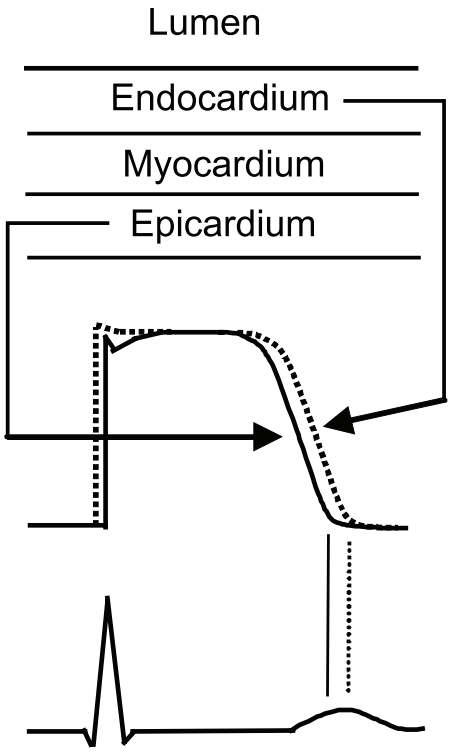

Fig. 6 *Cellular mechanism behind Brugada.*

The Brugada Electrocardiogram. The main ECG findings in Brugada syndrome are ST-segment elevation in the right precordial leads (V_1 through V_3), right bundle branch block, and ventricular tachycardia. A few cases involving the inferior and the right precordial leads have also been described, and these patients are thought to have a unique missense mutation.[54] Three patterns of ST-segment elevation have been described: the classic Brugada ECG (type 1), in which the elevated ST segment (≥2 mm) descends with an upward convexity to an inverted T wave. This pattern is referred to as the "coved-type" Brugada ECG (Fig. 7A). The type 2 and type 3 patterns have a "saddle-back" ST-T wave configuration: the elevated ST segment descends toward the baseline, and then rises again to an upright or biphasic T wave. The ST segment is elevated 1 mm or more in the type 2 pattern and less than 1 mm in the type 3 pattern (Fig. 7B).[55,56] Of note, in patients with Brugada syndrome, a widened S wave characteristic of right bundle branch block (usually seen in the left lateral leads) is absent, suggesting the presence of a J wave that is mimicking right bundle branch block.[45]

The sporadic and dynamic nature of the Brugada ECG makes the diagnosis somewhat challenging. Because of this, provocation testing with selected class IC antiarrhythmic drugs has been used. The flecainide provocation test has been shown to be highly sensitive and specific in unmasking the Brugada ECG pattern in affected subjects.[57] Other agents that can be used to unmask the Brugada ECG are procainamide, ajmaline, β-blockers, and lithium.[58-60] It is important to note that

the diagnosis of Brugada syndrome depends on both ECG and clinical findings. A patient who presents with the Brugada ECG criteria but without the clinical characteristics is said to have the Brugada *pattern* but not the syndrome.[55] The Brugada ECG pattern is seen up to 9 times more frequently in men than in women,[44] most likely because of a more prominent I_{to}-mediated notch in the epicardium of males.[61]

Supraventricular tachycardias can develop in Brugada patients, and many of these arrhythmias are atrial fibrillation.[62] One study reported up to a 20% incidence of spontaneous atrial fibrillation in patients with Brugada syndrome, compared with controls.[62]

It has been noted that, in Brugada syndrome, the epicardial layer (with a higher concentration of I_{to}) is more likely to have a "spike and dome" or even a premature termination ("dwarfing") configuration of the AP (Fig. 8).[41] A spike and dome or dwarfed epicardial AP, when combined with the more normal M-cell and endocardial APs, changes the gradients across the myocardial tissue (transmural voltage gradient) in such a manner that the ST segment develops an upward shift. This shift leads to the ST-segment elevation seen in the Brugada ECG (Fig. 9).[41] The AP dome is lost in some areas of the myocardium and is normal in other areas, creating the conditions for a possible phase-2 reentry as described previously, and leading to torsades de pointes or ventricular tachycardia and fibrillation.

Diagnosis of Brugada Syndrome. Although characteristic ECG patterns are suggestive of Brugada syndrome, it is the presence of specific clinical features in addition to these ECG findings that leads to the diagnosis of Brugada syndrome.[55] Brugada syndrome has been classified into 3 different categories. 1) The patients have an ECG with the coved-type ST-segment elevation (in >1 lead [in V_1–V_3]) and at least one of the following: unexplained syncope, self-terminating polymorphic ventricular tachycardia, documented ventricular fibrillation, family history of SCD at less than 45 years of age, type-1 ST elevation in a family member, nocturnal agonal respiration, and inducibility of ventricular tachycardia by electrophysiologic study.[55] Category 2) and 3) patients must meet the type-2 and type-3 ECG patterns; have one of the clinical features noted above; and show saddle-back ST-segment elevation in more than 1 right precordial lead, with conversion to type 1 after a drug challenge with a sodium channel blocker.[55] Despite all these diagnostic indicators, it is important to note that the definitive diagnosis of Brugada syndrome has yet to be determined.

Management of Patients with Brugada Syndrome

To date, no pharmacologic treatment has been shown to be completely effective in preventing SCD associated with Brugada syndrome. However, data suggest some benefit from quinidine and hydroquinidine.[63,64] The effect of these medications may be mediated by blockade of I_{to}, which is the transient outward current that increases heterogeneity and promotes premature ventricular beats that act as triggers for ventricular tachycardia and ventricular fibrillation.[42] Given the underlying mechanism of arrhythmogenesis in Brugada, I_{to} blockade could possibly improve the epicardial dwarfing of the AP and resolve the electrical imbalance responsible for the clinical manifestations of Brugada

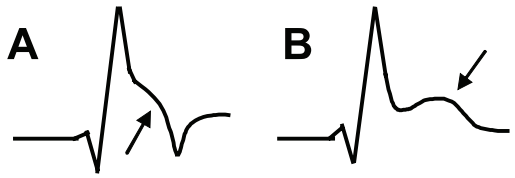

Fig. 7 *Brugada ECG patterns.*

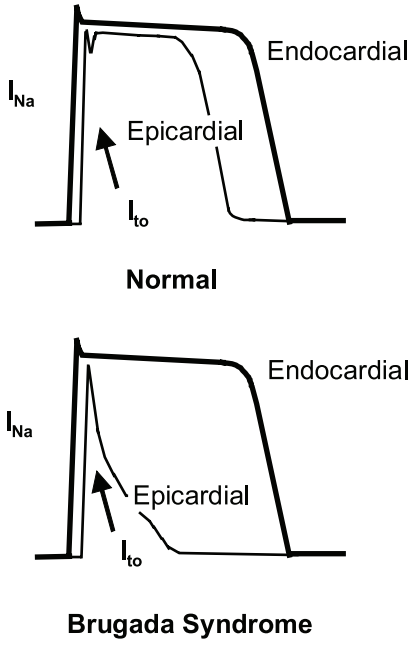

Fig. 8 *"Spike and dome" configuration seen in Brugada syndrome.*

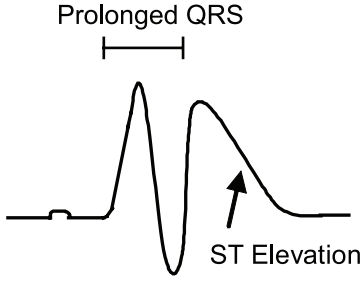

Fig. 9 *ST segment elevation in Brugada.*

syndrome. Newer agents that may aid in the management of Brugada syndrome are cilostazol (a phosphodiesterase III inhibitor) and tedisamil (a cardioselective I_{to} blocker).[65] Routine monitoring of serum potassium (and magnesium) levels in patients presenting with QT prolongation after arrhythmic events is warranted to eliminate secondary causes.[48] Despite the encouraging results recently seen with pharmacotherapy alone, there are not yet sufficient data to recommend antiarrhythmic therapy as an alternative to an ICD. Interestingly, antiarrhythmic drugs may have a positive application in patients with an ICD who continue to have frequent discharges.[25] Implantation of an ICD has shown a clear benefit in the prevention of SCD in patients with Brugada syndrome.[34,56]

The presence of a spontaneous Brugada type-1 ECG, along with ventricular fibrillation, syncope, or sudden death in a 1st-degree relative, warrants ICD placement. However, that benefit is less established in asymptomatic patients with inducible ventricular arrhythmias (class IIb), and there is no evidence of benefit in asymptomatic patients without inducible arrhythmias (class III).[25] The SCN5A mutations in Brugada syndrome are also distinguished by profound bradyarrhythmias[66]; however, the concept that pacemakers might prevent SCD by preventing bradycardia is still investigational. The use of programmed electrical stimulation to identify individuals with Brugada who are at increased risk of cardiac arrest remains a subject of debate.[67] Although some studies have shown that programmed electrical stimulation may be a good predictor of major cardiac events in Brugada patients, others have demonstrated conflicting results.[32]

In conclusion, long QT and Brugada syndromes have different phenotypes, but they share a common final pathway in causing sudden cardiac death. Brugada syndrome provides a model for understanding the pathogenesis of inherited arrhythmic syndromes. In the future, a more thorough knowledge of the disease processes of these syndromes may enable us to use targeted therapy alone and minimize the need for defibrillators.

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Case Series

Takotsubo Cardiomyopathy, or Broken-Heart Syndrome

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Takotsubo cardiomyopathy mimics acute coronary syndrome and is accompanied by reversible left ventricular apical ballooning in the absence of angiographically significant coronary artery stenosis. In Japanese, "tako-tsubo" means "fishing pot for trapping octopus," and the left ventricle of a patient diagnosed with this condition resembles that shape. Takotsubo cardiomyopathy, which is transient and typically precipitated by acute emotional stress, is also known as "stress cardiomyopathy" or "broken-heart syndrome."

Herein, we describe the clinical angiographic characteristics of 4 patients who exhibited this syndrome, and we review the existing literature and propose reasons to conduct prospective studies. ***(Tex Heart Inst J 2007;34:76-9)***

Key words: *Cardiomyopathies/diagnosis/etiology/physiopathology; catecholamines/secretion; chest pain/etiology; coronary angiography; coronary disease/physiopathology; echocardiography; electrocardiography; heart/physiopathology; myocardial ischemia/diagnosis; stress, psychological/complications/physiopathology; takotsubo cardiomyopathy; ventricular dysfunction, left/diagnosis/etiology/physiopathology*

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Takotsubo cardiomyopathy mimics acute coronary syndrome. It is accompanied by reversible left ventricular (LV) apical ballooning in the absence of angiographically significant coronary artery stenosis. In Japanese, "tako-tsubo" means "fishing pot for trapping octopus," because the LV of a patient diagnosed with this condition resembles that shape. A transient entity typically precipitated by acute emotional stress, takotsubo cardiomyopathy is also called "stress cardiomyopathy" or "broken-heart syndrome." Several cases of this interesting cardiomyopathy have been reported in Japan,[1-8] and more recently in the United States[9-13] and Belgium.[14] Herein, we describe the clinical and angiographic characteristics of 4 patients diagnosed with takotsubo cardiomyopathy, and we review the existing literature.

Case Reports

Patient 1

A 57-year-old black woman with a history of hypertension and dyslipidemia was hospitalized because of the sudden onset of angina-like chest pain and dyspnea. Auscultation revealed bilateral basilar crackles and an S_3 gallop. Electrocardiography (ECG) showed ST-segment elevation of 1 mm in leads V_1 through V_3. The QT interval was prolonged. Levels of creatine kinase-MB and troponin T were mildly elevated. Echocardiography showed substantial apical dysfunction, preserved basal function, and no intraventricular pressure gradient. The patient underwent emergency cardiac catheterization, which disclosed no substantial epicardial coronary artery stenosis. Left ventriculography showed systolic ballooning of the apex and hypercontraction of the basal segment (Fig. 1). The patient was treated with aspirin, an angio-

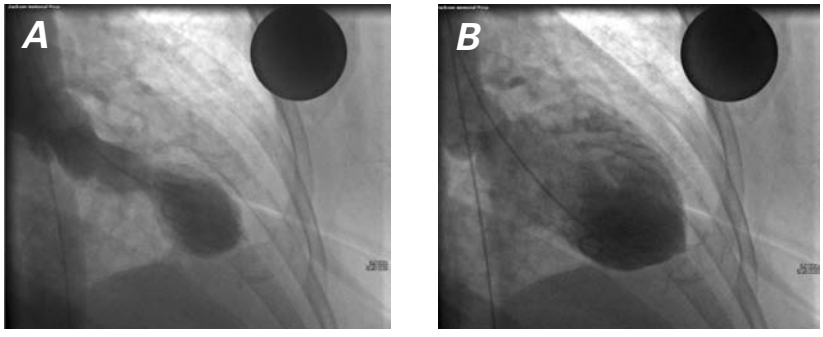

Fig. 1 *Patient 1. Left ventricular angiography in systole (**A**) and diastole (**B**) shows apical ballooning and hypercontraction of the basal segments.*

tensin-converting enzyme inhibitor, a diuretic, and statins. Two weeks later, the ECG showed complete resolution of the ST-segment elevation and no Q-wave formation. Echocardiography revealed remarkable improvement of the apical wall motion abnormality and normalization of the ejection fraction. It was concluded that acute emotional stress after the death of a relative had precipitated the initial symptoms.

Patient 2

A 64-year-old black woman with a history of diabetes mellitus presented with severe angina-like chest pain. Deep negative T waves were seen on ECG. Her cardiac enzyme levels were mildly elevated. The patient was admitted with a diagnosis of acute non-ST-segment-elevation myocardial infarction. An echocardiogram showed apical dyskinesis, an ejection fraction of 0.45, and no intraventricular pressure gradient. The patient's ongoing chest pain prompted emergency coronary angiography with intra-aortic balloon pump support. The angiogram revealed apical ballooning in systole with concomitantly increased contractility in the basal segments. The overall LV systolic function (LVSF) was mildly depressed. With medical therapy, the patient's symptoms improved. Echocardiography after 1 week showed normalization of the systolic apical ballooning and the LVSF. When questioned, the patient revealed that she had recently experienced severe emotional stress due to financial instability.

Patient 3

A 44-year-old white man without a pertinent medical history underwent urgent coronary angiography because of acute chest pain and marked precordial T-wave inversions suggestive of acute myocardial ischemia. Coronary angiography showed no significant stenosis of the coronary arteries. A challenge with acetylcholine elicited no spasm of either the right or the left coronary artery. Left ventriculography showed systolic apical ballooning with mild basal hypercontraction. Levels of creatine kinase-MB and troponin T were mildly elevated. One week later, echocardiography showed complete resolution of the wall motion abnormality. Severe occupation-related emotional stress had preceded the onset of this patient's symptoms.

Patient 4

A 64-year-old black woman with a history of hypertension and hyperlipidemia presented after 1 day of severe nausea and vomiting. An ECG showed ST-segment elevation and deep T-wave inversion in the anterior leads. The QT interval was also prolonged (Fig. 2). The cardiac enzyme levels were mildly elevated. Emergency cardiac catheterization disclosed no obstructive coronary artery disease. Left ventricular angiography revealed apical ballooning in systole with mild basal hypercontraction. The patient's LVSF was moderately reduced. Two weeks later, results of echocardiography showed resolution of the apical wall motion abnormality and the LV systolic dysfunction. The patient had not experienced emotional distress before the onset of symptoms.

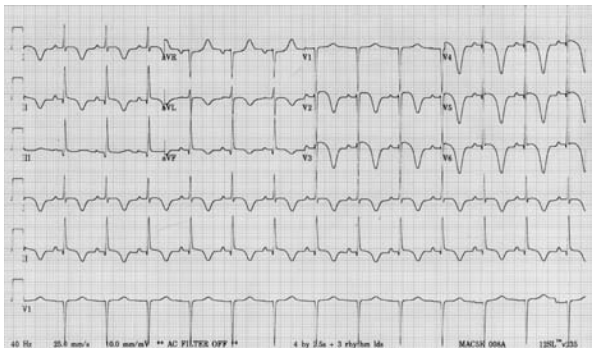

Fig. 2 *Patient 4. A 12-lead electrocardiogram of a patient diagnosed with takotsubo cardiomyopathy shows ST-segment elevation and deep T-wave inversions in the anterior leads, in association with a prolonged QT interval.*

Discussion

These 4 cases exhibited most of the characteristics of takotsubo cardiomyopathy that have been described in the literature:

- A preponderant occurrence of the syndrome in elderly or postmenopausal females[2,8-10]
- Onset consequent to acute emotional stress or an acute medical condition[2,7,8,11]
- ST-segment elevation or depression, or T-wave changes[1-11]
- A prolonged QT interval[2,11]
- A mild increase in cardiac enzymes[2,9,10]
- Typical akinesis of the apical and distal anterior wall together with hypercontraction of the basal wall[2,8-10]
- The occasional presence of transient intracavitary pressure gradients in some patients[2,8,10]
- A need for acute hemodynamic support in some cases[2,8,10]
- Complete resolution of the apical wall motion abnormality and the depressed LVSF.[2,3,8,9,11]

Although the exact pathogenesis of takotsubo cardiomyopathy remains unclear, various mechanisms have been proposed. Dote and associates[1] suggested coronary vasospasm as the pathogenic mechanism; however, induction of coronary vasospasm by acetylcholine or ergonovine has yielded mixed results. In some series, vasospasm in at least 1 epicardial coronary artery was present in most patients,[3,8] whereas Akashi and colleagues[2] found no coronary vasospasm in patients who underwent an acetylcholine challenge. Multivessel

coronary spasm would be required to account for the apical wall motion abnormality seen in this syndrome. Similarly, the duration of wall motion abnormality in takotsubo cardiomyopathy typically is longer than would be expected in conventional cases of coronary vasospasm.

The possibility of myocardial injury due to microvascular spasm has also been suggested.[3] Ako and coworkers,[15] by the use of an intracoronary Doppler wire technique, demonstrated microcirculation impairments in instances of transient LV hypocontraction. Although this is an interesting explanation, several factors challenge its causative potential. First, microscopic findings in some patients who had LV apical ballooning were different from those in patients who had myocardial ischemia. The most common pathologic finding in takotsubo cardiomyopathy, focal myocytolysis, is not typically seen in patients with myocardial infarction.[2] Second, in several cases, coronary angiography failed to reveal the slow-flow phenomenon, even in the presence of ST-segment elevation. Finally, impaired microcirculation during the acute phase is not direct evidence of causation, because microcirculatory impairment can result from a primary myocardial injury.

Another putative mechanism is neurogenic stunned myocardium. This condition is also observed during acute cerebrovascular accidents[16,17] and during the catecholamine-induced cardiomyopathy in patients with pheochromocytoma.[18-20] Enhanced sympathetic activity appears to play a very important role in the pathophysiology of takotsubo cardiomyopathy. Triggering factors, such as intense emotional stress, are frequently seen in patients with this syndrome. Excessive levels of catecholamines have been observed in patients with takotsubo cardiomyopathy.[2] Catecholamines have been shown to induce myocardial damage,[21,22] and excessive stimulation of cardiac adrenergic receptors has led to transient LV hypocontraction in animal models.[23] A 2005 case series[12] showed a strong relationship between stress-induced cardiomyopathy and increased plasma catecholamine levels, suggesting that exaggerated sympathetic activation may be important in the development of the cardiomyopathy.

The possibility that myocarditis leads to transient LV dysfunction has also been suggested, but results of biopsies and paired serum tests for viral serology have been negative in the patients studied.[2]

Another intriguing question surrounding takotsubo cardiomyopathy is that of why the apical wall is affected but the base is spared. Several explanations have been proposed.[8] The apex is structurally vulnerable because it does not have a 3-layered myocardial configuration, it has a limited elasticity reserve, it can easily become ischemic as a consequence of its relatively limited coronary circulation, and it is more responsive to adrenergic stimulation.[24] All of these factors might make the apex more sensitive to the catecholamine-induced surge frequently observed in takotsubo cardiomyopathy.

Transient intraventricular pressure gradients have also been detected in some patients diagnosed with takotsubo cardiomyopathy.[2,8,10] However, the absence of significant LV hypertrophy in takotsubo cardiomyopathy, along with the distinctive histologic features, rules out the possibility of an acute midventricular obstruction, as seen in patients who have hypertrophic cardiomyopathy.

Although short-term outcomes are excellent, with complete resolution in all reported cases,[2,8,9,11] there are no data in the literature regarding long-term outcome in patients who have experienced takotsubo cardiomyopathy.

Takotsubo cardiomyopathy has important implications, because its clinical presentation mimics that of an acute coronary syndrome. Increased awareness of takotsubo cardiomyopathy will likely result in its being diagnosed more frequently. Prospective studies are needed in order to determine more accurately the incidence of takotsubo cardiomyopathy and to ascertain the long-term outcomes. Studies are also needed to elucidate the specific pathophysiologic mechanisms responsible for this cardiomyopathy.

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Case Series

Intravenous Adenosine for Surgical Management of Penetrating Heart Wounds

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Accurate suturing of penetrating cardiac injuries is difficult. Heart motion, ongoing blood loss, arrhythmias due to heart manipulation, and the near-death condition of the patient can all affect the outcome. Rapid intravenous injection of adenosine induces temporary asystole that enables placement of sutures in a motionless surgical field. Use of this technique improves surgical conditions, and it is faster than other methods. Herein, we describe our experience with the use of intravenous adenosine to successfully treat 3 patients who had penetrating heart wounds. ***(Tex Heart Inst J 2007;34:80-1)***

The management of penetrating cardiac wounds can be especially difficult due to the urgent nature of the surgery and the consequences of handling a beating heart. Sudden malignant arrhythmias in an already hypovolemic patient can cause rapid circulatory derangement and death. We successfully used intravenous adenosine to induce temporary circulatory arrest in 3 patients who had penetrating cardiac wounds.

Case Reports

Patient 1

A 22-year-old man arrived at our emergency department in near-death condition with a 2-cm penetrating knife wound to the lower left thoracic wall. The patient was hypotensive, with a systolic blood pressure of 50 mmHg. He had decreased heart sounds, dyspnea, and tachycardia of approximately 180 beats/min.

A rapid flow of intravenous fluid was started, and the patient was transferred to the operating room without delay. We performed a median sternotomy and relieved the pericardial tamponade. The entry wound, which was covered with thrombus, was approximately 1 cm in length on the anterior wall of the right ventricle.

Patient 2

A 24-year-old man was brought to our emergency department with 3 penetrating wounds to his left lateral thoracic wall, from an unknown instrument. His condition gradually deteriorated, even after the evacuation of 250 cc of blood through a thoracic drainage tube. The patient had sinus tachycardia (120 beats/min) and was hypotensive (85/60 mmHg). Ultrasonography of the heart revealed pericardial tamponade. The patient was transferred to the operating room. After performing a median sternotomy, we found the source of the bleeding—an approximately 0.5-mm-diameter wound that extended into the root of the pulmonary artery.

Patient 3

A 48-year-old man was transferred to our emergency department in stable condition with a 4-cm-long wound to his upper left abdominal wall, after an explosion. Abdominal and thoracic computed tomographic scans revealed a metal pellet that was embedded in his diaphragm. General surgeons had investigated the wound, but they had not found the piece of metal. Cardiac ultrasonography disclosed the location of the metal pellet and showed a bloody pericardial collection without tamponade. We performed a median sternotomy and removed the metal pellet, which was embedded in the inner surface of the diaphragm and was projecting into the pericardial space. There was a tear in the apex of the heart.

Key words: *Adenosine/administration & dosage; cardiac surgery; emergencies; heart arrest/induced; heart injuries/surgery; infusions, intravenous; wounds, penetrating/surgery*

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Surgical Management

In these 3 patients, our 1st goal was to control the blood loss, which we did digitally. The anesthetist then injected 3 mg of adenosine through a large-bore vein catheter. After about 20 to 40 seconds, asystole occurred long enough (10–25 sec) to enable accurate placement of simple Prolene 5-0 sutures (Ethicon Inc., a Johnson & Johnson company; Somerville, NJ) reinforced with Teflon felt pledgets. The adenosine was administered 2 to 4 additional times, as needed, until the final repair was completed. After uneventful postoperative courses of 4 to 6 days, all 3 patients were discharged from the hospital.

Discussion

The outcome for patients with penetrating heart injuries depends upon rapid on-site resuscitation and prompt transport of the victim to the closest cardiothoracic surgical center. The patient must be taken to the operating room without delay. The nature of the injury dictates the choice of repair technique. Current techniques include simple sutures with or without Teflon felt pledgets; the use of both the instruments and the experience gained from beating-heart operations; the use of automatic-suture instruments, at least as a temporary solution; and the application of extracorporeal circulation. Extracorporeal circulation with cardioplegic arrest is used mainly for traumas to multiple heart chambers, or for wounds that involve the coronary circulation.[1]

We have used adenosine to achieve brief asystole, in order to provide enough time for accurate suturing in a motionless surgical field. Rapid intravenous injection of adenosine causes temporary atrioventricular block and asystole, because adenosine inhibits sinus and atrioventricular node function. Asystole is usually apparent after 20 to 40 sec.

Adenosine has a very brief effect. In our patients, asystole lasted for 10 to 20 sec. Sinus rhythm was easily restored after that period. Two to 4 administrations of 3 mg allowed time not only for the precise placement of sutures, but for the checking of all cardiac chambers for concurrent injuries.[2,3]

Side effects of adenosine include facial flushing (44% of cases), thoracic discomfort (40%), dyspnea (28%), headache (18%), 1st- and 2nd-degree atrioventricular block (3%), and hypotension (2%). Acute bronchoconstriction has also been reported.[4] Our patients experienced no side effects.

Proper and expeditious suturing of heart wounds is crucial. Adenosine-induced asystole occurs quickly and allows sufficient time for accurate suturing in a motionless surgical field. Our case series and another report[4] describe very good outcomes from this application of intravenous adenosine. We consider this easily learned and implemented technique one that affords substantial advantages over other approaches.

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Case Series

Isolated Chylopericardium after Intrapericardial Procedures

Possible Role of Inadvertent Right Efferent Lymphatic Trunk Injury

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Chylopericardium after an intrapericardial procedure is rare, and satisfactory explanations of its possible causes are lacking.

Herein, we present 4 cases of chylopericardium that developed after intrapericardial surgery, and we review the literature.

Our literature review revealed 29 cases of chylopericardium that complicated intrapericardial operations, to which we added our 4 cases for analysis. The 33 surgical procedures involved repair for congenital heart disease (n=21), valve surgery (n=5), coronary artery bypass grafting (n=6), and other (n=1). Causes were verified in 7 patients: small lymphatic injury in 3 and high venous pressure or venous thrombosis in 4. Of the 26 patients with chylopericardium of unknown origin, 15 had congenital heart disease. Ten of these 15 had chromosomal abnormalities, especially trisomy 21 (Down syndrome); these patients typically had increased lymphatic permeability, which raised the likelihood of chylopericardium. Five revascularizations for coronary artery disease required harvesting of the left internal thoracic artery for reconstruction, incurring a risk of damage to the drainage site of the right efferent lymphatic trunk. In addition, all 26 patients with chylopericardium of unknown origin underwent dissection of the ascending aorta and the main pulmonary artery, near the right efferent lymphatic trunk. Inadvertent injury to the trunk during the dissection would have increased the risk of chylopericardium. Accordingly, even though the overall incidence of chylopericardium during intrapericardial procedures is low, we recommend a meticulous dissection of the ascending aorta from the main pulmonary artery. ***(Tex Heart Inst J 2007;34:82-7)***

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Chylopericardium is rare after an intrapericardial procedure, because the sites of surgical dissection are usually anatomically remote from the thoracic duct. Even though some procedures may impede thoracic duct drainage to the subclavian vein, with the resultant elevation in venous pressure, the usual manifestation is chylothorax rather than chylopericardium. A 2002 cadaver study of the intrathoracic tributaries of the thoracic duct revealed that tributaries from the heart arrive at the thoracic duct via 2 routes.[1] Injury to these tributaries along their course within the pericardium may account for postoperative chylopericardium. Nevertheless, chylopericardium arising from post-intrapericardial procedures is described in few reports in the medical literature.[2-20] Herein, we present our experience with 4 patients, review the relevant literature, and refer to the cadaver study as we speculate on probable injury sites.

Case Reports

Patient 1

A 3-year-old boy was admitted with a diagnosis of a secundum-type atrial septal defect. To facilitate accurate cross-clamping of the aorta during the operation, we performed limited dissection of the ascending aorta (AAo) from the main pulmonary artery (MPA), separating the connecting soft tissues for clamping purposes. Forty-eight hours postoperatively, the mediastinal fluid drainage increased and became opalescent. The cholesterol and triglyceride levels of the effusion were 53 and 1,515 mg/dL, respectively. A diet of milk rich in mid-chain fatty acids was prescribed.

By day 6, the chylous fluid turned transparent, and its total daily volume decreased substantially. On the basis of these observations, the mediastinal tube was removed on day 7. No recurrence of the fluid accumulation was noted during regular echocardiographic follow-up over the next 5 years.

Patient 2

A 2-year-old boy was admitted for corrective surgery for tetralogy of Fallot. The AAo was dissected from the MPA extensively because of the expectation that a transannular patch would be required. The ventricular septal defect was repaired, and a transannular patch was used for right ventricular outflow tract reconstruction. The persistence of a moderate amount of serosanguineous pericardial effusion (>400 cc/day) was noted immediately after the operation. The effusion turned milky in color on day 14, and the levels of cholesterol and triglycerides therein were 42 and 202 mg/dL, respectively. A diet of mid-chain fatty-acid milk was administered to the patient until the effusion decreased; the mediastinal tubes were removed on day 20.

Patient 3

A 1-year-old boy with known Down syndrome and severe pulmonary hypertension (Qp/Qs=5.3) was admitted for surgical correction of an atrioventricular septal defect (complete form), and a small patent ductus arteriosus. The routine dissection of the AAo from the MPA was extended to encircle the patent ductus arteriosus before cardiopulmonary bypass was instituted. The atrioventricular septal defect was repaired by means of a 2-patch technique, with the coronary sinus draining into the left atrium. On postoperative day 10, massive pericardial effusion was observed on echocardiography. Subxiphoid pericardial drainage was begun immediately. The cholesterol and triglyceride levels of the milky fluid were 33 and 278 mg/dL, respectively. Chylopericardium was diagnosed, and a diet rich in mid-chain fatty acids was promptly implemented. After 18 days of dietary control, the drainage volume decreased, with no recurrent fluid accumulation noted during follow-up.

Patient 4

A full-term newborn boy was transferred to our hospital due to an imperforate anus, and an urgent colostomy was performed. On the basis of the infant's facial dysmorphism, Down syndrome was suspected, and trisomy 21 was confirmed upon subsequent chromosomal examination. Echocardiography and cardiac catheterization revealed a large ventricular septal defect, severe tricuspid valve regurgitation, and pulmonary artery hypertension. At the age of 4 months, the infant underwent surgical correction of the ventricular septal defect. The AAo was dissected from the MPA in standard fashion. Although the postoperative course was smooth, the pericardial discharge turned milky-yellow on day 3. The levels of cholesterol and triglycerides in the effusion were 28 and 185 mg/dL, respectively. A diet rich in mid-chain fatty acids was prescribed. Seven days later, the drainage volume decreased, and the pericardial tubes were removed.

Review

We reviewed the English-language medical literature, searching for the key word "chylopericardium." Studies that provided insufficient individual patient data were excluded; we considered only the 29 cases from 19 reports that exclusively dealt with isolated chylopericardium that had developed after intrapericardial procedures. Including our 4 patients, our review encompassed 33 cases.

Table I summarizes the demographic data. Twenty patients (61%) were male, and 19 were children (58%). Surgical procedures comprised repair for congenital heart disease (n=21), valve surgery (n=5), coronary artery bypass surgery (n=6), and correction of idiopathic hypertrophic subaortic stenosis (plus a myomectomy) (n=1). After we excluded 7 patients for whom no clinical symptoms were mentioned, the most prevalent presentations were cardiac tamponade (10/26) and persistent or increased drainage volume with the fluid becoming opalescent (9/26) after postoperative food intake. Twenty-seven patients were diagnosed with chylopericardium within 30 days of surgery; the late-onset average for the other 6 patients was 62.5 days. Eighteen patients were prescribed dietary regimens involving foods rich in medium-chain fatty acids, low-fat intake, or nothing by mouth. Five patients underwent low thoracic duct ligation or additional pericardioperitoneal shunt surgery, 2 underwent re-exploration for suture repair, and 1 received conservative therapy with additional somatostatin treatment. The causes of the chylopericardium were determined to be small lymphatic injury (n=3; cases 7, 14, and 29) and high venous pressure or venous thrombosis (n=4; cases 1, 5, 15, and 19). The remaining 26 cases were of unknown origin.

We explored the possible causes of chylopericardium in these 26 patients. Ten of the 15 congenital heart disease patients (cases 9, 21-27, 30, and 32) had chromosomal abnormalities; 9 of these patients had trisomy 21. Increased lymphatic permeability due to congenital lymphatic dysplasia probably led to the postoperative chylopericardium that was reported in the Down syndrome patients and in the other patient with a chromosomal anomaly. Five of the 6 patients who underwent coronary artery bypass had the left internal thoracic artery harvested as a conduit (cases 8, 10, 11, 13, and 20), and these dissections were extended to the 1st intercostal space near the drainage site of the right efferent lymphatic trunk (RET)—a possible site of injury that

TABLE I. Summary of Cases of Chylopericardium after Intrapericardial Surgery

Year	Reference	Case No.	Diagnosis; Operation	Pt. Age/ Sex	ChrA	Management	Postop Onset (d)	Cause
1971	Thomas CS and McGoon DC[2]	1	PA; PDA/VSD repair, homograft reconstruction	31 y/F	–	TDL –	60	Thrombosis at jugular–subclavian venous confluence
1977	Kansu E, et al.[3]	2	AR, AS; AVR	53 y/F	–	Conservative	35	Unknown
1981	Pollard WM, et al.[4]	3	IHSS; myotomy, myomectomy	23 y/M	–	Conservative	3	Unknown
		4	PS; pulmonic valvotomy	4.5 y/M	–	Conservative	10	Unknown (mediastinal lymph increase)
		5	CAD; CABG	57 y/M	–	Conservative	4	Left subclavian vein obstruction
		6	–; VSD repair	22 y/M	–	TDL	3	Unknown
1982	Rose DM, et al.[5]	7	Infundibular PS; MRS	20 y/F	–	Suture repair	12	Lymphatics of periaortic fat transected
1982	Fudge TL, et al.[6]	8	CAD; CABG	57 y/M	–	Conservative	9	Unknown
1984	Papaioannou Y, et al.[7]	9	TOF; total correction	9 y/M	tri 21	Conservative	5	Unknown
1984	Bakay C and Wijers TS[8]	10	CAD; CABG	41 y/M	–	PP fistula	35	Unknown
1984	Schiessler A, et al.[9]	11	CAD; CABG	45 y/M	–	Conservative	1	Unknown
1985	Tchervenkov CI and Dobell AR[10]	12	AS; aortic valvotomy	12 y/M	–	Conservative	34	Unknown
1987	Lee Y, et al.[11]	13	CAD; CABG	49 y/M	–	TDL, DPS	8	Unknown
1988	Pereira WM, et al.[12]	14	–; ASD II repair	4 y/F	–	TDL	17	Lymphatics injured at IVC
1989	Denfield SW, et al.[13]	15	TGA; Mustard	9 m/M	–	Conservative	180	SVC obstruction
		16	–; ASD repair	1 y/M	–	Conservative	5	Unknown
1989	Bar-El Y, et al.[14]	17	MS; MVR	39 y/F	–	Conservative	31	Unknown
1994	Schactman M, et al.[15]	18	AS; AVR (concomitant CABG)	77 y/M	–	Conservative	4	Unknown
1998	Rimensberger PC, et al.[16]	19	TGA; atrial switch	4 m/M	–	Conservative + somatostatin	2	Increasing central venous and left atrial pressure
1999	Sharpe DA, et al.[17]	20	CAD; CABG	63 y/F	–	Conservative	11	Unknown
2001	Campbell RM, et al.[18]	21	–; TOF repair	3 m/M	22q–	Conservative	7	Unknown
		22	–; AVSD repair	3 m/F	tri 21	Conservative	23	Unknown
		23	–; AVSD repair	4 m/F	tri 21	Conservative	19	Unknown
		24	–; AVSD repair	5 m/F	tri 21	Conservative	13	Unknown
		25	–; AVSD repair	5 m/F	tri 21	Conservative	6	Unknown
		26	TOF; AVSD repair	2 y/M	tri 21	Conservative	28	Unknown
		27	TOF; AVSD repair	2 y/F	tri 21	Conservative	22	Unknown
2002	Sasaki A, et al.[19]	28	MR; MVR	49 y/M	–	Conservative	2	Unknown
2003	Shanmugam G, et al.[20]	29	–; ASD repair	8 y/F	–	Suture repair	3	Thymic lymphatic leakage
2007	Kan C-D, et al.*	30	AVSD; PDA repair	1 y/M	tri 21	Conservative	10	Unknown
		31	–; ASD repair	3 y/M	–	Conservative	3	Unknown
		32	–; VSD repair	4 m/M	tri 21	Conservative	4	Unknown
		33	–; TOF repair	2 y/M	–	Conservative	14	Unknown

*Current study

AR = aortic valve regurgitation; AS = aortic valve stenosis; ASD = atrial septal defect; AVR = aortic valve replacement; AVSD = atrioventricular septal defect; CABG = coronary artery bypass grafting; CAD = coronary artery disease; ChrA = chromosomal anomaly; DPS = Denver pleuroperitoneal shunt; IHSS = idiopathic hypertrophic subaortic stenosis; IVC = inferior vena cava; m = months; MR = mitral regurgitation; MRS = muscular resection; MS = mitral stenosis; MVR = mitral valve replacement; PA = pulmonary atresia; PDA = patent ductus arteriosus; PP = pericardioperitoneal ; PS = pulmonary valve stenosis; SVC = superior vena cava; TDL = thoracic duct ligation; TGA = transposition of great vessels; TOF = tetralogy of Fallot; tri 21 = trisomy 21 (Down syndrome); 22q–=chromosome 22q deletion syndrome; VSD = ventricular septal defect; y = years

would cause chylopericardium. Of the remaining 6 patients, cases 2, 3, 12, and 18 underwent an aortotomy, and cases 17 and 28 underwent mitral valve replacement. No single procedure appeared to jeopardize the lymphatic trunk in these 6 patients. However, all 26 patients underwent varying degrees of dissection of the AAo from the MPA, in proximity to the RET. An inadvertent injury to the RET during blunt dissection would engender chylopericardium.

Discussion

Chylopericardium that complicates intrapericardial surgery is extremely rare. Thomas and McGoon[2] first reported this problem in 1971 after procedures involving cardiopulmonary bypass. Chylopericardium has been reported after valve replacement, myocardial revascularization, and corrections of congenital heart anomalies[2-20]; the overall incidence in the literature is less than 0.22%.[4,7,18,21] Upon retrospective review of all of the surgical patients in our hospital from September 1988 through February 2004, we calculated an incidence of 0.12% (4 of 3,332).

Normally, the lymphatic system drains chylous fluid, which is filtered by the capillaries from the interstitial spaces into the thoracic duct. The thoracic duct passes through the chest near the aorta and azygos vein and then terminates at or near the junction of the left subclavian artery and the jugular veins, into which the chyle drains. It is generally accepted that direct injury to the thoracic duct results in chylothorax rather than chylopericardium because the thoracic duct is located in the region of the descending aorta, and direct injury to the thoracic duct during a purely intrapericardial procedure is unlikely. Identifying the mechanism responsible for the development of chylopericardium is of interest to surgeons; however, due to the paucity of clinical experience with chylopericardium, few satisfactory explanations have been forthcoming to account for its occurrence.

Causes for chylopericardium could be established in only 7 of the patients who underwent intrapericardial procedures. Injury to the lymphatic system near the inferior vena cava during re-exploration was diagnosed in case 14. Small lymphatic leaks in the thymic tissues or periaortic fat were noted during reoperation in cases 7 and 29; both were treated by direct suture ligation. In cases 1, 5, 15, and 19, the chylopericardium was related to obstruction of normal thoracic ductal flow, as confirmed by venography, actual symptoms, or pressure tracing. Both direct obstruction of the systemic venous return (as seen in cases 1, 5, and 15) and abnormally elevated systemic venous pressure transmitted into the lymphatic channels (case 19) may increase the pressure within the thoracic duct; the same is true when patients undergo a Fontan procedure for tricuspid atresia and develop chylothorax, which results in pericardial chyle accumulation. Whereas in adults the thymus is nearly devoid of lymphatic tissue, in children the thymus is rich in lymphatic tissues. This may explain why chylopericardium develops more often after pediatric surgery, and why most such instances involve the anterior mediastinum of the thymic tissue.

Although many patients in our literature review were surveyed for possible pathogenesis, in most it remained undetermined. Previous researchers[18,22] have concluded that an important cause of postoperative chylopericardium is the increased lymphatic permeability due to congenital lymphatic dysplasia that contributes to the chylous effusions present in Down, Noonan, and Turner syndromes. Ten patients in our survey were found to have a chromosomal anomaly, mainly trisomy 21. However, the pathogenesis was unclear in the other 16 patients. We analyzed the general clinical manifestations in this subgroup. All 16 patients had undergone either some degree of dissection of the AAo from the MPA (to facilitate accurate aortic cross-clamping) or harvesting of the left internal thoracic artery (for coronary artery bypass).

In a study of the intrathoracic tributaries of the thoracic duct in 530 cadavers, 8.9% of lymphatic vessels were found to arise from the heart and connect with the thoracic duct.[1] There are 2 routes for these tributaries—the RET and the left efferent lymphatic trunk (LET). The RET, which often drains lymph from the right ventricle, ascends cephalad between the AAo and the MPA and joins the upper part of the left anterior mediastinal node chain, which is located at the level of origin of the internal thoracic artery. The RET then travels to the left of the thymus gland and drains into the arch of the thoracic duct (Fig. 1). The LET, which drains lymph from the left ventricle, ascends behind the MPA, joins the right paratracheal node, and drains into the thoracic duct at the mediastinum or arch. This confirms the observation of Pollard and colleagues,[4] who demonstrated the phenomenon of increased numbers of superior mediastinal lymphatics in 1 patient with chylopericardium (case 4).

Riquet and associates[1] have suggested that injury to an incompetent RET along its course within the pericardium is a possible cause of isolated postoperative chylopericardium.[1] (Note: We frequently dissect the AAo from the MPA in order to cross-clamp the AAo accurately after cardiopulmonary bypass. Inadvertent injury to the RET might be unavoidable during this dissection or the subsequent clamping; however, backflow from the thoracic duct actually occurs only if the integrity of the RET is compromised and results in leakage of chyle. This may explain why the incidence of isolated chylopericardium is so low even though dissection of the AAo from the MPA is a routine procedure.)

In patients who have undergone coronary artery bypass grafting, harvesting of the left internal thoracic artery above the left subclavian vein with ligation of

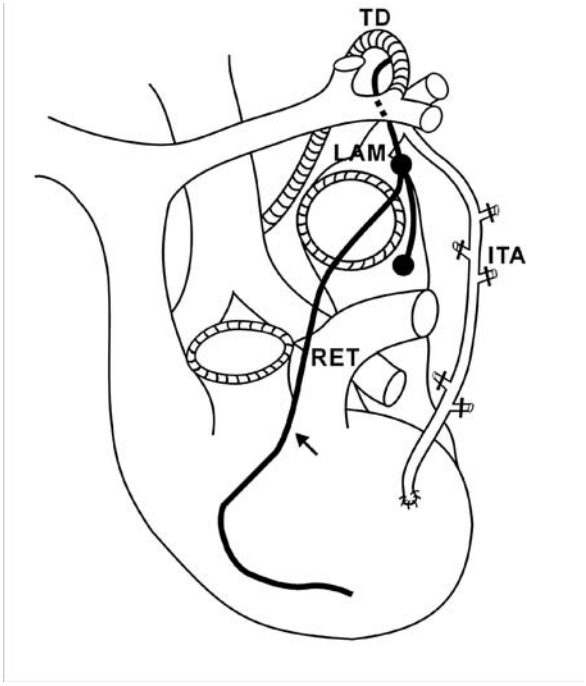

Fig. 1 *The right efferent lymphatic trunk (RET), which drains the lymph from the right ventricle, arises between the ascending aorta and the main pulmonary artery (arrow), joins the upper part of the left anterior mediastinal node chain (LAM) located at the origin of the internal thoracic artery (ITA), and empties into the arch of the thoracic duct (TD).*

the upper intercostal branch may incur an additional risk of chylopericardium or chylothorax if the pleural membrane is opened. The risk may be increased because the anterior mediastinal node chain is easily jeopardized during proximal dissection of the internal thoracic artery, and chylous leakage may ensue. This complication is under-reported and shows the danger of high dissection of the internal mammary artery. The intrapericardial collection of pericardial effusion after cardiac surgery is primarily related to not opening the pleural membrane.

Two research groups[7,23] showed improvements in patients with chyluria and chylothorax who were prescribed a medium-chain triglyceride diet. This regimen has since proved effective in many cases, under varied conditions. Therefore, we recommend treating chylothorax and chylopericardium with 2 weeks of conservative therapy: decompression of the thoracic lymphatics by parenteral hyperalimentation or oral medium-chain triglycerides, together with decompression of the pericardial space by closed chest-tube suction. To avoid prolonged hospitalization, we recommend outpatient drainage of a chylous effusion with the use of a soft silastic catheter (Pleurx; Denver Biomedical, Inc.; Golden, Colo) that is tunneled to prevent infection. More than half of the patients whose cases we reviewed were successfully treated by use of this method.

Control of chyle output with somatostatin has also been advocated.[25,26] Surgical reintervention was required in only 6 of 34 patients so treated. Generally, the indications for surgery are drainage of more than 1,000 mL/day in adults, or 100 mL × years of age in children, for the first 7 days, or persistent chylous drainage for longer than 2 weeks.[26-29] Ligating the thoracic duct at the diaphragmatic level confers the advantage of stopping flow from accessory ducts that may be unrecognized[30,31]; however, sometimes the thoracic duct cannot be found intraoperatively, or ligation fails to control the leak.[28,32] Other surgical options include pleurodesis, pleurectomy, low ligation of the thoracic duct by video-assisted thoracoscopic surgery, and pericardial–peritoneal shunting,[28,30,33,34] but the results are not always satisfactory.[24]

Summary

Chylopericardium after simple intrapericardial surgery is a rare entity, but one that is associated with potentially serious problems. Chylopericardium can result from injury to the lymphatic branches of the thymus, increased lymphatic permeability associated with the lymphatic dysplasia in patients with Down syndrome, or thrombosis of the great venous system. An inadvertent injury to the RET during dissection can also lead to chylopericardium. We advise caution when dissecting the tissues between the AAo and the MPA, and we discourage harvesting the internal mammary artery as far as the upper intercostal branches. Although surgical reintervention may be required for refractory chylopericardium, a conservative treatment strategy is still the 1st choice.

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Case Reports

Pericardial Effusion as an Expression of Thyrotoxicosis

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Patients who have either hyperthyroidism or hypothyroidism can present with cardiovascular complications. These manifestations of thyroid disease—congestive heart failure, atrial tachyarrhythmias, atrioventricular conduction disorders, and mitral valve dysfunction—are well known to the clinician. Pericardial effusion is considered a complication of hypothyroidism; as an expression of thyrotoxicosis, it is extremely rare.

Herein, we present the case of a 76-year-old woman who had pericardial effusion associated with thyrotoxicosis. She was treated with high-dose β-blockers, methimazole, diuretics, and short-term steroids. She recovered completely, which precluded the need for pericardiocentesis. We suggest that thyrotoxicosis be considered in the differential diagnosis of pericardial effusion. ***(Tex Heart Inst J 2007;34:88-90)***

In patients with hyperthyroidism, accelerated thyroid function results in secretion of excessive levels of thyroid hormones. The resulting signs and symptoms can be particularly severe in elderly patients. The most common symptoms are weight loss, irritability, heat intolerance and sweating, fatigue, weakness, gastrointestinal hypermotility, and diarrhea. Common signs are tachycardia and atrial fibrillation, congestive heart failure, tremor, goiter, warm moist skin, and muscle weakness.[1] A very rare complication is pericardial effusion, which is more commonly seen in cases of hypothyroidism. Herein, we discuss the case of a 76-year-old woman who presented at our hospital with pericardial effusion.

Case Report

On 8 May 2005, a 76-year-old woman was admitted to our hospital with palpitations and chest pain. Her medical history included type 2 diabetes mellitus (treated with insulin), osteoporosis, peptic ulcer, and a cerebrovascular accident in 1996. On admission, her physical examination was normal, with a blood pressure of 130/70 mmHg and a pulse rate of 95 beats/min. Electrocardiography revealed sinus rhythm with no signs of ischemia. Results of blood analysis were normal except for thyroid function: the thyroid-stimulating hormone (TSH) level was 0.03 μIU/mL (normal range, 0.25–4 μIU/mL), the free thyroxine (FT_4) level was 41.1 ng/dL (normal range, 0.9–1.9 ng/dL), and the triiodothyronine (T_3) level was 4.22 pg/dL (normal range, 2.57–4.43 pg/dL). These results led to a diagnosis of hyperthyroidism. Radioiodine uptake and thyroid scanning revealed a toxic, multinodular goiter. Treatment with oral atenolol (50 mg per day) was begun. Eleven days after the initial evaluation, she returned for radiotherapy and received 27 mCi of radioiodine I-131.

Eight days later, the patient was readmitted with rapid atrial fibrillation. She received 5 mg of intravenous verapamil, and sinus rhythm was restored. A blood analysis revealed a TSH level of <0.05 μIU/mL, an FT_4 of 6.32 ng/dL, and a T_3 of 11.6 pg/dL. The patient's dosage of atenolol was increased to 100 mg per day, and 20 mg of oral methimazole per day was begun at the recommendation of the consulting endocrinologist. The patient was discharged from the hospital, feeling well, on the same day.

Five days later, the patient was again admitted, this time with dyspnea, palpitations, and edema of the lower extremities. On physical examination, her body temperature was 36.8 °C; respiratory rate, 26 breaths/min; blood pressure, 130/70 mmHg; and pulse rate, 90 beats/min and irregular. She had mild congestion of the jugular veins. On auscultation, bilateral crepitant rales were heard over the lung bases. No cardiac murmur was heard. An abdominal examination revealed liver enlargement (a

Key words: *Echocardiography; heart diseases/diagnosis/etiology/therapy; hyperthyroidism/complications; hypothyroidism/complications; middle aged; pericardial effusion/diagnosis/etiology; thyroid hormones/blood; thyrotoxicosis/complications/diagnosis*

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span of 12 cm), and +2 bilateral edema of the lower extremities was noted. Electrocardiography revealed rapid atrial fibrillation. A chest radiograph (Fig. 1) showed mild bilateral pleural effusion and mild enlargement of the cardiac silhouette. Results of blood tests were normal except for thyroid function, which again was typical of hyperthyroidism, although the T_3 levels were improved (TSH, <0.05 μIU/mL; FT_4, 4.97 ng/dL; T_3, 8.59 pg/dL). Intravenous treatment with 0.5 mg of digoxin restored sinus rhythm. Treatment with intravenous furosemide (40 mg, twice daily) was added. The next day, echocardiography (Fig. 2) revealed mild-to-moderate pericardial effusion and normal global and regional left ventricular function, consistent with left ventricular diastolic dysfunction. The ejection fraction was 0.65. Despite diuretic treatment, her condition did not improve. Chest radiography and echocardiography 1 week later (Figs. 3 and 4) revealed moderate-to-severe pericardial effusion without evidence of cardiac tamponade. Pericardiocentesis was not required at this point. A consulting cardiologist recommended a regimen of oral steroids, which is an option for therapy in the case of thyrotoxic crisis after radioiodine treatment for partially treated hyperthyroidism. The patient was given 60 mg of oral prednisone daily for 3 days, and her condition improved.

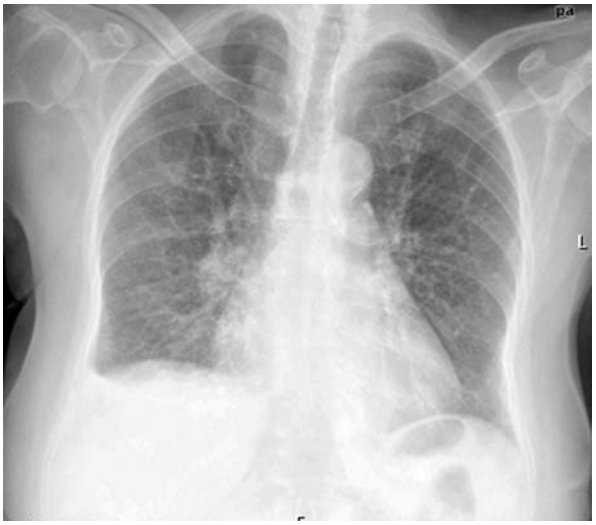

Fig. 1 *Chest radiography shows mild bilateral pleural effusion and mild enlargement of the cardiac silhouette.*

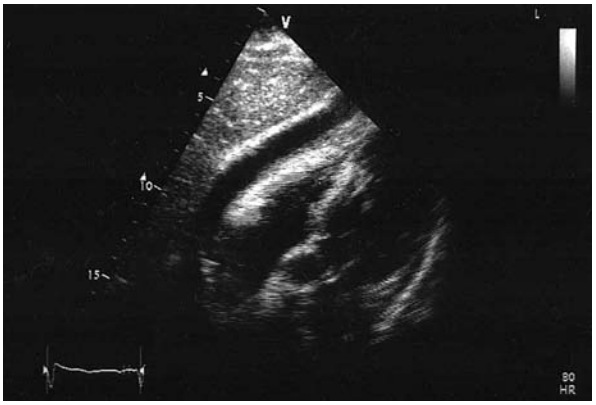

Fig. 2 *Echocardiography shows mild-to-moderate pericardial effusion and normal global and regional left ventricular function, consistent with left ventricular diastolic dysfunction.*

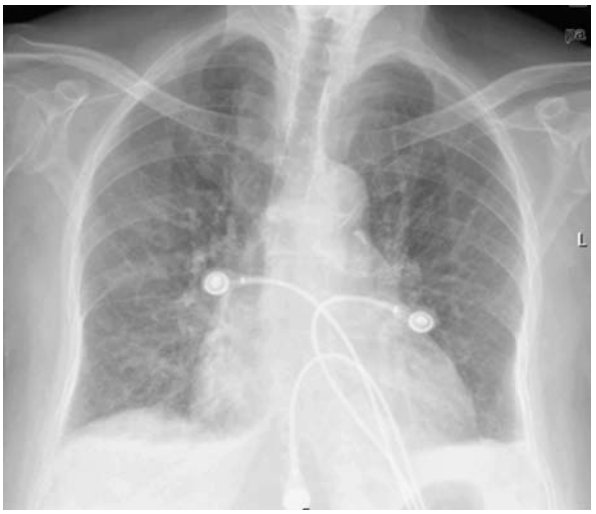

Fig. 3 *Chest radiography shows moderate-to-severe pericardial effusion without evidence of cardiac tamponade.*

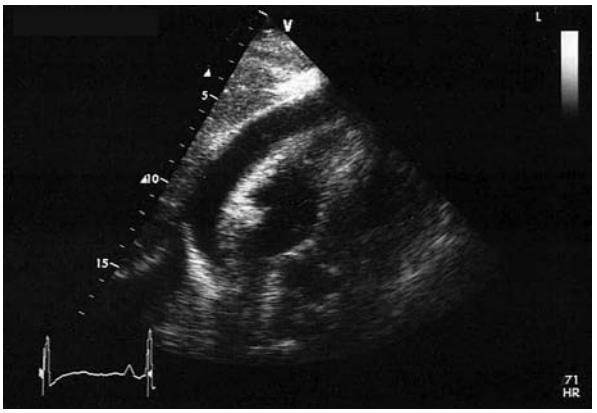

Fig. 4 *Echocardiography shows moderate-to-severe pericardial effusion without evidence of cardiac tamponade.*

During this hospitalization, the cause of the pericardial effusion was investigated; this included blood analyses and a Mantoux test. The results revealed an increase in C-reactive protein from 0.5 mg/dL to 7.48 mg/dL, and a lengthened erythrocyte sedimentation rate of 90 mm/h. The oncologic markers that we examined were normal except for cancer antigen 125, which was 102 U/mL (normal range, 0–35 U/mL). As a result, a gynecological consultation was requested, and abdominal ultrasonography was performed. Neither revealed any disorder. Results of immunoelectrophoresis were normal, as were the complement and antinuclear

factors. The Mantoux diameter was 4 mm, negative for any risk group. The patient's treatment with β-blockers, diuretics, methimazole, and prednisone was continued. Her condition gradually improved, and she was discharged from the hospital after 22 days (June 20).

During the next 6 months, as the results of the patient's thyroid function tests and repeat echocardiography returned to normal, she was gradually weaned from methimazole and β-blockers. At her 6-month and 1-year follow-up examinations, she had normal thyroid function and no cardiac symptoms.

Discussion

Our patient initially presented with thyrotoxicosis, with no particularly striking features. Our research of the literature supported this diagnosis. Because of her refractory cardiac arrhythmia and the development of congestive heart failure, we performed echocardiography to rule out other possibilities, such as mitral valve insufficiency and myopericarditis. As a result, pericardiocentesis was unnecessary, and the syndrome was resolved by pharmacotherapy alone.

Cardiac complications often dominate clinical presentations in middle-aged and older patients who have thyrotoxicosis. The more common complications are atrial fibrillation, congestive heart failure, mitral valve dysfunction, and atrioventricular block.[2-4] Pericardial effusion is evidently a very rare complication of thyrotoxicosis—in our search of the literature, we found only 1 report of 5 such cases.[2] A 2003 investigation into the causes of pericardial effusion in 204 patients resulted in a definitive diagnosis in 107 (52.4%), with no thyrotoxicosis among them.[5]

The reported mortality rate for thyrotoxicosis due to cardiac failure and arrhythmia is 30%, even with treatment.[6] The lack of published evidence linking pericardial effusion with thyrotoxicosis does not mean that these conditions do not coexist; the clinician must ascertain it.

All cases of pericardial effusion should be investigated for alternative origins of pericardial disease. Testing routinely involves multiple blood cultures, urine cultures, inflammatory and oncologic markers, the Mantoux test, direct-smear and tuberculosis cultures of pericardial fluid, pericardial fluid cytology, acute and convalescent serology, antinuclear and antineutrophil cytoplasmic antibody tests, and rheumatoid factor tests. We further recommend that thyroid function tests be part of the investigation of pericardial effusion, without limitation solely to cases of suspected hypothyroidism.

In cases of thyrotoxicosis, the primary cause of hyperthyroidism must always be investigated. When thyrotoxicosis is complicated by cardiac arrhythmia or congestive heart failure, we recommend that echocardiography be included in the investigation to rule out pericardial effusion as a contributing factor, since—if this were the case—the use of steroid treatment might facilitate the patient's recovery.

Acknowledgments

We express our deepest appreciation to Karin Lee Ovadia and Mary Clare Rosenberg for their assistance in translating and editing our manuscript.

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Case Reports

Infective Coronary Aneurysms

A Complication of Percutaneous Coronary Intervention

We present the case of a patient who developed infective coronary artery aneurysms after percutaneous coronary artery intervention. We describe the patient's clinical presentation, diagnosis, and treatment, and we review the pertinent medical literature. ***(Tex Heart Inst J 2007;34:91-4)***

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Key words: *Aneurysm, infected/diagnosis/etiology/surgery; angioplasty, transluminal, percutaneous coronary/adverse effects; bacteremia/diagnosis/etiology; coronary aneurysm/etiology/surgery; staphylococcal infections/etiology/drug therapy; stents/adverse effects*

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Inapparent bacteremia occurs frequently (in approximately 30% of cases) after complex percutaneous coronary intervention (PCI); however, clinical sequelae rarely occur.[1,2] Cardiac catheterization itself carries a negligible bacteremic risk.[3] Percutaneous coronary intervention has a greater bacteremic potential, presumably due to the prolonged procedural time and the repeated insertion of interventional devices into the vascular system.[3] When septic complications occur after PCI, morbidity and death often result.[4] We present the case of a patient who had infective coronary artery aneurysms that developed after PCI, and we discuss the possible contributing factors.

Case Report

A 43-year-old man presented with recurrent fever, chills, chest pain, and a persistent dry cough of 4 days' duration. He had a history of coronary artery bypass grafting 10 years earlier, end-stage renal disease with a functioning left-arm arteriovenous fistula, and chronic hepatitis C. The patient had undergone multiple stenting and balloon angioplasty procedures; the most recent was balloon angioplasty on a protected left main coronary artery 5 months before the current admission. Seven days after that procedure, he had developed methicillin-resistant *Staphylococcus aureus* (MRSA) bacteremia without an identifiable source. Intravenous vancomycin and gentamicin were given for 6 weeks. Shortly thereafter, the patient presented with unstable angina and underwent right coronary artery balloon angioplasty. He was asymptomatic for the next 3 months.

At the current presentation, he was febrile to 40 °C during hemodialysis and was admitted to the hospital. The physical examination showed nothing unusual. His white blood cell count was 14,900/cm^3 with a left shift. The total creatine kinase was 76 U/L (normal range, 33–194 U/L) with an MB isoenzyme of 11.1 ng/mL (normal, <5.0 ng/mL). The troponin I was 9.96 ng/mL (normal range, 0–1 ng/mL). Chest radiography showed bilateral infiltrates. Electrocardiography showed sinus rhythm with a left ventricular hypertrophy pattern, 2-mm ST-segment depression in leads V_3 through V_6, 1-mm ST-segment depression in lead I, and T-wave inversion in lead aVL. The presumptive diagnoses on admission were pneumonia and acute coronary syndrome. The patient was started on gentamicin, vancomycin, aspirin, clopidogrel, metoprolol, and heparin. Admission blood cultures grew MRSA. The patient improved clinically but remained bacteremic. Transesophageal echocardiography, ultrasonography of the arteriovenous fistula, and bone scanning revealed no evidence of infection. A technetium-99m white-blood-cell–tagged scan showed an area of white-blood-cell uptake in the mediastinum (Fig. 1). Chest computed tomographic scanning showed mediastinal fluid collection with 2 round foci, isodense to the aorta in the area of the right coronary artery, suggestive of coronary pseudoaneurysms (Fig. 2). Aortography showed bi-lobed aneurysmal dilatation of the right coronary artery. Coronary arteriography revealed very large sequential aneurysms of the mid-left circumflex (Fig. 3) and right coronary arteries (Fig. 4), and patent grafts to the left

anterior descending and 1st diagonal arteries. Because of the size of the aneurysms and the possibility of their being infected, we decided to operate in order to drain the infection, excise the aneurysms, and revascularize the coronary arteries. Intraoperative transesophageal echocardiography revealed severe mitral regurgitation due to a flail posterior leaflet. The aneurysms were resected, the surrounding abscesses drained, the necrotic tissue débrided, and the 2 coronary arteries bypassed with saphenous vein grafts. The circumflex artery abscess was found to be eroding into the mitral valve annulus (Fig. 5). Therefore, a mitral valve bioprosthesis was implanted, and a bovine pericardial patch was used to close the atrioventricular separation. The patient was removed from extracorporeal circulation with an intraaortic balloon pump in place. Despite these measures, cardiogenic shock ensued and the patient died in the operating room shortly thereafter.

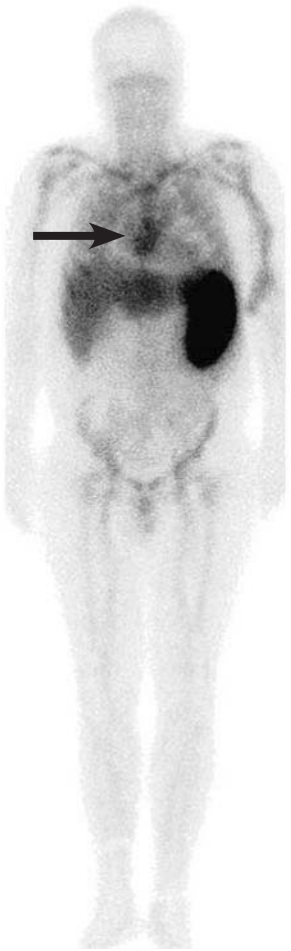

Fig. 1 *Technetium-99m white-blood-cell–tagged scan. Arrow indicates increased uptake in the mediastinum.*

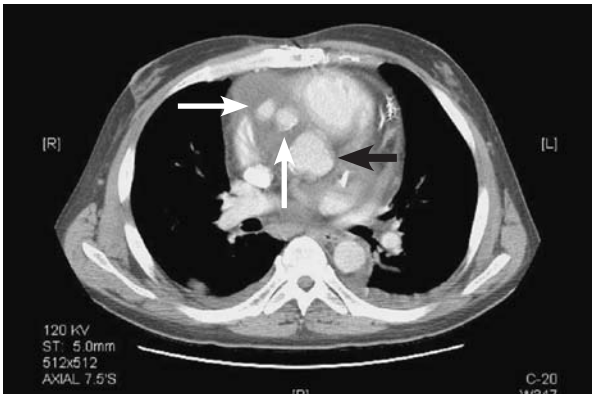

Fig. 2 *Computed tomographic scan shows 2 round foci (arrows) isodense with the aorta (black arrow), raising the suspicion of right coronary artery pseudoaneurysms.*

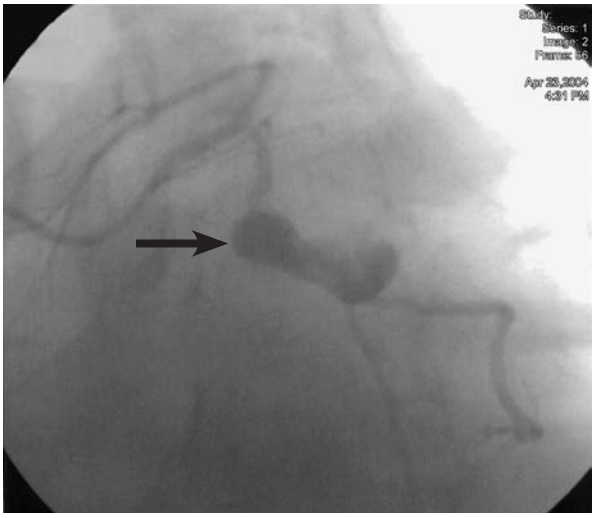

Fig. 3 *Aortography (left anterior oblique caudal view) shows very large sequential aneurysms of the mid -circumflex coronary artery (arrow).*

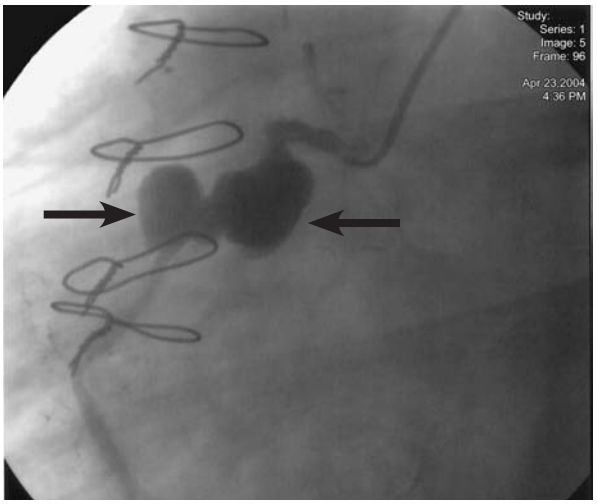

Fig. 4 *Coronary angiography (left anterior oblique view) of the right coronary artery shows large sequential aneurysms (arrows).*

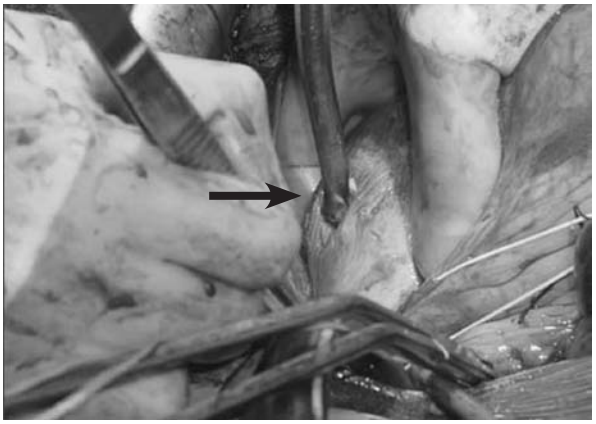

Fig. 5 *Intraoperative photograph shows the aneurysm of the circumflex artery, after it was opened to be drained, held between the surgeon's fingers (arrow).*

Discussion

Infectious cardiac complications after PCI are rare; such complications include coronary abscess,[5] pericarditis,[4] mycotic aneurysms, and valvular endocarditis,[6] and are often fatal.[5,6] Noncardiac infectious complications of PCI are also rare and include septic arthritis, infected groin hematoma, femoral endarteritis, and sternal osteomyelitis.[3,7]

Multiple risk factors for infections after PCI have been suggested. Evans and Goldstein[8] noted that any of these events—repeat PCI with repuncture of the ipsilateral femoral artery within 3 to 7 days of the initial procedure, access site hematoma, or skin drainage—increased the periprocedural risk of infection to 30%. It has been suggested that small soft-tissue hematomas may impair local host defense mechanisms.[9] McCready and co-authors[10] described repuncture of the ipsilateral artery and indwelling of the vascular sheath for more than 24 hours after the procedure as major risk factors for post-PCI septic complications. Other predisposing factors may include duration of the procedure, number of passages of the catheters through the femoral sheath, bleeding at the puncture site, and pseudoaneurysm.[2,4,10] In our patient, none of these risk factors was clearly operative.

Only a few cases of coronary artery abscess after PCI and stent placement have been reported,[3,5,9] and mycotic coronary aneurysms have been described even less often.[3,6] Timsit and colleagues[9] reported the 1st case of probable balloon angioplasty-related myocardial abscess. Liu and coworkers[3] described 5 cases of coronary artery abscesses after stenting, 2 of which developed into aneurysms. Two other cases of coronary artery abscess after PCI and stenting have been published since that report.[5,9] *S. aureus* and *Pseudomonas aeruginosa* seem to be the most frequently infective organisms.[3,6] Coronary infection after stenting can present days to weeks after intervention,[11] most frequently as an acute coronary syndrome.[3] Both surgical and medical mortality rates can be as high as 50%,[11,12] which emphasizes the dilemmas of therapeutic decision-making in individual patients.

Our patient developed MRSA bacteremia 7 days after balloon angioplasty of the left main coronary artery. Later, he had balloon angioplasty of the right coronary artery. The aneurysms subsequently developed at different sites. During the right coronary artery intervention, no wire manipulation was performed on the left coronary system, which raises the question of whether the abscesses and aneurysms were a complication of the interventional procedure or of systemic infection. Our patient had end-stage renal disease and underwent frequent hemodialysis, a combination that predisposes patients to bacteremia and systemic infection.[13,14]

Mycotic aneurysm formation may be due to microembolization to the vasa vasorum, pathogen invasion of the arterial wall, or immune complex deposition, any of which can result in medial injury and destruction. Complications include thrombosis, distal embolization, and rupture.[15] Aneurysms more than 1 to 2 cm in diameter are unlikely to resolve, and they may enlarge and eventually rupture even when the lesions have been sterilized with antibiotics. Most aneurysms are clinically silent; however, some patients present with angina or infarction. The frequency of these complications is difficult to determine, because of the extremely low prevalence.[16] Although angiography remains the gold standard for diagnosis, coronary aneurysms can also be detected by transesophageal echocardiography, contrast-enhanced computed tomography, and magnetic resonance imaging.[17] Osevala's group described 15 cases: of those, 4 patients had *S. aureus* and 1 had viridans streptococcus; the infective agent in the remaining cases was not identified.[18] One other case of viridans streptococcus and one of *Salmonella enteritidis* have been described.[15,19]

The treatment for mycotic coronary aneurysms is not clear-cut. Its presence does not indicate the need for immediate surgery. Antiplatelet and antithrombotic therapy may be administered to prevent thrombus formation and distal embolization.[20] Surgery should be considered for patients with large aneurysms because of the high risk of rupture. Surgical revascularization procedures include saphenous vein grafting alone or in combination with aneurysm resection.[18]

In our patient, the occurrence of bacteremia shortly after coronary artery intervention suggests a causal effect of the procedure on the formation of the aneurysms; however, the source was never determined.

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Case Reports

Aspergillus Endocarditis of the Mitral Valve in a Lung-Transplant Patient

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A 57-year-old man underwent bilateral lung transplantation at our hospital. On histopathology, aspergillomas were identified in the upper lobes of the explanted lungs. After being treated and discharged from the hospital, he returned 4 months later with ischemic chest pain, which was due to a myocardial infarction complicated by cardiogenic shock. He also had a large vegetation on the anterior mitral leaflet. Herein, we describe the patient's symptoms, complications, treatment, and recovery. To the best of our knowledge, ours is only the 2nd report of a patient who developed Aspergillus *endocarditis after lung transplantation and the 1st such patient to have undergone successful mitral valve replacement.*
(Tex Heart Inst J 2007;34:95-7)

Mitral valve endocarditis of a native valve with *Aspergillus fumigatus* is rare. We present a case of *Aspergillus* endocarditis of the mitral valve in a double-lung transplant recipient. He had a postoperative embolism to the left anterior descending coronary artery (LAD). The patient was treated with percutaneous coronary angioplasty, aggressive antifungal treatment, coronary artery bypass, and mitral valve replacement.

Case Report

A 57-year-old man was referred to us for bilateral lung transplantation. He had end-stage pulmonary disease with chronic obstructive airway disease and interstitial pulmonary fibrosis, for which he was on home oxygen therapy. He also had type 2 diabetes mellitus. He underwent sequential double-lung transplantation through a median sternotomy with cardiopulmonary bypass (CPB). Prednisolone, azathioprine, and tacrolimus were used for immunosuppressive therapy. The procedure was uncomplicated, and the patient was extubated on postoperative day 1.

On histopathology, aspergillomas were identified in the upper lobes of the explanted lungs. The patient's postoperative course was complicated by the development of acute renal failure. On postoperative day 8, he was found to have right-side empyema, which was treated with the insertion of a pleural drain and intrapleural instillation of streptokinase. *Aspergillus fumigatus* was identified on cultures grown from pleural fluid and from bronchial washings. We performed video-assisted thoracoscopic decortication of the right lung. The patient was given antifungal drugs in the form of caspofungin acetate, amphotericin B, and voriconazole. He was discharged from the hospital 6 weeks postoperatively with no evidence of residual infection.

Four months later, the patient presented with ischemic-type chest pain. He had sustained an extensive ST-elevation anterior-wall myocardial infarction, which was complicated by cardiogenic shock. A transthoracic echocardiogram showed severe hypokinesia of the mid-anterior left ventricular wall, septal wall, and apex. A large vegetation was found on the anterior mitral valve leaflet, and there was grade 3/4 mitral regurgitation. A coronary angiogram showed total occlusion of the LAD. There was evidence of an aneurysm of the left circumflex coronary artery. The patient underwent successful percutaneous transluminal coronary angioplasty of the LAD, with intra-aortic balloon pump (IABP) support and with dopamine (5 μg/kg per min) for inotropic support.

Blood cultures did not grow any organisms. On the basis of a clinical diagnosis of *Aspergillus* endocarditis, the patient was treated with liposomal amphotericin B, caspofungin acetate, and voriconazole. The IABP was removed the next day. Anti-

Key words: *Amphotericin B; aspergillosis/complications/diagnosis/surgery; Aspergillus fumigatus; endocarditis/complications/diagnosis/etiology/microbiology/surgery; heart valve diseases/diagnosis/etiology; heart valve prosthesis; immunocompromised host; mitral valve/surgery; opportunistic infections/diagnosis/drug therapy; organ transplantation*

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coagulation with warfarin was started. In view of the large size of the vegetation, the patient was scheduled for surgery.

Operative findings included dense intrapericardial adhesions, a dilated left ventricle, and a large vegetation (2.5 × 2.5 cm) on the anterior mitral leaflet (Fig. 1). There was a thick-walled aneurysm involving the 1st obtuse marginal artery. The patient underwent mitral valve replacement with a 29-mm Carpentier-Edwards® Perimount® valve (Edwards Lifesciences; Irvine, Calif), and a single coronary artery bypass graft with a segment of the great saphenous vein to the 1st obtuse marginal artery. *Aspergillus* endocarditis was confirmed upon culture and histopathology of the excised mitral valve (Fig. 2). Postoperatively, the patient experienced coagulopathy and respiratory failure, which were managed successfully. His stay in the intensive care unit was 7 days. Echocardiography showed a normally functioning prosthetic valve. The patient received antifungal treatment with amphotericin and caspofungin for 6 weeks. The voriconazole was discontinued during the 1st week of treatment because the patient developed thrombocytopenia; this condition improved thereafter. After 3 months of follow-up and close monitoring, the patient was recovering well without any evidence of prosthetic-valve endocarditis. He is not on any long-term antifungal prophylaxis.

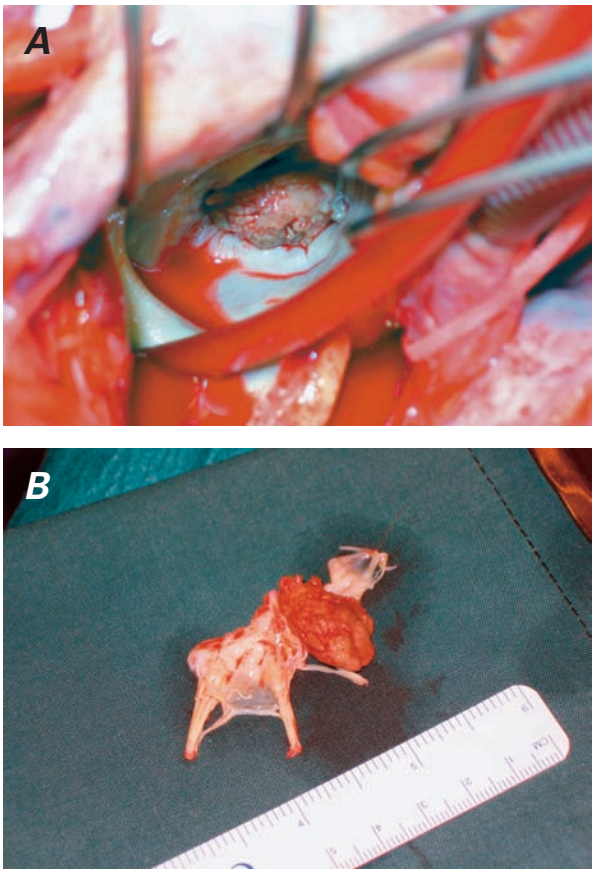

Fig. 1 ***A****) Large vegetation on the anterior leaflet of the mitral valve.* ***B****) The excised valve with vegetation.*

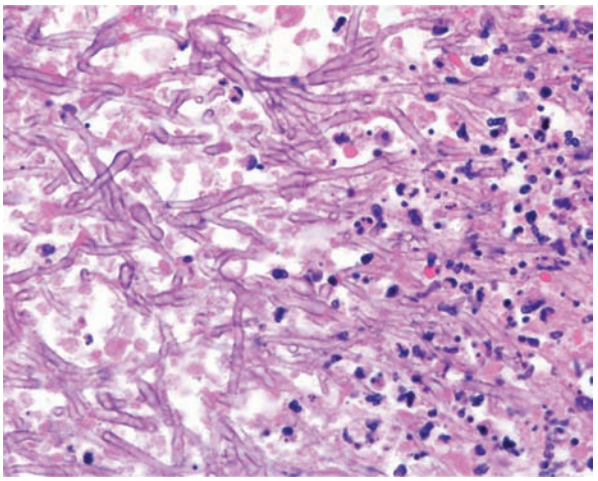

Fig. 2 *Photomicrograph of the mitral valve with* Aspergillus *hyphae (H & E, orig. ×200).*

Discussion

Fungal infection is a rare cause of infective endocarditis. There is an association of fungal endocarditis with cellular immune deficiency.[1] Characteristics of fungal endocarditis include large vegetations with an increased potential for systemic embolization, a tendency to grow on prosthetic valves, and a poor outcome despite adequate medical and surgical treatment.[1] The patient can acquire *Aspergillus* endocarditis during heart surgery when operating-room air and CPB equipment are contaminated.

Aspergillus infection may be difficult to diagnose clinically. Blood cultures that test positive for this organism are uncommon.[2] A high degree of suspicion is required for an early diagnosis. Our patient underwent sequential bilateral lung transplantation with extracorporeal circulation. Although aspergillomas were found incidentally upon histopathology of the native lung, there was no evidence of this infection clinically on pre-transplantation evaluation. In addition, this patient developed *Aspergillus* empyema after lung transplantation. Seeding of the mitral valve occurred either during transplantation or during the immediate postoperative period, when the patient developed empyema. Moreover, CPB has been associated with transient immunosuppression.[3] In addition, the patient's concomitant diabetes certainly would have contributed to the development of the invasive *Aspergillus* infection.

Aspergillus endocarditis has been described in patients who are on immunosuppressive therapy.[4] Endocarditis

of the native mitral valve in patients who have an anatomically normal valve and who have not received immunosuppressive therapy has been described in only a few cases.[5,6] Treatment should begin as soon as the diagnosis is suspected. *Aspergillus* endocarditis is associated with an extremely high mortality rate of 80% to 96%. Poor health of the patients, recurrent and severe embolic episodes, and diagnostic delays are the main factors responsible for the dismal outcomes.[1] Surgical treatment was indicated for our patient in order to confirm the clinical diagnosis, to reduce the risk of further embolization from the large vegetation, and to treat the severe mitral regurgitation. To the best of our knowledge, ours is only the 2nd report of a patient who developed *Aspergillus* endocarditis after lung transplantation and the 1st such patient to have undergone successful mitral valve replacement.

In a case described by Gilbey and coworkers,[7] a diagnosis of *Aspergillus* endocarditis was made 20 months after bilateral lung transplantation. Their patient had experienced multiple episodes of peripheral embolization before he was diagnosed with mitral valve endocarditis. This patient received only palliative treatment because of his poor clinical condition, and he later died. *Aspergillus* endocarditis of the native valves is an extremely rare condition in transplant patients. Two types of *Aspergillus* endocarditis have been identified. In the 1st type, the infection is very aggressive, and it leads to early death. Our patient had the 2nd type, which is a less fulminant infection. Patients with the 2nd type may present with embolic phenomena.[8]

Another interesting observation regarding our patient is the treatment of his occluded LAD with percutaneous coronary intervention. Because our patient was very sick from severe mitral regurgitation, sepsis, ongoing myocardial ischemia, and cardiogenic shock, our cardiology colleagues decided to proceed with percutaneous intervention of the LAD with IABP support in order to stabilize the patient before we undertook more definitive treatment. We have not found any reports of previous use of this intervention in the setting of presumed aspergilloma embolism to a coronary artery.

Our case illustrates a rare and interesting association of bilateral lung transplantation with *Aspergillus* endocarditis of the native mitral valve. Any focus of *Aspergillus* colonization or infection should be treated aggressively with use of a prolonged course of appropriate antifungal agents after transplantation.

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Case Reports

Transvenous Right Atrial and Left Ventricular Pacing after the Fontan Operation

Long-Term Hemodynamic and Electrophysiologic Benefit of Early Atrioventricular Resynchronization

J. Alberto Lopez, MD

We report a case of long-term, successful, endocardial atrioventricular pacing in a 32-year-old man who had severe heart failure and ascites after having undergone a Fontan procedure for tricuspid atresia 9 years earlier. The patient was referred to our hospital for Fontan revision. However, electroanatomic mapping of the right atrium revealed viable tissue at the interatrial septum above the os of the coronary sinus, and it appeared that the left ventricle could be paced from a coronary sinus branch. Therefore, instead of Fontan revision, an endocardial atrioventricular pacemaker was implanted transvenously.

On 5-year follow-up, the patient remained in New York Heart Association functional class I and had not been readmitted to the hospital for congestive heart failure or arrhythmias. His atrial and ventricular leads continued to show excellent pacing and sensing results. ***(Tex Heart Inst J 2007;34:98-101)***

Key words: *Fontan procedure/adverse effects; heart conduction system; heart failure; pacing, endocardial atrioventricular; pacemaker, artificial; postoperative complications; tricuspid atresia*

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After a Fontan operation, loss of atrioventricular (AV) synchrony usually results in severe systemic AV valve regurgitation, ventricular failure, and congestive heart failure, with a poor outcome.[1] The case presented herein involves a patient who was referred to our hospital for Fontan revision. When electroanatomic mapping of the right atrium revealed viable tissue at the interatrial septum above the os of the coronary sinus, it appeared that the left ventricle could be paced from a coronary sinus branch. Therefore, instead of Fontan revision, an endocardial atrioventricular pacemaker was implanted transvenously. Treatment and outcome are discussed. This case is particularly unusual because of its 5-year follow-up results.

Case Report

In August 2001, a 32-year-old patient was referred to our institution for surgery. The patient had been born with tricuspid atresia, an atrial septal defect, and a small perimembranous ventricular septal defect. He received a Pott's shunt (side-to-side anastomosis between the descending aorta and the left pulmonary artery) at age 3 months. At 3 years of age, because of recurrent congestive heart failure due to an oversized shunt, he required pulmonary banding in order to protect the pulmonary circulation for future Fontan conversion. During childhood and adolescence, he remained in reasonably good health.

At age 23 years, the patient began to have increasing polycythemia and cyanosis. Heart catheterization confirmed the previous diagnosis and showed well-preserved hemodynamic values. The patient underwent a classic Fontan procedure and closure of the Pott's shunt. His cardiac condition improved substantially, with total resolution of the cyanosis; however, he developed atrial tachycardia with a rapid ventricular rate response. Amiodarone, atenolol, and digoxin were prescribed, which resulted in good control of his arrhythmias.

Two years later, the patient was readmitted with syncope and documented bradycardia, and implantation of an epicardial pacemaker was recommended. At that time, the treating physicians decided to place a ventricular epicardial system from a subxiphoid approach. Before the implantation, the patient's left ventricular systolic function and

dimensions were normal, and no mitral regurgitation or intracardiac shunt was detected. During the next 7 years, the patient was admitted to the hospital several times for congestive heart failure with progressive left ventricular dysfunction and mitral regurgitation, as well as ascites, peripheral edema, and abnormal hepatocellular function. He was diagnosed with paroxysmal atrial flutter and fibrillation, and he was placed on long-term anticoagulation.

When the patient presented at our hospital at age 32, he had been referred to us for revision of his Fontan operation because of syncope and congestive heart failure. During a 72-hour monitoring period, no arrhythmias were documented. The pacemaker mode was VOO at a rate of 65 beats/min due to battery end-of-life, with retrograde conduction. Echocardiography showed left ventricular global hypokinesis, dimensions of 72 mm at end diastole and 59 mm at end systole, and a calculated ejection fraction of 0.30 to 0.35. Moderate-to-severe mitral regurgitation was also documented.

The patient underwent heart catheterization and electrophysiologic evaluation, which showed 100% V-wave pacing with slow retrograde conduction, a systolic V wave of 35 mmHg, a pulmonary artery pressure of 38/28 mmHg, and no intracardiac shunting. No ventricular tachycardia was induced. The patient had a poor AV conduction reserve (AV block at rates faster than 90 beats/min) during atrial pacing. The coronary sinus was cannulated from the right atrium, and left ventricular pacing was performed using an electrophysiology catheter.

Electroanatomic mapping of the right atrium revealed viable tissue at the interatrial septum, above the os of the coronary sinus (Fig. 1). This position was marked to guide atrial lead placement.

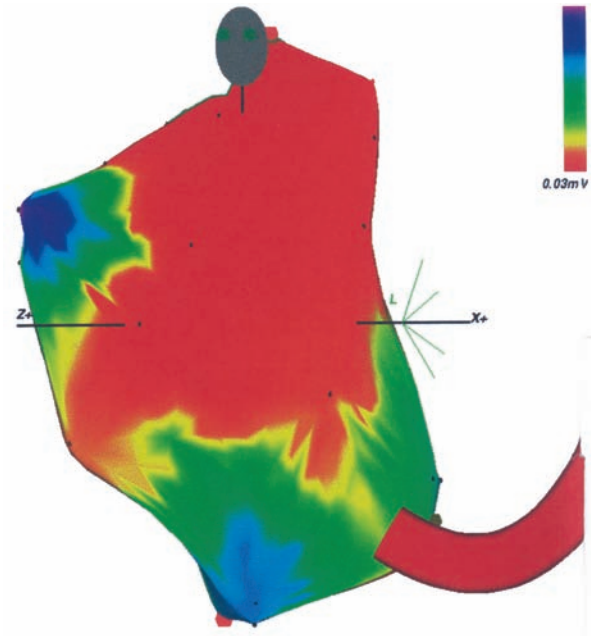
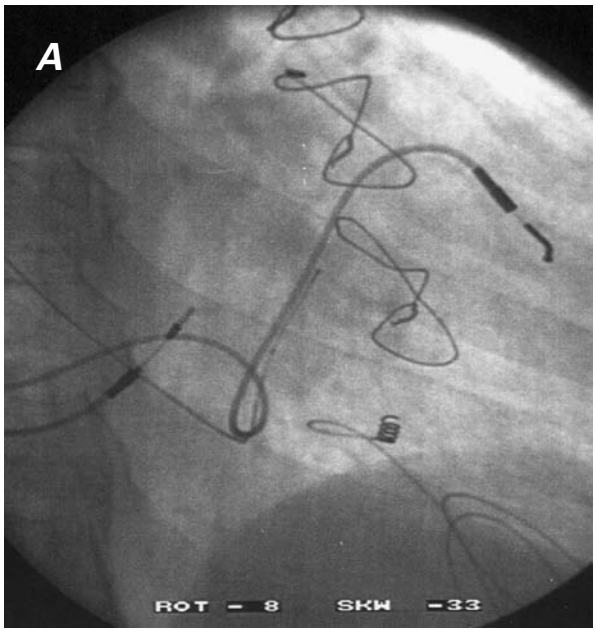


Fig. 1 *Three-dimensional electroanatomic map identifies viable atrial myocardium (greenish-blue) in the interatrial septum.*



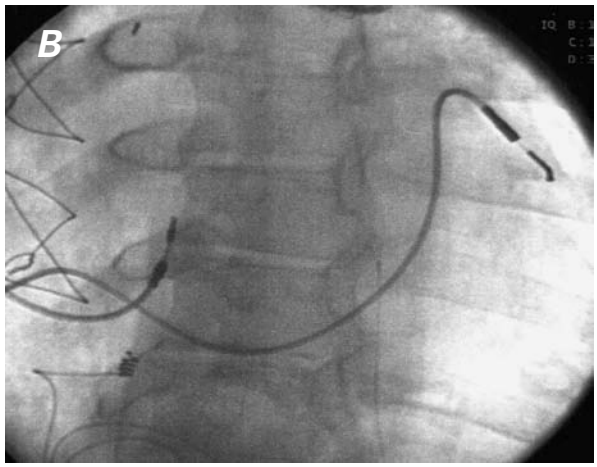


Fig. 2 *Right anterior oblique (**A**) and left anterior oblique (**B**) angiographic projections show a lead in the anterolateral vein (epicardial left ventricular pacing), and a 2nd lead in the low atrial septum above the os of the coronary sinus.*

During AV sequential pacing with an AV delay of 180 ms, the systolic V wave disappeared. The pulmonary capillary wedge pressure was 15 mmHg, the pulmonary artery pressure decreased to 27/14 mmHg, and the systolic arterial pressure increased from 95 to 120 mmHg.

After documentation of this significant acute hemodynamic improvement, from the left axillary approach, a bipolar lead (Model 2188-68, Medtronic Inc.; Minneapolis, Minn) was placed in the lateral vein (Fig. 2), resulting in excellent ventricular pacing. We placed a 2nd lead (model 4068-45, Medtronic) in the interatrial septum, immediately above the os of the coronary sinus

(Fig. 2). A Kappa DR pulse generator (Medtronic) was used for AV sequential pacing. The pulse generator in the epigastric region was removed with the patient under local anesthesia and sedation. He remained on amiodarone, atenolol, and lisinopril, but diuretics were discontinued after a few days. Warfarin was initiated on the 2nd day after pacemaker implantation.

The patient's edema and ascites resolved completely. Five years later, he remained in New York Heart Association functional class I, with no hospitalization for congestive heart failure or arrhythmias, and no thromboembolic complications (no anticoagulation was given after the first 3 months). He had a left ventricular end-diastolic dimension of 60 mm, an ejection fraction of 0.50, trivial mitral regurgitation, and a normal mitral inflow pattern. Atrial and ventricular leads showed excellent pacing and sensing thresholds.

Discussion

In cases of tricuspid atresia, the total venous return crosses a large atrial septal defect to the left side of the heart, producing severe cyanosis. In 1968, Fontan and Baudet[2] used a prosthetic conduit from the right atrial appendage to direct the systemic return to the pulmonary artery and then closed the atrial septal defect.

The reported incidence of AV block after the Fontan procedure is only 2% to 3%, but with sinus node dysfunction, atrial tachyarrhythmias (incidence, 20%–45%),[3] and the use of antiarrhythmic drugs, the need for ventricular pacing progressively increases with time and can reach 16%.[4]

Because the Fontan operation excludes the right ventricle from the venous circulation, conventional placement of endocardial ventricular pacing leads is not possible. The overall rate of epicardial lead failure at 5 years is reported to be 17%, but atrial lead failure may be as high as 40%.[5] In patients who have had multiple thoracotomies, the presence of scarring and adhesions makes implants more challenging and more likely to fail.

Atrial epicardial pacing requires a sternotomy or lateral thoracotomy, which can lead to recurrent or chronic left pleural effusion.[5,6] In patients with intact AV conduction, endocardial atrial pacing has better long-term results and fewer complications than does epicardial pacing.[7] In patients who require dual-chamber pacing, 1 hybrid approach involves subxiphoid epicardial ventricular pacing and an endocardial atrial lead that is tunneled to the epigastric area. This approach also requires general anesthesia and longer hospitalization than does endocardial pacing.

As Warnes and coworkers first reported in 1986,[8] the coronary sinus drainage remains accessible for left ventricular epicardial pacing when it has not been modified. If a total endocardial or a hybrid (endocardial/epicardial) approach is being considered, complete understanding of the relevant anatomy and physiology is extremely important. This knowledge is crucial, because some of the newer and more common modified Fontan procedures preclude later access to the right atrium or coronary sinus without the creation of a bidirectional or right-to-left shunt. Moreover, a residual right-to-left shunt would make the risk of systemic thromboembolic complications an important contraindication to these approaches.

We believe that, if possible, transesophageal echocardiography, magnetic resonance imaging, or both should be performed on all adults with corrected congenital heart disease. We usually perform a detailed hemodynamic and angiographic evaluation, as well as electroanatomic mapping of the right atrium, to identify areas of atrial tissue that are likely to have adequate sensing and capture thresholds, and to guide atrial lead placement. We document access to the coronary sinus from the right atrium, evaluate access to the right atrium from the SVC, and obtain an angiogram of the coronary sinus to document the presence of an accessible tributary for left ventricular lead placement.

Loss of AV synchrony and particularly atrial flutter are associated with severe AV valve regurgitation and left ventricular deterioration.[9] These can markedly worsen arrhythmias and inferior vena cava stasis, resulting in hepatic congestion, ascites, thrombosis, and exudative enteropathy.[10] Any of these complications may be considered an indication for cardiac transplantation[11] or for Fontan revision with total cavopulmonary connection and arrhythmia surgery.[12] Our case clearly illustrates the importance of restoring AV synchrony and chronotropic competence before substantial deterioration occurs, particularly if it can be accomplished by a minimally invasive and otherwise low-risk procedure.

A recent publication from Dodge-Khatami and colleagues[13] concluded that dual-chamber pacing with restoration of AV synchrony significantly improved single-ventricle hemodynamics and helped decompensated Fontan patients, in whom arrhythmias improved or disappeared, heart failure was controlled, and exercise tolerance increased.[13]

The Fontan operation increases the risk of thromboembolic complications, particularly systemic venous thrombosis, probably because of increased venous pressure, turbulence, the presence of prosthetic material, and potential protein C deficiency.[14,15] Long-term systemic anticoagulation has been recommended after a Fontan procedure, particularly during the 1st postoperative year, but its use remains controversial and there is no consensus with regard to type or duration of prophylactic therapy.[16,17] We believe such anticoagulation to be particularly important in the presence of multiple intracardiac pacing leads, and we start warfarin therapy after lead placement. We also believe that the increased

risk of thrombosis and warfarin therapy compares favorably with the morbidity and mortality rates of a repeat thoracotomy for pacemaker implantation, and our approach could delay the need for Fontan revision or cardiac transplantation for many years.

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Case Reports

C-Ring Mitral Annuloplasty

27-Year Follow-Up

Tomer Z. Karas, MD
George J. Reul, MD
Denton A. Cooley, MD

We report the long-term follow-up of a patient with rheumatic mitral valve disease who underwent annuloplasty with a specially developed C-ring (the Cooley C-ring) for mitral valve repair in 1977. The repaired valve remained competent and unobstructed for 27 years before requiring replacement. ***(Tex Heart Inst J 2007;34:102-4)***

During the 1970s, mitral valvuloplasty was commonly performed without an annular support device, because surgeons were concerned that placing a rigid, circular prosthesis too close to the aortic valve could lead to mitral and left ventricular dysfunction. We developed the Cooley C-ring prosthesis to avoid this problem and reported our 1st series of repairs in 1976.[1] There have been few opportunities to examine these devices after long-term use. We describe a case in which a Cooley C-ring, implanted as part of a mitral valvuloplasty in 1977, kept the mitral valve functional for 27 years before the valve required replacement.

Case Report

In March 1977, a 24-year-old man with rheumatic heart disease underwent open mitral commissurotomy and C-ring mitral annuloplasty for noncalcific mitral stenosis and mitral valve insufficiency. A #20 Cooley C-ring was sewn to the fibrous annulus around the posterior leaflet and commissural leaflets of the mitral valve, with 2-0 Ticron horizontal mattress sutures. The patient recovered well and was discharged from the hospital on postoperative day 7.

Twenty-seven years later, the patient developed progressive dyspnea on exertion. Cardiac catheterization revealed pulmonary hypertension with a systolic pulmonary artery pressure of 50 mmHg, severe tricuspid insufficiency, severe mitral insufficiency and stenosis, and an extremely large left atrium (Fig. 1).

In August 2004, the patient, now 51 years old, was returned to the operating room. The mitral valve was found to be severely calcified and stenotic (Fig. 2). The previously placed C-ring was removed (Fig. 3), and the mitral leaflets and their chordal attachments were excised because of severe subvalvular obstruction. A 27-mm pyrolite bileaflet prosthetic valve (St. Jude Medical, Inc.; St. Paul, Minn) was implanted. The left atrium was debulked to reduce the enlargement. The left atrial appendage was excluded. A DeVega-type tricuspid annuloplasty was performed to correct the tricuspid insufficiency. The hospital course was uncomplicated, and the patient was discharged from the hospital on postoperative day 5. At 1-year follow-up, the patient continued to do well.

Discussion

Early controversies surrounding the use of mitral valve repair in patients with rheumatic heart disease have been quieted by numerous reports of successful series.[2-6] The paradigm shift from replacement to repair appears to have occurred during the early 1980s.[6] A variety of repair techniques have been used, supported by several types of commercially available annuloplasty rings.

The original series of patients who underwent Cooley C-ring mitral valve annuloplasty was reported by surgeons at our institution in 1976 and was the 1st series in which a rigid C-ring was applied only to the posterior annulus.[1] All 12 patients had myxomatous degeneration of the native mitral valve, and all had complete relief of mitral regurgitation after the surgery. The C-shaped open ring was constructed from titanium wire covered with knitted double velour polyester (Dacron) (Fig. 4). The prosthesis was rigid and strong enough to maintain the desired shape for the recon-

Key words: *Heart valve prosthesis; mitral valve/surgery; mitral valve insufficiency/complications/surgery; reoperation; rheumatic heart disease/surgery*

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structed annulus. The anterior section of the annulus was left open because of concerns that rigidity adjacent to the aortic valve could cause subsequent dysfunction of the mitral valve and left ventricle. (Concern about systolic anterior motion resulting from the use of rigid rings did not arise until much later.[7]) With the open-ring design, the annulus adjacent to the mitral ring remained mobile during systole and diastole, improving left ventricular filling and ejection.

As the use of rigid and semirigid rings expanded, there was growing concern (later supported by case reports[8]) that the rigid ring caused hemolysis when direct blood flow was exposed to the ring, which protruded into the mitral inflow orifice. Subsequently, flexible C-rings were developed. Successful series of annuloplasties using bovine pericardium,[9] universally flexible polyester velour bands,[10] and even transverse sections of Dacron tube grafts[11] were reported.

Annuloplasty with some type of prosthetic support is now a part of virtually all techniques for mitral valve repair. This case shows the success and longevity of one of the 1st C-rings in a patient with rheumatic disease in an era when repair of rheumatic mitral valves was considered inadvisable. The case also shows the durability of the C-ring prosthesis; this patient retained his native mitral valve for 27 years without incident. When he eventually required valve replacement, presumably it was because the degeneration associated with the patient's rheumatic heart disease had progressed.

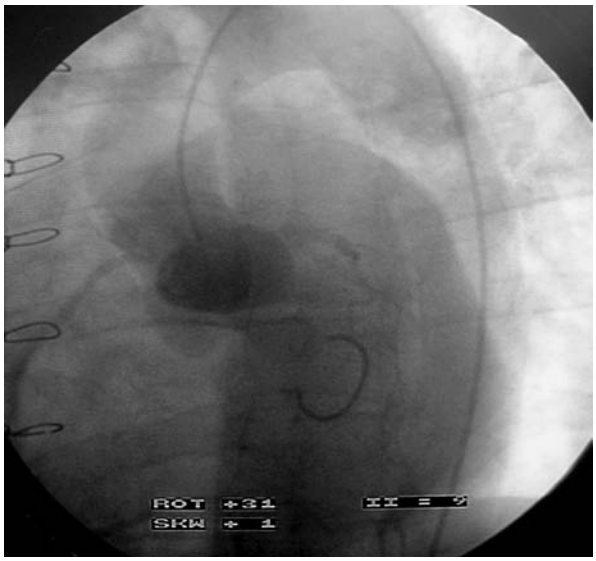

Fig. 1 *Fluoroscopic image shows the position of the mitral C-ring in situ.*

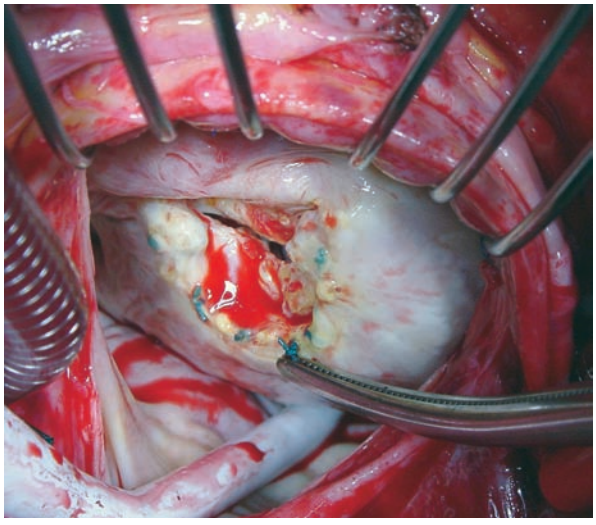

Fig. 2 *C-ring viewed through a left atriotomy at reoperation.*

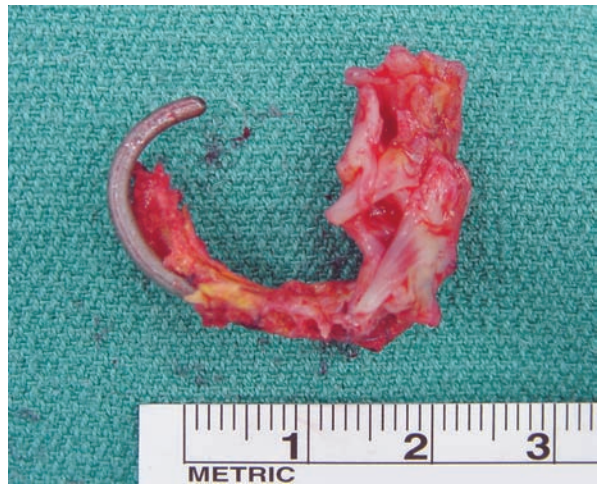

Fig. 3 *Excised C-ring with exposed titanium core. Divided posterolateral chordae tendineae from the posterior leaflet are seen on the right.*

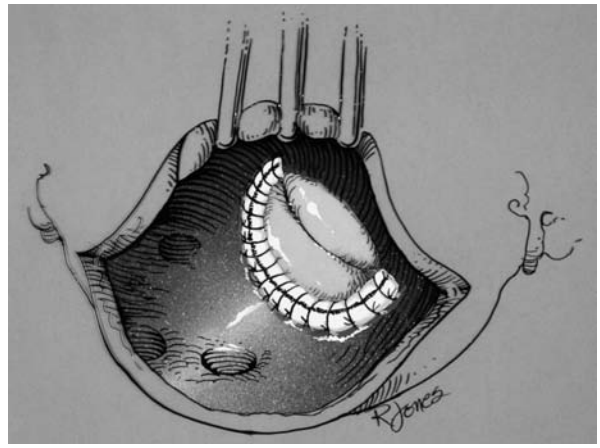

Fig. 4 *C-ring mitral prosthesis of the type used in our patient in 1977. It consisted of titanium wire covered with double velour polyester.*

Acknowledgment

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Case Reports

Color Doppler Imaging of the Ophthalmic Artery

during Antegrade Selective Cerebral Perfusion

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Postoperative brain damage is a major sequela of cardiovascular surgery. Different methods—such as transcranial Doppler imaging, carotid echography, and fluorescein angiography—can be used to monitor cerebral blood flow, but they present specific limitations.

High-resolution color Doppler imaging of the ophthalmic artery is a useful, noninvasive, and inexpensive technique for the evaluation of cerebral blood flow during cardiac surgery; signal changes can represent hypoperfusion of cerebral vessels and can thereby indicate inadequate cerebral perfusion during cardiac surgery, especially surgery of the aortic arch.
(Tex Heart Inst J 2007;34:105-7)

Postoperative brain damage is a major sequela of cardiac surgery; the incidence of severe brain injury varies from 3% to 11%.[1-3] This damage can be due to multiple factors: unrecognized carotid artery stenosis, nonpulsatile flow during cardiopulmonary bypass (CPB), circulatory arrest, deep hypothermia, or occurrence of embolism.[3,4]

Transcranial Doppler imaging (TCD) is a useful method for the evaluation of cerebral hemodynamics in cases of steno-occlusive lesions, or for the study of collateral flow or blood-flow reserve.[5-7] However, TCD does not provide a good signal when blood perfusion pressure is low; and in such an instance, it is difficult to determine whether signal attenuation is due to hypoperfusion or is simply a technical problem.[7,8]

Several authors have reported that impaired flow of the orbital vessels reflects stenosis or occlusion of the carotid artery.[6] Because the ophthalmic artery arises from the carotid artery, low flow velocity in retrobulbar vessels probably indicates reduced hemispheric flow.[4]

We report the results of our evaluation of ophthalmic artery flow during replacement of the ascending aorta and aortic arch.

Key words: *Aneurysm, dissecting; aortic aneurysm; ophthalmic artery/ultrasonography; ultrasonography, transcranial*

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Case Report

In May 2000, a 72-year-old man was admitted to our hospital for follow-up on a diagnosis of chronic aneurysm of the ascending aorta—an incidental finding upon chest radiography at another center. Computed tomographic scanning and digital subtraction angiography revealed a 55-mm-diameter dilatation of the ascending aorta and aortic arch. Upon transthoracic echocardiography, the aortic valve was seen to be competent and the left ventricle was mildly hypertrophic. At coronary angiography, no additional severe lesions were detected. General anesthesia was induced with fentanyl and midazolam and was maintained with a continuous infusion of propofol. Through a median sternotomy, an arterial cannula was placed in the femoral artery, and a venous cannula was placed in the right atrium; CPB was established with a roller pump and a membrane oxygenator. To provide antegrade selective cerebral perfusion (ASCP), 2 separate cannulas were inserted under profound hypothermic circulatory arrest (16 °C): one in the brachiocephalic artery and the other in the common carotid artery. By means of a single roller pump separate from the systemic circulation, ASCP was established at the rate of 500 to 700 mL/min.

The ascending aorta and arch were replaced with an elephant trunk conduit that was placed in the proximal descending aorta. Intraoperative ultrasonographic monitoring was started before aortic cross-clamping. The eyes were imaged by a 7.5-MHz linear array transducer connected to an Acuson 128/128 XP (SOMA Technology, Inc; Cheshire, Conn). The transducer was applied with contact jelly through the

closed upper eyelid, and the examiner's hand was rested on the orbital margin to minimize pressure on the globe (Fig. 1). By imaging the optic nerve for the orientation of the probe, we placed a sample volume (the ultrasonic beam) nasally and superior to the optic nerve (25 mm posterior to the globe).[7] When the ophthalmic arteries were visualized, they displayed a pulsatile flow, with peak systolic velocity of 18 cm/sec (Fig. 2). During ASCP, a relatively nonpulsatile spectral signal was detected with blood flow velocity above 20 cm/sec (Fig. 3). When blood flow in the ophthalmic artery became undetectable because of low perfusion pressure, we increased pump flow to 700 to 900 mL/hr, thereby obtaining a signal in the ophthalmic artery (Fig. 4). To minimize damage to the orbital tissues, we covered the patient's eyes with polyethylene patches, maintained the power output at a level below 200 ISPTA (spatial peak temporal average intensity, mW/cm^2), and performed intermittent examinations. The patient was discharged on the 18th postoperative day in good clinical condition, with no neurologic or ocular injury.

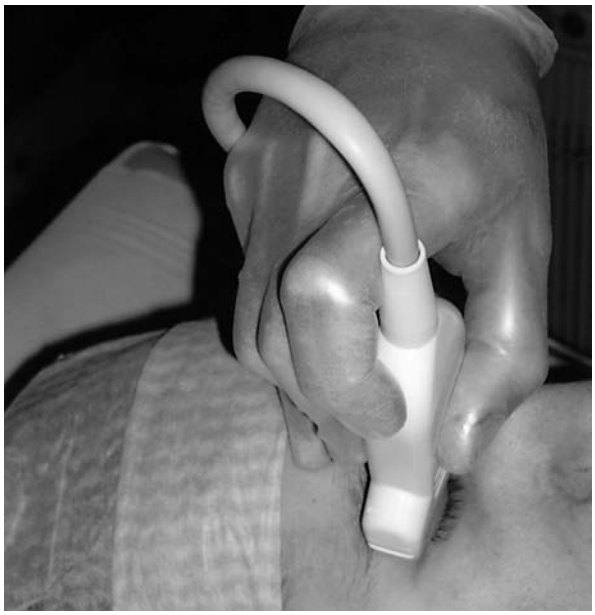

Fig. 1 *Photograph shows how the ultrasound probe is positioned on the globe through the closed upper eyelid, to detect and monitor blood flow velocity in the ophthalmic artery.*

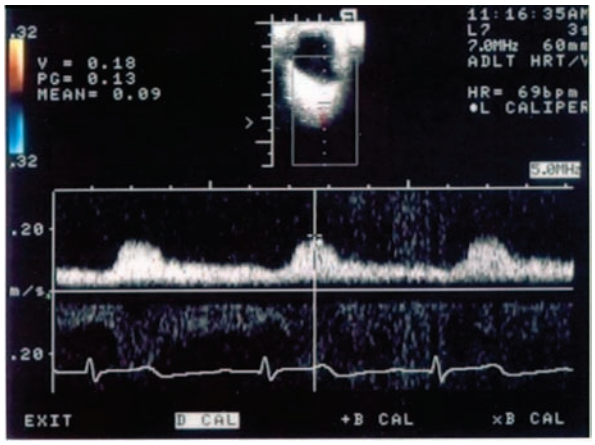

Fig. 2 *Color Doppler imaging of the ophthalmic artery, before aortic clamping, displays a pulsatile and positive waveform with peak systolic velocity of 18 cm/sec.*

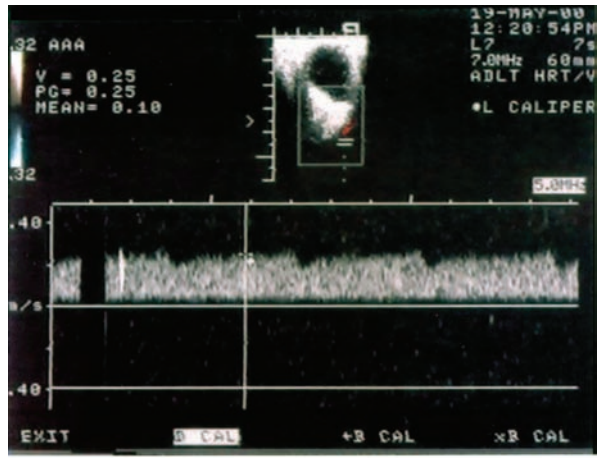

Fig. 3 *Color Doppler imaging of the ophthalmic artery during antegrade selective cerebral perfusion. A relatively nonpulsatile spectral signal was detected with blood flow velocity above 20 cm/sec.*

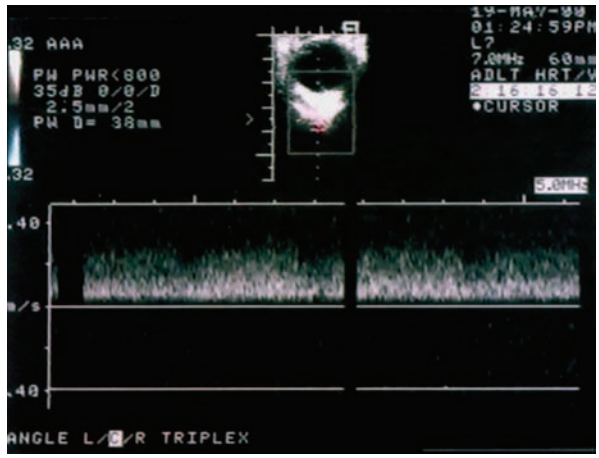

Fig. 4 *Reappearance of the signal in the ophthalmic artery after an increase of pump flow to 700–900 mL/h.*

Discussion

By means of TCD, Sakahashi and associates[9] could detect blood flow velocity in the middle cerebral artery during retrograde cerebral perfusion in 3 of the 6 patients examined. After examining blood flow in the central retinal artery and in retrobulbar vessels in 28 consecutive patients during CPB, Orihashi and colleagues[4] concluded that orbital-vessel monitoring provides the "critical closing pressure" (blood pressure–axis

intercept) of the central retinal artery and confirms the patency of the circle of Willis. During retrograde cerebral perfusion using the color Doppler technique, Voci and coworkers[8] described the pattern of blood-flow velocity in the peripheral, intrabulbar retinal vasculature and pointed out its usefulness as an indicator of cerebral blood flow. Harris and Martin[7] showed that ultrasonographic monitoring of the ophthalmic artery overcomes some of the technical limitations of TCD, and they confirmed its anatomic and physiological importance as an indicator of cerebral perfusion during cardiovascular surgery. The ophthalmic artery is easily visualized deep in the orbital cavity, in the area where it crosses the optic nerve; the spectral analysis is typical, displaying a pulsatile and positive waveform with blood flow velocity of 35 ± 11 cm/sec.[10] Reliability problems can arise when blood flow monitoring is performed in small ocular arteries or in veins, because the lower velocities found in these vessels are close to the resolution limit for detection by the ultrasonographic system (when the flow rate, for example, falls below 1–3 cm/sec in central retinal vein occlusion).[10] Ultrasonographic waves can damage the eye tissues, particularly from heat; although hypothermia probably protects the retina from the effects of prolonged imaging, the avoidance of prolonged imaging is recommended, as is the reduction of output energy.

In the present study, we monitored, by ultrasonography, blood flow in the ophthalmic artery during ASCP, in accordance with the indications proposed by Harris,[7] and we obtained important information about the adequacy of the perfusion.

Color Doppler imaging of the ophthalmic artery can be a useful method, which can be applied routinely for monitoring cerebral perfusion during aortic arch surgery and all cardiac operations, in order to detect impaired cerebral blood flow.

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Case Reports

Transfusion-Free Cardiac Reoperation in an 11-kg Jehovah's Witness Child

by Use of a Minimized Cardiopulmonary Bypass Circuit

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Herein, we describe the design of a perfusion system for a complex cardiovascular reoperation in an 11-kg Jehovah's Witness patient. The goal of safe, transfusion-free surgery was achieved chiefly by minimizing the priming volume of the cardiopulmonary bypass circuit to 200 mL while providing adequate flow and standard safety features. ***(Tex Heart Inst J 2007;34:108-11)***

Cardiac surgery involving cardiopulmonary bypass (CPB) in Jehovah's Witness patients presents a challenge to the surgical team. Particularly in pediatric cardiac surgery, the goal of safe, transfusion-free surgery is often defeated by the extreme hemodilution caused by the relatively large priming volume of the CPB system and by the potential blood loss during complex surgical procedures.

Herein, we describe the successful performance of complex cardiac reoperation in an 11-kg Jehovah's Witness patient. Safe, transfusion-free surgery was enabled by extreme minimization of the CPB system through the use of a modified small-volume neonatal circuit.

Key words: *Blood circulation; blood transfusion, autologous/contraindications; cardiac surgical procedures; cardiopulmonary bypass/instrumentation/methods; child, preschool; equipment design; hematocrit; hemoglobins/analysis; Jehovah's Witnesses; pulmonary artery; treatment outcome*

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Case Report

A 2-year-old girl, a child of Jehovah's Witness parents, was admitted to our institution in February 2006 with corrected tetralogy of Fallot and absent pulmonary valve syndrome. When the child was 7 days old and weighed 3.55 kg,[1] we had closed the ventricular septal defect, implanted a 12-mm valved Contegra conduit (Medtronic, Inc.; Minneapolis, Minn), and resected a left pulmonary artery (PA) aneurysm—all without blood transfusion. After 2 years and a tripling of body weight, the child now had a grown-out stenosis with a gradient of 60 mmHg between the right ventricle and the main PA, pulmonary valve regurgitation, and dilation of the right PA to 35 mm. We replaced the 12-mm Contegra conduit with a 16-mm conduit, and we further reduced the aneurysmal right PA.

The patient weighed 11 kg, and her height was 88 cm. Her calculated body surface area was 0.5 m^2, and her calculated blood volume was 850 mL. Her preoperative hemoglobin value (Hb) was 12.8 g/dL (hematocrit [Hct], 38.4%). Accordingly, the use of our standard CPB circuit for an infant who weighed more than 7 kg would have required a priming volume of approximately 450 mL (Table I), resulting in a maximum Hb value of 7.5 mg/dL (Hct, 22.5%) during CPB (Fig. 1). Because this was a reoperation, and because of the likelihood of increased blood loss during reoperation and of subsequent hemodilution before CPB, we believed that the safety margin for use of this CPB circuit would be too small. Therefore, we decided to modify our neonatal CPB system so that it would require a priming volume of only 200 mL, to allow for the higher flow needed for this child.

The CPB circuit was redesigned as follows. Cannulation was performed with a 12F aortic cannula, and bicaval cannulation was done with 16F and 18F metal-tipped cannulas. We then modified a Stöckert SIII mast-mounted console (Stöckert Instrumente GmbH; Munich, Germany), which we usually use for neonates and infants. We made short tubing connections from the venous reservoir outlet to the arterial pump head and to the oxygenator/heat-exchanger inlet, and from the sucker-pumps to the cardiotomy reservoir inlet. We used polyvinylchloride tubing of 3/16-inch in-

TABLE I. Characteristics of Conventional and Modified Infant/Child CPB Systems

Console	Conventional Circuit* Standard Stöckert SIII	Modified Circuit** Stöckert mast-mounted
Oxygenator	Dideco D 902 (105 mL)	Terumo Capiox RX05 (43 mL)
Arterial filter	Dideco D 736 (40 mL)	Dideco D 736 (40 mL)
Arterial tubing size (ID)	1/4-inch	3/16-inch
Venous tubing size (ID)	3/8-inch	3/16-inch
Arterial roller pump tubing (ID)	5/16-inch	1/4-inch
Suction lines (ID)	1/4-inch	3/16-inch
Venous drainage method	Gravity	Vacuum-assisted
Maximum flow rate	2 L/min (limited by arterial filter)	1.5 L/min (limited by oxygenator)
Priming volume, total	≥450 mL	≤200 mL

CPB = cardiopulmonary bypass; ID = internal diameter
* Conventional circuit, for children weighing 7 to 20 kg
** Modified neonatal circuit (with standard set-up <7 kg)

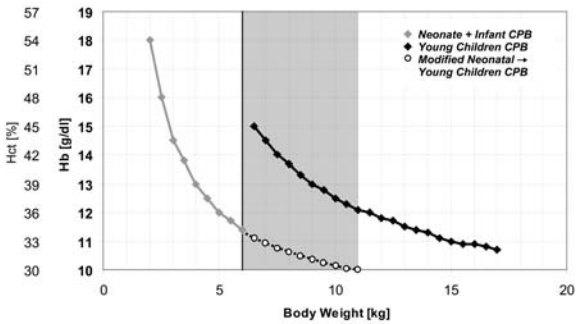

Fig. 1 *Relationship between patient weight, CPB system, and pre-CPB hemoglobin (hematocrit) levels necessary to achieve a hemoglobin value of 8.0 g/dL on CPB.*

CPB = cardiopulmonary bypass; Hb = hemoglobin; Hct = hematocrit

ternal diameter (ID) in the entire extracorporeal circuit except for the arterial pump runway, where we used 1/4-inch-ID silicone tubing. In the 1st operation on the child, we had used the Polystan Safe Micro oxygenator (Polystan A/S, a Maquet Inc. company; Vaerløse, Denmark), which requires a priming volume of 52 mL. The maximal blood flow rate of this oxygenator is 0.8 L/min, which, if used in this reoperation, would have resulted in a maximal blood flow of only 1.6 L/m^2. We therefore replaced this system by using the Capiox Baby RX05 oxygenator (Terumo Cardiovascular Systems; Ann Arbor, Mich), which requires a priming volume of 43 mL but allows a higher maximum blood flow of 1.5 L/min, resulting in a maximal blood flow of 3 L/m^2 in our patient. In addition, we implemented vacuum-assisted venous drainage with a maximum negative pressure of 40 to 50 mmHg in order to achieve a venous return of 3 L/min per m^2, and an arterial filter (Dideco D 736, Sorin Group Italia S.r.l.; Mirandola Modena, Italy) with a priming volume of 40 mL, resulting in a total priming volume of 200 mL. For this system, the calculated Hb value on CPB was calculated to be 10 g/dL (Hct, 30%).[2,3]

The patient was taken to surgery. To provide maximal protection of her coagulation system during CPB, we managed heparin and protamine dosages by use of the Hepcon HMS™ system (Medtronic), and administered aprotinin (Trasylol®, Bayer; Frankfurt, Germany) in accordance with a high-dose regimen (500,000 KIU) in the pump and a continuous infusion of 75,000 KIU/hr during perfusion.

The patient's Hb value immediately before CPB was 11.6 g/dL (Hct, 34.8%). During the 84 minutes of CPB, the highest Hb value was 11.4 g/dL (Hct, 34.2%), and the lowest was 9.4 g/dL (Hct, 28.2%). The rate of blood flow ranged from 2.6 to 3 L/m^2, and the blood lactate levels were within the normal range of less than 2 mg/dL. Venous oxygen saturation, which ranged from 67% to 85% in intermittently drawn samples, correlated well with near-infrared spectroscopic measurements (NIRO-200, Hamamatsu Photonics K.K.; Hamamatsu City, Japan) taken at the child's head. Despite the relatively small diameter of the tubing of the venous line, the negative pressure required to augment the venous return was consistent with the values reported by others.[2,3] With respect to hemolysis, the very small diameter of the arterial line was at the limit of acceptability, but arterial line pressures, measured before the line entered the oxygenator, remained between 350 and 450 mmHg (departmental standard range, 350–470 mmHg). The

intensive use of cardiotomy suction in this special reoperation was potentially a major cause of hemolysis; however, no macrohematuria was noted. The replacement of the 12-mm Contegra conduit with a 16-mm conduit and the reduction of the aneurysmatic right PA to 12 mm from the pulmonary hilus to the bifurcation were performed with the patient on normothermic, beating-heart CPB. After venous decannulation, we infused the volume of the venous line, reservoir, and oxygenator into the patient, then directly reinfused the residual volume from the arterial filter and the arterial line.

After the administration of protamine, desmopressin (0.04 μg/kg) was given to stimulate tissue-factor release and improve coagulation. Modified ultrafiltration was not performed, because priming of the filter system would have caused additional hemodilution. After the completion of CPB and the complete re-transfusion of the CPB blood, the circuit was flushed with 1,000 mL of saline solution, which was then processed with a cell saver (Autolog; Medtronic). The 135-mL product, which had a Hb value of 5.5 g/mL (Hct, 16.5%), was returned to the patient after the stimulation of diuresis.

The patient was transferred to the intensive care unit with a Hb level of 10.1 g/dL (Hct, 30.3%). The postoperative activated clotting time was 125 sec, and the postoperative 24-hr blood loss was 20 mL. The patient was weaned from mechanical ventilation on the same day. The postoperative course was uneventful, and the patient was discharged from the hospital after 10 days. Therapy with supplemental iron and recombinant erythropoietin, which had been started 4 weeks before surgery, was continued postoperatively for 4 weeks.

Discussion

Reducing the hemodilution of the CPB circuit is the key to safe cardiac surgery in pediatric Jehovah's Witness patients. Our patient's case was complicated by a low preoperative Hb value, so the dilution imposed by a larger system would have created the need for transfusion. In a selected group of patients with cyanotic malformations, a high preoperative Hb value often facilitates safe, transfusion-free cardiac surgery.[4] However, in patients with non-cyanotic malformations, the composition of the CPB circuit and the resultant priming volume becomes the central determinant for such surgery.

At our institution, we use CPB systems with a priming volume of 180 to 200 mL for neonates and small children with body weight of 2 to 6 kg. In children who weigh 7 to 20 kg, we usually apply an oxygenator with a higher capacity in combination with extracorporeal tubing of larger diameter, which increases the priming volume to approximately 450 mL. Consequently, a patient's higher preoperative weight can be associated with a higher degree of hemodilution and a subsequent reduction of intraoperative Hb values (Fig. 1). In 2003, Jonas and colleagues[5] found impaired neurocognitive development in infants whose intraoperative Hct levels had fallen below a critical value of 20% to 25% during hypothermic CPB.

These data and the Hb values expected in our patient if a conventional circuit were used prompted our decision to modify the system used for neonates. We considered our modified system safe, because the maximal blood flow rate in our patient was increased to 3 L/m^2 (1.5 L/min) by replacing the standard oxygenator and using vacuum-assisted venous return—and, in contrast with systems described by other groups, ours incorporated safety features such as an arterial filter. Despite a reduction of the priming volume to 200 mL, the calculated Hb value was 10 g/dL (Hct, 30%).[6]

As evidenced by the baseline blood lactate levels, venous oxygen saturation, and near-infrared spectroscopic data, use of this circuit maintained homeostasis in the patient during the entire course of extracorporeal circulation. Blood flow was in the range of 2.5 to 3 L/m^2, and Hb levels stayed within a safe range—between 9.5 and 11 g/dL (Hct, 28.5%–33%).

We believe that our modified CPB system and a priming volume of 200 mL allows the safe performance of normothermic CPB in patients who weigh approximately 11 kg and have a body surface area of 1 m^2 or less, corresponding to a maximum calculated blood flow of 1.5 L/min. On the basis of our earlier experience with pediatric Jehovah's Witness patients[7] and with our current patient, we conclude that optimized, low-prime CPB circuits enable safe, transfusion-free, complex cardiac surgery regardless of the patient's weight. Therefore, particular emphasis should be placed on the development of such specially designed circuits for pediatric patients of all weights.

Acknowledgment

We thank Anne Gale for her editorial assistance.

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Case Reports

Gastric Volvulus after Ventricular Assist Device Explantation and Cardiac Transplantation

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Diaphragmatic herniation has been recognized as a complication of unrepaired diaphragmatic defects after left ventricular assist device explantation and cardiac transplantation. We believe this to be the 1st report of diaphragmatic herniation that resulted in gastric volvulus in a cardiac transplant recipient. The presentation, diagnosis, and treatment of this potentially fatal condition are discussed herein.

Nine months after removal of a Thoratec HeartMate® II left ventricular assist device and orthotopic cardiac transplantation, the patient presented with intermittent upper abdominal and lower chest discomfort of 3 weeks' duration. Physical examination was notable for fullness in the upper abdomen. Plain radiographs and computed tomographic scans of the chest and abdomen without contrast were unexceptional. Two weeks later, the patient's pain began to worsen rapidly, and an upper gastrointestinal barium study revealed partial herniation of the stomach into the chest and omento-axial gastric volvulus without luminal obstruction. The patient underwent uncomplicated laparotomy for repair of the diaphragmatic defect and reduction of the herniated stomach.

This case highlights the need for increased awareness of diaphragmatic herniation as a complication of unrepaired diaphragmatic defects so that diagnosis is not delayed, and underscores the importance of primary repair of all such defects to prevent future complications. ***(Tex Heart Inst J 2007;34:112-4)***

Key words: *Cardiac transplantation; device removal; stomach volvulus; heart assist devices/adverse effects; hernia, diaphragmatic/diagnosis/etiology/surgery; postoperative complications*

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Diaphragmatic herniation has recently been recognized as a complication of unrepaired diaphragmatic defects after left ventricular assist device (LVAD) explantation and cardiac transplantation.[1-3] When LVADs are implanted in the peritoneum, the creation of these defects is necessary to channel the inlet conduit from the left ventricle and the outlet conduit to the ascending aorta. Ours is the 1st reported case in which such an unrepaired diaphragmatic defect resulted in gastric volvulus.

Case Report

In December 2005, a 50-year-old man presented at the Texas Heart Institute with a 3-week history of poor appetite and discomfort in the left lower chest and left upper abdomen. He described the discomfort as a bloating sensation in the abdomen that was intermittent, not related to eating, and not associated with nausea, vomiting, change in bowel habits, urination, cough, or fever. A year before presentation, he had undergone placement of a HeartMate® II LVAD (Thoratec Corporation; Pleasanton, Calif) due to refractory ischemic cardiomyopathy. Three months later, he underwent orthotopic cardiac transplantation with a protracted postoperative course. During mediastinal exploration on the day after transplantation, the lower lobe of the left lung was noted to be atelectatic and necrotic; therefore, it was surgically removed. A hernia through the left hemidiaphragm was resected and repaired with GoreTex dual mesh (W.L. Gore & Associates, Inc.; Flagstaff, Ariz). This mesh was removed 2 weeks later to mobilize omentum into the chest for omentopexy closure of the skin incision over the thorax. The patient also had a history of hypertension, hyperlipidemia, depression, and 50 pack-years of smoking. Notable medications included prednisone, 5 mg/day; tacrolimus, 4 mg 3 times a day; and oral trimethoprim-sulfamethoxazole, 160/800 mg, 3 times a week.

On presentation, the patient's vital signs were normal. The only notable findings on physical examination were mild abdominal tenderness and very poorly defined fullness in the left upper quadrant. Laboratory results comprised normal cell counts and serum chemistries, including liver function tests, amylase, and lipase. Radiologic studies, including plain films and noncon-trast computed tomographic scans of the chest and abdomen, revealed only increased volume loss in the left lower lung (Fig. 1). Bronchoscopy of the left lower lung showed a healthy stump of the left-lower-lobe bronchus with unremarkable bronchial biopsies and negative cultures and cytologic results from the lavage fluid. The patient was treated conservatively, and his pain worsened over the next 2 weeks. At this time, an esophagogram identified partial herniation of the stomach into the chest and more than 180° omento-axial gastric rotation without luminal obstruction (Fig. 2). The patient was diagnosed with secondary omento-axial gastric volvulus, and laparotomy was performed to reduce the herniation and to repair the defect with GoreTex mesh. He recovered well and remained free of symptoms postoperatively.

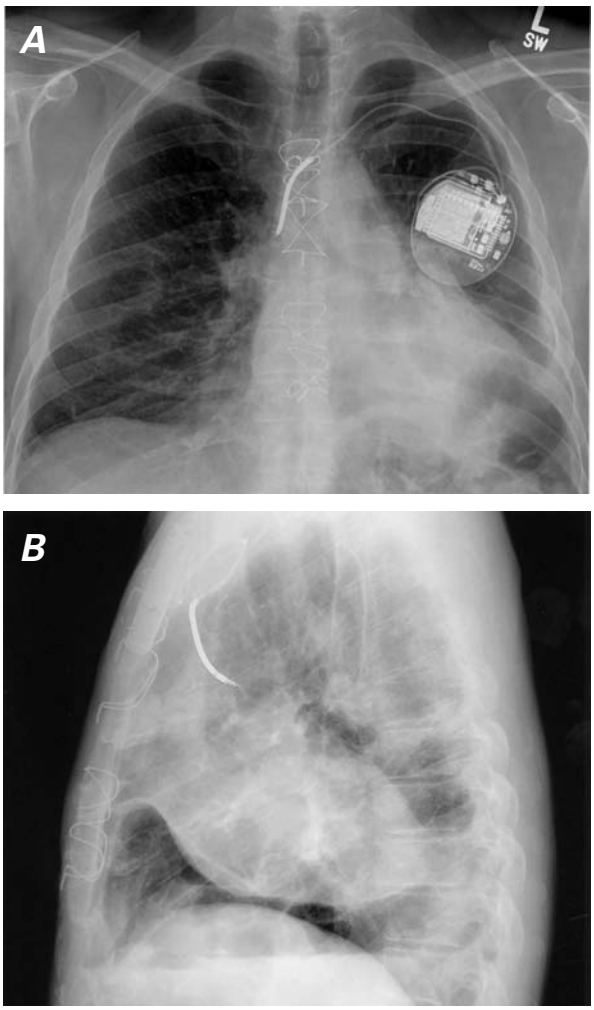

Fig. 1 *Chest radiograph on presentation demonstrates volume loss at the base of the left lung:* ***A****) anteroposterior view and* ***B****) lateral view.*

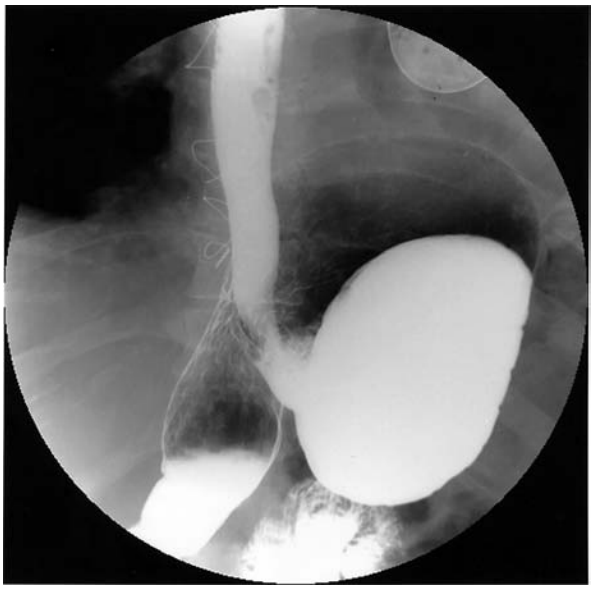

Fig. 2 *Upper gastrointestinal esophagogram reveals omento-axial volvulus of the stomach. Contrast medium was seen draining into the duodenum, which ruled out gastric luminal obstruction due to the volvulus.*

Discussion

Gastric volvulus implies torsion of the stomach to 180° or more along 1 of its 2 axes: the vertical axis connecting the esophagus to the greater curvature (omento-axial), or the horizontal axis between the greater and lesser curvatures (mesentero-enteric).[4] Gastric volvulus can be primary or secondary. Primary gastric volvulus (one third of cases) occurs below the diaphragm in the absence of any diaphragmatic or intra-abdominal abnormality and results from slack gastric stabilizing ligaments. Secondary gastric volvulus (the other two thirds of cases) develops above the diaphragm, usually in the setting of a pre-existing diaphragmatic defect. Six percent of cases of gastric volvulus occur in pediatric patients.[4] Most, however, occur in the 5th decade of life due to predisposing conditions, such as a paraesophageal hiatal hernia, trauma to the diaphragm, or diaphragmatic paralysis.[4] The prevalence of diaphragmatic herniation, recently recognized as a complication after LVAD explantation, has been reported to be as high as 15.9% for unrepaired defects versus 4.3% for defects that are repaired at the time of explantation.[1-3] To the best of our knowledge, gastric volvulus in such a patient has not previously been reported.

The clinical symptoms of gastric volvulus vary from acute to chronic, depending on the degree of obstruction of the lumen and on the presence or absence of

strangulation of the blood supply to the gastric wall.[5] Patients who have acute symptoms tend to present with sudden, severe pain localized to the upper abdomen or lower chest. On physical examination, the upper abdomen is often distended and is occasionally tympanic. Untreated, these patients can die of such complications as ulceration, perforation, hemorrhage, pancreatic necrosis, and omental avulsion.[5,6] Of note, rare cases of cardiac tamponade due to a severely distended intra-thoracic stomach have also been reported.[7,8] The chronic symptoms usually include vague upper abdominal or respiratory complaints, which are difficult to directly ascribe to underlying gastric volvulus.

Gastric volvulus is generally diagnosed by means of radiology. Initial suspicion arises from the identification of abnormal gas shadows in the upper abdomen or lower chest on plain radiography. Computed tomographic scanning with oral contrast medium or esophagogram can then be used to establish the diagnosis and define the gastric anatomy.[9] Laboratory test results, including elevated amylase or alkaline phosphatase, are not sufficiently specific to be useful in the diagnosis.

Early recognition and prompt surgical correction are the mainstays of therapy for gastric volvulus.[10] Mortality rates as high as 30% to 50% have been reported when complications of unoperated gastric volvulus develop. Surgical options include open or laparoscopic reduction of the hernia.[11] If the stomach is found to be necrotic intraoperatively, partial or full resection also becomes necessary. Otherwise, reduction of the volvulus should be followed either by fixation of the stomach within the abdomen or by correction of the predisposing factors mentioned above. A midline abdominal laparotomy is generally the preferred approach.[1] In patients who have acute obstruction, decompression of the stomach via nasogastric suction can help relieve symptoms before surgery.

This case highlights the need for increased awareness of the diaphragmatic complications that can occur after LVAD explantation so that appropriate tests can be ordered to make an early diagnosis. It also emphasizes the need for primary repair of all diaphragmatic defects remaining after LVAD explantation in order to prevent this life-threatening complication.

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Case Reports

Bivalirudin Anticoagulation for Cardiopulmonary Bypass

An Unusual Case

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The standard agent used for systemic anticoagulation during cardiopulmonary bypass is heparin. Alternative methods of anticoagulation are required for patients with heparin hypersensitivity. We present the case of a patient with heparin hypersensitivity who was anticoagulated with bivalirudin during cardiopulmonary bypass for coronary artery bypass grafting. This presented unusual challenges surrounding the monitoring of anticoagulation and the method of myocardial protection. ***(Tex Heart Inst J 2007;34:115-8)***

Key words: *Anticoagulants/administration & dosage; bivalirudin; cardiopulmonary bypass/adverse effects; heparin/adverse effects; hirudins/analogs & derivatives; kidney/drug effects; thrombocytopenia/chemically induced*

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Heparin remains the gold standard for anticoagulation during cardiopulmonary bypass (CPB) because of its rapid onset of action, reliable effect, low cost, and reversibility. However, hypersensitivity to heparin poses substantial challenges for cardiac surgical interventions. An alternative approach for hypersensitive patients who need coronary artery bypass grafting (CABG) is off-pump coronary artery bypass (OPCAB); nevertheless, a reserve strategy needs to be in place, in case hemodynamic instability during OPCAB should necessitate the institution of CPB.

Alternatives to heparin are ancrod,[1,2] danaproid,[3] lepirudin,[4] argatroban,[5] platelet IIb/IIIa inhibitor (trifiban),[6] and prostacyclin.[7] All of these drugs have been used, but they have limitations. A recent alternative, bivalirudin, is a direct thrombin inhibitor with rapid anticoagulative effect; excreted renally, bivalirudin has a short half-life. To date, bivalirudin is licensed for use only in percutaneous coronary interventions (PCI),[8] and only a few published reports exist for its use in CPB in patients with heparin-induced thrombocytopenia.[7,9,10] We describe a case of a patient with heparin hypersensitivity who required CABG using bivalirudin anticoagulation.

Case Report

A 42-year-old man who was a smoker with a 6-month history of exertional angina presented with acute inferolateral myocardial infarction associated with ventricular fibrillatory arrest. The patient was successfully resuscitated, and his thrombi were lysed with streptokinase. Coronary catheterization showed an occluded posterior descending branch of the right coronary artery, an occluded left anterior descending artery, and severely narrowed intermediate and diagonal arteries. There was moderate left ventricular systolic dysfunction on transthoracic echocardiography. The patient's medical history included asthma, hypertension, and morbid obesity (100 kg; body mass index, 39.1 kg/m^2). During hospitalization, he developed an abdominal eczematous rash at the site of low-molecular-weight heparin (LMWH) injection. Dermatological consultation and subsequent skin biopsies confirmed hypersensitivity to LMWH. The rash did not improve when unfractionated heparin was tried. Discontinuation of heparin resulted in a gradual resolution of the skin reaction. Preoperatively, the patient had normal liver and renal function and normal hemoglobin and platelet values. He remained as an inpatient until surgery.

Surgery was undertaken 9 weeks after the myocardial infarction. In view of the patient's coronary anatomy and ventricular function, we elected to undertake CABG with CPB, rather than use the OPCAB approach. Anticoagulation monitoring was undertaken by measuring activated clotting time (ACT), activated partial thromboplastin time ratio (aPTTR), and international normalized ratio (INR), and by

obtaining a thromboelastogram (TEG). The baseline measurements during anesthetic induction were: ACT, 122 (Fig. 1); aPTTR, 1.46 (Fig. 2); INR, 1.1 (Fig. 2); and a normal TEG (Figs. 3 and 4). All of the above measurements were taken before, during, and after the bivalirudin infusion, at specific time intervals.

Bivalirudin (Angiomax®, The Medicines Company; Parsippany, NJ) was started as a bolus dose and infusion

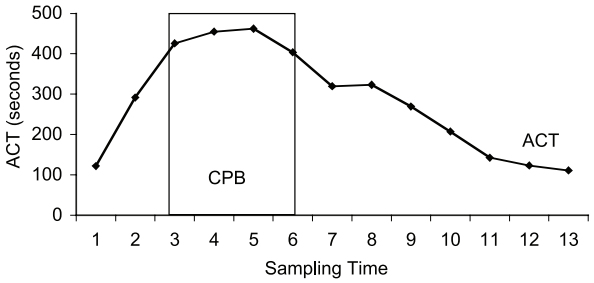

Fig. 1 *Activated clotting time.*

ACT = activated clotting time; CPB = cardiopulmonary bypass

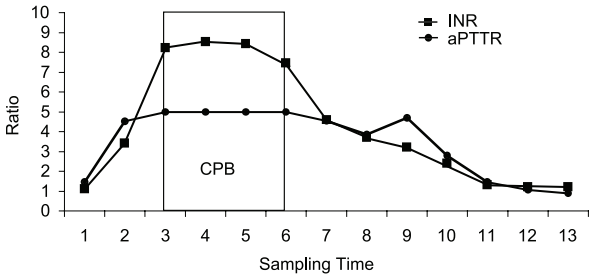

Fig. 2 *aPTTR and INR over time.*

aPTTR = activated partial thromboplastin time ratio; CPB = cardiopulmonary bypass; INR = international normalized ratio

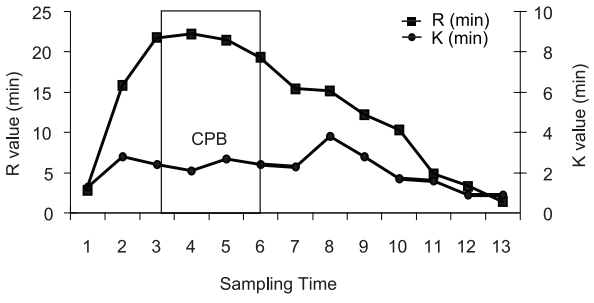

Fig. 3 *Thromboelastogram R and K values over time.*

CPB = cardiopulmonary bypass; K = clot formation time, as measured by the thromboelastogram; R = reaction time (clotting time) as measured by the thromboelastogram

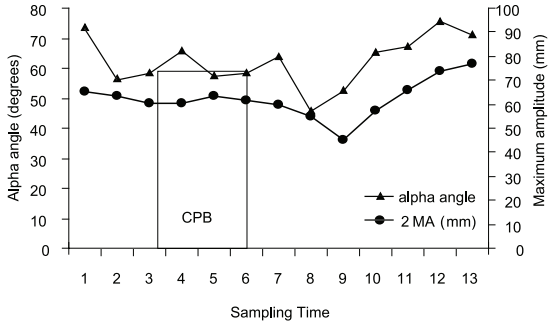

Fig. 4 *Thromboelastogram: alpha angle and sampling time.*

Alpha angle = measure of rate of clot formation by thromboelastogram; CPB = cardiopulmonary bypass; MA = maximum amplitude as measured by thromboelastogram

while we prepared for CPB. Published data suggested that a bolus of 1 mg/kg would result in an ACT of approximately 350 sec. Our ACT target for initiation of CPB was derived from previous reports[10] and was ACT >400 sec and <500 sec, to avoid either clot formation in the CPB circuit or excessive anticoagulation. Initially, 100 mg (1 mg/kg) of bivalirudin bolus and an infusion of 2.5 mg/kg per hr was given. This resulted in an ACT of 291, an aPTTR of 4.52, and an INR of 3.4. A repeat bolus of 50 mg (0.5 mg/kg) and an increase in the infusion rate to 5 mg/kg per hr resulted in a rise in the ACT to 322; in the aPTTR, to 4.98; and in the INR, to 4.2. A further bolus of 100 mg (1 mg/kg) was given, and the infusion was continued at 5 mg/kg per hr. Repeat measurements were: ACT, 362; aPTTR, >5; and INR, 5.4. A final bolus of 100 mg (1 mg/kg) with the same rate of infusion (5 mg/kg per hr) increased the ACT to 426 and the INR to 8.52, and left the aPTTR at >5. We initiated CPB and continued the bivalirudin infusion at 5 mg/kg per hr. The ACT during the 61 min on CPB ranged between 404 and 462 sec.

Myocardial protection was undertaken using the cross-clamp fibrillation technique, in order to avoid a protracted period of cross-clamping and intravascular stasis. Four bypass grafts were performed (left internal mammary artery to the left anterior descending artery, and vein grafts to the diagonal, intermediate, and posterior descending arteries). The CPB time was 61 min. The patient was then weaned from CPB using low-dose dopamine support. In the post-CPB period, bivalirudin was reversed spontaneously by renal excretion. The ACT values declined from 404 to 270 one hr after termination of the infusion and, 2 hr afterwards, to 207. At the same points in time, the aPTTR declined from >5 to 4.7 and 2.78, and the INR fell from 7.46 to 3.2 and 2.4. During this period, the patient was transfused with 1 unit of platelets for persistent mediastinal oozing. Satisfactory hemostasis was achieved,

and the operation was completed 2 hr after the end of CPB. During the early postoperative phase, there was a progressive normalization of the anticoagulation values (Figs. 1–4), and no substantial mediastinal bleeding was observed. The patient was discharged 7 days postoperatively with no morbidity.

Discussion

Delayed-type hypersensitivity reactions to subcutaneously injected unfractionated heparin or LMWH are relatively common. Particularly, extensive cross-reactivity between different heparins and heparinoids often occurs. It presents as eczema-like, infiltrated plaques at injection sites. The pathogenesis of heparin hypersensitivity is not fully understood. Heparin may act as a hapten by binding to dermal or subcutaneous structural proteins. Although intravenous administration of heparin may be tolerated, susceptible patients are at risk of developing a systemic reaction. It is therefore preferable to use alternative methods of anticoagulation when CPB is required.

Bivalirudin is a relatively new alternative anticoagulant. It is a semi-synthetic, specific, and reversible direct thrombin inhibitor.[8] The active substance is a synthetic, 20-amino-acid peptide. Bivalirudin directly inhibits thrombin by specifically binding both to the catalytic site and to the anion-binding exosite of circulating and clot-bound thrombin. Bivalirudin does not bind to plasma proteins (other than thrombin) or to red blood cells. In vitro studies have found bivalirudin to inhibit both soluble (free) and clot-bound thrombin, which is not neutralized by products of the platelet release reaction. Bivalirudin prolongs the activated partial thromboplastin time, thrombin time, and prothrombin time of normal human plasma in a concentration-dependent manner.

Bivalirudin is cleared from plasma by a combination of renal mechanisms and proteolytic cleavage, with a half-life of approximately 25 min in patients with normal renal function. The disposition of bivalirudin was studied in PCI patients with mild, moderate, and severe renal impairment.[7,11] Drug elimination was related to the glomerular filtration rate. Total body clearance was similar for patients with normal renal function and with mild renal impairment (60–89 mL/min). Clearance was reduced by approximately 20% in patients with moderate and severe renal impairment and by approximately 80% in dialysis-dependent patients.[7,11] Bivalirudin should therefore be used with caution in the presence of renal dysfunction in order to avoid protracted postsurgical bleeding.

In our patient, 3 intravenous boli of bivalirudin and an infusion rate of 5 mg/kg per hr were required to achieve an ACT of above 400 sec. Although the recommended infusion rate is 2.5 mg/kg per hr for PCI, the dose requirement is patient-dependent and needs to be tailored to the anticoagulative response. We elected to monitor the anticoagulant status using both laboratory-based (aPTTR and INR) and operating-room-based (ACT and TEG) tests. All measured values showed similar responses to changes in bivalirudin administration. The TEG was used because it is a useful adjunct to monitor whole blood clotting and fibrinolysis and because it can provide rapid bedside information on the coagulation status (Figs. 3 and 4). The "R" value is the clotting or "reaction" time, and it indicates factor deficiency or thrombocytopenia; the "K," or clot-formation time, depends upon fibrinogen and platelets. The alpha angle (measure of rate of clot formation by TEG) is abnormal in the presence of clotting-factor deficiencies, platelet dysfunction, thrombocytopenia, and hypofibrinogenemia; the maximum amplitude of the TEG is affected by platelet function and number and by fibrinogen.[12] The case that we report here shows that TEG can be used in conjunction with ACT to monitor anticoagulation with bivalirudin in a predictable manner.

The main clinical drawback of bivalirudin is that it has no known antidote. Excessive bleeding is the main risk from this drug, although it may be hemodialyzed out of the circulation in patients with renal failure. In addition, because of the relatively short half-life of bivalirudin, we elected to avoid a protracted period of coronary stasis, by using a cross-clamp fibrillation technique for myocardial preservation, as opposed to the intermittent administration of cold-blood cardioplegic solution. Alternative strategies include continuous retrograde administration and frequent intermittent antegrade administration of cardioplegic solution, although occluded vessels rely initially on a collateral supply.

Moreover, clot formation in the CPB circuit shortly after discontinuation of CPB has been described.[10] Therefore, after discontinuation of CPB and decannulation, we reconnected the circuit and continued circulating fluid through the pump-oxygenator, with ongoing infusion of bivalirudin into this circuit. This ensured the availability of the CPB circuit in case the patient became hemodynamically unstable.

Finally, the interaction of aprotinin and bivalirudin is unknown. Bivalirudin is a thrombin inhibitor, which is a serine protease, and aprotinin is a nonspecific serine protease inhibitor.[13] In our patient, we elected not to use aprotinin, although it would usually be part of our CPB protocol.

Conclusion

Our case shows that bivalirudin can be used safely for CPB, and its anticoagulant effect monitored, with the aid of currently available laboratory- and operating-room-based tests of anticoagulation.

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Key to Sampling Times

Baseline, after induction of anesthesia

After bolus of 1 mg/kg and infusion of 2.5 mg/kg per hr of bivalirudin

On cardiopulmonary bypass (CPB), with bivalirudin infused at 5.0 mg/kg per hr

20 min after initiation of CPB

40 min after initiation of CPB

60 min after initiation of CPB

20 min after termination of CPB

40 min after termination of CPB

60 min after termination of CPB

2 hr after termination of CPB

6 hr after termination of CPB

16 hr after termination of CPB

24 hr after termination of CPB

Case Reports

Intimal Sarcoma of the Pulmonary Artery

with Retrograde Extension into the Pulmonic Valve and Right Ventricle

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Aylin Orgen Calli, MD
Ali Gurbuz, MD

We describe the case of a 42-year-old man who presented with dyspnea on exertion and a history of anticoagulation therapy for what was thought to be pulmonary arterial thromboembolism. He underwent surgery for obstruction of the right ventricular outflow tract. This is a very rare case of an intimal sarcoma of the pulmonary artery, which we confirmed by pathologic studies. ***(Tex Heart Inst J 2007;34:119-21)***

Primary intimal sarcoma of the pulmonary artery (PA) is a very rare tumor, and it is highly lethal. Retrograde extension of the sarcoma to the pulmonic valve and the right ventricle is reported to be an extremely rare condition frequently mistaken for pulmonary thromboembolism.[1] We report a case—initially diagnosed as PA thromboembolism—of an intimal sarcoma of the PA with retrograde extension to the pulmonic valve and the right ventricle.

Case Report

In July 2005, a 42-year-old man with exertional dyspnea and chest pain was referred to our clinic after having been diagnosed with PA thromboembolism. He had taken an anticoagulant agent for this presumed condition for 3 months. Except for a systolic ejection murmur in the pulmonary area, the results of the patient's physical examination were normal.

Results of the laboratory tests and chest radiography revealed no abnormalities. Electrocardiography showed sinus rhythm. Transthoracic echocardiography showed a mobile thrombus-like mass (60 × 20 mm) in the PA. The mass protruded into the right ventricular outflow tract. The patient's PA pressure was 50 mmHg. The peak and mean gradients across the pulmonic valve were 71 and 42 mmHg, respectively. The right ventricular diameter was 59 mm, and the right atrial diameter was 64 mm. There was a moderate degree of tricuspid insufficiency. The ejection fraction was 0.70. On the basis of these findings, the patient was scheduled for surgery.

The patient was placed under general anesthesia. After median sternotomy and aortic arterial and bicaval venous cannulation, a vent was placed into the right superior pulmonary vein. Cardiopulmonary bypass was instituted. Then the aorta was clamped, and isothermal, hyperkalemic blood cardioplegic solution was infused into the antegrade cardioplegic cannula. Cardiac arrest was maintained by retrograde infusion of cardioplegic solution.

A longitudinal pulmonary arteriotomy was performed. In the lumen of the PA was a huge round mass (Fig. 1A) that extended distally to the main PA branches; most of it was adhered to the vascular wall. The mass, which almost completely occluded the artery, was also firmly adhered to the pulmonic valve. A longitudinal right ventriculotomy was extended to the infundibulum. A polypoid mass (Fig. 1B), seen protruding from the PA into the ventricular cavity, was resected. Because of the adherent nature of the mass, part of the PA wall and the pulmonic valve were also resected. The right ventriculotomy was closed primarily; the pulmonary arteriotomy was closed with a polytetrafluoroethylene patch. Cardiopulmonary bypass was discontinued, with the patient receiving minimal inotropic support.

After the mass was excised, the patient's condition improved. He experienced no complications and was discharged from the hospital on the 6th day. Postoperative transthoracic echocardiography at discharge showed a peak transpulmonary gradient

Key words: *Antineoplastic combined chemotherapy protocols; diagnosis, differential; epirubicin; ifosfamide; prognosis; pulmonary artery/pathology; pulmonary embolism/diagnosis; sarcoma/complications/diagnosis/drug therapy/pathology/surgery; vascular neoplasms/diagnosis/drug therapy/pathology/surgery*

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of 11 mmHg, with a mild degree of tricuspid insufficiency.

The pathology evaluation was done by means of a Nikon Eclipse E600W light microscope (Nikon Corporation Co., Ltd.; Kanagawa, Japan). The biopsy material contained markedly atypical spindle and oval cells with varying degrees of atypia and nuclear polymorphism. The mitotic activity was extremely high (Fig. 2A). Pleomorphic tumor cells surrounded the endothelium, in particular (Fig. 2B). Smooth-muscle actin, myoglobin, and factor VIII were immunohistochemically positive, whereas striated-muscle actin, CD31, and CD34 were negative. Accordingly, a diagnosis of primary intimal sarcoma was made. The patient was referred to the medical oncology clinic for further evaluation; he underwent 4 cycles of chemotherapy with ifosfamide and epirubicin in combination. One month, 6 months, and 16 months after his surgery, screening by magnetic resonance imaging, computed tomography, and echocardiography revealed no metastasis or recurrence of the malignancy.

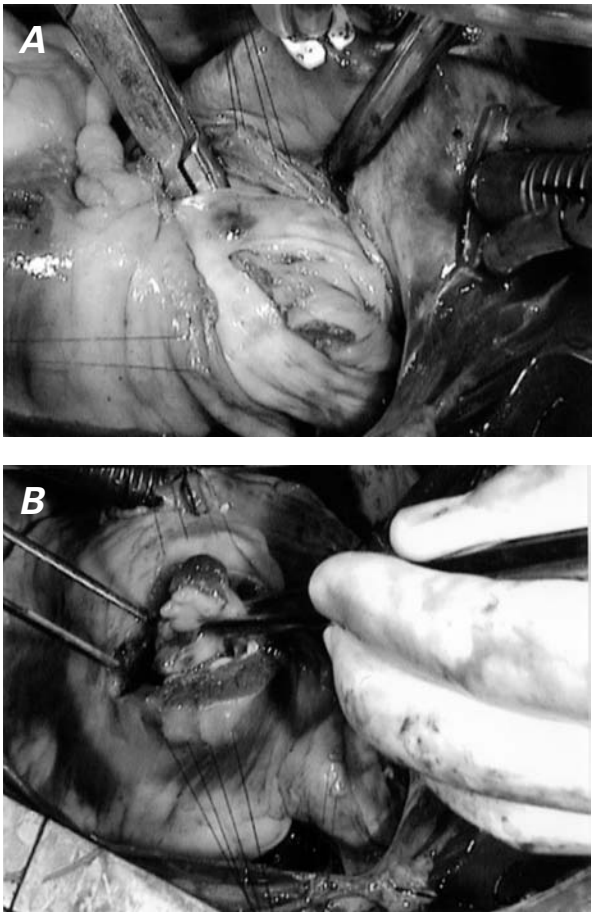

Fig. 1 ***A****) The large tumor took the shape of the main pulmonary artery and extended to its branches, adhering to the vascular wall and the pulmonic valve.* ***B****) The polypoid mass—protruding from the pulmonary artery into the ventricular cavity—is seen through the right ventriculotomy.*

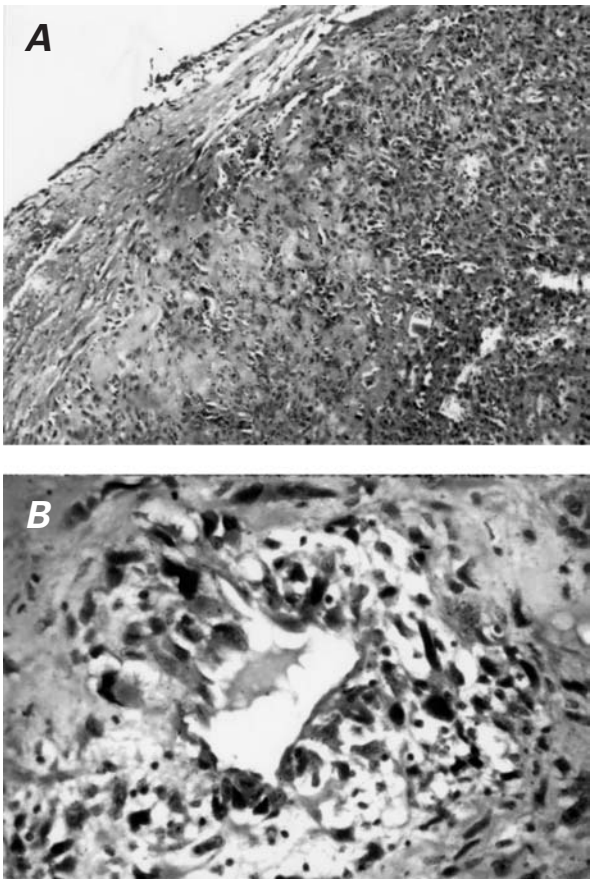

Fig. 2 ***A****) The tumor originated in the intimal layer of the pulmonary artery (H & E, orig. ×10).* ***B****) The endothelially lined vascular cleft, surrounded by pleomorphic cells (H & E, orig. ×40).*

Discussion

Intimal sarcomas are malignant mesenchymal tumors that arise in large arteries. The defining features of these tumors are intraluminal growth with obstruction of the lumen and seeding of emboli. The incidence of pulmonary intimal sarcoma is almost twice that of aortic origin. The mean age of diagnosis is 48 years for patients with pulmonary intimal sarcoma and 62 years for those with aortic intimal sarcoma.[2]

Intimal sarcoma of the aorta is a rare condition that is usually diagnosed postoperatively or at autopsy. The median survival time is only a few months.[3-6] Primary intimal sarcomas of the aorta are aggressive tumors that can metastasize to bones and visceral organs, including the liver, kidneys, adrenal glands, and lungs.[5]

Few reports describe intimal sarcoma of the PA. Primary intimal sarcoma of the PA is also rare.[2,6-8] Most commonly diagnosed at surgery or autopsy,[1] this sarcoma can metastasize to the brain, pancreas, adrenal glands, and lungs.[7] The prognosis after the onset of symptoms is unfavorable; life expectancy is usually 12 to 18 months.[1,2]

Intimal sarcoma of the PA is often mistaken for pulmonary thromboembolism, as it was in our patient.[2,9] This mistaken diagnosis can lead to inappropriate therapy, such as anticoagulation or thrombolysis. Surgical resection of the tumor offers the best chance of prolonged survival.[2,10] After performing surgery on a 63-year-old woman, Uchida and colleagues[10] detected the persistence of an intraluminal mass, and they successfully treated the patient with combination ifosfamide and epirubicin chemotherapy.

Herein, we have reported a very rare case of PA intimal sarcoma that was misdiagnosed as PA thromboembolism. If a mass has invaded the vascular structures or neighboring tissues, or if malignancy is suspected, the mass should be extensively resected. Such resection might prolong the patient's life. In addition, it is important that the patient be evaluated postoperatively for metastasis.

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Case Reports

Left Atrial Myxosarcoma with Previously Detected Intestinal Metastasis

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Primary cardiac myxosarcoma is a rare disease; it is exceedingly rare for symptoms of systemic metastasis to precede diagnosis of the primary cardiac tumor. We describe the case of a previously healthy 60-year-old man with left atrial myxosarcoma, who had first presented with jejunal intussusception due to intestinal polyposis. Three months after resection of the jejunum, the patient experienced cerebral infarction and pulmonary edema. Further physical evaluation, which included echocardiography for the 1st time, revealed a mass in the left atrium that protruded through the mitral valve into the left ventricle.

At emergency cardiac surgery, we found that the tumor involved multiple sites of the left atrium, the pulmonary veins, and the mitral anterior leaflet. Two months after surgery, the patient died of massive cerebral hemorrhage. Necropsy disclosed multiple recurrences of the cardiac myxosarcoma and widespread metastatic lesions. The intestinal polyps that had been resected originally were diagnosed, on retrospective histopathologic examination, as metastases of the myxosarcoma. In this unusual case, the metastatic lesions were the 1st clinical manifestations of a malignant cardiac tumor. ***(Tex Heart Inst J 2007;34: 122-5)***

Key words: *Heart neoplasms/diagnosis/surgery; intestinal neoplasms; intestinal polyps; intussusception/diagnosis/etiology/surgery; metastasis; myxosarcoma/surgery; neoplasm metastasis*

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Primary cardiac tumors are rare, with a frequency that ranges from 0.002% to 0.33%.[1] Approximately 75% of all cardiac neoplasms are benign histologically; of these, myxomas are the most common.[2] Despite advances in imaging methods, it is difficult to make a definitive diagnosis of cardiac neoplasms, whether they are benign or malignant. Usually, only surgical specimens can yield a differential diagnosis of cardiac tumors. In addition, due to histologic similarities, a myxosarcoma may be misdiagnosed as myxoma.[3,4] Patients with any cardiac tumor, benign or malignant, usually have cardiac manifestations at the time of diagnosis, including heart failure, arrhythmia, embolism, and precordial pain, depending on the location of the tumor within the heart. Few patients have metastatic disease at the time of cardiac tumor diagnosis. We report the case of a patient whose manifestations of metastatic disease preceded those of left atrial myxosarcoma.

Case Report

A 60-year-old man with no relevant medical history presented at our hospital because of frequent vomiting. Physical examination revealed abdominal distention with moderate tenderness and a palpable mass cranial to the navel. Abdominal radiography with the patient in the upright position revealed an obstruction of the small bowel; with the patient in the supine position, a defect indicating the absence of gas in the dilated small bowel was seen (Fig. 1A). Computed tomographic scanning of the abdomen showed a classic bull's-eye sign, which suggested intussusception of the small bowel (Fig. 1B). At urgent laparotomy, we found a jejunal retrograde intussusception at a site 60 cm below the ligament of Treitz; we suspected that this condition might be caused by a small tumor (Fig. 2A). A 100-cm segment of jejunum that included many polyps was resected, followed by primary end-to-end anastomosis. The polyps had a uniform, smooth, round surface contour. On microscopy, they showed tortuous, cystic, and inflamed glands interspersed in a predominantly myxomatous stroma (Fig. 2B). Because the polyps were multiple, the pathologic diagnosis was juvenile polyposis. The postoperative course was uneventful, and the patient was discharged from the hospital 17 days after the laparotomy. Cardiac examination was not performed during this hospital stay.

Approximately 3 months after discharge, the patient presented with dysarthria. Brain magnetic resonance imaging revealed fresh cerebral infarction of the frontal cortex. The dysarthria improved gradually, and the patient was discharged from the hospital 9 days after admission. Three days later, however, the patient was readmitted because of worsening dyspnea and orthopnea. On physical examination, auscultation revealed coarse crackles over the bilateral chest wall. Pulse oxymetry showed an oxygen saturation of 91% on room air. Electrocardiography showed the patient to be in sinus rhythm. Chest radiography revealed cardiomegaly with a cardiothoracic ratio of 0.57, pulmonary congestion, and pleural effusion. Echocardiography revealed a 4 × 3-cm mass within the left atrium, which was protruding through the mitral valve (Fig. 3). Emergency surgery was performed to resolve the congestive heart failure that was caused by the mitral valve obstruction.

At surgery, with the patient under moderate hypothermic cardiopulmonary bypass (CPB), the aorta was cross-clamped, and the left atrium, the right atrium, and the atrial septum were incised to expose the tumor. We found multiple tumors that involved the atrial septum, the posterior wall of the left atrium, the anterior leaflet of the mitral valve, and the upper right pulmonary vein. The largest tumor, which obstructed the mitral valve, protruded from the atrial septum on a short pedicle. After 4 tumors (Fig. 4A) were excised, along with the tissue margins, we replaced the mitral valve with a 25-mm mechanical valve (St. Jude Medical, Inc.; St. Paul, Minn) because of mitral valve incompetence. In addition, we reconstructed the right and left free atrial walls and the atrial septum with an equine pericardial patch (XAG-400, Edwards Lifesciences; Irvine, Calif). The patient was weaned from CPB smoothly and was discharged from the hospital after an uneventful postoperative course. Predischarge magnetic resonance imaging showed no evident tumors in the left atrium.

The resected tumors weighed 51.7 g, 2.9 g, 1.3 g, and 0.2 g (Fig. 4A). Histopathologically, the tumors had a diffuse myxoid background with a focal cellular area showing pleomorphism and high mitotic activity (Fig. 4B).

Approximately 2 months after cardiac surgery, the patient was readmitted with dizziness, headache, and dysarthria. A computed tomographic scan of the head revealed cerebral hemorrhage in the lateral cortex. Warfarin (2.5 mg per day) had been given after valve replacement, and the international normalized ratio (INR) value of prothrombin time was 1.81 at this readmission. Three days after his return to the hospital, the patient developed a severe headache and suddenly lost consciousness. He went into a coma and died 3 days later.

Postmortem examination revealed multiple recurrences of the tumor within the left atrium and no thrombus around the mechanical mitral valve (Fig. 5A). Macroscopic and microscopic examination disclosed metastatic lesions in the stomach (Fig. 5B), small intestine, colon, kidneys, spleen, and mesentery of the small bowel. Histopathologic findings of myxosarcoma in all of these lesions were similar to the findings in the cardiac tumors. Retrospectively, we found that the pathologic features of the polyps that had caused the jejunal retrograde intussusception coincided with the features of the cardiac tumors and the other metastatic lesions.

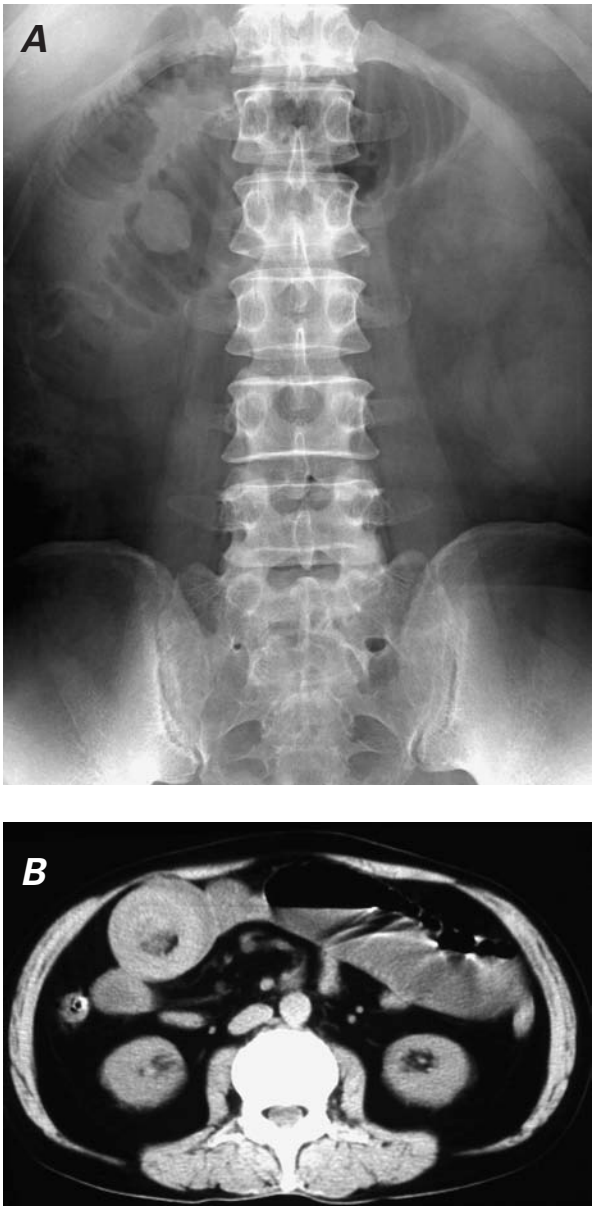
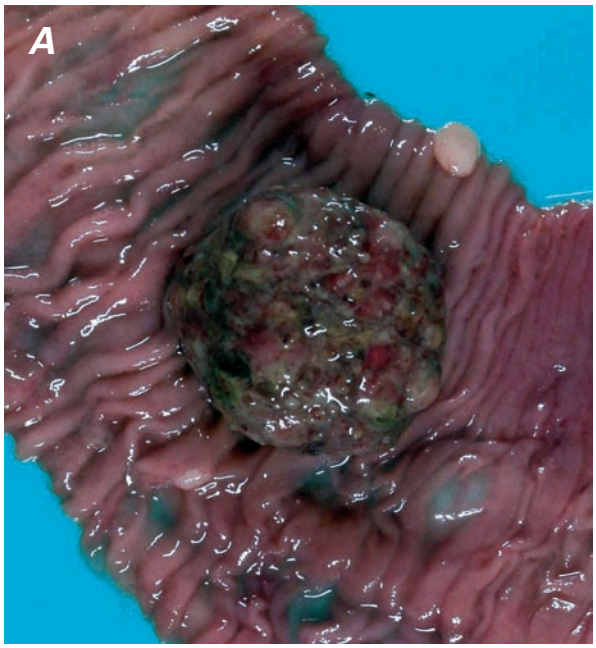


Fig. 1 ***A****) Abdominal radiograph of the patient in the upright position on admission to the hospital with frequent vomiting.* ***B****) Abdominal computed tomographic scan, used in the diagnosis of intussusception of the small bowel, shows a thick-walled loop of bowel with infolding bowel, indicated by a bull's-eye sign.*



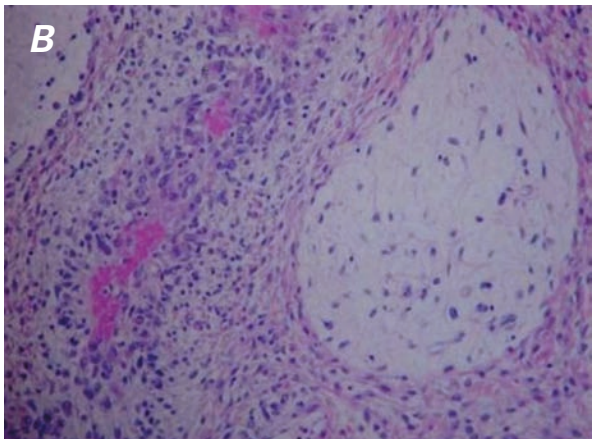


Fig. 2 *Jejunal polyp that caused retrograde intussusception:* ***A****) a resected specimen, and* ***B****) a histopathologic specimen (H & E, orig. ×200).*

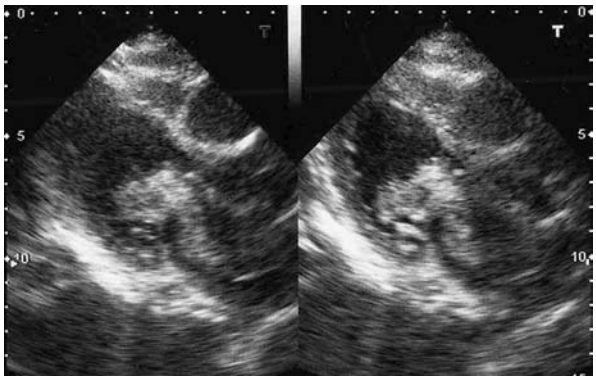
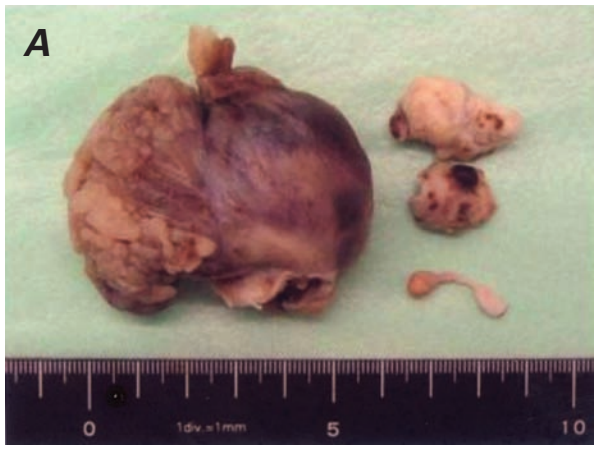


Fig. 3 *Diagnostic echocardiography shows the left atrial tumor and mitral valve obstruction.*



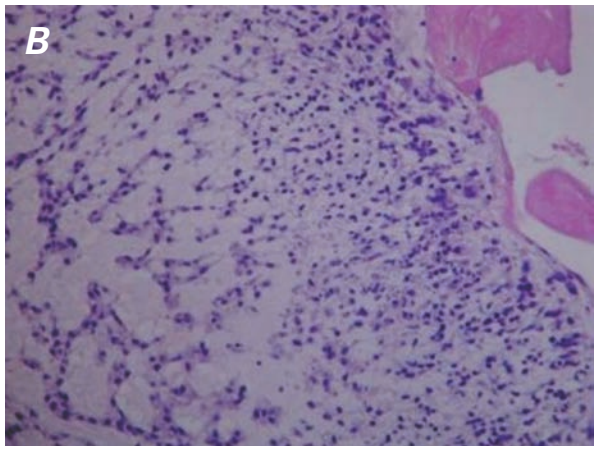


Fig. 4 ***A****) Photograph of the excised tumors.* ***B****) Histopathologic specimen of the left atrial tumor (H & E, orig. ×200).*

Discussion

Myxosarcomas are rare, constituting less than 5% of cardiac sarcomas,[2,5] and are usually found in the left atrium with myxoid margins. Therefore, myxosarcomas can be confused with the much more common, benign cardiac myxomas. The histologic criterion in identifying myxosarcomas is the absence of the typical cords, rings, and capillary structures formed by myxoma cells. However, the degree of cellularity of myxosarcomas varies, and some myxomas also can be quite cellular.[1,2]

It is difficult to fully characterize cardiac tumors noninvasively. Therefore, surgery is important in the definitive diagnosis of such tumors—in addition to the palliation of symptoms—even though it is not effective for complete eradication of malignant tumors. Another factor contributing to the difficulty of preoperative differential diagnosis is that few patients have metastatic disease at the time of diagnosis of a primary cardiac tumor. Alternatively, as in our patient, the cardiac origin of the tumor may not be recognized when the atypical metastatic disease is found.

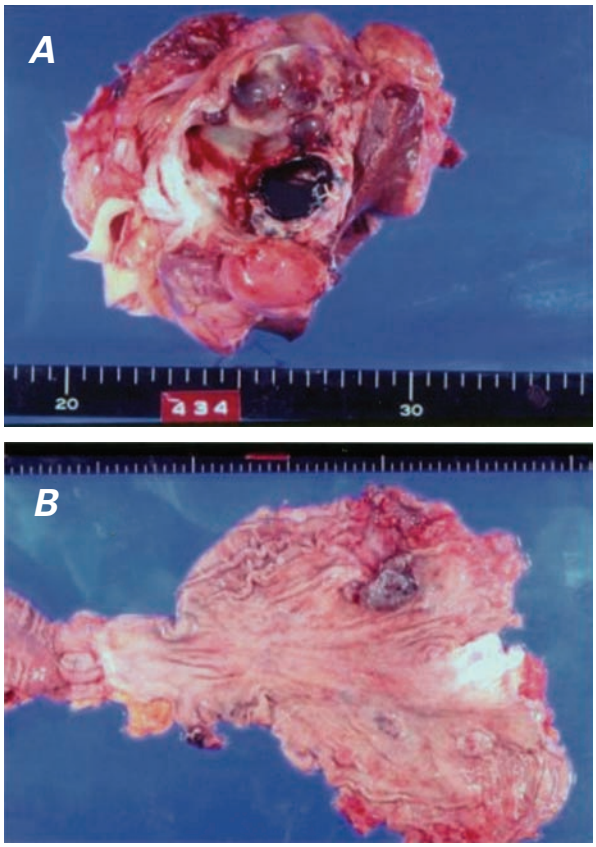


Fig. 5 *Photograph at necropsy reveals* ***A****) the recurrence of the left atrial tumors and* ***B****) a metastatic lesion of the stomach.*

Although the frequency of metastasis of cardiac tumors is low, the most frequent metastatic sites of malignant cardiac tumors are the lungs, thoracic lymph nodes, mediastinum, and vertebral column.[5] Our patient's case is rare, in that the metastasis was intestinal and presented as intussusception due to polyps, and it was treated before the cardiac tumors were diagnosed. It is also rare for multiple metastatic lesions to have spread to the abdominal organs, stomach, small intestine, colon, kidneys, spleen, and mesentery of the intestine, which was the case by the time our patient died.

The intussusception in our patient was unusual in 3 respects: it occurred in an adult, it was jejunojejunal, and it was retrograde. Intussusception most commonly occurs in children, without identifiable causes, and is rare in adults. However, in a study by Begos and colleagues,[6] more than 90% of adult patients with intussusception had an organic lesion or tumor, as did our patient. Moreover, most intussusceptions in adults involve the colon and are of the antegrade type.[7] Retrograde jejunojejunal intussusception in an adult is extremely rare.

Metastatic tumors can induce intussusception of the small bowel in an adult. However, at the 1st presentation of our patient, we did not perform systemic examinations—such as echocardiography—for other tumors, which delayed diagnosis of the cardiac tumor. We conclude that it is quite important to search for systemic lesions when any tumor is first recognized.

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Images in Cardiovascular Medicine

Left Atrial Hemangioma Presenting as Cardiac Tamponade

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A 43-year-old man presented at the emergency department with weakness and dyspnea. He was hypotensive and hypothermic. Physical examination revealed prominent jugular venous distention, muffled heart sounds, and a palpable pulsus paradoxus. Transthoracic echocardiography confirmed the presence of a concentric pericardial effusion that was causing tamponade (Fig. 1). Emergency pericardiocentesis resulted in the drainage of 500 cc of bloody effusion. Hemodynamic stability ensued.

Echocardiography after the procedure showed resolution of the pericardial effusion and revealed a 4-cm left atrial mass. Computed tomography (CT) showed a heterogeneously contrast-enhanced soft-tissue density in the right atrium (Fig. 2). Subsequent cardiac magnetic resonance imaging (MRI) showed a right atrial mass arising from the atrial septum and exerting pressure on the left atrium (Fig. 3).

After median sternotomy, a large, firm mass was found in the left atrium. The mass involved the atrial septum, distorted the dome of the left atrium superiorly and anteriorly, and extended between the aorta and the right atrium (Fig. 4). Analysis of frozen sections from a transseptal biopsy provided no immediate diagnosis. When final results of pathologic studies revealed a cavernous hemangioma, the patient underwent resection of the mass, the dome of the left atrium, and almost the entire atrial septum. The dome and the septum were reconstructed with bovine pericardium. The patient was discharged from the hospital on postoperative day 3. A postoperative echocardiogram was normal.

Comment

Hemangiomas are benign endothelial tumors found throughout the body; they most commonly involve the skin. The natural history of cardiac hemangiomas is characterized by slow growth, with eventual compression of the surrounding structures. Although patients may be asymptomatic, the tumors can cause conduction abnormalities and hemodynamic instability. Cardiac hemangiomas usually arise from the anterior wall of the right ventricle and the lateral wall of the left ventricle (although they have been described within each chamber of the heart), and they can involve the tricuspid and mitral valves.[1,2] Echocardiography is the imaging method typi-

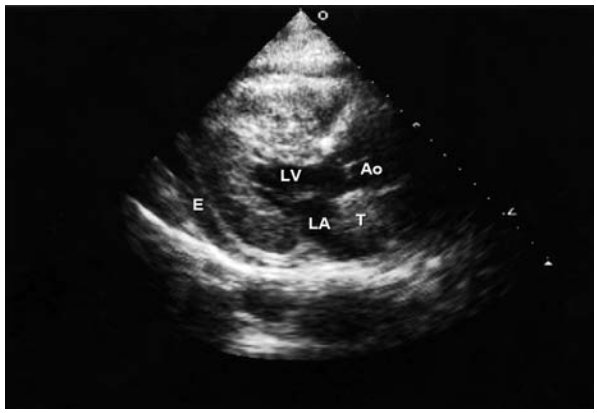

Fig. 1 *Transthoracic echocardiography (parasternal long-axis view) shows a mass in the left atrium.*

Ao = aorta; E = pericardial effusion; LA = left atrium; LV = left ventricle; T = tumor

cally used to identify a cardiac mass initially; however, Kemp and colleagues[3] consider CT and MRI superior to echocardiography for further characterizing cardiac hemangiomas. Typical CT imaging of a cardiac hemangioma reveals intense contrast enhancement due to the vascularity of the tumor. Findings on MRI include isointensity on T_1-weighted images and hyperintensity on T_2-weighted images.

Surgical excision of a cardiac hemangioma is the accepted standard of care; however, spontaneous regression or recurrence has been reported.[4] Patients typically do well postoperatively, but their risk of developing hemangiomas elsewhere in the body is not known. In 1 case, after excision of a left atrial hemangioma, the patient developed an intracardiac angiosarcoma.[5] In light of these findings, we recommend periodic examinations and echocardiograms for patients who have undergone cardiac hemangioma resection.

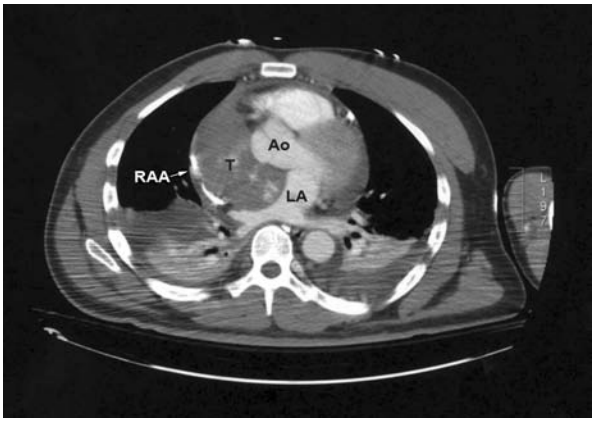

Fig. 2 *Contrast-enhanced axial computed tomographic scan shows a soft-tissue mass (8.6 × 4 × 7 cm) that extends rightward from the left atrium and compresses the right atrium.*

Ao = aorta; LA = left atrium; RAA = right atrial appendage; T = tumor

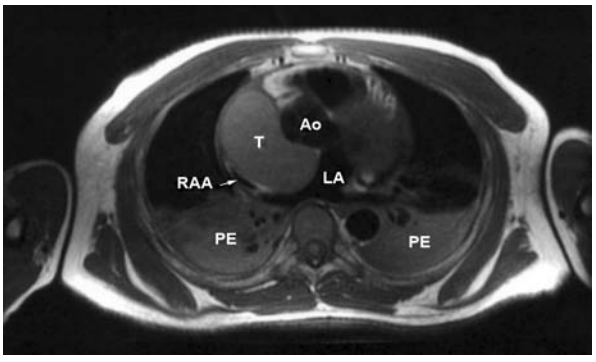

Fig. 3 *Axial image through the heart, using double inversion recovery (T_1-weighted) magnetic resonance imaging, shows a large soft-tissue mass, appearing to be in the right atrium and exerting mass effect on the left atrium without evidence of invasion. Bilateral pleural effusions are also visible. The mass is homogeneously isointense on T_1-weighted imaging and hyperintense on T_2-weighted imaging.*

Ao = aorta; LA = left atrium; PE = pleural effusions; RAA = right atrial appendage; T = tumor

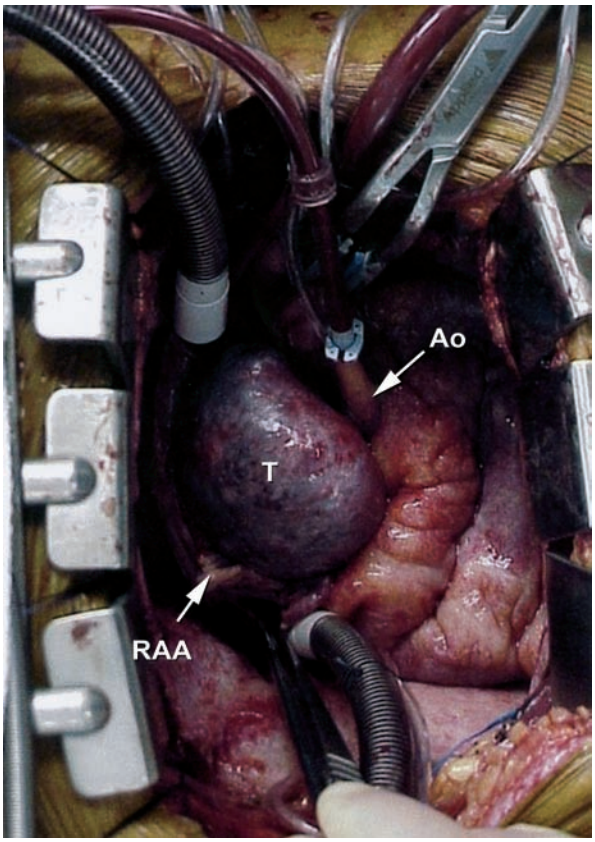

Fig. 4 *Intraoperative photograph reveals a large left atrial mass that displaces the normal right atrium laterally.*

Ao = aorta; RAA = right atrial appendage; T = tumor

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Images in Cardiovascular Medicine

Large Left Ventricular Capillary Hemangioma

with Cavernous Areas

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A 34-year-old man presented with palpitations, headaches, and a history of supraventricular arrhythmias. Transesophageal and transthoracic echocardiography and magnetic resonance imaging (Fig. 1) showed a large non-pedunculated mass in the inferoposterior and lateral walls of the left ventricle. Coronary angiography and left ventriculography showed normal coronary vessels and a large filling defect in the aforementioned walls of the left ventricle. The mass was supplied primarily by the circumflex coronary artery and partially by the right coronary artery (Fig. 2).

Under bicaval, normothermic cardiopulmonary bypass and crystalloid cardioplegic arrest, the patient underwent complete removal of a solid transmural tumor (4 × 6 × 4 cm). The tumor originated in the endocardium between the anterior and posterior papillary muscles of the mitral valve, and it extended through the myocardium to the epicardium. The marginal branches of the circumflex coronary artery were ligated during the excision. The cardiac defect, enormous for an otherwise normal ventricle, was closed primarily in 2 layers with Teflon felt pledgets, as in aneurysmal repair. The microscopic diagnosis was mural capillary hemangioma of the heart, with cavernous areas, and without evidence of malignancy (Figs. 3 and 4).

The patient's postoperative course was uneventful, with no compromise in ventricular or valvular function despite the tumor's proximity to the papillary muscles of the mitral valve. He was discharged from the hospital on the 6th postoperative day. Over the last 8 years, the patient has undergone serial follow-up echocardiography; the results have shown mitral sufficiency, satisfactory ventricular function, and no recurrence of the tumor.

Comment

Hemangiomas of the heart comprise 5% to 10% of benign cardiac tumors in surgical series[1]; fewer than 100 surgically discovered cases have been reported in the world literature. Histologically, hemangiomas are classified as cavernous, capillary, and arteriovenous.[1] They are localized in the atria, the ventricles, the ventricular septum, the pericardium, and very rarely the mitral valve. They can reach a large size, and, in 75% of cases, they are mural. Although most hemangiomas are asymptomatic, they can present with arrhythmias, conduction disturbances, pericardial effusion, coronary insufficiency, outflow tract obstruction, or congestive heart failure. Sudden cardiac death, consequent to conduction disturbances or rupture and

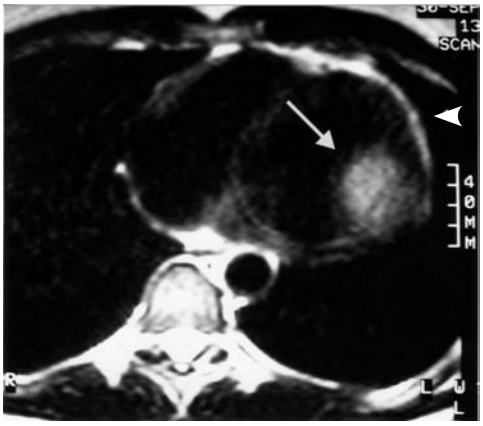

Fig. 1 *Left ventricular magnetic resonance image of a capillary hemangioma, with cavernous areas. The axial T_2-weighted image at the ventricular level shows a high-signal mass projecting within the left ventricle (large arrow) and the transmural location of the mass (arrowhead).*

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tamponade, has been reported.[1,2] Echocardiography is a sensitive diagnostic method[3,4] that can be supplemented by coronary angiography, ventriculography, and magnetic resonance imaging.[5-7] The differential diagnosis is

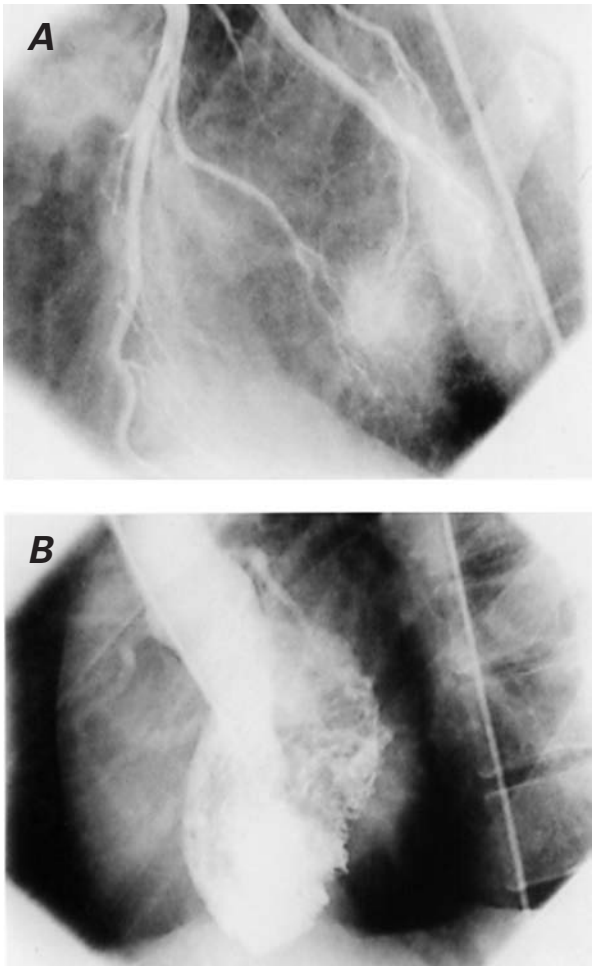

Fig. 2 ***A****) Coronary angiography shows that the mass is supplied by the circumflex coronary artery.* ***B****) Left ventriculography shows the large filling defect from the mural, non-pedunculated mass in the inferoposterior and lateral walls of the left ventricle.*

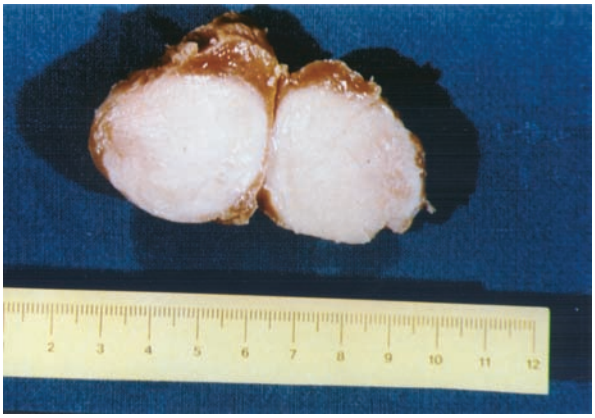

Fig. 3 *Macroscopic view of the tumor (dimensions, 4 × 6 × 4 cm).*

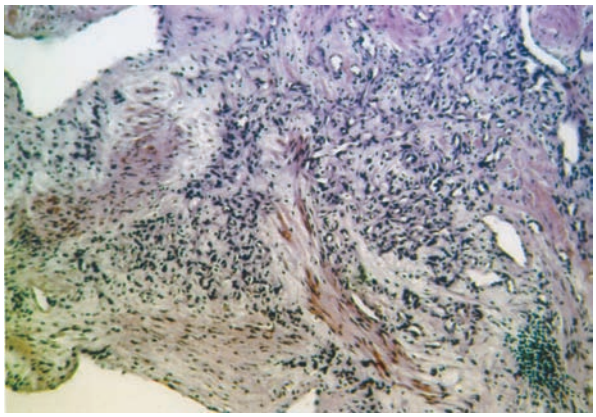

Fig. 4 *Photomicrograph of a representative area of the tumor. Numerous and relatively uniform capillary-sized vessels are arranged in groups. A mild inflammatory reaction is also present.*

myxoma or hemangiosarcoma. When diagnosed, hemangiomas should be removed because of the possibility of rupture[8,9] and tamponade.[10] In most cases, as with our patient, excision is considered curative.

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Images in Cardiovascular Medicine

Inferolateral Left Ventricular Aneurysm

Preventing Mitral Regurgitation

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An 80-year-old asymptomatic man who had experienced an inferior myocardial infarction 2 years earlier was admitted for preoperative cardiovascular evaluation in preparation for noncardiac surgery. His blood pressure was 140/80 mmHg; his heart rate was 80 beats/min. His electrocardiogram indicated sinus rhythm, abnormal Q waves, and T-wave inversion in leads aVF, II, and III. Chest radiography showed cardiomegaly. Transthoracic echocardiography revealed left ventricular (LV) enlargement, a large (4.8 × 4.6 cm) inferolateral LV wall aneurysm (Fig. 1), and normal left atrial size. It also showed that the posterior mitral leaflet was tethered by its papillary muscle (Fig. 2). Transesophageal echocardiography (TEE) showed a large LV aneurysm that compressed the mitral annulus (Fig. 3); it also confirmed the papillary tethering (Fig. 4). Color-flow Doppler TEE showed minimal mitral regurgitation (MR). The neck of the aneurysm was wide, suggesting a true aneurysm.

The patient was given an angiotensin-converting enzyme inhibitor, a β-blocker, aspirin, and spironolactone. Because the patient was asymptomatic and elderly, surgical treatment of the aneurysm was not considered.

Comment

True aneurysm of the LV is the most common mechanical sequela of acute myocardial infarction; it occurs in approximately 15% of all such infarctions (range, 3%–38%). Only 9% of all infarct-related aneurysms involve the inferior wall, and they are rarely extensive.[1,2] Post-infarction LV aneurysm is a serious disorder that can lead to congestive heart failure, lethal ventricular arrhythmia, and premature death. Application of Laplace's law indicates that LV wall tension increases as diameter, intracavitary pressure, and thinning of the LV wall increase. A large, thin-walled aneurysm is worsened by high wall tension, poor coronary perfusion, and further dilation. The ultimate stage of LV aneurysm is enlargement—not only of the aneurysm, but of the entire LV. As a result, most such patients develop heart failure.[3] Our patient had LV dilatation and LV failure.

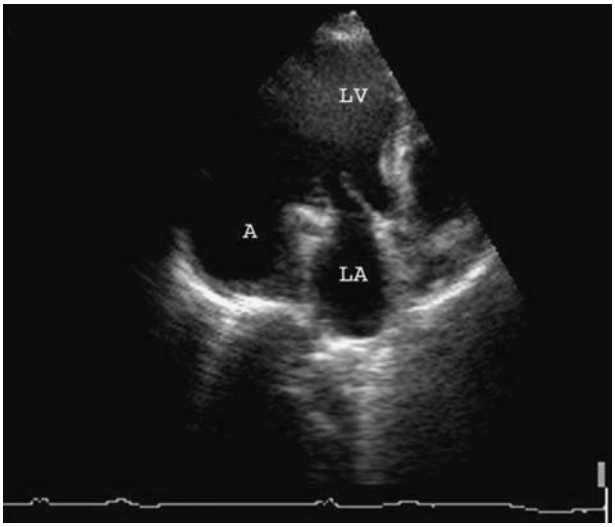

Fig. 1 *Transthoracic echocardiography shows the inferolateral aneurysm.*

A = aneurysm; LA = left atrium; LV = left ventricle

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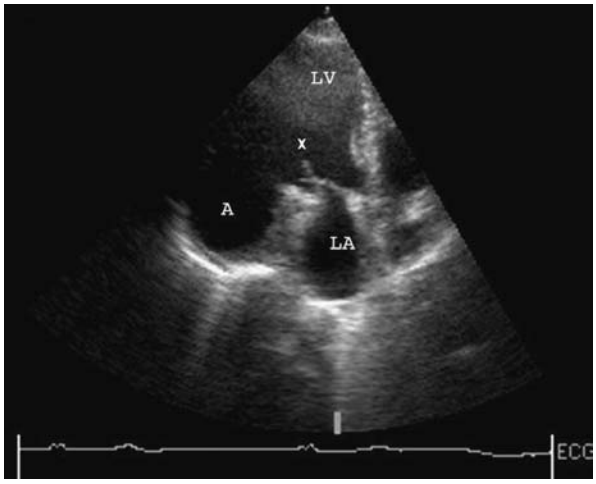

Fig. 2 *Transthoracic echocardiography shows that the posterior mitral leaflet is tethered by its papillary muscle.*

A = aneurysm; LA = left atrium; LV = left ventricle; X = posterior mitral leaflet

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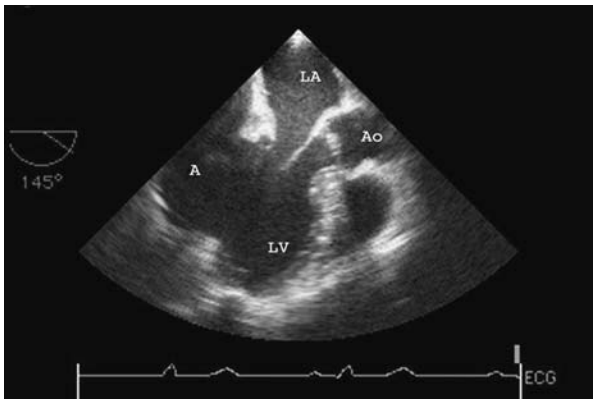

Fig. 3 *Transesophageal echocardiography shows the inferolateral aneurysm.*

A = aneurysm; Ao = ascending aorta; LA = left atrium; LV = left ventricle

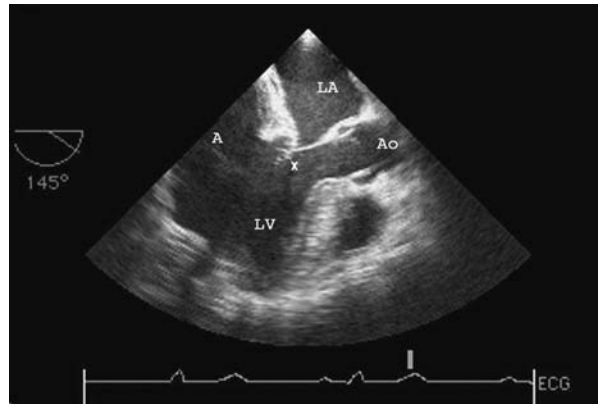

Fig. 4 *Transesophageal echocardiography shows that the posterior mitral leaflet is tethered by its papillary muscle.*

A = aneurysm; Ao = ascending aorta; LA = left atrium; LV = left ventricle; X = posterior mitral leaflet

Real-time motion images are available at texasheart.org/journal.

Mitral regurgitation is a severe problem in patients with heart failure. The MR is functional and secondary to both annular and LV dilatation. In general, patients with lateral wall LV aneurysm have severe MR due to papillary muscle tethering or annular dilatation. In addition, papillary muscle tethering increases MR and renders it severe in these patients. Patients with secondary MR experience a worsening of LV function, LV dilatation, and MR.[4] Despite apparent overtethering of the posterior mitral leaflet due to papillary muscle displacement, MR was not present in our patient. Presumably, this was due to compensatory systolic expansion of the large aneurysmal cavity, which seemed to compress the mitral annulus, thereby preserving mitral leaflet coaptation. Consequently, our patient's aneurysm treated itself.

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Images in Cardiovascular Medicine

Metastatic Cardiac Carcinoid

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A 58-year-old man with metastatic carcinoid tumor of the liver was referred to the Interventional Cardiology Department at our hospital for a cardiac biopsy. Four years before, he had gone to his primary care physician because of facial flushing, occasional diarrhea, and right flank pain. His only relevant history was medically treated hypertension. He did not drink alcohol or smoke. His father had died of lung cancer. Physical examination of the patient at that time had revealed hepatomegaly. Results of laboratory tests had shown normal hematocrit, white blood cell count, liver function, and prothrombin time. Ultrasonography and subsequent computed tomography of the abdomen showed multiple hepatic lesions, and a liver biopsy showed carcinoid tumor. His urine 5-hydroxyindoleacetic acid level was 1700 mg/24 hr (normal, 0–6 mg/24 hr). The primary tumor could not be found. An echocardiogram performed as a part of that initial evaluation was normal. He was treated with octreotide, with partial improvement of symptoms. The primary tumor was later found to be in the small bowel, and small-bowel resection was performed. He received staged chemoembolization to the liver with cisplatin, adriamycin, and mitomycin. Subsequent treatments included capecitabine and interferon. He then developed decompensated liver disease with ascites that required multiple paracenteses during the course of his illness. He was being considered for liver transplantation at the time of his initial referral to Interventional Cardiology.

Because of his increasing ascites, the patient underwent echocardiography for evaluation of possible valvular disease. The echocardiogram revealed normal left ventricular function, with no evidence of valvular heart disease and no pericardial effusion (Fig. 1); however, there was a 30 × 12-mm mass in the inferior basilar interventricular septum. Magnetic resonance imaging confirmed the presence of a mass (26 × 14 × 26 mm) in the inferior interventricular septum (Fig. 2). The patient was not experiencing dyspnea, chest pain, palpitations, or syncope.

We performed a percutaneous right ventricular endomyocardial biopsy of the septal mass. Histopathologic results showed nests of uniform cells containing round nuclei, with small nucleoli and abundant cytoplasm; these results were consistent with metastatic cardiac carcinoid. Chromogranin staining, a marker of endocrine tumors, was strongly positive (Fig. 3). The finding of extrahepatic metastatic disease resulted in the patient's removal from the liver transplant list. Currently, he is being treated palliatively with bevacizumab (a vascular endothelial growth factor antibody) and octreotide.

Comment

Carcinoid metastasis to the heart is rare; the reported incidence among patients with metastatic carcinoid disease is about 4%.[1] In 2002, Pandya and colleagues[2] described 11 patients with metastatic cardiac carcinoid tumors. All of the patients had carcinoid syndrome. The average time from the diagnosis of carcinoid syndrome to the diagnosis of metastatic cardiac carcinoid was 5.6 ± 3.9 years. The diagnosis of metastatic cardiac carcinoid was made by means of echocardiography in 55% of patients; in the remaining cases, the diagnosis was not determined until autopsy. The metastatic cardiac carcinoid tumors on echocardiography appeared as a homogenous, circumscribed non-infiltrating mass. The tumor involved the left ventricle in 53% of those patients, the right ventricle in 40%, and the ventricular septum in only 7%. There was cardiac valvular involvement in most of the patients (73%). The average duration of survival after the diagnosis of metastatic cardiac carcinoid tumor was 6.3 ± 5

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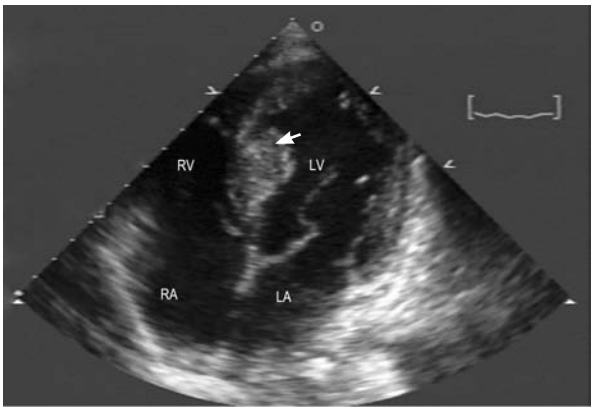

Fig. 1 *Transthoracic echocardiogram (apical 4-chamber view) shows a mass (arrow) in the inferior basilar interventricular septum.*

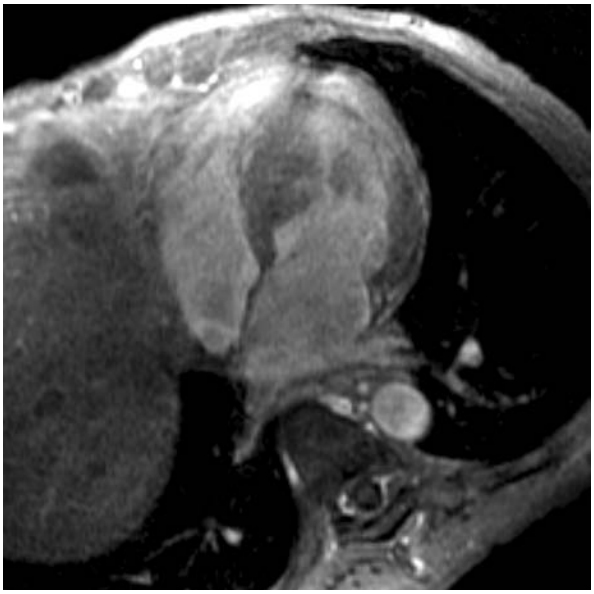

Fig. 2 *Magnetic resonance image (steady-state, free precession, horizontal long-axis view) shows a mass in the inferior basilar interventricular septum.*

years.[2] We conclude that cardiac metastasis as the only manifestation of carcinoid heart disease, as found in our patient, is uncommon.

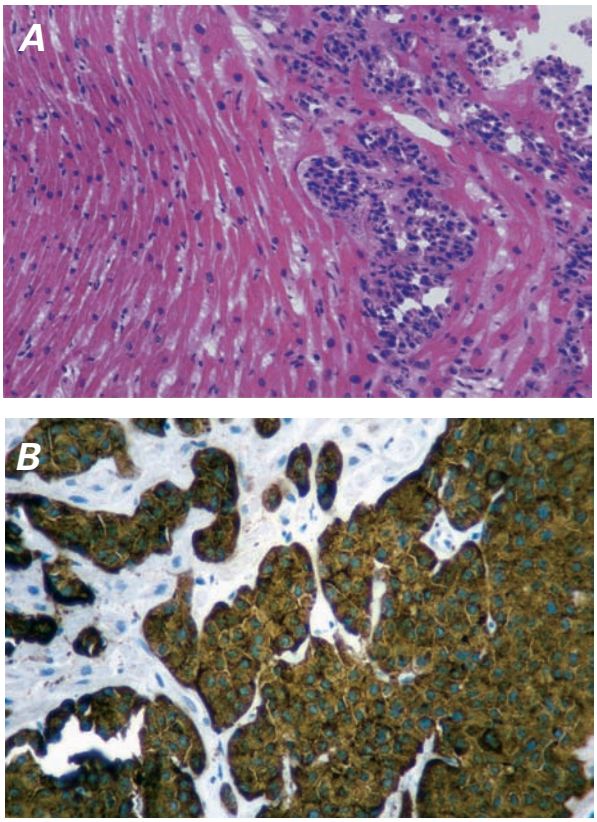

Fig. 3 *Metastatic carcinoid tumor in cardiac muscle shown by histopathologic staining: **A**) H & E, orig. ×100, and **B**) chromogranin, orig. ×400.*

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CORRESPONDENCE

Acute Spinal Cord Ischemia during Aortography

To the Editor:

We read with utmost interest the report from Restrepo and Guttin[1] that described a case of acute spinal cord ischemia, which resulted from aortography in a patient with severe systemic atherosclerosis. In their patient, the injury occurred during apparently straightforward aortography for the evaluation of an aneurysm of the abdominal aorta. The patient was successfully treated with intravenous recombinant tissue plasminogen activator within 3 hours after the onset of symptoms, and he was discharged 3 days after thrombolysis, able to walk unassisted.

We had a 79-year-old patient with recent-onset angina pectoris, severe aortic and systemic atherosclerotic disease, and chronic moderate renal failure, who developed extensive spinal cord ischemia after a much more demanding right femoral coronary angiography, because of severe full-length aortic and iliac tortuosity. Our case was never reported in the literature, but it was presented and discussed during some meetings in Europe.[2]

We were forced to use a 45-cm-long 6F introducer, ultra-stiff 0.35″ Amplatz exchange wires (Cook Medical Inc.; Bloomington, Ind), and 6F coronary angioplasty catheters in order to opacify the coronary tree. Moderately severe disease of the right coronary and left circumflex arteries, suitable for coronary angioplasty, was discovered. We did not proceed, because the patient had dull back pain and felt exhausted despite the fact that the procedure did not last too long (29 minutes), considering the technical difficulties that we had faced.

When we moved him from the catheterization table to the stretcher, we realized that he had complete flaccid paralysis of the legs associated with sensory loss, and a livedo reticularis extending from the umbilical line to the feet. The femoral pulses were brisk. We hypothesized that there had been a plaque dislodgement, with embolization of a costal artery that supplied the spinal cord, caused by the long sheath or by passage of the stiff wires or catheters. In the hope that some fresh, platelet-rich thrombi were present with the chronic plaque material and cholesterol crystals, we decided to inject a full bolus (180 μg/kg) and a half bolus (90 μg/kg) 10 minutes apart, instead of 2 full boli (because of the patient's age and renal failure), followed by a continuous infusion of 2.0 μg/kg per min for 12 hours. Low doses of dopamine, nitroprusside, and pentoxifylline were also given. Soon afterwards, the patient underwent emergency computed tomographic scanning and intravenous aortography, which ruled out an aortic dissection. Some 40 minutes after the end of the last eptifibatide bolus, the patient started moving his legs, with gradual recovery of his sensory function and regression of the livedo.

It took some days for him to walk unassisted. His renal function deteriorated (creatinine level from 3.5 up to 4.5 mg/dL), but that reversed in a matter of 3 weeks. The diagnosis of spinal cord injury was confirmed by the neurologist on duty and also by nuclear magnetic resonance imaging 1 week after the procedure. The patient was discharged from the hospital, asymptomatic for angina, on medical treatment, and he has been well since then.

The occurrence of spinal cord ischemia during angiography is a very serious matter. Excluding the 2 cases discussed here,[1,2] 5 have been described in the English literature since 1972—4 occurring during aortography and 1 during coronary angiography.[3] Our colleagues have showed us that this dreadful complication can be treated successfully with antithrombotic drugs,[1] without hemorrhage in the spinal cord. The 2 types of drugs are probably both effective: IIb/IIIa glycoprotein inhibitors may be preferred if they are used, as in our present case, immediately after the insult, when the presence of a white thrombus is more likely. The therapeutic window for thrombolytic agents is probably wider. It would be interesting to know whether these drugs can be successfully used in at least some cases of acute spinal ischemia observed after the percutaneous implantation of an aortic prosthesis, or even after thoracoabdominal aortic surgery. In this last situation, the potential benefit might be obscured by the risk of serious bleeding from the sutures. Perhaps lower-dose local therapy could be given, for a lower risk of hemorrhage.

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Acute Myocardial Infarction with Normal Coronary Arteries in a Patient with Hodgkin's Disease

To the Editor:

The article by Letsas and colleagues (Letsas KP, Korantzopoulos P, Evangelou D, Pappas LK, and Kardaras F. Acute myocardial infarction with normal coronary arteries in a patient with Hodgkin's disease. Tex Heart Inst J 2006;33:512-4) raises the question of the possible direct relationship between Hodgkin's disease and the associated acute event (myocardial infarction). Nevertheless, acute myocardial infarction in the presence of radiographically patent coronary arteries occurs often enough to warrant the consideration that the association is one of chance: witness the frequency of documented acute myocardial infarction with patent coronary arteries in the CASS registry, more often in young females. Nevertheless, the mechanism has eluded detection thus far, leaving the possibility of multiple mechanisms—any one or more of which could be exacerbated by conditions such as Hodgkin's disease in which multiple factors, including those related to endothelial dysfunction, are in disarray. Calling the patent coronary arteries "normal" may be part of the problem, when they may only *appear* normal, even at autopsy.

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For Further Reading

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