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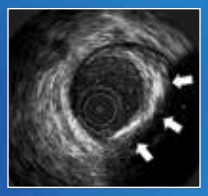

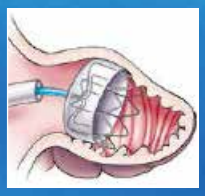

Cleveland Clinic

Cardiac Consult

Heart and Vascular News from Cleveland Clinic | Fall 2015 | Vol. XXV No. 3

New Lessons on the Great Vessel:

Insights into complex aortic disease

p. 6

Dear Colleagues:

Strength lies in numbers. For centuries that's been true in everything from warfare to social movements, and it's increasingly the case in healthcare, albeit with a twist: The more times you perform a procedure or treat a certain disease or patient type, the better you become and the more insights you gain.

That's the notion behind the cover story of this issue of *Cardiac Consult*. Cleveland Clinic's Aorta Center performs more aortic surgeries each year than any other program in the world, and all that experience affords opportunities to perfect techniques, innovate new approaches, and accumulate data to conduct studies and generate novel research questions. The story, which starts on p. 6, shares a few such recent insights on the great vessel, which range from a new system for classifying aortitis to discovery of an autoantigen that appears to play a role in aortitis pathogenesis.

Strength in numbers is likewise the notion behind this issue's final article (p. 18). That piece profiles a study that drew on over a quarter century of mitral valve repair procedures at Cleveland Clinic (more than 5,900 in all) to conclude that watchful waiting rarely makes sense for asymptomatic patients with severely regurgitant mitral valves. Not surprisingly, this review of Cleveland Clinic's vast experience with these procedures reveals that the benefits of earlier referral for mitral valve repair have been experienced by a larger and larger proportion of mitral valve surgery patients over time.

Insights from large data analyses like this are facilitated by the work of the Cleveland Clinic Coordinating Center for Clinical Research (C5Research). This academic research organization helps harness the full power of research data by leading large-scale trials and conducting high-powered pooled analyses. One example is the analysis profiled on p. 4, which has upended thinking about the relationship between coronary artery calcification and atheroma volume.

C5Research grew out of many decades of meticulous computerized record-keeping of procedures and outcomes by Cleveland Clinic's heart team. When such an ethic of data collection is paired with the volumes of one of the world's largest and busiest heart programs, powerful research insights result. So do effective continuous quality improvement efforts.

This issue is full of evidence that numbers — in terms of both volumes and quantifiable practice-related data — can help us all provide better care for patients and understand their diseases (and potential cures) more clearly. Strength in numbers indeed.

Respectfully,

Amar Krishnaswamy, MD
Staff Cardiologist, Invasive Cardiology

Michael Rocco, MD
Medical Director, Cardiac Rehabilitation and Stress Testing

W. Michael Park, MD
Staff Surgeon, Vascular Surgery

Joseph F. Sabik III, MD
Chairman, Thoracic and Cardiovascular Surgery

Cardiac Consult offers updates on advanced diagnostic and management techniques from specialists in Cleveland Clinic's Sydell and Arnold Miller Family Heart & Vascular Institute. Please direct correspondence to:

Medical Editors

Amar Krishnaswamy, MD
krishna2@ccf.org

W. Michael Park, MD
parkm3@ccf.org

Michael Rocco, MD
roccom@ccf.org

Joseph F. Sabik III, MD
sabikj@ccf.org

Managing Editor
Glenn R. Campbell

Art Director
Michael Viars

Marketing Manager
Martha Makar

Photography & Illustrations
Cleveland Clinic Center for Medical Art and Photography

Russell Lee Photography

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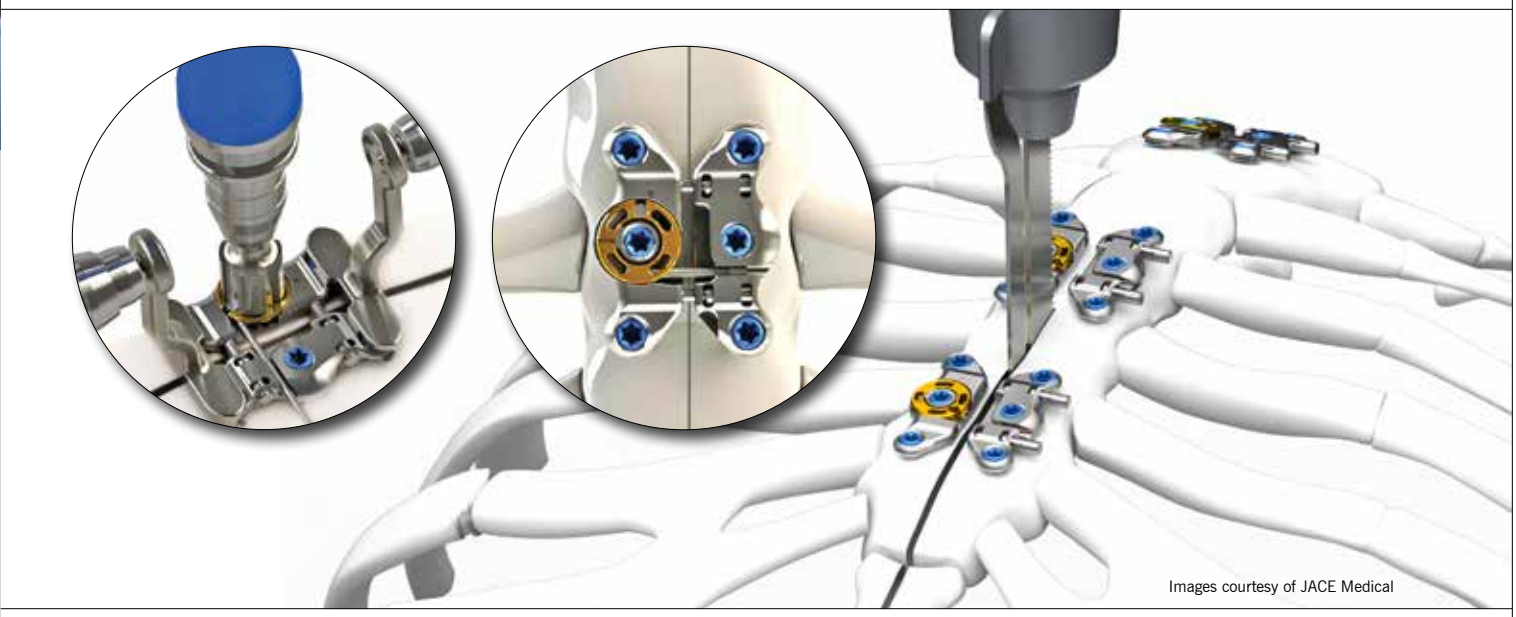
Image of the Issue



Images courtesy of JACE Medical

THE DAYS OF WIRE-BASED STERNAL CLOSURE MAY BE NUMBERED

Cardiothoracic surgery is one of the only surgical specialties still using wires to close bones, but the days of wire-based sternal closure may be numbered, thanks to an innovative device developed by Cleveland Clinic surgeons.

In high-risk patients undergoing cardiothoracic surgery, wires may not produce a tight closure or stable union at the sternum, thereby delaying recovery and causing chronic pain or audible clicks.

This spurred cardiothoracic surgeons Douglas Johnston, MD, and Edward Soltesz, MD, and orthopaedic surgeon Wael Barsoum, MD, to team with colleagues from Cleveland Clinic's commercialization arm, Cleveland Clinic Innovations, to develop a rigid sternal closure device that perfectly realigns the bone and eliminates the motion that can occur with wire closure.

The device, called The Grand Pre Sternal Closure System (JACE Medical), received FDA approval in January 2015. Cleveland Clinic is currently using it primarily on patients at high risk for sternal nonunion.

The device, which employs plate-and-screw technology that's standard in orthopaedics, is the first designed specifically for sternal closure. Existing devices occasionally used for this purpose are placed at the end of the operation and often leave a gap between the two halves of the sternum, raising the risk of bleeding. In contrast, The Grand Pre uses a ratchet system to close the space tightly, which promotes healing and helps avoid bleeding.

The preloaded plate is placed on the sternum before surgery and secured with screws in less than a minute. The pre-positioned plates provide a template for sternal incision (large image above) that aids in achieving true anatomical alignment during closure.

After surgery, the bones are brought together, a locking element is placed between the two halves of the plate, and the ratchet (first inset image) brings the two halves of the sternum together with perfect alignment (second inset image).

The Grand Pre can be used in reoperations as well as first-time sternotomies. It is biocompatible and MRI-compatible. ■

FOR MORE INFORMATION, CONTACT DOUGLAS JOHNSTON, MD, AT JOHNSTD3@CCF.ORG.

Plaque Paradox:

Even While Shrinking Atheromas, Statin Therapy Increases the Calcium Within Them

The relationship between coronary artery calcification and atheroma volume is not what it seems. So indicates a recent Cleveland Clinic analysis of serial coronary intravascular ultrasound (IVUS) images of patients participating in eight large clinical trials.

Findings of the analysis, published in the *Journal of the American College of Cardiology* (2015;65:1273-1282), include the following:

- Patients with coronary artery disease (CAD) who are treated with statins experience an increase in coronary calcification, an effect that is independent of plaque progression or regression.
- Paradoxically, high-intensity statin therapy is associated with the largest increases in coronary calcification despite promoting atheroma regression.

"Patients prescribed the highest doses of statins, despite achieving low levels of cholesterol and demonstrating marked plaque regression, had changes in plaque calcification that were nearly double the changes in patients who received no statins, and greater than the changes in those who received low-intensity statin therapy, both of which were associated with plaque progression," says the study's principal investigator, Rishi Puri, MBBS, PhD.

Dr. Puri is a consultant with the Atherosclerosis Imaging Core Laboratory within the Cleveland Clinic Coordinating Center for Clinical Research (C5Research) (see box). The studies included in the pooled analysis were run through C5Research.

Calcification as a Mechanism of Plaque Stabilization?

The increase in calcification revealed by the analysis may represent a means by which statin therapy stabilizes coronary plaque to reduce the risk of cardiovascular events, says the study's senior investigator, Steven Nissen, MD, who adds that this hypothesis remains to be proved.

"We found that as plaques were getting smaller with statins, they were calcifying," explains Dr. Nissen, Chairman of the Robert and Suzanne Tomsich Department of Cardiovascular Medicine at Cleveland Clinic.

"It's exactly the opposite of what you might think intuitively," he continues. "This is an important observation that tells us that statins work to stabilize plaques by converting softer, cholesterol-laden plaques that are prone to rupture into more stable calcified plaques that are relatively inert. It explains the paradox of why serial measurement of calcium doesn't necessarily work to track the progression of disease, and it explains to some extent how statins work."

Not All Calcium Is the Same

"These findings show that not all calcium within the coronary arteries is necessarily the same," Dr. Puri notes. "Rather, it likely depends on the context of a patient's therapy and its duration, as well as the specific clinical situation. Our findings strongly suggest a calcium-related healing effect following high-dose therapy with potent statins, which could be considered atheroprotective. Our imaging laboratory, along with others, has demonstrated in the past the possible adverse effects of 'spotty calcification' found within the coronary tree, the plaques of which seem more resistant to therapies and more frequently found within culprit lesions of patients presenting with acute coronary syndromes."

Leading Research to Impact Clinical Care

Cleveland Clinic Coordinating Center for Clinical Research (C5Research) is an academic research organization (ARO) within the Miller Family Heart & Vascular Institute. It provides clinical trial operational services to the pharmaceutical and medical device industries. It also supports NIH- and Cleveland Clinic investigator-initiated studies and collaborates with other AROs and contract research organizations to conduct clinical trials. C5Research has more than 100 dedicated clinical trial specialists who combine scientific and clinical expertise in cardiovascular disease with operational excellence to conduct phase II-IV multicenter trials. For more, visit c5research.clevelandclinic.org.

C5Research
Cleveland Clinic Coordinating Center for Clinical Research

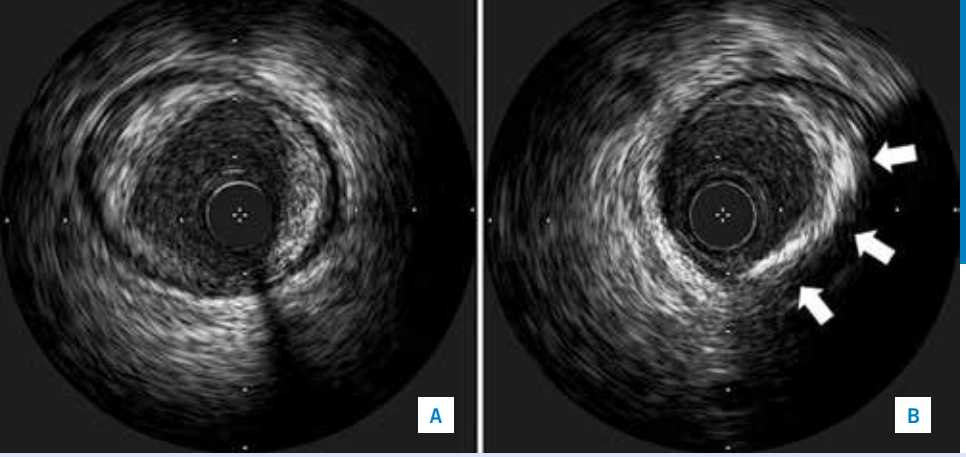


Figure. Intravascular ultrasound images representing cross-sections within the left anterior descending artery of **(A)** a noncalcified atheroma and **(B)** a calcified atheroma characterized by ultrasonographic shadowing in the region of the arrows.

CT measurement of coronary calcium has traditionally been used to predict future CAD events. A total calcium score is derived from the extent of calcification detected in the coronary arteries, with higher scores representing more extensive CAD and thus a greater risk of CAD events. Calcium scoring via CT, however, has a much lower resolution compared with IVUS, which can elucidate subtle but significant changes in atheroma calcification (Figure) as well as plaque volume.

Essentials of the Analysis

As part of the pooled analysis, serial IVUS measures of coronary calcification were obtained over 18 to 24 months in 3,495 patients with CAD who received either no statins (n = 224), low-intensity statin therapy (n = 1,726) or high-intensity statin therapy (n = 1,545).

An IVUS calcium index was calculated from each of the IVUS images. The multiple IVUS assessments enabled measurement of both plaque volume change and calcified tissue change across the different patient groups — the first time both measures had been tracked over time and in a substantial number of patients, Dr. Puri says.

All groups had statistically significant increases in plaque calcium indices from baseline; the increases ranged from 0.020 in the no-statin group to 0.038 in the low-intensity statin group to 0.044 in the high-intensity statin group. Models adjusted for atheroma volume showed that changes in calcium indices were significantly greater in the high-intensity and low-intensity statin groups compared with the no-statin group, but the difference between the high- and low-intensity groups did not quite reach statistical significance.

"What struck me were the differences in changes in plaque calcification between the no-statin and low-intensity statin groups," says Dr. Puri. "Both groups achieved relatively similar LDL-C levels and demonstrated the same degree of plaque progression over time, yet the increase in calcium index in the low-intensity group was nearly double that in the no-statin group. This observation in itself is somewhat telling regarding the possible pro-calcific properties of statins."

Coronary artery calcification progressed independent of changes in plaque regression or progression, and changes in calcium indices were significantly greater in those with plaque progression than in those with nonprogression or regression.

Implications for Coronary Calcium Measurement Practices

An accompanying editorial (*J Am Coll Cardiol.* 2015; 65:1283-1285) notes the potential importance of the analysis for portraying coronary artery calcification "in a new light," particularly regarding whether attenuation of coronary artery calcification progression remains a useful goal of statin therapy.

Dr. Nissen says a coronary calcium measurement may be performed once to define a patient's risk of cardiovascular events, but not when a patient initiates therapy "because the change in calcium isn't necessarily an accurate predictor of whether or not the patient is benefiting from the therapy."

Dr. Puri concurs. "More recent findings on CT have confirmed our findings with IVUS," he says. "Moreover, other groups have shown that the actual density of calcium measured with CT is perhaps more important than simply the total amount of calcium."

Next Research Questions

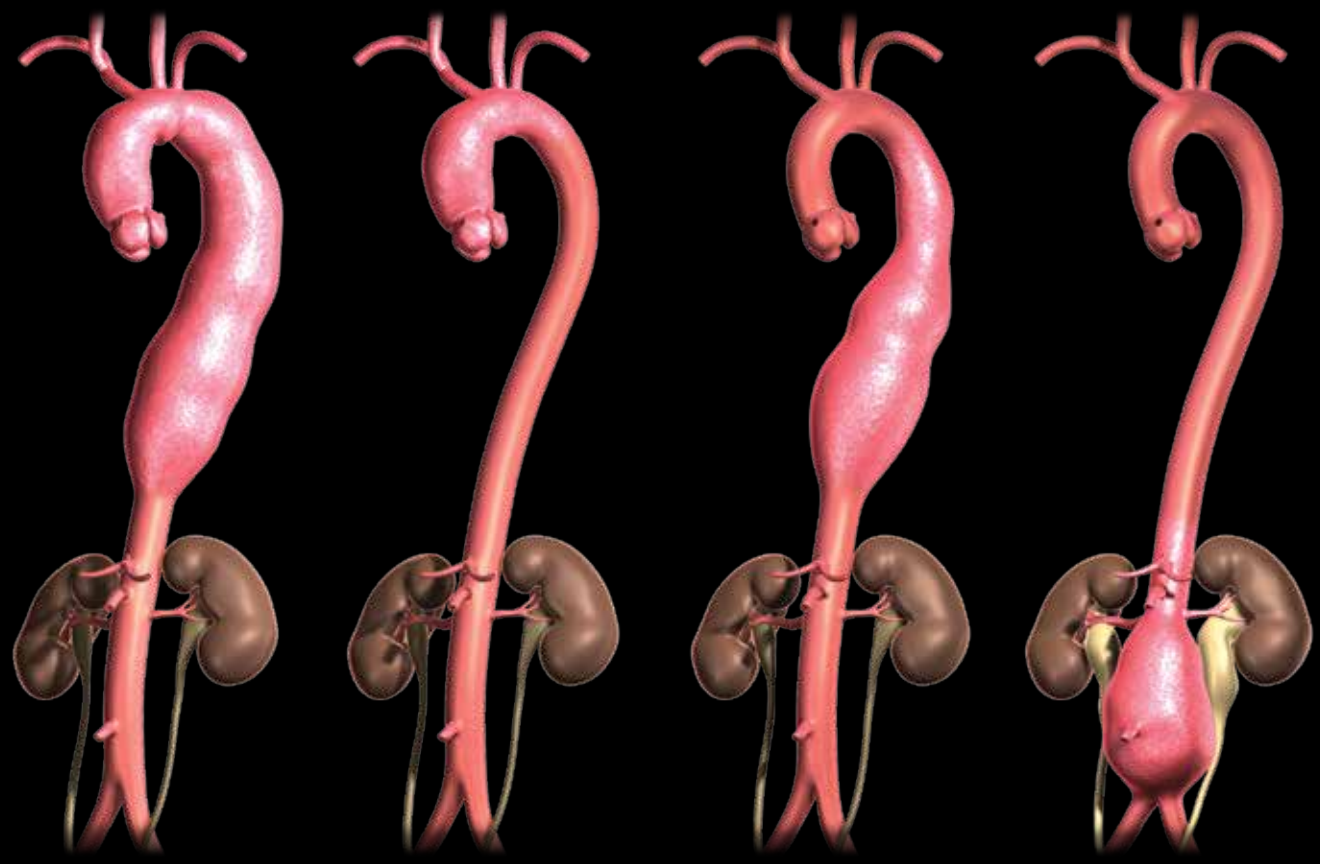
The authors of the editorial call for further investigations to get at the question of whether coronary artery calcification is indeed protective and a sign that further progression of high-risk, low-density plaque is being impeded.

Dr. Puri sees identification of the underlying biological mechanisms of his group's observations as a focus for future research. "We must explore whether our current and future imaging modalities could be better utilized to more accurately assess calcium morphology within the arterial wall as a means of honing risk prediction for future cardiovascular events," he says. ■

Contact Dr. Puri at purir@ccf.org or 581.984.7748.
Contact Dr. Nissen at nissens@ccf.org or 216.445.6852.

New Lessons on the Great Vessel:

How Large Volumes Yield Novel Insights in Complex Aortic Diseases



When a center performs the world's largest volume of aortic surgeries, the abundance of cases offers unique opportunities to study underlying causes of aortic disease and new therapeutic approaches. Cleveland Clinic's Aorta Center is running with those opportunities, as reflected in a flurry of new research papers on diverse aspects of inflammatory disease of the aorta.

A Multidisciplinary Imperative

Over the past 20 years, Cleveland Clinic has grown its thoracic aorta surgical volumes sixfold, making its aortic surgery program the largest in the world. The program's 4 percent operative mortality rate (in-hospital or 30-day, whichever is longer) is likewise one of the lowest in the world despite a challenging patient mix: 29 percent of the 1,196 aorta operations performed in 2014 were emergency procedures.

Yet surgery is only the capstone of the Aorta Center's multi-disciplinary offerings, which draw on the expertise of Cleveland Clinic rheumatologists, pathologists, genetic counselors and others in addition to cardiologists and cardiothoracic and vascular surgeons.

"We believe aortic disease should be treated like cancer, with a multidisciplinary team and lifelong care," says thoracic and cardiovascular surgeon Eric Roselli, MD, Director of the Aorta Center. "This approach is particularly valuable for inflammatory and autoimmune diseases of the aorta, where we collaborate with world leaders in vasculitis."

Leveraging Premier Vasculitis Expertise

He's speaking of the Center for Vasculitis Care and Research in the Department of Rheumatic and Immunologic Diseases, directed by Carol Langford, MD, MHS.

"When our surgical colleagues make an unexpected diagnosis of aortitis during surgery, they can reach our vasculitis specialists immediately," says Dr. Langford. "We work closely with

our vascular pathology colleagues to confirm the diagnosis and plan the patient's medical evaluation and any needed medical management."

Aortitis is seen in 5 to 15 percent of thoracic aneurysms and is speculated to be an autoimmune process. It may occur as a process limited to the thoracic aorta, as a secondary vasculitis due to a range of illnesses or as a component of primary systemic large-vessel vasculitis, most commonly giant cell arteritis (GCA) or Takayasu arteritis (TAK).

"In patients with known GCA or TAK, we consult with the surgeon to coordinate the timing of surgery with ongoing medical treatment to optimally manage their blood vessel inflammation and damage," Dr. Langford notes.

New Classification of Aortitis Patterns

This intersection of leadership in vasculitis and aortic surgery enabled Cleveland Clinic staff to recently publish the largest reported series of patients undergoing surgery for ascending or aortic arch disease — 7,551 such patients from 1996 to 2012 (*J Thorac Cardiovasc Surg.* 2015;149[2 suppl]:S170-S175).

They found that 156 patients (2 percent) had histologically confirmed aortitis. Combining observations in these patients with earlier reports, the researchers developed a classification of aortitis types to improve treatment targeting. Their four aortitis types are depicted (in order) in the illustration on the facing page and outlined in the table below.

The researchers concluded that good results are achievable with surgery and that intervention should be based on clear understanding of the histologic pattern and extent of disease. "The aim of surgery is to correct the anatomic problem, reduce risk of pseudoaneurysm formation, prevent paravalvular leaks, prevent continued destruction from the disease and prepare for disease progression," says Dr. Roselli, who was a co-author.

Anticipating Future Surgeries

In view of the chronic nature of aortic disease, Dr. Roselli and his fellow Aorta Center surgeons also take a "great vessel tailored" approach that plans for the likelihood of future surgeries.

Because many patients with an aneurysm in one section of the aorta have disease in other segments, they may need another surgery within five years. The surgeons often prepare for the second operation during the first one.

"Extending the repair into the arch with bypasses to the carotid arteries and leaving a cuff of graft or performing a prophylactic elephant trunk repair eliminates the need for two more open surgeries," says Dr. Roselli. It also allows the second operation to be done endovascularly with placement of a stent graft into the previously placed surgical graft.

Choice of surgical approach is always individualized. High-risk patients and those unlikely to need a second repair may be treated with less-invasive techniques. In patients with multiple comorbidities, only the immediate threat may be addressed.

continued next page

Classification of Aortitis Types

	INVOLVEMENT	COMMON ETIOLOGIES	TREATMENT
Type 1	• Primarily ascending aorta and arch with variable degrees of descending or thoracoabdominal dilatation • Variable proximal branch vessel involvement	Focal idiopathic aortitis (primary thoracic aortitis)	• Ascending and total arch replacement with prophylactic elephant trunk repair • Aortic valve replacement for moderate or severe aortic valve disease
Type 2	• Ascending aortic aneurysm with variable branch vessel stenosis, but often includes (A) carotid disease at bifurcation or more distally or (B) proximal innominate or subclavian involvement	Giant cell or Takayasu arteritis	• Aortic replacement with branch vessel bypasses with prosthetic material beyond the branch artery stenoses • Aortic valve replacement for moderate or severe aortic valve disease
Type 3	• Thoracoabdominal disease with variable dilatation, atheroma or atherosclerosis • Proximal greater arch vessel or visceral branch vessel occlusive disease	Giant cell or Takayasu arteritis	Pathology-specific procedures directed at the branch vessel stenoses, such as bypasses or covered stenting of the greater vessels or visceral arteries
Type 4	• Subdiaphragmatic aorta with variable visceral artery involvement	Possible lymphatic vessel disease	Pathology-specific procedures directed at the stenoses, such as bypasses or covered stenting of the greater vessels or visceral arteries

Derived from Svensson et al, *J Thorac Cardiovasc Surg* (2015;149[2 suppl]:S170-S175).

Identifying a Novel Autoantigen in Aortitis

Other collaborations between the Aorta Center and Dr. Langford's team of vasculitis experts include ongoing studies of biomarkers and clinical trials of new treatments. "We're focused on understanding the underlying basis of these diseases," Dr. Langford says. "There's much we have yet to learn, and knowing the triggers could provide insights into better treatments."

One avenue of research initiated and being advanced by Center for Vasculitis Care and Research founder Gary Hoffman, MD, recently culminated in the discovery of a novel autoantigen that appears to play a role in the pathogenesis of aortitis (*Arthritis Rheumatol.* 2015;67:1913-1921).

"We found that 78 percent of patients with large-vessel vasculitis produced antibodies to aortic proteins in the 14-3-3 family," says the paper's lead author, Ritu Chakravarti, PhD, of Cleveland Clinic's Lerner Research Institute. "In contrast, patients with noninflammatory aortic conditions were usually 14-3-3 antibody-negative." (The 14-3-3 family of proteins perform important cell signaling functions.) "We're hopeful this novel finding may lead to use of 14-3-3 antibodies as a noninvasive biomarker for diagnosis and disease activity."

Another avenue of investigation in large-vessel vasculitis has involved international collaborations with the NIH-funded Vasculitis Clinical Research Consortium. These involve biomarker/genetic studies and investigations of patient-reported outcomes, imaging techniques and novel therapeutics. A recent NIH-funded clinical trial is evaluating the safety and effectiveness of the biologic abatacept (CTLA4-Ig) in GCA and TAK.

Another Focus: Marfan and Other Genetic Syndromes

Care of patients with Marfan syndrome and other connective tissue disorders is another focus of the Aorta Center's multidisciplinary team. Because these patients are at heightened risk for aortic aneurysms and valve disease, they are treated with appropriate medications and monitored closely. When surgery is needed to repair an aneurysm or repair or replace a valve, Aorta Center surgeons provide innovative, expert care.

Aortic root aneurysms are a common complication of Marfan syndrome. Affected patients are offered the modified David reimplantation procedure. Developed by Lars Svensson, MD, PhD, Chairman of Cleveland Clinic's Miller Family Heart & Vascular Institute, this technique enables the aneurysm to be repaired while preserving the patient's native valve. It improves outcomes by determining the appropriately sized aorta graft and maintaining the left ventricular outflow tract.

The diagnosis of Marfan syndrome is confirmed with a genetic test, after which close medical supervision is provided to manage complications. The Aorta Center advises patients' family members to be tested as well, and genetic counselors work with families to help them understand how the syndrome may be passed to future generations.

The gene mutations responsible for Marfan syndrome are among a group of at least eight mutation types associated with aortic disease. For this reason, tissue and blood samples are preserved from aortic surgery patients who agree to participate in one of several tissue banking efforts offered by the Miller Family Heart & Vascular Institute. "If we learn of a new gene mutation, we can screen the samples again," Dr. Roselli explains.

Enhancing Follow-Up and Data Collection

Genetic counselors likewise figure into the Aorta Center's efforts to enhance its Aortic Follow-Up Clinic, where patients are closely monitored after surviving an aortic emergency. "Thirty to 40 percent of these patients will require another surgery, so they need to be followed by their surgeon and by a cardiologist for blood pressure management," says Dr. Roselli. "We also engage genetic counselors to advise patients and families, and we've been working to make that process more seamless and improve preventive care for patients and family members."

The Aorta Center has also begun collecting data on patients who haven't yet had surgery, to better understand the natural history of aortic disease. That effort aligns with a new database specifically for patients with aortic disease that features a structured reporting mechanism created in concert with Cleveland Clinic cardiac imaging specialists. "It allows us to harvest and analyze data more easily," Dr. Roselli notes. The aim is accelerated research efforts. So stay tuned: More insights are likely on the way. ■

Contact Dr. Roselli at roselle@ccf.org or 216.444.0995.

New Guidance on Surgical Pathology of Inflammatory Aortic Disease

Portions of the aorta resected during surgical repair of aortic aneurysms and dissections contain important diagnostic information about underlying aortic diseases. Two Cleveland Clinic vascular pathologists, E. Rene Rodriguez, MD, and Carmela Tan, MD, were among a team convened by the Society for Cardiovascular Pathology and the Association for European Cardiovascular Pathology to develop the first consensus classification of inflammatory aortic disease based on histologic features. Check it out in *Cardiovascular Pathology* (2015;24:267-278).

Old Meets New in Novel Hybrid Approach to Restorative Vascular Surgery

Combining remote and direct techniques to avoid bypass

Aortobifemoral bypass (ABF) grafting is the traditional treatment for extensive aortoiliac occlusive disease. But endarterectomy and its modern incarnation, remote endarterectomy (EndoRE-ABF), offer an important option in revascularization.

The advantages, according to Cleveland Clinic vascular surgeon W. Michael Park, MD, include the following:

- Native vessels are reopened by removing obstructive plaque and even occluded stents.
- The approach is minimally invasive, typically done via an incision in the groin.
- No artificial materials are relied on, which makes this option suitable for cases involving infection.
- Results are durable, with acceptable primary/primary assisted patencies superior to those with stents or PTFE graft bypass.

Old Meets New

Dr. Park is one of only a few U.S. surgeons performing this procedure that restores the superficial femoral artery to its original state without incisions, and he is the only one with extensive experience removing occluded stents. The hybrid technique is based on an established technique of open remote endarterectomy dating back to the 1960s.

"It's a revival of an old way of doing things," he says. "It's a lost art because everyone is doing stents. The problem is that they block up. After that, bypass with autologous vein typically is performed, but when that fails, options are limited."

A Case Example

That's when having this third option, after stenting and bypass, matters most. "It offers another avenue of revascularization," Dr. Park says, noting that this restorative therapy option is used extensively in Europe.

He cites the case of a 70-year-old woman who had diffuse bilateral iliac atherosclerotic plaque with occlusion of the right common femoral artery and left common and external iliac artery. Severe leg pain left her unable to walk. He was able to restore function by performing a hybrid common femoral and profunda femoris endarterectomy, external iliac artery EndoRE-ABF and common iliac artery stenting (Figures 1 and 2). Full case details are at Dr. Park's blog, vascsurg.me/category/endore-2/.

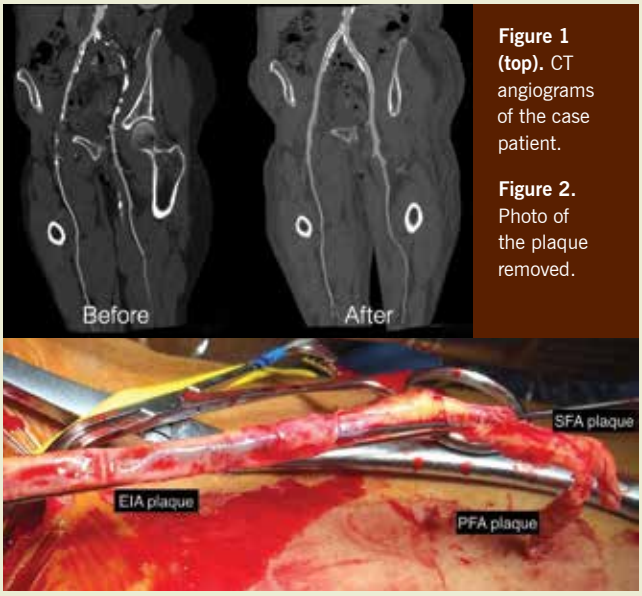


Figure 1 (top). CT angiograms of the case patient.

Figure 2. Photo of the plaque removed.

Taking EndoABF to the Next Level

Endovascular ABF (EndoABF) is an established hybrid procedure involving an open endarterectomy of the common femoral and profunda femoris/superficial femoral arteries with iliac balloon angioplasty and stenting. Often the stents are taken distally into the common femoral artery and the patch to deal with complex distal external iliac artery plaque.

Taking it a step further, Dr. Park removes plaque from the common femoral artery and also does an iliac endarterectomy. He uses a slight variation with the EndoRE-ABF, which removes a great deal of external plaque surgically, reopening the previously occluded artery. By combining remote and direct techniques, he is able to avoid using bypass, which can involve nominal and substantial blood loss, as well as remove occlusive stents.

This hybrid procedure is also an excellent option for patients who have undergone multiple prior procedures and those with infections who need revascularization, Dr. Park notes. ■

Contact Dr. Park at parkm3@ccf.org or 440.878.2500.

Stroke Prevention in Atrial Fibrillation:

With a WATCHMAN Now on Duty, How Much Has the Landscape Changed?

The left atrial appendage (LAA) has been called "our most lethal human attachment,"[1] but you'd never guess it from appearances: The LAA is a modest hollow sac that hangs from the left atrium, filling with blood and emptying along with the atrium. Its lethal reputation derives from the fact that in the 15 percent of patients with atrial fibrillation (AF) who suffer strokes, 90 percent of the culprit emboli are believed to originate in the LAA (see sidebar).

Anticoagulants: Still First-Line, but Limitations Linger

The first-line treatment for stroke prevention in patients with nonvalvular AF remains warfarin despite its reputation as a high-maintenance anticoagulant with numerous food and drug interactions and the need for frequent monitoring to avoid gastric or cranial bleeding. Large numbers of patients who are prescribed warfarin cease to use it within a year, and it is contraindicated in many others.

The demand for alternatives to warfarin has brought about a wave of new oral anticoagulants in the past five years. Although these agents — direct thrombin inhibitors or direct factor Xa inhibitors — are useful for certain subgroups of patients, none yet seriously threatens warfarin's dominance, in part because of their higher costs and their lack of an antidote to reverse active bleeding.

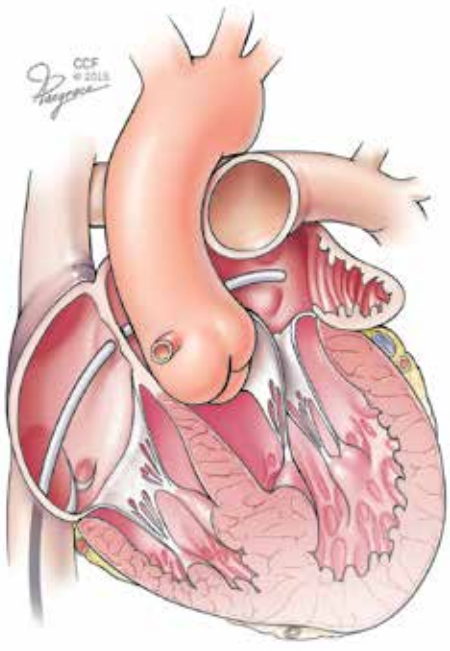


Figure 1. The transvenous, transseptal approach used for implantation of the WATCHMAN device in the LAA (upper right).

LAA: A Tempting Target for Intervention

The ostium of the LAA has long been a tempting target to innovators seeking a nonpharmacologic alternative to warfarin. The LAA can be surgically removed, sutured, stapled or clipped closed during open surgery, with differing degrees of efficacy. Less invasively, several catheter-delivered devices for occluding the LAA have been developed and have undergone various degrees of testing.

In March 2015, after many years of review, the FDA approved the percutaneously implanted WATCHMAN™ Left Atrial Appendage Closure Device (Boston Scientific) for stroke risk reduction in patients with nonvalvular AF.

"WATCHMAN is a big development," says Oussama Wazni, MD, Co-Director of the Ventricular Arrhythmia Center and Director of Outpatient Electrophysiology at Cleveland Clinic. "It's implanted via a simple catheter-based procedure, and if there's a good seal, there's a very high likelihood the patient can be taken off oral anticoagulants."

WATCHMAN Implantation at a Glance

The WATCHMAN device is implanted in an interventional lab, under fluoroscopy. Transesophageal echocardiography (TEE) is used to assess the size and shape of the LAA.

During the procedure, a guidewire catheter is advanced through the femoral vein to the heart, where it is passed through a transseptal puncture to the left atrium (Figure 1). An access sheath and dilator are advanced into the left atrium, and a pigtail catheter is advanced into the LAA. In the final step, the device is inserted through the access sheath and aligned with the neck of the LAA. Once in position, the device is opened like a bulbous umbrella. Its flexible, fabric-covered nitinol frame conforms to the shape of the LAA (Figure 2).

The procedure takes about an hour. The patient may go home the next day. Over the next several months, tissue overgrows the plug.

Evidence Base and Experience

WATCHMAN has been commercially available in Europe since 2005 and is the leading percutaneous LAA closure device worldwide, with more than 10,000 patients having been treated.

Its U.S. approval was based on two major clinical trials, PROTECT AF and PREVAIL. The aggregate of the two trials showed the device to be noninferior to warfarin in reducing the rate of stroke from any cause.

Several Cleveland Clinic investigators participated in these studies, including Dr. Wazni and fellow electrophysiologist Walid Saliba, MD, Medical Director of the Center for Atrial Fibrillation, as well as Samir Kapadia, MD, Director of the Sones Cardiac Catheterization Laboratory, and fellow interventional cardiologist Murat Tuzcu, MD, Vice Chair of the Department of Cardiovascular Medicine.

Drs. Kapadia and Tuzcu likewise published a systematic review and analysis of relevant observational studies that echoed these results, concluding: "Percutaneous LAA occlusion for stroke prophylaxis was comparable to historical controls for adjusted-dose warfarin and comparable to other anticoagulation agents."[2]

These physicians also teamed with Dr. Saliba and interventional cardiology colleague Amar Krishnaswamy, MD, to publish a method for using CT-based imaging to potentially help plan the LAA occlusion procedure.[3] TEE and CT scan are complementary for image guidance before and during the procedure.

The Lethal Appendage

While the left atrial appendage (LAA) is an artifact of the embryonic left atrium, it is composed of different tissue from the left atrium and comes in a variety of shapes whose descriptions range from windsock to chicken wing to cactus to cauliflower.[4]

It is not precisely the "appendix of the heart," as it seems to function as an active contractile chamber and may serve as a kind of volume reserve for the left atrium. It also has receptors sensitive to stretch that can influence heart rate in response to atrial pressure. In addition, the LAA has its own pattern of contraction, particularly during atrial fibrillation, when it can create pools of stagnant blood that generate emboli.

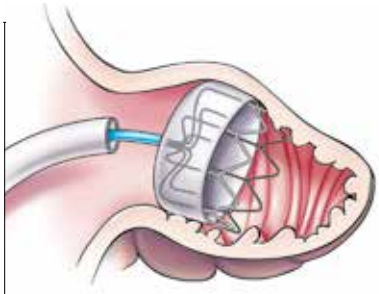


Figure 2. The WATCHMAN device opens like an umbrella to conform to the shape of the LAA. Figures 1 and 2 are reprinted from *Cleveland Clinic Journal of Medicine* (2015;82:167-176).

Weighing WATCHMAN Against Traditional Options

The FDA has approved WATCHMAN for patients with nonvalvular AF who:

- Are at increased stroke risk and have been recommended for long-term anticoagulation therapy
- Are deemed suitable for warfarin by their physicians
- Have an "appropriate rationale" to seek a nondrug alternative to warfarin

That indication gives physicians and patients considerable latitude for discussion. For Dr. Wazni, the "appropriate rationale" includes having a history of bleeding when taking oral anticoagulants or being deemed to have a high future risk of bleeding.

"WATCHMAN is a second-line therapy for a selected group of patients," he says. "But for those patients, this is a very important option, as it can prevent stroke while avoiding the risk of bleeding."

His colleague Dr. Saliba concurs, noting that patient preference looms large and additional experience should help refine decision-making. "It will take more education, more data and more time to see how it's going to pan out," Dr. Saliba says.

Dr. Kapadia adds: "Valvular AF refers to patients with rheumatic heart disease. As percutaneous treatment of valvular heart disease is expanding with transcatheter aortic valve replacement and the use of MitraClip®, many elderly patients with AF and nonrheumatic valvular heart disease can also benefit from this new advance." ■

Contact Dr. Wazni at waznio@ccf.org, Dr. Saliba at salibaw@ccf.org, Dr. Kapadia at kapadis@ccf.org, Dr. Tuzcu at tuzcue@ccf.org and Dr. Krishnaswamy at krishna2@ccf.org.

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Cardiac Amyloidosis:

Successful Dual Heart/Stem Cell Transplants Reflect Progress Against Once-Incurable Malady

Case Study

In October 2013, a 65-year-old male physician from Dallas diagnosed with hypertrophic cardiomyopathy saw Cleveland Clinic heart failure specialist Mazen Hanna, MD, for a second opinion. The former marathoner had been treated for heart failure for about a year but was rapidly declining.

Finding the patient's test results inconsistent with the diagnosis, Dr. Hanna ordered more-sensitive tests, which revealed cardiac amyloidosis (Figures 1 and 2) — specifically, AL amyloidosis — that was soon confirmed by biopsy. Chemotherapy was promptly started. The patient returned to Texas, and with a Cleveland Clinic hematologist coordinating his chemotherapy, he achieved very good partial remission.

Despite an amyloidosis-specific cardiac care regimen, however, his heart failure worsened. Dr. Hanna proposed an aggressive treatment: heart transplantation followed by stem cell transplantation. The patient agreed. Through Cleveland Clinic's cardiovascular clinical and research alliance with Baylor Scott & White Health in Dallas, he was listed for a heart transplant at Baylor in July 2014 and received a new heart five days later. Chemotherapy was continued during his recovery. In February 2015, he underwent an autologous stem cell transplant at Cleveland Clinic. Within a few months, he was in complete remission, returned to work full time and resumed running.

Cardiac Amyloidosis: No Longer Hopeless, but Still Daunting

Cleveland Clinic is one of the few U.S. centers offering heart and stem cell transplantation for selected patients with cardiac amyloidosis. The approach is emblematic of a commitment to changing the outlook for patients with a once-incurable disease.

"The prognosis for cardiac amyloidosis is not hopeless," says Dr. Hanna. "Once diagnosed, however, it requires significant expertise to treat. A multidisciplinary team like the one we have here is an enormous asset."

Two Types, with Very Different Treatments

Amyloid deposits can occur in any organ in the body. Approximately 50 new patients with cardiac involvement are among those seen in Cleveland Clinic's Amyloidosis Center every year. The center includes specialists from multiple disciplines — cardiology, hematology-oncology, nephrology, neurology, gastroenterology, pathology, transplantation and palliative care — who meet bimonthly to discuss cases.

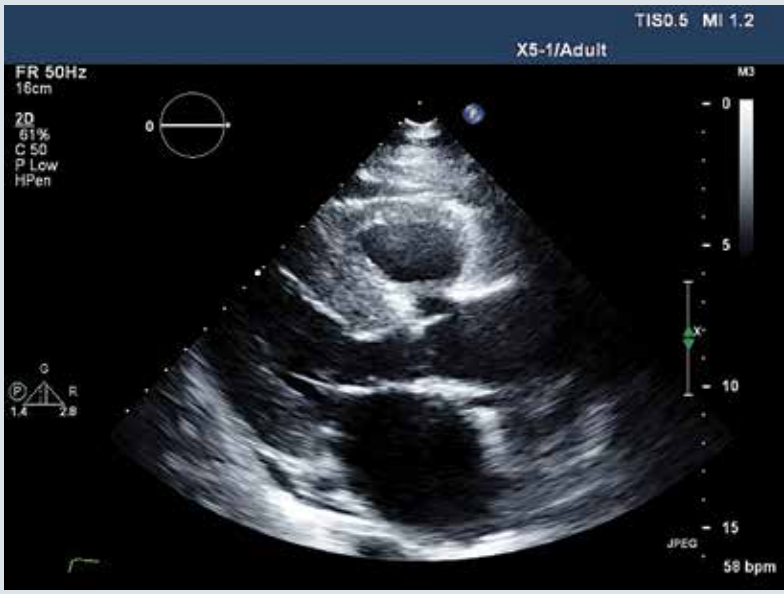


Figure 1. Echocardiogram of the case patient (parasternal long axis view) showing diffuse thickening of the left and right ventricular walls.

Of the patients with cardiac amyloidosis, about 40 percent have light chain amyloidosis due to a plasma cell dyscrasia (AL amyloidosis) and 60 percent have transthyretin-related (TTR) amyloidosis. "The distinction is critical," says Dr. Hanna, "because the two forms require very different treatments."

AL amyloidosis is a rapidly progressing, life-threatening disease. Several types of chemotherapy, used with or without transplantation, are reserved for this form. Cleveland Clinic is taking part in clinical trials of NEOD001, a humanized monoclonal antibody designed to potentiate the effects of chemotherapy against AL amyloidosis. "We're excited about the potential of this biologic, which may clear existing amyloid deposits," Dr. Hanna notes.

For patients with TTR amyloidosis, investigational drugs are showing promise in slowing disease progression. Cleveland Clinic offers participation in clinical trials of two such agents:

- Tafamidis, a stabilizing agent that prevents misfolding of the circulating TTR protein in the plasma
- Revusiran, a small RNA interference (RNAi) therapeutic that specifically reduces hepatic production of TTR by blocking translation in the cytoplasm

More Interest = More Diagnoses

Knowledge about cardiac amyloid disease is being advanced at Cleveland Clinic by a $2 million gift in 2014 from an anonymous donor. Dr. Hanna is using the funds to support research projects and a research fellow dedicated to the subspecialty.

These developments reflect growing interest in the disease among Cleveland Clinic cardiologists and colleagues in other specialties. "We have two cardiology fellows specializing in amyloid, and all our cardiologists are invested in the condition," says Dr. Hanna. "As a result, amyloidosis is being diagnosed with increasing frequency."

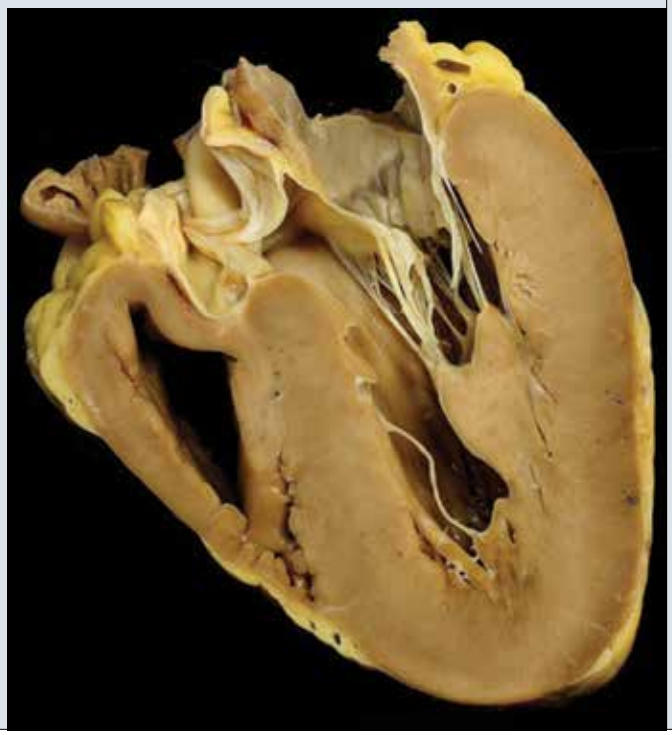
And when patients are diagnosed with amyloidosis in other organs, Dr. Hanna — who directs cardiac amyloidosis care at Cleveland Clinic — is routinely asked to screen them for cardiac involvement.

Therapy Addresses Both HF and Underlying Amyloid Disease

Once cardiac amyloidosis is identified, early referral to an experienced center is not only recommended — it may be lifesaving.

"Treatment is generally complex and requires managing the patient's heart failure while treating the underlying disease," Dr. Hanna explains. "Amyloid patients cannot be treated like other heart failure patients. It's as important to know what not to give them as what to give them, since many common heart failure drugs will be poorly tolerated or detrimental, and patients may not respond to medications as expected."

Figure 2. The case patient's explanted heart. Note the dramatic thickening of all chambers, which is typical of cardiac amyloidosis.



For patients with AL amyloidosis, an individualized, aggressive chemotherapy regimen must be initiated to stop production of abnormal light chains in the plasma. Individual patients may be candidates for additional therapy with stem cell transplantation. Some patients may be candidates for heart transplantation, which can be considered in highly selected AL amyloidosis cases with advanced cardiac amyloid and no severe involvement of other organs.

For some patients with TTR amyloidosis, heart transplant or combined heart and liver transplant may be feasible. "We have performed seven heart transplants in these patients, one with combined liver transplant," Dr. Hanna notes. "All have had very good outcomes."

Not as Rare as Once Thought

According to Dr. Hanna, cardiac amyloidosis is not rare; it is underdiagnosed. He says any of the following findings should prompt a high index of suspicion for amyloidosis:

- Left ventricular hypertrophy (LVH) without defined cause
- Low/normal voltage on ECG in the setting of LVH on echo
- Bilateral carpal tunnel with no apparent explanation
- Hypertrophic cardiomyopathy in an older adult

He recommends screening for a monoclonal process with serum free light chain assay (kappa and lambda) and serum and urine immunofixation. He advises against ordering routine serum protein electrophoresis (SPEP) and urine protein electrophoresis (UPEP) when cardiac amyloidosis is suspected. "They are not sensitive enough; even when results are negative, a patient can have AL amyloidosis."

Patients whose lab tests show no monoclonal protein can still have TTR amyloidosis. Imaging techniques such as cardiac MRI, echocardiography (Figure 1) with longitudinal strain analysis, and technetium pyrophosphate scanning are noninvasive workup methods. Definitive diagnosis is made by endomyocardial biopsy.

Collaboration and Momentum

Cleveland Clinic cardiologists collaborate with amyloidosis centers at other institutions to improve outcomes for patients of all ages with the disease. The clinicians and researchers have monthly conference calls and meet yearly with patients and families. "It's all about helping each other fight this disease," Dr. Hanna says.

He is encouraged by rapid progress in all areas of diagnosis and treatment. "When I started in medicine, we saw so many patients with no options. Now this area of cardiology is progressing and expanding." ■

Contact Dr. Hanna at hannam@ccf.org or 216.444.3490.

Revamping Processes Around Registry Data Boosts Physician Trust — and CABG Outcomes

The latest in a series profiling how Cleveland Clinic's Miller Family Heart & Vascular Institute works with allied and affiliated provider organizations across the U.S. to improve their clinical or operational functions

Context and Challenge

In January 2014, Cleveland Clinic formed a cardiovascular surgery and cardiology affiliation with CHRISTUS St. Michael Health System, a Catholic health system and part of CHRISTUS Health, which has served the Texarkana region of Arkansas, Texas, Louisiana and Oklahoma since 1916. The relationship evolved from a consulting agreement that began in 2012.

At the start of the affiliation, the two institutions identified an opportunity to enhance feedback on quality and improve mortality and morbidity outcomes among cardiovascular surgery patients. CHRISTUS St. Michael enjoys strong physician and administrative engagement and leadership, yet key stakeholders questioned the validity of registry data for the Society of Thoracic Surgeons (STS) Adult Cardiac Surgery Database, which created an environment of mistrust around reported cardiovascular outcomes. As a result, this high-functioning, patient-focused cardiovascular program was experiencing less-than-desirable outcomes because it lacked adequate processes to accurately collect, validate, analyze and communicate results across clinical disciplines to engage physicians in quality improvement.

Approach and Solutions

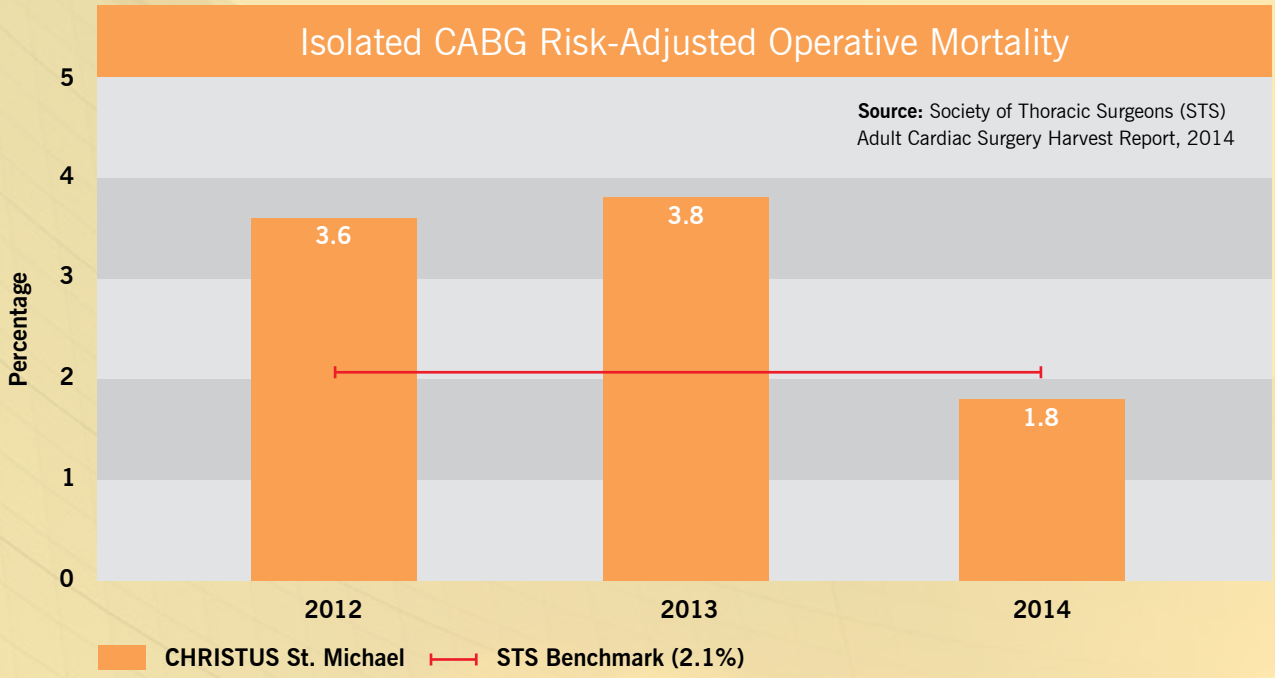
CHRISTUS St. Michael's physician leaders and administrators worked with Cleveland Clinic's affiliate program team to identify key obstacles to improving surgical outcomes and feedback on quality metrics, and they developed strategies to overcome them, as outlined in the following paragraphs.

> "This affiliation has allowed our physicians to have real-time consultation with our partners at Cleveland Clinic."
>
> – **Mike Finley, MD** | CHRISTUS St. Michael Health System

1) Ensuring data validation and accuracy through a Cardiac Registry Boot Camp. As a first step, CHRISTUS St. Michael's cardiac registry team attended a three-day cardiac registry boot camp hosted by Cleveland Clinic's Miller Family Heart & Vascular Institute for its affiliated hospitals. The camp is designed for beginner abstractors and enabled direct contact with Cleveland Clinic registry experts. This training and guidance empowered the cardiac registry team to fill gaps in their processes for registry data review and validation. The result has been improved data accuracy and a better understanding of key competencies central to registry reporting.

2) Establishing processes for second opinions and mortality review. This step has given CHRISTUS St. Michael surgeons and cardiologists access to Cleveland Clinic call schedules on a daily basis, allowing them to connect rapidly for second opinions or consultations on complicated or high-risk cases. This access is enhanced by electronic image transfer for use in second opinion reviews. The result is better-informed patient selection and a collaborative approach to challenging cases. Additionally, inpatient documents were submitted for all CHRISTUS St. Michael 2014 cardiovascular surgery mortality cases and reviewed by leading Cleveland Clinic cardiac surgeons.

3) Enhancing quality infrastructure and outcomes analysis. After multiple iterations, a comprehensive cardiovascular surgery scorecard was produced and is now reviewed routinely. The scorecard includes core metrics pertinent to improving STS ratings. Its adoption has enabled the cardiac registry team to provide physicians with real-time data feedback, which promotes discussion of patient fallouts. Also, regularly occurring quality meetings have been established among a multidisciplinary team from both CHRISTUS St. Michael and Cleveland Clinic. In addition to physician discussion of best practices, these meetings center on reviewing the cardiovascular surgery scorecard, prioritizing specific metrics and identifying process changes to improve metrics.



Outcomes in Brief

Under the leadership of Regional Chief Medical Officer Mike Finley, MD, as well as cardiothoracic surgeon Michael Cannon, MD, and the CHRISTUS St. Michael administrative team, these changes have brought about the following:

- Improved data collection and validation
- Improved transparency of STS outcomes data among physicians
- Greater physician trust

Notably, they've also brought about a substantial improvement in CHRISTUS St. Michael's coronary artery bypass graft surgery (CABG) mortality for 2014 relative to the two prior years and to the STS benchmark, as detailed in the graph above. The observed-to-expected mortality ratio for 2014 (0.89) was likewise substantially improved from the ratios for 2012 (1.78) and 2013 (1.91).

In addition to improved data quality and transparency and greater physician trust, two other factors likely help explain this improvement in mortality:

- A concentrated emphasis on preoperative risk assessment and determination of appropriateness and timing of surgery
- Greater appreciation of the need to consider referring patients deemed high-risk (based on STS preoperative risk score or clinical judgment) to a major facility for surgery

Reflections on the Relationship

"This affiliation has allowed our physicians to have real-time consultation with our partners at Cleveland Clinic," says Dr. Finley. "Cases are discussed and studies are reviewed, sometimes with multiple physicians. This collaboration has provided our physicians with input and confidence when making decisions about treatment options and patient selection, which has been invaluable to patient care.

"Just as important has been the opportunity to validate and improve our data collection so that it accurately reflects our patient experience," he adds. "Our surgical team has benefited greatly from Cleveland Clinic's site visits, the processes we've implemented have been highly successful, and the assistance in strategically evaluating new technology and services has been extremely helpful. We could not be more pleased with this affiliation." ■

For more on advisory services from Cleveland Clinic's Miller Family Heart & Vascular Institute, visit affiliatenetwork.clevelandclinic.org.

Minimally Invasive Thoracic Surgery:

Clues to When It's Appropriate and When It's Not

BY DANIEL RAYMOND, MD

Figure 1. Minimal scarring was encountered on initial inspection of the case patient's chest at the time of completion pneumonectomy in 2015.

Case Vignette

In 2011, a 66-year-old woman diagnosed with primary adenocarcinoma of the lung underwent a left lower lobectomy with video-assisted thoracoscopic surgery (VATS) at Cleveland Clinic. Her recovery was uneventful, and she subsequently stopped smoking. In 2015, she was diagnosed with an unrelated cancer in the remaining left upper lobe; this time, it was squamous cell carcinoma. Because her prior resection resulted in minimal scar formation in the chest (Figure 1), we were able to perform a completion pneumonectomy using VATS (Figures 2 and 3). Her postoperative course was uncomplicated, and she was discharged after five days. She continues to do well.

The Expanding Reach of Minimally Invasive Procedures

Increasing utilization of thoracic CT scans by a host of healthcare providers, together with the advent of Medicare reimbursement for screening CT scans in smokers, has led to the diagnosis of growing numbers of early lung cancers.

These cancers require a multidisciplinary treatment team that includes a thoracic surgeon. In many cases the patient and referring physician expect the surgeon to treat the cancer with a minimally invasive procedure, as such procedures have been shown to reduce postoperative pain and hasten recovery from surgery.

Indeed, the majority of patients with early-stage lung cancers can be treated with VATS or robotic surgery. In fact, virtually every oncologic disease of the lung and esophagus — as well as benign disease of the chest — can be treated with a minimally invasive approach. Likewise, minimally invasive techniques are widely used for mediastinal surgery and for biopsies of masses and lymph nodes. As a result, I perform 80 to 90 percent of my thoracic operations with video assistance.

At the same time, although the indications for minimally invasive thoracic procedures continue to expand, there remain clear indications for open surgery. My goal in choosing between the two is to achieve the necessary diagnostic and therapeutic outcomes for each patient while ensuring safety and a rapid recovery.

Three Key Benefits of a Minimally Invasive Approach

1) Improved functional outcomes. Compared with open surgery, less-invasive options such as VATS and robotic surgery result in reduced postoperative discomfort and quicker patient recovery. In turn, patients stay fewer days in the hospital and return to normal activities, including work, sooner.

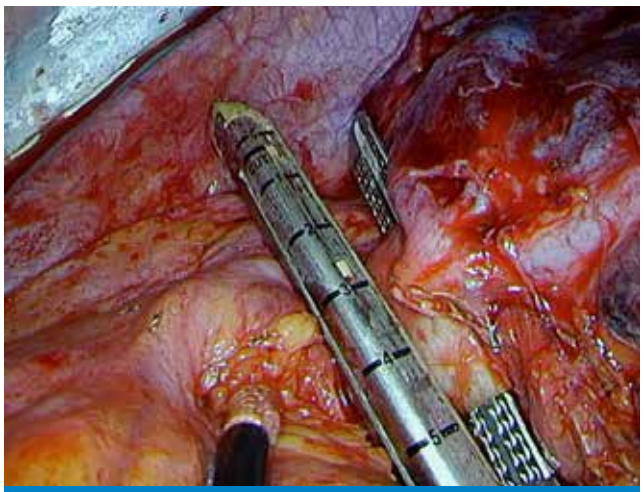


Figure 2. Completion pneumonectomy in the case patient was performed using video-assisted thoracoscopic surgery. This intraoperative photo shows a surgical stapler around the main artery entering the left lung.

2) Easy conversion to open surgery when needed. We expect minimally invasive thoracic surgery to become the gold standard for treating lung cancer. In addition to being easier on patients, minimally invasive techniques do not compromise the safety or quality of the cancer operation when applied appropriately. These procedures are easily converted to an open thoracotomy if the surgeon should encounter any issue that might compromise the operation's quality or safety.

3) Less-compromised anatomy if future procedures are needed. The case study above illustrates an overriding consideration in favor of minimally invasive thoracic surgery: leaving the patient better prepared for a possible future surgery. Because our patient's initial cancer had been treated with VATS, she had minimal scar tissue in her chest (Figure 1). Although the appearance of an unrelated cancer four years later was unanticipated, lack of scar tissue meant the remaining portion of her lung could be successfully removed in a second minimally invasive procedure.

An overriding consideration in favor of minimally invasive thoracic surgery is that it leaves the patient better prepared for a possible future surgery.

When Minimally Invasive Approaches Don't Make Sense

The optimal choice for an individual patient is dictated by his or her presenting anatomy, cancer stage, underlying physiologic status and history of prior chest surgeries and lung diseases.

Factors that may lead to preference for an open operation over a minimally invasive technique include:

- Previous open chest surgery
- Prior radiation to the chest
- History of pulmonary infections
- Prior coronary artery bypass graft surgery (CABG). The vascular grafts are often proximate to lung tissue, so there is a risk of injury during lung surgery. While this is not an absolute contraindication to a VATS lung procedure, it increases the probability that a thoracotomy will be needed.

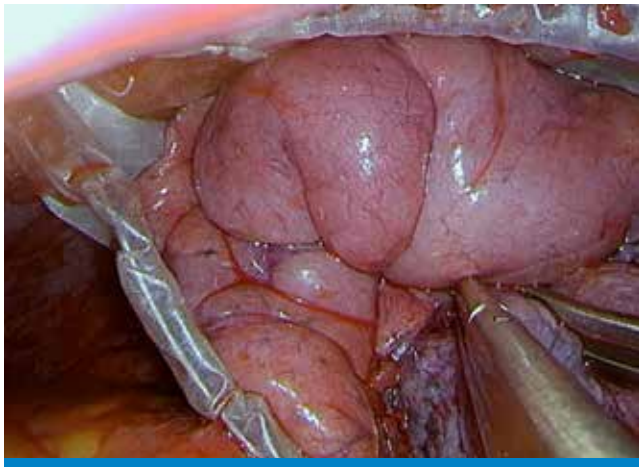


Figure 3. Intraoperative photo showing the remaining portion of the case patient's lung being placed in a bag for extraction from the chest.

Additionally, operations for mesothelioma and chest wall resections require open surgery at this time.

The surgeon's experience and preference play a large role in patient selection, since the appropriate choice of any method depends on good surgical judgment. Individual surgeons and institutions must monitor their own outcomes, and such monitoring is enhanced by voluntary participation in the Society of Thoracic Surgeons (STS) General Thoracic Surgery Database. These outcomes data, together with the publicly reported STS quality ratings derived from them, can help patients make informed decisions.

Considerations for Referral

The referring physician is wise to inquire whether a thoracic surgeon employs minimally invasive techniques, as the ability to offer a spectrum of options can help ensure the most appropriate oncologic care for a given patient.

Patients should be reassured that it is perfectly acceptable to ask a surgeon what percentage of procedures he or she performs minimally invasively — as well as the criteria used to decide when to use these techniques.

Consideration should also be given to whether the thoracic surgeon is part of a multidisciplinary team, since all oncologic surgeries benefit from a team approach. A team where the thoracic surgeon works closely with a medical oncologist, a radiation oncologist and a pulmonologist is best equipped to provide optimal care. ■

Dr. Raymond (raymond3@ccf.org; 216.636.1623) is a surgeon in the Department of Thoracic and Cardiovascular Surgery.

Forget Watchful Waiting for Severely Regurgitant Mitral Valves

Large analysis shows early repair to be safe and effective

Treating degenerative mitral valve (MV) disease earlier and with less-invasive techniques is more beneficial to patients than watchful waiting. So concludes a new analysis of more than 5,900 repair procedures for degenerative MV disease performed at Cleveland Clinic over 26 years (*Ann Thorac Surg*. 2015;99:1992-2000).

"An aggressive strategy is successful, safe and effective," says Joseph Sabik III, MD, Chairman of Thoracic and Cardiovascular Surgery at Cleveland Clinic and the study's senior author. "Less-invasive technology has enabled more patients to benefit from mitral valve repair before experiencing symptoms such as atrial fibrillation or heart failure."

Assessing Practice Changes over Time

Dr. Sabik and colleagues reviewed the records of 5,902 patients who underwent MV repair for regurgitation at Cleveland Clinic from 1985 to 2011. They divided the study period into three segments — 1985 to 1997, 1997 to 2005, and 2005 to 2011 — and compared trends in patient characteristics, timing of intervention and surgical techniques.

They found that nearly twice as many patients treated from 2005 to 2011 were asymptomatic (NYHA class I) compared with those treated from 1985 to 1997. Moreover, patients from 2005 to 2011 were far less likely to have heart failure, atrial fibrillation or moderate or severe left ventricular dysfunction, suggesting a trend toward referral earlier in the disease course.

Additionally, the more recent patients were less likely to have comorbidities such as peripheral artery disease, carotid disease, prior stroke or myocardial infarction, or chronic obstructive pulmonary disease.

Patients treated in the later years were also discharged about two days sooner than those treated in the earlier years. This was attributed to fewer full sternotomies and increased use of less-invasive surgery.

Outcomes Improved with Time

Moreover, rates of in-hospital mortality and reoperation on the repaired valve were initially low and became progressively lower over time. Rates of residual regurgitation were minimal throughout the overall study period.

"We recommend that patients with severe mitral valve regurgitation undergo surgical evaluation, even if they have not developed symptoms," says Dr. Sabik. "At this time, however, asymptomatic patients with severe regurgitation should be referred to high-volume centers for mitral repair, where successful repair with no or minimal residual regurgitation and low mortality can be expected."

An 'Important Shift' Toward Earlier Referral

In an invited commentary accompanying the study (*Ann Thorac Surg*. 2015;99:2000), James S. Gammie, MD, of the University of Maryland School of Medicine states that the study documents an important shift toward referral for MV repair earlier in the disease process, before the effects of mitral regurgitation compromise long-term outcomes.

"The authors' institution is ahead of the national curve, where fewer than 10 percent (compared with 44 percent in this report) of referred patients are asymptomatic," writes Dr. Gammie. He adds that the study serves as a "reminder that highly reliable and durable mitral repair is probably best achieved by surgeons with a dedicated subspecialization in mitral valve repair." ■

Contact Dr. Sabik at sabikj@ccf.org or 216.444.6788.

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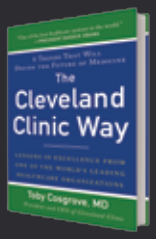

The Cleveland Clinic Way
By Toby Cosgrove, MD, CEO and President, Cleveland Clinic

Great things happen when a medical center puts patients first. Visit clevelandclinic.org/ClevelandClinicWay for details or to order a copy.

About Cleveland Clinic
Cleveland Clinic is an integrated healthcare delivery system with local, national and international reach. At Cleveland Clinic, more than 3,200 physicians and researchers represent 120 medical specialties and subspecialties. We are a main campus, more than 80 northern Ohio outpatient locations (including 16 full-service family health centers), Cleveland Clinic Florida, Cleveland Clinic Lou Ruvo Center for Brain Health in Las Vegas, Cleveland Clinic Canada, Sheikh Khalifa Medical City and Cleveland Clinic Abu Dhabi.

In 2015, Cleveland Clinic was ranked one of America's top five hospitals in *U.S. News & World Report*'s "Best Hospitals" survey. The survey ranks Cleveland Clinic among the nation's top 10 hospitals in 13 specialty areas, and the top hospital in heart care for the 21st consecutive year.

Cleveland Clinic

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Cardiac Consult

CME Calendar

Contemporary Management of Cardiovascular Disease

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