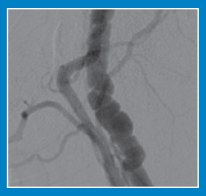
INSIDE THIS ISSUE



Cleveland Clinic

Cardiac Consult

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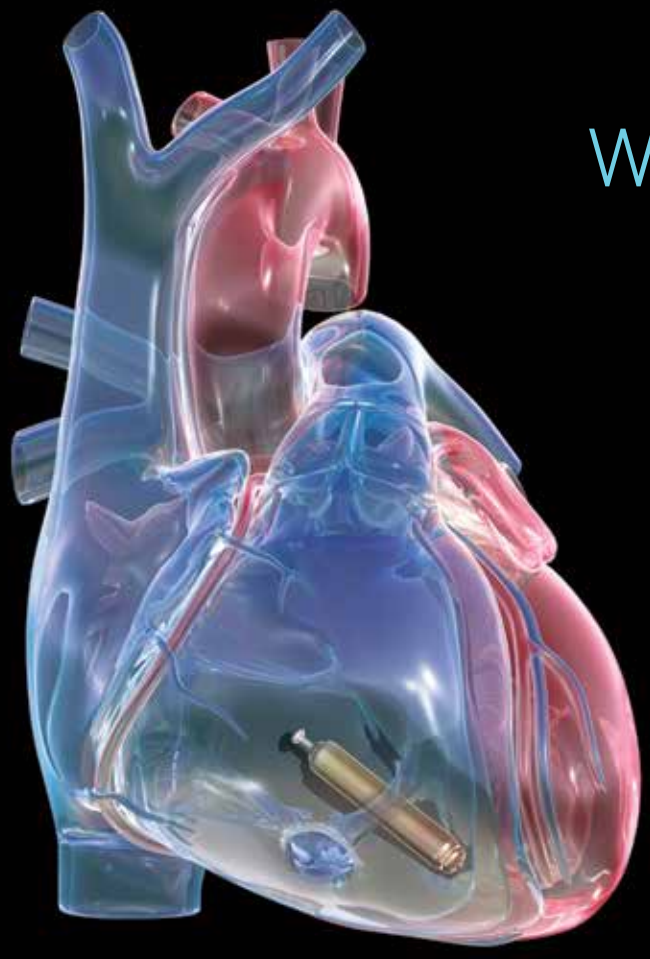

Who Needs Leads?

Pursuing Leadless Pacemaking While Perfecting the Art of Lead Extraction

– p9

Dear Colleagues:

Two steps forward and one step back. That's how progress often occurs in medicine. New findings override old beliefs, and the old wisdom makes way for the new. We offer a vivid example in this issue of *Cardiac Consult*.

Research by Cleveland Clinic cardiologist and researcher Stanley Hazen, MD, PhD, and his team has changed our view of HDL cholesterol. For years, we believed that high levels of HDL were cardioprotective. Now we know that under certain circumstances, HDL can promote inflammation and atherosclerosis. This may explain why drugs that have managed to raise HDL levels have so far failed to reduce cardiac risk. So much for the "good" cholesterol. The bright side is that we now have an accurate new biomarker for cardiac risk — for which Dr. Hazen has already developed a new test.

Implantable cardiac devices were a big step forward in treating rhythm disorders. The benefits have been only somewhat mitigated by the occasional need to remove dysfunctional or infected lead wires. But as you'll read, the need for lead removal has grown steadily as more patients are living with implanted devices. Cleveland Clinic electrophysiologists are steering efforts to disseminate advances in navigating the complexities of transvenous lead extraction, and they're at the forefront of research that suggests the holy grail — leadless pacemakers — may not be far off.

The symptoms of infective endocarditis are often mistaken for influenza or pneumonia. Unless it's caught early enough, this often deadly condition calls for surgical treatment. The procedures involved are complex and delicate. As you'll read, they call for experienced specialists working as part of an integrated team at a comprehensive medical center. Cleveland Clinic surgeons like Gösta Pettersson, MD, PhD, have raised the treatment of infective endocarditis to an art.

We're pleased to get the word out about infective endocarditis as well as another often-overlooked condition: fibromuscular dysplasia. We're proud of the leadership of Heather Gornik, MD, in establishing greater awareness of and research into this nonatherosclerotic vascular disease.

We hope you find these snapshots of progress — complete with all its real-world complexities — to be of interest. And we urge you to visit page 14 for the first installment of our new series on surgical decision-making. Thank you for reading *Cardiac Consult*.

Respectfully,

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3 Stars in 3 STS Categories for 3+ Years Running

Cleveland Clinic's main campus was one of just 17 U.S. hospitals and surgical groups to receive a three-star (highest) rating in all three categories of the Society of Thoracic Surgeons' (STS) risk-adjusted quality ratings for adult cardiac surgery for calendar year 2013 among more than 550 participating programs rated. The three categories are CABG, aortic valve replacement (AVR), and a composite of both CABG and AVR.

Cleveland Clinic has achieved three stars in all three categories in all STS rating reports dating back to the July 2010-June 2011 reporting period.

A **New View** of HDL's Role in Heart Disease

Despite HDL's reputation as a cardiovascular protectant, it increasingly appears to have a dark side.

Is "good" cholesterol really good? Not necessarily so. High-density lipoprotein (HDL) — the molecule that normally scours from cells of vessel walls the excess cholesterol deposited there by low-density lipoprotein (LDL) — is itself vulnerable to corruption and conversion into a destructive form.

Stanley Hazen, MD, PhD

The modified, oxidized HDL and its major structural protein, apolipoprotein A1 (apoA1), not only are rendered dysfunctional, losing their cholesterol-scavenging capability, but gain potent pro-inflammatory capacities that activate endothelial cells and potentially contribute to vulnerable plaque development. Dysfunctional apoA1 is abundant in atherosclerotic plaques, and elevated levels of the oxidized, malevolent protein in patients' blood have been shown to be associated with increased coronary artery disease (CAD) risk.

This profoundly altered view of HDL and its role in heart disease results from more than a decade of investigation by Cleveland Clinic cardiovascular researcher Stanley Hazen, MD, PhD, Head of the Section of Preventive Cardiology and Rehabilitation and Vice Chair of Translational Research, Lerner Research Institute.

His research team's latest study, published in February's *Nature Medicine* (2014;20[2]:193-203), reveals at the structural level how HDL is corrupted. Using innovative techniques, the researchers determined the HDL molecule's complex atomic structure. Next they identified a targeted site (Trp72) on apoA1 where oxidation occurs, which disrupts apoA1/HDL cholesterol acceptor function. Then they genetically engineered an antibody that specifically recognizes the corrupted form of HDL and apoA1. The findings may soon produce a new diagnostic test to quantify patients' dysfunctional HDL — and may eventually have therapeutic implications.

"We're slowly decoding the structure and modifications that happen to apoA1 and HDL in the artery wall and understanding how that leads to changes in function," Dr. Hazen says. "We're starting to understand what's going on at a very detailed, structural level, and the next step is figuring out how to block that."

> "We're starting to understand what's going on at a very detailed, structural level, and the next step is figuring out how to block that."
>
> – Stanley Hazen, MD, PhD

New Insight on the HDL Paradox?

HDL's susceptibility to conversion from beneficial to harmful may help explain the HDL paradox that has baffled researchers.

Epidemiologic studies repeatedly have shown an inverse association between circulating HDL cholesterol or apoA1 levels and CAD: the higher the level of HDL cholesterol or apoA1, the lower the prevalence of CAD and risk of cardiovascular problems. But several interventional studies testing HDL cholesterol-raising drugs failed to show a reduction in cardiac risk, and studies testing direct infusions of different HDL formulations have yielded mixed results.

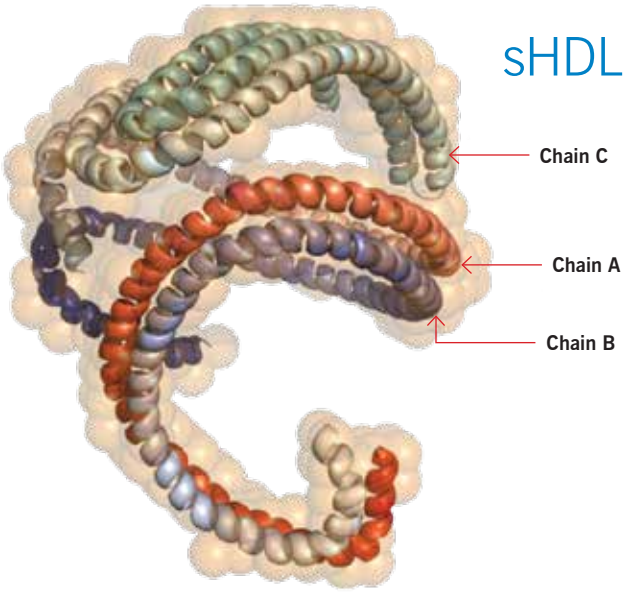


Figure 1. Hazen and colleagues recently reported the first structure of spherical HDL (sHDL), the most abundant form of HDL in blood. Spherical HDL has three apoA1 chains (labeled), which are shown within the low-resolution shape of protein that was directly visualized (semitransparent). (For image credit, see end of article.)

To Dr. Hazen, that strongly suggests the HDL particle's functionality (or dysfunctionality), not its bulk amount, is more clinically important — a hypothesis his latest findings support.

Studying Inflammation Pathways

Dr. Hazen, whose training is in biochemistry as well as internal medicine, didn't set out to study HDL. His research had been focused on deciphering the inflammation pathways and processes in atherosclerosis.

His particular interest has been myeloperoxidase (MPO), an enzyme secreted by activated neutrophils and monocytes at sites of inflammation, including within atherosclerotic lesions. MPO churns out free radicals and diffusible oxidants that are toxic to microbes. But MPO also promotes oxidative damage of host tissues. Since MPO accumulates in the subendothelial space of the artery wall, that damage fosters development of CAD. Elevated MPO levels are associated with increased risk for CAD and coronary events.

Dr. Hazen's team began trying to identify the major targets that MPO oxidizes and modifies in artery walls. HDL — and specifically apoA1 — emerged as the bull's-eye. "If you quantify the degree of MPO's oxidation of apoA1 vs. other proteins in its surroundings within the artery wall, it's more than 500-fold selectively targeted," Dr. Hazen says.

> "HDL has evolved to bind to and sequester heme proteins like MPO that can make reactive species. You need a way to get rid of the land mines. I call HDL the bomb squad."
>
> – Stanley Hazen, MD, PhD

Why the selective targeting? It happens because MPO binds directly to HDL in the artery wall. One of HDL's jobs appears to be snaring potentially harmful enzymes and carrying them away for elimination. So it needs an accessible docking mechanism. "HDL has evolved to bind to and sequester heme proteins like MPO that can make reactive species," Dr. Hazen says. "You need a way to get rid of the land mines. I call HDL the bomb squad."

In this case, though, the hazardous cargo disables its transporter while also turning it toxic. Dr. Hazen's research shows that MPO's oxidation of apoA1 and HDL severely impairs the lipoprotein's cholesterol-accepting ability and converts it into a pro-inflammatory particle.

Defining HDL's Structure: Surprising Results from a Novel Technique

Confirming MPO's selective affinity for HDL/apoA1 and understanding the process and disastrous consequences of oxidation required deeper knowledge of HDL's structure. Dr. Hazen's team needed to determine the lipoprotein's shape and the architecture of its binding sites.

The traditional method for visualizing protein structures, X-ray diffraction, would require crystallizing HDL, which no one has been able to do. So for more than a decade, Dr. Hazen worked on alternative visualization means. His team was the first to use a technology called contrast variation neutron scattering to systematically map HDL. The results were a surprise.

Computational models of HDL had suggested it was a bilayered disc, like a coin, with a ring of protein around its rim. Neutron scattering revealed a much more complex structure. The protein and lipid components of spherical HDL, the most abundant form of HDL in the blood, were directly visualized, revealing a complex shape where the apoA1 surrounded a lipid core (Figures 1 and 2).

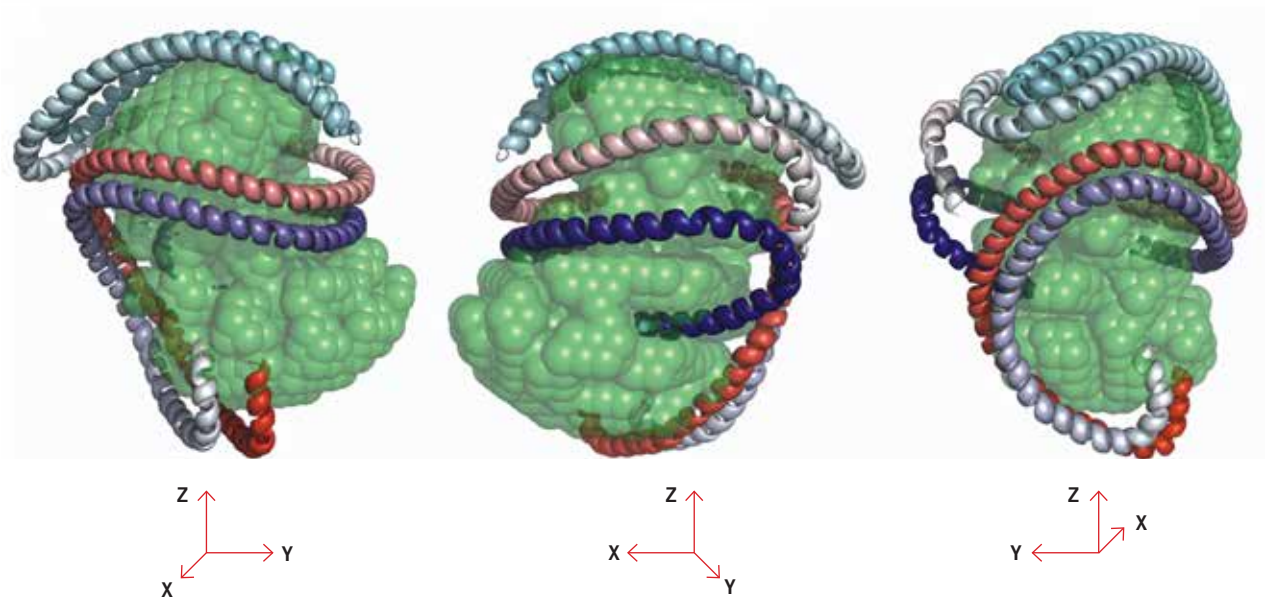


Figure 2. Superimposition of the model from Figure 1 within the low-resolution structure of the lipid component that also was directly visualized (green). (For image credit, see end of article.)

"HDL used to be thought of as just an oil slick with a protein like a serpent inside it," Dr. Hazen says. "But it's nowhere near that uncontrolled. It has a very defined structure, and the protein is not highly rigid; it's highly dynamic. But it follows set rules of structure."

Another analytical method called hydrogen/deuterium exchange enabled the team to map key contact sites on the apoA1 molecule of HDL with HDL-associated proteins. Proteomic studies of apoA1 from lesions identified the site at Trp72 where MPO oxidatively modifies apoA1.

Targeting Dysfunctional HDL

Armed with that structural and binding site knowledge, Dr. Hazen began developing a monoclonal antibody to recognize MPO-oxidized apoA1. This would allow the researchers to determine diagnostically how much dysfunctional HDL was present in vivo. It also might function as a therapeutic aid, facilitating the corrupted lipoprotein's removal.

Dr. Hazen's team screened more than 30,000 candidate antibodies before identifying one with the right binding characteristics. But the antibody's affinity was too low to be diagnostically reliable. The researchers had to carefully genetically modify the antibody to amplify its affinity without altering its binding characteristics. "In the end, we increased the antibody's affinity more than 1,600-fold," Dr. Hazen says.

Using this superantibody, the researchers confirmed in 2013 that atherosclerotic plaque-laden human aortas are teeming with dysfunctional apoA1, while there is far less in healthy vessel walls. And unlike in circulating blood, where apoA1 rides within HDL, the dysfunctional apoA1 in atherosclerotic plaque is lipid-free, unassociated with HDL.

What's Next? A Diagnostic Test and Future Research

Cleveland HeartLab, a spinoff company from Cleveland Clinic, is developing a diagnostic test for arterial inflammation and cardiac risk based on the antibody biomarker for dysfunctional apoA1. The company hopes to have the assay commercially available by the end of 2014, Dr. Hazen says.

Though several pharmaceutical companies are testing potential MPO-inhibiting drugs — which presumably would block inflammation — none currently is approved for use. So patients who test positive for dysfunctional apoA1 probably would be advised to take preventive steps to reduce cardiovascular risk, Dr. Hazen says, such as lowering LDL levels, increasing exercise, and controlling weight, blood pressure and diabetes.

Going forward, Dr. Hazen's team will attempt to identify additional HDL sites where oxidation-induced dysfunctionality can occur.

"We used to have good and bad cholesterol," he says. "I think we're now going to have dysfunctional HDL, and that may be a composite of several things. The real question is what you do about it. That will be the next five, 10 years of work." ■

Direct comments to Dr. Hazen via coffmaj@ccf.org.

Figures 1 and 2 were originally published in *Journal of Biological Chemistry.* 2009;284(52):36605-36619.

Infective Endocarditis:

This Insidious Process Demands an Experienced Management Team

Infective endocarditis (IE) affects 20,000 to 50,000 U.S. adults a year. Without prompt diagnosis and proper treatment, damage to the valve and myocardium may be irreversible and lead to complications such as heart failure, sepsis, stroke and renal failure.

In IE, microorganisms adhere to areas of damaged endocardium and form vegetations. Infected tissue can split off emboli, which may occlude arteries in the brain and other organs, causing local infarcts, mycotic aneurysms and infection. Bacteria also produce toxins and enzymes that kill normal cells and disintegrate the tissue, damaging leaflets and preventing cusps from healing.

"The diagnosis and management of patients with IE requires a multidisciplinary, team-based approach involving clinicians with knowledge about the disease process and experience treating patients at each step," says Steven Gordon, MD, Chairman of the Department of Infectious Disease and a member of Cleveland Clinic's IE team.

The team — which also comprises clinical and interventional cardiologists, cardiothoracic surgeons, pathologists, microbiologists, neurologists and psychiatrists — has accrued one of the largest single-center IE experience bases in the world.

An Easily Overlooked Diagnosis

Challenges start with making a diagnosis early, before damage advances.

Patients commonly present with fever and may complain of muscle and joint aches and poor appetite, making IE an easy diagnosis to overlook. Risk factors for IE include previous heart disease, interventional procedures, implanted prosthetic devices or dental work.

"You have to have a high level of suspicion and avoid jumping to the conclusion that the patient has influenza with pneumonia and immediately prescribe antibiotics," says Gösta Pettersson, MD, PhD, Vice Chairman of the Department of Thoracic and Cardiovascular Surgery.

Such suspicion is particularly important if the patient has a prosthetic valve or other cardiac device, he adds. "Any patient with a history of valve surgery who becomes febrile and does not improve quickly should be referred to a center with experience diagnosing IE."

Even when echocardiography shows no sign of infection, infected tissue may be lurking. Three separate blood cultures from different venipuncture sites should be obtained at least one hour apart to confirm the diagnosis and identify the pathogen, Dr. Pettersson notes.

"The pathology is important, because it describes the stage of disease as it relates to the damage caused by the infection and predicts which problems will develop," he explains.

In acute cases, antibiotic treatment should be started within two hours, during which time the blood cultures are being obtained. "To prevent valve damage, antibiotics have to be started before destruction begins," Dr. Pettersson says.

Why Rapid Evaluation and Treatment Matter

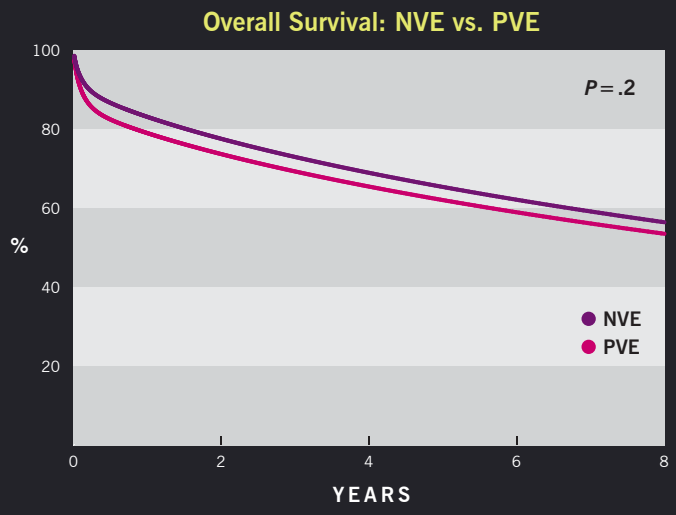
Waiting for antibiotics to clear the infection before taking further action is a classic mistake, say the IE experts. The antibiotic may not be effective, and the disease will worsen. Prompt removal of infected tissue may be required.

"Not every patient needs surgery, but every case should be evaluated with an experienced cardiac surgeon," says Dr. Gordon.

Knowing when to operate before damage occurs requires experience. "The surgeon is often involved too late, when valve destruction is advanced," says Syed Hussain, MD, a cardiothoracic surgeon on the IE team.

If infection is not entirely debrided, the patient will have an increased risk of recurrent infection and death. Risk is further increased in patients with a prosthetic valve. Unfortunately, some physicians are hesitant to send these patients for a second surgery.

"By the time we see them, they are often extremely sick and need a more complex operation," says Dr. Hussain.



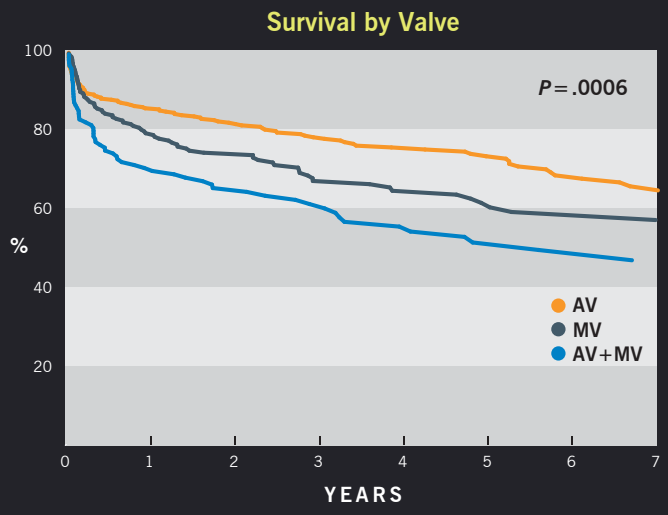


Figure 1 (left). Survival among 1,195 patients who had surgery for IE at Cleveland Clinic from 2002 through 2010 was comparable regardless of whether patients had prosthetic (PVE) or natural (NVE) valve endocarditis. Overall survival in the combined groups was 92 percent at 30 days, 81 percent at one year, 72 percent at three years and 60 percent at seven years.

Figure 2 (right). Among the same cohort of patients as in Figure 1, survival varied significantly by whether IE involved the aortic valve (AV), the mitral valve (MV) or both.

Lessons from a Large Experience Base

Early referral may save the valve, avoid an operation and lower the risk of death. In experienced centers, surgery in patients with active IE is today associated with much lower mortality than before. In a review of 1,195 consecutive patients who underwent surgery for IE at Cleveland Clinic from 2002 through 2010, 30-day survival was 92 percent, with similar survival for patients with prosthetic and natural valve infections (Figure 1).

For patients with destruction and invasive IE, outcomes are better if the IE affects the aortic valve rather than the mitral valve (Figure 2). Reasons include the typically poor condition of patients with mitral valve IE, the mitral valve anatomy and less-than-optimal mitral valve prostheses.

"If you postpone surgery on the presumption that operating on a patient with active infection is too risky and technically demanding, you may expose the patient to risk of further destruction of cardiac tissue and potential development of heart failure, heart block and repeat embolic events," says Dr. Pettersson. "It also increases the possibility that the patient may subsequently be ineligible for surgery due to complications of the disease or its treatment." ■

Contact Dr. Pettersson at petterg@ccf.org or 216.444.2035, Dr. Hussain at hussais2@ccf.org or 216.444.3604, and Dr. Gordon at gordons@ccf.org or 216.444.8976.

Infective Endocarditis:
What Every Cardiothoracic Surgeon Needs to Know

Understanding the pathophysiology of IE is critical to understanding its natural progression and choosing the optimal operation for the best outcome. Dr. Pettersson, Dr. Hussain and colleagues have condensed this information into nine pearls of wisdom in a liberally illustrated atlas of IE disease progression published in the April 2014 *Journal of Thoracic and Cardiovascular Surgery* (2014;147[4]:1142-1149).

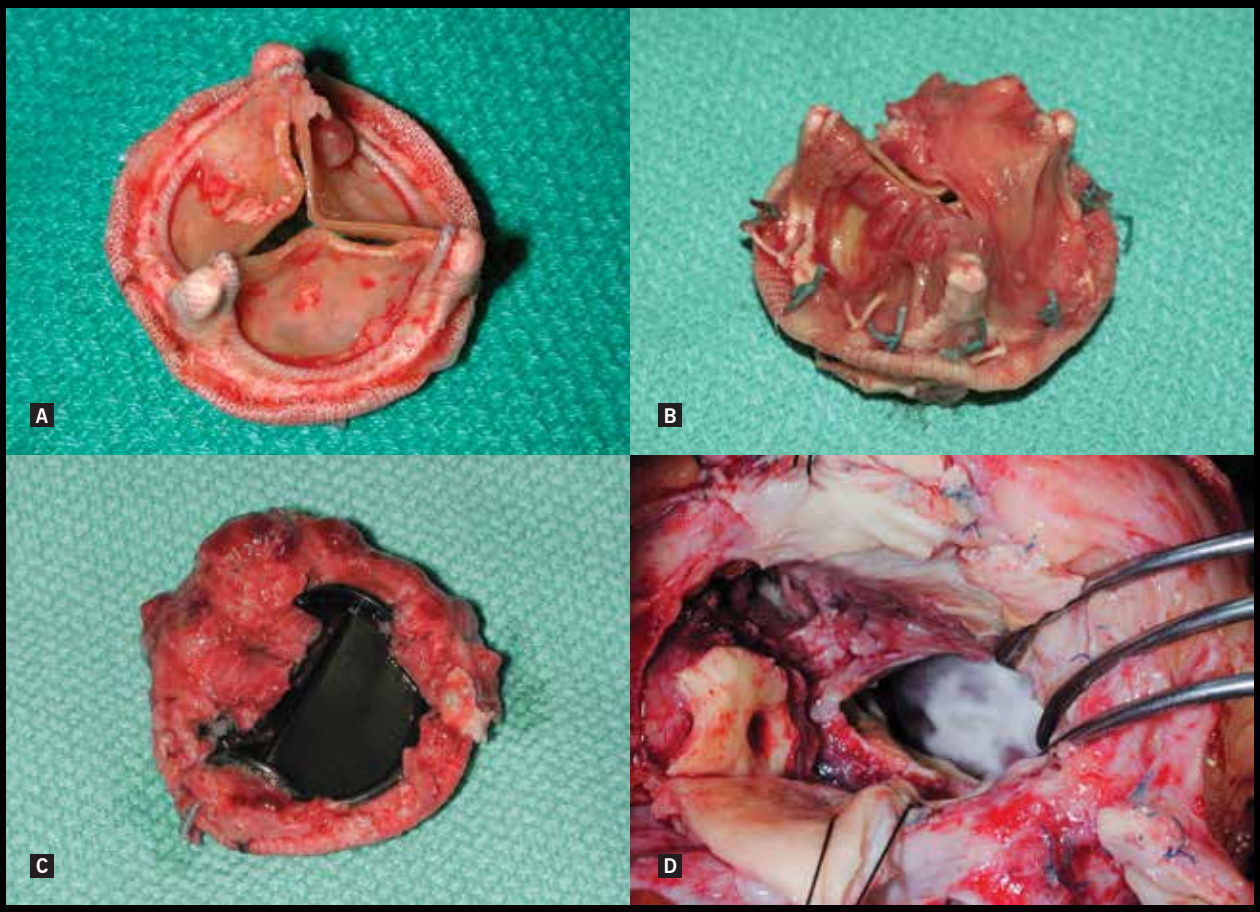
"The atlas presents major concepts that collectively describe the main features and basic facts about endocarditis every surgeon needs to know," Dr. Pettersson says.

The concepts are:

1. Vegetations in endothelial defects or injuries are the primary manifestations of IE.
2. Extra-aortic invasion of native valve endocarditis is localized.
3. Extra-aortic invasion of prosthetic valves is often circumferential.
4. Heart block is caused by bacterial destruction of the atrioventricular node and bundle of His.
5. All organisms are not equally destructive (see next page).
6. Congenital heart defects, repaired or not, are associated with increased risk of endocarditis.
7. Mitral valve endocarditis has specific features related to its anatomy and degenerative pathologic features.
8. Right-sided IE is characterized by vegetations and disintegration of valve leaflets or cusps, but almost never by invasion.
9. Complete debridement is the basic principle of successful reconstructive surgery for invasive IE.

Image of the Issue

FROM SYED HUSSAIN, MD, AND GÖSTA PETTERSSON, MD, PhD



INFECTIVE ENDOCARDITIS: DESTRUCTION DIFFERS DRAMATICALLY BY ORGANISM

The organisms causing infective endocarditis are not equally destructive or invasive. (A) This explanted tissue valve was infected with a less-aggressive organism such as an *Enterococcus* species. Such organisms are generally minimally invasive, causing formation of small vegetations, with recurrent episodes of sepsis. (B-D) In contrast, aggressive organisms, such as *Staphylococcus aureus*, can cause rapid, extensive tissue destruction, usually within a few weeks, with formation of large vegetations. These images show a tissue valve (B) and a mechanical valve (C) infected by *S. aureus* and extensive tissue destruction with aortic root abscess (D) caused by *S. aureus* prosthetic valve endocarditis.

ADDITIONAL REVEALING IMAGES ARE AVAILABLE IN THE AUTHORS' NEWLY PUBLISHED ATLAS OF INFECTIVE ENDOCARDITIS, AS DISCUSSED IN THE PRECEDING ARTICLE. FOR MORE INFORMATION, CONTACT SYED HUSSAIN, MD, AT HUSSAIS2@CCF.ORG OR 216.444.3604.

Leading from Experience

in Transvenous Lead Extraction

As indications for cardiac pacemakers and implantable cardioverter-defibrillators (ICDs) increase, ever more patients are requiring lead extraction for complications or replacement of the leads for these implanted electronic devices. An estimated 10,000 to 15,000 transvenous lead extractions are now performed yearly worldwide. Complications requiring lead removal are varied and include infection, lead malfunction or breakage, and vein occlusion. Additionally, lead removal is needed when leads become dislodged or are no longer necessary.

No Substitute for Experience

Yet lead extraction is complex, and recent years have seen a parallel rise in patients whose extraction procedures have failed or were improperly performed — or in whom infection has been treated incompletely. As a major cardiac referral center, Cleveland Clinic sees a large number of these patients.

Averaging 250 lead extractions a year for the past 15 years, Cleveland Clinic's lead extraction team has developed unsurpassed expertise in performing difficult and complex extractions. In a new study of 5,521 leads removed in 2,999 transvenous extraction procedures at Cleveland Clinic from 1996 to 2011 (*Heart Rhythm.* 2014 Jan 17 [Epub ahead of print]), the team reported the following outcomes in a complex patient population with multiple comorbidities:

- 95.1 percent complete procedural success
- 98.9 percent clinical success
- 1.1 percent failure
- 3.6 percent rate of minor complications
- 1.8 percent rate of major complications
- 2.2 percent all-cause mortality within 30 days

"Quality is related to volume. You must have a multidisciplinary team that performs lead extractions consistently and often," says the study's senior author, Cleveland Clinic electrophysiologist Bruce Wilkoff, MD, who has been performing lead extractions since 1988 and heads the lead extraction team. The team comprises clinicians from cardiology, nursing, anesthesiology, infectious disease and cardiothoracic surgery.

Figure. Large vegetation on a right ventricular ICD lead removed at the time of surgery with a second large embolized vegetation removed from the pulmonary artery.

Infection — Uncommon but Gravely Serious

Though the rate of lead infection is only 1 in 100 patient-years, infection is associated with significant morbidity and mortality. "Infection is extremely serious and should not be dismissed," says Steven Gordon, MD, Chairman of the Department of Infectious Disease and a member of the lead extraction team. He plays a key role in the diagnosis of infection and management of infected patients, as well as in determining when reimplantation is safe.

Incomplete or improper treatment of infection is common. "Antibiotics alone will not cure a device infection, which will return when treatment is stopped unless both device and leads are removed," says electrophysiologist Khaldoun Tarakji, MD, MPH, another team member.

Infection is a class I indication for lead extraction. Patients can present with pocket infection or endovascular infection; in either case, the entire system must be removed since any remaining lead will act as a nidus for infection and cause relapse. Once the infection is cleared, a new system can be implanted on the opposite side.

With Fever, Assuming Device Involvement Is Prudent

Febrile patients with an intact pocket who present in the emergency department or in a different hospital system often are given multiple courses of antibiotics before the possibility of device infection arises. Dr. Gordon advises physicians to have a low threshold for evaluating these patients.

"They are at high risk for bacteremia," he says. "When any patient with a device presents with a staph infection or fever, assume the device is involved until proven otherwise."

Although some physicians hesitate to operate on extremely sick patients, the mortality rate for lead extraction is minimal compared with the risks posed by infection. "Major complications of transvenous lead extraction occur in about 1.4 percent of patients," says Dr. Wilkoff, "and the procedure carries a 0.3 percent risk of death. In contrast, the mortality risk with infection is very high." Antibiotics are often required for six weeks after extraction of the system.

When Lead Removal Is Less Clear

The decision to remove a malfunctioning lead is less clear and should be made on an individualized basis.

"If the patient is old or frail, the risks of extraction are weighed against the risks of capping and ignoring the lead and simply adding a new lead," says Dr. Tarakji. "In younger patients, dealing with multiple leads over time might become problematic, so lead removal should be considered."

Regardless of the factors involved, the patient should be involved in the decision. "Sometimes we see patients who've had multiple leads added over the years to stand in for malfunctioning leads but who have never been given the option of having the abandoned leads removed," Dr. Tarakji notes.

Emergent Interventions for Catastrophic Complications

Complications of lead removal occur most commonly with older leads, which can become anchored by fibrous tissue and require dissection from the venous wall and myocardium. In these cases, major vascular injury or cardiac perforation — although rare — carries significant in-hospital mortality.

A recently published study of 5,973 leads extracted during 3,258 consecutive procedures at Cleveland Clinic (*Heart Rhythm*. 2014;11[3]:419-425) found that 25 patients (0.8 percent) experienced catastrophic complications requiring emergent intervention. Of those 25 patients, 64 percent were able to be rescued with immediate response and surgical or endovascular intervention.

As a result of this experience, Cleveland Clinic has made available during extraction cases an "endovascular intervention cart" with equipment needed for such interventions.

"Catastrophic complications are uncommon but can happen at any point during lead extraction," says Dr. Tarakji. "Experience-based preparation for responding to them is of utmost importance." ■

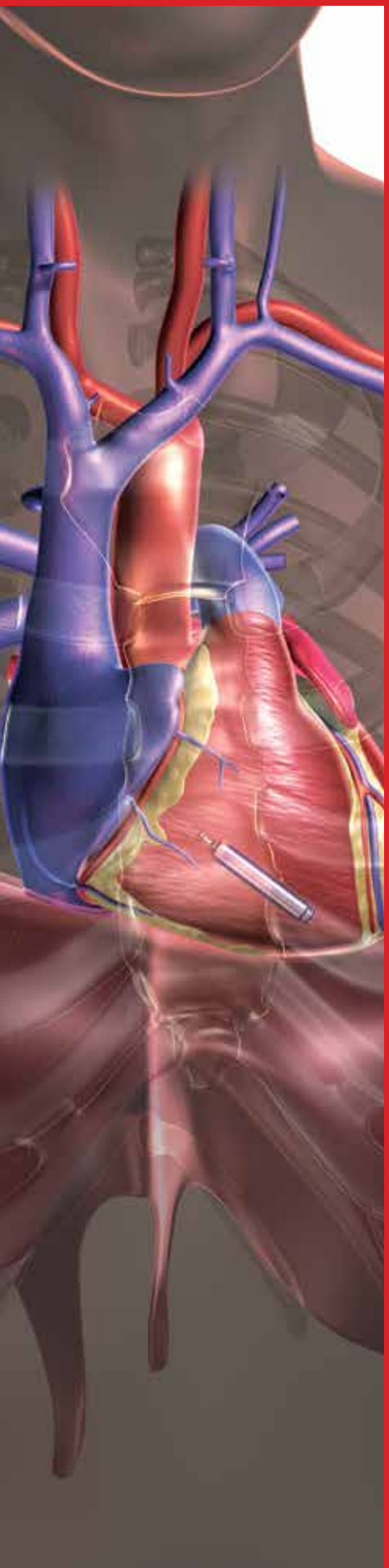
Contact Dr. Wilkoff at wilkofb@ccf.org or 216.444.4975, Dr. Tarakji at tarakjk@ccf.org or 216.445.9225, and Dr. Cantillon (see next page) at cantild@ccf.org or 216.445.9220.

Going Global to Disseminate Lead Extraction Expertise

With relatively few electrophysiologists practicing worldwide, those who perform transvenous lead extraction have limited opportunity to share their ideas and approaches with one another.

To foster such communication, Cleveland Clinic's Bruce Wilkoff, MD, has organized a collaborative community of physicians and surgeons (LeadConnection.org, launching summer 2014) with a shared interest in working together to solve common pacemaker and ICD management and extraction issues. "We are working to discover the best ways to limit complications, provide safe and effective care, and communicate and implement practice changes," he says.

Initial efforts are focused on reducing lead and device infection rates through an international clinical trial. Participation by the majority of device experts worldwide has a distinct advantage, says Dr. Wilkoff: "Once we have the answer, it will be simultaneously distributed, and practices will change worldwide."



Who Needs Leads?

Pursuing the Promise of Leadless Pacemakers

Given the complications associated with implanted cardiac pacemaker leads, the prospect of leadless pacemakers has long enticed electrophysiologists. Now, with multiple leadless pacemakers entering late-stage U.S. trials, that prospect seems near at hand.

"By eliminating pockets and leads, we hope to improve the safety profile of pacemakers," says Cleveland Clinic electrophysiologist Daniel Cantillon, MD. "We expect to see fewer infections, lead dislodgements and failures, which would sweep the bulk of pacemaker complications off the table."

In February, Dr. Cantillon performed one of the first U.S. placements of St. Jude Medical's investigational Nanostim™ leadless pacemaker, and he is enrolling single-chamber pacemaker candidates in the multicenter LEADLESS II clinical trial of that device, which is already cleared for use in Europe. Dr. Cantillon is principal investigator for Cleveland Clinic and serves on the study's steering committee for the North American trial.

Cleveland Clinic is one of three U.S. sites training investigators from other sites how to implant and remove the Nanostim.

Clinical trials of another investigational leadless pacemaker, Medtronic's Micra™ Transcatheter Pacing System, are expected to begin at Cleveland Clinic this summer under the direction of Bruce Wilkoff, MD, and Khaldoun Tarakji, MD, MPH.

SMALL BUT MIGHTY

These first entries into the leadless pacemaker field are single-chamber, programmable devices delivered by catheter via the femoral vein. The Nanostim (left photo) and Micra (right photo) each contain a lithium battery, electrode and fixation device in a body one-tenth the size of a traditional pacemaker.

The Nanostim is tipped with a small screw that secures the device into the heart muscle. A sensor and stimulatory electrode sense the heart's activity and determine when to deliver or withhold stimulation. The device's battery life depends on the amount of pacing required but is estimated to be seven to 10 years.

The Micra anchors to the myocardium with three curved prongs. Like the Nanostim, it can adjust to the patient's changing activity level. Its estimated battery life of 10 years will be tested during human trials.

Dr. Wilkoff expects leadless pacemakers to eclipse traditional pacemaker technology before long. "Soon leadless pacemakers will be married with subcutaneous defibrillators and we'll have a device that paces and shocks," he says. "A leadless pacemaker could even be used in the left ventricle and a traditional pacemaker in the right ventricle for cardiac resynchronization."

Images courtesy of St. Jude Medical and Medtronic.

From the Shadows to the Spotlight:

Giving Fibromuscular Dysplasia Its Due

Heather Gornik, MD, MHS

Heather Gornik, MD, MHS, has been practicing at Cleveland Clinic for less than a decade, but her work surrounding one of her specialty passions — fibromuscular dysplasia (FMD) — is already punctuated by a long series of firsts. These include opening the world's first dedicated FMD clinic, becoming one of the first clinicians to enroll patients in a national FMD registry and co-chairing the first international conference on the disease (see sidebar for details).

Earlier this year Dr. Gornik blazed another trail in FMD when she co-chaired the American Heart Association's (AHA's) first scientific statement on FMD, which is also the first FMD guidance published in the United States. The statement, "Fibromuscular Dysplasia: State of the Science and Critical Unanswered Questions," was published in the March 4 *Circulation* (2014;129[9]:1048-1078) after nearly five years of development.

Another — and more unfortunate — first served as the impetus for Dr. Gornik's role in the multidisciplinary statement: the fact that she is often the first physician to diagnose FMD in patients who were previously mis- or underdiagnosed.

"Cardiovascular specialists are on the front lines of recognizing and diagnosing FMD," says Dr. Gornik, Medical Director of Cleveland Clinic's Noninvasive Vascular Laboratory and a staff physician in the Vascular Medicine Section. "FMD is an underrecognized disease that's more common than many physicians think. Our goals were to increase awareness and share accurate information to guide FMD diagnosis and treatment."

State of the Science on a Misunderstood Disease

The causes and prevalence of FMD — a rare nonatherosclerotic vascular disease that may result in arterial stenosis, occlusion, aneurysm or dissection — are unknown. The disease most commonly affects the renal and extracranial carotid and vertebral arteries. More than 90 percent of patients are women, often in their 40s and 50s.

"The disease tends to affect people who don't have a lot of other medical issues and are healthy from a cardiovascular standpoint," Dr. Gornik says. "The symptoms are nonspecific, and providers don't tend to think about FMD, so there is often a significant delay from the first presentation to the diagnosis."

The AHA scientific statement emphasizes the top signs and symptoms in patients with FMD, which include:

- Hypertension
- Headaches, especially migraines
- Dizziness
- Pulsatile tinnitus (swooshing noise in the ear)
- Cervical bruit

"The reality is that all clinicians are seeing patients with FMD," she says. "It's just a question of whether they are ready to recognize it."

The statement introduced a new classification system and nomenclature for two types of FMD, developed by the AHA writing group. The system designates FMD as either multifocal or focal based on angiographic appearance ("string of beads" [Figure] or "non string of beads").

Busting Myths About FMD

The AHA statement follows a 2011 European consensus document and data from the first 447 patients enrolled in the U.S. Registry for Fibromuscular Dysplasia (see sidebar). "These recent publications have added new information about FMD and dispelled some myths that continue to be taught in medical schools and during postgraduate education," Dr. Gornik and co-authors wrote.

For example, the statement clarifies that not all coronary, carotid and renal artery disease is caused by atherosclerosis. Many patients with FMD have few or no atherosclerotic risk factors, and FMD occurs in the mid and distal part of the artery — rather than in the origin or proximal portion of the vessel, as with atherosclerosis. The guidance also emphasizes that there is no indication for stent placement in FMD under most circumstances.

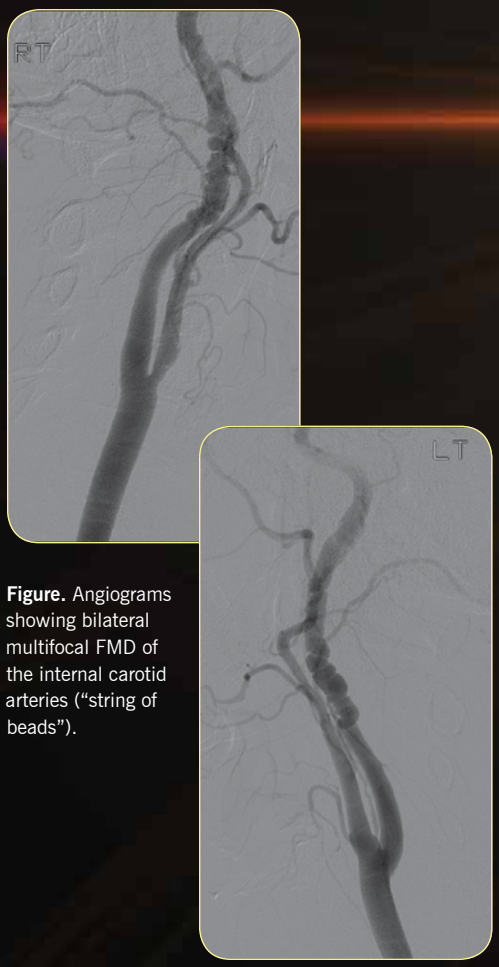


Figure. Angiograms showing bilateral multifocal FMD of the internal carotid arteries ("string of beads").

Prioritizing Tomorrow's FMD Research

Future research is needed into the pathogenesis, diagnostic approach, natural history and outcomes of FMD. No randomized controlled trials have been conducted of medical therapies or endovascular treatment for the condition.

Dr. Gornik and colleagues identified 11 research priorities, including fundamental questions such as determining the prevalence of FMD in the general population of women ages 18 to 65 and understanding the unique biological and genetic determinants of FMD.

Until those questions are tackled, Dr. Gornik has a challenge for her colleagues: "I call on cardiovascular specialists to learn about FMD and to not miss the disease when it walks through your door. This is critical to saving patients years of waiting for a proper diagnosis and treatment." ■

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Fibromuscular Dysplasia Firsts

Dr. Gornik's activities have helped establish Cleveland Clinic as an international leader in treating FMD, drawing patients from across the country and from Africa, India, Latin America, Europe and Canada. Below is a rundown of areas in which she and Cleveland Clinic have broken new ground in FMD.

Opening the world's first dedicated FMD clinic in 2008. Dr. Gornik, Esther Kim, MD, and Natalia Fendrikova Mahlay, MD, now follow more than 400 patients with FMD at the twice-weekly clinic, one of the world's largest FMD patient populations. As vascular medicine specialists, they coordinate the patients' multidisciplinary care with nephrologists, neurologists, vascular surgeons, interventional cardiologists, geneticists, radiologists and pathologists. "We bring the big-picture perspective," Dr. Gornik says. "Our FMD clinic has become a 'medical home' for these patients."

Pam Mace, Executive Director of the Fibromuscular Dysplasia Society of America (FMDSA), says there are now more than a dozen FMD clinics in the U.S. "Dr. Gornik was able to get others on board across the country," Mace says. "She elevated and recognized the need for FMD-specific clinics and care."

Pioneering participation in the national patient registry. FMDSA's U.S. Registry for Fibromuscular Dysplasia, with information on 1,000+ patients, began enrolling patients in 2009, with a focus on learning about FMD's natural history. Cleveland Clinic participated from the outset and remains the highest-enrolling center.

"There are many things we still don't understand about FMD, but through the registry and doctors like Dr. Gornik who specialize in FMD, we're starting to see what's common," Mace says.

Building a biorepository. Cleveland Clinic is collecting blood samples from consenting FMD patients (and their first-degree relatives) for future analyses to help determine the disease's pathogenesis.

Hosting an international conference. Dr. Gornik co-chaired (with Jeffrey Olin, DO) Cleveland Clinic's International Fibromuscular Dysplasia Research Network Symposium, held in Cleveland this past May, the first-ever international conference focused on FMD. The symposium convened leading U.S. and international FMD experts to educate other providers and plan future research initiatives.

When LV Outflow Tract Obstruction Presents with Minimal Hypertrophy

A customized approach to diagnosis and corrective repairs can overcome this clinical conundrum.

By Nicholas Smedira, MD

Nicholas Smedira, MD

Classically, left ventricular outflow tract obstruction (LVOTO) was identified when symptomatic patients were found on echocardiography to have a septum measuring approximately 20 mm and had LVOTO at rest or when provoked by a Valsalva maneuver or administration of amyl nitrate.

When LVOTO due to this severity of septal hypertrophy is identified, treatment is straightforward: A myectomy or an alcohol septal ablation is performed, which eliminates the obstruction. The patient's symptoms improve or completely disappear.

At Cleveland Clinic we are identifying increasing numbers of patients who have LVOTO with minimal to mild left ventricular (LV) hypertrophy (septum of 13-17 mm) (Figure 1). It is not known whether these patients with mild or no hypertrophy represent (1) a unique form of hypertrophic obstructive cardiomyopathy (HOCM), (2) a very early presentation of what we have labeled adult HOCM defined by the magnitude of the hypertrophy or (3) intrinsic mitral valve abnormalities that cause obstruction and then secondary hypertrophy.

While these cases can be much more difficult to diagnose, our imaging experience has grown and our surgical arsenal has expanded, yielding more tools than ever to diagnose and treat these clinically challenging symptomatic patients who present with relatively normal resting echocardiographic images.

Limited Options Breed New Techniques

Patients in this subgroup with LVOTO and minimal or no hypertrophy often present a diagnostic dilemma. The lack of hypertrophy and absence of a resting gradient mean a more aggressive diagnostic approach (such as with amyl nitrate or exercise stress testing) is needed. Moreover, if such tests are performed and the LVOTO is identified, options are limited because there is insufficient hypertrophy for alcohol ablation or substantial myectomy to open the outflow tract.

These constraints have prompted us to develop new diagnostic approaches and surgical techniques to identify and treat LVOTO with minimal hypertrophy. In such cases, often seen in young and healthy patients, we typically perform a stress echocardiogram during vigorous exercise on an upright bicycle. This avoids the rapid heart rate recovery seen with standard treadmill testing and increases the chance we will provoke obstruction. We also employ MRI to look at the septal and subvalvular anatomy.

Surgical Resourcefulness Can Avoid Valve Replacement

Once LVOTO is documented and the anatomy defined, we consider what surgical options can be used to eliminate the obstruction. While valve replacement can effectively address all cases of LVOTO caused by systolic anterior motion of the mitral valve, we favor repair techniques that avoid prosthetic valve replacement — especially in young, healthy patients.

The surgical options we use include:

- Limited myectomy based on detailed measurements of septal thickness
- Resection of anomalous structures, including muscle bands, fibrous bands, abnormal chordae and abnormally inserting papillary muscles
- Shortening the anterior leaflet of the mitral valve, resecting tethering secondary chordae, and reorienting and then reanchoring mobile papillary muscle heads to prevent systolic anterior motion (see Figure 2 and case vignette)

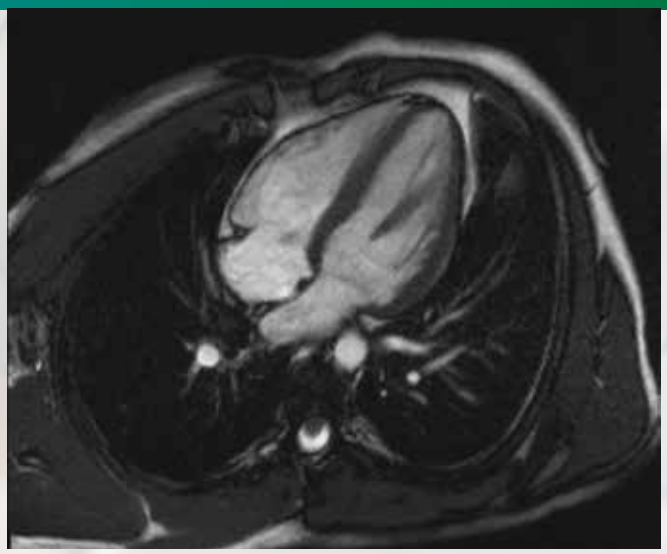

Figure 1. MRI of a patient with severe obstruction with minimal septal hypertrophy.

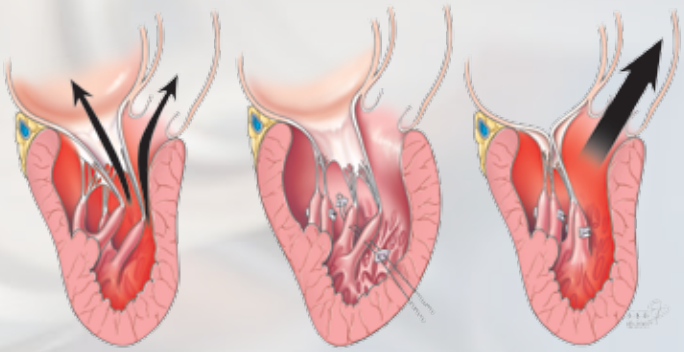

Figure 2. Mobile papillary muscle heads being reoriented away from the septum.

In our experience, about 75 percent of patients who have severe LVOTO with minimal or no LV hypertrophy are candidates for corrective repair that avoids valve replacement.

The accompanying sidebar presents a composite case vignette illustrating some of the innovative approaches employed by surgeons in Cleveland Clinic's Department of Thoracic and Cardiovascular Surgery when a patient presents with symptoms of LVOTO and minimal septal hypertrophy. ■

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Editors' note: We are pleased to introduce this *Cardiac Consult* series on surgical decision-making to give colleagues a window into how our surgeons sort through the always-evolving interventional options for surgical candidates. In each issue a Cleveland Clinic Heart & Vascular Institute surgeon will lay out factors that guide the choice of surgical approaches for a given condition in a given patient. We hope you enjoy this debut installment. Send ideas for future topics to coffmaj@ccf.org.

LVOTO Case Vignette:
Avoiding Valve Replacement in a 25-Year-Old Athlete

HISTORY AND PRESENTATION

The patient is a previously healthy 25-year-old male and a former NCAA Division I athlete. Over the 18 months following college graduation, he noted a gradual progression of exertional dyspnea, to the point that he was unable to play recreational sports. Symptoms progressed to shortness of breath when walking up hills and then while walking on level ground.

DIAGNOSIS

Diagnostic evaluation included normal resting transthoracic and transesophageal echocardiogram, with measurements of the LV septum ranging from 9 to 13 mm. Treadmill stress echo suggested systolic anterior motion of the mitral valve without a detectable outflow tract gradient. Upright bicycle stress echocardiogram at peak exercise capacity revealed severe systolic anterior motion of the anterior mitral valve leaflet with a peak gradient of 120 mm Hg and development of severe (grade IV) posteriorly directed mitral regurgitation. MRI confirmed normal septal thickness and suggested elongation of the anterior mitral valve leaflet and a multiheaded papillary muscle complex.

SURGICAL INTERVENTION

At the time of surgery we found that (1) the anterior leaflet was elongated, (2) there was an anomalous inserting head of the anterior lateral papillary muscle into the A1 segment of the mitral valve, and (3) there was excessive mobility of the two papillary muscle heads. We eliminated the inducible LVOTO by resecting the anomalous papillary muscle head, shortening the anterior leaflet of the mitral valve and fixating the two papillary muscle heads posteriorly.

OUTCOME

After an uneventful recovery, the patient is now NYHA class I and has resumed prior athletic endeavors without difficulty.

Taking **TAVR** to the Next Level

As transcatheter aortic valve replacement comes into its own, buzz begins around a new generation of valve systems.

As an active participant in clinical trials of transcatheter aortic valve replacement (TAVR), Cleveland Clinic has access to an expanding array of valve options, including the newest valve systems with smaller delivery sheaths to accommodate patients with otherwise poor vascular access due to small vessels or a diseased arterial system.

TAVR Finds Its Rightful Place

Catheter-based aortic valve replacement offers therapeutic options for patients with aortic valve disease who are deemed inoperable or are at high risk of complications from the gold standard of surgical AVR.

For a three-year period ending in December 2013, 30-day mortality among the 956 patients who underwent isolated surgical AVR at Cleveland Clinic, usually by a minimally invasive approach, was 0.6 percent. "While these results of open surgery are excellent, there was a group of patients who were inoperable or were at very high risk from surgery for whom we had no good options," says cardiothoracic surgeon Lars Svensson, MD, PhD. "But with the advent of TAVR, we now have more options for elderly patients who are not candidates for minimally invasive keyhole operations."

Outcomes data from all patients with severe symptomatic aortic stenosis deemed inoperable or at high surgical risk who were treated with transfemoral-approach TAVR at Cleveland Clinic from 2006 through 2012 revealed extremely low rates of 30-day mortality (0.4 percent) and stroke (1.6 percent) (*Catheter Cardiovasc Interv.* 2014 Mar 21 [Epub ahead of print]). This compares favorably with results from the PARTNER IB trial, which randomized inoperable patients to TAVR or standard medical therapy across 23 U.S. centers (Figure).

In a separate study of 150 patients who underwent transapical-approach TAVR at Cleveland Clinic from February 2007 to May 2013, the 30-day mortality of 3.3 percent was the lowest reported of any similar series; for those patients operated on after January 2011, it was only 1.2 percent.

"This experience shows that TAVR can be accomplished with excellent safety in a tertiary center with a well-developed infrastructure and team taking care of these sick patients," says interventional cardiologist Samir Kapadia, MD, lead author of the above transfemoral-approach TAVR study.

Potential Strengths of Second-Generation Valves

Emerging against this backdrop is a new generation of TAVR valve systems with smaller delivery sheaths. A key advantage of these newer technologies is a reduction in the risk of paravalvular aortic regurgitation (PAR), notes Amar Krishnaswamy, MD, an interventional cardiologist on the TAVR team. "In the initial experience with TAVR, we realized that leakage around the valve is a contributor not only to patients' symptoms but also to higher mortality," he says.

The newer valve systems' smaller sizes also permit placement via the less-invasive transfemoral approach — as opposed to transaortic or transapical approaches — in a larger number of patients.

The New Generation at a Glance

The second-generation TAVR valve system farthest along the U.S. regulatory path is the Edwards SAPIEN XT, which is available in Canada and Europe and currently under consideration for FDA approval. Cleveland Clinic took part in initial trials of the system that now form the basis for its application for market approval.

Cleveland Clinic interventional cardiologists are likewise involved in ongoing clinical trials of the following second-generation valve systems — and share perspectives on each.

Direct Flow Medical® transcatheter aortic valve system. "This valve is unique in that it is designed to minimize PAR and is repositionable after deployment," says Cleveland Clinic interventional cardiologist E. Murat Tuzcu, MD, who

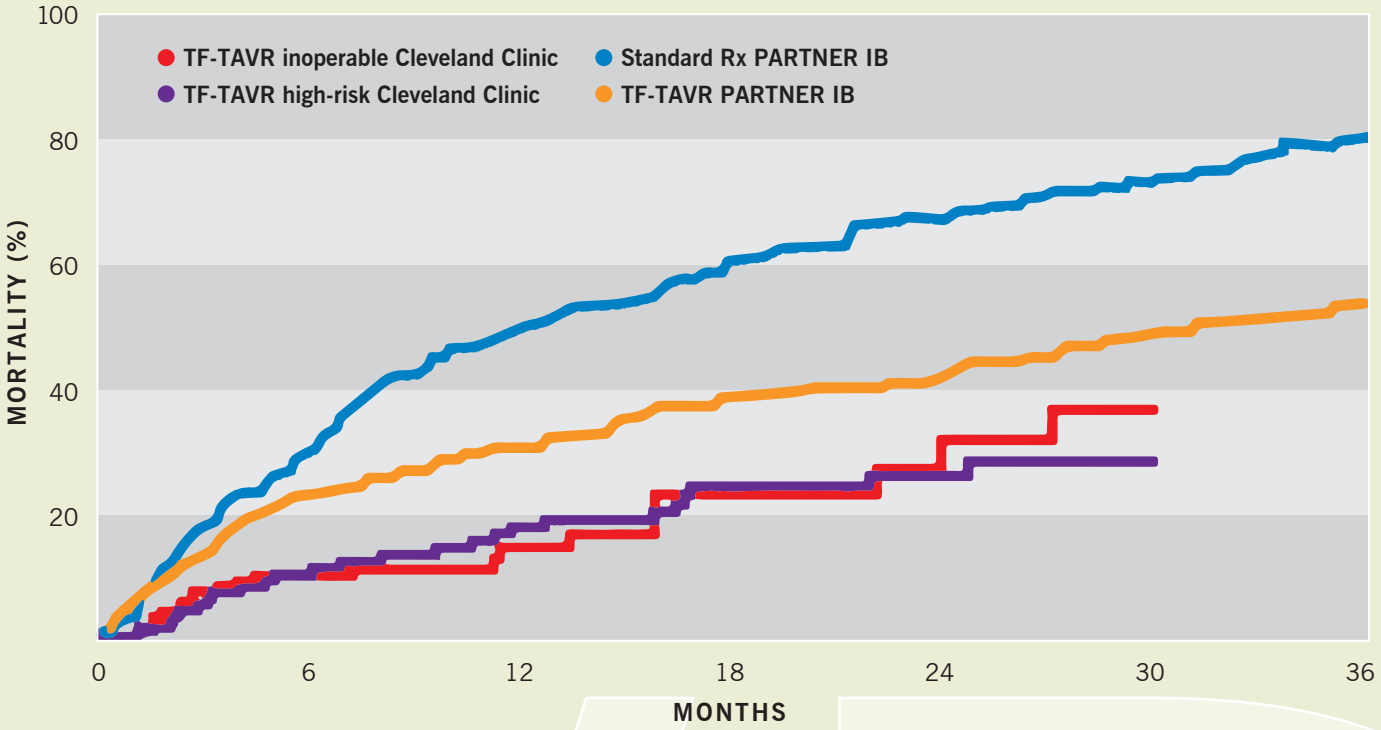

Figure. Mortality among patients considered inoperable or at high surgical risk treated with transfemoral (TF) TAVR at Cleveland Clinic vs. patients in the national PARTNER IB trial that randomized patients to transfemoral TAVR or standard medical therapy.

was national co-principal investigator for a U.S. feasibility study of the valve. "This allows the operator to continuously evaluate and re-evaluate the degree of paravalvular leakage after the valve is deployed and to reposition it if needed."

A European study of this valve in approximately 100 patients with severe aortic stenosis found moderate to severe PAR to occur in 2 to 3 percent of cases, which compares favorably with the approximately 15 percent seen in clinical trials of first-generation TAVR valves.

The U.S. feasibility study in 30 patients "has shown that the Direct Flow valve can be implanted with extraordinary safety, with very low mortality related to the procedure or the valve," notes Dr. Tuzcu, who is also co-principal investigator for its U.S. pivotal trial, which aims to enroll more than 400 inoperable patients.

Edwards SAPIEN 3. The SAPIEN 3, though not repositionable, is also designed to minimize PAR with the introduction of a "sealing skirt" at the bottom of the valve stent. It also has the smallest delivery sheath of any transcatheter valve system, allowing TAVR to be applied to patients who are not candidates for other valves, notes Dr. Krishnaswamy. European data suggest that TAVR in patients at intermediate risk of surgical complications has a safety and efficacy profile comparable to that of surgical AVR. In view of those findings, he adds, Cleveland Clinic is using this valve system in the intermediate-risk population as part of a clinical trial known as S3 Intermediate.

St. Jude Medical Portico™ system. The Portico is a repositionable valve with a self-expanding frame, and it too employs a smaller delivery catheter than the first-generation valves. In European studies, the risk of PAR has been very low with the Portico, notes Dr. Kapadia, who is on the steering committee for the U.S. clinical trial of the valve.

A Quest for More Options

"Completion of these trials will be an important milestone toward offering promising new valve technology to the overall population with aortic valve disease — and allowing selection of an appropriate device for a given patient," observes Dr. Tuzcu.

Dr. Svensson adds: "This is a flooding tide that will float all boats, both for these complex patients and for the physicians taking care of them." ■

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Median Arcuate Ligament Syndrome:

Collaboration Brings Relief After a Long Diagnostic Journey

By W. Michael Park, MD; Kevin M. El-Hayek, MD; and Matthew Kroh, MD

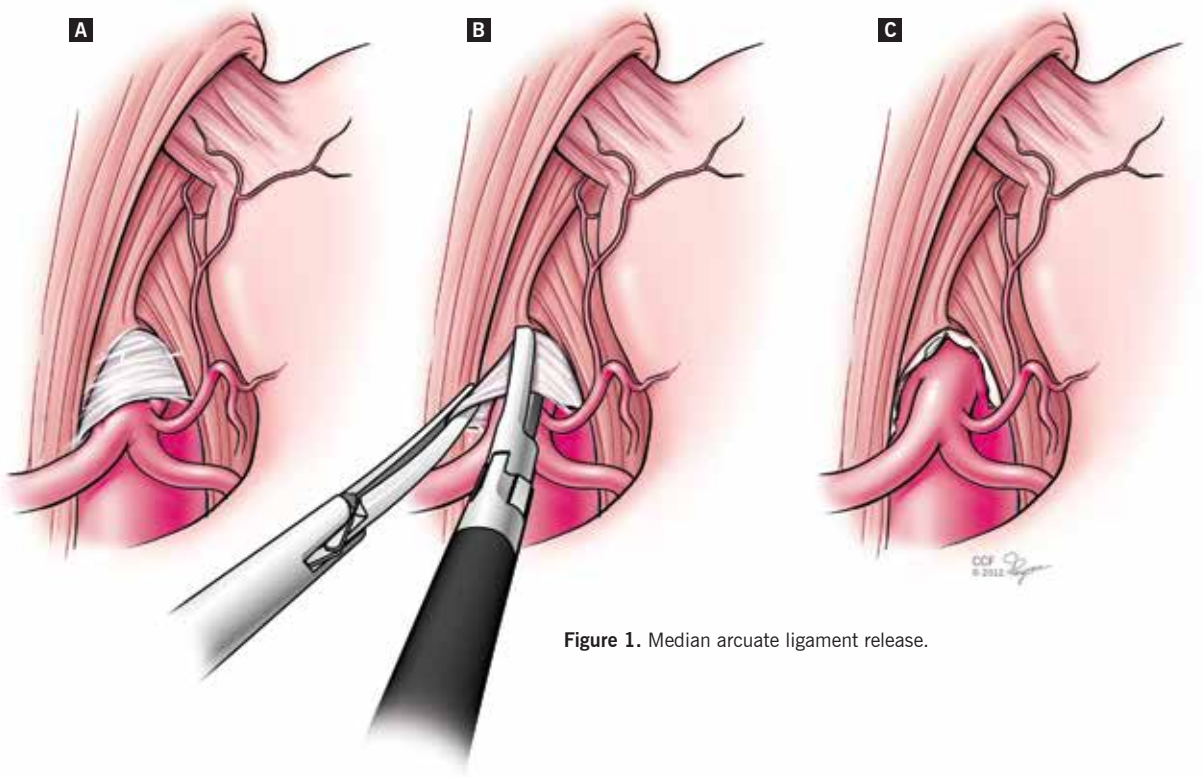

Figure 1. Median arcuate ligament release.

Case Presentation: Abdominal Pain with Major Weight Loss

Ms. A is a 28-year-old woman who had upper abdominal pain of 18 months' duration and an associated 70-pound weight loss. The pain was intense and triggered by eating.

She underwent an extensive gastroenterology workup — including esophagogastroduodenoscopy, endoscopic ultrasound, capsule enteroscopy, hepatobiliary iminodiacetic acid (HIDA) scan, CT and MRI — which suggested compression of her celiac axis by her median arcuate ligament. Vascular ultrasound confirmed this and showed velocities in the celiac axis of 450 cm/sec without inspiration and 215 cm/sec with inspiration. Flows were normal in the superior mesenteric artery.

Vascular surgery and general surgery consultation confirmed that she would benefit from laparoscopic release of the median arcuate ligament. The combined team performed the surgery, which involved full release of the ligament (Figures 1 and 2) and lysis of the celiac plexus. She recovered well and was discharged on postoperative day 2, tolerating a regular diet without pain for the first time in over a year.

MALS: Often the End of a Long Diagnostic Road

For many patients, median arcuate ligament syndrome (MALS) is the final diagnosis of a medical journey. It usually starts with abdominal pain that soon becomes incapacitating. Food may trigger or exacerbate it, and meals are avoided, resulting in weight loss. Some will lose more than 50 pounds, but average loss is about 20 pounds. Lying facedown or crouching will sometimes relieve the pain, which occurs in the upper abdomen.

Because of the pain's location, coincidence with eating and associated weight loss, an extensive workup including blood tests and wide-ranging imaging studies (radiographic, magnetic

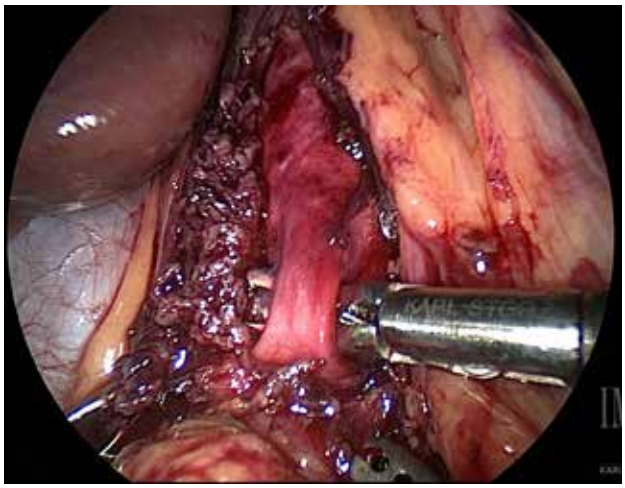

Figure 2. Intraoperative photo of the release procedure in the case patient.

The evidence for MALS lies primarily in the relief patients get from release of the median arcuate ligament when more common and potentially deadly diagnoses are ruled out.

resonance, ultrasound, nuclear and endoscopic) is typically done. Not infrequently, the gallbladder is removed without pain relief. A referral is made when compression of the celiac axis by the median arcuate ligament of the diaphragm is diagnosed.

A Diagnosis of Exclusion

Controversy surrounds this diagnosis because of the lack of proved mechanism. Some surgeons do not believe this malady exists, noting justifiably that for the great majority of patients without atherosclerotic occlusive disease, intermittent occlusion of the celiac axis should not cause mesenteric ischemia because of the usually excellent collateral circulation present between the celiac axis and superior mesenteric artery beds.

The evidence lies primarily in the relief patients get from release of the median arcuate ligament when more common and potentially deadly diagnoses are ruled out. MALS is therefore a diagnosis of exclusion. This means many more common diagnoses (gastroesophageal reflux disease, gastritis, gastroparesis, hepatobiliary disease, and disorders of the pancreas, liver, gallbladder, spleen and intestine) are considered and worked up before the patient is referred to a center that treats MALS.

MALS shares some characteristics with mesenteric ischemia, but it affects a younger population, generally women. It is related to compression of the celiac axis by the median arcuate ligament of the diaphragm, resulting in stenosis of the celiac axis. The pain may be due to regional ischemia brought on by increases in postprandial demand, but it may also result from pathologic compression, inflammation and fibrosis of the nerve fibers of the celiac plexus. Sometimes a celiac plexus block is used to help refine the diagnosis in cases that do not present with classic symptoms.

Weighing Surgical Risks and Outcomes

The decision to proceed with surgery balances risk of harm against likelihood of success. The latter is related to the presence of weight loss, being younger to middle age, the absence of significant atherosclerosis and the absence of significant foregut pathology. The risk of conversion to open repair for bleeding or other reasons is about 5 percent. When laparoscopic release alone fails to relieve symptoms, treatment of any residual stenosis involving the celiac axis is considered. The vast majority of patients report improvement in pain after treatment.[1]

Traditionally, open surgical release of the median arcuate ligament and, if necessary, reconstruction of the celiac axis were the gold standard, but laparoscopic release and subsequent endovascular repair, if necessary, offer a minimally invasive set of options for potential relief.

At Cleveland Clinic, a multidisciplinary team including members from vascular surgery and general surgery is engaged in the evaluation and treatment of MALS. This collaboration and the combined institutional experience enhance the safety and outcomes of patients with this relatively rare but debilitating disease. ■

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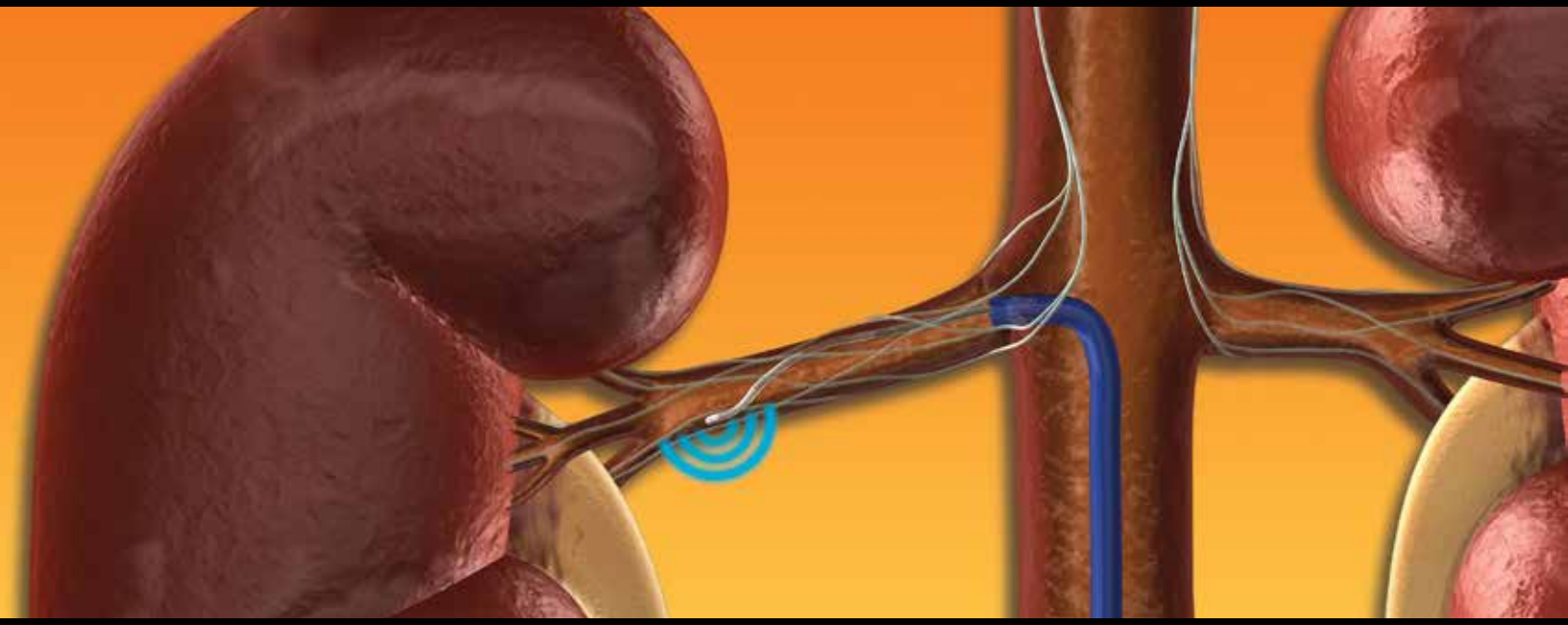
Reference: 1. El-Hayek KM, Titus J, Bui A, Mastracci T, Kroh M. Laparoscopic median arcuate ligament release: are we improving symptoms? *J Am Coll Surg.* 2013;216(2):272-279.

Resistant Hypertension Therapy After SYMPLICITY HTN-3: Where to Now?

Cleveland Clinic's site PIs reflect on lessons from the landmark renal denervation trial and the road ahead.



"A COLOSSAL DISAPPOINTMENT." That's how Mehdi Shishehbor, DO, MPH, described the SYMPLICITY HTN-3 trial when its sponsor, Medtronic, announced in January that the study missed its primary efficacy endpoint. He served as site co-principal investigator for the trial at Cleveland Clinic, which enrolled 13 patients, one of the highest counts among U.S. centers in the study of catheter-based renal denervation for resistant hypertension.

The full study results have since been published in the *New England Journal of Medicine*, but the medical community is still grappling with their implications. That's because the findings contradict previously published clinical data on renal denervation, which is in clinical use in more than 80 countries although it remains investigational in the United States. Several device manufacturers in addition to Medtronic have developed renal denervation systems.

Why the Disconnect with Prior Results?

The SYMPLICITY HTN-3 study was highly anticipated because it was the first large, randomized, blinded and sham-controlled study of renal denervation, which was seen as a promising leap forward in the quest for effective therapies for resistant hypertension. Yet it found no significant reduction in systolic blood pressure at six months in patients with resistant hypertension who underwent renal denervation as opposed to a sham procedure.

"This study brings the concept of renal denervation into question," says Dr. Shishehbor, Director of Endovascular Services in the Miller Family Heart & Vascular Institute. He identifies several potential reasons for SYMPLICITY HTN-3's discordance with previous studies:

- **Sample size.** "With 535 patients, this study was more than five times bigger than the largest previous study of renal denervation," he notes.
- **Design rigor.** "Not only was this the first blinded trial of renal denervation with a sham control, but everything about the study was rigorous, from the inclusion criteria to patient monitoring and follow-up."
- **Patient heterogeneity.** "Because this was a large, multicenter, multistate trial, it had a more heterogeneous mix of patients than previous studies, which probably better reflects the population with resistant hypertension."

"SYMPLICITY HTN-3 highlights why we always need to do proper randomized controlled trials for devices — with sham controls when possible — to understand whether they are truly effective. We don't typically do so, and that should change."

– Mehdi Shishehbor, DO, MPH

What's Next in Resistant Hypertension Therapy?

The findings put development of renal denervation on hold, which is unwelcome news to the approximately 10 percent of hypertension patients with resistant disease. In fact, Dr. Shishehbor had 60+ patients waiting to enroll in other renal denervation studies when the negative trial results emerged.

"Many of these patients take three to five antihypertensive medications a day and still can't achieve blood pressure control," he notes. "Adherence to all these drugs is burdensome, yet the patients are still at risk of stroke, myocardial infarction and other events."

Yet Dr. Shishehbor doesn't believe renal denervation for resistant hypertension is necessarily dead, noting that its underlying theoretical mechanism is still sound and six-month safety results in SYMPLICITY HTN-3 were favorable. "We need to go back to the drawing board and try to understand what happened," he says, through closer assessment of the technique and physiology involved and which patients may stand to benefit most.

Medtronic announced that it is not abandoning its Symplicity™ renal denervation system and will continue enrolling patients in its Global SYMPLICITY Registry. At the recent American College of Cardiology 2014 Scientific Session, researchers reported larger blood pressure reductions among that registry's first 1,000 patients than were observed in SYMPLICITY HTN-3, but the registry was not blinded and did not include a sham control.

Meanwhile, Dr. Shishehbor notes that other modalities for treating resistant hypertension show promise. One involves modulating bioreceptors in the carotid arteries. That approach is the basis for several investigational devices, including Vascular Dynamics' catheter-delivered MobiusHD™ implant. Dr. Shishehbor is currently enrolling patients in the multicenter CALM-FIM_US trial, the first study of MobiusHD in humans.

His colleague George Thomas, MD, a hypertension specialist in Cleveland Clinic's Glickman Urological & Kidney Institute, adds this advice for the near term: "In the absence of approved device therapy for resistant hypertension in the U.S, we must focus on thorough evaluation of patients with this diagnosis and find the appropriate combination of medications to use."

Vital Lessons from SYMPLICITY HTN-3

Despite its disappointing results, SYMPLICITY HTN-3 yielded valuable lessons, Dr. Shishehbor notes. "It highlights why we always need to do proper randomized controlled trials for devices — with sham controls when possible — to understand whether they are truly effective. We don't typically do so, and that should change.

"Also, the FDA is often criticized for approving products long after they're cleared for use in Europe and Australia," he says, noting that this experience vindicates the FDA's meticulousness, at least in the case of renal denervation devices. "The FDA deserves kudos for mandating a randomized, sham-controlled trial."

"For such trials, identifying patients who are truly resistant to optimal pharmacologic treatment is critical," adds Dr. Thomas, who served as site co-principal investigator for SYMPLICITY HTN-3. "Device therapy, if approved, will likely be an adjunct to medications to achieve better blood pressure control, but not necessarily replace them." ■

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Barcelona, Spain
European Society of Cardiology

At this satellite dinner symposium to the European Society of Cardiology meeting, international experts will explore recent lipid guideline changes, HDL functionality, the science behind CETP and PCSK9 inhibitors, and more.

For information/registration, visit ccescsatellite.eventbrite.com.

21st Century Treatment of Heart Failure: Synchronizing Surgical and Medical Therapies for Better Outcomes

Oct. 16-17, 2014

InterContinental Hotel & Bank of America Conference Center, Cleveland, Ohio

This two-day program's diverse national faculty will examine current and future heart failure therapies. Focused sessions include optimizing medical therapy, decision-making around mechanical circulatory support, cardiac transplant, refining outcomes in destination therapy and more.

For information/registration, visit ccfcme.org/heartfailure.

More CME ... at Your Convenience

Cleveland Clinic is working with **theheart.org/Medscape Cardiology** to offer engaging online educational programs on high-interest cardiology topics. For the activities below, visit medscape.org and enter "Cleveland Clinic" in the site's search box.

- **Ischemic Events in ACS: Unmet Needs in the Antiplatelet World**, a video expert panel discussion of the pros and cons of antiplatelet therapy for ACS patients undergoing PCI
- **A Systems Approach to VTE: Highlighting Best Practices to Ensure Optimal Outcomes**, a video expert panel discussion of anticoagulation therapy in VTE and systems-based barriers to optimal treatment

theheart.org | Medscape EDUCATION CARDIOLOGY

Beyond this collaboration, the Cleveland Clinic Center for Continuing Education website offers an abundance of complimentary CME activities — webcasts, case-based lessons, online journal articles and more — in all aspects of cardiovascular practice. Some take as little as 15 minutes. Check them out at **ccfcme.org** and choose "Cardiology" under "Browse by Specialty."

CLEVELAND CLINIC RESOURCES

About Cleveland Clinic

Cleveland Clinic is an integrated healthcare delivery system with local, national and international reach. At Cleveland Clinic, more than 3,000 physicians and researchers represent 120 medical specialties and subspecialties. We are a nonprofit academic medical center with a main campus, eight community hospitals, more than 75 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 2013, Cleveland Clinic was ranked one of America's top 4 hospitals in *U.S. News & World Report*'s annual "America's Best Hospitals" survey. The survey ranks Cleveland Clinic among the nation's top 10 hospitals in 14 specialty areas, and the top in heart care for the 19th consecutive year.

24/7 Referrals

Referring Physician Hotline
855.REFER.123

Live help connecting with our specialists, scheduling and confirming appointments, and resolving service-related issues.

Hospital Transfers
800.553.5056

New patients, in most cases, can be seen within one week of calling for an appointment.

On the Web at clevelandclinic.org/heart

Download Today! Physician Referral App

Contacting us is easier than ever before. With our free Physician Referral App, you can view all our specialists, transfer a patient and get in touch immediately with one click of your iPhone®, iPad®, or Android™ phone or tablet. Download today at the App Store or Google Play.

Resources for Physicians

Physician Directory
View our staff online at clevelandclinic.org/staff.

Same-Day Appointments
Cleveland Clinic offers same-day appointments to help your patients get the care they need, right away. Have your patients call our same-day appointment line, **216.444.CARE (2273)** or **800.223.CARE (2273)**.

Track Your Patients' Care Online
Establish a secure online Dr**Connect** account for real-time information about your patients' treatment at Cleveland Clinic at clevelandclinic.org/drconnect.

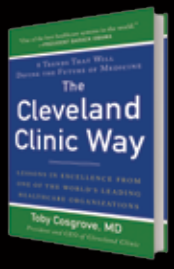
Critical Care Transport Worldwide
To arrange a critical care transfer, call **216.448.7000** or **866.547.1467**. For STEMI (ST elevated myocardial infarction), acute stroke, ICH (intracerebral hemorrhage), SAH (subarachnoid hemorrhage) or aortic syndrome transfers, call **877.379.CODE (2633)**. Learn more at clevelandclinic.org/criticalcaretransport.

Outcomes Data
View Outcomes books at clevelandclinic.org/outcomes.

Consult QD Blog for Physicians
Discover the latest research insights, innovations, treatment trends and more. Visit consultqd.org.

CME Opportunities: Live and Online
Visit ccfcme.org to learn more about the Cleveland Clinic Center for Continuing Education's convenient, complimentary learning opportunities.

Executive Education
Learn about our Executive Visitors' Program and two-week Samson Global Leadership Academy immersion program at clevelandclinic.org/executiveeducation.



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.

Cleveland Clinic

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Cleveland, OH 44195

Cardiac Consult

INTRODUCING

Consult QD – Heart & Vascular

A blog for healthcare professionals on heart, vascular and thoracic care

Get your daily dose of insights and perspectives on our specialty with this new open, online forum from Cleveland Clinic's Heart & Vascular Institute, the nation's No. 1 heart program.

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