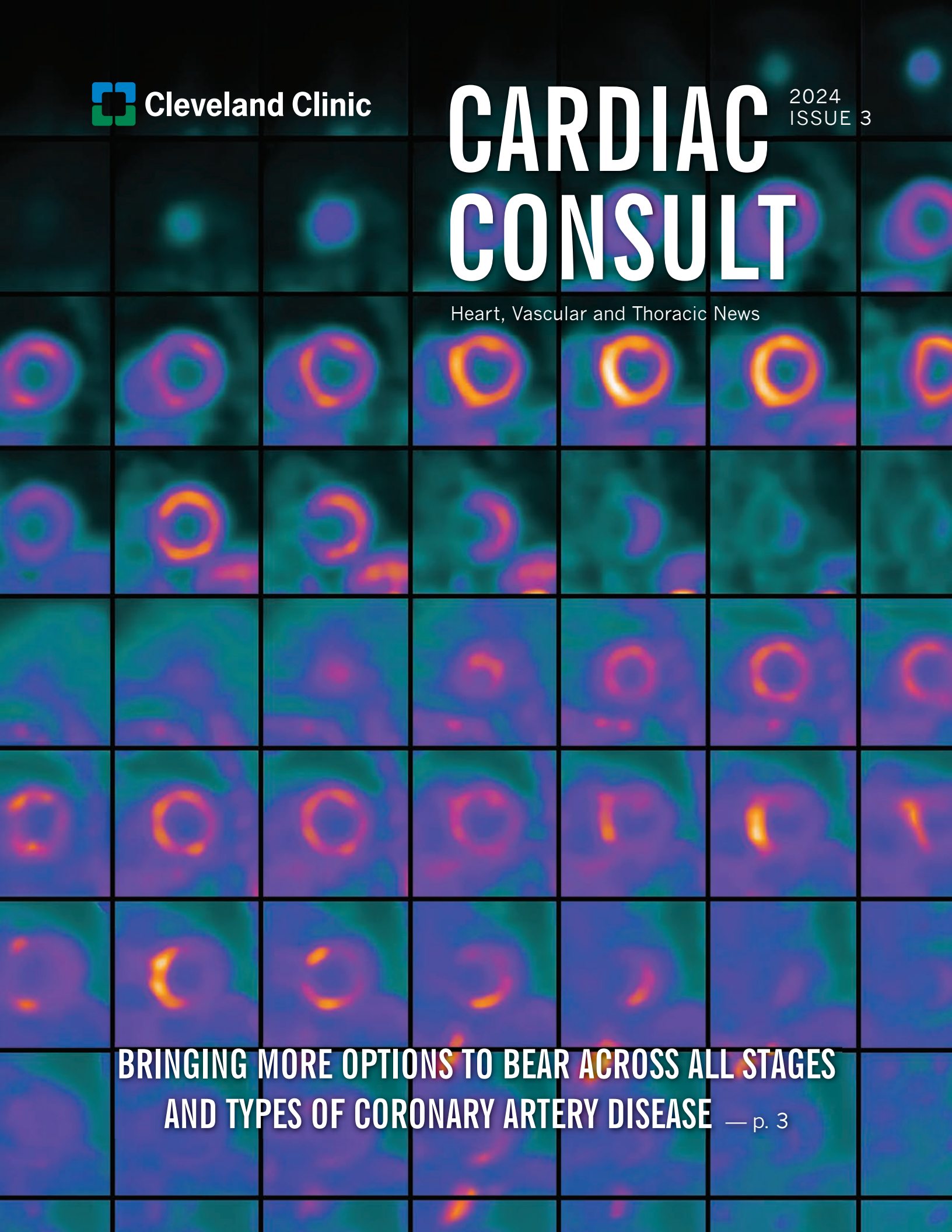

Cleveland Clinic

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ISSUE 3

Heart, Vascular and Thoracic News

BRINGING MORE OPTIONS TO BEAR ACROSS ALL STAGES AND TYPES OF CORONARY ARTERY DISEASE — p. 3

DEAR COLLEAGUES,

If I mentioned that a patient was referred to Cleveland Clinic for coronary artery disease (CAD), you'd likely figure it was for coronary artery bypass grafting (CABG) or another intervention to treat advanced disease.

While there's an abundance of ways that patients benefit from our CABG program — such as its exemplary operative mortality rate and strong commitment to multiarterial grafting — it's also true that many CAD patients come to Cleveland Clinic earlier in their disease course, seeking expertise to delay or even prevent a need for CABG.

The cover story of this *Cardiac Consult* issue profiles a few of the ways our Heart, Vascular & Thoracic Institute helps patients optimally manage CAD at all stages of disease by offering options not always available elsewhere. One example is our forward-looking approach to noninvasive functional testing for obstructive disease, such as our leadership in the use of PET with flow measurement. Another example is our wide range of diagnostic and treatment alternatives for patients with microvascular disease and nonobstructive CAD. The article also covers the many options we offer patients with elevated lipoprotein(a) levels and challenging cases of chronic total occlusion. And it concludes with the ways our CABG program goes above and beyond when revascularization is needed, including with minimally invasive options bolstered by our growing volume of robotically assisted CABG operations.

The common denominator across these examples is a resourceful team approach that brings new options to bear and a commitment to helping patients decide the best type and timing of treatment. When you entrust Cleveland Clinic with a referral, this is what you can expect for your patient.

Respectfully,

Lars G. Svensson, MD, PhD
Chief, Sydell and Arnold Miller Family Heart, Vascular & Thoracic Institute

ON THE COVER — PET imaging for assessment of myocardial hibernation in a patient with obstructive coronary artery disease (CAD). Broad use of PET stress testing with flow measurement is one of various ways in which Cleveland Clinic offers patients abundant and often innovative options for managing CAD at all stages of disease, not just when surgical or interventional revascularization is needed. For more, see the cover story starting on page 3.

Cleveland Clinic's Miller Family Heart, Vascular & Thoracic Institute is nationally and internationally renowned as a leader in cardiovascular care. Its teams are dedicated to continuously improving upon their standard-setting clinical outcomes, unsurpassed volumes and experience, and rich legacy of innovation and research leadership.

Cardiac Consult is produced by Cleveland Clinic's Sydell and Arnold Miller Family Heart, Vascular & Thoracic Institute.

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BRINGING MORE OPTIONS TO BEAR ACROSS THE SPECTRUM OF CORONARY ARTERY DISEASE

Novel approaches are available for all stages of CAD and various patient subpopulations

To many patients and clinicians, seeking out expert care for coronary artery disease (CAD) brings to mind referral for coronary artery bypass graft surgery (CABG) in cases of challenging anatomy or when a minimally invasive approach is desired.

Yet an innovative, high-volume heart program like Cleveland Clinic's can offer patients with CAD distinctive care options at all stages of disease, including long before they may need revascularization. "Our Heart, Vascular & Thoracic Institute takes a comprehensive and highly integrated approach to CAD," says Samir Kapadia, MD, Chair of Cardiovascular Medicine. "We have standout expertise in helping patients prevent or ameliorate various forms of CAD and advising them on the very best timing and method of intervention."

This article shares a few selected examples of such expertise, from noninvasive functional testing for obstructive CAD to the care of special patient populations and to refinements in revascularization care for chronic total occlusion and patients requiring CABG.

Noninvasive Functional Testing for CAD

Because stress imaging offers greater sensitivity than exercise ECG testing alone, it is advantageous for diagnostic confirmation in many patients with symptoms suggestive of obstructive CAD. "Although stress testing is well established, it is not done equivalently everywhere," says Wael Jaber, MD, a cardiologist in the Section of Cardiovascular Imaging.

Expert use of stress echo

A key consideration is volume-based experience, which looms large in stress echocardiography. At its main campus and family health centers in Northeast Ohio alone, Cleveland Clinic performs approximately 550 stress echo tests each month — about 500 with exercise and 50 with dobutamine. Most are done to evaluate for known or suspected CAD, though valvular heart disease, cardiomyopathy and use in metabolic stress testing are growing indications.

A big advantage of stress echo testing is its safety and freedom from ionizing radiation. "Stress echo has been performed since the late 1970s, so there's a wealth of diagnostic data as well as prognostic/outcomes data with long-term follow-up," says Patrick Collier, MD, PhD, a cardiologist in the Section of Cardiovascular Imaging.

Patients with intermediate probability of CAD are most likely to have their management altered by the results of stress testing, Dr. Collier notes. Among stress testing options, stress echo is known to have relatively high specificity (a low false-positive rate). "Most experienced physicians will choose stress echo for intermediate-risk patients who they deem less likely to have ischemia," he says, "as such patients are more likely to have a true negative test in this context." Due to changes in referral patterns, stress echo results that are "positive for ischemia" are less common, he adds, which poses challenges for both training and reporting.

"Stress echo testing requires deep experience on the part of sonographers and readers," Dr. Collier says. "It's important for patients and referring physicians to ensure that such testing is done at an accredited, experienced echo lab that performs a high volume. At Cleveland Clinic, we pride ourselves on the expertise of our sonographers (which is crucially important, as with all ultrasound-based tests) and the depth of knowledge and training of our physician readers, who stand out in terms of volume and experience. This is all the more important with the healthcare workforce challenges everyone has seen in the post-COVID-19 era."

Broad capabilities in nuclear stress testing

For patients in whom radionuclide myocardial perfusion imaging (i.e., nuclear stress testing) is indicated, a center's depth and breadth of technological capabilities is key, says Dr. Jaber, who has a specialty interest in nuclear imaging.

> "Without flow measurement, the sensitivity of traditional SPECT or PET is about 70% to 85%. When you add flow measurement, sensitivity improves to 95% to 98%. It's rare for PET to miss a problem when flow measurement is performed."
>
> — WAEL JABER, MD

SPECT is the most widespread imaging modality for both exercise and pharmacologic nuclear stress testing, but it is limited by artifacts, which can lead to false-positive results in up to 30% or 40% of cases. To overcome this limitation, Cleveland Clinic is one of a small number of centers that perform CT attenuation correction on SPECT images.

"Ours is the only U.S. heart center that does CT attenuation correction on all our SPECT images," Dr. Jaber says. "This enables us to remove many of the artifacts and improve image accuracy exponentially. This, in turn, reduces false-positive results and can spare patients the risk of unnecessary downstream testing."

In addition to SPECT, Cleveland Clinic offers PET imaging for nuclear stress testing. Dr. Jaber says that while SPECT is a good choice for patients who prefer treadmill exercise over pharmacologic stress and for those whose insurance doesn't cover PET (which is more expensive), PET is a more advanced imaging modality that offers several advantages over SPECT:

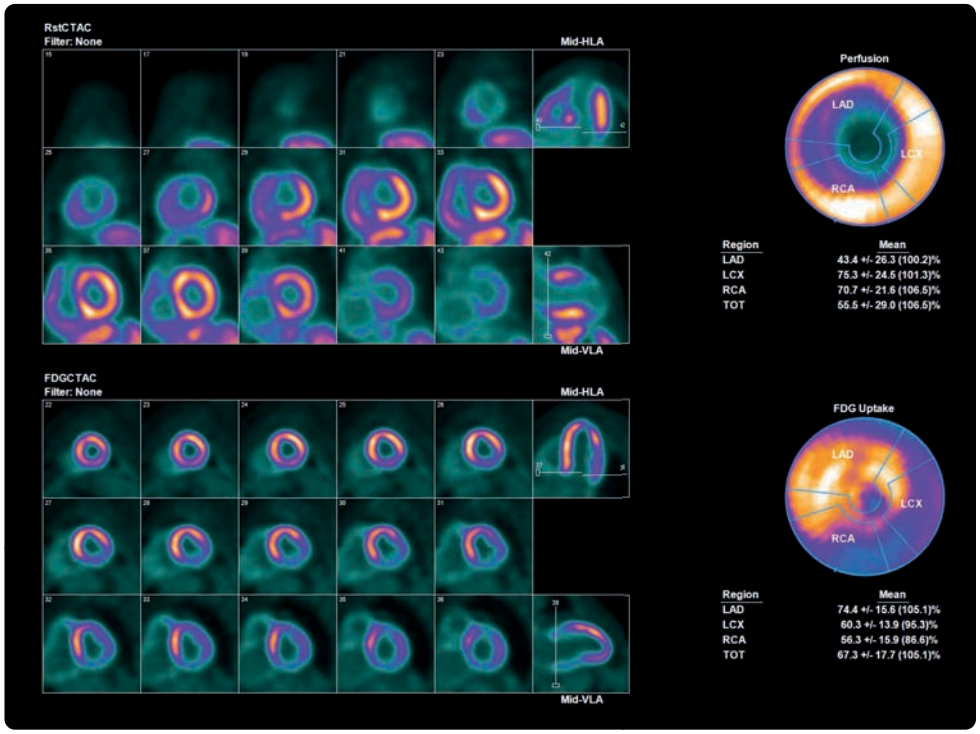
- Greater imaging accuracy through higher resolution
- Higher-energy tracers with brief radiopharmaceutical half-lives, which reduce radiation exposure and enhance image quality
- Built-in attenuation correction
- A markedly shorter imaging protocol (24 minutes versus at least 2.5 hours with SPECT)
- The ability to quantify myocardial blood flow and myocardial blood flow reserve

The latter feature — blood flow measurement — is an important advantage. "Not only can we measure whether blood is getting to the heart, but we can measure how much is getting there," Dr. Jaber explains. "Without flow measurement, the sensitivity of traditional SPECT or PET is about 70% to 85%. When you add flow measurement, sensitivity improves to 95% to 98%. It's rare for PET to miss a problem when flow measurement is performed."

As a result, every PET stress test at Cleveland Clinic is done with flow measurement. And because Cleveland Clinic's main campus has three PET scanners dedicated solely to cardiovascular cases, it performs 15 to 19 PET stress tests every day. "This is the largest single-center volume anywhere in the country," Dr. Jaber notes. "At most other major institutions, cardiologists borrow PET cameras from their oncology departments to do stress tests, which means they can do only a handful per week, resulting in long wait times. We have virtually no wait time here."

Patients benefit from these advanced PET capabilities via greater diagnostic certainty as well as reduced radiation exposure and shorter testing time compared with SPECT.

PET with flow measurement also enhances the ability to guide revascularization. One example is through evaluation of myocardial viability, specifically with assessment of myocardial hibernation. "This enables us to determine, before any revascularization procedure, whether a section of heart wall that's not moving is



RIGHT — PET imaging for assessment of myocardial hibernation in a patient with obstructive CAD. Because it has three PET scanners dedicated to cardiac care, Cleveland Clinic is able to perform 15 to 19 PET stress tests daily.

"CT-FFR can potentially be useful in determining ... whether a 50% to 70% stenosis on CT is flow-limiting or nonobstructive." — MILIND DESAI, MD, MBA

capable of recovery even with restored blood flow," Dr. Jaber explains. "This allows us to spare patients the risk, pain and cost of having a procedure that may not benefit them.

"For all these reasons," he says, "contemporary patients who need nuclear stress testing are best advised to go to a center that can readily offer PET to ensure the most comprehensive evaluation."

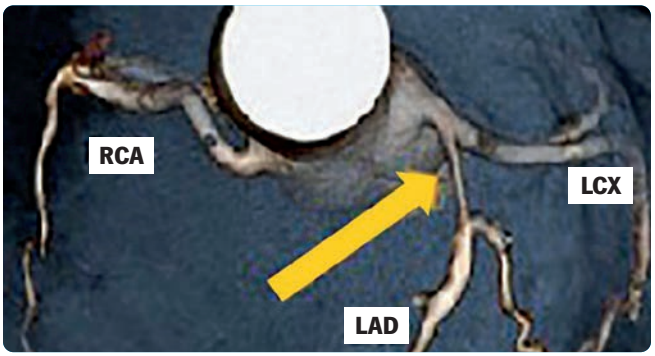
Making the most of coronary CT angiography

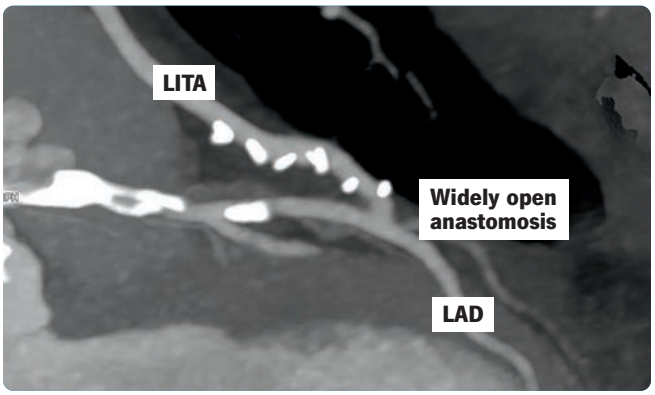
Coronary CT angiography (CTA) is an increasingly used noninvasive imaging technique that plays a significant role in the assessment and management of CAD. It differs from stress testing in that it directly visualizes the coronary arteries and can quantify the extent of stenosis and assess plaque characteristics. In the latest multisociety chest pain guidelines, coronary CTA carries a class 1 indication for assessment of symptomatic patients with stable chest pain.

At Cleveland Clinic, coronary CTA currently plays a multitude of roles in CAD management for appropriate patients, according to cardiologist Milind Desai, MD, MBA, Vice Chair of Education for Cleveland Clinic's Heart, Vascular & Thoracic Institute:

- *Diagnosis of CAD and evaluation of chest pain.* By providing detailed images of the coronary arteries, coronary CTA has demonstrated high sensitivity and specificity for detecting CAD and ruling out significant stenosis. "This supports its use as a noninvasive diagnostic alternative to invasive coronary angiography," Dr. Desai notes.
- *Assessment of coronary anatomy and use in preprocedural planning.* Coronary CTA is distinctly good at offering a detailed view of the coronary anatomy, including the size and location of coronary plaques. "This can be crucial for planning treatment strategies," Dr. Desai observes, "providing a clear picture of the arteries and any anatomical variations in patients undergoing cardiac surgery or interventional procedures."
- *Postprocedural assessment.* For patients who have undergone CABG, coronary CTA is valuable for evaluating the patency of the grafts and the condition of native coronary arteries.
- *Risk stratification and monitoring.* Coronary CTA shows considerable utility in assessing the risk of cardiovascular events in patients with suspected CAD, helping guide treatment decisions and manage risk factors more effectively. It also helps monitor CAD progression and treatment effectiveness over time.

BELOW — Two applications of coronary CTA at Cleveland Clinic. Top image is a 3D rendering showing stenosis (arrow) of the proximal left anterior descending artery (LAD). Bottom image was taken in a separate patient after a bypass operation. It shows a patent left internal thoracic artery (LITA) with clips on its branches (bright white) anastomosed to the LAD beyond its diseased and calcified segments (also bright white).





"The prognostic and monitoring value of coronary CTA in patients with stable disease has been demonstrated by improved outcomes in large prospective investigations such as the SCOT-HEART trial," Dr. Desai notes.

He adds that newer techniques like CT fractional flow reserve (CT-FFR) use coronary CTA-derived data to simulate blood flow through the coronary arteries and calculate the FFR to assess the functional significance of a moderate coronary lesion. "CT-FFR can potentially be useful in determining, for example, whether a 50% to 70% stenosis on CT is flow-limiting or nonobstructive," Dr. Desai explains. "This helps guide decisions related to revascularization."

Meeting Needs of Special Patient Populations

Shifting much-needed attention to microvascular disease

One traditionally underserved subpopulation of CAD patients includes those with microvascular disease, or ischemia with non-obstructive coronary artery disease (INOCA). Cleveland Clinic's long-standing interest in INOCA grew in late 2020 when Khaled Ziada, MD, joined the Section of Interventional Cardiology, where he is one of three staff cardiologists with a specialty interest in the condition.

"We consider INOCA when patients present with angina but have little or no evidence of plaque in the coronary arteries," Dr. Ziada explains. "Although it is quite common, there's a significant need for better diagnosis, which is the foundation of proper management. Cleveland Clinic is one of just a few centers in the middle of the country with expertise in INOCA diagnosis and treatment."

In the three years from 2021 through 2023, Cleveland Clinic conducted diagnostic testing for suspected INOCA in over 400 patients. Patients are evaluated via specialized catheterization lab testing for the two major forms of INOCA, microvascular angina and vasospastic angina, with most patients tested for both.

To assess for vasospastic disorders, Cleveland Clinic favors provocative testing with an intracoronary agent over the intravenous agents traditionally used. "We find intracoronary provocative agents to be more accurate and more diagnostic," Dr. Ziada notes.

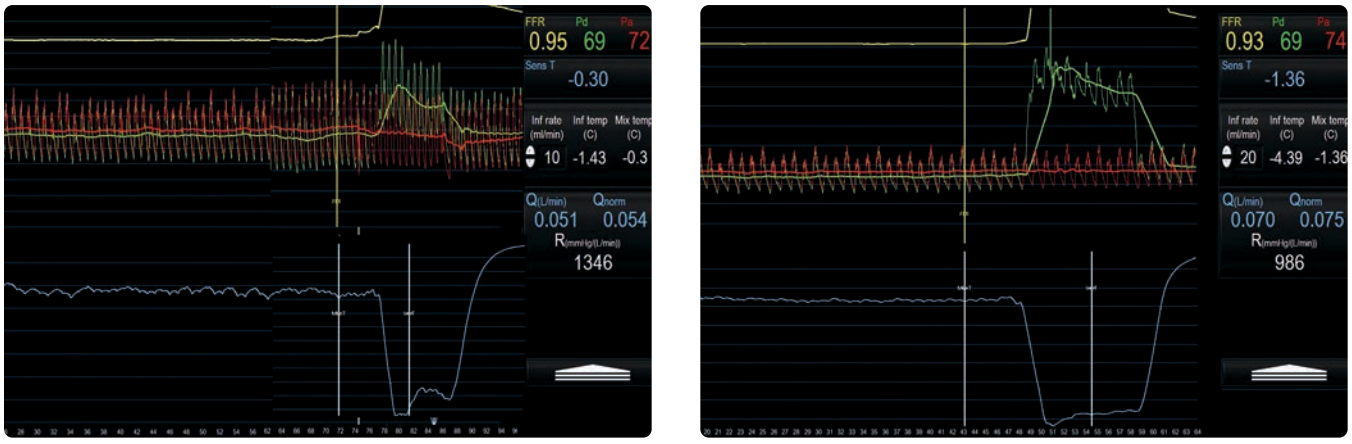
Typical assessment of microvascular function in the cath lab includes intracoronary injections of saline and use of adenosine to assess flow reserve. Cleveland Clinic cardiologists increasingly supplement this with a newer method, continuous thermodilution, that uses a microcatheter to infuse saline inside the coronary artery at different rates and without need for adenosine.

Continuous thermodilution was pioneered in Europe; Cleveland Clinic was the first center to use it in the U.S. "Evidence indicates that it's more accurate and reproducible than standard microvascular function testing," Dr. Ziada says. "We've been using both the traditional measurements and continuous thermodilution to better understand the differences between them, but we are shifting to continuous thermodilution for all patients. We believe it will become the standard measurement used by everyone."

Cleveland Clinic is also pioneering another promising diagnostic tool for microvascular disease — magnetocardiography. This noninvasive test records magnetic fields produced by the heart's electrical activity.

"Testing shows that magnetocardiography scans reveal abnormality in the magnetic fields in patients with microvascular dysfunction, even at rest," Dr. Ziada says. "They appear to be 70% to 80% accurate. We are working with the developer of the scanner to conduct validation studies that could support regulatory approval. Magnetocardiography is a simple, noninvasive scan that takes only about five minutes to do. If validation testing supports approval, it could be an appealing new screening option."

Once diagnosed with INOCA, patients are offered contemporary therapy for the condition, which is aimed at alleviating angina symptoms and addressing long-term risk of cardiac events. Traditional anti-anginal medications are less effective in INOCA, so pharmacotherapy options for microvascular angina include beta-blockers, calcium channel blockers, ranolazine and ivabradine, while those for vasospastic angina include calcium channel blockers and long-acting nitrates. These are often used against a backdrop of statin, aspirin and ACE inhibitor/ARB therapy. Management of risk factors (hypertension, dyslipidemia and diabetes) is emphasized, along with



ABOVE — An example of the continuous thermodilution method for assessing microvascular function in a patient with INOCA. Absolute coronary flow and resistance are measured using continuous saline infusion at rest (left) and after inducing hyperemia (right). Both coronary flow reserve and microvascular resistance reserve are abnormal, indicating microvascular dysfunction.

nutrition, exercise, weight management, smoking cessation and stress reduction.

"Most patients achieve significant improvement in symptoms and quality of life on contemporary therapy for INOCA," Dr. Ziada says. "The improvement is dramatic in some and more measured in others. But there's no question that we need better and more specific therapies for INOCA."

To that end, Cleveland Clinic has begun exploring use of the SGLT2 inhibitor dapagliflozin, which improves outcomes in heart failure with preserved ejection (HFpEF), in patients with microvascular dysfunction who have HFpEF. "About 75% of patients with HFpEF have microvascular dysfunction, and it's believed that HFpEF is a form of microvascular dysfunction affecting the myocardium that leads to heart muscle stiffness and heart failure symptoms," Dr. Ziada explains. "Based on those observations, we consider dapagliflozin in these patients and have seen relatively good symptom relief and quality-of-life gains. We are now exploring a clinical study of SGLT2 inhibitors for microvascular dysfunction."

Additionally, Cleveland Clinic offers selected patients with INOCA potential enrollment in the multicenter COSIRA-II randomized trial of an investigational coronary sinus reducing device for refractory angina. "While this study predominantly includes patients with nonrevascularizable obstructive CAD, there is an arm specifically for patients with microvascular dysfunction," Dr. Ziada notes.

Cleveland Clinic also participates in the multicenter DISCOVER INOCA registry that's following patients for five years after INOCA diagnosis to better characterize outcomes. "Most outcomes data for INOCA are from the early 2000s," Dr. Ziada says. "This registry should help us better understand outcomes and issues for contemporary INOCA patients."

Preparing to take on elevated Lp(a)

Once a week, Steven Nissen, MD, holds a clinic in which almost every patient has elevated levels of lipoprotein(a), or Lp(a). Most of the clinic's patients have seen multiple family members suffer a cardiac event and/or undergo revascularization by their 40s or 50s.

"These patients typically say, 'I just had my Lp(a) checked and it's really high; I'm scared to death,'" says Dr. Nissen, Chief Academic Officer for Cleveland Clinic's Heart, Vascular & Thoracic Institute. He adds that while there are no FDA-approved therapies for lowering Lp(a) levels, four promising investigational therapies are in clinical trials, and Cleveland Clinic is leading several of the trials.

"We are a focal point for much of the research into treating Lp(a)-related cardiovascular risk," Dr. Nissen says, "and we are advocates for patients getting their Lp(a) levels checked. In addition to raising awareness of Lp(a) as an important risk factor, this identifies people at elevated risk of cardiovascular events. We can then treat all their other risk factors super aggressively and consider enrollment in a clinical trial of an investigational therapy if appropriate."

He and his colleagues have focused on Lp(a) because of the emergence of the investigational therapies and because the clinical impacts of Lp(a) elevation, once underappreciated, have grown increasingly apparent.

Those impacts manifest as a heightened risk — and often an accelerated course — of CAD-related events and conditions, particularly premature myocardial infarction, venous thrombo-embolism and calcific aortic stenosis. "Elevated Lp(a) can nearly double the risk of atherosclerotic cardiovascular disease and aortic stenosis," observes Leslie Cho, MD, Co-Section Head of Preventive Cardiology, "and it tends to lead to disease at a younger age."

Elevated Lp(a) is a genetically determined risk factor. Normal Lp(a) levels are < 25 mg/dL. Significant risk of atherothrombotic events begins between 50 and 70 mg/dL and rises thereafter. Over 3 million Americans have levels ≥ 180 mg/dL, which confer extremely high risk.

Notably, Lp(a) levels are unaffected by available lipid-lowering therapies or by lifestyle interventions. "Elevated Lp(a) is one of the last untreatable frontiers of cardiovascular risk," Dr. Nissen notes.

That may soon change, however, in view of the investigational therapies, known as nucleic acid therapeutics. Both classes of these therapeutics, antisense oligonucleotides and short interfering RNAs (siRNAs), act by degrading the messenger RNA that codes for apolipoprotein(a).

Four nucleic acid therapeutics — all given subcutaneously, from once monthly to once or twice a year — are now in clinical testing:

- Pelacarsen is an antisense oligonucleotide being studied in the phase 3 Lp(a) HORIZON outcomes trial coordinated by the Cleveland Clinic Coordinating Center for Clinical Research (C5Research). Results may be available in 2025.
- Olpasiran is an siRNA being assessed in the phase 3 OCEAN(a) outcomes trial. Results are expected in 2027.
- Zerlasiran is an siRNA being studied in a phase 2 trial coordinated by C5Research.
- Lepodisiran is an siRNA being evaluated in the large phase 3 ACCLAIM-Lp(a) trial, an outcomes study led by C5Research.

Because Lp(a) HORIZON, OCEAN(a) and ACCLAIM-Lp(a) are outcomes trials, they should help determine whether significant Lp(a) lowering reduces major cardiovascular events in people with Lp(a) elevation and the magnitude of Lp(a) reduction needed.

"We want clinicians to start assessing Lp(a) now so that when Lp(a)-targeted therapies become available, we'll be ready to treat the patients who need them," says Dr. Cho.

Refining Revascularization Care

CTO demands both expertise and judiciousness

For many patients with chronic total occlusion (CTO) in the coronary circulation, percutaneous coronary intervention (PCI) is a good but often challenging option. As a result, only a small share of patients with CTOs undergo PCI, and rates of technical success (< 30% stenosis with TIMI 3 flow) are low — about 50% to 70% nationally, compared with about 95% for non-CTO PCI.

At expert centers, those rates can be considerably higher. "At Cleveland Clinic, the technical success rate for CTO PCI is 87% on the first attempt and 94% overall," says Laura Young, MD, a cardiologist in the Section of Interventional Cardiology. She and colleague Jaikirshan Khatri, MD, have performed all CTO PCIs at Cleveland Clinic's main campus in recent years, which number from 130 to 150 annually.

"By concentrating that considerable volume in this way, we've developed a high level of technical expertise to ensure that cases are done effectively and safely," Dr. Khatri says. He notes that Cleveland Clinic's 2.1% incidence of in-hospital major adverse cardiac events compares well with the rate in the global PROGRESS CTO registry, in which Cleveland Clinic participates. He also attributes avoidance of complications to the team's high utilization of biradial access for CTO PCI, which reduces the risk of serious bleeds, facilitates early ambulation and reduces radiation exposure.

Beyond the concentrated expertise in CTO PCI, the team-based approach of Cleveland Clinic's CTO program is a point of distinction, notes Dr. Young. "We have the depth and breadth of expertise among our general cardiologists, imaging specialists, interventionalists and cardiac surgeons to advise patients on when to defer treatment, go for CTO intervention or go for surgery with open sternotomy or a minimally invasive approach," she says. "This expertise is complemented by Cleveland Clinic's group practice model in which staff aren't paid based on personal procedural volumes. That aligns incentives with what's best for patients."

"We have the depth and breadth of expertise … to advise patients on when to defer treatment, go for CTO intervention or go for surgery with open sternotomy or a minimally invasive approach."

— LAURA YOUNG, MD

This team-based approach means expert cardiac surgeons and critical care specialists are readily available to help rescue patients who may encounter a serious complication during a PCI attempt. It also means many patients with CTO can be successfully managed for years with medical therapy alone.

"Many patients come to Cleveland Clinic after a CTO is discovered as an incidental finding," Dr. Khatri says. "They've been told something needs to be done about it and are concerned about their prognosis. However, if these patients are asymptomatic and don't have significant disease along the left main coronary artery, some can do quite well for up to five or six years with medical management and monitoring alone. If symptoms develop, we reevaluate their care and can offer PCI or surgery if indicated. It can be a dynamic situation that requires confidence to lean on the literature and our experience base to defer treatment when it's not yet appropriate."

When more than medical therapy is needed but conventional revascularization isn't viable, Cleveland Clinic offers appropriate patients with CTO access to clinical trials to manage refractory angina. These include the multicenter COSIRA-II trial of an investigational coronary sinus reducing device that's been commercially available in Europe since 2015. The hourglass-shaped device is placed percutaneously in the coronary sinus to redirect blood flow and thereby reduce angina. Cleveland Clinic is the top-enrolling center in this randomized, sham-controlled trial.

Cleveland Clinic also participated in the EXACT trial that assessed intramyocardial injection of a recombinant vascular endothelial growth factor to induce therapeutic angiogenesis in patients with refractory angina. Now completed, the trial yielded promising findings, so the therapy's developer is starting a new study in which the growth factor is injected in the heart percutaneously. "We are exploring participation in this new study as well," Dr. Young says.

"We're equipped to help patients with CTO and angina regardless of disease stage," she concludes. "We can monitor them until symptoms develop. We can explore operating on or stenting the artery. We can consider whether they're candidates for a trial of a novel therapy. We have the expertise to present a whole gamut of possibilities."

Raising the bar in CABG with greater complexity, less invasiveness

Despite all the promising approaches for earlier and less invasive management outlined above, some patients with CAD will ultimately still need CABG or a related form of surgical revascularization.

Since completing the world's first successful series of coronary vein graft surgeries in 1967, Cleveland Clinic has remained in the vanguard in this realm. It now performs 1,000 isolated CABG operations annually, including many reoperations and other cases referred from other cardiac centers because of their high risk and complexity. Despite this significant risk and acuity,

LEFT — *(First image)* Placement of an arterial graft in a multiarterial CABG procedure. Such procedures represent the preferred approach to CABG at Cleveland Clinic. *(Second image)* Dr. Bakaeen at the robot console during one of the two to four CABG operations now performed with robotic assistance each month at Cleveland Clinic.

Cleveland Clinic's overall operative mortality rate for isolated CABG approaches 0.5%. "This is less than half the rate predicted by the Society of Thoracic Surgeons (STS) risk model," notes Faisal Bakaeen, MD, Director of Cleveland Clinic's Coronary Artery Bypass Surgery Center. "The morbidity rate is also very low, which gives our CABG program a high score and a three-star rating in the STS Adult Cardiac Surgery Database."

To extend these strong short-term results to the best possible long-term outcomes, the Cleveland Clinic CABG team uses multiple arterial conduits for all important target coronary vessels whenever possible. As a result, 34% of CABG cases at Cleveland Clinic involve multiarterial grafts. "This is three times higher than the STS benchmark despite the complexity of our patient mix," Dr. Bakaeen says.

"We use bilateral ITAs [internal thoracic artery grafts] and radial artery grafts very frequently," adds Kenneth McCurry, MD, another surgeon on the CABG team. "This is consistent with guideline recommendations and has been shown, by us and others, to be associated with longer patient survival. We can often safely use bilateral ITAs on patients well into their 60s and 70s, which many centers consider too risky to attempt."

The program readily takes on other forms of case complexity as well, including performing CABG in selected patients with failing hearts by using preemptive advanced mechanical circulatory support to reduce the risk of postcardiotomy cardiogenic shock. The team also has deep experience performing CABG in patients with multiple previous coronary stents or other challenges, such as poor vessel targets. And its expertise in reoperative CABG is unsurpassed, with reoperations representing 9% to 11% of its overall CABG procedures in recent years. "Many of our redo CABG patients have been declined elsewhere," Dr. McCurry notes.

The team is committed to offering patients CABG via the least invasive operation possible, for quicker recovery and smaller scars. One option is minimally invasive direct coronary artery bypass (MIDCAB), a sternum-sparing, typically off-pump approach in which a small incision is made between the ribs, after which long instrumentation and special retraction devices are used to place the left ITA as the bypass graft to the left anterior descending artery (LAD). MIDCAB is also offered as part of hybrid revascularization for patients who additionally need to undergo stenting for lesions in non-LAD vessels not readily accessible via mini-thoracotomy.

Now the Cleveland Clinic team also can offer selected patients MIDCAB with robotic assistance, which typically allows for an even smaller incision and perhaps even faster and less painful recovery. "We have been doing two to four robotically assisted CABG procedures per month," says Dr. Bakaeen. "That number is quickly rising as the robotic technology allows us to expand the patient pool and we undertake more robotically assisted hybrid procedures. Patients appreciate the cosmetic results and quicker return to full activity."

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TAVR EXPLANTATION: GUIDANCE FOR MANAGING A GROWING CLINICAL NEED

TAVR explant demands multidisciplinary expertise

All bioprosthetic valves, whether placed by surgical or transcatheter insertion, have a specific life span. While explantation of surgical aortic valves has been safely performed for many decades, removing transcatheter aortic valve replacement (TAVR) valves is a recent development that carries increased risk.

A 2022 Cleveland Clinic study of 59 consecutive patients who underwent cardiac surgery after TAVR revealed that 78% of the operations involved TAVR explantation (*Ann Thoracic Surg.* 2022;114:52-60). Moreover, the interval between TAVR implantation and explantation decreased substantially over the course of the study period, which ran from 2012 to 2020.

The Cleveland Clinic cardiac surgeons behind this research have updated data for publication, and they say the trend of more and earlier TAVR explantations has continued. They attribute the trend largely to inappropriate patient selection, patient-prosthesis mismatch, infective endocarditis or failure to address concurrent problems, such as coronary artery disease or mitral valve disease.

"TAVR was initially developed as an alternative to surgical aortic valve replacement [SAVR] in patients at high to medium risk from surgery," says Marijan Koprivanac, MD, MS, a cardiac surgeon specializing in aorta and aortic valve surgery. "As indications have expanded to low-risk patients, a significant percentage of TAVR recipients are now younger and healthier. They love the option of a less-invasive procedure that lets them go home the next day, but these patients are likely to outlive their replacement valves, whether they be TAVR or SAVR valves. Heart teams should fully consider patients' long-term needs when deciding between SAVR and TAVR for initial valve replacement, with an eye toward potential future replacement procedures. One approach may set the stage for future procedures better than the other, but this is often determined on a case-by-case basis after factoring in patient age, overall health, life expectancy and specific anatomic considerations usually based on CT imaging. It's an individualized decision that requires a heart team approach and shared decision-making with the patient."

Options when a TAVR valve fails

Today's TAVR valves may last 10 years or more, but long-term durability is unknown and longer-term follow-up will be needed. Reasons for TAVR prosthesis failure include stenosis/regurgitation, paravalvular leak and endocarditis. Further, some patients may require cardiac surgery after TAVR for another reason, even if the TAVR valve is still working properly, in which case the TAVR valve is often still explanted and replaced with a surgical bioprosthesis.

When a TAVR valve needs to be replaced, the options are insertion of a second valve inside the first (valve-in-valve TAVR) or surgical explantation followed by SAVR. In cases where endocarditis is present, the infected tissue must be removed, making SAVR the sole option.

Dr. Koprivanac considers SAVR to generally be the better treatment option for a failing TAVR valve in many patients at lower surgical risk. "With valve-in-valve TAVR, the second valve makes the annulus smaller and creates a higher pressure gradient, so it is not ideal in many cases and is not possible in others," he says.

"Valve-in-valve TAVR can be a great option when the initial TAVR is a large valve and there is appropriate space around it," notes Amar Krishnaswamy, MD, Section Head of Interventional Cardiology. "The same considerations regarding sizing need to be made when placing a SAVR valve. That is why it is vitally important that an expert multidisciplinary team work together to provide the best option for each patient."

Dr. Koprivanac says there is growing evidence that, in general, when SAVR follows TAVR, outcomes tend to be worse than when TAVR follows SAVR. "In most cases, the sequence should be planned so that TAVR is the last intervention," he says. "SAVR can provide an ideal foundation for valve-in-valve TAVR."

Endocarditis in a TAVR patient

When infective endocarditis develops in a TAVR prosthesis, there is no question about treatment. "The valve must be removed, along with all traces of infection," says Haytham Elgharably, MD, Surgical Director of Cleveland Clinic's Endocarditis Center.

"Explantation can be complex, especially if the surgeon doesn't do a large number of aortic root procedures," he continues. "A high-volume center like Cleveland Clinic can handle the pathology and avoid destroying the root."

"The good news," adds Samir Kapadia, MD, Chair of Cardiovascular Medicine and an interventional cardiologist, "is that the risk of endocarditis is similar in trials that compare TAVR and SAVR, so it does not appear that TAVR itself increases endocarditis risk."

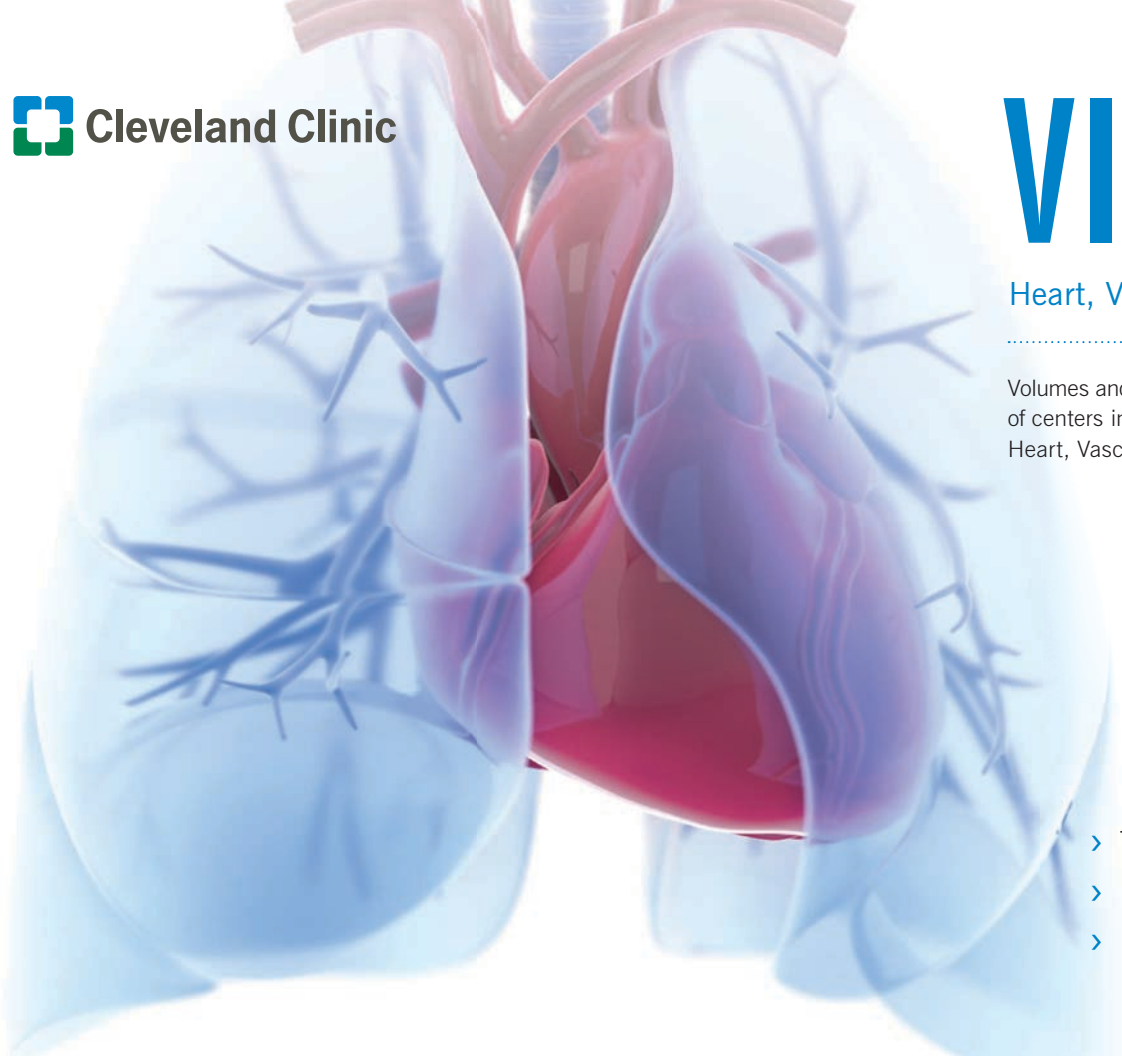
Cleveland Clinic

VITALS

2024 | ISSUE 3

Heart, Vascular and Thoracic

Volumes and outcomes from a sampling of centers in Cleveland Clinic's Miller Family Heart, Vascular & Thoracic Institute



- Thoracic Surgery
- Lung Transplantation
- HOCM and Pericarditis

THORACIC SURGERY

2023 DATA HIGHLIGHTS

2,016
Number of general thoracic operations performed

275
Number of robotically assisted thoracic surgery procedures

94%
Proportion of all lobectomies for stage I lung cancer (N = 120) that used video/robot-assisted thoracoscopic surgery

82.5%
Proportion of thymectomy/thymic mass resections completed robotically (N = 33)

STS QUALITY RATINGS

From the Society of Thoracic Surgeons (STS) General Thoracic Surgery Database (3-year period ending December 2023):

Lobectomy for Lung Cancer — Composite Overall Quality Rating			
Eligible procedures	Participant score	STS mean participant score	Participant rating
466	98.78%	98.40%	★★

Lung Cancer Resection — Composite Overall Quality Rating			
Eligible procedures	Participant score	STS mean participant score	Participant rating
731	98.9%	98.57%	★★★ (highest)

Esophagectomy — Composite Overall Quality Rating			
Eligible procedures	Participant score	STS mean participant score	Participant rating
221	95.01%	91.01%	★★★ (highest)

Of 106 rated participants in this STS category, Cleveland Clinic was **one of 14** that achieved a 3-star rating.

LUNG TRANSPLANTATION

2023 DATA HIGHLIGHTS

129

Total lung transplants performed, including 1 heart/lung and 5 lung/liver

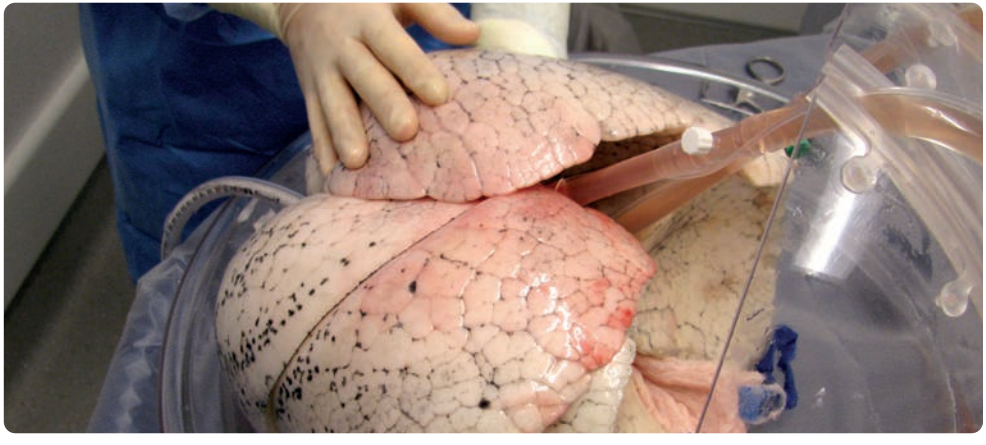
34

Lung transplants performed after ex vivo lung perfusion (EVLP)

97%

30-day survival rate following EVLP lung transplant

Lung Transplant Patient Survival Rates				
	Observed	Expected	National	Report period
1-year survival (N = 255)	87.65%	88.49%	88.85%	1/1/2021-6/30/2023
3-year survival (N = 254)	72.22%	71.17%	72.36%	7/1/2018-3/12/2020, 6/13/2020-12/31/2020
Source: Scientific Registry of Transplant Recipients (SRTR) data release of 7/9/2024 (amended 7/18/2024)				



RIGHT — Donor lungs undergoing ex vivo lung perfusion (EVLP).

HOCM AND PERICARDITIS

2023 DATA HIGHLIGHTS FOR HYPERTROPHIC OBSTRUCTIVE CARDIOMYOPATHY (HOCM)

4,847
Outpatient visits for HOCM

787
New HOCM patients seen

177
Septal myectomy procedures (with or without other procedures) performed for HOCM

0.0
Observed-to-expected mortality ratio for septal myectomy*

* *According to Vizient® Clinical Data Base/Resource Manager. Used by permission of Vizient. All rights reserved.*

2023 DATA HIGHLIGHTS FOR PERICARDITIS

3,048
Patients seen by our Pericardial Diseases Center

573
New patients seen by the Pericardial Diseases Center

305
Pericardial procedures performed

56
Pericardiectomies performed

› For more data like this, visit **clevelandclinic.org/hvtioutcomes** and **clevelandclinic.org/e15**.

Dr. Elgharably notes that the explant procedure generally carries high mortality, citing a report from the EXPLANT-TAVR international registry detailing outcomes of 269 patients undergoing TAVR explantation at 42 centers (*JACC Cardiovasc Interv.* 2021;14[18]:1978-1991): 30-day mortality was 13.1%, and 54.6% of patients required a concomitant cardiac procedure. Importantly, most patients in this series were elderly and at high surgical risk, which limits how broadly these data can be extrapolated.

Diagnosing TAVR valve failure

At Cleveland Clinic, patients with symptoms of TAVR failure are examined with transthoracic echocardiography. If the findings suggest a problem, transesophageal echocardiography (TEE) and/or cardiac CT may be done.

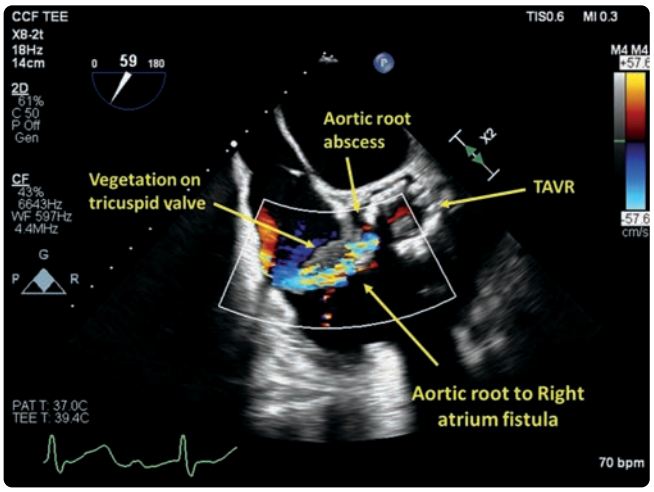
"These are complementary tools," says cardiologist Serge Harb, MD. "Both have excellent spatial resolution. TEE also has excellent temporal resolution, so we use it to assess the valve leaflets and to determine the severity of valve dysfunction. CT provides excellent anatomic definition of the valve and its surrounding area, and it also helps in planning potential interventions."

Not uncommonly, a patient with suspected endocarditis may present with recurrent positive cultures but no visible vegetation on echocardiography and perhaps just thickening of the leaflets. Without a clear diagnosis of endocarditis on initial imaging, some cardiologists hesitate to refer and will start the patient on antibiotics. Dr. Elgharably discourages this practice.

"These patients should be referred to a specialized endocarditis center," he says, "as they may need specialized imaging for diagnosis, such as a PET scan. If endocarditis is present in the prosthetic valve, explanting the prosthesis is the only way to cure the infection. However, if the patient is at prohibitive risk for surgical extraction (as some TAVR patients are), they will need antibiotics indefinitely. If you stop the treatment, the infection will get worse."

Managing complications

As a major referral center for complex valve replacements and endocarditis surgery, Cleveland Clinic sees the results of inadequate attempts at treating failing TAVR valves. One case, published by Dr. Elgharably and colleagues in the *Annals of Thoracic Surgery* (2023;1[2]:316), was marked by TAVR valve embolization to the aortic arch. Instead of removal, a second TAVR valve was implanted, but residual paravalvular leak was detected. Failing to find symptom relief, the patient sought treatment at Cleveland Clinic, where



ABOVE — A transesophageal echocardiogram from a patient with complex infective endocarditis involving a TAVR prosthesis. The coexistent abscess, fistula and vegetation illustrate the complexity of cases like these.

both prostheses were carefully removed and successful SAVR was performed.

Such cases underscore recommendations that TAVR explantation be performed only by a team with experience and expertise in valve replacement, aorta and aortic root surgery, multimodality imaging and endocarditis.

"The aorta grows into the nitinol cage, and it is easy to damage the aorta when peeling it away from the prosthesis," Dr. Koprivanac notes. "In addition to replacing the valve, the surgeon must be prepared to replace the aortic root and repair or replace the ascending aorta as well.

"TAVR is unquestionably a fantastic development," he continues, "but in those cases when an implanted valve is failing, referral to a center with high volume-based experience in TAVR explantation can mitigate some of the risk inherent in this increasingly frequent presentation."

Contact Dr. Koprivanac at 216.444.2035, Dr. Krishnaswamy at 216.636.2824, Dr. Elgharably at 216.444.1824, Dr. Kapadia at 216.444.6735 and Dr. Harb at 216.444.3316.

A TRANSAORTIC APPROACH TO MIDVENTRICULAR AND APICAL SEPTAL MYECTOMY

Large single-center series demonstrates safety and efficacy for extending procedure

Midventricular and apical septal muscle can be resected successfully and safely with a transaortic approach by experienced surgeons aided by specialized instruments and detailed imaging, concludes a large new Cleveland Clinic study.

This strategy for relieving obstruction and enlarging the left ventricular chamber is employed at Cleveland Clinic for patients with obstructive hypertrophic cardiomyopathy (HCM) who are unresponsive to or intolerant of maximal medical therapy. The study was published online in the *Journal of Thoracic and Cardiovascular Surgery* and presented at the recent 104th annual meeting of the American Association for Thoracic Surgery.

"In our experience, the transaortic approach can be used to reach the midventricular and apical regions, allowing extended myectomy to be conducted without ventriculotomy," says the study's senior and corresponding author, Nicholas Smedira, MD, MBA, a Cleveland Clinic cardiothoracic surgeon with a specialty interest in septal myectomy. "The transaortic approach is more comfortable than the transapical approach for most cardiothoracic surgeons, offers a more conventional anatomical viewpoint and provides easy access for mitral valve repair."

Extension of a familiar technique

While myectomy for isolated basal septal hypertrophy is usually performed via a transaortic approach, transapical entry — requiring left ventriculotomy to access the septum — is usually recommended for midventricular and apical hypertrophy. Over the past several years, Dr. Smedira has used the transaortic approach to extend resection from the base as far as the apex, thereby avoiding the need for repeat myectomy due to inadequate resection.

"Cleveland Clinic has been performing myectomies for over 40 years, during which time we have continually refined the operation," Dr. Smedira notes. "This has included designing and developing instruments to facilitate the operation. It also includes collaborating with our cardiovascular imaging colleagues to gain a comprehensive understanding of septal anatomy and function, guide how much muscle to remove, and assess the efficacy of the procedure. This extension of the transaortic approach evolved from that ongoing process of refinement."

The new retrospective study was undertaken to examine this strategy with regard to operative features, safety and efficacy.

Series characteristics and outcomes

From January 2018 to August 2023, transaortic septal myectomy was performed in 940 patients at Cleveland Clinic. Of these, 258 patients (27%) underwent isolated basal myectomy and were excluded from this analysis. The final cohort consisted of 682 patients who underwent myectomy of the midventricular and/or apical septum using the transaortic approach.

Anatomy varied among the patients, requiring different amounts and areas of muscle to be resected. Most patients had 5 to 15 grams of muscle removed (median, 10 g), with the largest resection weighing 32 grams.

The following combinations of septal areas were most commonly resected:

- Basal (defined as opposite the mitral valve to the leaflet tips) plus midventricular (leaflet tips to just beyond the papillary muscle heads) (n = 582; 85%)
- Basal plus midventricular plus apical (apical third of ventricle) (n = 78; 11%)

Small numbers of patients underwent either isolated midventricular, midventricular plus apical, or basal plus apical resections.

The median total cardiopulmonary bypass time was 41 minutes, and the median cross-clamp time was 32 minutes.

The primary endpoint was obstruction relief as assessed by intraventricular gradient. Mean intraventricular gradient improved from 102 ± 41 mmHg preoperatively to 16 ± 10 mmHg on intraoperative postmyectomy transesophageal echocardiography. Almost all patients (96%) achieved a gradient of 36 mmHg or less, the prespecified threshold for adequate myectomy.

Operative and postoperative complications included the following:

- One patient died (0.1%) due to an intraoperative ventricular septal defect.
- Permanent pacemaker placement was required in 38 patients (5.6%). Of these, 30 had preoperative right bundle branch block and eight (1.2%) had normal preoperative conduction.

"The transaortic approach is more comfortable than the transapical approach for most cardiothoracic surgeons, offers a more conventional anatomical viewpoint and provides easy access for mitral valve repair." — NICHOLAS SMEDIRA, MD, MBA

- Stroke occurred in eight patients (1.2%), four patients (0.6%) had renal failure requiring dialysis, 13 (1.9%) required prolonged ventilation and seven (1.0%) required reoperation for bleeding/tamponade.

No aortic or mitral valve injuries occurred.

"The safety profile and the aortic cross-clamp times are similar to those reported for the transapical approach," Dr. Smedira observes.

Concomitant mitral valve procedures

Among the cohort, 145 patients (21%) underwent successful concomitant mitral valve repairs, 137 of which were performed via the transaortic approach. Most mitral valve repairs were indicated primarily for HCM-related pathology (85%); 13% of cases involved intrinsic mitral valve disease, and 2.1% of cases involved both issues.

In addition, 16 patients (2.3%) had concomitant mitral valve replacement (15 with a bioprosthesis and one with a mechanical valve). Two were performed after failed attempts at mitral valve repair.

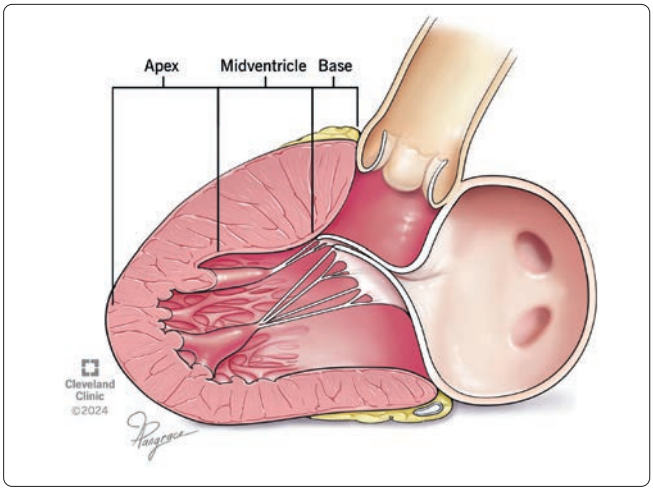
Essentials for a successful extended transaortic approach

The authors note that elongated anterior leaflets should be resected or plicated at the time of myectomy. Further operative techniques have been described by these Cleveland Clinic authors in the *Journal of Thoracic and Cardiovascular Surgery* (2019;157[6]:2289-2299), *Innovations (Philadelphia)* (2023;18[1]:4-6) and *Operative Techniques in Thoracic and Cardiovascular Surgery* (2023;28[4]:272).

In general, Dr. Smedira emphasizes that the following are critical to surgical success in this context:

- Surgeon experience in resecting midventricular and apical muscle
- A complete understanding of the patient's septal anatomy using 3D imaging
- Use of a strong LED headlight and specialized instruments, as detailed in the published study report

"More than 70% of patients in our study period who underwent septal myectomy for relief of obstruction required resection beyond the basal septum," Dr. Smedira concludes. "Our overarching goal is the safe removal of the maximum amount of muscle to relieve obstruction and enlarge the left ventricular cavity if needed."



ABOVE — The transaortic approach investigated in the study extends resection from the basal septum to as far as the apex.

An additional perspective

"Surgical therapies are well established for relief of dynamic left ventricular outflow tract obstruction in the setting of basal septal hypertrophy and systolic anterior motion of the mitral valve in a symptomatic patient with obstructive HCM," notes Milind Desai, MD, MBA, Director of Cleveland Clinic's Hypertrophic Cardiomyopathy Center. "However, they are less established for mid- and distal cavity hypertrophy in other patients with symptomatic 'nonobstructive' HCM or in those with midcavitary obstruction.

"This study represents a step in the right direction using a conventional transaortic approach versus an apical myectomy, which requires a transapical approach and, in turn, a repair of the left ventricular apex," he continues. "At the same time, this landscape is going to evolve in the next decade with the emergence of effective nonsurgical therapeutic options, including the new class of cardiac myosin inhibitors such as mavacamten."

Contact Dr. Smedira at 216.445.7052 and Dr. Desai at 216.445.5250.

RESEARCH MOUNTS LINKING SUGAR SUBSTITUTES TO HEIGHTENED CARDIOVASCULAR RISK

Public health implications loom large for use of xylitol and erythritol as food additives

Two new papers by Cleveland Clinic researchers add to mounting evidence that at least two sugar alcohols used as non-nutritive sweeteners substantially enhance platelet reactivity and thrombosis potential in humans. The papers report on studies that also included observational cohort components additionally showing an elevated incident risk of major adverse cardiovascular events (MACE).

The research, which involved the sugar alcohols xylitol and erythritol, has prompted concern that these additives may not be as safe as their food regulatory classifications suggest and that they should be reevaluated for use as ingredients in foods and beverages.

"These investigations indicate an immediate need for evaluating sugar alcohols and other sugar substitutes," says principal investigator Stanley Hazen, MD, PhD, Co-Section Head of Preventive Cardiology and Chair of Cardiovascular and Metabolic Sciences in Cleveland Clinic Lerner Research Institute. "This is underscored by the fact that food products with these compounds continue to be recommended for combating conditions like obesity and diabetes despite findings that they appear to actually *increase* patients' cardiometabolic risk."

Natural compounds in unnatural quantities

Xylitol and erythritol are sugar alcohols found naturally in small quantities in fruits and vegetables. They are also produced endogenously by humans in very small amounts as a side product of glucose metabolism. In recent years, they have been manufactured for use in much larger quantities as zero-calorie sweeteners in processed foods marketed as healthier alternatives to sugar-sweetened baked goods or confections.

"Sugar alcohols, also known as polyols, are sugar derivatives that can come from natural sources, so they are technically not considered nonsugar or artificial sweeteners," says co-investigator W.H. Wilson Tang, MD, Research Director for Heart Failure and Transplantation in the Department of Cardiovascular Medicine. "Interestingly, polyols have not been included as added sugars in products' nutritional labeling, which allows manufacturers to describe polyol-containing foods as 'sugar free' or 'reduced sugar' in their claims."

Indeed, xylitol and erythritol are classified by the U.S. FDA and the European Food Safety Authority as GRAS ("generally recognized as safe") ingredients, allowing their use without restriction in food products.

"Many professional societies and clinicians recommend that people at high cardiovascular risk — those with obesity, diabetes or metabolic syndrome — consume foods that contain sugar substitutes rather than sugar," Dr. Hazen notes. "It is incumbent on us to ensure that we are not unwittingly provoking adverse events with this advice."

Xylitol studies

His team's research on xylitol, published in the *European Heart Journal* (2024;45[27]:2439-2452), was a multicomponent investigation comprising large-scale patient analyses, preclinical functional studies and a clinical intervention study. It stemmed from analyses of fasting blood samples taken from over 3,300 adults undergoing elective cardiac evaluations who were followed for MACE over the next three years. The blood samples were screened for chemical signatures that predicted future MACE independent of traditional risk factors.

The analyses included an untargeted metabolomics study in a discovery cohort ($n = 1,157$) that identified circulating levels of xylitol as being associated with incident MACE risk. A subsequent targeted study in a separate validation cohort ($n = 2,149$) confirmed xylitol's association with incident MACE, with an adjusted hazard ratio of 1.57 (95% CI, 1.12-2.21) ($P < .01$) over three-year follow-up for subjects with the highest tertile of xylitol levels versus those with levels in the lowest tertile.

The researchers then conducted functional studies to directly observe whether xylitol is causally linked to cardiovascular pathogenesis. In vitro studies using human whole blood showed that xylitol substantially enhanced platelet reactivity at levels observed in fasting plasma from the initial cohort studies. "In the presence of xylitol, platelets showed a much lower threshold for clotting," Dr. Hazen says.

This in vitro work was complemented by in vivo murine studies that demonstrated parallel enhancement of thrombosis formation with xylitol, again at levels equivalent to fasting plasma levels in humans.

The researchers then tracked baseline versus postprandial platelet activity in 10 healthy volunteers who ingested a drink sweetened with 30 grams of xylitol (roughly the amount in a scoop of keto-friendly ice cream). Plasma levels of xylitol rose 1,000-fold in these subjects within 30 minutes, and every measure of platelet responsiveness significantly increased immediately after ingestion in every subject. Xylitol was rapidly excreted, returning to near-baseline levels within six hours of ingestion.

"This intervention study suggests that the fasting plasma levels of xylitol seen in our observational cohort represent variations in endogenous levels of xylitol, not levels impacted by food consumption," Dr. Hazen notes. He says this underscores just how great the clotting risk from food-related elevations in plasma xylitol may be, given how greatly endogenous xylitol levels are dwarfed by the xylitol levels added to foods.

Erythritol intervention study

The Cleveland Clinic team has made parallel observations with erythritol. Last year they published findings in *Nature Medicine* (2023;29:710-718) prompted by fasting blood samples from the same discovery and validation cohorts from the xylitol investigations above. That paper revealed the following:

- At-risk cardiac patients with high plasma erythritol levels were about twice as likely to have a cardiac event over the next three years compared with similar patients with low erythritol levels.
- Adding erythritol to blood products in vitro to achieve concentrations seen in patients led to increased platelet aggregation and adhesion.
- Increasing circulating erythritol levels in a murine model of arterial injury led to a faster rate of clot formation.

Dr. Hazen's group followed up that work with an intervention study of erythritol (*Arterioscler Thromb Vasc Biol.* [Epub 2024 Aug 8]) similar to the xylitol intervention study reported above. After blood was drawn following overnight fasting, 20 healthy volunteers consumed water mixed with 30 grams of erythritol (about what's in an erythritol-sweetened soda or baked good) or 30 grams of glucose. Blood was drawn again after 30 minutes, and plasma levels of erythritol were assessed, as were multiple indicators of platelet function. Among the key findings:

- Postprandial mean erythritol level increased more than 1,000-fold in the erythritol group compared with baseline (from 4 μM to 6,480 μM, $P < .0001$).
- Circulating erythritol levels remained similar before and after glucose consumption, and mean glucose level increased modestly (from 87 to 127 mg/dL, $P = .002$).
- Measures of platelet aggregation showed a striking increase after erythritol ingestion for each subject and agonist examined but did not change after glucose consumption.

KEY FINDINGS

- **Diverse studies indicate that the sugar alcohols xylitol and erythritol (chemical structure illustrated at left) increase incident cardiac event risk and promote platelet reactivity and thrombosis.**
- **Intervention studies show that ingestion of either sugar alcohol increases plasma levels of the compound 1,000-fold within 30 minutes and significantly raises all measures of platelet responsiveness.**

- Measures of platelet dense granule and alpha granule release showed significant increases following erythritol ingestion but did not change after glucose consumption.

Next steps, near-term advice

"These findings raise concern that standard servings of erythritol- or xylitol-sweetened foods and beverages may acutely stimulate a direct prothrombotic effect," Dr. Tang observes. "They highlight the need for rigorous, prospective clinical trials with sufficient duration and clinically relevant endpoints to establish the cardiovascular and metabolic safety — or risk — of these widely consumed sugar substitutes in direct comparison to consuming sugar itself."

"The effects we observed were significant and were confirmed across many different types of studies," Dr. Hazen adds. "This is a health concern on a population scale. We need more research and reappraisal of regulatory guidelines so we can make sure we're not inadvertently urging people to reach for something they think is a healthy choice when it's not."

Meanwhile, until further clarifying research or regulatory guidance is forthcoming, Dr. Hazen advises his patients to avoid all highly processed "sugar free" foods.

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Contact Dr. Hazen at 216.444.9426 and Dr. Tang at 216.444.2121.

INFECTIVE ENDOCARDITIS DUE TO OPIOID ADDICTION: TWO DISEASES, HIGHLY DIVERGENT OUTCOMES

Cleveland Clinic study points to need for new strategies to curb addiction relapse

Surgery for infective endocarditis (IE) in people who use injected opioids is as successful as in nonusers of opioids, yet most patients soon relapse to opioid use and die within three to five years of surgery, a Cleveland Clinic study has found.

The study, published in the *Journal of the American College of Cardiology* (2024;83:811-823), concludes that opioid addiction is considerably more lethal than IE surgery itself and requires enhanced and comprehensive rehabilitative efforts.

"It is disheartening and draining when we hear that a patient has been readmitted for relapse or has overdosed and died," says corresponding author Haytham Elgharably, MD, Surgical Director of Cleveland Clinic's multidisciplinary Endocarditis Center. "We view these cases as involving two diseases — endocarditis and addiction — and treatment for endocarditis cannot ultimately be effective unless the addiction is overcome. We remain committed to refining efforts to combat the addiction and will continue to track outcomes in these patients."

Study backdrop and key findings

Cleveland Clinic has one of the nation's most active IE surgery programs, and a large share of its IE cases result from use of injected opioids. To prevent addiction relapse and avoid IE recurrence, the Endocarditis Center supports patients who inject drugs with a multidisciplinary program of pre-, peri- and postoperative care, with a focus on preventing return to addiction.

Despite these efforts, addiction relapse and death rates have not slowed in recent years, according to the results reported in *JACC*. The retrospective study included 227 persons who injected drugs (mean age, 36) who underwent IE surgery at Cleveland Clinic from January 2010 to June 2020. Of the 227 operations, 67 (30%) were reoperations, seven were second reoperations and one was a third reoperation.

Psychosocial comorbidities were common, with 66% of patients reporting arrest, incarceration or other involvement with the justice system; 25% being unhoused; and 52% and 46% having diagnosed depression or anxiety, respectively.

The most commonly used injected drug was heroin, reported by 81% of patients, although the study notes that drug enforcement agencies believe "heroin" is now more likely to be a fentanyl derivative with fillers.

Early surgical outcomes in the cohort were excellent and equivalent to those of IE patients without opioid addiction. However, a sizable share of patients was lost to follow-up, and rates of relapse to opioid use were high, particularly in the first year, peaking at nine months after surgery.

Because of the high loss to follow-up, the researchers calculated patient outcomes as conditional probabilities. They estimated that, at one year after surgery, 16% of patients had been lost to follow-up, 32% had relapsed and 21% had died. By five years, the estimates were 59% lost to follow-up, 79% having relapsed and 68% having died, with a median time to death of 3.2 years.

Relapse was the only factor significantly associated with death. Predictors of relapse were younger age, heroin use and lower educational attainment.

Addiction far more lethal than endocarditis

"At Cleveland Clinic, we have a large experience in all areas of surgery for endocarditis and have consistently published our results," says study co-author and cardiothoracic surgeon Shinya Unai, MD. He cites recent study publications in the *Journal of Thoracic and Cardiovascular Surgery:* (2024;167[1]:127-140), (2024;168[2]:440-452) and (2023;165[4]:1303-1315). "However, even if the surgical outcomes are good, patients will not have a good long-term result if the addiction is not treated appropriately. We have more work to do."

There is controversy about how to manage these patients — and even whether surgery for IE is appropriate. Cleveland Clinic surgeons believe surgery is not futile.

"Because short-term outcomes are excellent, clinically and ethically we cannot refuse to offer surgery to these patients," Dr. Elgharably says. "Of the two potentially lethal diseases these patients have, opioid addiction is far more lethal than advanced IE treated with surgery. Although we can prevent immediate death, heart failure, shock and sepsis with surgery, we cannot break the cycle of addiction with what is currently being done. It's just not enough."

One encouraging finding was that patients were less likely to be lost to follow-up if they reported having depression or anxiety. "The theory is that we did a better job of treating those psychiatric conditions, and the patients benefited," says psychiatrist and study co-author David Streem, MD, part of the Endocarditis Center team.

Newer strategies emerging

At the center of Cleveland Clinic's current efforts to treat IE patients who inject drugs is a program called MOSAIC that uses standardized protocols for pre-, peri- and postoperative care. Patients are evaluated preoperatively by a psychiatric addiction specialist, a cardiologist, a cardiac surgeon and an infectious disease physician, who collectively work with patients to put in place a clear plan for postoperative rehabilitation.

"A structured team-centered approach with community involvement and support is essential for optimal long-term outcomes among patients with this daunting treatment challenge," says Brian Griffin, MD, a cardiologist with the Endocarditis Center.

In 2017, Cleveland Clinic partnered with a long-term acute care hospital where patients receive treatment for addiction and underlying psychiatric issues while physically recovering from surgery. "This allows our psychiatrists to improve postoperative discharge follow-up and management, and it positions patients to have a better outcome and lower likelihood of returning to drugs," Dr. Streem explains.

The arrangement was a big win for Endocarditis Center patients, since insurers often refuse to pay for physical rehabilitation services at a facility that provides addiction treatment, due to higher costs.

In 2019, the state of Ohio launched Project SOAR (Supporting Opioid Addiction Recovery), a program promoting community response for people with addiction. By the end of the Cleveland Clinic study in 2020, 100% of IE patients who injected drugs were enrolled in MOSAIC and SOAR, and 100% were discharged on medications for opioid use disorder, versus 0% in 2010. After discharge, nurses call patients on a regular schedule to see how they are doing and ask if they need support.

These measures had not slowed the rate of relapse and death during the study period, but the researchers note that there may not have been enough time for an effect to be seen, given that the 10-year study ended in mid-2020.

The Endocarditis Center team continues to try new approaches. Recently, they launched an innovative effort aimed at preparing patients for successful recovery. In the Bridge to Surgery program, patients presenting with right-sided endocarditis — for which immediate surgery is generally unnecessary — begin addiction recovery along with antibiotic therapy for IE prior to surgery.

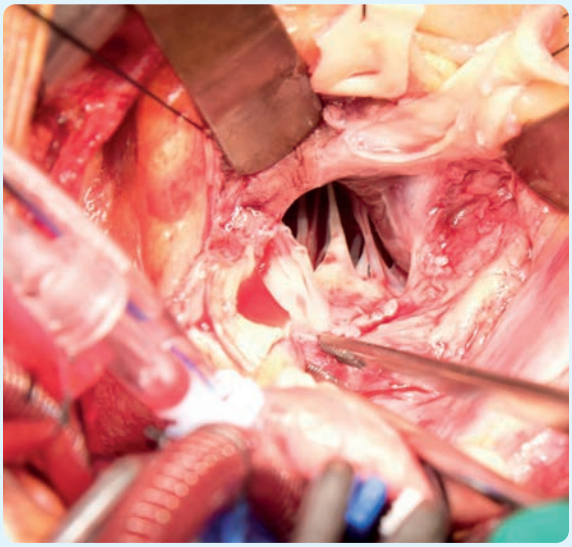
Another focus is extending the duration of recovery programs, in view of the study's finding that the risk of addiction relapse peaks at nine months after IE surgery.

Although the opioid epidemic shows little sign of easing, the team believes it's only a matter of time before they find a protocol that reduces the relapse rate and saves lives.

Meanwhile, they invite other centers dealing with the same problem to join the effort. "Those dying are mostly people in the prime of life," Dr. Elgharably says. "This is a problem affecting communities nationwide."

Contact Dr. Elgharably at 216.444.1824, Dr. Unai at 216.445.5902, Dr. Streem at 216.425.7413 and Dr. Griffin at 216.444.6812.

KEY FINDINGS



- **Surgery for infective endocarditis can be performed with low mortality in people who inject opioids, but the risk of addiction relapse within one year is high.**
- **Continued innovation is needed to identify effective strategies to prevent postsurgical addiction relapse.**

CME PREVIEW

MATCHLESS CASE-BASED LEARNING IN MITRAL AND TRICUSPID DISEASE IS IN STORE THIS DECEMBER

Join us in New York Dec. 6-7 for a broadened version of a CME crowd-pleaser

Case-Based Management of Tricuspid and Mitral Valve Disease 2024

Fri.-Sat., Dec. 6-7, 2024
JW Marriott Essex House, New York City
Information/registration: ccfcme.org/mitralvalve

For several years running, Cleveland Clinic has offered a valve-focused CME event in the heart of New York City in the lead-up to the December holidays, with the focus alternating from year to year between the aortic and mitral valves. This year the spotlight returns to the mitral valve, but now with a broadened scope to include detailed discussion of tricuspid valve disease as well.

"We've expanded the agenda to the tricuspid valve to address the evolving management of tricuspid valve disease with the emergence of new interventional therapies," says course co-director Brian Griffin, MD, Section Head of Cardiovascular Imaging at Cleveland Clinic.

"The landscape for management of mitral and tricuspid valve disease is changing rapidly," adds course co-director Marc Gillinov, MD, Chair of Thoracic and Cardiovascular Surgery. "Using a case-based approach, a multidisciplinary faculty will highlight the complex decision-making involved in choosing the best therapy for each patient."

More case-focused than ever

In fact, the popular course's case-based nature is stronger than ever this year, with case-based discussion comprising a large majority of each of its nine sessions. The sessions are focused on the following topics:

- Evolution of the mitral valve disease landscape
- Management of tricuspid valve disease
- Ventricular arrhythmias and mitral regurgitation
- Atrial arrhythmias and mitral regurgitation
- State of the art in transcatheter edge-to-edge repair
- Ischemic mitral regurgitation
- Torrential tricuspid regurgitation
- When and how to address the mitral valve in hypertrophic obstructive cardiomyopathy

Additionally, the final session of the day-and-a-half course consists exclusively of five complex case-based scenarios.

Imaging, interventional, surgery, EP and more

What makes the course's case-based discussions distinctive is that most include management perspectives from multiple subspecialties, including cardiovascular imaging, interventional cardiology, cardiac surgery, electrophysiology (EP) and others. These perspectives come from a faculty of 12 experts in these areas from Cleveland Clinic and leading institutions in the New York metro area.

"We have designed this meeting to combine case-based, cutting-edge discussions in all aspects of the diagnosis and management of mitral and tricuspid valve disease," notes course co-director Milind Desai, MD, MBA, Vice Chair of Education for Cleveland Clinic's Heart, Vascular & Thoracic Institute and a leading cardiologist in its Valve Center. "It will include lively discussions on multimodality imaging and on state-of-the-art surgical and structural interventions, including implications of the latest trial data."

The agenda is notable for its frequent integration of imaging and EP considerations into virtually all the subtopics covered, ensuring comprehensive exploration of all case scenarios discussed. Other agenda highlights include a review of lessons from recent trials of various transcatheter tricuspid interventions, a debate on surgery versus interventional management of ischemic mitral regurgitation, and discussions around surgical management of combined mitral and tricuspid valve disease.

"This course will be a great resource for those interested in the latest on complex mitral and tricuspid valve surgery and the many nuanced clinical considerations leading up to it," comments course co-director Lars Svensson, MD, PhD, Chief of the Heart, Vascular & Thoracic Institute. "We look forward to engaging discussions with colleagues from near and far."

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Register or learn more at ccfcme.org/mitralvalve.
Early-bird pricing ends Oct. 15.

This activity has been approved for *AMA PRA Category 1 Credit™*.

ROBOTIC MITRAL VALVE REPAIR: REFLECTIONS AFTER 2,400-PLUS CASES

Robotically assisted mitral valve repair surgery holds clear appeal for patients: Its minimally invasive nature means shorter recovery and better cosmetic results compared with full or partial sternotomy. For surgeons, it additionally offers unparalleled visualization into the heart.

This appeal has translated to continued embrace of the procedure at Cleveland Clinic, which performed its 2,400th robotically assisted mitral valve repair surgery in May 2024. This series of robotic procedures, which began nearly 20 years ago, was achieved with a 99.7% rate of repair (versus replacement) for isolated degenerative mitral valve disease and a mortality rate of 0.04%.

"Many patients with mitral valve disease come to us asking specifically for a robotically assisted repair," says A. Marc Gillinov, MD, Chair of Thoracic and Cardiovascular Surgery. "While many are good candidates, some are not. What we can assure patients is that we'll work with them to judiciously determine which option — robotic assistance, another minimally invasive approach, or partial or full sternotomy — will give them the best chance of a safe and lasting mitral valve repair."

In lieu of sternotomy, robotically assisted mitral valve repair involves tiny incisions for each of three arm ports and one working incision about 3-4 cm long between the ribs. The cameras housed in the robotic system enable the surgeon, seated at a console, to see parts of the valve at 10× magnification and with 360-degree orientation.

"The motions of the robot arms and articulation of the instruments are so precise that they mimic exactly the motions we direct from the console," says cardiac surgeon Tarek Malas, MD, whose interests include robotic and minimally invasive surgery.

Postoperatively, patients have shorter length of stay than their open-surgery counterparts. Overall recovery is shorter too, though it still takes two to four weeks for most patients. Patients are particularly pleased that they can drive within a week of robotic surgery, versus four to six weeks of no driving after standard surgery.

Beyond acquisition of a robotic surgical system, these procedures require specialized training. "Robotic heart surgery isn't something you learn in medical school or a regular residency," Dr. Gillinov says. "Our large team of experienced surgeons allows us to teach this new skill set to interested trainees."

Cleveland Clinic's approach is guided by a homegrown screening algorithm used to assess patients' candidacy for robotic mitral valve repair. Candidates must fulfill the following requirements based on imaging findings:

- *From transthoracic echocardiography:* mild or no aortic regurgitation, no significant mitral annular calcification, good left ventricular function and no significant pulmonary hypertension
- *From CT of the chest, abdomen and pelvis:* minimal aortoiliac atherosclerosis, femoral artery diameter ≥ 7 mm and absence of severe pectus excavatum

ABOVE — Dr. Gillinov at the robot console during a mitral valve repair.

A 2022 study in the *Journal of Thoracic and Cardiovascular Surgery* evaluated use of the algorithm across a 1,000-patient sample. It showed that 60% of screened patients qualified for robotic surgery and that their postoperative outcomes were just as good as those of patients undergoing mitral valve repair with sternotomy. More recently, 70% of patients with isolated degenerative mitral valve disease have qualified for the robotic approach, Dr. Gillinov notes.

Although the study wasn't randomized, it showed that patients who underwent robotic surgery also had significant reductions in new-onset atrial fibrillation, red blood cell transfusions and hospital length of stay compared with sternotomy patients.

As experience has grown, Dr. Gillinov adds, the team has extended robotic surgery to patients with some degree of left ventricular dysfunction, mild mitral annular calcification and the need for concomitant procedures. "We're also exploring robotic assistance in other types of cardiac surgery," he says. "For instance, we now offer robotically assisted coronary artery bypass grafting for selected patients with coronary artery disease."

Contact Dr. Gillinov at 216.445.8841 and Dr. Malas at 216.445.1652.

Cleveland Clinic

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SAVE THE DATES FOR CME

Cardiovascular Update 2024

Thu.-Fri., Oct. 31-Nov. 1, 2024

Hilton Cleveland Downtown
Cleveland, Ohio

Information/registration: ccfcme.org/cvupdate24

Advancing Cardiovascular Care 2024

Fri., Nov. 8, 2024

Hyatt Regency Columbus
Columbus, Ohio

Information/registration: ccfcme.org/columbuscvcare24

Dimensions in Cardiac Care

Sun.-Tue., Nov. 10-12, 2024

InterContinental Cleveland
Cleveland, Ohio

Information/registration: ccfcme.org/cardiaccare24

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(see detailed preview on page 18)

These activities have been approved for *AMA PRA Category 1 Credit™*.

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