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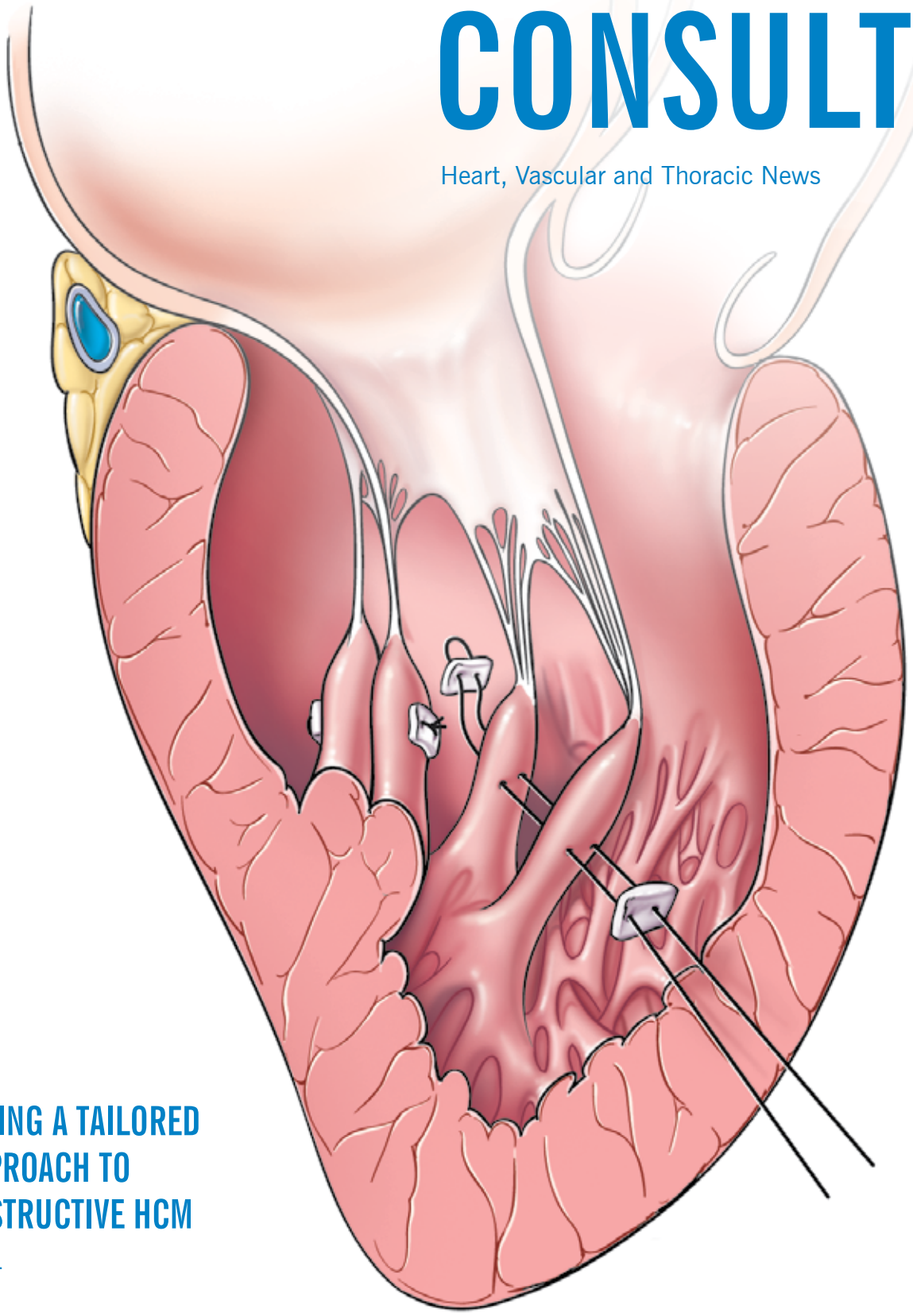


TAKING A TAILORED APPROACH TO OBSTRUCTIVE HCM

p. 4

DEAR COLLEAGUES,

One size does not fit all. That's the takeaway of the cover story of this issue of *Cardiac Consult* (page 4). For most patients with symptomatic hypertrophic cardiomyopathy, septal myectomy is sufficient to relieve left ventricular outflow tract obstruction, but in some patients other anomalies contribute to the obstruction, requiring a carefully tailored approach.

In Cleveland Clinic's Sydell and Arnold Miller Family Heart, Vascular & Thoracic Institute, we specialize in tailored approaches. That commitment to tailoring care is what prompted development of what we call the "Convergent Plus" approach to persistent atrial fibrillation (AF). As detailed on page 8, this strategy builds on the Convergent procedure — a hybrid epicardial/endocardial approach to AF ablation — by adding ablation of the ligament of Marshall and a left atrial appendage clip to further reduce AF burden and stroke risk in appropriate patients.

The same commitment to tailored care is at the heart of the story on page 14 profiling our recently published series of advanced interventions for esophageal perforation in critically ill patients. This report, the largest single-institution series published to date, shows that even patients requiring esophageal diversion can now benefit from surgical intervention, with excellent long-term survival. Our article outlines how best to match advanced interventions to specific patient characteristics.

If you have a challenging case requiring referral for highly specialized care, be assured that we will take a similarly tailored approach to finding the best solution. At Cleveland Clinic, we make it our mission to find just the right fit for each of our patients.

Respectfully,

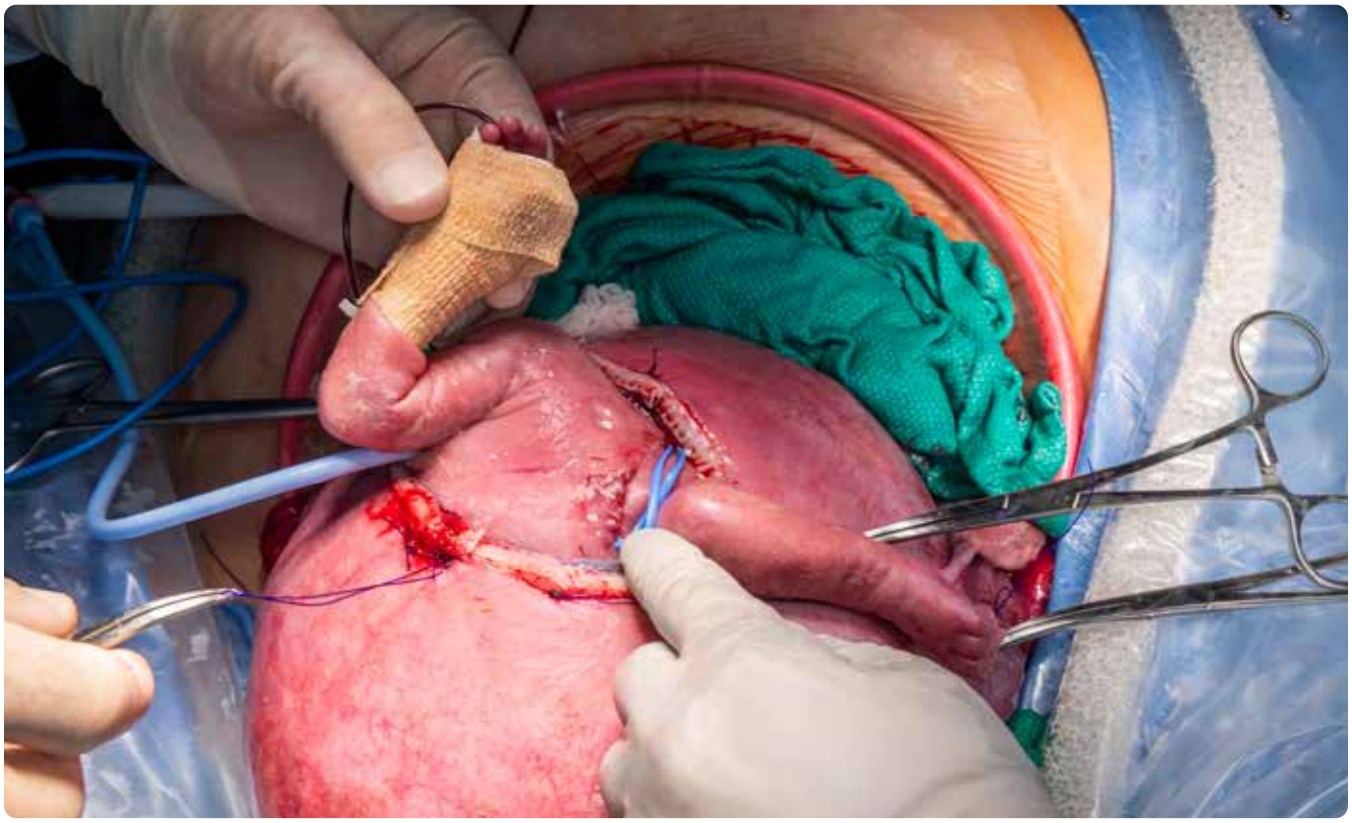
Lars G. Svensson, MD, PhD
Chairman, Sydell and Arnold Miller Family Heart, Vascular & Thoracic Institute

Cleveland Clinic was named a top U.S. hospital in *U.S. News & World Report*'s "Best Hospitals" rankings for 2021-22, as well as the No. 1 hospital in cardiology and heart surgery for the 27th consecutive year.

IMAGE OF THE ISSUE —

SUCCESSFUL FETAL SURGERY TO RESECT RARE INTRAPERICARDIAL TERATOMA

BELOW — Photo showing the fetus's exposed chest to allow resection of the pericardial teratoma.



"I knew that if my surgical colleagues could safely get me access to the fetus's chest, I could remove the tumor, because the technical part would be feasible." So says Hani Najm, MD, Chair of Pediatric and Congenital Heart Surgery at Cleveland Clinic, about his role in a landmark fetal surgery.

Dr. Najm was part of a multidisciplinary Cleveland Clinic team led by fetal surgeon Darrell Cass, MD, that successfully performed a challenging fetal surgery to remove a fast-growing pericardial teratoma that posed imminent lethal risk to a nearly 27-week-old fetus.

The operation in May 2021 to excise a 3-centimeter tumor affixed to the left side of the fetus's heart relieved severe cardiac and other physiologic problems and enabled the baby boy to be delivered at term 10 weeks later. The infant is now thriving at home.

Only one previous instance of extended survival after fetal intrapericardial teratoma resection is documented in the world's medical literature. "This case is as hard as they come," says Dr. Cass, who founded Cleveland Clinic's fetal surgery program in 2018 and is its director.

Dr. Najm had successfully resected intrapericardial teratomas in neonates several times, but he had never attempted the procedure in utero. "What you need is knowledge, teamwork and courage," he says. "There is nothing wrong with a calculated risk. This is how we advance medicine."

Buoyed by the successful intrapericardial teratoma resection, Dr. Najm and his congenital heart surgery colleagues plan to collaborate with Dr. Cass and his team on other advanced fetal cardiac surgeries at Cleveland Clinic.

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For a detailed account of this Cleveland Clinic fetal heart surgery, see **ccf.org/fetalheart**.

IN OBSTRUCTIVE HYPERTROPHIC CARDIOMYOPATHY, ONE SIZE DOES NOT FIT ALL

Why we favor a tailored approach to relieve LVOT obstruction

For most cases of symptomatic hypertrophic cardiomyopathy (HCM), septal myectomy is adequate to relieve left ventricular outflow tract (LVOT) obstruction. However, some patients have other anomalies causing LVOT obstruction, with or without septal hypertrophy, necessitating a more personalized strategy to address the problem.

"Obstructive hypertrophic cardiomyopathy is a very heterogeneous disease with a varied phenotype," says Milind Desai, MD, MBA, Director of Cleveland Clinic's Hypertrophic Cardiomyopathy Center. "An individualized treatment plan, informed by thorough evaluation with multimodality imaging and multidisciplinary collaboration, is essential for achieving optimal outcomes."

Experience-informed evaluation is essential

Dr. Desai recommends that patients diagnosed with or suspected of having HCM be referred to a center with expertise in the condition. While classic cases may be easy to recognize (i.e., patients with a characteristic provokable gradient and thick basal septum), some patients lack significant septal hypertrophy but have LVOT obstruction, which still puts them at risk for progression to severe heart failure and sudden death.

Maximum LVOT pressure gradient is assessed at rest and with provocation. Any and all means should be used to provoke an LVOT gradient in a symptomatic patient, including amyl nitrite, the Valsalva maneuver and treadmill/bicycle testing, as clinically indicated.

"Determining that someone does not have HCM based on lack of left ventricular hypertrophy is not appropriate," says Dr. Desai. "Furthermore, diagnosing someone with nonobstructive HCM without the full extent of provocation is also inappropriate."

Multimodality imaging pinpoints correctable problems

Patients should be evaluated with transthoracic echocardiography and cardiac magnetic resonance imaging, with special attention to the following features:

- **Basal septal thickness.** Thickness of 18 mm is the usual threshold for prompting myectomy. However, a mini-myectomy can be considered in selected cases with basal septum > 15 mm.
- **Mitral valve.** Focus should be on leaflet length, severity of mitral regurgitation and presence of systolic anterior motion.
- **Papillary muscles.** These should be checked for location, multiplicity and laxity. Finding apical displacement, abnormal chordal attachment, or bifid hypermobile or double bifid papillary muscles should raise suspicion for dynamic LVOT obstruction.

A Cleveland Clinic series of 121 patients with HCM and LVOT obstruction but without basal septal hypertrophy published in *Circulation: Cardiovascular Imaging* (2015;8[7]:e003132) found that abnormalities of the mitral valve, chordae and papillary muscles were associated with LVOT obstruction and that procedures to correct these problems, with or without myectomy, may be of benefit.

How to manage these complex patients

Nicholas Smedira, MD, MBA, Surgical Director of the Hypertrophic Cardiomyopathy Center, has extensive experience with complex HCM, having operated on about 2,500 cases. He notes that even with that experience, surgeries on these patients continue to pose new challenges. "One size does not fit all," he says. "In many cases, you need to be creative."

A mitral valve or below-valve intervention is often combined with myectomy in patients with LVOT and only moderate septal hypertrophy. Procedures may include the following, some of which are illustrated in Figures 1-3 on the opposite page:

- **Resection of secondary chordae.** This allows the zone of coaptation to move posteriorly, away from the outflow tract. It relieves heart failure symptoms, abolishes left ventricle outflow gradient, and avoids mitral valve replacement in patients with obstructive HCM and mild septal thickness.
- **Papillary muscle reorientation.** This is performed by tacking hypermobile anterior papillary muscle heads to posterior heads, moving the papillary muscles and mitral valve zone of coaptation away from the outflow tract.

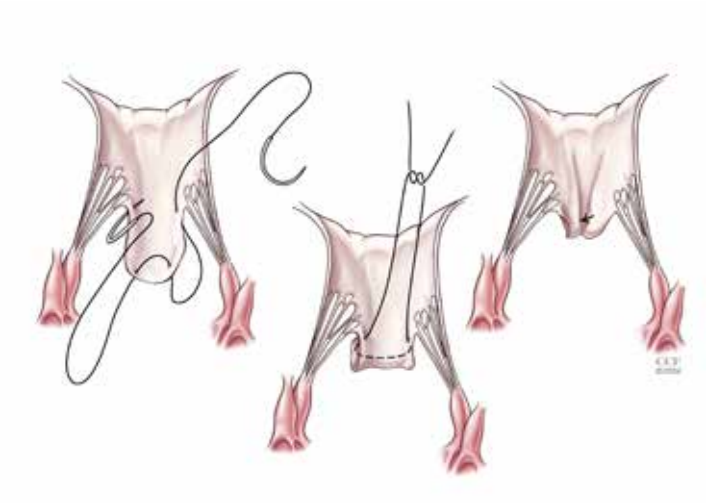

FIGURE 1

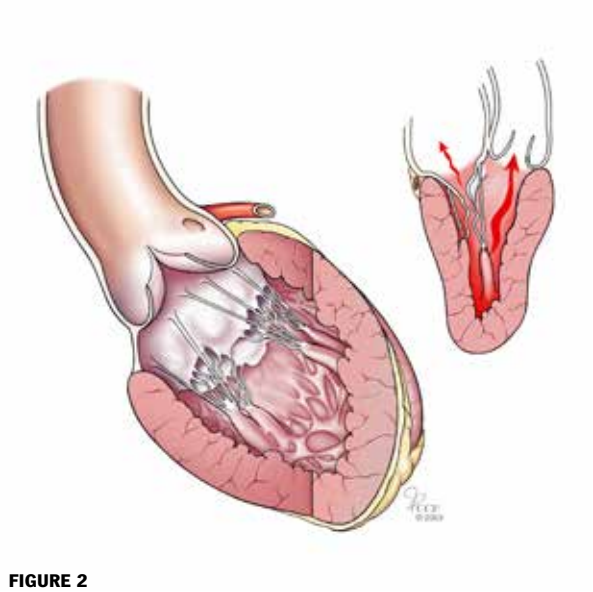

FIGURE 2

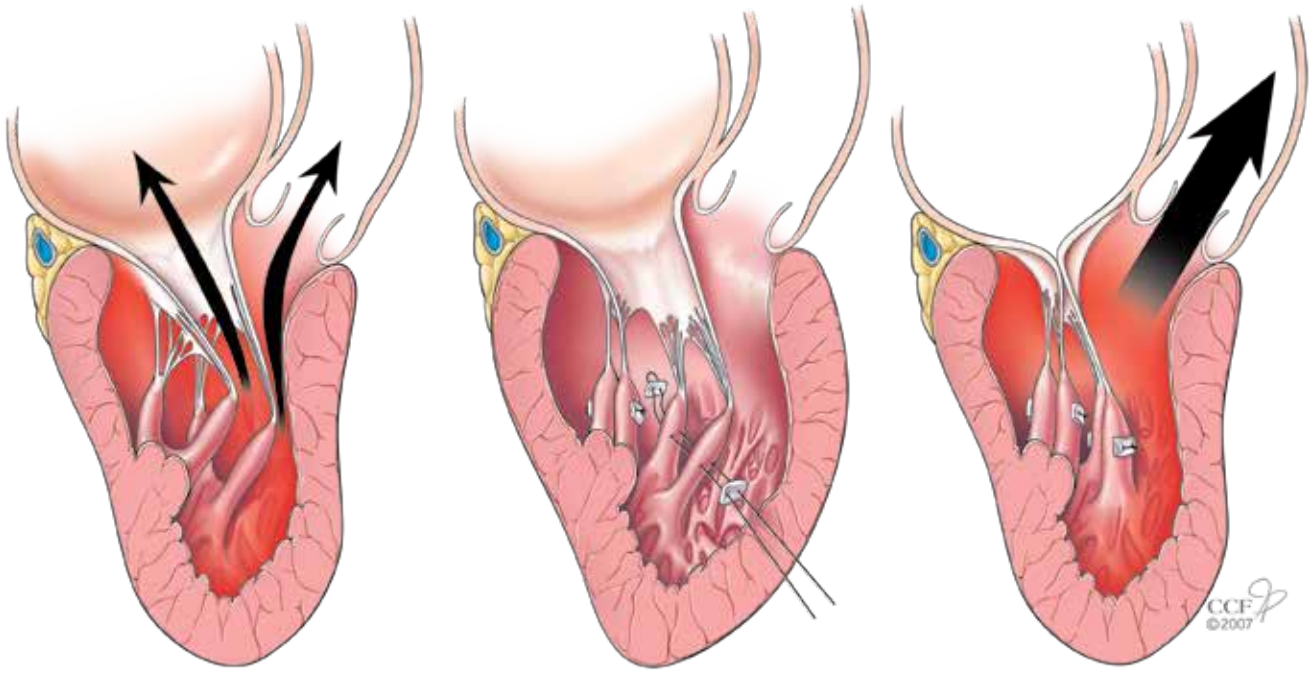

FIGURE 3

FIGURES — Mitral valve operations commonly combined with myectomy in patients with LVOT and only moderate septal hypertrophy. **(1)** Plication of an elongated anterior mitral valve leaflet. **(2)** Resection of secondary chordae to allow the zone of coaptation to shift posteriorly and away from the outflow tract. **(3)** Papillary muscle reorientation to move the papillary muscles and mitral valve zone of coaptation away from the outflow tract.

- **Plication of an elongated anterior mitral leaflet.**
- **Anomalous mitral valve bundle resection.** Anomalous muscle bundles are common in HCM, possibly leading to mid-apical obstruction.

"These interventions can be safely undertaken with long-term relief of LVOT obstruction when performed by an experienced surgeon in a high-volume, specialized center," says Dr. Smedira.

He cites a recent article in the *Journal of Thoracic and Cardiovascular Surgery* (2019;157[6]:2289-2299) analyzing over 1,500 operations performed at Cleveland Clinic between 2005 and 2015 for LVOT obstruction, about one-quarter of which were myectomies combined with a mitral valve or subvalvular apparatus intervention. Overall, in-hospital permanent pacemaker insertion was needed in 5.3% of cases and operative mortality was 0.38%.

When a mitral valve procedure is required, repair is preferred over replacement. If repair is not possible, however, Dr. Smedira performs careful placement of a biological valve, ensuring that struts do not protrude and cause obstruction, avoiding the need for lifelong warfarin with a mechanical valve.

Dr. Desai notes that a recent Cleveland Clinic study (*J Am Heart Assoc.* 2021;10:e016210) of 2,268 patients with obstructive HCM undergoing either a myectomy or any of the additional procedures described above found that there is no outcome penalty for performing these procedures along with myectomy. "The long-term outcomes of these patients were similar to those of the age- and gender-matched general population," he says.

Nonsurgical options also available

For patients who cannot tolerate or are refractory to medical therapy but are not candidates for open-heart surgery, two catheter-based options — one old and one new — can relieve LVOT obstruction.

Alcohol septal ablation, introduced in the mid-1990s, involves injecting a small amount of alcohol percutaneously into one or more arteries supplying the septum. This induces myocardial necrosis, with subsequent scarring and widening of the LVOT. The procedure is associated with symptomatic improvement and good long-term survival, but it may induce arrhythmias that may require a pacemaker.

"Although alcohol ablation is now performed in many centers, experience is critical so that it is done in appropriate patients in an appropriate way," says Samir Kapadia, MD, Chair of Cardiovascular Medicine. "It is important to understand a patient's anatomy and options before committing the patient to alcohol ablation. For this reason, a heart team approach — with HCM expert clinicians, surgeons and interventional cardiologists — is essential for selecting appropriate candidates for alcohol ablation."

The MitraClip™ device, the newer option, is designed to address primary mitral regurgitation and has started to be used in HCM. The percutaneous device grasps and coapts the mitral valve leaflets, accomplishing a tailored repair. Dr. Desai notes that further data on its use in this setting will be forthcoming.

Contact Dr. Desai at 216.445.5250, Dr. Smedira at 216.445.7052 and Dr. Kapadia at 216.444.6735.

"Determining that someone does not have HCM based on lack of left ventricular hypertrophy is not appropriate. Furthermore, diagnosing someone with nonobstructive HCM without the full extent of provocation is also inappropriate."

— MILIND DESAI, MD, MBA

PDE-5 INHIBITORS MAY BENEFIT PATIENTS AFTER CENTRIFUGAL-FLOW LVAD IMPLANT

Patients with a contemporary centrifugal left ventricular assist device (LVAD) who received phosphodiesterase-5 inhibitor (PDE-5i) therapy after LVAD implant had lower rates of death and ischemic stroke than comparable patients not taking a PDE-5i.

So finds a retrospective analysis of more than 7,200 patients in the STS (Society of Thoracic Surgeons) Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS). The study was published in *JACC: Heart Failure* by Cleveland Clinic investigators.

"This study provides intriguing preliminary evidence that adjunctive PDE-5i therapy could provide additional benefits for patients with a contemporary LVAD," says heart failure cardiologist Randall C. Starling, MD, MPH, the study's corresponding author. "If these results are confirmed in a randomized controlled trial, we expect that PDE-5i therapy will become standard of care in this setting."

Mounting evidence of cardiovascular benefit

PDE-5is, which are FDA-approved for erectile dysfunction and pulmonary arterial hypertension, have multiple effects that theoretically could improve outcomes for LVAD patients. They have antiplatelet and antithrombotic effects, facilitate right ventricle unloading in patients with LVADs and have been shown experimentally to improve right ventricular contractile function.

A previous observational study from Cleveland Clinic researchers (*J Am Heart Assoc.* 2020;9[14]:e0158897) found fewer thrombotic events and improved survival in LVAD patients if they were receiving a PDE-5i. However, that study mostly included patients with a HeartMate II™ LVAD, an axial-flow device that is no longer implanted.

LVADs have evolved from first-generation pulsatile-flow devices to continuous-flow devices, including second-generation (axial flow) and third-generation (centrifugal flow) pumps. The third-generation HeartMate 3™ is now the only durable LVAD approved for use in the U.S. While that device is associated with improved stroke and mortality profiles, additional improvements may be possible with effective adjunctive therapy.

Study design and results

The new study included 7,229 patients registered in STS INTERMACS between September 2017 and March 2020. All had been implanted with a continuous-flow centrifugal LVAD and had data on pharmacologic treatment. The devices were the HeartMate 3 (n = 4,628) and HeartWare™ VAD (n = 2,601). The latter has since been removed from the market by its vendor.

Of the total cohort, 2,173 patients (30.1%) were taking a PDE-5i post-implant. Propensity matching was used to adjust for differences between patients who were and were not taking a PDE-5i. Dr. Starling notes that current clinical trial evidence does not support use of PDE-5i therapy by registry patients to improve post-LVAD outcomes, adding that such therapy is usually given because the patient has pulmonary hypertension.

The primary endpoint — a composite of all-cause mortality, ischemic stroke or pump thrombosis — occurred in 410 patients (18.9%) in the PDE-5i group versus 1,071 (21.2%) in the non-PDE-5i group. This translates to lower risk for patients taking a PDE-5i (adjusted hazard ratio [HR] = 0.77; 95% CI, 0.69-0.86; $P < 0.0001$). Results were similar whether patients had received a HeartMate 3 or HeartWare device.

Among the study's secondary endpoints, all-cause mortality and ischemic stroke were significantly lower in the PDE-5i group, while rates of LVAD thrombosis were comparable between the two groups. However, PDE-5i use was associated with increased gastrointestinal bleeding (adjusted HR = 1.18; 95% CI, 1.04-1.34; $P = 0.01$).

Findings bolster earlier evidence

"These results with the newer LVADs are consistent with findings from our prior study that analyzed patients with the obsolete models," observes co-investigator Edward Soltesz, MD, MPH, Surgical Director of Cleveland Clinic's Kaufman Center for Heart Failure Treatment and Recovery. "They support the idea that adding PDE-5i therapy merits a randomized clinical trial."

"Cleveland Clinic is actively exploring initiating a multicenter randomized trial for patients with a contemporary LVAD," Dr. Starling adds. "This is critical before PDE-5i therapy can be endorsed for this use."

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Contact Dr. Starling at 216.444.2268 and Dr. Soltesz at 216.444.5680.

'CONVERGENT PLUS' OPTIMIZES HYBRID STRATEGY FOR PERSISTENT ATRIAL FIBRILLATION

Taking a combined surgical/electrophysiologic strategy to the next level

Convergent, the hybrid epicardial/endocardial approach to atrial fibrillation (AF) ablation, is increasingly used to provide more durable and reliable posterior wall isolation with significantly reduced risk of esophageal injury. "Convergent Plus" adds ablation of the ligament of Marshall and a left atrial appendage (LAA) clip to further reduce stroke risk and AF burden.

This more complete strategy has been pioneered at Cleveland Clinic and is now offered at its Complex AF Clinic.

"Surgeons and electrophysiologists each bring unique capabilities to the table to optimize strategies for persistent AF," says Ayman Hussein, MD, Medical Co-Director of Cleveland Clinic's Atrial Fibrillation Center. "The collaborative hybrid approaches are improving outcomes while reducing risks."

Persistent AF involves substrate abnormalities

While excellent outcomes can typically be achieved with endocardial catheter ablation alone in patients with paroxysmal AF, success rates for a first-time procedure for persistent AF tend to be only around 65%.

Dr. Hussein explains that AF is mainly paroxysmal early in its course, with triggers from the pulmonary veins being the main culprit. As time goes on, the role of the substrate becomes increasingly important as the left atrium changes: mechanical stress due to pericardial tethers and cardiac motion causes inflammation, leading to fibrosis and increased susceptibility to fibrillation, especially along the posterior wall.

"Many strategies have been tried to improve the outcomes of ablation in patients with persistent AF, with only modest success," says Walid Saliba, MD, Director of Cleveland Clinic's Electrophysiology Lab and Medical Co-Director of the Atrial Fibrillation Center. He identifies several likely explanations:

- **Pulmonary vein conduction recovers.** The created lesions might not be transmural or may have gaps, which can be invisible during the procedure because of edema.
- **Ablation is incomplete due to fear of injury.** The electrophysiologist may limit energy delivery to the posterior wall of the left atrium to avoid causing an atrioesophageal fistula.
- **Non-pulmonary vein triggers exist.** Areas beyond the pulmonary veins may trigger AF, including the ligament of Marshall, the superior vena cava, the LAA and the coronary sinus. These areas are not routinely ablated; it is best to wait for evidence that triggers come from within these areas before ablating them.

CONVERGE establishes superiority of hybrid approach

The multicenter CONVERGE (Convergence of Epicardial and Endocardial Ablation for the Treatment of Symptomatic Persistent AF) trial assessed the efficacy and safety of adding epicardial left atrial posterior wall ablation (done by a cardiac surgeon) to endocardial catheter ablation to isolate the pulmonary veins (done by an electrophysiologist). Results were published in late 2020 in *Circulation: Arrhythmia and Electrophysiology*.

Freedom from atrial arrhythmia absent new or increased medications was reached at 12 months in 67.7% of patients who underwent the hybrid approach versus 50.0% of those who received endocardial catheter ablation alone (risk ratio = 1.35; $P = 0.036$). Off-antiarrhythmic drug success was achieved in 53.5% versus 32.0%, respectively (risk ratio = 1.67; $P = 0.013$). No deaths, cardiac perforations or atrioesophageal fistulas occurred.

"The hybrid Convergent procedure needs no cardiopulmonary bypass, and it spares the sternum and protects the esophagus," says cardiothoracic surgeon Edward Soltesz, MD, MPH, Surgical Co-Director of the Atrial Fibrillation Center. "By targeting triggers and substrate, it provides a viable treatment option for complex atrial fibrillation."

Cleveland Clinic's approach to the hybrid procedure

Cleveland Clinic's Complex AF Clinic offers state-of-the-art mapping and ablation techniques for patients with challenging AF cases, especially those who failed prior ablation procedures.

Epicardial ablation of the posterior wall is conducted first by a cardiothoracic surgeon via subxiphoid or transdiaphragmatic access to the pericardium. The posterior left atrium contributes minimally to left atrial ejection, Dr. Soltesz explains, with multiple studies demonstrating little ill effect of complete ablation.

Next, the endocardial procedure is conducted by an electrophysiologist in standard fashion.

The "Plus" indicates additional management with a thoracoscopic LAA clip and ligament of Marshall ablation.

"Applying a left atrial appendage clip may have benefits in terms of both stroke prevention and arrhythmia control," says Oussama Wazni, MD, Section Head of Cardiac Electrophysiology and Pacing.

He notes that LAA clipping is one of the main advantages of Convergent Plus, citing the recently published Left Atrial Appendage Occlusion Study (*N Engl J Med.* 2021;384:2081-2091). In patients who underwent surgery for AF, closing the appendage led to reduced incidence of stroke or systemic embolism after a mean follow-up of 3.8 years relative to those who did not have LAA closure (4.8% vs. 7.0%, respectively; hazard ratio = 0.67; 95% CI, 0.53-0.85; $P = 0.001$).

"We also target the ligament of Marshall because that has been shown to contribute to atrial fibrillation physiology in many cases," Dr. Wazni adds.

Candidates for Convergent Plus

Patients with any of the following should be considered for a hybrid procedure:

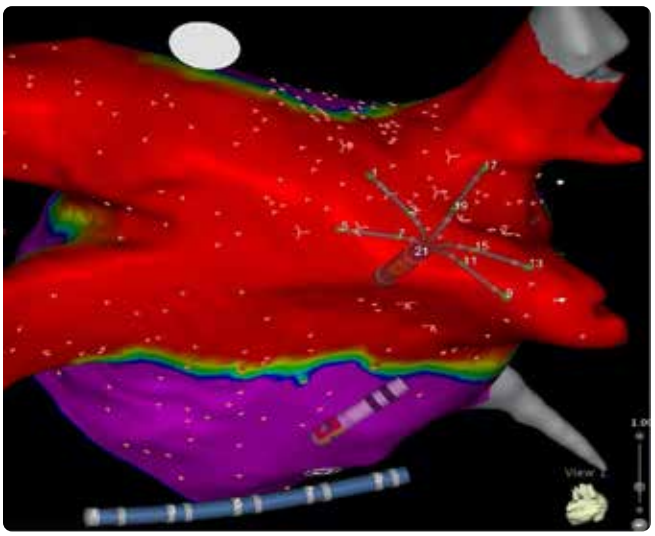
- Persistent AF and failure of one or multiple antiarrhythmic drugs
- Failure of multiple ablations
- Severely dilated atria
- Inability to undergo posterior wall ablation due to proximity to the esophagus

Absolute contraindications are either a documented LAA thrombus or significant valvular or coronary heart disease. These findings should prompt an open surgical approach and a concomitant Cox-Maze IV lesion set.

Staged vs. single-day approach

Hybrid procedures can be performed staged or in a single day. "At Cleveland Clinic, we prefer a staged approach, which allows resolution of postsurgical acute edema before the endocardial procedure is started," Dr. Soltesz notes. "It also enables the epicardial lesions to mature."

FIGURE — A map of the left atrium showing electrical isolation (red) of the pulmonary veins and the posterior wall that is characteristic of results with the Convergent Plus procedure.



Moreover, he adds, staging allows time to determine whether a patient actually needs a second procedure, which can be helpful for patients who have had prior catheter ablations with good control of the pulmonary veins.

More questions to be answered

Cleveland Clinic's Complex AF Clinic also has a research component, as it collects prospective data on patient characteristics and outcomes, with the goal of assessing new technologies.

Dr. Saliba identifies several issues that deserve further research:

- ***Candidacy for the procedure:*** Might the hybrid approach also benefit patients with paroxysmal AF?
- ***Staged vs. simultaneous timing:*** Which produces the best outcomes?
- ***Anticoagulation:*** What are optimal strategies?

"Our Complex AF Clinic presents a great opportunity to move science forward," Dr. Hussein concludes. "We anticipate that we'll soon have longitudinal data on patient outcomes to share."

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Contact Dr. Hussein at 216.444.6171, Dr. Saliba at 216.444.6810, Dr. Soltesz at 216.444.5680 and Dr. Wazni at 216.444.2131.

SAFETY OF PACLITAXEL-COATED BALLOON FOR PAD CONFIRMED THROUGH FOUR YEARS OF FOLLOW-UP

Patient-level meta-analysis of ILLUMENATE trials finds no increased mortality with Stellarex DCB

A systematic meta-analysis using patient-level data shows comparable all-cause mortality through four years between the Stellarex DCB paclitaxel-coated balloon and percutaneous transluminal angioplasty for treatment of peripheral artery disease (PAD).

The findings, published online in the *Journal of Vascular Surgery*, bolster the case for long-term safety of this paclitaxel-coated balloon in the treatment of PAD.

Rationale for paclitaxel-coated devices in symptomatic PAD

Endovascular therapy is the mainstay of treatment for patients with symptomatic PAD, which most commonly affects the superficial femoral artery and popliteal arteries. Percutaneous transluminal angioplasty (PTA) produces good short-term outcomes in this setting but has been associated with 12-month restenosis rates of nearly 50% in some reports.

Efforts to avoid restenosis led to the development of several devices that deliver the anti-restenotic drug paclitaxel via drug-coated balloons (DCBs) or drug-eluting stents. Multiple studies have shown these devices to consistently yield better patency and less need for target lesion revascularization compared with PTA.

Questions from an earlier meta-analysis

Despite consistent evidence of early efficacy and safety of paclitaxel-coated devices in clinical trials, a meta-analysis published by Katsanos and colleagues in December 2018 suggested an increased mortality signal. These researchers pooled summary-level data from 28 randomized controlled trials of paclitaxel-coated balloons and stents for treating femoropopliteal PAD. They reported a significantly increased rate of all-cause death at two and five years in claudicants receiving paclitaxel-coated devices relative to controls, as well as a potential dose-related signal.

KEY FINDING

14.0% vs. **14.4%**

four-year mortality estimates for DCB and PTA groups, respectively

These findings prompted controversy, in view of the lack of a suggested plausible mechanism of harm and the fact that a large share of patients — up to 30% — had been lost to follow-up, as the studies were not designed to assess long-term mortality. A subsequent meta-analysis (*Circulation.* 2020;141:1859-1869) was conducted that used individual patient-level data and captured more of the patients lost to follow-up. It showed a smaller increase in mortality with the paclitaxel-coated devices relative to the summary-level meta-analysis, and did not validate the dose-response relationship between paclitaxel dose and mortality risk detected by Katsanos and colleagues.

Subsequent outcomes data from reviews of a German insurance claims database (*Eur J Vasc Endovasc Surg.* 2020;59[4]:587-596) and a Medicare database (*JAMA Intern Med.* 2021;181[8]:1071-1080) have not shown an increased mortality risk with paclitaxel-coated devices. Moreover, data from randomized patients in the VOYAGER PAD trial (*J Am Coll Cardiol.* 2021;78[18]:1768-1778) showed no increased mortality risk with these devices.

"We have seen no evidence from randomized clinical trials or from insurance or Medicare databases to support the conclusions of the initial summary-level meta-analysis suggesting an increased mortality risk with use of paclitaxel-coated devices in the lower extremity," says Sean Lyden, MD, Chair of Vascular Surgery at Cleveland Clinic.

"One piece of evidence we still lacked was late data from the ILLUMENATE trials," he adds, referring to two large randomized trials of the Stellarex DCB paclitaxel-coated balloon.

A meta-analysis focused on Stellarex randomized trials

These trials are specifically known as the ILLUMENATE Pivotal Trial, conducted in the U.S. and Europe, and the ILLUMENATE EU RCT, conducted solely in Europe. Dr. Lyden is national principal investigator of ILLUMENATE Pivotal.

Both trials are prospective, multicenter, single-blind investigations that randomized patients to the Stellarex DCB coated with paclitaxel 2 $\mu g/mm^2$ or to standard balloon PTA. All patients had either de novo or restenotic Rutherford class 2-4 lesions in the superficial femoral and/or popliteal arteries.

To supply the late outcomes data Dr. Lyden referred to, he and co-investigators continue to monitor outcomes of these two ILLUMENATE trials. Four-year data are now available, with those from ILLUMENATE Pivotal recently published online in the *Journal of Endovascular Therapy*, and those from the ILLUMENATE EU RCT presented at the 2020 Vascular InterVentional Advances (VIVA) meeting.

These latest outcomes from the two trials were combined in the new systematic meta-analysis in the *Journal of Vascular Surgery*. The analysis was performed by an independent third party that pooled homogenous patient-level data and cause-specific adjudicated deaths through four years of follow-up from the index procedure. The outcome assessed was time to death, with Kaplan-Meier analysis used to estimate all-cause mortality.

Results: No mortality difference

The pooled analysis included 589 patients, of whom 419 were treated with the Stellarex DCB and 170 with PTA. Median follow-up was 4.75 years and was slightly longer in the DCB group. Overall, 401 patients completed four-year follow-up (292 in the DCB group and 109 in the PTA group). Vital status compliance was >95% in each of the two pooled randomized trials.

Total deaths through four years were 58 of 419 in the DCB group (13.8%) versus 23 of 170 in the PTA group (13.5%). Kaplan-Meier estimates of all-cause mortality did not differ significantly between the groups ($P = 0.864$) and shifted toward slightly favoring the DCB group in absolute terms over time, as follows:

- One-year estimate, 1.9% ± 0.7% for DCB vs. 1.2% ± 0.9% for PTA
- Two-year estimate, 6.6% ± 1.2% for DCB vs. 4.9% ± 1.7% for PTA
- Three-year estimate, 9.3% ± 1.4% for DCB vs. 9.9% ± 2.4% for PTA
- Four-year estimate, 14.0% ± 1.7% for DCB vs. 14.4% ± 2.8% for PTA

> "The absence of an association between paclitaxel and late mortality in this analysis … is consistent with meta-analyses of other FDA-approved DCBs using patient-level data and with several large real-world datasets."
>
> — SEAN LYDEN, MD

Multivariate analysis showed that significant predictors of mortality at four years included greater age, renal insufficiency and lesion length but did not include paclitaxel exposure or paclitaxel dose.

Reassurance as follow-up continues

"These findings of similar four-year mortality rates in the DCB and PTA arms reinforce the long-term safety profile of the Stellarex DCB," observes Dr. Lyden, first author of the new meta-analysis. "The absence of an association between paclitaxel and late mortality in this analysis of two concordant ILLUMENATE trials is consistent with meta-analyses of other FDA-approved DCBs using patient-level data and with several large real-world datasets."

"These results are very reassuring for physicians and patients when discussing safe and effective treatment options for peripheral artery disease," says Jai Khatri, MD, a cardiologist with appointments in Cleveland Clinic's Section of Invasive and Interventional Cardiology and Section of Vascular Medicine. "Furthermore, this analysis offers a cautionary tale about the potential limitations of drawing conclusions about patient outcomes using summary-level pooled data rather than patient-level data."

Patient follow-up in the two ILLUMENATE trials will continue through five years.

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Contact Dr. Lyden at 216.444.3581 and Dr. Khatri at 216.445.3991.

SOCIOECONOMIC DISPARITIES IN STEMI CARE: A PROMISING BLUEPRINT FOR LEVELING THE PLAYING FIELD

Study shows STEMI protocol closes traditional gaps in care metrics and mortality

In an unprecedented study finding, a standardized care protocol has been shown to reduce socioeconomic disparities in care processes and clinical outcomes for a high-acuity, urgent condition like ST-elevation myocardial infarction (STEMI).

Specifically, a comprehensive STEMI protocol adopted by Cleveland Clinic was associated with improved guideline-directed medical therapy (GDMT) across a spectrum of socioeconomic deprivation levels and with reductions in in-hospital mortality that were particularly pronounced in patients with high and moderate levels of socioeconomic deprivation.

"Many prior studies have demonstrated higher mortality after STEMI among patients with lower socioeconomic status, but no previous study has assessed an intervention to mitigate this disparity," says Umesh Khot, MD, Head of Regional Cardiovascular Medicine at Cleveland Clinic and senior author of the study, published in the *Journal of the American Heart Association* (2021;10:e024540).

Disparities are well established, solutions are not

Indeed, multiple studies show that use of GDMT before percutaneous coronary intervention (PCI), use of revascularization procedures and achievement of recommended door-to-balloon time (D2BT) for STEMI are significantly less common in patients with lower socioeconomic status. They further show that this results in worse clinical outcomes for these patients, i.e., higher rates of mortality and rehospitalization and lower quality of life.

"When we developed our comprehensive STEMI protocol several years ago, we knew that care disparities related to socioeconomics were an issue nationally and locally," explains Dr. Khot. "We wanted to see if we as a health system could improve the care of our most vulnerable patients at their most vulnerable times, such as during a heart attack. We sought to transform the care of these patients by eliminating care variability to ensure the highest level of standardized care for every patient with STEMI."

Protocol and study design at a glance

Cleveland Clinic implemented the STEMI protocol across its Northeast Ohio facilities in July 2014 to minimize variability in care. It did so by way of four key changes and principles:

- Standardizing criteria by which emergency department physicians can activate the catheterization lab
- Using a "STEMI safe handoff checklist" defining roles of all caregivers involved
- Immediately transferring patients to an available cath lab at all times to avoid delays
- Adopting a "radial artery first" approach for vascular access in primary PCI for all appropriate candidates

The current observational cohort study compared care processes and outcomes of consecutive patients with STEMI from January 2011 to July 2019, thereby capturing several years before and after protocol implementation.

To evaluate the impact of socioeconomic status, the researchers used the Area Deprivation Index (ADI), a summary metric for accurately quantifying socioeconomic position at the neighborhood level. The ADI — which draws on 17 data elements reflecting education, employment, housing and poverty derived from the U.S. Census Bureau and American Community Survey data — is a more granular metric than ZIP code. "This makes it a better indicator of neighborhood-level socioeconomic position," notes Dr. Khot. Higher ADI scores denote higher levels of deprivation, corresponding to lower socioeconomic status.

Key findings

The 1,761 patients with STEMI included in the study were classified by ADI score as residing in low-deprivation neighborhoods (29.0%), moderate-deprivation neighborhoods (40.8%) or high-deprivation neighborhoods (30.2%). Patient distribution among these groups was statistically similar between the periods before and after STEMI protocol implementation.

Comparative analysis of care metrics and outcomes by patients' neighborhood deprivation level before and after protocol implementation yielded four major findings:

FIGURE — Cleveland Clinic cath lab staff in action. The health system implemented a protocol across all its Northeast Ohio facilities to minimize variability in STEMI care. Analyses have shown that not only has the protocol improved STEMI care and outcomes overall, but it has significantly reduced long-standing socioeconomic disparities in STEMI care and outcomes.

- Increasing degrees of socioeconomic deprivation correlated with higher proportions of patients of Black race, of female sex and with cardiovascular comorbidities in spite of younger median age.
- Following protocol implementation, significant improvements in D2BT — the primary process outcome measure — were seen for patients in all three deprivation levels ($P < 0.001$ for pre-/post-implementation comparisons for all). Notably, in the period after protocol implementation, D2BT was statistically noninferior between the high and low deprivation groups among patients presenting to the emergency department or with in-hospital STEMI.
- Improvements in the use of GDMT and transradial PCI were observed following protocol implementation in all deprivation groups, although GDMT improvement was most modest in the high deprivation group.
- In-hospital mortality — the primary clinical outcome measure — was reduced significantly following protocol implementation across the overall study cohort. This was due largely to significant pre-/post-protocol reductions in the high and moderate deprivation groups (odds ratio [OR] = 0.42 [95% CI, 0.25-0.72], $P = 0.002$ in unadjusted analysis; OR = 0.42 [95% CI, 0.23-0.77], $P = 0.002$ in risk-adjusted analysis).

'Leveling the playing field' in STEMI care

"These findings support our hypothesis that strategies to minimize STEMI care variability can improve care delivery and reduce mortality in patients at all socioeconomic levels and lessen care disparities," says Grant Reed, MD, MSc, Director of Cleveland Clinic's Enterprise STEMI Program. He notes that the paradoxical finding that post-protocol D2BT improvements were smallest in the high deprivation group suggests that strategies designed to standardize STEMI care more broadly may eclipse D2BT alone.

"A narrow focus on door-to-balloon time may exclude some patients from realizing the benefits of STEMI quality improvement programs," adds Amar Krishnaswamy, MD, Section Head of Invasive and Interventional Cardiology. "Our STEMI protocol's multicomponent nature is its strength, which has been shown in previous analyses to yield incremental value beyond the benefits achieved from reductions in door-to-balloon time alone."

An additional recent analysis, published in *European Heart Journal Open*, found the Cleveland Clinic STEMI protocol to be associated with reductions in sex-related disparities in STEMI care and outcomes as well. "Together, these studies suggest that taking a comprehensive, multifaceted approach to standardizing STEMI care has strong potential to level the playing field with regard to STEMI care disparities, whether they stem from a patient's neighborhood or sex or some other demographic factor," observes Samir Kapadia, MD, Chair of Cardiovascular Medicine. "We believe this protocol can be a model for other organizations aiming to improve the equity of their care delivery."

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ESOPHAGEAL PERFORATION: EFFECTIVE OPTIONS EXIST FOR EVEN THE MOST SEVERE CASES

Large single-center series details outcomes of several advanced interventions

Critically ill patients with uncontained esophageal perforation have several advanced therapy options, from esophageal repair to esophagectomy and complete alimentary tract diversion with the possibility of eventual reconstruction for the most severe cases.

Advanced interventions — and characteristics of 166 patients on whom they were performed at Cleveland Clinic — were recently described in the *Annals of Surgery* (2021;274[5]:e417-e424). The report, which covers cases over a 20-year period, represents the largest single-institution series of advanced intervention for esophageal perforations published to date.

"With more options available, the paradigm for treating esophageal perforation has changed over the years, as have outcomes," says the paper's senior author, Sudish Murthy, MD, PhD, Section Head of Thoracic Surgery at Cleveland Clinic. "Despite severe illness, even patients requiring esophageal diversion can now benefit from operative intervention, with excellent long-term survival."

A critical event with no set solution

Esophageal perforation (Figure 1) is often fatal without invasive intervention. Because of its rarity and heterogeneous etiology and presentation, optimal management strategies have not been well defined.

This study was designed to characterize patients who underwent an advanced intervention (see example in Figure 2) for esophageal perforation at Cleveland Clinic to identify factors associated with therapy decisions and treatment outcomes.

Cohort and interventions

Patients who had an esophageal perforation managed by advanced surgical intervention at Cleveland Clinic from 1996 to 2017 were included in the study (N = 166; mean age, 61 ± 16 years; 54% female).

The following interventions were performed:

- **Primary repair** with tissue flap in 74 patients (of these, three later underwent resection and five underwent resection-diversion). This group had the most iatrogenic perforations, the fewest cancer perforations and the shortest time from perforation to surgery.
- **Resection** (esophagectomy and gastric pull-up) in 26 patients.
- **Resection-diversion** (esophagectomy with complete alimentary tract diversion and planned delayed reconstruction) in 66 patients. (Among these patients, plus five of the patients with primary repair leading to resection-diversion, 39 later underwent reconstruction.) This group had more spontaneous perforations involving the lower esophagus compared with the other groups.

Illness severity was retrospectively quantified using the Pittsburgh Severity Score (PSS; range, 0-18), which takes into account risk factors at presentation that are associated with mortality (i.e., age, tachycardia, leukocytosis, pleural effusion, fever, uncontained leak, respiratory compromise, time to diagnosis, cancer, hypotension). A validation study from another institution found that a score over 5 is associated with an in-hospital mortality rate of about 40%.

The mean PSS in the entire cohort was 5.0 ± 3.3; 25% had a PSS > 7. Mean PSS was 3 points for both the repair and resection groups versus 6 points for the resection-diversion group ($P = 0.002$).

Intervention results

Outcomes following interventions were as follows:

- 90-day mortality was 11% with repair, 7.7% with resection and 23% with resection-diversion ($P = 0.13$).
- Five-year survival was 71% with repair, 63% with resection and 47% with resection-diversion ($P = 0.12$).

Risk of death following resection-diversion was highest within the first year. However, 52% of patients with this intervention went on to undergo reconstruction of the upper alimentary tract within two years.

FIGURE 1

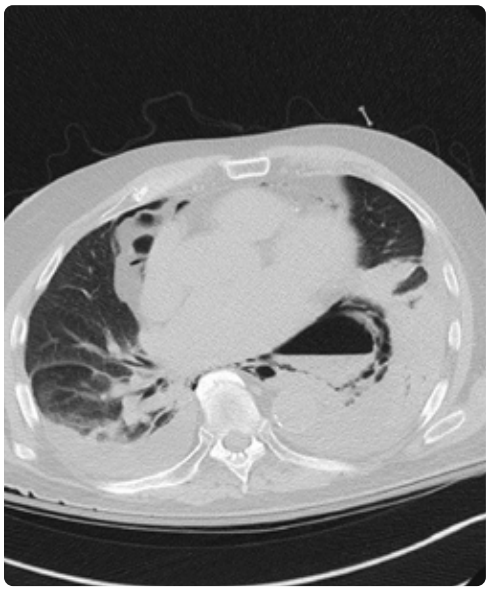

FIGURE 2

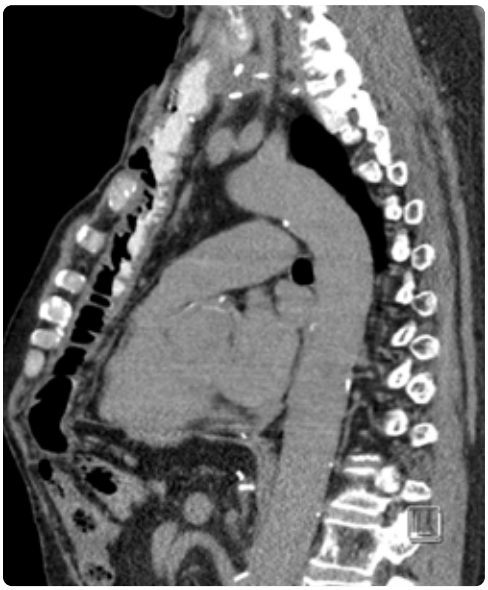

FIGURE 1 — Chest CT showing an esophageal perforation.

FIGURE 2 — Imaging study showing substernal colon interposition to repair an esophageal perforation.

"The risk of death was high for the most severe cases during the first year, but for those who survived this period and underwent reconstruction, survival was excellent," Dr. Murthy says.

A treatment strategy

Severity of disease at presentation should determine treatment, the study authors emphasize. Dr. Murthy notes that the PSS is a reasonable method for assessing severity and can help guide intervention and management, although other factors also must be considered.

At one end of the spectrum, patients with a small contained perforation often can be managed expectantly, and endoscopic stent placement plus pleural drainage may be sufficient even for full-thickness perforations if soilage is limited.

For more severe presentations and for patients who do not respond to nonoperative management, the authors recommend the following general strategy for advanced intervention:

- **For patients at the low end of severity** (e.g., limited mediastinal necrosis, a salvageable esophagus): Manage with primary repair and tissue buttress. Patients should still have limited follow-up with the goal of preserving normal deglutition. More than half of patients in the series with a PSS of 2 points or less were managed this way; the rest underwent either resection or resection-diversion.
- **For patients with moderately severe disease** (e.g., uncontained perforation with lower severity at presentation, and possibly other esophageal pathology): Manage with primary resection and gastric pull-up. Patients should have longer follow-up and will likely need more interventions, such as anastomotic dilatation, in the future.
- **For patients with very severe disease:** Treat with esophagectomy and complete diversion, then reconstruction after recovery. These patients will need intensive follow-up. More than half of study patients with a PSS of more than 5 points underwent resection-diversion.

Guidance for future cases

"Repair and organ preservation are always preferred, if possible," observes study co-author Siva Raja, MD, PhD, of the Section of Thoracic Surgery. "However, extensive mediastinal and pleural soilage, in addition to hemodynamic instability, often make this impractical." In such cases, he says, resection-diversion can be an important lifesaving option.

"Despite advances in minimally invasive and endoscopic surgery, life-threatening problems like esophageal perforations sometimes require big operations to start, as we may not have a second chance to salvage critically ill patients," Dr. Raja concludes. "Studies such as ours can provide guidance to surgeons who are debating between the various options to treat esophageal perforations based on the clinical picture."

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Contact Dr. Murthy at 216.444.5640 and Dr. Raja at 216.444.4063.

CASE STUDY IN COLLABORATION —

COLLABORATIVE ALLIANCE WITH CLEVELAND CLINIC YIELDS CATH LAB EFFICIENCIES FOR A NEW JERSEY HOSPITAL

How we helped Deborah Heart and Lung Center care for more patients

A commitment to continuous improvement becomes no less important after a healthcare organization has established a record of high-quality care. In fact, it is the factor that's likely to be most responsible for maintaining that record.

This was the mentality that guided Deborah Heart and Lung Center in Browns Mills, New Jersey, when it recently undertook an effort to improve operational efficiencies of its cardiac catheterization laboratories with assistance from Cleveland Clinic.

As a hospital focusing on cardiac, vascular and lung disease, Deborah is a premier provider of innovative, compassionate and patient-focused care for the Delaware Valley region of southern New Jersey. Since August 2019, Deborah has maintained an alliance relationship with Cleveland Clinic's Miller Family Heart, Vascular & Thoracic Institute (HVTI). The relationship is designed to offer value through a variety of in-depth services provided by Cleveland Clinic, including the sharing of clinical best practices to maximize quality and efficiency.

A focus on cath lab efficiencies

Early in the alliance, Deborah's cardiovascular service line leadership identified and prioritized areas of opportunity for Cleveland Clinic's HVTI Advisory Services team to provide insights and clinical expertise. As a result, Deborah and the Cleveland Clinic Advisory Services team launched a project aimed at promoting standardization and operational efficiency in order to optimize cath lab capacity and room utilization — and thus potentially allow for treatment of more patients.

To identify specific opportunities for improving efficiency, the Cleveland Clinic team requested time stamp data from Deborah cath lab management on each of a series of key steps in cath lab cases.

Specific challenges identified

Deborah's cardiac cath lab manager and team conducted a manual audit of patient case documentation to identify reasons for any delays. When they analyzed the data with the Cleveland Clinic advisors, they identified delayed start times — particularly for the first procedure of the day — as a key challenge.

Whereas the scheduled start time for the first case of the day was 7:30 a.m., the average first-case start time from January through September 2020 was 9:07, with average times ranging from 8:51 to 9:26 across Deborah's four cath labs.

The Deborah and Cleveland Clinic teams also reviewed lab utilization, finding that the Deborah cath labs had a utilization rate of 65% for the same period of January through September 2020.

Formulating a plan

The Cleveland Clinic team then conducted interviews with the Deborah cath lab team, including physician and nursing leaders, administrators, schedulers, nurses and radiology technologists. Next they combined insights from these interviews with information from the data analysis into a report that provided targeted, prioritized recommendations for the Deborah cath lab team and leaders. The Deborah and Cleveland Clinic teams then jointly developed a work plan and established time frames for implementation.

Operations team drives improvements

In collaboration with Cleveland Clinic's interventional cardiology consultant, Deborah's cath lab leaders formed an interdisciplinary cath lab operations team comprising the physician cath lab director, nursing manager, department administrators and additional personnel involved in cardiac cath lab procedures. The operations team reviewed the data and designed specific interventions to address the root causes of delays.

This systematic, multidisciplinary approach helped reduce cath lab inefficiencies and streamline processes, as detailed below:

- From January to November 2021, the average first-case start time improved to 8:32 a.m. (from the prior average of 9:07) (see Table 1). One of the four labs improved its average first-case start time by 55 minutes from the prior-year period.

TABLE 1 | AVERAGE FIRST-CASE START TIMES		
Lab	**Jan.-Sept. 2020**	**Jan.-Nov. 2021**
1	8:51 a.m.	8:16 a.m.
2	8:59 a.m.	8:57 a.m.
3	9:10 a.m.	8:25 a.m.
4	9:26 a.m.	8:31 a.m.

TABLE 2 | CARDIAC CATH LAB UTILIZATION RATES		
Lab	**Jan.-Sept. 2020**	**Jan.-Nov. 2021**
1	69.5%	72.5%
2	70.6%	62.8%
3	63.3%	71.5%
4	57.9%	72.0%

> "These improvements are allowing the talented Deborah team to increase access to their catheterization lab services to care for more patients in their community without additional strain on hospital resources."
>
> — CHRISTOPHER BAJZER, MD

- This improved timeliness helped the cath lab team provide care to more patients. Prior to the project (January-September 2020), Deborah cath labs averaged 11.0 patients per day. From January 2021 to November 2021, the cath labs averaged 14.8 patients per day. This increase in access translates to nearly 20 more patients per week and just shy of 1,000 more patients per year.
- The increase in patient volumes corresponded with an increase in cath lab utilization, with the overall utilization rate rising from 65% in the prior-year period to 70% in the January-November 2021 period (see Table 2).

"These preliminary results are promising and a testament to the tireless collaboration between our cardiac cath lab team and HVTI's Advisory Services team," says Joseph R. Manni, Executive Vice President and Chief Operating Officer of Deborah Heart and Lung Center. "Both teams look forward to continued improvement and engagement in order to bring Deborah's high-quality cardiac care to as many patients as possible."

"This is an excellent example of how collaboration between Deborah Heart and Lung Center and Cleveland Clinic's HVTI Advisory Services can identify opportunities to enhance overall efficiencies," notes Cleveland Clinic interventional cardiologist Christopher Bajzer, MD, who is part of the HVTI team that works with Deborah. "These improvements are allowing the talented Deborah team to increase access to their catheterization lab services to care for more patients in their community without additional strain on hospital resources. It's a win-win for the hospital and the community."

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For information on affiliation and alliance opportunities with Cleveland Clinic, email Amanda Lesesky at leseska@ccf.org.

CME PREVIEW

GET UP TO SPEED ON THE LATEST IN SPORTS CARDIOLOGY GUIDANCE AT VIRTUAL CME SYMPOSIUM

Detecting Cardiovascular Disease in the Athletic Heart

Virtual symposium offered by livestream
(complimentary registration)

Sat., May 14, 2022, 10 a.m. to 3:30 p.m. ET

Information/registration: ccfcme.org/sportscardiology

If you're a provider looking to help your cardiovascular patients safely enjoy the benefits of sports, Cleveland Clinic has a free CME-certified virtual symposium in store that will equip you to give the most current guidance possible.

"Detecting Cardiovascular Disease in the Athletic Heart" is the debut offering of a sports cardiology course from Cleveland Clinic focused on the diagnosis and management of individuals with cardiovascular disease and the related effects on athletic training.

Safely reaping the benefits of athletics

"Contemporary pre-participation and return-to-play evaluations are more than just 'screening,'" notes course co-director Michael Emery, MD, Co-Director of Cleveland Clinic's Sports Cardiology Center. "They are geared toward a shared decision-making process that allows people to make informed decisions about their lives and enables those with cardiac disease to reap the benefits of sports and exercise with the minimum possible risk."

"Our virtual symposium will be a chance for all those involved in the care of athletes to gain up-to-date knowledge on the diagnosis and management of adults with cardiovascular diseases and the implications for athletic training," adds course co-director Tamanna Singh, MD, also Co-Director of the Sports Cardiology Center. "We are bringing together experts in sports cardiology, inherited cardiovascular diseases and sudden cardiac death to examine contemporary issues and the latest developments in this field."

Symposium content will be delivered by a faculty of at least a dozen Cleveland Clinic experts in various cardiovascular subspecialties — sports cardiology, electrophysiology, cardiovascular imaging, adult congenital heart disease, preventive cardiology — as well as in genetic counseling and primary care sports medicine.

Comprehensive but efficient coverage of essentials

The bulk of the 5.5-hour course is devoted to three 90-minute sessions, each divided into four 15-minute focused presentations followed by a 30-minute panel discussion with questions from course attendees. These sessions explore the following areas:

- **Contemporary screening of the athletic heart.** This portion covers the essentials of sports medicine evaluation and cardiac screening, the preparticipation evaluation, sudden cardiac death in athletes, and using guidelines and shared decision-making to assess risk of sports participation.
- **Etiology, risk stratification and evaluation of common cardiac problems in athletes.** Topics here include structural, electrical and acquired cardiac abnormalities as well as congenital heart disease in adult athletes.
- **Considerations for return to play.** After starting with a discussion of when athletes stand to benefit from genetic testing, this session examines preventive cardiology and cardiac rehab for athletes, the role of heart monitoring in this setting, and the use of implantable cardioverter-defibrillators in sports.

Rapid-fire ECG case review

The symposium concludes with a 60-minute session focused on ECGs in athletes. The centerpiece will be a 45-minute rapid-fire case review devoted to interpreting ECGs in diverse cases presented by expert cardiologists. Course attendees will be encouraged to participate via audience response to apply what they've learned.

"The information shared in this symposium will help caregivers identify patients who may benefit from consultation with a sports cardiologist," says Dr. Singh. "It will also empower them to advocate for patient-athletes to find a safe balance between the implications of cardiovascular pathology and ensuring a healthy, active lifestyle for overall cardiovascular benefit and quality of life."

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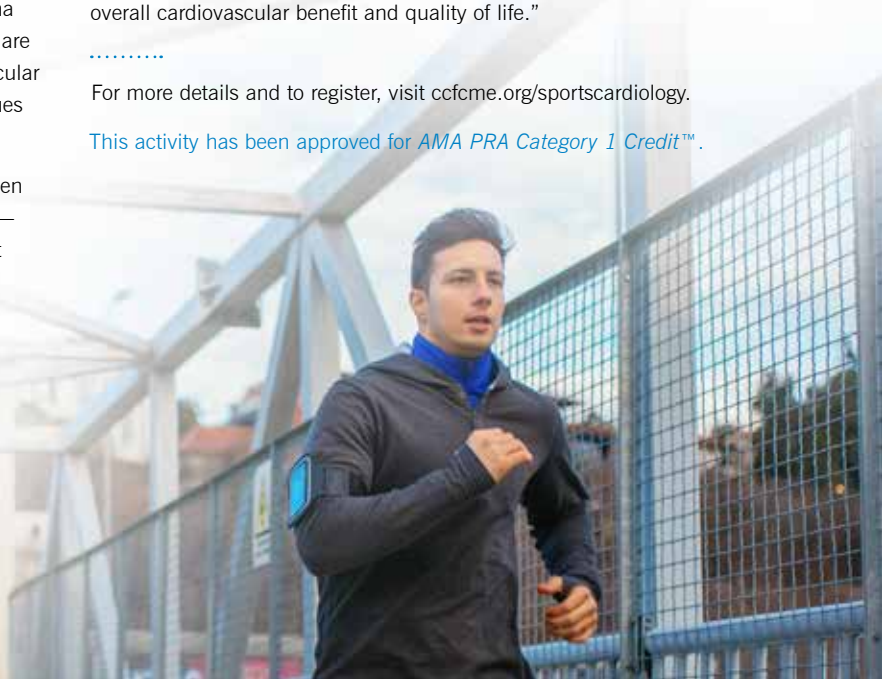
For more details and to register, visit ccfcme.org/sportscardiology.

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



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SAVE THE DATES FOR CME

The Present and Future of EP Practice: The Cleveland Clinic Perspective

Thu., April 28, 2022, 6-8:30 p.m.

Satellite symposium at Heart Rhythm 2022
San Francisco, California
Information/registration: ccfcme.org/eppractice2022

Cardiovascular Disease in the Athletic Heart

Sat., May 14, 2022, 10 a.m. to 3:30 p.m. ET

Virtual symposium offered by livestream
Information/registration: ccfcme.org/sportscardiology
(see page 18 for a detailed preview)

Heart, Vascular & Thoracic Institute Advanced Practice Provider Symposium

Fri.-Sat., May 20-21, 2022

Virtual symposium offered by livestream
Information/registration: ccfcme.org/appcvupdate

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

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