

CardiacConsult

Heart, Vascular and Thoracic News from Cleveland Clinic | 2021 | Issue 2



> CARDIAC CONSULT FEATURE

The Tools and Spaces Behind Our Care:
A Photo Essay – p. 4



Dear Colleagues,

The best patient outcomes and experience tend to result from the optimal combination of high-tech and high-touch caregiving. At Cleveland Clinic, we strive to be in the vanguard of both of these essential components of clinical excellence.

In this issue, we offer a window into a few ways we are advancing high-tech caregiving in cardiac, vascular and thoracic disease through the photo essay featured as our cover story. With the pandemic restricting travel opportunities in recent months, we wanted to give you, our colleagues across the nation, a chance to “visit” our main campus in Cleveland by visually showcasing a few examples of the advanced tools and spaces we use to deliver exceptional care to our patients.

While it’s no substitute for an in-person visit, we hope it may prompt you to inquire about how we might collaborate with you on the care of a particularly challenging case that requires the most leading-edge equipment or deepest experience.

And while these visual examples illustrate only the high-tech component of clinical excellence, we trust you know from your own experience that no photographer can achieve the intimate access and serendipity to predictably capture the magic of high-touch caregiving. If you entrust Cleveland Clinic with referral of a patient with highly complex disease, we pledge to do our best to deliver that magic while they are under our care.

Respectfully,

Lars G. Svensson, MD, PhD

CHAIRMAN | Sydell and Arnold Miller Family Heart, Vascular & Thoracic Institute



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

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Cleveland Clinic was named a top U.S. hospital in *U.S. News & World Report’s* “Best Hospitals” rankings for 2020-21, as well as the No. 1 hospital in cardiology and heart surgery for the 26th consecutive year.

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Research Roundup: Takeaways From Recent Studies of Note



Intermediate-Term Outcomes of Endoscopic or Open Vein Harvesting for CABG

► *JAMA Netw Open.* 2021;4(3):e2111439

The safety of endoscopic vein harvesting for coronary bypass operations got a boost from intermediate-term results of the multicenter REGROUP randomized controlled trial. Over median follow-up of 4.7 years, there was no significant difference in major adverse cardiac events between coronary artery bypass graft (CABG) patients who underwent endoscopic vein harvesting versus open vein harvesting. The updated results follow similar findings through 2.7 years reported two years ago. “Some data have suggested that endoscopic harvesting might be associated with elevated mortality,” says REGROUP co-investigator Faisal Bakaeen, MD, a Cleveland Clinic cardiothoracic surgeon. “REGROUP’s findings to date offer reassurance about the safety of endoscopic harvesting.” Follow-up will continue through 10 years. ■

Long-Term Outcomes in Patients With a Left Ejection Fraction $\leq 15\%$ Undergoing CRT

► *JACC Clin Electrophysiol.* 2021;7(1):36-46

Cardiac resynchronization therapy (CRT) can be a valuable treatment option even in patients with severe left ventricular (LV) dysfunction, concludes this retrospective study led by Cleveland Clinic researchers. The study, which included 420 patients with an ejection fraction $\leq 15\%$ and a QRS duration ≥ 120 ms who underwent CRT, revealed that individuals with severe LV dysfunction respond to CRT, albeit it at a lower rate than traditional CRT candidates. Smaller LV size and left bundle branch block predicted positive outcomes in this group. No procedural deaths occurred across the cohort. “We are now more likely to offer CRT to appropriate patients with low LV ejection fraction,” says lead author John Rickard, MD, MPH. ■

Peroral Endoscopic Myotomy Provides Effective Palliation in Type III Achalasia

► *J Thorac Cardiovasc Surg.* 2021 Feb 6 (online ahead of print)

Peroral endoscopic myotomy (POEM) should be considered as first-line therapy for patients with type III achalasia, concludes this single-center retrospective investigation from Cleveland Clinic. The study — one of the largest ever focused on type III achalasia, a rare and difficult-to-treat subtype — found the minimally invasive procedure yielded symptom relief and im-

proved esophageal manometry, radiograph measurements and drainage studies, all with low associated morbidity. “We saw excellent perioperative outcomes and sustained postoperative palliation with POEM at one year,” says co-first author Monisha Sudarshan, MD. “Outcomes were superior to those historically reported after laparoscopic Heller myotomy and other treatments, suggesting a paradigm shift in initial management.” ■

Five-Year Outcomes of the COMMENCE Trial of a Novel Tissue Bioprosthesis for AVR

► Presented at the 2021 annual meeting of the Society of Thoracic Surgeons

Favorable safety and hemodynamic results with a new tissue valve designed to reduce structural valve deterioration in surgical aortic valve replacement (SAVR) continued through five years of follow-up, report investigators with the multicenter COMMENCE trial. The latest data from this single-arm study covered 471 patients through exactly five years, revealing 89.2% freedom from mortality, 94.5% freedom from stroke and 100% freedom from valve thrombosis and structural valve deterioration. The study is assessing a trileaflet bioprosthesis mounted with the bovine pericardial tissue known as Resilia. “If these results are maintained through 10 or 15 years, this will be an important development for our younger SAVR patients, who stand to benefit from a more durable valve,” says COMMENCE co-investigator Lars Svensson, MD, PhD, Chair of Cleveland Clinic’s Heart, Vascular & Thoracic Institute. ■

Off-Label Use of DOACs in Patients Receiving Surgical Mechanical and Bioprosthetic Heart Valves

► *JAMA Netw Open.* 2021;4(3):e2111259

Use of direct oral anticoagulants (DOACs) following surgical heart valve replacement is not insignificant in the U.S. even though satisfactory safety data on DOACs in this setting are lacking. So finds this retrospective cohort study by Cleveland Clinic researchers who extracted data from the Society of Thoracic Surgeons Adult Cardiac Surgery Database on all patients who underwent surgical aortic or mitral valve replacement with a mechanical or bioprosthetic valve from mid-2014 to mid-2017. Rates of DOAC use at discharge were approximately 5% among bioprosthetic valve recipients and greater than 1% among mechanical valve recipients. “These findings call for a pause and caution from clinicians,” says lead author Ankur Kalra, MD. “We should wait until more data accrue on DOACs’ efficacy and safety in these patient subsets.” ■



the Tools and Spaces Behind Our Care: A PHOTO ESSAY

In Cleveland Clinic's Heart, Vascular & Thoracic Institute, our core strength is our caregivers, who deliver unsurpassed outcomes and experience to our patients day in and day out. Their achievements stem mostly from qualities involving the science and art of medicine — intangibles like training, dedication and empathy. But those intangibles require spaces and tools to be put into action, and we are proud to offer our patients the finest facilities and technologies to meet their needs. To show how these tools help our caregivers do what they do best every day, *Cardiac Consult* presents this photo essay over the next six pages. Although far from comprehensive, it shares a few examples of how our teams are leveraging leading-edge equipment and facilities to realize every advancement possible for patients who come to us from around the globe.





DEDICATED CARDIAC SURGERY ROBOT

Cleveland Clinic cardiac surgeons have completed over 2,000 operations using a state-of-the-art robotic surgical platform dedicated solely to cardiac surgery. The robot's high-definition camera and advanced instrumentation enable unmatched visualization and mobility with minimal invasiveness for the patient. We are now expanding use of the robotic platform beyond mitral valve repair to procedures including myectomy and more. ■



BUSTLING ELECTROPHYSIOLOGY LABS

Our main campus is home to nine leading-edge electrophysiology (EP) labs, where expert electrophysiologists have performed nearly 30,000 EP procedures over the past five years. These labs include multiple 3D mapping and ablation systems using the most advanced technologies, allowing our staff to contribute to the latest research protocols exploring new strategies for ablation. One of the labs is a hybrid operating room and EP lab, and all are equipped to allow backup support from Cleveland Clinic cardiac surgeons if a complication should arise. An additional preclinical EP lab is kept busy by researchers pursuing translational research advancements. ■



IN-HOUSE PRINTING OF 3D HEART REPLICAS

Our clinicians take advantage of the 3D printing lab in Cleveland Clinic's Lerner Research Institute to produce a steady stream of 3D-printed heart replicas to facilitate planning for procedures in patients with especially complex anatomic features. The models are based on advanced multimodality imaging. Replicas like the examples shown here have enabled new, innovative surgical and interventional repairs of complex congenital heart defects. Additional applications include use in planning percutaneous interventions for structural heart disease. ■

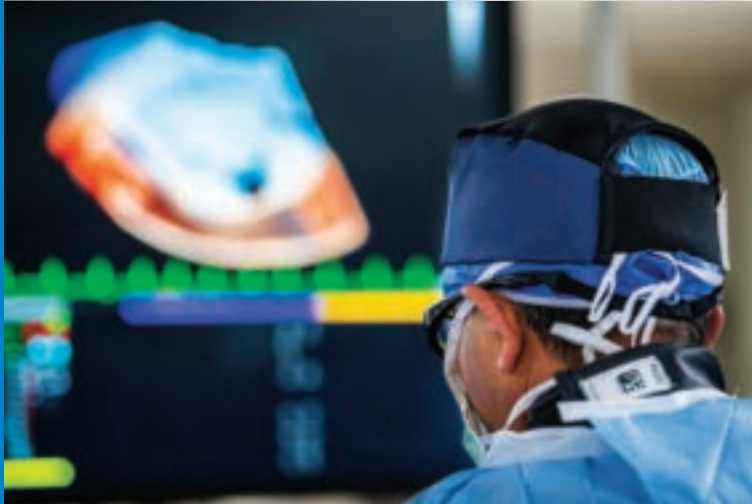




ROBOTICS IN THE CATH LAB

Our interventional cardiologists continue to expand their use of the robotic system installed in our cath labs in 2019. Current applications include a full range of coronary interventions, including those for chronic total occlusions, with more applications potentially on the horizon. The system benefits operators by drastically reducing their radiation exposure and lowering risk of orthopaedic injury by allowing them to avoid prolonged standing wearing lead aprons. Along with the potential for more accurate lesion measurement, the technology promises to eventually enable remote treatment via “telestenting.” ■





HYBRID OPERATING ROOMS

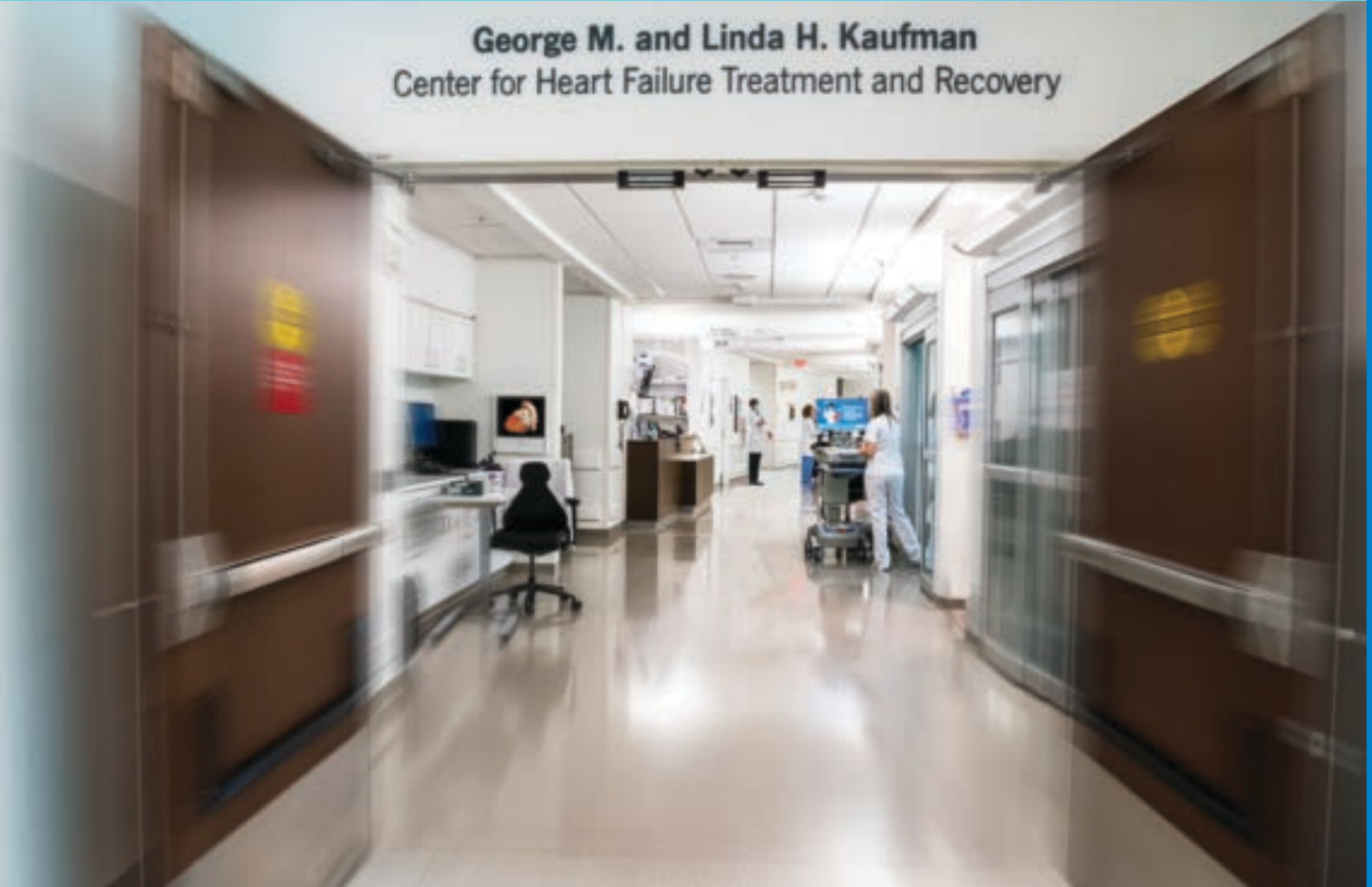
Several Cleveland Clinic hospitals house hybrid operating rooms (ORs). The six hybrid ORs on our main campus include the two largest in any U.S. health system. Thanks to their size, our hybrid ORs can accommodate both open surgery cases and complex interventional cases that rely on advanced imaging using state-of-the-art biplane fluoroscopy or robotic fluoroscopy arms. The rooms' unique layout provides immediate access to surgical tools for hybrid cases and interventional emergencies, including ready-to-use cardiopulmonary bypass equipment and optimal anesthesiology support. Multiple monitors enable procedural flexibility, allowing approaches from any side of the body. The rooms are designed to integrate various imaging technologies, including vessel fusion, DynaCT, 3D transesophageal echocardiography, IOPS radiation-free navigation, intra-vascular ultrasound and OCT imaging. Our hybrid ORs facilitate coordinated care delivery by interdisciplinary teams to treat some of the most complex cases of aortic, cardiac, peripheral vascular and heart rhythm disease. ■



EXTENSIVE ICU RESOURCES FOR CRITICAL CASES

Cleveland Clinic's main campus hospital serves cardiovascular patients' critical care needs through a 24-bed cardiac intensive care unit (ICU), a 10-bed heart failure ICU and a 95-bed postoperative cardiovascular ICU. Here a wide spectrum of patients receive intensive monitoring and care, including the latest in temporal mechanical circulatory support. Beds are spacious, with state-of-the-art monitoring systems that facilitate bedside nursing and clinical care. All the ICUs have dedicated procedure rooms staffed by a procedure nurse for expeditious initiation of interventions within the unit itself. Care of the patients in all units is multidisciplinary, with physician and nursing teams supported by nutrition, respiratory therapy, bioethics, palliative care, cardiac pharmacy, and occupational and physical therapy specialists. ■

George M. and Linda H. Kaufman Center for Heart Failure Treatment and Recovery



EX VIVO LUNG PERFUSION

A dedicated team of physicians, nurses and perfusionists keeps Cleveland Clinic's XPS™ system for ex vivo lung perfusion (EVLP) in frequent use, allowing our surgeons to perform more than 75 lung transplants involving EVLP to date. By prolonging lung preservation outside the body, allowing marginal donor lungs to be treated to make them transplantable, and enabling rapid assessment of lungs from last-minute organ offers, our EVLP system is helping narrow the gap between donor lung supply and demand. ■



Ventricular Switch: A New Paradigm May Be at Hand for ‘Unseptatable’ Hearts

Refinements introduced to a Cleveland Clinic-developed approach to a rare defect.

In congenital heart surgery, paradigm shifts are few and far between. The rarity of most congenital defects has kept opportunities for such shifts relatively limited. As a result, milestone developments like the atrial switch and arterial switch procedures are now well established, having been practiced for multiple decades.

Yet a Cleveland Clinic team led by Hani Najm, MD, MSc, Chair of Pediatric and Congenital Heart Surgery, suspects a new paradigm shift may be at hand with their development of a novel approach to biventricular conversion in “unseptatable” hearts, which they have termed the *ventricular switch*.

The team reported positive results of the approach in their first five patients at the 2020 American Association for Thoracic Surgery scientific session early last year, and they recently published those results in full in *Seminars in Thoracic and Cardiovascular Surgery* (2021;33[1]:172-180). They have since used the approach in several additional patients, incorporating some new refinements they believe will further enhance its impact.

A novel paradigm

The term *unseptatable* has been applied to the hearts of patients with complex systemic and pulmonary venous anatomy commonly characterized by atrioventricular canal defects and conotruncal anomalies. These patients are traditionally treated with univentricular palliation, which leaves them subject to poor long-term survival and few rescue options if the univentricular circulation begins to fail.

The ventricular switch involves biventricular conversion, or septation, in these so-called unseptatable hearts. “We use both ventricles, with the morphologic left ventricle serving as the subpulmonary ventricle to basically recapitulate the physiology of congenitally corrected transposition of the great arteries,” explains Dr. Najm, who led development of the novel approach. “We have formalized a combination of procedures that lead to a systemic right ventricle, as opposed to a single ventricle, in patients whose hearts have multiple abnormal connections.”

Initial series

The team’s recently published initial series of ventricular switch cases involved five consecutive patients with challenging anatomic configurations, severe cyanosis and extreme functional limitations. The patients, who ranged in age from 11 months to 46 years, all required complex atrial septation informed by comprehensive planning using 3D-printed heart models.

The ventricular switch was successful in all five cases:

- All patients were alive at last follow-up (median, 0.6 years; range, 1 month to 2.7 years).
- Left ventricular recruitment substantially improved functional status in all patients.
- Hypoxemia was resolved, with mean systemic oxygenation saturation improving from $79\% \pm 7\%$ to $95\% \pm 5\%$ ($P = 0.003$).

New refinements

The Cleveland Clinic team has subsequently applied the ventricular switch to four additional patients — with some refinements, as enumerated below.

1) Staging. Dr. Najm notes that the ventricular switch is actually a series of five sequential steps (Figure) outlined in the team’s published report of their initial series:

- Septation of the atrioventricular valves
- Repair of anomalous pulmonary venous connections
- Atrial conversion
- Rerouting of extracardiac systemic venous connections
- Left ventricle-pulmonary artery (LV-PA) conduit insertion

“This is not a single procedure but rather multiple procedures that culminate in the use of the right ventricle for systemic circulation,” he explains. “We believe it is better for these components of the ventricular switch to be staged into two or three operations rather than all done in a single operation.” The specifics of the staged breakdown of procedures should be left to the surgeon and informed by the child’s development and overall management, he adds.

2) Earlier intervention. “As we gain experience, we believe the ventricular switch should be done early in life — ideally before age 2 years,” Dr. Najm observes. “The idea is to set these patients up with an alternative to the univentricular heart and undertake the ventricular switch as part of the planning



Figure. Illustrations showing the key sequential components of the ventricular switch. Steps 3 and 4 are combined in the fourth illustration. CAVSD = complete atrioventricular septal defect; TAPVC = total anomalous pulmonary venous connection; LV-PA = left ventricle-pulmonary artery

for their long-term care. The heart that's prepared early in life is apt to fare better than the heart prepared later." He adds, however, that this is currently only a clinical impression that has not been evaluated in clinical trials. And he emphasizes that it does not mean the ventricular switch should not be considered later, as four of the five initial patients were well beyond age 2 and have had positive results thus far.

3) Systemic atrioventricular valve ring. When the right ventricle becomes the systemic ventricle as a result of the ventricular switch, the atrioventricular valve, which is usually on the right side, may dilate and leak as a result of being pressurized. In response, the team has begun routinely adding a left atrioventricular valve ring as a prophylactic measure to preserve the competency of the valve.

4) Branch pulmonary artery band in selected cases. In patients requiring one-and-a-half ventricle repair, a pulsatile bidirectional Glenn procedure is required. The team is now adding a branch pulmonary artery band before performing the Glenn to reduce the pulsatility of the Glenn and thereby reduce the risk of postoperative pleural effusion.

Readily adoptable with proper imaging guidance

A key appeal of the ventricular switch is that it can be readily adopted without significant training, as the individual component procedures are familiar to virtually all congenital heart surgeons. What's novel is the deliberate, proactive planning to use the procedures in coordinated combination to create a systemic right ventricle.

Key to that planning is multimodality imaging, which plays an important role in optimizing patient selection, notes Tara Karamlou, MD, MSc, a staff pediatric and congenital heart surgeon who works with Dr. Najm. "We have used both CT

and MRI with 3D model building to facilitate operative planning," she says. "These models are extremely important since surgical procedures usually consist of multiple components that must be coordinated. Part of our iterative approach has also been informed by the retrospective review of models in situations where modifications have been suggested."

All eyes on the right ventricle

Moving forward, the team will continue following their initial five cases and subsequent patients, with a particular focus on function of the right ventricle over time. They'll also be watching what potential failure of the ventricular switch's systemic circulation may look like. "Our new approach offers patients a better quality of life through a biventricular circulation, and we're hopeful it will offer greater survival than with univentricular circulation," Dr. Najm says. "But we also expect it will set patients up for a better failure model if and when failure develops."

He explains that when failure sets in with a univentricular heart after a Fontan procedure, it manifests as multiorgan failure, with high risk of liver cirrhosis, kidney failure, protein-losing enteropathy and more. "In contrast," he says, "patients with biventricular circulation will fail with a heart failure pathophysiology, without all the multisystem components. That means they can be considered for heart transplant or mechanical circulatory support or other heart-specific options. These patients are set up for a more manageable failure model if needed — one with alternatives." ■

Contact Dr. Najm at 216.444.5819 and Dr. Karamlou at 216.442.8278.



Dr. Rakesh Suri Returns to U.S. Practice While Setting His Sights on Expanding Access Abroad

This spring, cardiothoracic surgeon **Rakesh M. Suri, MD, DPhil**, returned to the United States from Cleveland Clinic Abu Dhabi to take on a new Cleveland Clinic role, President of International Operations, and resume surgical practice at Cleveland Clinic's main campus in Ohio.



“We can now offer our patients located anywhere access to the specialized expertise of our caregivers across the globe when they need us.”

– Rakesh Suri, MD, DPhil

He made the move after serving as CEO of Cleveland Clinic Abu Dhabi since 2017 and serving as its Chair of Thoracic and Cardiovascular Surgery since the hospital opened its doors in the United Arab Emirates (UAE) in 2015. He has overseen Cleveland Clinic Abu Dhabi's overall strategy and operation as the first U.S. multispecialty hospital to be replicated outside North America with more than 5,000 caregivers.

The move adds Dr. Suri's extensive and pioneering clinical expertise — particularly in robotic and minimally invasive cardiac surgery, mitral valve repair and transcatheter valve therapies — to the deep bench of Cleveland Clinic's Department of Thoracic and Cardiovascular Surgery in Cleveland.

“I'm excited to be directly working with the most experienced heart team in the world, with the best outcomes,” says Dr. Suri. “I look forward to contributing to the group however I can. My passion lies in valve repair, preserving valves to benefit patients, and determining the right time to operate

so that patients are spared the challenges of heart failure and myocardial dysfunction associated with severe, persistent valve regurgitation.”

“We are delighted that Dr. Suri has returned to our main campus to contribute to our outstanding robotic mitral valve repair program,” says Lars Svensson, MD, PhD, Chair of Cleveland Clinic's Heart, Vascular & Thoracic Institute. “Rakesh has been recognized as a great leader, innovator and researcher in mitral valve repair. We look forward to how he will further increase our team's expertise, help serve our patients from across the nation and contribute to future publications.”

“It is a pleasure to work in the OR with Dr. Suri,” adds Marc Gillinov, MD, Chair of Thoracic and Cardiovascular Surgery. “He is one of the finest mitral valve surgeons in the world, and adding his expertise to our program — which is already the world's premier mitral valve service — helps us keep advancing therapies for those with mitral valve disease.”



A new international role

When Dr. Suri is not caring for patients, his energies are devoted to leading Cleveland Clinic's overall international strategy as its new President of International Operations.

"Our new mandate is to work with our teams across the globe to create an integrated and inspiring vision for delivery of care to patients outside the U.S.," he explains. "That includes those who travel to any Cleveland Clinic care hub around the globe — whether in Northeast Ohio, Florida, Toronto, Abu Dhabi or soon London — and those who access our care virtually. We will articulate a team-based vision that guides Cleveland Clinic's growth in a manner aligned with our organization's goal to double the number of lives we serve in a way that's centered on care value.

"Cleveland Clinic is now an integrated global healthcare network of over 70,000 connected caregivers," he continues, "and hunger for our services is greater than ever. The best way to meet that demand is to adopt a proactive and visionary approach where we closely coordinate expansion outside the U.S. with our enterprise-wide strategy. That means ensuring that care is consistently standardized at the highest level across our system, regardless of where or how patients access us."

Key to those goals is exemplary care coordination, within and across sites. "Once a patient is in our system," Dr. Suri says, "we must be focused on getting them to the right service in the right place and the right way at the right time. Our unique value proposition is that we can now offer our patients located anywhere access to the specialized expertise of our caregivers across the globe when they need us, preventing them from having to travel long distances."

Building on successes in Abu Dhabi

Despite the demands of this new role, Dr. Suri views maintaining his cardiac surgery practice as a key to his success in it, based on his experience as an executive leader at Cleveland Clinic Abu Dhabi.

"It was very clear in Abu Dhabi that working side by side with other caregivers and being on the front lines of innovation was instrumental to building our reputation with patients, referring providers, the community and the nation," he says.

This was true, he notes, for himself as well as his predecessor as CEO of Cleveland Clinic Abu Dhabi, fellow cardiothoracic surgeon Tom Mihaljevic, MD, who is now CEO and President of the overall Cleveland Clinic enterprise. "We took in-house call, we stayed with our patients, we were responsible for operations from opening the skin to closing the chest to transporting our patients to the ICU," Dr. Suri explains. "This kept us familiar with all aspects of patient care, made us aware

of challenges for patients and caregivers, built trust with families and kept us attuned to the importance of teamwork in delivery of the Cleveland Clinic model of care 8,000 miles from where we learned how to practice medicine."

The results speak for themselves. Over the past four years Cleveland Clinic Abu Dhabi expanded its robust multispecialty offerings, including the launch of the UAE's first multiorgan transplant program in 2017. The hospital saw 20% year-over-year growth in clinical outpatient, surgical and inpatient volumes despite the COVID-19 pandemic — all while achieving the highest overall quality score (five stars) from the UAE's Department of Health.

Similarly notable are the team's accomplishments in cardiothoracic surgery, including creation of Cleveland Clinic Abu Dhabi's transcatheter cardiac programs and the most sophisticated minimally invasive and robotic cardiac surgery program in the region. "We've been able to innovate on both the surgical and transcatheter fronts," Dr. Suri says, "performing several new transcatheter mitral valve procedures — leaflet and annuloplasty procedures — that hadn't even been performed in North America."

What's particularly gratifying, he notes, is that seeking care for adult heart disease went from being the No. 1 reason people traveled from the UAE to now being extremely rare. "Cleveland Clinic Abu Dhabi has essentially fulfilled all the adult cardiac surgery needs for the nation and the region," he says. "That's been one of the highlights of our professional journeys."

Enduring lessons from abroad

Dr. Suri says his six years in Abu Dhabi left him with enduring lessons that will serve him well in his roles back in the U.S. One stemmed from the experience of tackling the COVID-19 pandemic, which arrived in Abu Dhabi before it reached the U.S. He notes that the pandemic required his team to "make bold decisions leveraging our Cleveland Clinic team-of-teams network across the globe" before traditional Western regulatory bodies weighed in.

"What the pandemic taught us," he says, "is that we're only as healthy and able to pursue our day-to-day lives as are the least protected communities across the planet. It made clear that healthcare moving forward will not be a zero-sum game. It will demand a new degree of collaboration and connectedness that we hope to help foster with partners and colleagues across the U.S. and around the world. We are inspired by the power of 100 years of Cleveland Clinic caregiver contributions to improve the lives of millions of people on the other side of the planet and meaningfully redirect the course of their future." ■

Contact Dr. Suri at 216.444.5007.



Cleveland Clinic-Led Trial Suggests a Role for Targeting GM-CSF in Hyperinflammatory COVID-19

Results of the first placebo-controlled study of the monoclonal antibody mavrimumab in hospitalized patients with COVID-19 pneumonia and heightened systemic inflammation are encouraging enough to merit further investigation. So conclude investigators with the trial, known as MASH-COVID, whose results were recently published in *Lancet Rheumatology*.

“This small study did not demonstrate a statistically significant outcomes benefit, but it showed a numeric benefit for patients treated with mavrimumab, as well as no safety concerns,” says lead investigator Paul Cremer, MD, a Cleveland Clinic cardiologist. “These encouraging hypothesis-generating findings are consistent with other studies suggesting a potential role for these therapies in this setting.”

A focus on GM-CSF

The signal-of-efficacy trial was initiated by Dr. Cremer and coordinated by Cleveland Clinic’s academic research organization, C5Research. The aim was to assess whether inhibiting granulocyte-macrophage colony-stimulating factor (GM-CSF) with mavrimumab would improve clinical outcomes in some of the sickest COVID-19 patients — those with COVID-19 pneumonia and systemic hyperinflammation. “It was not intended to be definitive for treatment effect,” explains Dr. Cremer.

GM-CSF is a pro-inflammatory cytokine that drives innate immune response and is particularly important in how the lungs respond to inflammatory stimuli. In the first phase of serious COVID-19 cases, viral clearance is key. “GM-CSF may actually be advantageous in clearing the virus early on,” Dr. Cremer says.

During the second phase of COVID-19, which can be characterized by an overwhelming inflammatory response, GM-CSF becomes a bad actor, perpetuating lung injury. “That’s why we thought GM-CSF might mediate the hyperactive inflammatory response associated with respiratory failure and death in COVID-19,” Dr. Cremer notes. “Mavrimumab targets GM-CSF, attenuating this overactive inflammatory response.”

MASH-COVID essentials

Dr. Cremer assembled a consortium of colleagues to discuss testing this theory, and they decided to undertake a randomized controlled trial. Between May 28 and Sept. 15, 2020, 40 patients were enrolled in the trial — 37 of them at Cleveland Clinic hospitals in Northeast Ohio and Florida — and randomized to a single intravenous infusion of either mavrimumab or placebo.

At day 14, 57% of patients in the mavrimumab group and 47% of those in the placebo group met the primary endpoint of being alive and off supplemental oxygen therapy (odds ratio = 1.48; 95% CI, 0.43-5.16).

At 28 days, 95% of patients on mavrimumab and 79% of those on placebo were alive and without respiratory failure. By study completion at day 60, one patient (5%) randomized to mavrimumab had died, compared with four (21%) randomized to placebo.

Adverse events were comparable between the groups, and no safety concerns were seen. “This is important when giving a treatment to patients who are already critically ill,” says Dr. Cremer. “There was concern about the effect of so much immunosuppression, but we haven’t seen an increase in secondary infections.”

More insights expected

Patients who become very ill with COVID-19 pneumonia represent a subset who experience an overactive inflammatory response. Because various therapies block immune response through different pathways, mavrimumab is one of several with potential for treating these very sick patients.

Tocilizumab is an anti-IL-6 monoclonal antibody that has some supportive evidence for use in patients hospitalized with COVID-19 pneumonia with low oxygen levels and high levels of inflammation. “Patients who don’t meet these criteria are not likely to respond,” notes Dr. Cremer.

As for mavrimumab, initial results of a larger trial are expected soon. Additionally, a phase 3 study of lenzilumab, another monoclonal antibody against GM-CSF, reported top-line results showing significantly greater odds of ventilation-free survival compared with placebo in hospitalized patients with COVID-19, and results from further studies are due soon.

“I think we’ll know shortly whether targeting GM-CSF with these agents is effective or not,” Dr. Cremer concludes. ■

Contact Dr. Cremer at 216.444.6765.



More From the Intersection of COVID-19 and the Heart

A Model for Uninterrupted Cardiac Rehab

Scalable delivery of safe, uninterrupted phase II cardiac rehabilitation (CR) is achievable across a regional health system in the face of the COVID-19 pandemic. That's the takeaway from a commentary by a team of Cleveland Clinic clinicians published in the *Journal of Cardiopulmonary Rehabilitation and Prevention* (2021;41[2]:88-92). The article shares an experience-based overview of how Cleveland Clinic's nine CR centers in Northeast Ohio worked to provide patients with safe, routine and effective access to phase II CR services. It outlines two major initiatives:

- Swift development of a standard-of-care model for CR telemedicine that prioritized access and inclusivity for all types of patients. No patients have experienced adverse cardiac events or other complications from participating in home-based exercise consistent with their treatment plan.
- Adaptation of universal safety precautions for COVID-19 to the demands of a medically necessary exercise setting. Through January 2021, no COVID-19 cases were traced back to any of Cleveland Clinic's nine CR centers despite resuming phase II CR sessions at 50% to 80% of pre-pandemic capacity.

› Details of specific actions taken are available at ccf.org/covidcardiacrehab.

Taking on the Heart Effects of Long COVID

Cleveland Clinic has launched the Post-COVID Cardiovascular Recovery Center in collaboration with its multidisciplinary reCOVer Clinic to provide evaluation and treatment for post-acute sequelae of SARS-CoV-2 infection, or “long COVID.” “These programs provide the opportunity to better understand the long-term sequelae of COVID-19 and establish best management practices,” says cardiologist Jerry Estep, MD, Co-Director of the Post-COVID Cardiovascular Recovery Center.

Patients with persistent symptoms following COVID-19 that may have a cardiovascular etiology undergo a focused evaluation to screen for cardiovascular complications. The center also evaluates patients with preexisting heart disease who had COVID-19 of any severity to assess for changes in cardiovascular status. Patients have access to subspecialists and resources from electrophysiology, sports cardiology, heart failure, cardiovascular imaging and vascular medicine.

After evaluation, a personalized care plan is offered, including initiation of cardiovascular treatments if appropriate. Individuals are followed until cardiovascular symptoms resolve. Patient-reported outcome measures are captured, and smart forms within the electronic health record are used to document outcomes in support of research efforts to illuminate the long-term burden of COVID-19.

› More at ccf.org/postcovidheart.

Guidance on COVID-19 and the Athlete's Heart

Providers wishing to keep current on cardiac testing and return-to-play considerations for athletes following COVID-19 infection can turn to two recent reports co-authored by Michael Emery, MD, Co-Director of Cleveland Clinic's Sports Cardiology Center:

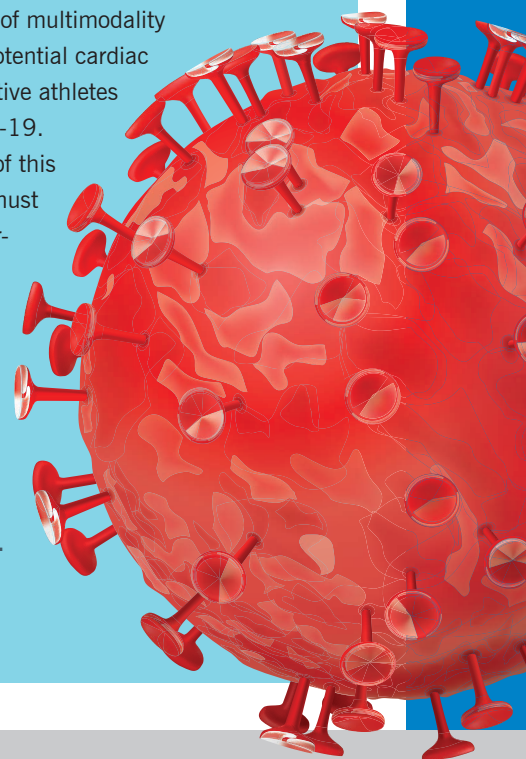
- “Coronavirus Disease 2019 and the Athletic Heart,” a special communication in *JAMA Cardiology* (2021;6[2]:219-227) by a group of leading sports cardiologists, advises consideration of comprehensive cardiovascular testing before resumption of practice or play for various subgroups of athletes. The report outlines recommendations for first-line testing, shares return-to-play algorithms and identifies near-term research priorities.

- An expert consensus statement in *JACC: Cardiovascular Imaging* (2020;13[12]:2635-2652) distills evidence from a review of multimodality imaging to screen for potential cardiac involvement in competitive athletes recovering from COVID-19.

“An important message of this statement is that care must be taken not to misinterpret exercise-induced cardiac remodeling as cardiac injury related to COVID-19,”

Dr. Emery notes.

› More on both publications is available at ccf.org/covidinathletes.





Ex Vivo Lung Perfusion: Insights From a Fast-Growing Program

How the technology helped maintain transplant volume during a pandemic year.

Cleveland Clinic's ex vivo lung perfusion (EVLP) program is now the highest-volume program in the U.S. and growing rapidly. Whereas just 1% of Cleveland Clinic's total lung transplants in 2016 involved lungs that underwent EVLP, that percentage rose to a robust 25% in 2020. In fact, the technology was instrumental in making Cleveland Clinic one of only four U.S. centers to perform more than 100 lung or heart-lung transplants during 2020 in the midst of the challenges of COVID-19.

Q&A

with Kenneth McCurry, MD

Kenneth McCurry, MD, Surgical Director of Lung and Heart-Lung Transplantation, has been the leader of Cleveland Clinic's EVLP efforts since they were initiated a decade ago. *Cardiac Consult* caught up with him to discuss what EVLP brings to lung transplantation and emerging developments in the field.

Q: Why is EVLP important to modern lung transplantation?

Dr. McCurry: Donor lungs remain in high demand, with many patients dying while waiting for organs. Unfortunately, only 20% of available donor lungs are actually used, despite acceptance of marginal donors and aggressive donor organ management. EVLP allows us to increase the pool of organs, helping to close the wide gap between supply and demand.

It does so in three main ways. First, a donated lung can be preserved outside the body while it is better evaluated to determine its likelihood to function successfully after transplantation. Second, lungs that are truly marginal for transplantation can be treated with techniques and therapeutic agents to improve function and make them transplantable after EVLP. Third, the extended organ preservation provided by EVLP allows assessment and utilization of organs that would otherwise go unused due to logistical factors such as last-minute organ offers.

One surprising role of EVLP we have discovered is that it allows us to determine that a lung that appears promising by traditional criteria may not, in fact, be suitable for transplantation. On rare occasions we have an organ that, despite meeting all the standard requirements, is found through EVLP assessment to have problems that would make it likely to fail.

Because of this, EVLP has spared a few patients the experience of undergoing an ultimately unsuccessful transplantation.

For those interested in more detail, our team has summarized the fundamentals of EVLP in a review article in *Current Transplantation Reports* (2019;6:251-264).

Q: Has Cleveland Clinic developed techniques or protocols for EVLP that can be useful to others?

Dr. McCurry: We have conducted considerable research on how best to assess lungs for likelihood of successful function after transplantation. We developed a technique using ultrasound to assess lungs undergoing EVLP called CLUE (DireCt Lung Ultrasound Evaluation), which is described in the *Journal of Heart and Lung Transplantation* (2020;39[11]:1220-1227). It is a highly sensitive method of assessing extravascular lung water content, which correlates well with lung suitability for transplant.

EVLP at Cleveland Clinic

- > 1 of 4 U.S. programs to perform
> 100 lung/heart-lung transplants in 2020
- > 30 lungs transplanted after EVLP in 2020,
representing 25% of our lung transplant cases
- > 100% survival at 30 days and 93% survival
at 1 year for cumulative EVLP transplant recipients
through 2020



“Therapeutic interventions administered while a lung is on EVLP — to optimize organ function and resilience and reduce the likelihood of recipient rejection — are being explored.”

– Kenneth McCurry, MD

We have also investigated methods of saving marginal lungs. One study evaluated the role of EVLP in salvaging lungs from donors with a high body mass index, which tend to have more atelectasis and a lower PaO₂/FiO₂ ratio. We found that using an aggressive protocol with EVLP can allow transplantation of some of these lungs, resulting in good outcomes (*Ann Thor Surg.* 2020;109[6]:1663-1669).

Therapeutic interventions administered while a lung is on EVLP — to optimize organ function and resilience and reduce the likelihood of recipient rejection — are also being explored by us and other groups. Current topics of investigation include use of antibiotics to treat infection, as well as use of other biologic agents, including gene therapy, which can be inhaled by or injected into a donor organ while on EVLP. At Cleveland Clinic, we are focused on the potential benefits of therapies — including nitric oxide, nitrite and others — that are important to the immune response and may make the lung more resistant to rejection.

Q: Should all lung transplant centers be adopting EVLP?

Dr. McCurry: Having this program has benefited our lung transplant program enormously. Since the challenges of COVID-19 began early last year, EVLP has significantly enhanced our ability to maintain a good organ supply, which helped us perform 118 lung transplants in 2020, one of the highest volumes in the nation.

But such a program can't be undertaken successfully without resources and commitment. The equipment and personnel costs are considerable. At Cleveland Clinic, we are fortunate to have strong institutional support that provides the necessary funding, dedicated staff and space. We are also fortunate to have an outstanding team — including Toshihiro Okamoto, MD, PhD, Associate Director of EVLP, and Kamal Ayyat, MD, PhD, Assistant Director of EVLP — who help provide great leadership, as well as fellows, respiratory therapists and perfusionists who contribute greatly to the team effort.

Experience is the other critical factor. Since our program started in 2016, we have performed more than 75 lung transplants involving EVLP, with 100% survival at 30 days and 93% survival at one year. This level of experience is invaluable for acquiring the ability to make good clinical decisions surrounding EVLP.

One of our goals is to assist others, and we have conducted several on-site education programs on EVLP for international and domestic transplant centers. In 2019, we initiated an annual EVLP symposium to bring together transplant clinician leaders, transplant center financial leaders and organ procurement organization leaders to discuss the financial, logistical and experience hurdles that are currently an impediment to broader application of this technology. We hope these efforts will make more lungs available for transplantation and save more lives. ■

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Contact Dr. McCurry at 216.445.9303.



Optimizing Length of Stay for Cardiac Surgery Through Preoperative Workflow Redesign

An affiliated hospital adopts same-day admissions to boost patient satisfaction and reduce costs.

Optimizing hospital length of stay (LOS) has many advantages, such as lower risk of hospital-acquired conditions, increased patient satisfaction and reduced hospital costs. These advantages loomed large when Cleveland Clinic's Heart and Vascular Advisory Services team performed an initial assessment of the cardiovascular service line of Kaweah Health (KH), recognizing an opportunity to significantly shorten preoperative LOS for patients undergoing elective cardiac surgery through process improvements and workflow redesign.

The assessment took place in the early stages of an affiliation relationship that KH, which serves California's Central Valley, entered into with Cleveland Clinic's Heart, Vascular & Thoracic Institute in 2019 to promote quality outcomes and share best practices pertaining to patient experience and efficiency.

Backdrop to the project

For years, cardiac surgeons at KH had arranged for their elective surgery patients to be admitted to the hospital prior to the day of surgery as a "courtesy admission" during which the surgical team could finalize the preoperative evaluation and provide formal presurgical education to the patient and family. The aim was to afford surgeons better control of elective surgery start times since patients would already be in-house.

In practice, courtesy admission patients could spend anywhere from 12 hours to several days waiting to go to surgery as a result of incomplete preoperative tests or being delayed for more urgent cases. The resulting prolonged hospitalization time waiting for an elective procedure became a significant source of patient dissatisfaction.

This dissatisfaction was exacerbated in the spring of 2020 when the COVID-19 pandemic brought new restrictions limiting family members from visiting their loved ones in the hospital. This proved to be a huge stressor to patients prior to surgery. The need to shorten or eliminate preoperative LOS was more apparent than ever from patients' standpoint. Unnecessary presurgical admissions also reduced access to limited hospital beds, as some were occupied by preoperative patients who didn't yet need them.

Identified preoperative inefficiencies related to patient satisfaction, efficiency and cost

Mapped current elective surgery workflows from cardiovascular surgery office consultation to operating room

Formed stakeholder team to develop workflow redesign

Redesigned workflows and provided education to outpatient personnel

Developed ideal-state pathway and optimized new process to address barriers

Figure. Steps involved in the development of Kaweah Health's same-day admission process for elective cardiac surgery patients.

Essentials of the process redesign

Challenges and opportunities related to this courtesy admission process were identified in Cleveland Clinic's initial review of KH cardiovascular operations. Working with Cleveland Clinic consultants who performed the review, KH cardiac surgery leadership undertook an initiative to eliminate preoperative admissions for elective surgery patients in order to (1) promote patient satisfaction, (2) increase preoperative workup efficiency and (3) reduce the cost of elective surgery cases by avoiding expenditures for unnecessary preoperative hospital stays.

After thorough communication to the teams involved about expected benefits of the project for patients and the hospital, KH cardiac surgery leadership and a Cleveland Clinic consultant initiated discussions about how best to redesign the process and workflow for presurgical workup of elective surgery patients. All affected areas were covered, from surgical offices to the preoperative and cardiovascular care units to the preadmission testing area.



“Sharing best practices lies at the foundation of our affiliate arrangements.”

– Edward Soltesz | MD, MPH | DIRECTOR OF CARDIAC SURGERY AFFILIATE SERVICES

Through a series of interviews and formation of a stakeholder team, the Cleveland Clinic consultant worked with KH to:

- Create “current state” productivity timelines to visually display productive versus nonproductive portions of the presurgical admission process
- Recommend “ideal state” pathways to incorporate key steps into the surgical evaluation process
- Create an ideal-state process map as a visual aid for workflow transparency once workflows were agreed upon and adopted

Under the leadership of Christine Aleman, Director of Cardiovascular Operations at KH, and with support from Leheb Araim, MD, Cardiac Surgery Director, education on the workflow redesign was provided to the cardiovascular surgery nurse practitioners and preoperative nursing teams. Patient evaluation, testing and presurgical education were then transitioned to be done on an outpatient basis by existing preoperative hospital personnel.

Initial impacts of the same-day admission pathway

The result was a redesigned process — the same-day admission pathway — with outpatient workflows that eliminated the need for admission prior to surgery. This allows KH personnel to provide necessary patient education on the procedure and expectations for postoperative recovery several days prior to surgery rather than the day before, giving patients and families time to formulate questions and fully prepare for the operation.

“All our elective cardiac surgery patients’ preoperative work is now completed through phone calls and outpatient communication,” says KH’s Aleman. “Paperwork is completed before their arrival at the hospital, and expectations for their surgery and recovery have already been discussed with them in detail. Patients are appreciative of our new process because it allows them to be at home where they are most comfortable until the day of surgery. Patients are now more at ease because they have already met most of the healthcare professionals they will see the day of surgery and have had a chance to

process all the educational information with their families. This tends to reduce patients’ stress, which should ultimately result in better outcomes and faster recovery.”

Implementation of the same-day admission pathway has been too recent to allow comprehensive assessment of its impact on patient satisfaction, but it is expected to have positive effects. In addition, the new pathway has provided an efficient and effective process for surgical evaluation, with no negative impact on quality.

Moreover, preoperative testing on an outpatient basis has proved less expensive than inpatient testing due to savings realized through shorter inpatient stays, elimination of facility charges, and reduced use of labor, supplies and textiles. “Since implementing the same-day admission process, our hospital is saving thousands of dollars per patient by avoiding costs typically associated with an increased length of stay,” says Aleman.

“Working with Cleveland Clinic was a worthwhile strategic move that provided insights, evaluations and resources to bring the same-day admission process to life for our cardiac surgery patients,” she adds. “We have been able to take the concept and turn it into a process that works across multiple departments in our hospital.”

“Sharing best practices lies at the foundation of our affiliate arrangements,” notes Edward Soltesz, MD, MPH, cardiothoracic surgeon and Director of Cardiac Surgery Affiliate Services at Cleveland Clinic. “The same-day admission process has been shown to not only improve efficiency and patient satisfaction but also encourage a protocol-driven approach to the multidisciplinary evaluation that is the cornerstone of surgical quality. We are excited that KH has operationalized this important program, and we look forward to seeing its positive results.” ■

For information on affiliation and alliance opportunities with Cleveland Clinic’s Heart, Vascular & Thoracic Institute, email Amada.Leseska@ccf.org.



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