The past year was an exciting one at the Vanderbilt Heart and Vascular Institute (VHVI). We continued the expansion of our clinical and academic programs, set new records for procedural volume in multiple areas, and launched several new research programs.

Our advanced heart failure and transplantation program reached a rare milestone, performing 100 adult heart transplants in 2018. This achievement allowed Vanderbilt to maintain the distinction of being the second busiest heart transplant center in the country, for the third consecutive year.

Electrophysiology saw continued clinical growth. Much of the recent growth has been attributable to our complex ablation program. Referrals for VT ablation, in particular, have doubled since 2017 (see article by Dr. William Stevenson and colleagues, page 8). We also continue to be among the national leaders in left atrial appendage closure and lead extraction.

Our comprehensive structural heart disease program was bolstered by the addition of 2 interventionalists, Drs. Kashish Goel and Jared O'Leary. They will be joined in the spring by Dr. Colin Barker, the new director of Interventional Cardiology and a national leader in percutaneous valve therapies. As described in the article by Dr. Goel and colleagues (page 6), a key advance in the field has been the publication of the COAPT trial, demonstrating the benefit of percutaneous mitral valve repair for secondary mitral regurgitation. The national trial was co-led by Dr. JoAnn Lindenfeld at Vanderbilt.

Another important development was the recruitment of Dr. Matthew Bacchetta to thoracic and cardiac surgery. Dr. Bacchetta is a surgeon-investigator, nationally recognized for his work in extracorporeal membrane oxygenation (ECMO), whole organ preservation, and the treatment of pulmonary vascular disease. Other recent additions to the surgical team include Drs. Keki Balsara (Cardiac Surgery) and Patrick Stone (Vascular Surgery).

Our research program continued its expansion, with total NIH funding increasing by 162% since 2013. In that time, VHVI faculty have received 4 Strategically Focused Research Network grants from the American Heart Association, 2 program project grants, and 4 major training grant renewals. Our faculty also continue to play leading roles in national precision medicine efforts, including the NIH’s “All of Us Research Program,” for which Vanderbilt serves as the Data and Research Center.

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Emerging Therapies for Cardiac Amyloidosis

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Amyloidosis is a disorder of protein misfolding, leading to the deposition of insoluble protein aggregates within the heart, resulting in heart failure, arrhythmias, and sudden cardiac death. Of more than 100 known amyloidogenic proteins, light chain (AL) and transthyretin (ATTR) explain the majority of cases. ATTR may be mutant (mATTR) or senile, wild type (wtATTR). Cardiac amyloidosis may be accompanied by involvement of the gastrointestinal, renal, or autonomic systems. Preexisting heart disease often confounds the clinical workup, leading to failure to consider amyloidosis as the unifying diagnosis. Despite an increasing recognition of amyloidosis, it is still common to see delays in diagnosis of 6 or more months from onset of symptoms, and diagnosis may require the expertise of 3 or more physicians. Patients with amyloidosis often show poor tolerance of standard heart failure therapies (angiotensin converting enzyme inhibitors, angiotensin receptor blockers, and beta blockers), so diuretics are the mainstay of symptom management.

Clinical Presentation: Cardiac amyloidosis typically presents as heart failure with preserved ejection fraction (HFpEF) and may be accompanied by atrial arrhythmias and conduction abnormalities, requiring permanent pacing. Left ventricular hypertrophy (Figure 1) in the absence of left ventricular dilation results in small stroke volumes with relative hypotension, which may be exacerbated by autonomic dysfunction.

Diagnosis and Clinical Course: The finding of low voltage on the electrocardiogram is a classic finding; however, it is present in only 50% of cases and thus cannot be relied on to exclude the diagnosis of cardiac amyloidosis. Late gadolinium enhancement and T1 mapping on cardiac MRI can help support the diagnosis. Elevations in natriuretic peptides and troponins in the absence of epicardial coronary disease are common. On endomyocardial biopsy, congo red staining reveals the characteristic apple green birefringence of amyloidosis (Figure 2). Fibrillary typing using mass spectrometry should then be performed to identify the specific amyloid protein to direct appropriate therapy.

AL amyloidosis, derived from a clonal expansion of plasma cells, carries the gravest prognosis with a median survival of 6 months in the most advanced cases. All evaluations of cardiac amyloidosis must include a laboratory assessment for AL (serum and urine protein electrophoresis/immunofixation and serum free light chain). Well-tolerated chemotherapy regimens, based on proteasome inhibitors and immunomodulators, lead to rapid and durable

Figure 1: Cardiac MRI demonstrates left ventricular hypertrophy with small stroke volume.

Figure 2: Cardiac amyloidosis (Hematoxylin and eosin stain, top; Congo red stain under polarized light, bottom).
reductions in light chain levels, necessary for hematologic remission and survival. Autologous stem cell transplant provides deeper remission in select patients.

With a slower clinical course despite similar imaging findings, TTR amyloidosis is the other common cause of cardiac amyloidosis. Compared to AL amyloidosis, median survival is longer, ranging from 4 to 6 years after the onset of symptoms. The TTR complex dissociates into unstable monomers that misfold into amyloid. A history of carpal tunnel syndrome, spinal stenosis, low gradient aortic stenosis, or late onset hypertrophic cardiomyopathy should raise suspicion. wtATTR, representing half the ATTR cases in the US, can be found in Caucasian males over age 65, and rarely presents in women. Scintigraphy using 99mTc-pyrophosphate labeled bone avid tracers allows diagnosis of cardiac ATTR without the need for invasive endomyocardial biopsy (Figure 3). Intense tracer uptake in the heart (heart to contralateral chest ratio > 1.5) identifies ATTR with high sensitivity and specificity, but requires single photon emission computed tomography (SPECT) localization to avoid false positives. Once the diagnosis of ATTR has been established, genetic testing can distinguish between mATTR and wtATTR.

**Vanderbilt Amyloid Multidisciplinary Program:** With the emerging therapeutic options for a disease with an inexorable, and in some cases rapidly fatal, course, early diagnosis and prompt initiation of therapy remain imperative. The Vanderbilt Amyloid Multidisciplinary Program provides comprehensive evaluation of multisystem amyloidosis with access to clinical trials for both AL and ATTR. At Vanderbilt Heart, we are particularly excited to offer access to tafamadis for mATTR cardiomyopathy in the open-label extension phase of the ATTR-ACT trial. For patients whose disease may be too advanced to benefit from stabilizing therapies, cardiac transplantation remains a therapeutic option at experienced transplant centers such as Vanderbilt. There is increasing recognition that cardiac amyloidosis is greatly underdiagnosed, with early interventions now available to improve both quality of life and survival.

**Figure 3:** Grade 3 uptake of 99mTc-pyrophosphate demonstrates cardiac infiltration by transthyretin.
Interventional Cardiology Program

Percutaneous Mechanical Circulatory Support:
Current Perspectives and Future Horizons

The cardiology community has done a remarkable job addressing optimal STEMI care. However, the management of cardiac insults complicated by pump failure continues to be incredibly heterogeneous with highly variable outcomes. The next frontier in the management of cardiac emergencies will be to reduce the variability in the care of patients who could benefit from mechanical circulatory support. A confluence of factors has resulted in the increased use of percutaneous, non-durable mechanical circulatory support for the management of cardiogenic shock and in high-risk coronary intervention. These factors include advances in the understanding of cardiogenic shock physiology, recognition of the deleterious effects of vasopressors and inotropes, technological advancements in devices and device management, and more options for definitive therapies if native heart recovery is not feasible.

Cardiogenic Shock: Hospitalization for cardiogenic shock is increasing, and the portfolio for device use in cardiogenic shock is also changing, with an observed decline in the use of intra-aortic balloon pumps (IABP). This change has been driven by data suggesting the IABP may have no advantage over medical therapies in acute myocardial infarction with cardiogenic shock. To avoid tactical errors, a team-based approach to shock guided by evidence-based algorithms and multi-disciplinary case reviews to hard-wire process improvement is vital. This requires familiarity and experience with the current portfolio of devices, including the Impella family of catheters for left and right ventricular support (ABIOMED, Inc., Danvers, MA), the TandemHeart (TandemLife/LivaNova, Pittsburgh, PA), and several variations of a veno-arterial (VA) ECMO circuit. The deployment of these therapies requires an understanding of the nuances of each device in relation to the physiology of each individual patient. For example, in the use of VA ECMO in patients with ischemic heart disease-related shock, native heart recovery can be promoted by unloading or “venting” the left ventricle. This is due to the significant afterload created by retrograde perfusion of the aorta from the arterialized limb of the circuit, leading to left ventricular distension and driving further ischemia. Venting of the left ventricle can be performed in several variations, including surgical vent placement in the left ventricle, use of a pre-pulmonary cannula to decrease left heart blood return, use of an Impella device (the so-called ECPELLA circuit), or left atrial cannulation via a trans-septal puncture for the venous limb of the ECMO circuit. In addition, the early recognition of shock and the appropriate early initiation of support prior to metabolic insults to the liver, kidneys, and other end-organs is the key to survival. The potential of this philosophy to improve outcomes is recognized in several recent studies.

Complex Ischemic Heart Disease: Percutaneous mechanical circulatory support has also played an important role in the management of complex, high-risk ischemic heart disease. Patients who would have previously been managed medically or palliatively are now often offered percutaneous options for revascularization that are only possible with circulatory support. This includes patients with unprotected left main lesions, complex multi-vessel coronary artery disease with decreased left ventricular ejection fraction and/or need for atherectomy, single-remaining coronary conduits in need of intervention, or chronic total occlusion interventions with need to use dominant collaterals for retrograde approaches. An example of such an intervention is displayed in (Figure 1), in which a 68-year-old woman with systolic dysfunction and clinical heart failure (left ventricular ejection fraction 25-30%) was declined for coronary artery bypass graft surgery (CABG) at both the referring institution and at VUMC due to significant co-morbidities including a severe decubitus ulcer. The Vanderbilt Complex Coronary Revascularization and Management (CCRM) Team successfully managed the needs of this patient with complex atherectomy and PCI to the LAD followed by same-setting CTO PCI to the RCA, accomplishing complete revascularization and...
an excellent clinical outcome. Circulatory support was provided using an Impella CP device. During LAD atherectomy, aortic pulsatility decreased significantly, but recovered fully after completion of LAD PCI (Figure 2). This response reminds us that such an intervention would not be feasible without the use of percutaneous circulatory support tools and a multi-disciplinary team approach to revascularization planning.

Building Systems of Care: The delivery of complex care in shock and for complex ischemic heart disease patients has been moving towards coordinated networks of care. In fact, the process of network development has been legislated in some states, such as Georgia, by designating a tiered system of cardiac emergency centers akin to the trauma center designations. The goal is to facilitate the delivery of care in a streamlined and efficient manner, to avoid delay in recognition of the disease process and to institute an appropriate management plan. In some situations this means the patient must receive circulatory support at the referring institution to facilitate safe transport to quaternary cardiac emergency centers. Vanderbilt has implemented a retrieval service for cardiopulmonary emergencies since 2016 in collaboration with Vanderbilt LifeFlight. The services have included on-site cannulation for ECMO, in-the-field critical care management, and patient transport to Vanderbilt University Medical Center. The service has reached a radius of care delivery of nearly 400 miles.

Percutaneous circulatory support has become an essential tool in complex cardiovascular care. The use of circulatory support in shock patients will continue to be refined via systems of care planning similar to the early days of primary PCI for STEMI. In the complex revascularization field, the use of support devices can be viewed as "on-pump" PCI, providing benefits analogous to that seen with on-pump rather than off-pump CABG.

Figure 1: Before and after angiographic images of complex PCI with hemodynamic support in a patient with ischemic cardiomyopathy. LAD atherectomy assisted PCI as well as CTO PCI of the RCA were performed in the same setting.

Figure 2: Series of hemodynamic tracings during PCI on the patient shown in Figure 1. The upper (red) tracing is central aortic pressure. The far left frame indicates baseline tracings. The middle frame is taken during LAD atherectomy. Note the loss of aortic pressure pulsatility. The far right tracing shows recovery of aortic pulsatility after completion of LAD PCI.
The prevalence of mitral regurgitation (MR) increases with age, rising from 0.5% for 18-44 year olds to 9.3% for those age 75 years and older. Current guidelines dichotomize therapeutic management strategies for MR based on the presence of primary or secondary regurgitation. In primary mitral regurgitation, some component of the valve itself is dysfunctional and repair/replacement of the valve can therefore be curative. By contrast, in secondary MR the valve itself is essentially normal, and regurgitation results from tethering of the valve due to underlying myocardial pathologies. As a result, in the setting of secondary MR, repair or replacement of the valve is not by itself curative. Optimal management of secondary MR is therefore less well defined compared with primary MR. Secondary MR in patients is best managed initially by a heart failure specialist to maximize medical therapy of heart failure and consider cardiac resynchronization (CRT) as indicated. Medical management and CRT may both significantly decrease the severity of MR. Once medical and device management are maximized, the decision for MitraClip therapy should be determined by a team of heart failure specialists, structural interventionalists, and surgeons.

Until recently, there were no proven therapies for patients with moderate-severe or severe secondary MR. The current AHA/ACC valve guidelines recommend surgical valve replacement in patients with persistent symptoms despite optimal medical therapy with a weak class IIb indication, and for patients undergoing other cardiac surgery (class IIa). However, there has been a paucity of data addressing whether “fixing the valve” would change the prognosis or result in symptomatic improvement.

Recently, a national group of investigators including Dr. JoAnn Lindenfeld from Vanderbilt University Medical Center performed one of the first randomized controlled trials in patients with secondary MR. The Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients with Functional Mitral Regurgitation (COAPT) trial randomized symptomatic patients with moderate-severe or severe secondary MR 1:1 to guideline-directed medical therapy (GDMT) alone versus GDMT plus transcatheter mitral valve repair with MitraClip (Abbott). MitraClip was successfully implanted in 95% of the patients, and 82% of patients had ≤1+ MR at discharge. At 2 years follow-up, the primary efficacy endpoint of heart failure hospitalizations was significantly reduced (47% relative reduction) in the MitraClip arm compared with medical therapy. Based on these results, 3 patients meeting the inclusion criteria of COAPT trial need to be treated with MitraClip to prevent 1 heart failure hospitalization. In addition, there was a significant 38% relative reduction in all-cause mortality (number needed to treat, 6). All other secondary outcomes, including reduction in MR grade to <2+ at 12 months, improvement in quality of life, 6-minute walk duration, and left ventricular remodeling were also significantly better in the device arm. Overall, the COAPT trial showed that transcatheter mitral valve repair with the MitraClip device along with GDMT improves prognosis and symptoms in patients with secondary MR.

It is important to note that the European MITRA-FR trial reported contradictory results to COAPT regarding the management of secondary MR. Compared with GDMT, MitraClip plus GDMT did not yield a significant reduction in all-cause mortality. There were significant differences in the COAPT and MITRA-FR trials, which may explain the discordant results. In MITRA-FR, the degree of baseline MR (effective regurgitant orifice 0.31 cm2 vs. 0.41 cm2) was less and left ventricular volumes were significantly larger (left ventricular end diastolic volume 135 mL/m2 vs. 100 mL/m2) compared with the COAPT trial. These data are extremely important in the assessment of patients with secondary MR and will help us target the group of patients who may benefit from transcatheter therapy.

Transcatheter mitral valve repair represents one of the first strategies designed to improve outcomes in secondary MR. Transcatheter
mitral valve replacement (TMVR) is also now on the horizon. At Vanderbilt, we are currently participating in the APOLOO trial of the Intrepid TMVR device (Medtronic). The valve team at Vanderbilt offers the complete array of interventions for mitral regurgitations, including advanced heart failure management, surgical repair/replacement, MitraClip, and TMVR. The future is bright for treatment of patients with secondary MR.

Figure 1: Primary MR with posterior leaflet prolapse.

Figure 2: Severe mitral regurgitation.

Figure 3: 3D Echo showing severe mitral regurgitation.

Figure 4: MitraClip deployment on 3D Echo.

Figure 5: Post-Clip residual trace mitral regurgitation.
Catheter Ablation for Treatment of Ventricular Arrhythmias

Heart rhythm disturbances that arise from the ventricles are an important cause of symptoms and sudden death. Ventricular arrhythmias can be caused by many different forms of heart disease but can also develop in people with no structural abnormalities of the heart. There have been substantial advances in the diagnosis and treatment of ventricular arrhythmias, with catheter ablation emerging as a major treatment option.

Almost any form of heart disease can lead to a rapid ventricular arrhythmia that can cause sudden cardiac death. Patients who have developed ventricular scar from a prior myocardial infarction or a cardiomyopathy are at greatest risk. Our ability to identify these people and protect them with an implanted cardioverter defibrillation (ICD) has revolutionized their management. The ICD is a safety net that terminates dangerous ventricular tachycardias (VT), but unfortunately ICDs do not prevent the arrhythmia from occurring. Many of the VT episodes will be terminated by rapid pacing from the ICD (antitachycardia pacing, referred to as ATP), but some episodes require a shock for termination. Preventing sudden death in patients with heart disease is always a success story, but shocks are painful and decrease quality of life. In addition, episodes of VT often worsen other aspects of the patients’ heart disease, including heart failure. Antiarrhythmic drugs can be helpful, but medications can fail or cause side effects in many people. For these reasons, therapies to prevent VT are important, even when an ICD is working well to restore normal rhythm.

Catheter ablation has the potential to prevent VT without the need to increase or add antiarrhythmic drug therapy. Our understanding of the anatomic causes of VT, commonly referred to as the “arrhythmia substrate,” has advanced substantially and now guides ablation efforts. The first consideration is whether the VT is monomorphic (organized with repeating QRS complexes) or polymorphic (disorganized) (Figure 1). This can be determined from inspection of recordings from the ICD or from an electrocardiogram (ECG). Monomorphic VTs usually emerge from an area of scar that can be identified using the ECG and advanced cardiac imaging, such as cardiac magnetic resonance imaging (MRI). Polymorphic, disorganized VTs can emerge from scar, but often have other causes, including ischemia, that need to be considered. In the electrophysiology (EP) laboratory, anatomically-detailed reconstructions of the ventricle are created to refine the localization of the arrhythmia origin. We now have substantial experience with VTs in all forms of heart disease, including coronary artery disease, different forms of cardiomyopathies, and repaired congenital heart disease, such as Tetralogy of Fallot. From this knowledge, specific arrhythmia substrates can be anticipated, identified, and targeted for ablation.

In most cases, ablation is performed by advancing the ablation catheter through an artery or vein to reach the endocardial (inside) surface of the heart and applying radiofrequency (RF) current to heat the abnormal area. Some VTs arise from regions deep within the wall of the heart, and getting close to these areas may require more advanced techniques. In some cases, inserting a needle into the pericardial space allows delivery of the ablation catheter to the epicardial (outside) surface of the heart. In others, identifying the artery that supplies blood to the VT substrate can be identified and alcohol injected for ablation. Cardiac surgery is required for some, facilitated by our hybrid operating room suite that provides advanced cardiac mapping and ablation capabilities. Other patients may benefit from the use of experimental ablation tools under investigation, including a needle ablation catheter and radiation therapy. Cardiac stimulation from the nervous system is an important aggravating factor for arrhythmia that can be treated with surgical cardiac sympathectomy. Vanderbilt Heart receives referrals of patients with difficult to control arrhythmias from across the country, most of whom have had a prior ablation procedure that was unsuccessful. One or more of these advanced techniques is often the best option for these patients.
For some patients, particularly those who also have heart failure, ventricular arrhythmias are a sign that their heart disease is entering a more serious phase, or that other factors are aggravating their heart disease. For all patients, we take a personalized approach to treatment that considers not only the type of arrhythmia, but also the underlying heart disease, and other potentially aggravating factors. Patients may benefit from coronary artery revascularization procedures, treatment of mitral regurgitation, and optimization of medical therapy for heart failure. For some with severe heart disease, cardiac transplantation or placement of a left ventricular support device is the best option. Our multidisciplinary team is committed to implementing the best treatment for each patient.

Premature ventricular beats or runs of nonsustained VT that occur in patients who do not have structural heart disease are usually benign and do not require treatment. However, some cause disturbing symptoms, such as palpitations, that reduce quality of life, and very frequent PVCs (with more than 20% of each day’s total heart beats being a PVC rather than a normal beat) can put additional strain on the heart, causing cardiomyopathy. Most of these arrhythmias arise from a region accessible to catheter ablation, which is an excellent treatment option for many patients.

Selecting the best therapy requires careful consideration of the risks and benefits. The risks of catheter ablation are largely those associated with manipulating catheters through blood vessels and in the heart. Despite the severe heart disease present in many patients who need ablation, serious complications are infrequent. A dedicated EP laboratory staff and close collaboration with cardiac anesthesia, surgery, heart failure specialists, and interventional colleagues are important for prompt detection and management of risks and are crucial for achieving the best outcomes.

Figure 1: A middle-aged woman with recurrent episodes of ventricular fibrillation (top panel) despite medications was emergently transferred to VUMC for management of recurrent episodes of ventricular fibrillation (VF). Coronary angiography was normal. VF was observed to be initiated by premature ventricular beats (PVCs) (telemetry ECG tracing). She was taken emergently to the EP laboratory where mapping of the endocardial left ventricle, aided by intracardiac ultrasound imaging (bottom right panel), was performed. The PVCs were found to originate from a site on the left ventricular septum (left panel region shown in red), where RF ablation (sites with red circles) abolished the initiating PVCs and episodes of ventricular fibrillation. VF is most commonly due to myocardial ischemia, but rare patients have idiopathic VF, as in this case, for whom catheter ablation of the PVCs that initiate the VF can be life-saving.
VHVI by the Numbers

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Left Atrial Appendage Closure Cases

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