Defining structural heart disease in the adult patient: current scope, inherent challenges and future directions

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Structural heart disease refers to non-coronary cardiovascular disease processes and related interventions. The last 10 years has seen tremendous advances in both the understanding of these processes and the therapeutic modalities aimed to treat them. Technology continues to evolve and clinical trials are ongoing to help delineate the appropriate role these therapies will play. Inherent challenges exist in training physicians in structural heart disease. Ultimately, credentialing societies and training programmes will emerge to help assure expertise within the cardiovascular community. This review focuses on the scope of structural heart disease, summarizes some of the current and future technologies available, highlights inherent challenges pertaining to structural heart disease and outlines future directions the field may take.

Introduction

‘Structural heart disease’ is a term first introduced by Martin Leon at the 1999 Transcatheter Cardiovascular Therapeutics meeting to provide an over-reaching term encompassing non-coronary cardiac disease processes and developing interventional techniques. As an entity, however, catheter-based interventions aiming to alleviate conditions related to heart structure have existed for over half a century. Indeed, the pioneering work by Rubio-Alvares and Limon in 1952 to relieve critical pulmonary valve stenosis1 heralded a cascade of procedural and technological advances that now contribute to our abilities to treat, and often cure, structural heart disease.

The past decade has seen tremendous advances in all forms of cardiovascular care, and this is especially true with structural heart disease. Increased recognition of disease, attention paid to the pathophysiologic mechanisms underlying these diseases, advanced imaging techniques to more finely elucidate anatomic abnormalities and catheter-based techniques and devices have each contributed to improved diagnosis and treatment of structural heart disease. As a result, structural heart disease is emerging as its own specialty within interventional cardiology. While the entirety of this issue is devoted to structural heart disease, this review focuses broadly on the field as a whole.

Current scope of structural heart disease

Atrial septal defect

Atrial septal defect (ASD) is one of the most common congenital heart defects. There are three types of ASDs: primum, secundum, and sinus venosus. Symptomatic patients present with dyspnea, fatigue, atrial arrhythmia, or right-sided heart failure. Indications for ASD closure include the presence of symptoms, a size of more than 10 mm to cause a significant left-to-right shunt, a Qp (= pulmonary blood flow) to Qs (= systemic blood flow) ratio of >1.5, and/or significant right atrial and ventricular enlargement (Figure 1).2
The optimal treatment of ASDs depends on the anatomic type of defect. Defects of the septum primum or sinus venosus are best treated by surgical means. However, the more common septum secundum defects are very effectively treated by percutaneous closure. The most frequently used percutaneous device to close the defect is the Amplatzer (AGA Medical, MN, USA) device, however, a number of other devices exist.

**Patent foramen ovale**

The foramen ovale is a congenital tunnel between the right and left atrium. Physiologically essential during the embryonic period, the septae effectively close soon after birth, and in the majority of people, they fuse together within 2 years. However, upwards of 35% of children have a small residual defect, termed a patent foramen ovale (PFO), and in autopsy studies of adult patients, the incidence of PFO is as high as 27%. Numerous studies have reported an association between PFO and various conditions including paradoxical thromboembolism, ischaemic stroke, migraine headaches, and decompression illness.

Since the first report by Bridges et al.4 in 1992, many studies have reported on the safety and efficacy of percutaneous PFO closure, and numerous devices to treat PFO are in varying stages of development and commercialization (Figure 2). Despite the intuitive attractiveness of PFO closure, controversy exists regarding the overall benefit of this therapy. A number of smaller studies suggest favourable results with PFO closure over medical therapy in preventing recurrent events in patients with cryptogenic stroke;5–7 however, no randomized study has been published to date. Therefore, widespread recommendation of routine PFO closure has not yet occurred.8

**Ventricular septal defect**

Ventricular septal defects (VSD) represent another common congenital heart abnormality. Anatomically, VSDs can be divided into perimembranous and muscular defects, the former of which being far more frequent. Often, large VSDs are diagnosed and treated in childhood, however, smaller defects can manifest in adulthood. Clinical presentations include infective endocarditis, arrhythmias, pulmonary hypertension, and aortic regurgitation.9–11 Indications for the closure are symptoms and a hemodynamically significant shunt (Qp:Qs > 1.5).

With regard to treatment, compared with surgical closure, percutaneous closure has a lower morbidity; however, percutaneous closure of VSD is technically more challenging than ASD closure. A number of
devices are available for VSD closure, including the Amplatzer Occluders [membranous, muscular, and muscular post-myocardial infarction (MI)] as well as the CardioSEAL STARFlex (NMT Medical Inc., MA, USA) device. In a prospective study with 83 procedures in 75 patients with a muscular VSD, the device could be placed in 86.7%. Importantly, 10.7% (8/75) of the patients suffered major device or procedure-related complications. The long-term follow-up showed a closure rate of almost 93% at 1 year.

With regard to perimembranous VSDs, Holzer et al. evaluated transcatheter closure in 35 patients. Six months follow-up showed complete closure in 96% of the patients. In total, 8.6% had serious adverse events, but no death or neurological event occurred. In another prospective but non-randomized study (100 patients, mean age 9 years), the authors concluded that VSD closure is safe and effective, comparable to surgical treatment.

**Patent ductus arteriosus**

The patent ductus arteriosus (PDA) is an essential foetal structure serving to allow oxygenated blood to pass from the pulmonary artery into the aorta, effectively bypassing the developing lungs. In the large majority of children, the ductus closes spontaneously shortly after birth; however, persistent patency occurs in approximately 1 in 2000 births. Ductus closure is indicated for patients with symptomatic left-to-right shunt through the PDA. If patients are asymptomatic, PDA closure should be performed in patients with significant shunting which results in left heart enlargement.

Most PDAs in children and adults can be closed by transcatheter technique. An occluder can be placed from either the pulmonary artery or the aorta with excellent results. Following the original report of transcatheter ductal occlusion in 1967 numerous devices have been developed and employed in the pursuit of the ideal occluder. The Amplatzer Ductal Occluder (AGA Medical, MN, USA) is probably the most well established for use in adult patients today.

**Left atrial appendage**

In patients with non-valvular atrial fibrillation, embolic stroke is associated with left atrial thrombi. The left atrial appendage (LAA) is the site of thrombus formation and the source of embolism in more than 90% of cases based on autopsy studies and echocardiography. Occlusion of the LAA may prevent thromboembolism by removing the site of thrombus formation. Currently available LAA occluder devices include the Watchman (Atritech, MN, USA) and the Amplatzer ACP device (Figure 3). In a randomized trial comparing the Watchman device vs. anticoagulation in 707 patients, the efficacy of percutaneous closure of the LAA with this device was non-inferior to that of anticoagulation therapy. Although there was a higher rate of adverse safety events in the intervention group than in the control group, events in the intervention group were mainly a result of periprocedural complications whereas complications in the control group were mainly due to bleeding related to long-term anticoagulation and consequently continued to occur during follow-up. The authors concluded that the closure of the LAA may provide an alternative strategy to chronic anticoagulation therapy for stroke prevention. In another prospective study of 64 patients with paroxysmal or permanent atrial fibrillation receiving a different device, the annualized stroke/transient ischaemic attack (TIA) rate was 3.8%. This was 42.5% less than the rate predicted by the CHADS2 scoring system (6.6%/year) after up to 5 years of follow-up. Based on these studies, percutaneous left atrial appendage closure may provide an alternative to anticoagulation in properly selected patients with non-valvular atrial fibrillation.

**Left ventricular aneurysm**

Postinfarction left ventricular aneurysm is a serious disorder that can lead to congestive heart failure, lethal ventricular arrhythmia, and death. For patients with congestive heart failure, angina pectoris, malignant ventricular arrhythmia, or recurrent embolization arising from the left ventricle, exclusion of the aneurysm may
provide significant benefit. The goal of the intervention, surgically or percutaneously, is to improve systolic function by downsizing and correcting the geometry of the left ventricle, reducing wall tension and paradoxical movement.

Traditionally, surgery has been the primary means by which to accomplish left ventricular reduction/restoration with a few case reports describing successful percutaneous implantation of a device. Primarily made for other congenital heart diseases. A novel device (Parachute, Cardiokinetix, CA, USA) developed especially for LV aneurysm is currently under study.

**Paravalvular leak**

Hundreds of thousands of prosthetic valves (mechanic and bioprosthetic) are implanted each year. Although long-term results follow valve replacement surgery are excellent, paravalvular leak (PVL) may be detected in up to 5% of the patients by contemporary echocardiographic imaging. It results from incomplete apposition of the implanted ring to the native tissue and is often benign and asymptomatic. Symptoms can occur, however, due to large regurgitant volume or haemolysis. Clinically significant PVLs occur most commonly with prosthetic implantation in the mitral position. Regarding treatment of PVL, medical therapy is palliative, and reoperation carries significant morbidity and mortality. Percutaneous transcatheter closure, therefore, is very attractive as an alternative to surgery. Small studies showed that percutaneous closure of PVLs is a feasible option for patients who are not candidates for surgery. Transcatheter closure of paravalvular leaks has been accomplished using a number of different devices. Its primary limitations relate to the fact that it is technically challenging, variably effective and may require multiple interventions to be clinically successful. Advances in imaging, such as real-time RT-3D transesophageal echocardiography, and the development of better occlusion devices specifically designed for closing paravalvular leaks may improve procedure results and outcomes.

**Post-MI ventricular septal rupture**

Since the introduction of early reperfusion techniques in MI, the incidence of VSD as a complication of a MI has decreased to <1%. However, post-MI VSD portends high mortality with both conservative and surgical therapy. In recent years, a number of reports have suggested the feasibility of percutaneous closure of post-infarction VSD with the Amplatzer (AGA Medical, MN, USA) device, and there may be a lower mortality rate with percutaneous closure when compared with the classical surgical approach. Thus, in patients with post-infarction VSDs that are not candidates for surgical closure or have hemodynamically significant residual shunts, percutaneous closure of the VSDs may offer an effective therapeutic option. Further investigation in a prospective manner is needed before any definitive statements can be made.

**Valvular heart disease**

**Mitral stenosis**

One of the most well-established interventional techniques within structural heart disease is percutaneous mitral valvuloplasty (PTMV). Since the first report by Inoue et al. in 1984, PTMV has become the treatment of choice for mitral stenosis. In symptomatic patients, indications include moderate to severe mitral stenosis or mild stenosis with accompanying pulmonary hypertension. When performed on appropriately selected patients with favourable anatomy, acute and long-term results of PTMV are excellent.

**Mitral regurgitation**

The mitral apparatus is a complex structure consisting of the mitral valve leaflets, the annulus, chordae, papillary muscles, and ventricle. A defect at any level may result in regurgitation of blood from the left ventricle to left atrium. Severe mitral regurgitation is associated with increased mortality regardless of symptoms, and the ACC/AHA have put forth extensive guidelines to help optimize the timing of surgery in patients with severe mitral regurgitation. Surgical therapy has long been the primary means by which to repair mitral regurgitation for indicated patients with repair being by far the preferred method when feasible.

From a percutaneous perspective, a myriad of devices designed to treat mitral regurgitation are currently under varying stages of development. Potential targets include the valve leaflets, annulus (by way of the coronary sinus or subvalvular), and the ventricle itself. Importantly, inherent challenge related to percutaneous therapy for mitral regurgitation result from the variety of underlying causes of mitral regurgitation, and the fact that individual devices can only target one mechanism.

The edge-to-edge repair method, which serves to mimic a surgical technique developed by Alfieri and colleagues in the 1990s is the farthest along of the mitral therapies. Via a transapical approach, a clip (Mitra-Clip, Evalve Inc., CA, USA) is implanted to approximate the anterior and posterior leaflets of the valve, reduce the regurgitant orifice and decrease the severity of mitral regurgitation. The recently completed EVEREST-II trial prospectively randomized patients with severe mitral regurgitation to percutaneous vs. surgical mitral valve repair. Preliminary results are encouraging in terms of symptomatic improvement, reduction of mitral regurgitation and LV remodelling.

Coronary sinus annuloplasty attempts to replicate the results of surgical annuloplasty by reducing the antero-posterior diameter of the mitral annulus. There are currently different device systems being tested to reduce the diameter. Early data suggest that mitral valve repair and annuloplasty is feasible, however, the safety and long-term effect is unproven. Multiple trials are currently underway and should provide us with useful information about the potential for percutaneous mitral repair.
Aortic stenosis
While surgical treatment of symptomatic, severe aortic stenosis remains the gold standard, there are a significant number of patients who are not ideal candidates for surgery due to high or prohibitive operative risk. Of these patients, many should not undergo any therapy, as their comorbid conditions are likely life limiting. However, there exist substantial subsets of high-risk patients who stand to improve significantly if the valve can be replaced via less invasive means. For these patients, percutaneous aortic valve implantation is an important alternative.

Since it was first performed by Alain Cribier in 2002, percutaneous aortic valve implantation (AVI) has seen tremendous progress. First, important strides have been made to simplify the procedure and reduce procedural morbidity. Second, the development and commercialization of two devices (Sapien, Edwards Lifesciences, CA, USA and CoreValve, Medtronic-CoreValve, MN, USA) (Figure 5) has lead to widespread European application of percutaneous AVI. Preliminary trials investigating these devices in patients considered high or prohibitive risk for surgery suggest that transcatheter aortic valve replacement is not only feasible but also effective, and pivotal trials are ongoing.

Hypertrophic obstructive cardiomyopathy
Hypertrophic obstructive cardiomyopathy (HOCM) is defined as a primary, frequently familial and genetically determined condition characterized by myocardial hypertrophy. It is relatively common, with an incidence of approximately 1 in 500. Of these, about 25% also have varying degrees of dynamic left ventricular outflow tract obstruction. For symptomatic patients, surgical myectomy has long been the gold standard. A number of less invasive treatments have been tried including medical therapy with beta-blockers, verapamil, or dysopyramide as well as dual chamber pacemakers. Over the past decade, the therapeutic options for symptomatic HOCM patients have increased due to the introduction of percutaneous transluminal septal myocardial ablation. This interventional method creates an alcohol-induced septal infarction resembling the anatomic and hemodynamic effect of surgical myectomy. Although there are no randomized studies comparing percutaneous and surgical septal ablation, it appears that both treatment options yield comparable hemodynamic and clinical results.

Other structural heart interventions
In adult patients, numerous additional structural heart disease processes are increasingly approached via percutaneous methods. Some of these include pulmonary valve implantation, closure of sinus of valsava aneurysm rupture, and treatment of vascular fistulae. Although many of these treatments are relatively novel, with emerging data, the face of structural heart disease will undoubtedly continue to evolve.

Challenges unique to structural heart disease
Interventional techniques for treatment of structural heart disease are evolving rapidly and have become established routine in a large number of centres worldwide. Over the last 10 years, the term ‘structural heart disease’ has become generally accepted as a category of disease by the medical community. The disease processes and devices outlined above and elsewhere in this issue highlights the fact that structural heart intervention encompasses a wide array of treatment modalities. As most of these procedures are based on catheter and wire manipulation skills already honed by the coronary and peripheral vascular interventionalist, it stands to reason that interventional cardiologists can also treat structural disease. However, there are a number of issues unique to structural disease that render the transition somewhat more difficult and pose inherent challenges to training.

The first issue is the role of adjunctive imaging and pre-procedural assessment in treating structural heart disease. Percutaneous treatment of these processes certainly relies heavily on hemodynamic and fluoroscopic assessment, with expertise commonplace among interventional cardiologists. However, optimization of structural heart intervention also often depends on soft-tissue imaging, therefore commanding mastery of additional modalities such as echocardiography. Furthermore, different disease processes are better served by various imaging modalities as intracardiac echocardiography is very well suited for PFO and ASD closure, while transesophageal echocardiography (conventional and RT
3-D appears to be better suited for percutaneous valve implantation. Dedication to and expertise in these imaging modalities is necessary to ensure optimal treatment of these defects.

A second issue relates to patient and procedural volume. While high-volume catheterization laboratories perform thousands of coronary interventions per year, structural heart volume is considerably less, and even recognized high-volume experts perform no more than 200–300 cases per year. More importantly, many respectable centres do not perform structural heart interventions, and while some centres may be considered ‘centres of excellence’ for one form of structural heart disease, the same centre may have minimal or even no experience for another. This has tremendous implication with regard to training and dissemination of technology as the purpose of training is to guarantee a minimum common standard with regard to cognitive understanding and technical skill. As a result, many interventional trainees therefore will not receive necessary training to perform these procedures once their training is complete. Additionally, once out of training, building necessary volume to remain current and proficient represents another issue altogether.

A third challenge relates to the wide spectrum of structural heart disease and subtle variability within each disease process. For instance, percutaneous treatment of ASD and PFO involve closing a communication between two chambers via similar devices and relatively similar implantation techniques. However, not all devices are suitable for every lesion, and it requires a certain level of expertise to understand the nuances and apply the best technology for each individual lesion. On another note, percutaneous treatment of valvular heart disease relies on a relatively different knowledge base and skill set. It is important to recognize the inherent difficulties involved in being a true expert in everything, which then paves the way for subspecialized centres and individuals to emerge even within the field of structural heart intervention.

Future directions

There is little doubt that catheter-based treatment of structural heart disease has become increasingly applicable over the past 10 years. Importantly, some centres have concomitantly emerged from traditional coronary catheterization laboratories into dedicated units with specialized personnel for catheter-based therapy of structural heart diseases. Furthermore, dedicated fellowship programmes have recently been developed such as the programme in the Massachusetts General Hospital. This
programme incorporates dedicated clinical exposure and hands-on training proctored by experienced physicians of the field as well as research platforms for fellows interested in turning empirical clinical understanding of structural heart diseases into pre-clinical research and subsequent novel catheter-based solutions. Additionally, in 2008, the Society of Cardiovascular Angiography and Interventions launched the first-of-its kind Council for structural heart disease. The goal is to facilitate pre-clinical and clinical research, expert communications and the development of guidelines and training standards for this subspecialty of interventional cardiology. However, looking beyond promising developments in research and training, one must consider that the prevalence of most structural heart diseases is comparably low. The number of potential patients in need of structural heart interventions is not at all comparable to that of percutaneous therapy for coronary heart disease and therefore should not be prematurely overestimated. On the contrary, the advent of technologies such as percutaneous aortic valve replacement potentially broadens the population of patients to whom treatment can be delivered. In this case, patients with severe, symptomatic aortic stenosis previously considered prohibitive candidates for surgery will likely be considered acceptable candidates for percutaneous therapy.

Furthermore, discussions concerning the balance between potential advances in catheter-based technology and the cost-effectiveness of patient treatment have been raised. For some catheter-based approaches, criticism may remain justified in the future. Novel percutaneous techniques may turn out to be less efficacious than surgical strategies or may not prove to have significant benefits in patient outcomes. However, particularly in the treatment of patients at high surgical risk, it is unquestionable that there is an overall need for less invasive alternatives to contemporary surgery.

In view of the above issues, it is clear that partnerships between cardiology and surgical divisions are essential. Undoubtedly, percutaneous therapy is changing and will continue to change the manner in which structural heart disease is approached. The evolution of technology and knowledge assures that fact. As with surgical intervention, complex anatomy and broad pathophysiologic spectrum of structural heart disease will make necessary a combination of different ideas, skills of therapeutic strategies in order to attain optimal percutaneous results.

Conclusions

As a field, structural heart disease has seen tremendous advances over the past 10 years. Increased recognition and understanding of the disease processes as well as the development of percutaneous approaches to treat these processes heralds a new era in cardiovascular medicine. The results of ongoing trials and the inevitable evolution of technology promise to shape the field over the next few years. Undoubtedly, the term ‘structural heart’ will continue to encompass the ever-expanding armamentarium of non-coronary heart disease and intervention.

Conflict of Interest: none declared.

References


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