

FOCUS REVIEW

Interventional cardiology: the future beyond the coronaries

Eric Horlick

It was not long ago that I was a medical student at McGill. I graduated in the class of 1996.

When I started to do interventional work as a Cardiology Resident at McGill, we were well into the era of coronary intervention. Almost every balloon angioplasty was followed by the implantation of a stent, which had been shown to improve the immediate and long-term results of interventional therapy. Life was becoming easier, dual antiplatelet therapy had emerged and replaced heparin, dextran, and warfarin which were initially used to treat every patient with a stent to prevent acute thrombosis. Our equipment had improved with better, less bulky balloons that allowed for smaller caliber guiding catheters and arterial access. This allowed vascular complications to diminish significantly. Stents were now being manufactured attached to balloon catheters decreasing the risk of stent embolization. There were also a number of pharmacologic strategies including 2B3A inhibitors which significantly reduced morbidity in high risk patients.

It has been about 8 years since I first scrubbed for an angioplasty and much has changed. We now know quite a bit about patient selection, risk management, and the outcomes after coronary interventions. Regular stents are still widely in use but drug eluting stents are being implanted in great numbers. The albatross around the neck of the stent era of coronary intervention was in-stent restenosis, an aggressive healing response to the arterial injury which occurs with both balloon angioplasty and stent implantation. This process results

in renarrowing of the stented segment over the course of the first 6 to 9 months of follow up. Restenosis generally presents as recurrent angina. The risk of restenosis is related primarily to the presence of diabetes, and the length and diameter of the stent implanted. The arrival of drug eluting stents has greatly diminished the risk of patients developing restenosis and thereby requiring repeat procedures and suffering recurrent symptoms. Drug eluting stents have encouraged a more aggressive percutaneous approach to the treatment of coronary artery disease in patients who would have previously been directed toward surgical revascularization. When only bare metal stents were available, it was hard to justify pursuing an angioplasty that would almost certainly result in restenosis.

Drug eluting stents have been implicated in an increased risk of stent thrombosis (a much more deadly acute occlusion of a stented segment) late after the index procedure. Drugs are likely to delay endothelialization of the stents by blocking the intense healing response which causes restenosis. A prolonged duration of dual antiplatelet therapy with ASA and Clopidogrel, longer than the 3-6 months recommended in the initial trials of these therapies, has been suggested by most interventional practitioners and is thought to be protective. The most recent analyses have suggested no increased risk of drug eluting vs bare metal stents in up to 4 years of follow up after a coronary intervention. They have also shown no difference in the rate of death or death/ myocardial infarction in these 2 groups calling into question the cost effectiveness of drug eluting stents, which are three to four times the cost of bare metal stents. Despite the above, I am unaware of any cardiologist who would not want a DES implanted at the time of their own angioplasty.

Coronary intervention has been compared to coronary artery bypass surgery in many populations both with bare metal stents and with drug eluting stents. In

*To whom correspondence should be addressed:

Eric Horlick MDCM FRCPC
Director; Structural Heart Disease Intervention Program
Assistant Professor of Medicine, Peter Munk Cardiac Centre
Toronto General Hospital – University Health Network
Room 6E-249, 200 Elizabeth Street, Toronto, Ontario, M5G 2C4
Email: eric.horlick@uhn.on.ca

summary, there is really no evidence of mortality benefit of one of these treatments versus the other. The angioplasty patients generally require repeat procedures versus the surgical patients. Despite an apparent advantage of surgery, most patients who have been given a full informed consent choose angioplasty for its less invasive properties and the shorter recovery times required.

A discussion of coronary disease could easily fill volumes with data, conjecture and opinion. Although coronary artery disease by far occupies the most time of any cardiac interventional program, many other interventions are currently being performed to treat cardiac disease and will be the focus of the remainder of this discussion.

Structural heart disease is an explosive area of cardiovascular interventional cardiology and can be alternatively defined as non-coronary cardiac intervention. Interventions in structural heart disease occupy increasing time at many scientific meetings and are seeing a rise in the number of practitioners carrying out these interventions.

ASD CLOSURE

The skills to perform structural procedures are based in pediatric cardiology and interventional radiology. By far the most common intervention is atrial septal defect closure. Patients born with a significant atrial septal defect go on to develop right ventricular dilatation and manifest symptoms or exercise intolerance and cardiac rhythm disturbances. As decades go by, the pulmonary pressure may rise to moderate levels. Symptoms worsen over time in relation to the stiffening of the left ventricle with age which promotes increased left to right flow through these defects. Probably the best marker of a significant defect is right ventricular enlargement. Surgery for atrial septal defects has been carried out since the 1950's. The catheter-based solutions came into common usage in the mid to late 1990's.

The method of closing any intracardiac defect with any device is similar. A device, usually with 2 discs or umbrellas is attached to a delivery cable. By virtue of the design or mechanical properties of the device it can be advanced through a narrow tube or catheter, usually less than 3 mm in diameter. The catheter is advanced across the defect and one side of the device is released. The catheter and exposed disc or umbrella are withdrawn until they make contact with the defect and then the other disk is exposed on the opposite side of the hole providing closure. The device can then be released from the delivery system. Using this method, atrial septal defects up to 40 mm in diameter can be closed.

Transcatheter ASD closure offers benefits over surgery. In an elegant study by Dhillon, decreased right

ventricular total excursion and peak lengthening rate was noted in patients undergoing surgery but not in those undergoing transcatheter closure. It is thought that this effect was related to poor myocardial preservation in the operating room, selective damage to longitudinal muscle fibers which compose the majority of the right ventricle and poor temperature regulation of the right ventricle intraoperatively. In our institution catheter based ASD closure is the preferred method of ASD closure.

PFO CLOSURE

About thirty percent of the population has a residual embryologic defect known as a patent foramen ovale. This connection between the right and left atrium served to shunt blood between the right atrium and left during fetal life in utero. During that period, the lungs were filled with fluid and oxygenated maternal blood would bypass the right-sided circulation to reach the fetal organs. PFOs have been implicated in a number of disease states including cryptogenic stroke, migraine headache, platypnea orthodeoxia, altitude sickness, and obstructive sleep apnea. Cryptogenic stroke i.e. stroke in the absence of classical vascular or cardioembolic sources, is usually implicated when patients under the age of 55 years present with prolonged or permanent neurologic dysfunction. The mechanism has been attributed to paradoxical embolism through this residual embryologic intratrial communication in some patients. There are currently several large randomized trials underway comparing medical therapy in the form of ASA or warfarin and percutaneous device closure for the prevention of recurrent cryptogenic stroke. The jury is clearly out in this particular patient population although there is a suggestion from single centre experiences and meta-analyses that device closure may offer some protection from recurrent events. Our practice is to offer patients a complete stroke investigation including MRI/MRA of the brain, thrombophilia screening, holter monitoring, and transesophageal echocardiography when the etiology of a stroke is unclear. Those patients with cryptogenic stroke after full investigation will be offered entry into a randomized trial. Should they not be candidates, individual consideration of device closure will be offered after informed consent.

PDA CLOSURE

Patent ductus arteriosus (PDA) is another residual embryologic structure that can persist in adults. Large defects usually present in childhood with heart failure. A PDA in adults usually manifests as a continuous murmur; i.e. a murmur which passes through the second heart sound unchanged. It is usually heard best in the

left infraclavicular space and can be missed if not specifically listened for. The indication for PDA closure is the presence of an audible murmur and the reason for closure is to prevent endarteritis which results in a systemic bacteremia. The transcatheter procedure is technically uncomplicated and involves crossing over the defect from the pulmonary artery and implanting either a coil or device in the ductus to promote thrombosis and occlusion.

PROCEDURAL IMAGING

The procedure for closure of ASDs, PFO and PDAs are well established and can usually be accomplished in well less than an hour. ASD closure procedures in our institution are performed with the use of fluoroscopy as well as intracardiac echo (ICE) guidance. Many sites around the world continue to close ASDs with patients under general anesthesia and transesophageal echo guidance. The advantages of intracardiac echo (a ten French or 3.33 mm diameter catheter) include: increased patient comfort, freedom from general anesthesia and the required recovery period, independence from busy echocardiographers, and unique views of the septum not available with TEE. Most importantly, the use of ICE requires and promotes the development of the echo skills of the operator who is ultimately responsible. Knowledge of echo anatomy allows translation to other structural heart disease interventions. PFO closure is generally performed with the use of fluoroscopy alone as is PDA closure.

There are a number of devices available for intracardiac use each with their own advantages and disadvantages. Probably the most relevant factor in device selection is operator comfort and knowledge of the system in question. There are particular anatomic situations where one device's features are clearly advantageous, arguing for operators to have a working knowledge of multiple devices or systems. Low volume operators in structural heart disease intervention are clearly a liability and while the optimal number of annual procedures is not well defined, it is quite clear that high volume operators are likely to have better outcomes and broader experience than low volume operators.

OTHER INTERVENTIONS

While the three lesions described above constitute the bulk of adult structural heart disease practice, there are countless lesions that require treatment in this patient population on a less frequent basis. They include stent placement for coarctation of the aorta, stenting of stenotic pulmonary arteries, pulmonary or systemic veins, surgically created baffles used to treat transposition of the great arteries, or conduits from the

ventricles to the great arteries to bypass inoperable subvalvular obstruction. We are often called upon to occlude venous or arterial collateral vessels from the aorta or great veins as well as pulmonary arteriovenous malformations. Coronary fistula closure is a regularly performed procedure. Pulmonary and aortic balloon valvuloplasty are not infrequently performed procedures for stenotic valves. With experience in device use and sophisticated techniques, closure of perivalvular leaks around mechanical valves, aortoatrial fistulas, aortic pseudoaneurysms, and ventricular septal defects of both congenital and post myocardial infarction etiology is possible.

TRANSCATHETER VALVE THERAPIES

Whereas as recently as five years ago, catheter-based treatment of valvular heart disease consisted only of balloon valvuloplasty, our present armamentarium of therapies allows treatment of pulmonary, aortic and mitral valve disease.

TRANSCATHETER PULMONARY VALVE REPLACEMENT

The earliest clinical experience with percutaneous heart valve therapy was for the treatment of pulmonary regurgitation. In certain patients with congenital heart disease, particularly those with Tetralogy of Fallot, a valved conduit from the right ventricle has been used as part of the definitive repair in patients with inoperable right ventricular outflow tract disease. Unfortunately, the natural history of these conduits is one of progressive regurgitation or stenosis or both. Conduit regurgitation/stenosis leads to right ventricular dilation and dysfunction, resulting in progressive symptoms of exercise intolerance, arrhythmia and right sided heart failure. Philip Bonhoeffer pioneered a technique which involved harvesting a bovine jugular venous valve and suturing it into a stent that could be placed into a surgical conduit to eliminate conduit regurgitation and improve stenosis. This therapy has the advantage of increasing the time between major cardiac operations in children with certain forms of congenital heart disease. The Medtronic Melody™ pulmonary valve is the product of this endeavour and has been implanted in well over 200 patients. I was fortunate to implant the first of these valves in North America with Dr. Lee Benson at the Hospital for Sick Children several years ago.

The challenge at present is to be able to offer percutaneous pulmonary valve therapy not only to the relatively few patients with conduits, but to the broader population of patients with congenital heart disease who have severe native pulmonary regurgitation, a common lesion. The challenge with the present technology is that

the largest bovine jugular venous valves are 22mm in diameter when fully expanded. Many native outflow tracts are significantly larger than this. There are a variety of strategies being considered to deal with this problem. For example, a “docking station” has been proposed: a larger “reducing” stent would be implanted first to decrease the diameter of a large native outflow tract. A smaller valve could then be implanted within. Only time will tell whether this will be successful. A second manufacturer has also produced a bioprosthetic valve that has been implanted in humans. Edwards Lifesciences has implanted the Harmony™ valve in the pulmonic position in 4 patients. This valve is a bovine pericardial bioprosthesis that at present comes in 2 sizes measuring 23 and 26 mm.

TRANSCATHETER AORTIC VALVE SOLUTIONS

Potentially the largest group of patients in need of a valvular heart disease solution is those with severe aortic stenosis. Aortic stenosis is generally a disease of the elderly. Concomitant coronary artery disease, pulmonary, renal, hepatic and cerebrovascular disease are also prevalent in this population. When expected surgical mortality exceeds 15%, both patients and surgeons are hesitant to accept and offer therapy respectively. The possibility of deploying a valve in a stent that could displace the patient’s native valve is an attractive alternative that has been hypothesized since the early 1980s. There are 2 potential routes to deliver an aortic valve on a stent. The antegrade approach, which involves a transeptal puncture and passage of the valve from the right atrium to the left atrium and through the left ventricle, has been abandoned. This route has been implicated in injury to the mitral valve and is technically demanding. A potentially less complicated approach is to deliver the valve via a retrograde approach, which involves passing the valve from the femoral artery around the aortic arch and into position.

At present there are 2 prostheses that have been implanted in humans; Edwards’ Sapien™ valve and Corevalve’s Revalving™ system are two different approaches to the challenge of aortic stenosis. The Sapien™ valve is mounted on a balloon, and deployed with a single balloon inflation during rapid pacing of the right ventricle to reduce cardiac output. The limitation of this valve at present is its large profile, a 23 mm valve and a 26 mm valve are available and require a 22 french and 26 french sheath to deliver respectively. In the elderly with aortic stenosis, it is a challenge to find patients with iliac arteries of between 8 and 9 mm required to deliver this valve. A novel alternative, using a minimally invasive surgical technique, involves the

performance of a left mini thoracotomy for delivery of the valve through the apex of a beating heart. Several hundred of these transapical procedures have been performed with quite reasonable results allowing for the infirmity of those patients who require this approach.

The Corevalve Revalving™ prosthesis is now approved in Europe with an 18 french system. The lower profile is achieved primarily through the use of a self-expanding stent platform as opposed to a balloon expandable system.

Over 20 other companies are working on the development of percutaneous aortic valve technologies. Key features of the next generation of technologies include the ability to reposition, remove, and exchange a new valve and the ability to deploy them through an arterial access that allows the majority of eligible patients to be treated. The ideal valve would have a low risk of infection, be easy to use, and not require anticoagulation. The future is bright and many new therapies are near human implantation.

TRANSCATHETER MITRAL VALVE SOLUTIONS

The mitral valve is by far the most difficult valve to treat percutaneously. While the aortic and pulmonary systems are fairly simple consisting of a relatively fixed annulus with attached leaflets, the mitral valve is of far greater complexity. For the mitral valve to function correctly, a synchronized effort on behalf of the mitral leaflets, annulus, chordae, papillary muscles and the walls of the left ventricle is required.

There are a number of strategies hypothesized to impact the regurgitant mitral valve. The most mature technology already in a randomized trial vs surgery is the Evalve MitraClip™. This technology is implanted using a specialized delivery catheter via a transeptal approach using primarily transesophageal echo for guidance. The clip is implanted on the A2 and P2 leaflets (mid portion of each mitral leaflet) for pathology ranging from functional, prolapse, flail and ischemic mitral insufficiency. The initial results are promising, demonstrating the ability to reduce mitral insufficiency from 4+ to <2+ in a majority of patients. The procedure is technically demanding but with experience, procedure times are falling as results improve.

The “leaflet” approach to mitral repair is but a single avenue of therapy. Several companies have utilized the relationship of the coronary sinus to the mitral valve annulus to advantage. By implanting a device which cinches the coronary sinus, it is possible to reduce the size of the annulus of the mitral valve. This mechanism for valve dysfunction occurs primarily in those patients with congestive heart failure and a dilated mitral valve

annulus. Early results are promising but whether or not sufficient MR reduction will occur with this type of therapy remains to be seen. A second obstacle is the variable relationship of the coronary sinus to the annulus and circumflex coronary artery.

Mitralign™ is a therapy designed to be delivered from a retrograde access. This technology employs a direct suture annuloplasty delivered from the inside of the ventricle. The first human procedure is expected soon.

Reshaping of the heart muscle into a more favorable geometric configuration for the mitral valve is the aim of the Myocor Coapsys system. This therapy, which has been used surgically, is being adapted as a percutaneous procedure. Access is obtained to the pericardial space, and two anchors, joined by a tether which runs through the ventricle, are implanted on the outer surface of the anterior and posterior surface of the left ventricle. The system aims to reduce the antero-posterior dimension of the ventricle to reapproximate mitral valve leaflets that no longer coapt because of annular dilation. Another innovative technology created by Ample Medical™ uses a novel technique to deliver a suture from the coronary sinus to an atrial septal occlusion device. Under TEE guidance, the AP diameter of the annulus can be reduced by tightening the suture and reapproximating mitral valve leaflets in a dilated annulus.

A NOTE OF CAUTION

The success of transcatheter structural heart disease therapies has been the ability to repair intracardiac defects that once required surgery in a minimally invasive fashion. In high-risk patients these therapies are readily accepted. In patients of low operative risk we must constantly re-examine and be critical of

transcatheter therapies with the availability of excellent surgical therapies with long-term track records. Although device closure of atrial septal defects is the standard of care, we have learned the importance of patient selection to avoid device erosion which almost uniformly leads to tamponade or important complications. Similarly, although the closure of perimembranous VSDs in children is almost uniformly successful, there is a small, but present, risk of heart block requiring permanent pacing. A pacemaker implant in a small child will require multiple revisions with attendant morbidity. A healthy respect for the complications of new and innovative therapy is critical for interventionalists. Careful evaluation, monitoring and reporting of outcomes of these new therapies are critical for further advancement and insight into ideal patient selection. A referral to a structural heart disease interventionalist should be a true consulting process where the relative indications for therapy are explored and the merits of conventional surgery vs a catheter intervention are discussed overtly with the patient.

CONCLUSION

The future of transcatheter therapies for structural heart disease is bright. There are a paucity of practitioners at present who are able to deliver these therapies in adult patients. As this subspecialty of cardiology evolves and matures, it will have a profound impact on the natural history of our patients and their families. It will only be through partnering with our surgical colleagues that we will optimize outcomes and improve decision-making. Collaboration with industry to modify, improve and develop future therapies is a critical part of the future. In 1996, when I graduated from medical school, many of the therapies I have described had not been conceived.

Eric Horlick, MDCM, FRCPC, is Director of the Structural Heart Disease Intervention Program and Assistant Professor of Medicine of the Peter Munk Cardiac Centre of Toronto General Hospital - University Health Network.