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The development of catheter techniques to treat native and acquired stenoses in congenital heart disease.

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Declaration

(a) this thesis has been composed by myself, (b) either the work is my own or if I have been a member of a research group I have made a substantial contribution to the work and my contribution is clearly indicated, (c) that the work has not been submitted for any other degree or professional qualification except as specified, and (d) that any included publications are my own work.

Signed Date 1/12/15

Abstract

Aim: To describe innovative uses of catheter based treatment in a variety of native and post surgical stenoses in children and young adults with congenital heart disease.

Background: Cardiac catheterization in man was first described 1929 and since then there has been a drive to develop endovascular techniques to investigate and treat both congenital and acquired heart disease. Many of the advances are being made in congenital heart disease.

Methods: A number of congenital cardiac stenotic lesions were studied including baffle obstruction after atrial switch for transposition of the great arteries, aortic stenosis in infants, coarctation of the aorta, peripheral pulmonary artery stenosis and superior vena caval obstruction. The use of angioplasty balloons, cutting balloons, stents and alternative catheter approaches were investigated for these lesions.

Results: Following atrial redirection surgery for transposition of the great arteries balloon angioplasty improved baffle haemodynamics. The technique of anterograde balloon dilation of the aortic valve was developed and had superior outcomes in terms of aortic insufficiency compared to a retrograde approach in neonates with severe aortic valve stenosis. In an animal model of peripheral pulmonary arterial stenosis, the application of cutting balloon angioplasty produced effective relief in a controlled

fashion. Balloon mounted stents were used in patients with native and post surgical coarctation of the aorta with significant relief of stenosis and relief of hypertension.

Finally, a group of patients with superior vena obstruction syndrome after surgical repair of partial anomalous pulmonary venous drainage had successful treatment using balloon mounted stents.

Conclusions: Catheter based treatment of congenital and post surgical vascular stenoses of the heart and great arteries using angioplasty balloons, cutting balloons and balloon mounted stents is safe and appears to be effective in the short and medium term. It may represent a useful alternative to surgery and will reduce the number of surgical procedures required over a lifetime. Future directions will include bio-absorbable stents and hybrid techniques involving surgery.

Lay summary

Congenital heart disease is the commonest birth abnormality with an incidence of 8 per 1000 live births. There is a wide spectrum of disease and in the majority of children the heart is the only organ affected. About half of these children will need treatment to correct or at least lessen the physical impact of their condition. In most cases, it is the structure of the heart which is affected and therefore treatment has to be in the form of an operation or in some children a series of operations which may extend over the individuals lifetime. In order to reduce the impact of surgery, which can be particularly significant in young babies, non surgical alternative treatments using cardiac catheter techniques are being developed. These techniques involve entry into the circulation usually via the artery and vein at the top of the leg followed by treating the defect in the heart or the great vessels close to the heart from the inside as opposed to treating from the outside which is what happens during surgery. The heart is reached by long fine plastic tubes called catheters supported by fine guide wires and the abnormality is addressed using different types of inflatable balloons and devices which are mounted at the ends of catheters or guide wires.

This thesis describes innovations in the use of catheter mounted balloons and particular devices called stents, which support vessel walls, to treat of a number of either native or post surgical obstructions within the heart or great vessels in children and adults affected by congenital heart disease. It also addresses how the application of this

technology can complement heart surgery, reduce the number of operations required over a lifetime and how it might develop in the future.

Table of contents

List of figures

List of tables

Publications arising from this work

MAGEE A.G., WAX D., NYKANEN D., BENSON L.N. (1997) Balloon dilatation of severe aortic stenosis in the neonate: comparison of antegrade and retrograde catheter approaches. *Journal of the American College of Cardiology*, 30, 1061-1066.

MAGEE A.G., WAX D., SAIKI Y., REBEKYA I., BENSON L.N. (1998) The application of "cutting" balloons in an animal model of branch pulmonary artery stenosis. *Canadian Journal of Cardiology,* 14, 1037-1041.

ZARTNER P., SCHNEIDER M.B.E., MAGEE A.G. (1999) Cutting balloon for treatment of severe peripheral pulmonary stenoses in an infant. *Heart,* 82, 108.

MAGEE A.G., BRZEZINSKA-RAJSZYS G., QURESHI S.A., ROSENTHAL E., ZUBRZYCKA M., KSIAZYK J., TYNAN M. (1999) Stent implantation for Aortic Coarctation and Recoarctation. *Heart,* 82, 600-606.

SCHNEIDER M.B.E., ZARTNER P., MAGEE A.G. (1999) Trans-septal approach in children after patch occlusion of atrial septal defect: first experience with the Cutting Balloon. *Catheter and Cardiovascular Interventions,* 48, 378-381.

MAGEE A.G., BLAUTH C., QURESHI S.A.(2001) Interventional and surgical management of aortic stenosis and coarctation. *The Annals of Thoracic Surgery,* 71, 713-714.

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Dedicated to my wife Annie and 3 children Kirsty, Rachel and Megan

What is not started will never get finished – Johann Wolfgang von Goethe.

Chapter 1

Introduction and rationale

Introduction

Historical perspective

Surgery. Performing procedures on the heart and great vessels has traditionally carried a degree of dread because of the vital nature of these structures. At the end of the 19th century, surgery on the heart was considered beyond the natural limits of medicine. The influential German surgeon Theodor Billroth, who pioneered abdominal surgery, stated in 1883 "A surgeon who tries to suture a heart wound deserves to lose the esteem of his colleagues." In 1896, the surgeon Stephen Paget writing in his textbook on surgery of the chest stated, “Surgery of the heart has probably reached the limit set by nature to all surgery; no new method and no new discovery can overcome the natural difficulties that attend a wound of the heart”. Nevertheless it was in that same year that the first successful operation on the heart was performed by Ludwig Rehn (1897) in Frankfurt when he repaired a stab wound to the right ventricle sustained by a wounded soldier and in doing so completely changed attitudes towards cardiac surgery.

The next landmark was the first surgical treatment of valvular heart disease which was performed in 1925 by the British surgeon Henry Sessions Souttar (1925) when he dilated a mitral valve using his finger inserted through an opening made in the left atrial appendage and in doing so saved the life of a young girl with severe rheumatic mitral stenosis. At the time, the procedure was heavily criticized by the medical community because of the perceived risk and was not repeated until 1948. Surgery for valvular heart disease only really began after the second world war the with the efforts of

surgeons such as Dwight Harken (1946) based on their experience as US Army surgeons. He had removed foreign bodies from in and around the hearts of over 100 soldiers who had been wounded in battle and his experience greatly increased to confidence of surgeons to undertake operations on the heart (Harken et al., 1948).

Although much less common than acquired heart disease, the really big breakthroughs in cardiac surgery were made in the treatment of congenital heart disease. Back in 1907, John Munro of Boston had proposed surgical treatment of the patent arterial duct through the sternum and was able to demonstrate technical feasibility by operating on the cadavers of 2 neonates, however he did not attempt the surgery in a living child. This fell to Robert Gross at Boston Children's Hospital who in 1938 reported the first successful ligation of a patent arterial duct between the descending aorta and left pulmonary artery via a left thoracotomy (Gross and Hubbard, 1939). It has since come to light than the first successful surgical ligation of a patent arterial duct had actually been performed earlier in the same year by Emil Karl Frey a surgeon in Dusseldorf (Kaemmerer et al., 2004). Frey had neglected to report his procedure probably on the assumption that it would be the first of many.

Only a few years later in 1944 saw the transformational Blalock-Taussig shunt carried out at Johns Hopkins Hospital to augment pulmonary blood flow in an infant with severe tetralogy of Fallot. This procedure was based on the collaboration between the surgeon Alfred Blalock and the cardiologist Helen Taussig (Blalock and Taussig, 1945).

It was only later recognized that much of the credit was due to the work of Vivien Thomas, Blalock's surgical assistant., who had developed the technique by operating on dogs in the laboratory. The classical Blalock-Taussig shunt involved division of the subclavian artery and anastomosis end to side onto the ipsilateral branch pulmonary artery in order to augment pulmonary blood flow (Fig. 1).

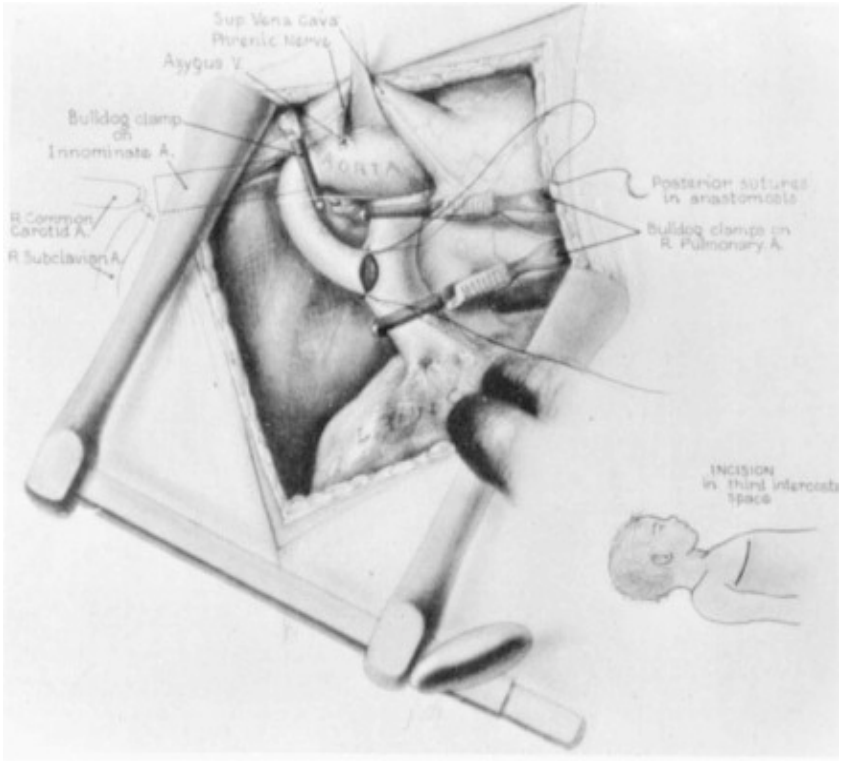


Figure 1. The classical Blalock-Taussig Shunt. Illustration from: *The surgical treatment of malformations of the heart in which there is pulmonary stenosis or pulmonary atresia. (1945) Journal of the American Medical Association,128,189-202.*

In the same year came the report of the first repair of coarctation of the aorta by Crafoord and Nyhlin (1945) in Sweden using the technique of resection with end to end anastomosis (Fig. 2). Crafoord had been safely cross clamping the aorta for short

periods while performing duct ligation and extended this application to coarctation repair by placing 2 clamps on either side of the obstruction before resecting the narrowed portion.

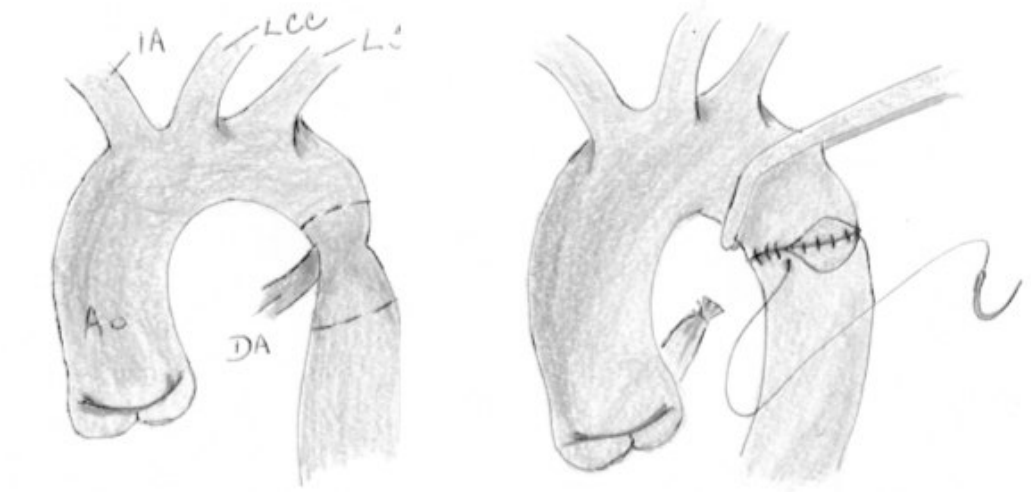


Figure 2. Resection and end to end anastomosis of coarctation of the aorta, as described by Crafoord and Nyhlin.

There remained the significant challenge of opening and operating on the beating heart itself. In 1950, Bigelow in Toronto reported the experimental use of surface hypothermia (Bigelow, Lindsay and Greenwood, 1950) and in 1952 John Lewis, at the University of Minnesota, used hypothermia to around 26^0 C to slow the heart sufficiently to allow repair of an atrial septal defect under direct vision in a 5 year old girl (Lewis and Taufic, 1953). To secure a bloodless field snares were placed around the inferior and superior vena cavae. Although this method did not gain popularity, it did stimulate progress and the further development of hypothermia and cardiopulmonary

bypass. Hypothermia itself provided only a small window of time in the order of 10 minutes to allow surgery on the heart before irreversible cerebral ischaemia would occur. While others such as Gibbon were working on membrane oxygenation (Gibbon, 1954), C. Walt Lillehei, who was part of Lewis's team at Minnesota, developed the technique of cross circulation where a donor, who was usually a parent, would provide oxygenated arterial blood to the infant being operated on via a pump (Fig. 3). The first patient was a 13 month old with a ventricular septal defect and although the operation was a success, the child died 11 days later with suspected pneumonia. During the next year, 44 open heart procedures were performed in this manner with 32 survivors (Lillehei et al., 1955) Lillehei himself said that it was the only operation with a potentially 200% mortality however only one donor suffered a significant complication, a stroke probably caused by air embolism.

Once the problem of cardiopulmonary bypass was resolved progress in cardiac surgery was rapid with the first coronary artery bypass graft performed in New York in 1960 (Konstantinov, 2000), the first mitral valve replacements in the same year (Braunwald, Cooper and Morrow, 1960) and of course the first heart transplant in 1967 (South African Medical Journal, 1967).

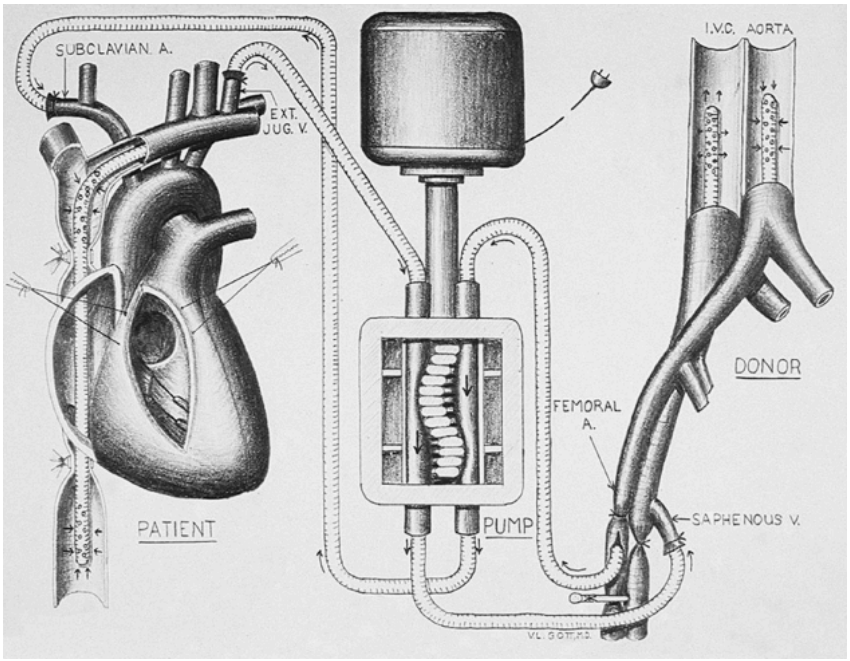


Figure 3. Schematic illustration of the first case of controlled cross circulation, 1954. Original drawing made by the intern on C. Walton Lillehei's service, GOTT V.L. (1994) *Section III: Cardiopulmonary bypass and myocardial protection. IN: STEPHENSON L.W., RUGGERO R., (Eds). Heart surgery classics, Boston: Adams Publishing Group, Ltd,130.*

Catheterization. As well as looking at the problem of the heart from the outside, others were finding ways to access the heart via the circulation for diagnostic purposes and potentially treatment. The first cardiac catheterization was credited to Stephen Hales (Lewis, 1994), an English clergyman who in 1733 cannulated the aorta of a horse using an instrument made of brass pipes, a glass tube and the trachea of a goose enabling him to directly measure systemic arterial pressure. In 1929, a German surgical trainee named Werner Forssman inserted a ureteric catheter into his own antecubital vein, advanced it under fluroscopy and then walked along a corridor and up two flights of stairs before

having a chest X-ray (Fig. 4) confirming the tip of the catheter to be in the right atrium (Forssmann, 1929). Once he published his findings, he was strongly condemned by his university for self experimentation and went into urology instead of cardiology but eventually achieved recognition when he jointly won the Nobel prize for Medicine in 1956.

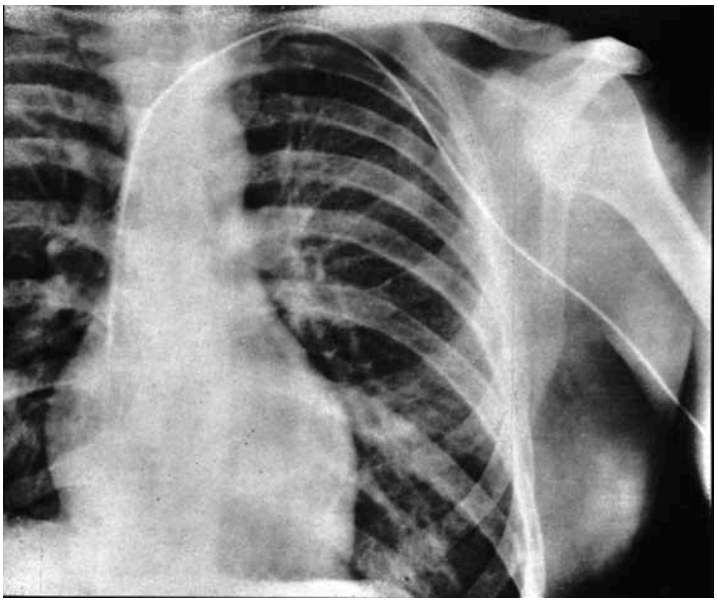


Figure 4. The Chest X-Ray of Dr Werner Forssman showing the catheter advanced from the left ante-cubital vein and lying with the tip within the right atrium.

In the 1940s, Andre Cournand and Dickinson Richards developed cardiac catheterization and used it to investigate right heart physiology. They subsequently shared the Nobel prize with Forssman in 1956. Retrograde left heart catheterization was first described by Zimmerman, Scott and Becker (1950) and selective coronary angiography was reported by Mason Sones (1959) after he accidentally selectively

entered the right coronary artery during a power injection of contrast into the aortic root in a 26 year old with rheumatic heart disease.

A non-surgical or minimally invasive approach to the treatment as well as diagnosis of many conditions is always an attractive option as there are obvious benefits in terms of a reduction in the amount of discomfort, the time spent in hospital, the risk of infection and the size of a surgical scar. This is all providing the approach can be as safe and effective as surgery. The case for using catheter based techniques for treatment as well as diagnosis in children is perhaps even more attractive as the prospect of surgery on the heart and great vessels can seem daunting to families. In addition for a sick child a catheter based treatment as either palliation or definitive treatment might be a safer option. Over the past 5 decades, surgery for congenital heart disease has improved markedly in terms of efficacy and safety however in the earlier decades the high risk of surgery was probably an added stimulus for the development of non surgical techniques in some centres. One further incentive to non surgical treatment is the fact that congenital heart disease is often a life long condition with the need for multiple re-interventions. It would be an advantage if some of these can be preformed in a manner that reduces the tissue trauma and catabolic load to the individual which in turn would mean a shorter recovery time. The first report of catheter based treatment of congenital heart disease was by Rubio-Alvarez and his colleagues in Mexico City in 1953 who described the use of a cutting wire mounted at the end of a ureteric catheter introduced via the femoral vein to relieve pulmonary stenosis in 3 patients (Rubio-Alvarez, Limon

and Soni, 1953). Cardiac surgery was still in its infancy, this was in the era before cardiopulmonary bypass and the only surgical treatment available for pulmonary valve stenosis was closed pulmonary valvotomy first described by Thomas Holmes Sellor (1948) and then independently by Lord Brock. In this procedure, which has become known as the Brock procedure (Fig. 5), the heart was exposed via a sternotomy and the main pulmonary artery entered using a trocar introduced through a controlling suture. A valvulotome (instrument for cutting a valve) was then inserted into the pulmonary artery and 2 valvulotomies were made in the region of the anterior 2 commissures of the valve in order to avoid the coronary arteries lying posteriorly.

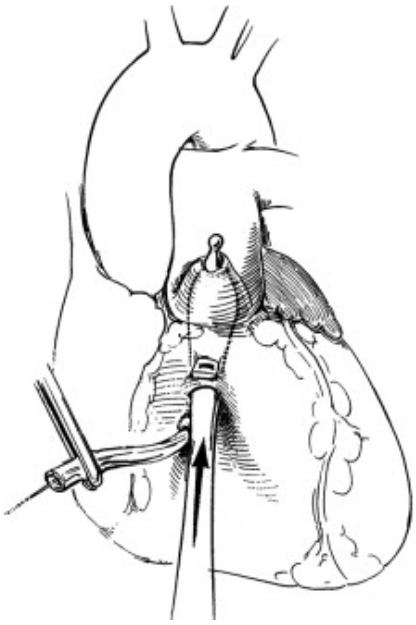


Figure 5. Diagram of transventricular pulmonary valvotomy developed by Sellors and Brock.

The technique developed by Rubio-Alvarez was an attempt to replicate this via an endovascular approach. The tip of a ureteric catheter was pre-shaped into a bend and

the wire kept straight allowing it to ‘saw’ through the fused commissures of the valve (Fig. 6). The procedure was first performed in a 10 month old child with severe pulmonary valve stenosis and produced a reduction in the invasive peak systolic pressure gradient across the valve from 72-59 mmHg. Although successful, the technique was challenging and hazardous and was only used in a few patients. Unsurprisingly, it did not gain acceptance and was not attempted by other operators.

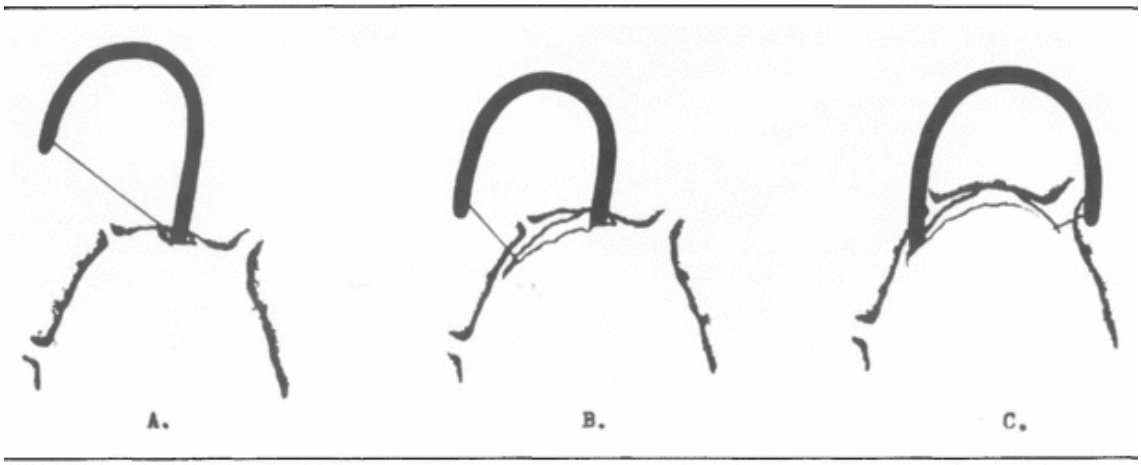


Figure 6. Illustration of the first successful transcatheter valvotomy by Rubio-Alvarez (*from Arch. Institut. Cardiol. Mexico 1953*).

At around the same time, guidewires were being developed and in 1953 Sven-Ivar Seldinger, a radiologist, described a unique method of establishing vascular access using a guidewire (Fig. 7) making interventional radiology and subsequently interventional cardiology a realistic possibility (Seldinger, 1953). Continued development of materials science especially of plastics and their formation into catheters by extrusion techniques made a huge contribution to progress. The concept of a sheath, which is a smaller indwelling catheter in the vessel often with a sidearm to

allow flushing, allowing easy exchanges of catheters and guidewires greatly contributed to the ease of which endovascular techniques could be performed.

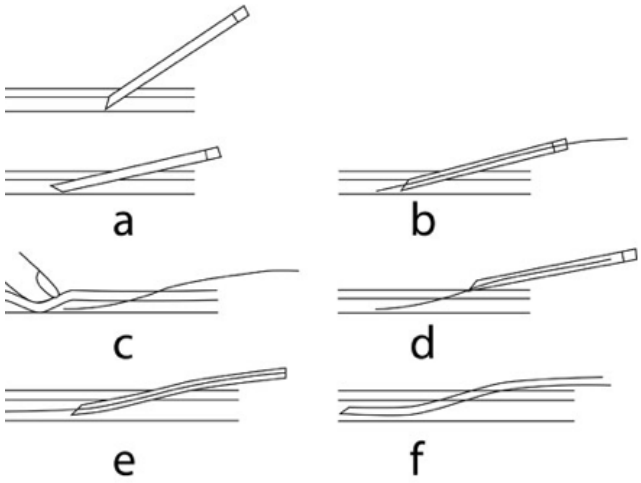


Figure 7. Reproduction of the original illustration from *SELDINGER S.I. (1953) Catheter Replacement of the Needle in Percutaneous Arteriography: A new technique. Acta Radiologica, 39(5), 368-376.*

No further reported attempts were made to treat congenital heart disease using non surgical approaches until the pioneering work by the cardiologist William Rashkind at Johns Hopkins Hospital, Baltimore in 1965 (Rashkind and Miller, 1966). By this stage cardiopulmonary bypass had been developed and one major success story in congenital heart disease was the surgical treatment of transposition of the great arteries (Fig. 8). In this condition, the pulmonary artery and aorta are wrongly connected to the two ventricles meaning that de-oxygenated blood is pumped back into the systemic circulation. Prior to 1959, the prognosis for this condition was so poor that few babies survived until the end of the first year of life.

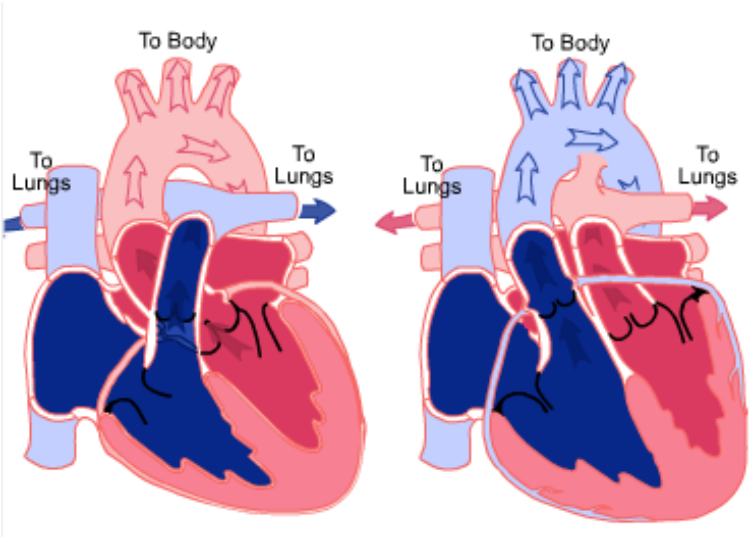


Figure 8. Diagram of the normal heart and a heart with transposition of the great arteries.

Then in 1959, Senning in Sweden described the atrial switch procedure which allowed redirection of the systemic and pulmonary venous inflow to the heart using flaps constructed from the right atrial wall and interatrial septum (Senning, 1959). Successful anatomical correction did not come for many years because of the technical difficulties of transferring the coronary arteries. Senning's technique meant that 2 circulations in parallel were converted into 2 in series. This was followed by the technically less demanding Mustard procedure in 1963 developed by William Mustard, who originally trained as an orthopaedic surgeon and was working at the Hospital for Sick Children in Toronto (Mustard et al., 1964). This procedure used patches of either pericardium or synthetic material to baffle the venous inflows and in doing so redirect the blood. However, these atrial switch procedures could not be performed at birth and therefore palliation to allow some mixing of the circulations was necessary to buy time unless an atrial or ventricular septal communication already existed. This palliation took

the form of the Blalock-Hanlon septectomy (Fig. 9), first described in 1950, where the surgeon excised the posterior aspect of the atrial septum via a right lateral thoracotomy so allowing blood to mix at atrial level and improve tissue oxygen delivery (Blalock and Hanlon, 1950).

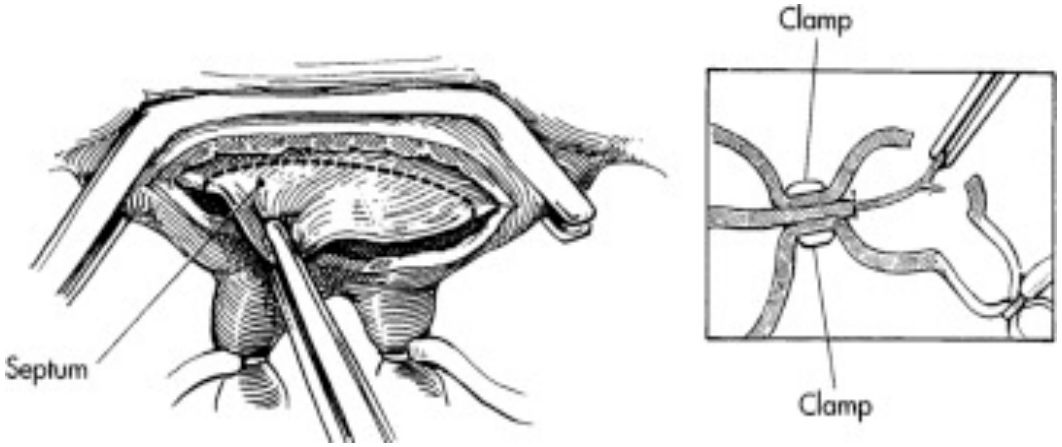


Figure 9. Illustration of Blalock-Hanlon sepectomy with specifically designed side biting clamp used to isolate part of right atrium allowing the surgeon to excise atrial septum.

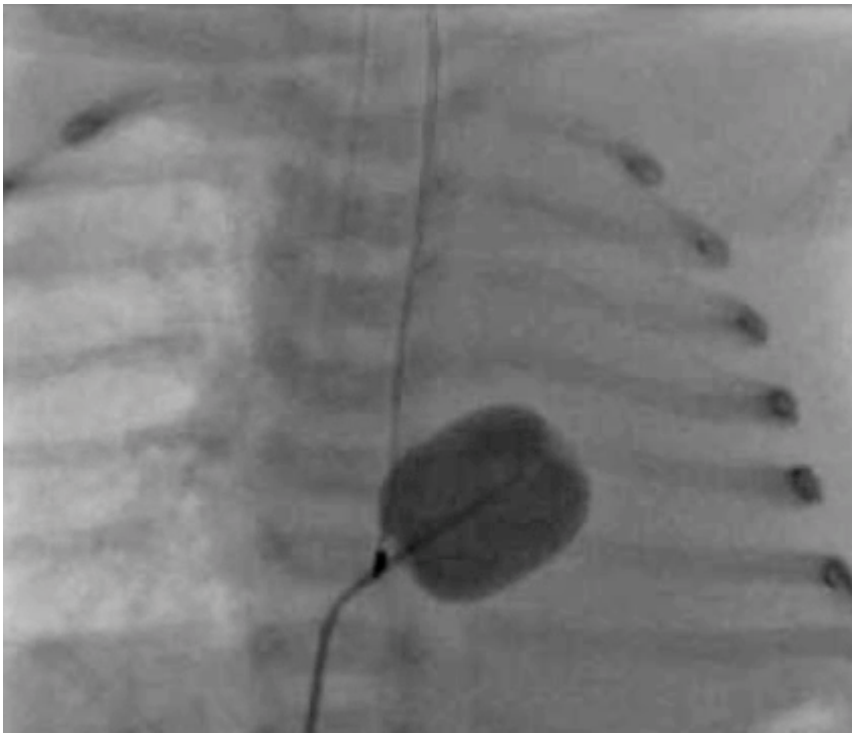


Figure 10. Still image of balloon atrial septostomy under fluoroscopic control in a neonate with transposition of the great arteries. The balloon filled with dilute contrast material is being withdrawn from the left to the right atrium in order to tear open the septum.

What Rashkind did was to replace the Blalock Hanlon procedure with an endovascular technique which could be performed via either the femoral or umbilical veins in newborn babies with transposition. This was a much less traumatic procedure than surgical septectomy especially in those sick neonates with profound desaturation because of a very restrictive interatrial communication. A balloon tipped catheter was advanced from the inferior vena cava across the patent foramen ovale into the left atrium, the balloon was then filled with dilute contrast agent and then abruptly pulled back under fluoroscopy X-ray guidance to tear open the fossa ovalis so creating mixing of the circulations (Fig. 10). This was a truly revolutionary technique and represented

the beginning of catheter based treatment for congenital heart disease inspiring many others to think along these lines.

"...The initial response to this report varied between admiration and horror but, in either case, the procedure stirred the imagination of the "invasive" cardiologists throughout the entire cardiology world and set the stage for all future intracardiac interventional procedures – the true beginning of pediatric and adult interventional cardiology." (Charles E. Mullins, 1998)

The next attempt to use a catheter in the treatment of congenital heart disease was by Semb in Sweden (Semb et al.,1979). Using the same concept as Rashkind, he used a Berman Angiographic Catheter with the balloon filled with carbon dioxide to relieve pulmonary stenosis by rapidly withdrawing it across the valve and in doing so tearing fused valve commissures. This was a particularly interesting neonate with the haemodynamically adverse combination of severe pulmonary valvar stenosis and severe tricuspid insufficiency. The baby was thought to be too unwell to undergo cardiac surgery and instead underwent this dynamic balloon dilation of the pulmonary valve. The result was excellent with effective relief of stenosis and only mild residual tricuspid regurgitation when the pressure load was relieved. However, similarly to the experience of Rubio-Avarez, this technique was not adopted for general use because of the unpredictability of the outcome and the fact that the valve leaflets could be completely avulsed producing free regurgitation.

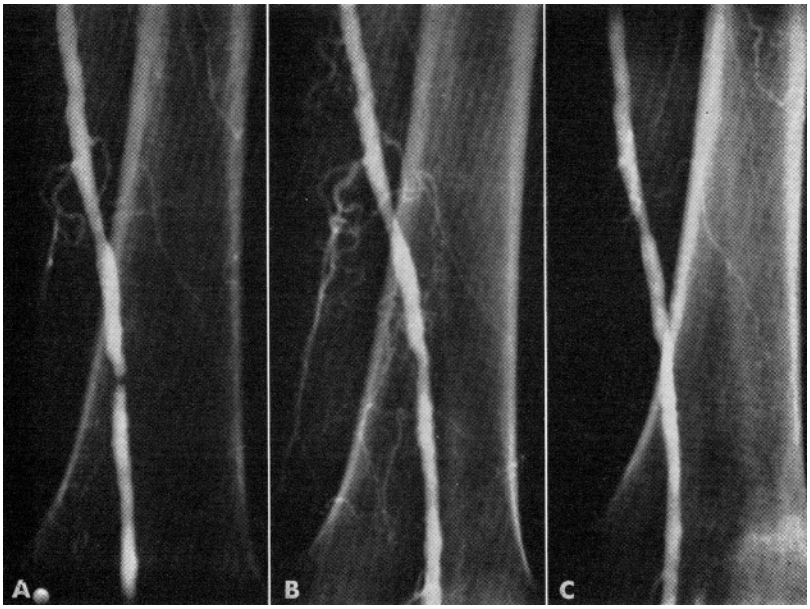


Figure 11. Angiograms before, immediately after and 6 months after angioplasty of the popliteal artery in an 82 year old patient with gangrene taken by Charles Dotter.

To understand the next step forward in catheter based treatment it is necessary to go back in time to 1963 when a radiologist named Charles Dotter accidentally recanalized a blocked iliac artery during an attempt to perform an aortogram in a patient with renal artery stenosis. Based on this experience he conceived the idea of sequential dilators for arterial stenoses. Their first successful use was in an 82 year old woman suffering from gangrene due to popliteal arterial stenosis (Fig. 11) who had refused amputation (Dotter and Judkins, 1964). It was Andreas Gruentzig, working in Zurich, who took this technology further by using balloons instead of dilators. The balloons were mounted at the end of double lumen catheters with one lumen for the supporting guide-wire and the other to allow inflation. The concept was different from that of Rashkind as the balloons were held in a static position during inflation and deflation instead of being abruptly

withdrawn to tear a structure. A number of different materials were tried for the balloon before polyvinyl chloride was chosen for it's non elastic properties. Greuntzig went on to use this system to dilate stenotic lesions in experimental animals and humans with peripheral vascular disease. In September 1977, he performed the first coronary angioplasty in a 37 year old man in Switzerland (Greuntzig, 1978) which heralded the era of coronary intervention for ischaemic heart disease.

Following on from the experience in peripheral and coronary arteries, it was only a matter of time before static balloon angioplasty was applied to congenital lesions. In 1982 Dr Jean Kan, also at Johns Hopkins, performed successful balloon dilation of the pulmonary valve in a 6 year old girl with pulmonary stenosis (Kan et al., 1982). Since then, balloon angioplasty (Fig. 12) became the treatment of choice for valvar pulmonary stenosis (Stanger at al., 1990) and was soon applied to the aortic valve in children (Lababidi, Wu and Walls, 1984).

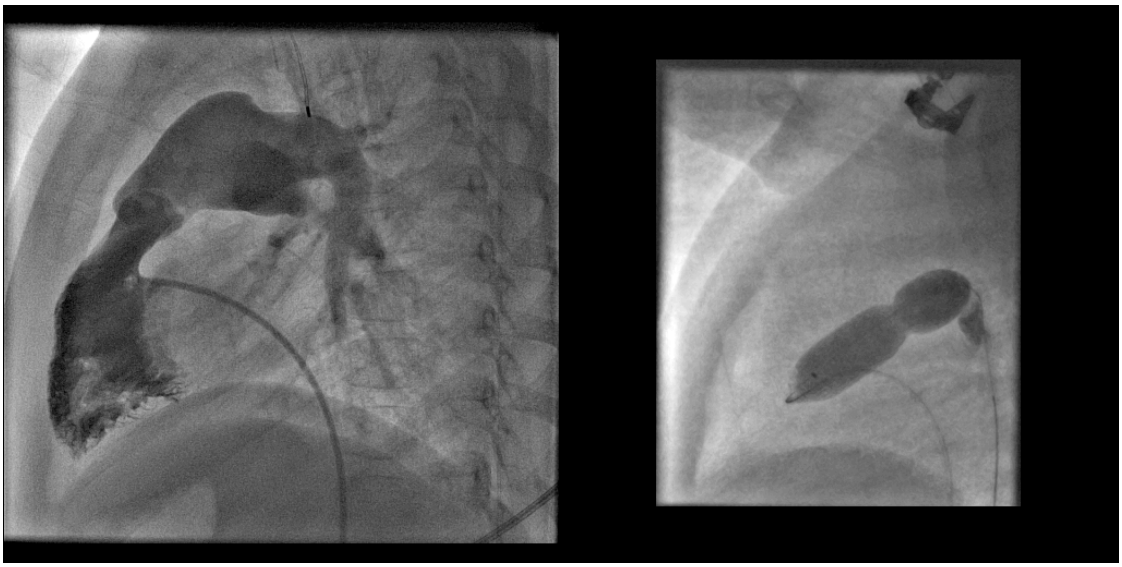


Figure 12. Lateral angiogram of balloon dilation of the pulmonary valve. The left hand panel shows a doming pulmonary valve with post stenotic dilatation of the pulmonary arteries, the right hand panel shows the balloon being inflated across the valve.

The mechanism of success of angioplasty must involve partial tearing of vascular structures either of valve commissures or vessel stenoses and as such it could be considered to be relatively uncontrolled when compared to surgery where there is the advantage of direct inspection. Potential complications of angioplasty could include complete vessel tears, false or true aneurysm formation and avulsion of valve leaflets as well as damage to sites of vascular access. In addition, elastic, kinked and non-discrete lesions may not respond as the improvement in diameter will not be maintained once the balloon is deflated. A vessel which is narrow over some distance might not be expected to respond favourably to angioplasty and overinflation of a balloon in this situation could lead to a longitudinal partial or complete vessel tears. In the situation of valvar stenosis, the tearing has to be along the congenitally fused valve commissures to

relieve stenosis without tearing through or avulsing the leaflets and thus causing significant regurgitation (Hawkins et al., 1995). If this were to occur, there is no way for the operator to acutely undo the damage which must be repaired surgically with the timing of surgical intervention depending on severity. Severe regurgitation of the aortic, mitral or tricuspid valve is poorly tolerated especially when the onset is acute.

In order to overcome recoil after angioplasty, some means has to be found to maintain support of the vessel walls using a device which is safe to use in prolonged contact with the bloodstream. Supporting a dilated vessel may also effectively treat long segment stenosis and reduce the risks of tearing or aneurysm formation. It could also be used to treat aneurysms by strengthening the wall so preventing further expansion. Again it was Dotter (1969) who came up with the original concept of supporting vessels when he published a technique to place endovascular spiral stents and proposed the use of such structures to treat aneurysms. Then in the early 1980s, Maass working at the surgical clinic of the University of Zurich, developed a double helix spiral prosthesis from self expanding spring coils which he used in animal experiments and eventually in 2 patients with dissecting aortic aneurysms-the first time that vascular stents were used in humans (Maass et al., 1984). These spring coils worked by decreasing in diameter when torque was applied and expanding to their original diameter when it was released. Incorporation of the stent into the vessel wall, so called endothelialisation, took around 3 weeks in animal experiments. Balloon expandable stents were invented by Julio Palmaz, a Argentinian vascular radiologist, who initially reported their use in the aortae

and peripheral arteries of dogs (Palmaz et al., 1985). These systems consisted of stainless steel grafts mounted onto and expanded by angioplasty balloons and were extensively used to treat peripheral vascular disease.

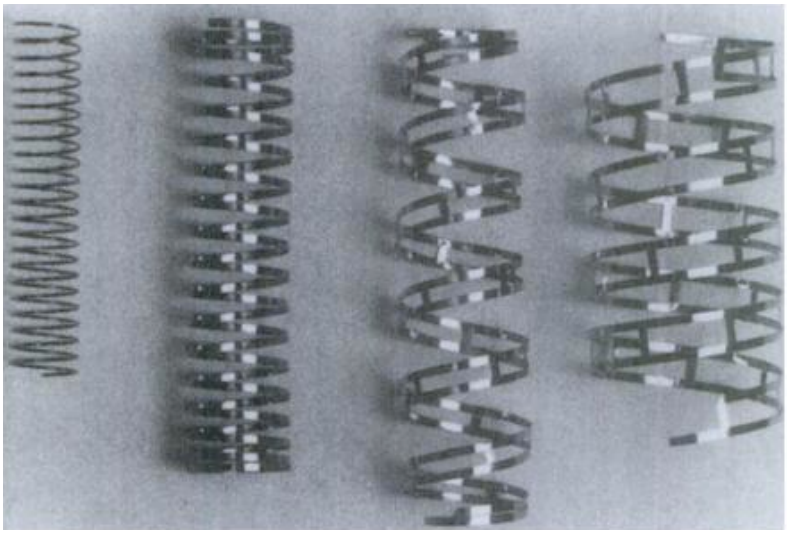


Figure 13. Spiral spring stents, single and double helex developed by Maass for endovascular implantation.

With increasing confidence in peripheral vascular stenting, the technique was then applied to the coronary arteries. The first coronary stent was implanted by Puel in Toulouse and shortly afterwards by Ulrich Sigwart in Lausanne in 1986 using self expanding Medinvent stents which became known as Wallstents.

They subsequently reporting their findings of the use of these stents to prevent vessel reocclusion after coronary artery angioplasty (Sigwart et al.,1987). A little later Palmaz teamed up with the cardiologist Richard Schatz and developed the balloon expandable Palmaz-Schatz stent for coronary use (Schatz et al., 1987).

In general, self expanding stents such as the Wallstent and stent grafts have less radial strength and are more suited to excluding aneurysms rather than dilating and supporting stenotic vessels. In children and adults with congenital heart disease, the main aim is to keep vessels open rather than to exclude aneurysms. After animal experiments to investigate the feasibility of Palmaz stent implantation in pulmonary arteries and systemic veins, the first balloon expandable stents were implanted in a child with stenosis of the branch pulmonary arteries in 1989 by Mullins using Palmaz stents originally designed for peripheral vascular disease in the iliac arteries (O'Laughlin et al., 1991). Since then stents have found increasing applications in congenital heart disease.

The derivation of the word stent provides a very good example of how words enter the language. It comes from Charles Thomas Stent, an English dentist who developed a material derived from the natural latex gutta-percha suitable for making dental impressions. This material went into commercial production under the name 'Stents' and was then used by Esser, a Dutch plastic surgeon, to stabilise skin grafts for soldiers who had sustained facial war wounds during the first World War. Eventually the term stent came to describe 'any kind of non-biological support used to give shape or form to biological tissue'.

One obvious major limitation of balloon mounted stents is that they have a finite expanded diameter and therefore will eventually cause relative stenosis in the growing

child unless they can self absorb or be disrupted by further inflation, as well as this stents quickly become incorporated into the vessel wall and would be very difficult to remove surgically without destroying the vessel. Therefore care must be taken when implanting stents in smaller children unless there is no realistic alternative or in an emergency situation.

For smaller branching vessels, where conventional angioplasty is not beneficial stent implantation may not affect outcome. For example in the lung periphery, the branching nature of the vasculature will mean that stents cross and possibly occlude side branches depending on the angle of incidence. In addition, the type of peripheral pulmonary stenosis for example that found in syndromes such as Williams (Geggel, Gauvreau and Lock, 2001) and Alagilles may not to respond the angioplasty with or without the support of stenting because of the significant thickness of the vessel wall.

Stenosed pulmonary veins, either due to native disease or following repair of total anomalous pulmonary venous drainage, are a particular problem because of the tendency to recur after surgery. They can be a cause of severe pulmonary hypertension and failure to thrive in infants. Attempted enlargement of these veins using stent implantation has been disappointing because of neo-intimal proliferation (Balasubramanian et al., 2012). Another solution in such patients and in peripheral pulmonary arterial stenosis might be cutting balloon angioplasty (Barath et al., 1991) which has been employed to treat stenotic arteriovenous fistulae used in patients with

chronic renal failure for dialysis and also to treat resistant coronary stenoses. By making controlled tears in the vessel wall it might be possible to relieve resistant stenoses without using excessive force.

From the above historical perspective, it is clear that while surgeons and cardiologists have different approaches the benefits intended for their patients are the same. Indeed both groups are faced with similar potential complications. Any procedure on the heart or great arteries can cause unrepairable damage to these structures as well as to vital organs such as the brain principally by the interruption of oxygenation. Therefore a thorough understanding of the morphology of lesions is necessary to define potential risks as well as the means to minimize them. It is essential that surgeons and cardiologists work together to provide the best long term outcomes with the lowest morbidity especially when patients have complex congenital lesions with little chance of a 'cure' after a single procedure.

Linked to the assessment of risks and benefits in applying new treatments such as those outlined above is the difficulty in applying evidence based practice. It is often not possible to compare treatment and control groups because to not offer treatment could be unethical if the new treatment was clearly advantageous. Randomised double blind controlled trials are not possible and in fact there have been very few randomised studies in the treatment of congenital heart disease. It could be

argued that some novel treatments could never have become established in the current regulatory environment because of the excess mortality and morbidity during the learning period. Therefore advances have been made incrementally by comparing outcomes of new treatments in terms of efficacy and complications with the natural history or results of previous treatments.

Rationale for thesis

Aims of each chapter

Chapter 1: To provide the historical background of catheter based techniques to treat stenoses of the heart and great vessels in children and adults with congenital heart disease.

Chapter 2: To determine the effects of balloon angioplasty to treat acquired baffle obstruction after the Mustard Procedure for Transposition of the Great Arteries. My contribution was to collect and analyze the data.

Chapter 3: To determine the gross anatomy, histology, efficacy and safety of cutting blade balloon angioplasty in an experimental animal model of pulmonary artery stenosis. My contribution was study design, surgical creation of the branch pulmonary artery stenosis (together with a Fellow in cardiothoracic surgery), cardiac catheterization of the animals, collection of data and analysis.

Chapter 4: To compare the results of balloon angioplasty of severe aortic stenosis in a cohort of infants using an antegrade catheter approach to a historical cohort in whom a retrograde approach was used with particular emphasis on technique. My contribution was study design, assisting with approximately one half of the antegrade catheter procedures, collection of data and analysis.

Chapter 5: To describe the early experience of balloon mounted stent implantation in both native and postoperative coarctation of the aorta in older children and adults. My contribution was study design, assisting with 4 of the procedures, formatting of 3D CT reconstruction (with medical physicist colleague), collection of data and analysis.

Chapter 6: To describe the use of balloon mounted stents in the treatment of acquired superior vena caval stenosis after surgical repair of partial anomalous pulmonary venous drainage. My contribution was to perform the procedures, design the study, follow up the patients and analyze the data.

Chapter 7: To bring the techniques described in chapters 2 to 6 up to date and describe the future direction of catheter based techniques in the treatment of native and acquired stenosis in congenital heart disease.

Timing of thesis

Original approval for this thesis was granted in 1993 meaning a considerable delay before submission. The research studies are mostly historical being performed between 1995 and 2013 however I have endeavored to link them together and bring them up date them using a search of the literature.

Chapter 2

The management of systemic venous obstruction after the Mustard Procedure.

Introduction

Since its introduction in 1963 (Mustard et al., 1964), the Mustard procedure to redirect pulmonary and systemic venous return in transposition of the great arteries (Fig. 14) had become the preferred operation in most congenital cardiac surgical centres until the introduction of the arterial switch in the early 1980s. Although revolutionary in its time saving many lives the Mustard procedure carried a number of potential problems. These included failure of the systemic right ventricle, sinus node disease and atrial arrhythmias together with obstruction of the venous pathways. In fact obstruction to systemic or pulmonary venous return had become one of the major complications following the Mustard operation for transposition of the great arteries, with a reported incidence of between 13-18% (Trusler et al., 1987).

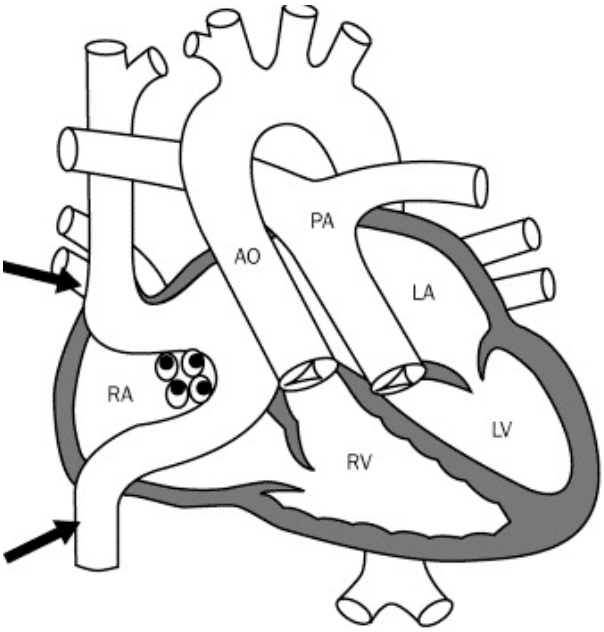


Figure 14. Diagram of the Mustard procedure for transposition of the great arteries, arrows indicate the superior and inferior systemic venous pathways (baffles).

In general, re-operation was recommended for cases of pulmonary, inferior systemic or symptomatic superior systemic venous pathway obstruction and involved replacement of the baffle material with Dacron® (polyethylene terephthalate) or Goretex® (expanded polytetrafluoroethylene). Operative revision is often hazardous in congenital heart disease because of the presence of adhesions and possibly impaired myocardial performance and appears to be especially hazardous following the Mustard procedure (Trusler et al., 1987; Wells and Blackstone, 2000) possibly because of a systemic right ventricle. It was particularly hazardous when some form of synthetic material has previously been used to form the baffle. Fortunately a less invasive percutaneous approach to these lesions may be feasible. In 1983 Waldman described a case of transposition of the great arteries following Mustard atrial redirection with mid cavity systemic venous atrium obstruction, balloon dilatation was performed twice with initial success but rapid recurrence of the obstruction (Waldman, Waldman and Jones, 1983). In 1984, Lock reported attempted balloon dilation in 4 children with systemic atrial baffle obstruction (Lock et al., 1984). Three out of the 4 cases were successful and two were followed for 6-7 months with persistence of relief. A larger series was provided by the Valvuloplasty and Congenital anomalies (VACA) Registry in 1990 (Tynan et al., 1990) with 13 out of 16 superior limb and 2 of 6 inferior limb obstructions successfully treated in the short term. The criteria for judging success and failure and longer term follow up data were not presented.

Venous pathway obstruction may present clinically or come to light as an unexpected finding during routine follow-up. It may also have implications for future endovascular pacing. Although lesions may be identified by precordial ultrasound, the addition of transoesophageal imaging provides consistent definition of the site and morphology of obstruction and is particularly useful when precordial ultrasound windows are restricted for example in older children and adolescents (Kaulitz et al., 1990).

Aims of the study

(1) to identify the substrate causing venous pathway obstruction following the Mustard procedure for transposition of the great arteries using a combination of angiography and transoesophageal ultrasound.

(2) to attempt balloon angioplasty of lesions in which morphology appeared favourable.

(3) when possible to follow-up the results of treatment.

Patients and methods

Patients: A search of the database revealed a total of 74 patients with transposition of the great arteries undergoing the Mustard procedure at the Royal Hospital for Sick Children Edinburgh, a total of 20 (15 male) were identified with systemic venous pathway obstruction on clinical grounds or on routine clinical and cardiac catheter follow-up. The original baffle was created from autologous or xenograft pericardium in all but one patient in whom Goretex® was used. Five patients presented with definite

clinical signs of obstruction and for the remainder the diagnosis was made at elective follow-up cardiac catheterization which at the time was part of routine follow-up.

Catheterization: Cardiac catheterization was performed under general anaesthesia in all patients with percutaneous access via a femoral vein. The criteria for treatment of pathway obstruction (Fig.15) were firstly a pullback catheter gradient of ≥ 5 mmHg.

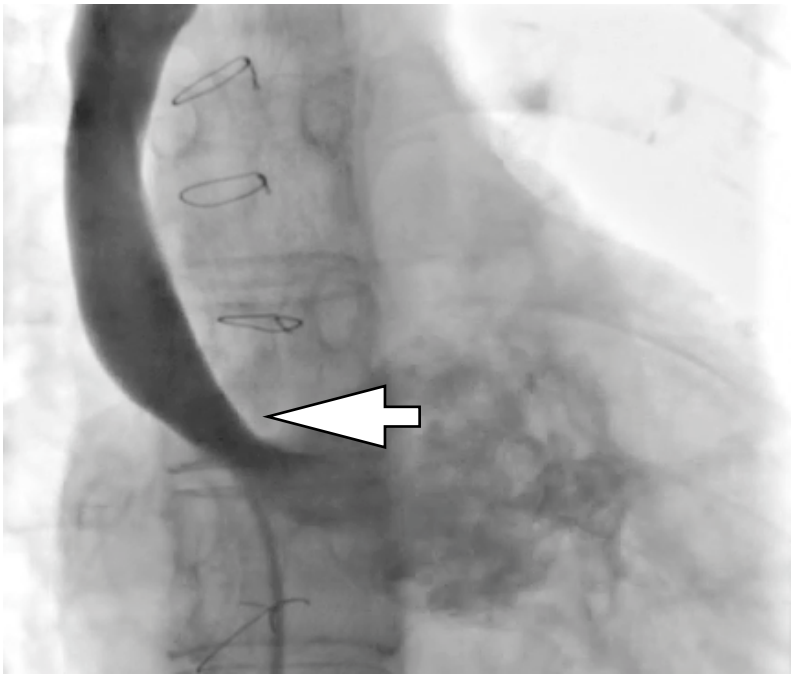


Figure 15. Angiogram of narrow superior systemic venous pathway following the Mustard procedure. Arrow points to site of original atrial septum.

in the absence of azygous run-off or the angiographic appearance of severe obstruction when azygous run-off or baffle leak was present. A decision to elect for catheter or surgical intervention was made on the basis of whether or not it was possible to pass a guide wire or if the morphology appeared favourable meaning that the obstruction was

relatively discrete. One child was found to have severe obstruction of both limbs together with very poor right ventricular function. It was felt that no treatment could be offered and he died shortly afterwards.

Transoesophageal ultrasound (TOE): was performed using a dedicated Toshiba biplane or a prototype Odelft single plane probe connected to a Toshiba SSH140A system. Evaluation of the systemic and pulmonary venous pathways was made according to previously described techniques (Kaulitz et al., 1990). Colour flow and pulse wave Doppler were used to detect obstructions and any baffle leaks. In the cases which were treated by balloon angioplasty, examinations were repeated after intervention and findings correlated with the angiographic appearance.

Balloon angioplasty: was performed using a series of Meditech balloons (Boston Scientific, MA, USA) with expanded diameters ranging between 10 and 20 mm. The ratio between balloon size chosen and estimated pathway diameter was 0.7-1.3:1. Inflation was by hand using dilute contrast (1 part contrast to 2 parts saline) with an inflation/deflation cycle of 10 seconds. Inflations were performed until balloon waisting disappeared or up until a maximum of 6 inflation/deflation cycles with persistence of waisting. Pullback mean pressure gradients were made with held respiration before and after intervention and off-line measurement measurements of minimum and maximum pathway diameter were made from the anteroposterior and lateral projections. The catheter diameter was used to correct for magnification. In 2 patients, the narrowest

point was only seen on transoesophageal echocardiogram because of overlapping of the dilated pathway on angiography in spite of the X-ray angulation employed.

Statistical analysis

Results are presented using medians and ranges or means with 1 standard deviation as appropriate and the Student t-test was used to compare groups of continuous data.

Results

A total of 13 children (10 male) underwent balloon dilation of systemic venous pathways following the Mustard procedure for transposition of the great arteries including one child who had previous Goretex® baffle revision. Of the patients who had baffle creation using pericardium, the morphology of the obstruction was discrete in 11 patients and tubular in one. There were 4 attempted inferior baffle limb dilations and 10 attempted superior baffle limb dilations as one patient had angioplasty to each limb on separate occasions. The median age at angioplasty was 4.8 years (range 1.3-12 years), median weight was 18.1 kg (range 9.4-36.7 kg) and median time following surgery was 4.3 years (range 0.6-11.3 years). A total of 11 dilations in 10 patients were judged to be successful at the time of the procedure with loss of balloon waisting, improved filling of the systemic venous atrium, reduction in pressure gradients and reduction in azygous and/or hemi-azygous run-off in those with SVC obstruction. Where small baffle leaks were identified (n=3) there appeared to be subjectively less shunting on colour-flow mapping than before the procedure.

Balloon dilation reduced the mean pull back pressure gradient (Fig. 16) across obstructions from a mean of 10.3 mmHg (SD 5.4, range 4-20) to mean of 4 mm Hg (SD 1.8, range 0-8, p=0.0001). The minimum diameter of the pathway (Fig. 3) averaged over 2 orthogonal planes increased from a mean of 5.1 mm (SD 1.6, range 3-8) to mean of 10 mm (SD 3.3, range 4.7-14.4, p<0.0001). The only complication encountered was a localised dissection identified by TOE alone during an otherwise successful procedure. A further study one month later showed that the neo-intimal flap had adhered to the baffle wall. Of the 10 successful procedures, 5 were followed-up with repeat cardiac catheterisation and TOE at a median interval of 1.6 years (range 1-3.2 years) with persistence of benefit.

Surgery: A total of 9 patients had surgery including 3 patients who had unsuccessful balloon dilation procedures. In one case with severe superior limb obstruction, the left superior vena cava was anastomosed to the left atrial appendage at the time of surgery. In a further patient with severe obstruction of both limbs a bidirectional cavopulmonary connection was performed and in the remaining patients the atrial baffle was refashioned with Goretex®. Three patients died, 2 could not be separated form cardiopulmonary bypass and the one who had bidirectional cavo-pulmonary connection died of multi-organ failure after 10 days.

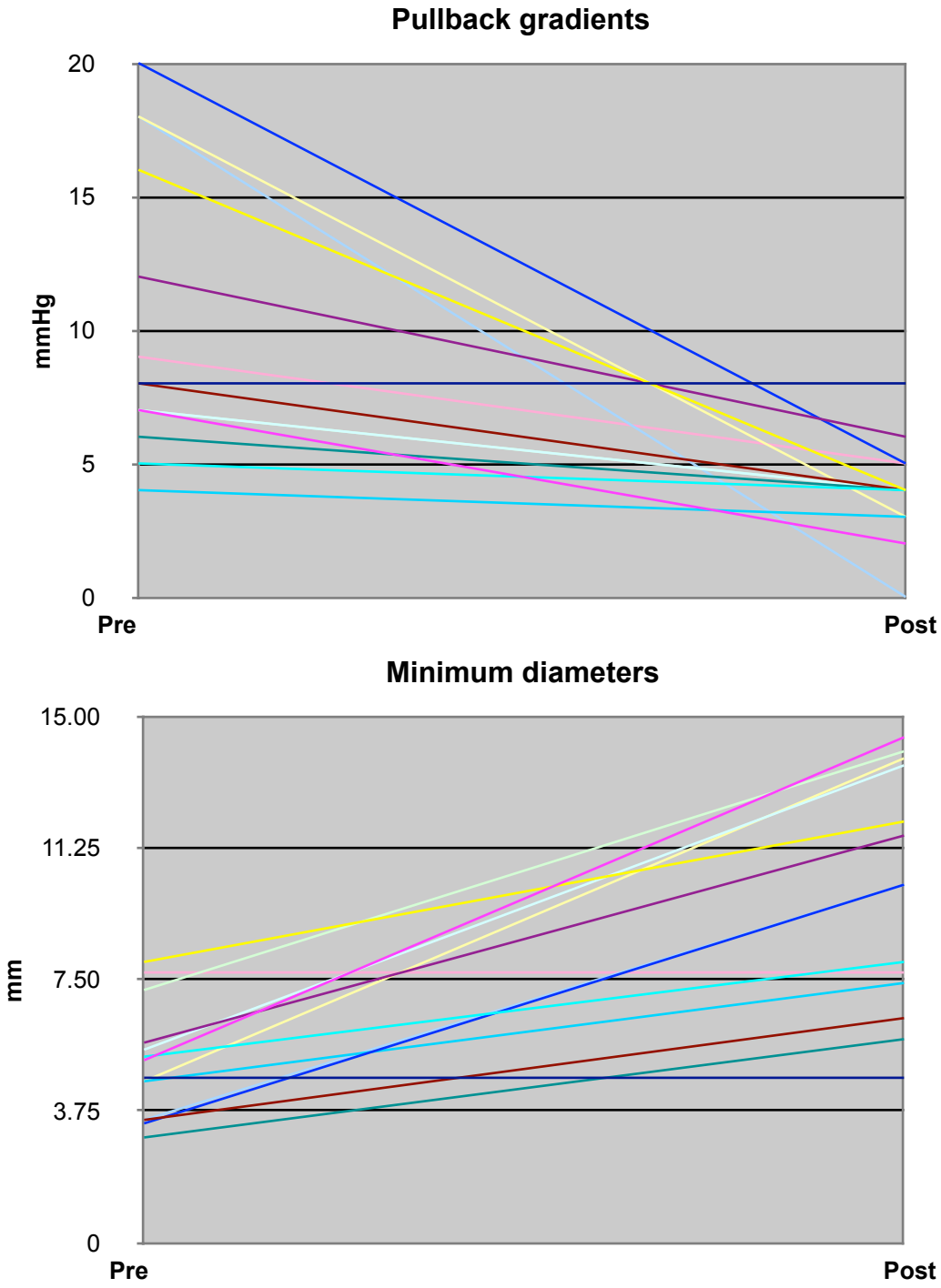


Figure 16. Pullback pressure gradients (above) and minimum pathway diameters (below) before and after angioplasty procedures.

Discussion

The incidence of baffle obstruction in this patient population was moderately high at 27% when compared to the literature (Trusler et al., 1987). Most obstructions were morphologically discrete and occurred at the site of the remnant of the atrial septum. Sub-total resection of the atrial septum during initial surgery might result from trying to avoid the incision extending into the inter-atrial groove and the artery to the sinus node superiorly or towards the atrioventricular node inferiorly. Obstructions presenting early after surgery tend to be of this type while those presenting later after surgery often have a tubular shape possibly due to shrinkage of pericardial baffle material. In some cases the mechanism of obstruction is a combination of both remnant of the atrial septum and baffle shrinkage. Most patents in the above series had baffles made of pericardium. Previous studies have suggested that baffle obstruction is more likely after the use of synthetic material which makes the prospect of surgical revision even less attractive.

In our series, ballon angioplasty appeared to be successful in around 75% of selected patients in the short term with a low incidence of side effects. The mechanism of relief is unclear but probably involves some splitting of remnant of the atrial septum. Therefore, balloon angioplasty would not effective for obstruction caused by redundant folds of synthetic material, calcified pericardium or lesions with a tubular morphology. In this series there was only one minor complication which was a neo-intimal flap which was only seen on trans-oesophageal echocardiogram.

As this is only an observational study, it is not possible to compare surgical revision to balloon angioplasty as the cases initially selected for surgery were ones in whom the the morphology was unsuitable for angioplasty and were often not contemporaneous. However this small series does highlight the risks of surgical re-intervention post Mustard procedure. In retrospect, the balloon sizes in 2 early unsuccessful attempts at 10 and 12 mm were probably inadequate and should have been larger. For obstructions with a tubular shape stent implantation either using balloon expanded or self expanding stents offers a useful alternative (BuLock et al., 1998).

Conclusion

Balloon angioplasty alone may have a place in the percutaneous treatment of some cases of Mustard baffle obstruction with a discrete morphology. It is possibly safer than surgical re-intervention in this population.

Study Limitations

1. This is a retrospective observational study offering no direct comparison with surgical treatment as no angioplasty attempt was made in patients when the stenosis was not judged to be favourable.

2. There was no differentiation between patients treated with clinical evidence of baffle obstruction and those whose baffle obstruction was found on routine catheter follow-up. In asymptomatic cases with superior limb obstruction and azygous run-off the need for intervention is questionable on clinical grounds.

3. It may be that subclinical baffle obstruction may have a place in limiting exercise tolerance in these patients and therefore intervention could be warranted however this was not tested.

Chapter 3

Experimental branch pulmonary artery stenosis angioplasty using a novel cutting balloon.

Introduction

Following experimental work in the early 1980s (Lock et al., 1981), balloon angioplasty of hypoplastic and/or stenotic branch pulmonary arteries has become an established practice in children (Lock et al.,1983; Rothman et al., 1990; Kan et al., 1990). However acute anatomical success of pulmonary artery angioplasty is seen in only 50% to 60% of patients, with a 16% restenosis rate at late follow-up (Rothman et al., 1990; Kan et al., 1990; Hosking et al., 1992). The natural elastic recoil of the vessel or a non distensible scar from previous surgical treatment may contribute to these results. Isolated congenital pulmonary artery branch stenosis occurring, for example, in Williams, Noonan or Alagille syndromes, can also be particularly difficult to dilate successfully (Beekman, Rocchini and Rosenthal, 1989; Ring el al., 1985; Gentles, Lock and Perry, 1993) because of the increased thickness of the tunica media. High pressure balloons (Gentles, Lock and Perry, 1993) and more recently endovascular stenting have been employed with impressive acute and intermediate term success (O'Laughlin et al., 1993; Fogelman et al., 1995). However this latter treatment is less applicable in the younger child as it's use is limited by stent maximal expandable diameter, the disadvantages of a foreign body and the requirements of long term management (Ing et al., 1995). In addition peripheral stenoses especially at branching points are less attractive lesions for stent implantation (Fogelman et al., 1995).

As an alternative to addressing resistant stenotic lesions with conventional balloons, a bladed balloon angioplasty catheter has been developed originally for resistant coronary stenoses (Barath et al., 1991). These bladed or cutting balloons have four longitudinally mounted blades with a cutting depth of 0.15 mm mounted at 90^0. Tough intimal atheromatous plaques can be incised, allowing dilation with less chance of vessel rupture (Unterberg et al., 1993). This current study was undertaken to determine the gross anatomy, histology and efficacy of balloon angioplasty using a cutting blade balloon angioplasty catheter in the setting of experimental pulmonary artery stenosis using an animal model.

Animals and Methods

Surgical creation of branch pulmonary artery stenosis was undertaken in nine two-week old pigs, each weighing approximately 5kg. The animals were premeditated with akmezine 0.25 ml/kg (97.9% ketamine, 2% acepromazine and 0.11% atropine) and general anaesthesia was maintained by a mixture of halothane, nitrous oxide and oxygen. A left lateral thoracotomy was performed in the fifth intercostal space, and an intercostal nerve block was induced with 4 ml of 0.5% bupivicaine diluted 1:1 with saline. The left lung was collapsed and the left pulmonary artery was identified by blunt dissection. In seven cases it was necessary to divide and ligate a left superior vena cava to provide access to the left pulmonary artery. A single 2-0 chromic catgut suture (Ethicon, Johnston and Johnston) was placed around the artery and three 6-0 prolene sutures (Ethicon, Johnston and Johnston) were placed circumferentially around the

vessel as previously described (Lock et al., 1981). Each prolene suture was passed through the adventitia and the media of the vessel twice and tied. The catgut suture was ligated over an angled forceps twice to reduce the vessel diameter by approximately 50%. An additional bupivicaine intercostal block was administered and the lung re-expanded. The chest was closed in layers with 2-0 Dexon (Ethicon, Johnston and Johnston), any remaining air in the left chest was evacuated via a chest drain placed through the wound and the skin was closed with 4-0 Dexon.

Antibiotic prophylaxis was provided with a single intramuscular dose of long acting benzylpenicillen 150,000 U for animals weighing less than 20kg and 300,000 U for those weighing more than 20kg. Postoperative pain relief was provided by the nerve block augmented by intramuscular buphenorphine (0.01 mg/kg). While all the animals survived surgery one died two weeks postoperatively. This animal, the smallest in the series had evidence of mediastinal lymphadenopathy and pleural adhesions at autopsy with infection being the presumed cause of death.

Balloon angioplasty. Cardiac catheterization was performed under general anaesthesia 41± 10 days after the surgical creation of branch pulmonary artery stenosis. The right femoral vein was entered percutaneously and a 7 French venous sheath together with a back bleed tap and sidearm was placed into the vein. A 5 French right coronary artery catheter (Judkins type, Cordis Inc, Florida) was advanced into the heart and pressures in the right atrium, right ventricle and left pulmonary artery proximal and distal to the area

of stenosis were recorded by fluid-filled pressure manometers zeroed at mid-atrial level. The right coronary artery catheter was replaced with a 7 French Gensini catheter and a selective angiogram was performed in the left pulmonary artery by hand injection (Isovue 300, Squibb Inc). Angiograms were recorded in the postero-anterior projection onto both videotape and hard copy. The diameters of the pulmonary artery at the level of stenoses were measured offline by using the known catheter diameter to correct for magnification.

Angioplasty of pulmonary artery stenoses was attempted in the eight surviving animals. One animal was found to have complete obstruction of the left pulmonary artery which could not be crossed with a guide wire and this was confirmed at autopsy. Of the remaining seven animals, five had angioplasty with a 6 mm diameter x 15 mm long cutting balloon (Interventional Technologies Inc, California, Fig. 17).

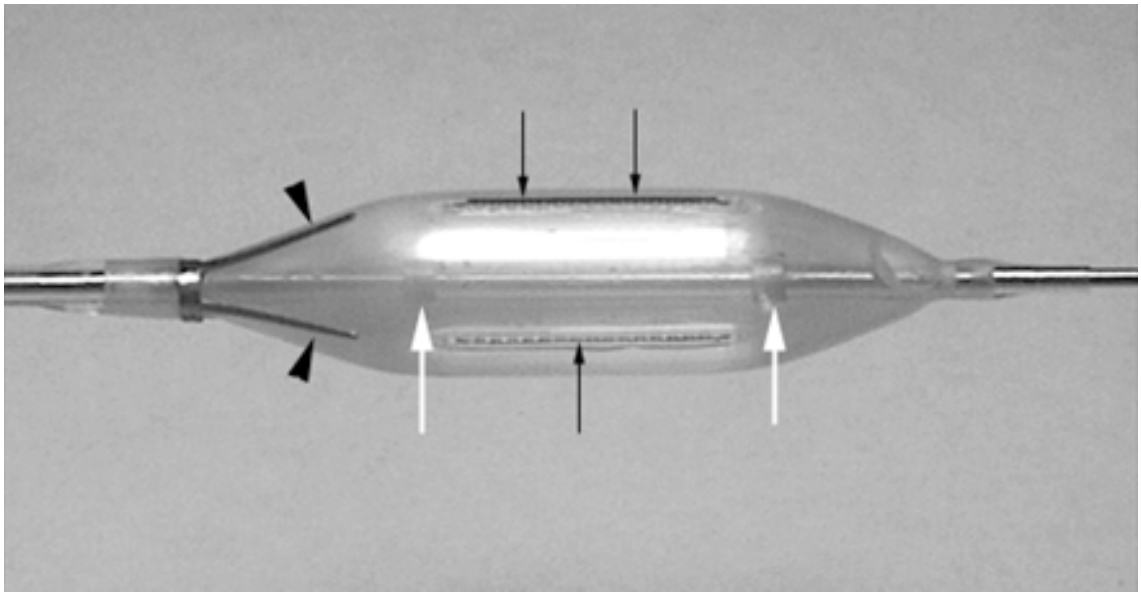


Figure 17. Diagram of Interventional Technologies cutting balloon. White arrows show radio-opaque markers, black arrows denote cutting atherotomes.

Because the supply of cutting balloons was limited and re-use was not always possible, two animals underwent balloon angioplasty in the standard fashion using catheter-mounted balloons (Cordis Inc.). Cutting balloons were introduced over a 0.014 “ guide wire for stability and through an 8 French long transseptal sheath (USCI Angiographic, Massachusetts) to protect both balloon and cardiac structures. The sheath with intraluminary balloon was positioned across the area of stenosis within the left pulmonary artery. The sheath was withdrawn to expose the balloon and a small amount of contrast was injected into the sheath (through the sidearm) to monitor position. After de-airing, the balloon was inflated with a singe inflation of dilute contrast. The balloon was deflated, carefully withdrawn into the sheath and removed. The lesion was recrossed with a 0.035” hydrophilic wire (Terumo Corp, Tokyo, Japan) and the 7 French Gensini catheter was advanced over the wire to the distal left pulmonary artery.

Pullback pressure gradients (Fig. 18 A and B) were repeated, as well as selective angiography with remeasuring of the diameters of the dilated segments.

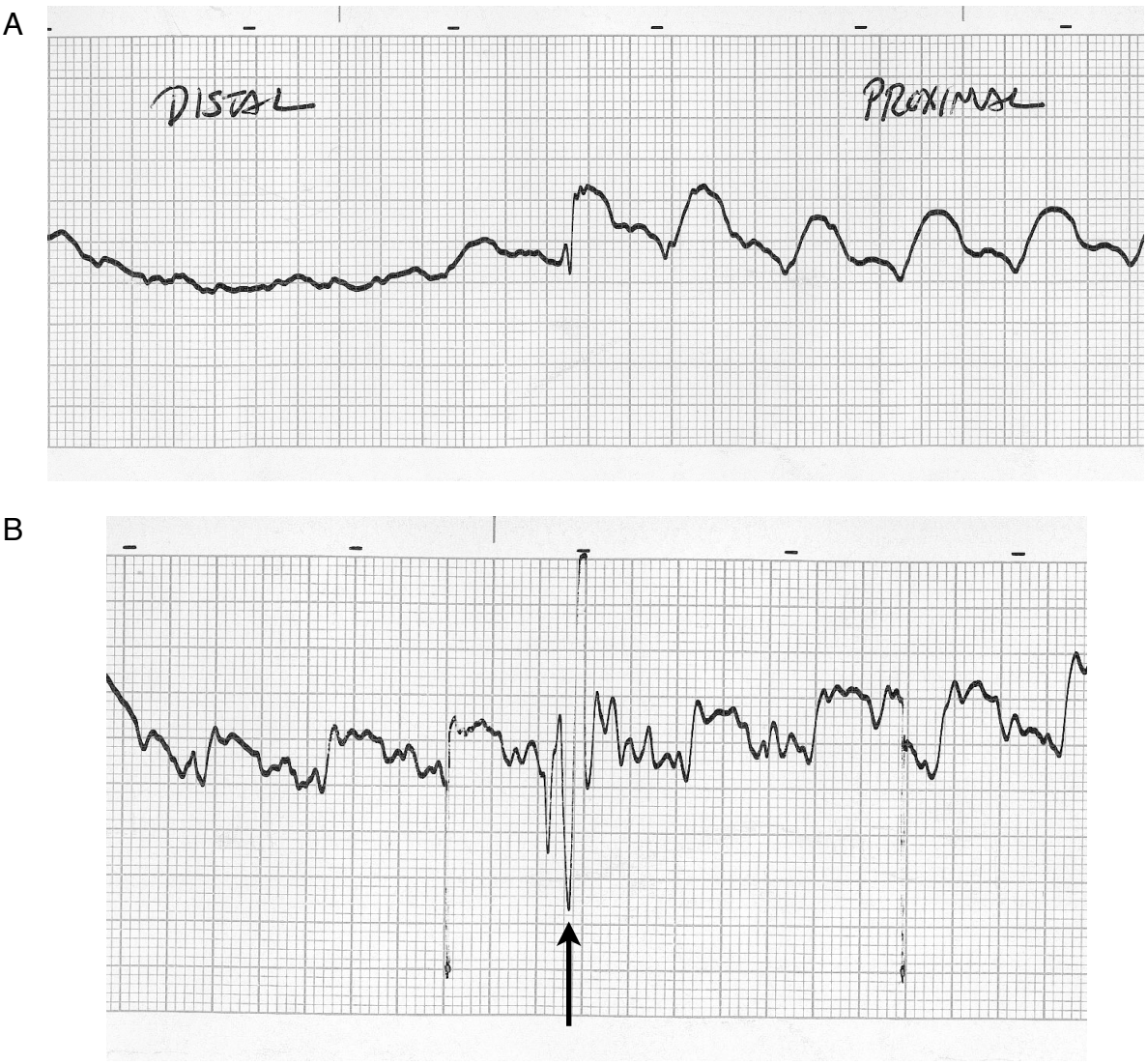


Figure 18. Pullback pressure tracing across the left pulmonary artery in animal 1 before (A) and after (B) cutting balloon angioplasty, arrow points to site of stenosis.

For standard balloon angioplasty, 2 cm long balloons were selected with a diameter approximately three times the diameter of the stenosis but not greater than two times the diameter of the normal pulmonary artery. One animal had standard balloon angioplasty following predilation with a cutting balloon. Both this animal and the one treated with a cutting balloon were killed immediately with a euthanasia solution (Euthanyl, MTC Pharmaceuticals). These animals had also undergone cutting balloon angioplasty in smaller branches to observe the effect on normal vessels. The distal branches chosen had a diameter of approximately 3 to 4 mm (i.e., less than the cutting balloon's expanded diameter).

Follow-up. Surviving animals had follow-up cardiac catheterizations after 42 ± 3 days. Percutaneous entry was from the femoral vein and pressures in the right heart, and proximal and distal pulmonary arteries were measured. Selective angiography was performed in the left pulmonary artery as before. Following catheterization, all animals were killed using euthanasia solution.

Pathological examination. The two animals killed immediately were prepared for electron microscopy. Immediately after death a window in the chest wall was created, and the aorta, superior vena cava and inferior vena cava were ligated. The main pulmonary artery and aorta were cannulated and the heart-lung preparation was perfused with saline followed by 2L of fixative containing 2% glutaraldehyde before removal of the left pulmonary artery (to prevent smooth

muscle contraction artefact). The pressure generated in the perfusion preparation was kept below 50 mmHg. The cut luminal surface of the artery was used for scanning electron microscopy.

For the remaining animals, the left pulmonary artery was dissected out and placed in 10% buffered formalin. The specimen of pulmonary artery was cut lengthways and the appearance of the luminal and adventitial surface was examined. Serial circumferential histological sections were cut from paraffin-embedded tissue, stained with hematoxylin and eosin, and examined by light microscopy.

Ethical approval was granted by the Animal Services Committee of the Hospital for Sick Children. Data are expressed as median with ranges or as mean ± 1 SD.

Results

The schedule of interventions and outcomes for each animal is given in Table 1. The median weight at angioplasty was 24 kg (range 14-39.2). In all animals, the mean peak systolic pressure gradient across the left pulmonary artery fell from 8.3 ± 2.3 mmHg to 3.2 ± 3.1 mmHg, and the mean diameter of stenoses increased from 4.5 ± 2 mm to 5.6 ± 2 mm at initial angioplasty. There was no change in peak right ventricular pressure before (25 ± 3 mmHg) or after (23 ± 5 mmHg) dilation. The only acute complication was rupture of a reused cutting balloon on inflation. This balloon could not be

Table 1. Schedule of interventions and outcomes for two-week old pigs in a model of left pulmonary artery stenosis

Animal	Surgery	Balloon	Gradient pre mmHg	Gradient post mmHg	Diameter pre mm	Diameter post mm	Outcome	Exam.
1	Survived	Cutting	10	1	5.5	6	F/U cath	Light
2	Survived	Cutting	12	9	3	3.5	F/U cath	Light
3	Survived	Cutting	6	3	4	5	F/U cath	Light
4	Survived	Standard	10	0	2	6	F/U cath	Light
5	Survived	Standard	7	2	2.5	3.5	Haemopericardium	Gross
6	Survived	LPA occluded						
7	Survived	Cutting	6	1	7	8	Sacrificed	E/M
8	Died 2 weeks							
9	Survived	Cutting	8	6	7	8	Sacrificed	E/M

withdrawn into the sheath and attempts to exteriorize led to the remnant being torn from the catheter shaft and left in the femoral vein. This animal had been scheduled to be killed immediately. One other animal died two weeks post angioplasty, after a regular balloon dilation had produced a poor result. At autopsy, there was blood in the pericardial sac; however the site of vessel perforation could not be identified. There were no rhythm disturbances during angioplasty.

Of the five animals treated with a cutting balloon, all showed a modest increase in vessel diameter although the measured pre-dilation diameters in two animals were greater than 6 mm. One of these animals underwent angioplasty with a regular balloon which produced no further increase in vessel diameter and both animals were killed immediately and prepared for electro microscopy. Naked eye examination revealed cuts in the luminal surface presumably because the blades added to the overall diameter (Fig. 17).

Scanning electron microscopy showed linear tears at the site of the angioplasty extending through the intima into the media (Fig. 19). These two animals also underwent cutting balloon angioplasties of normal distal vessels which produced no gross pathological or histological evidence of damage.

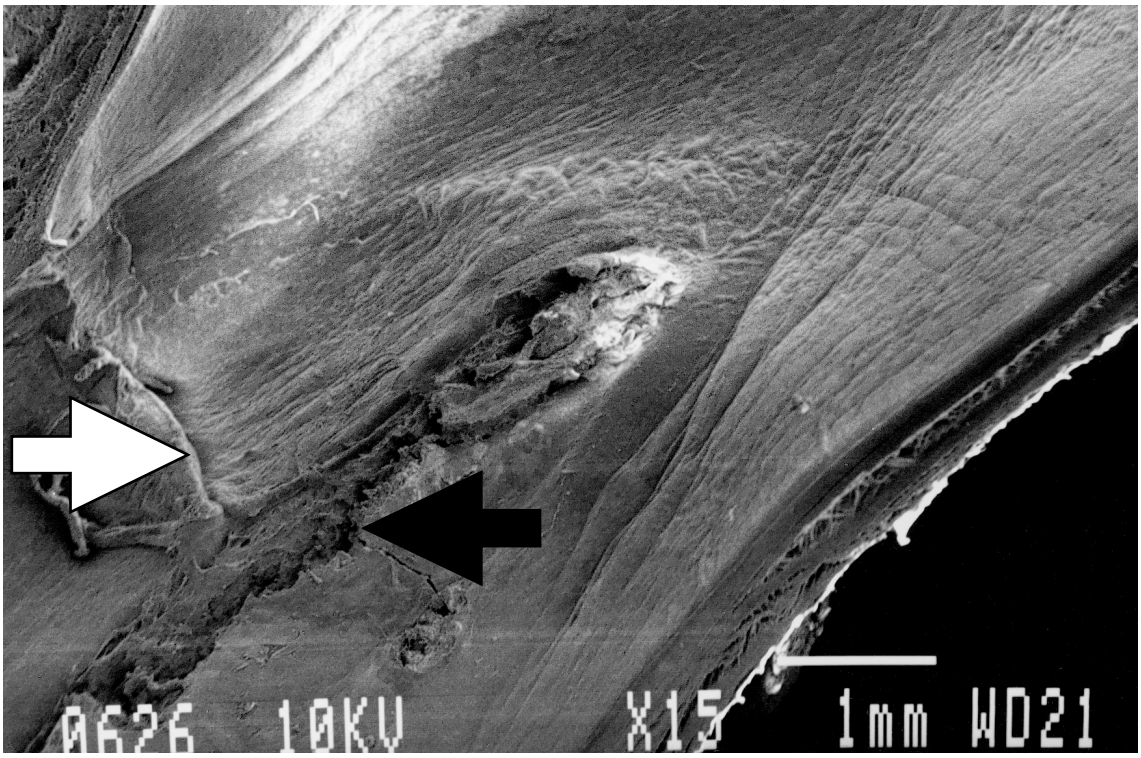


Figure 19. Scanning electron micrograph with 1 mm distance marker showing luminal surface of pulmonary artery. Key: white arrow points to stenotic ridge and black arrow to linear tear from cutting balloon.

The three surviving animals in which the cutting balloon had been employed continued to demonstrate growth of the stenotic area at follow-up, although in one animal this further increase was minimal. At follow-up, this latter animal underwent repeat angioplasty with a regular balloon with an increase in diameter of only 4.1 mm to 5.3 mm. The single survivor after regular angioplasty showed some evidence of restenosis at follow-up. No pulmonary artery aneurysms were seen at recatheterization in any of these four surviving animals. All were killed and underwent pathological and

histological examination, which showed healing of the cut luminal surface and no evidence of adventitial haemorrhage.

Discussion

This preliminary study shows that 'cutting' balloons may be employed through a long sheath for angioplasty of branch pulmonary artery stenoses without complications (haemorrhage or aneurysm formation). The mechanism of angioplasty appears to be creation of regular incisions of the intima and media, which may allow for a more controlled widening of the vessel than the tearing seen after standard balloon angioplasty (Edwards et al., 1985). These incisions were also shown to be healed completely by four to six weeks. One technical limitation of this study was that in several cases the diameter of stenoses was similar to the available balloon diameter and angioplasty by the cutting balloon produced only a modest acute increase in vessel diameter. In two of the three surviving animals however a further increase in vessel diameter at follow-up was seen, not unlike that noted after conventional angioplasty. Abrasions or cuts in the luminal surface of normal distal vessels in which the cutting balloon was deployed were not seen because these vessels were easily distensible.

One serious technical problem was rupture of a cutting balloon that could not be withdrawn into the sheath and eventually tore away from the catheter shaft.
Reuse of this balloon may have caused this complication. Because only two animals had angioplasty with regular balloons, comparison with cutting balloons was impossible;

however short term follow-up angiograms suggested that pulmonary artery stenotic areas treated with cutting balloons continued to grow.

Available cutting balloons are designed for use only in coronary angioplasty and as such have a maximum expanded balloon diameter of 6 mm but only track a coronary 0.014” guidewire. To further explore clinical applications, such as angioplasty of branch pulmonary artery stenoses or creation of atrial septal defects, redesign would be necessary to make balloon and catheter more robust. This might include increasing catheter size and allowing tracking over a stronger guidewire (such as 0.035”). Additionally, a larger catheter would be less likely to tear following balloon rupture.

Conclusion

In a case of branch pulmonary artery stenoses, where stenting or surgery are not justified, dilation with a cutting balloon may allow controlled tearing. It may be additionally useful in isolated or multiple congenital congenital branch pulmonary stenoses which tend to respond less well to regular angioplasty. In cases where the stenotic diameter is not much greater than the available cutting balloon expanded diameter, the cutting balloon can can be used to produce linear tears in the artery that can be further stretched (or torn) by standard angioplasty techniques.

Chapter 4

Balloon dilation of severe aortic stenosis in the neonate: comparison of anterograde and retrograde catheter approaches.

Introduction

Aortic stenosis is relatively uncommon and occurs in only 3-5% of all patients with congenital heart disease (Keith, Rowe and Vlad, 1967). Of these only around 10% will require treatment in the neonatal period either because the systemic circulation is duct dependent or because of heart failure (Sandor et al., 1980). The term 'critical' should only be applied when the stenosis is so severe that continued patency of the arterial duct is required to maintain life.

Balloon dilation of the aortic valve was first described by Lababidi (1984) and has since been applied successfully to infants and children as a alternative to surgical valvotomy (Vogel et al., 1989; McCrindle, 1996). In recent years, the technique has been used in neonates with severe or critical aortic valve stenosis with results comparable to surgical approaches (Zeevi et al., 1989) although in many centres surgery remains the preferred option. During the procedure, the left heart has generally been approached in a retrograde fashion through the femoral (Zeevi et al., 1989), umbilical (Beekman, Rocchini and Andes, 1991), or right common carotid arteries (Fischer et al., 1990; Donti et al., 1995). Femoral artery access in neonates carries the risk of damage to the vessel resulting in thrombosis and potential limb complications (Vogel et al., 1989; Burrows et al., 1990). Additionally, it is often necessary to exchange or withdraw catheters increasing the possibility of damage to the arterial wall.

An anterograde approach through the heart from the femoral vein would eliminate the risk of arterial compromise and would be superior to the retrograde approach, provided that the procedure was as effective as retrograde access, could be performed quickly and was free from neurologic complications due to wire manipulation. Additional benefits of this approach could result from the wire reliably crossing the hemodynamic orifice of the valve rather that potentially piercing a valve leaflet, leading to severe aortic incompetence on dilation. Also performing the procedure in the direction of blood flow might reduce the tendency of the balloon to 'bounce' in and out of the valve as blood is ejected from the heart. To this end, encouraging experience with an anterograde approach was reported (Hausdorf et al., 1993) in a group of nine children ranging in age from 1 day to 11 years. Reported here is our experience with an anterograde approach to aortic valve balloon dilation in a consecutive group of 11 neonates with severe aortic valve stenosis, with particular emphasis on the technique and comparison of results to a similarly matched group undergoing dilation in a retrograde fashion from the aorta.

Methods

Echocardiographic and clinical assessment: All patients underwent a complete two-dimensional echocardiographic study before intervention, including assessment of the ventricular morphology and the diameter (at the hinge points) of the mitral and aortic valves. In cases where the left ventricle did not reach the apex of the heart, a Rhodes score was measured (Rhodes et al., 1991). Left ventricular ejection was measured using

a biplane Simpson method. Severe aortic stenosis was defined as an arterial duct-dependent systemic circulation, symptomatic heart failure or a derived peak to peak Doppler gradient > 60 mmHg (Beekman et al., 1992).

Degree of aortic valve incompetence was measured semiquantitatively, using the ratio of regurgitant jet width to annulus size (Nishimura et al., 1992). Mitral valve incompetence was assessed qualitatively by Doppler colourflow mapping and categorized as nil, trivial, mild, moderate or severe. In two of the earlier group 2 patients, Doppler colour flow mapping of the mitral valve was not available. Unless otherwise stated, pressure gradients are those measured at cardiac catheterization. Echocardiography was repeated within 24 hours of the procedure to assess ventricular function and the degree of aortic and mitral valve incompetence.

Patients. *Group 1:* Between November 1994 and November 1995, 11 consecutive neonates with severe aortic valve stenosis underwent attempted balloon dilation of the aortic valve using an anterograde catheter approach. There were nine male and 2 female neonates, and all but one was < 28 days old (median age 6 days, range 1-42; median weight 3.5 kg, range 2.2-4.25). Four patients presented with congestive heart failure on day 1 of life; four had a murmur and congestive heart failure within the first week of life; and two had a murmur and congestive heart failure and presented at 2 weeks of life. The remaining patient, who presented with a murmur on day 1, remained well but developed an increasing aortic valve echocardiographic-Doppler gradient.

Six patients had a patent arterial duct: shunting was predominantly right to left in two and bidirectional in four. One patient had partial anomalous pulmonary venous drainage of the left upper pulmonary vein to the innominate vein, and two had mild hypoplasia of the aortic isthmus. Five patients had reduced left ventricular function (ejection fraction between 10% and 40%), and in four of these five patients, the mitral valve chordae and papillary muscle apparatus had a bright appearance on the echocardiogram, suggesting endocardial fibrosis. Three patients had hypoplasia of the left ventricle with a Rhodes score of -0.14, +0.3 and +1.4 respectively; in another two patients, the left ventricle was dilated (end-diastolic dimension 2.2 and 2.3 cm, respectively, both above the 95th percentile for age).

Group 2: Between April 1985 and April 1995, 15 patients underwent attempted balloon dilation of the aortic valve from a retrograde catheter approach, including two who had an unsuccessful attempt using an anterograde approach (median 3 days, range 1 to 35; median weight 3.5 kg, range 2.5 to 4.4). Five patients presented with heart failure and poor perfusion on day one of life, three with heart failure within the first week and one each at 10 days, 14 days and 1 month. Three patients were found to have a murmur within the first few days of life and the diagnosis was made by echocardiogram at 1, 6 and 20 days of age. One patient was diagnosed by fetal echocardiography and transferred to the catheter laboratory on day one of life while receiving a prostaglandin infusion. Of the six patients with evidence of right to left shunting across a patent

arterial duct, bidirectional shunting was present in one and two had coarctation of the aorta. Three patients had a hypoplastic left ventricle (end-diastolic dimensions 0.7, 1.5 and 1.55 cm, respectively, all below the fifth percentile for age), and one had a dilated ventricle (end-diastolic dimension 2.53 cm). In six patients, an echo-bright appearance of the mitral valve chordae and papillary muscle apparatus suggested endocardial fibrosis. One patient had surgical open valvotomy on day 1 but required further intervention at 9 days of age.

Procedures. All procedures were performed under general anaesthesia with mechanical ventilation.

Group 1: In the first patient, percutaneous entry was achieved from the right femoral vein and umbilical artery. After unsuccessful attempts to cross the valve retrogradely from the ascending aorta, a 4F right coronary catheter (Judkins type, Cook) with a 2.5 curve was advanced from the femoral vein and passed through the oval foramen and into the left ventricle. Counterclockwise rotation allowed the tip to turn towards the left ventricular outflow tract. A guide wire was passed across the aortic valve into the ascending aorta and snared (Amplatz, Cook) from the retrograde umbilical arterial catheter to stabilize its position. In the remaining 10 cases, stable wire position was achieved from the femoral vein via an antegrade approach with no attempted retrograde approach. A 4F right coronary catheter (2.5 curve) was used to enter the left ventricle through the foramen ovale in three cases, a 5F right coronary catheter (2.5 curve) in five cases and a 5F end-hole balloon catheter (Critikon, Inc., Ontario) in one case. In one

patient, percutaneous entry into the femoral artery was performed for pressure monitoring. Pressures in the left ventricle and aorta were measured and the aortic valve annulus diameter was measured from a left ventricular angiogram (n=7) or ascending aortogram (n=2) using the catheter diameter to correct for magnification. The initial guide wires used to cross the valve included a 0.014-in. coronary wire (C.R. Bard Inc.) (n=1), a 0.035-in. flexible tipped wire (Wholey, Mallinckrodt Medical) (n=5), a 0.035- or 0.018-in. hydrophilic wire (Terumo Corp., Tokyo, Japan) (n=2) or a 0.025-in. Teflon-coated wire (Cook Inc.) (n=1). If possible, the wire was directed into the descending aorta; however, in four patents, the soft tip of the guide wire was left in the innominate artery for stability. The coronary catheter was curled in the left ventricle and then advanced over the wire to either the ascending or descending aorta, and the initial wire exchanged for a 0.035-in. guide wire (Cook Inc.) (Fig. 20, left). A 2-cm long balloon (Cordis Corp.) with a diameter 90% to 100% of the estimated aortic annulus diameter was selected and advanced over the guide wire. Care was taken to position the balloon within the left ventricle clear of the mitral valve apparatus. After an inflation with ⅓ dilute contrast medium (Fig. 20, right), the balloon was withdrawn and replaced with the right coronary catheter.

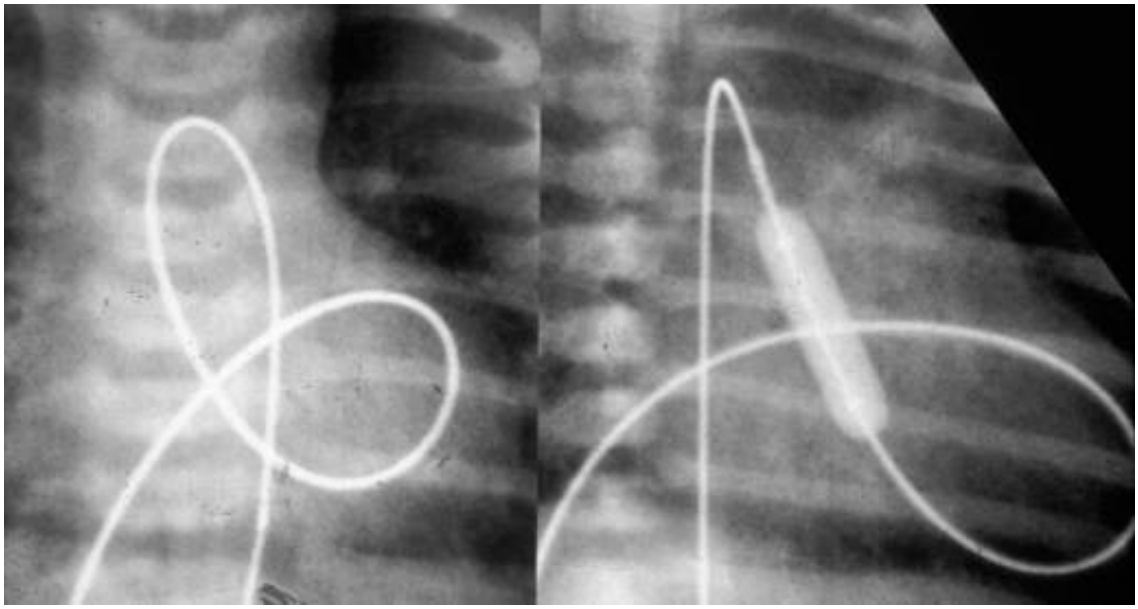


Figure 20. Left, Guide wire looped in the left ventricular apex, clear of the mitral valve apparatus, crossing the aortic valve and positioned in the descending aorta of a 3.8-kg neonate. Right, Balloon dilation of the aortic valve using a 6-mm × 2-cm balloon over a 0.035-in. wire, stabilized in the descending aorta. Inflation produced a decrease in peak systolic gradient from 100 to 26 mm Hg, with no residual aortic or mitral valve incompetence.

Pressures in the left ventricle and aorta were remeasured, and the procedure was repeated if no change in gradient was documented. In four patients, the balloon size was increased by 1 mm and in one patient by 2 mm. Ventriculography was performed before and after the dilation to assess valve mobility, chamber function and mitral regurgitation.

Group 2: Retrograde balloon dilation was from an umbilical artery approach in one patient and through the femoral artery in the remaining 14 patients. The aortic valve annulus diameter was estimated from the ascending aortogram, and the valve was

dilated using the appropriate balloon diameter (see Procedures, Group 1) introduced over a guide wire whose tip was curled in the left ventricular apex. In two patients, the balloon size was increased by 2 mm. Aortography was repeated to assess aortic valve mobility and degree of aortic regurgitation.

Statistics

Normally distributed continuous variables are presented as mean value ± 1 SD and other variables as medians with ranges or frequencies. Between-group comparisons were made with a Student t test, chi-square with Fisher exact test on Mann-Whitney U test, depending on whether data was parametric or nonparametric. A p value < 0.05 was considered significant.

Results

Group 1: Of the 11 attempted anterograde dilations, the aortic valve was successfully crossed in all but 2 patients. In the first of these, the balloon was successfully advanced across the valve but was poorly seated, and the dilation was ineffective; in the second, an anterograde approach was abandoned after the development of atrial flutter requiring overdrive pacing for termination. These two patients subsequently underwent retrograde dilation at the same catheterization and are included in group 2. Clinical and haemodynamic data for the remaining 9 group 1 patients are presented in Table 2.

		LVEF (%)				Peak systolic gradient (mmHg)	
Pt No/Age	Wt (kg)	Pre	Post	Annulus (mm)	Balloon size (mm)	Pre	Post
1/2	3.1	10	22	6	6	50	18
2/6	3.9	16	25	6	7	39	23
3/6	3.5	72	86	8	8	113	19
4/16	3.3	40	48	5	5	60	10
5/42	4.3	72	76	6	6	46	14
6/2	3.8	NA	NA	7	6	100	26
7/1	3.2	10	28	6	6	20	4
8/2	3.5	64	75	7	8	80	24
9/6	2.2	80	80	5	5	53	17

Table 2. Group 1 (antegrade approach to aortic valve): Clinical and Haemodynamic Data

LVEF = left ventricular ejection fraction; NA = not available; Pre = before the procedure; Post = after the procedure; Pt = patient; Wt = weight.

The median balloon diameter was 6 mm (range 5 to 8), the mean ratio of balloon diameter to aortic annulus diameter was 1 ± 0.0. The median fluoroscopy time was 40 min (range 22 to 63). Although ventricular ectopic activity was not uncommon no additional prolonged or haemodynamically compromising rhythm disturbances occurred during wire catheter or balloon manipulation. The initial and post-procedural peak to peak systolic gradients across the aortic valve were 62 ± 20 and 17 ± 5 mmHg, respectively (P=0.001).

Left ventricular ejection fraction, as estimated by echocardiography, changed from a mean of 45 ± 21% (range 10% to 80%) to a mean of 55 ± 19% (range 22% to 86%) within 24 h of the procedure ($p = 0.002$). Of the four patients presenting with poor left ventricular performance, three had normal function by 4 months and one continued to have poor ventricular function. This latter child developed a calculated peak to peak gradient of Doppler of 81 mmHg and had an uneventful surgical valvotomy at 4 months of age. One other patient with normalized left ventricular function has a Doppler peak to peak gradient of 56 mmHg at 6 months after the procedure and was scheduled for re-intervention.

Complications: Echocardiographically, of the 7 patients with no preceding aortic incompetence, 4 developed mild aortic insufficiency with the remaining 3 having none after the procedure. One patient with mild aortic incompetence before dilation had moderate incompetence after the procedure, and in one further patient the degree of regurgitation went from trivial to moderate. The ratio of regurgitant jet width to aortic annulus diameter increased from a mean of 0.03 to a mean of 0.16 ($p = 0.008$). From qualitative assessment using Doppler color flow mapping, the degree of mitral valve incompetence was unchanged in four patients, whereas in one it appeared to decrease from moderate to mild. In four patients the degree of mitral valve incompetence increased: two developed mild and two moderate mitral regurgitation. In the latter two patients, the mitral regurgitation jet appeared to arise from the anterior mitral leaflet and may have represented damage from the wire or balloon catheter. One patient was treated

with afterload reduction and diuretic drugs, and in both patients the degree of mitral regurgitation decreased to mild within 1 week.

All femoral pulses were normal after catheterization, except in the one patient (11%) in whom a catheter had been placed in the femoral artery for pressure monitoring. Gradual resolution of the compromised pulse in this patient occurred after thrombolytic therapy. The smallest patient (2.2 kg) had echocardographic evidence of a 1 cm x 0.4 cm thrombus within the left atrial appendage after the procedure and this was treated uneventfully with low molecular weight heparin. There were no acute deaths or neurological sequelae.

Group 2: The valve could not be crossed in the first 2 patients, leaving 13 who underwent dilation. Clinical and haemodynamic data for group 2 patients are presented in Table 3.

		LVEF (%)				Peak systolic gradient (mmHg)	
Pt No/Age (days)	Wt (kg)	Pre	Post	Annulus (mm)	Balloon size (mm)	Pre	Post
1/5	4.4	NA	NA	8	8	124	36
2/1	3.2	NA	NA	6	6	5	0
3/11	3.5	NA	NA	5	5	19	0
4/2	2.7	NA	NA	6	4/5/6	20	14
5/9	3.5	NA	67	7	7	63	20
6/3	3.5	78	78	6	6	50	20
7/25	3.0	79	85	8.8	8	54	14
8/1	3.8	10	32	6	6/8	49	7
9/3	3.5	67	56	8	8	95	17
10/35	3.3	36	42	7	7	61	26
11/7	3.5	69	84	6.5	7	45	16
12/1	2.9	54	NA	7.4	7	38	6
13/17	3.5	28	47	7	6	50	24

Table 3. Group 2 (retrograde approach to aortic valve): Clinical and Haemodynamic Data

Abbreviations as in Table 2.

The mean ratio of balloon diameter to aortic annulus diameter was 1 ± 0.06, and the median fluoroscopy time was 18 min (range 5 to 72). Fluoroscopy times are skewed by one of the unsuccessful anterograde dilation attempts. The initial and post-procedural peak to peak systolic gradients across the aortic valve were 52 ± 17 mmHg and 17 ± 5 mmHg respectively ($p = 0.001$). Measured left ventricular ejection fractions went from 53 ± 18% (range 10% to 79%) to 58 ± 12% (range 32% to 85%, $p = 0.1$).

Complications: There were six deaths after retrograde balloon dilation (mortality rate 46%). All deaths were related to the occurrence of severe (n = 5) or moderately severe (n = 1) aortic incompetence. Two patients underwent an emergency Ross procedure and one patient a Konno procedure 5 weeks after dilation. In the latter patient, complete detachment of an aortic valve leaflet was noted at operation. The degree of aortic incompetence was unchanged in four patients (nil in two, mild in two). In the remaining nine patients, all of whom had no incompetence before dilation, regurgitation increased and became severe in five and moderate in four. The ratio of regurgitant jet width to aortic annulus diameter increased from a mean of 0.02 to a mean of 0.51 ($p = 0.003$). Of the 11 patients in whom a qualitative assessment of mitral incompetence is available, 1 demonstrated a decrease from moderate to mild and 1 in whom anterograde dilation was attempted developed mild regurgitation after the procedure. In the remaining nine patients, the degree of mitral regurgitation was unchanged. Of the eight patients who developed femoral artery thromboses (62%), one also had laceration of the femoral artery that required surgical repair. In one patient, the pulse resolved with heparin therapy alone, and five underwent successful thrombolysis leaving two lesions unresolved. Other complications included ventricular fibrillation during balloon inflation in one patient, which also produced a small tear in the ascending aorta and an episode of bacterial endocarditis in another patient. There were no acute neurological events among survivors.

Comparison of groups 1 and 2 (Table 4): There were no significant differences between the two groups in age or weight at dilation, peak systolic pressure gradient before dilation, left ventricular ejection fraction or ratio of maximal diameter before and after the procedure. Although the anterograde approach took significantly longer, the retrograde approach was associated with significantly higher mortality, an increased incidence of arterial complications and more severe aortic regurgitation. There was no significant difference in degree of mitral regurgitation between the 2 groups after the procedure.

	Group 1 (n = 9)	Group 2 (n = 13)	p value
Age (days)			
Median	6	3	0.5
Range	1-42	1-35	
Wt (kg)			
Median	3.5	3.5	0.5
Range	2.2-4.25	2.5-4.4	
Before dilation			
Peak gradient (mmHg)	62 ± 20	52 ± 17	0.44
LVEF (%)	45 ± 21	53 ± 18	0.5
AI ratio			
Median	0	0	0.5
Range	0-0.13	0-0.12	
Balloon/annulus ratio	1 ± 0.06	1 ± 0.06	0.64
Fluoroscopy (min)	43 ± 9	25 ± 10	0.03*
After dilation			
Peak gradient (mmHg)	17 ± 5	17 ± 5.5	0.9
LVEF (%)	55 ± 19	58 ± 12	0.8
AI ratio	0.16 ± 0.08	0.51 ± 0.24	0.03*
Increase in MR	2.2-4.25	0	0.17
Arterial thrombosis	11%	62%	0.03*
Mortality rate	0%	46%	0.046*

Table 4. Comparison of Anterograde and Retrograde approaches to Aortic Valve Dilation. AI=Aortic regurgitation jet width/annulus ratio. Increase in MR number of patients who went from mild or less to moderate or more.

Discussion

Mortality: The present series compares retrograde and anterograde catheter approaches for dilation of severe aortic valve stenosis in neonates. Not all patients had arterial duct dependent systemic circulations: thus the term ‘severe’ is used in preference to ‘critical’. Because the present trial was not a randomized, controlled one, the two groups are not strictly comparable, and several of the retrograde dilation attempts were performed early in the evolving experience of catheter-directed therapies. In addition, three earlier patients had qualitatively small ventricles, predating attempts to assess candidacy for biventricular repair and may not have been suitable retrospectively for dilation but instead should have been treated with single ventricle palliation. Because these three patients predated formal echocardiographic application of the Rhodes scoring system (Rhodes et al., 1991), we were unable to retrospectively assign a reliable score and must accept this limitation of the retrospective control. Mortality rates from other series of retrograde balloon dilation of the aortic valve range from 10% to 20% (Zeevi et al., 1989; Beekman, Rocchini and Andes, 1991; Fischer et al., 1990). In our experience, if patients who underwent angioplasty before 1990 are excluded (which includes those with unequivocally small ventricles), the mortality rate for the retrograde group falls to 33% which is still significantly greater than the mortality for the antegrade group. In addition, the incidence of predominantly right to left shunting at the ductal level was higher in the retrograde group. Although the high mortality for the retrograde group may be peculiar to the operators or technically related as described later, the mortality is within the confidence limits of the published data, and all procedures were undertaken

by one of two primary operators, whether anterograde or retrograde. Nevertheless, the differences in mortality for the two approaches are striking and several of the patients who died after an attempted retrograde approach had normal ventricular size and function.

Aortic incompetence. We believe that the major factor leading to a poor outcome after retrograde dilation is the development of severe acute aortic incompetence. A sudden volume load, together with reduced coronary perfusion on the background of poor ventricular function or hypertrophy can rapidly lead to hypotension and acidosis despite prompt resuscitative measures. Three patients with severe aortic incompetence died after cardiac catheterization: two died after emergency surgery; and one whose valve incompetence was slightly less severe (ratio of echocardiographic regurgitant jet width to aortic annulus diameter of 0.9) died after attempted repair at 5 weeks of age. These results emphasize the importance of avoiding acute severe aortic incompetence in infancy, a situation that can rarely be successfully salvaged in the operating room.

In contrast, only two patients developed moderate aortic incompetence after an anterograde approach, although the ratio of balloon to annulus diameter was the same for both groups. No patients died in this group. Crossing the aortic valve in an anterograde fashion allows the wire to be advanced through the hemodynamic valve orifice and, together with the use of floppy-tipped guide wires, can reduce the risk of valve leaflet perforation. We speculate that it is this inadvertent valve perforation and

subsequent dilation that led to severe aortic incompetence (Fischer et al., 1990) in the present series but emphasize that this group of patients reflects procedures undertaken early in the overall experience.

Mitral incompetence. There was no progression of mitral valve incompetence after the retrograde approach. However after the anterograde approach, two patients developed moderate regurgitation which appeared to improve with time. Nevertheless, the anterograde approach to the mitral valve does carry potential risks of damage to the mitral valve apparatus. The catheter and wire may pass between chordae, resulting in injury to the tension apparatus when the balloon is withdrawn. Such injury may be avoided by utilizing an end-hole catheter to traverse the mitral valve in an effort to avoid the tension apparatus before achieving final wire position. If the total balloon length including taper is too long, it may also cross and potentially damage the anterior mitral valve leaflet during inflation. Looping and hand shaping the guide wire towards the apex of the left ventricle may help to avoid the mitral tension apparatus and reduce the potential for the guide wire to simultaneously prop open both the mitral and aortic valves, resulting in a marked reduction in forward flow. Hypoplastic ventricles may be more prone to these events but in any case should probably be excluded from consideration of balloon angioplasty. Although echocardiography during the procedure may help to identify an improperly placed wire across the mitral valve, this is not our current practice in the catheterization laboratory.

Arterial complications. A significant difference in morbidity was seen in arterial complications. The incidence of femoral artery thrombosis was 62% (n=8) when the arterial access was used and only 11% (n=1) with an anterograde approach. This latter case was early in the experience and was unrelated to the technique. Previously reported series (Vogel et al., 1989; Burrows et al., 1990) also report a high incidence of arterial complications when the femoral artery was used for vascular access. No neurological sequelae were seen after anterograde balloon dilation, although a thrombus within the left atrial appendage did develop in the smallest patient. This occurrence can be lessened by systemic heparinization. Avoidance of direct manipulation of the carotid artery removes the potential for acute and long-term neurologic sequelae due to vessel compromise.

In all but the first two attempted anterograde dilations, the valve was successfully crossed and dilated. Significant reductions in systolic pressure gradients were achieved with improvement in left ventricular function, when impaired. No deaths occurred, and there was a low incidence of mitral incompetence, only one arterial thrombosis and a single occurrence of thrombus in the left atrial appendage.

Conclusions

Compared with retrograde balloon dilation of the aortic valve, the anterograde approach has lower mortality and morbidity and should be considered for neonates in the biventricular repair category.

Chapter 5

Aortopathy

Part 1: Stent implantation for aortic coarctation and recoarctation.

Introduction

Balloon dilatation has largely been accepted as the treatment of choice for recoarctation of the aorta but is less well established in the treatment of native aortic coarctation despite similar results (McCrindle et al., 1996). Within the first year of life and particularly within the first month, the high restenosis rate and the rate of femoral arterial complications after balloon dilatation of aortic coarctation supports surgical repair as the preferred option (Mendelsohn et al.,1994; Rao et al., 1996; Fletcher et al., 1995). In older patients, however, balloon dilatation of both native and aortic recoarctation has a higher success rate with a lower incidence of restenosis than in infancy (McCrindle et al.,1996; Mendelsohn et al.,1994; Rao et al., 1996; Fletcher et al., 1995; Huggon et al., 1994; Hijazi et al., 1991; Hellenbrand et al., 1990; Anjos et al., 1992) but there are concerns about acute aortic dissection (Hellenbrand et al., 1990; Balaji, Oommen and Rees, 1991) and the late development of aneurysms (Aydogan et al., 1995; Tynan et al., 1990). It is of note that aneurysm formation is an increasingly recognized complication after various types of surgical repair (Pinzon et al., 1991; Bromberg et al., 1989), particularly when the results are evaluated by routine magnetic resonance imaging (Parks et al., 1995).

Balloon expandable endovascular stents have a long history in the treatment of peripheral (Palmaz et al., 1988) and subsequently atherosclerotic (Serruys et al., 1994) coronary artery disease. Since 1989, stent implantation has been applied in congenital heart disease principally in the pulmonary arteries and systemic veins (O'Laughlin et

al., 1991). After balloon dilatation, vessel recoil may lead to restenosis. Stents prevent this and thus maintain the effectiveness of dilatation within these structures. In addition, the integrity of the vessel is maintained by preventing the extension of any vessel tears or dissection between vessel layers that may have occurred after balloon angioplasty. Some studies have already described the application of endovascular stents in the treatment of aortic coarctation or recoarctation (Bulbul et al., 1996; Cheatham et al., 1998). While their use in younger children is limited by their ultimate maximum expanded diameter, their application in older children, adolescents and adults appears promising.

We report our experience of stent implantation in both native and postoperative coarctation of the aorta in older children and adults. In older patients with native coarctation or those postoperative patients who had no previous balloon angioplasty, we elected to proceed directly to stent implantation in order to reduce aneurysm risk. We wish to emphasize the role of staged dilatation in an attempt to further reduce the incidence of aneurysms that may still occur after stent implantation (Cheatham et al., 1998) and the use of spiral computed tomography (CT) in the non-invasive follow up evaluation.

Methods

Patient population: Between November 1983 and June 1998, 17 patients (3 female, 14 male) underwent stent implantation for aortic coarctation and recoarctation. The median age at the time of stent implantation was 17 years (range 4.4 to 45 years) and the median weight was 61 kg (range 17 to 92 kg). Six patients had native coarctation and 11 had aortic recoarctation (Table 5). Of those with aortic recoarctation, the initial type of surgical repair was subclavian flap aortoplasty in 5, onlay Dacron patch repair in two, resection of coarctation with end to end anastomosis in three, and insertion of a 12 mm conduit bypass graft in one. Of those initially repaired by subclavian flap aortoplasty, one had also undergone balloon dilatation of recoarctation followed by Dacron patch repair and subsequently implantation of a conduit from the left common carotid artery to the descending aorta. This patient has been described in an earlier case report (Huggon et al., 1994).

One patient had two previous balloon dilatations; two had one previous balloon dilatation, and one had resection of recoarctation with end to end anastomosis followed by balloon dilatation. Two of the three patients who initially had repair by resection of coarctation with end to end anastomosis and one of the two patients who previously had repair by Dacron patch also underwent unsuccessful ballon dilatation. Therefore 23 previous procedures in all had been performed in these 11 patients to treat coarctation.

Patient	Age	Wt	Diagnosis	Previous surgery	Previous balloon	Upper limb BP	Drug treatment
1	14	60	COA	SC Flap, Dacron patch, conduit	BD x 1	160/50	Captopril/nifedipine/ atenolol
2	29	67	COA, AS	SC Flap, E/E, AVR	BD x 1	160/90	Nifedipine/Aldactide
3	35	92	COA	E/E	None	160/100	None
4	6	20	COA, AS	None	None	138/88	None
5	8	22	COA	SC Flap	BD x 2	115/66	Atenolol
6	16	75	COA	Dacron patch	None	146/69	None
7	24	57	COA	Dacron patch	BD x 1	145/80	None
8	10	17	COA, supra AS	None	None	158/80	None
9	43	58	COA, AS	None	None	140/70	None
10	45	74	COA, AS	None	None	155/85	None
11	45	83	COA	None	None	180/110	None
12	26	64	COA	None	None	156/74	None
13	8	28	COA	E/E	BD x 1	120/70	Propranolol
14	18	62	COA, TOF	Conduit	None	160/80	Enalapril/nifedipine/ acebutolol
15	16	67	COA	SC Flap	BD x 1	155/100	Enalapril/nifedipine
16	4	19	COA	E/E	BD x 1	150/90	Nifedipine
17	13	45	COA	SC Flap	BD x 1	190/105	Amlodipine/ perindopril

Table 5. Patient details. Key: AS, aortic stenosis; AVR, aortic valve replacement; BD, balloon dilatation; BP, blood pressure; COA, coarctation of the aorta; E/E, resection end to end anastomosis; SC Flap, subclavian flap aortoplasty; Supra AS, supravalve aortic stenosis; TOF, tetralogy of Fallot.

Four patients also had additional aortic valve stenosis, one of whom had previous mechanical aortic valve replacement and two had undergone aortic valve replacement using pulmonary autografts after having had the coarctation treated with stent implantation. One patient had moderate aortic stenosis, which had not required treatment at the time of writing. One patient had Williams syndrome and mild supravalvar aortic stenosis. One patient had previous repair of tetralogy of Fallot and a double aortic arch. This patient was later noted to have a long segment coarctation which had been treated by the insertion of a 12 mm conduit bypass graft.

Indications for intervention: All patients had reduced femoral pulses and Doppler echocardiographic evidence of coarctation of the aorta. Fourteen patients had evidence of resting upper limb systolic hypertension (systolic blood pressure > 95th centile for age) and six of these also had significantly raised diastolic pressures (> 95th centile for age). The remaining three were normotensive, but one had evidence of significant aortic stenosis requiring treatment and the remaining two were on antihypertensive drugs. The blood pressures had been measured supine during outpatient clinic visits using standard mercury sphygmomanometers. Eight patients were receiving antihypertensive treatment with either a single drug (3 patients) or a combination of drugs (5 patients) before intervention.

Stent implantation technique: Written informed consent was obtained from the patients-or in the case of children, from their parents-for the procedures, all of which were performed under general anaesthesia.

Percutaneous entry was made into the femoral artery for angiography, as well as for the measurements of the ascending and descending aortic pressures and pullback gradients across the coarctation site. For stent delivery, percutaneous puncture was made into the contralateral femoral artery in 13 of the patients and a cutdown was performed onto the right common carotid artery in the remaining four. In these four youngest patients, a carotid artery approach was chosen in view of the diameter of the long introducing sheath required for stent deployment. Following the measurement of a pullback pressure gradient, an arch aortogram was performed (Fig. 21A) and the diameters of the transverse arch, minimum diameter of the coarctation site, and the diameter of the descending aorta at the level of the diaphragm, together with the length of the narrowed segment, were measured using electronic calipers. The measured catheter diameter or the 1 cm divisions on a ‘marker’ catheter (USCI Inc, Billerica, Massachusetts, USA) were used to correct for magnification. The angiographic catheter was left across the coarctation site for check angiography to aid positioning of the stent and was withdrawn just before deployment of the stent. Palmaz ‘iliac stents’ (7 x 308, 9 x 4014, 2 x 5014: Johnston and Johnston, Warren, New Jersey, USA) were manually crimped onto a variety of balloons (12 Olbert: Boston Scientific, Watertown, Massachusetts, USA; four

Cristal: E Merck Inc, Montmorency, France; one Blue-Max: Boston Scientific; and one Powerflex: Cordis Europa, Roden, Netherlands).

After dilating the site of arterial access, an 11 F Mullins long transeptal sheath (Cook Europe, Bjaeverskov, Denmark) was advanced over an Amplatz SuperStiff guidewire (Meditech, Watertown, Massachusetts, USA) through the femoral or common carotid artery and across the coarctation site. Depending on the diameter of the balloon on which the stent was to be mounted, it was occasionally possible to use a smaller sheath, for example 9F. The stent/balloon assembly was then advanced through the sheath to the desired site. After a final check angiogram, both the angiographic catheter and the sheath were withdrawn to uncover the stent, and the balloon was inflated using an Indeflator. In the first three patients stents were fully expanded to the diameter of the normal vessel on either side of the coarctation, but in subsequent patients care was taken not to fully expand the balloon, or else an undersized balloon was chosen intentionally in order to reduce the likelihood of aortic wall damage. After the stent was deployed, simultaneous pressure measurements were made using the angiographic catheter and the delivery sheath, and a further aortogram was performed (Fig. 21B). At the conclusion of the procedure, the carotid artery cutdown sites were repaired and haemostasis obtained.

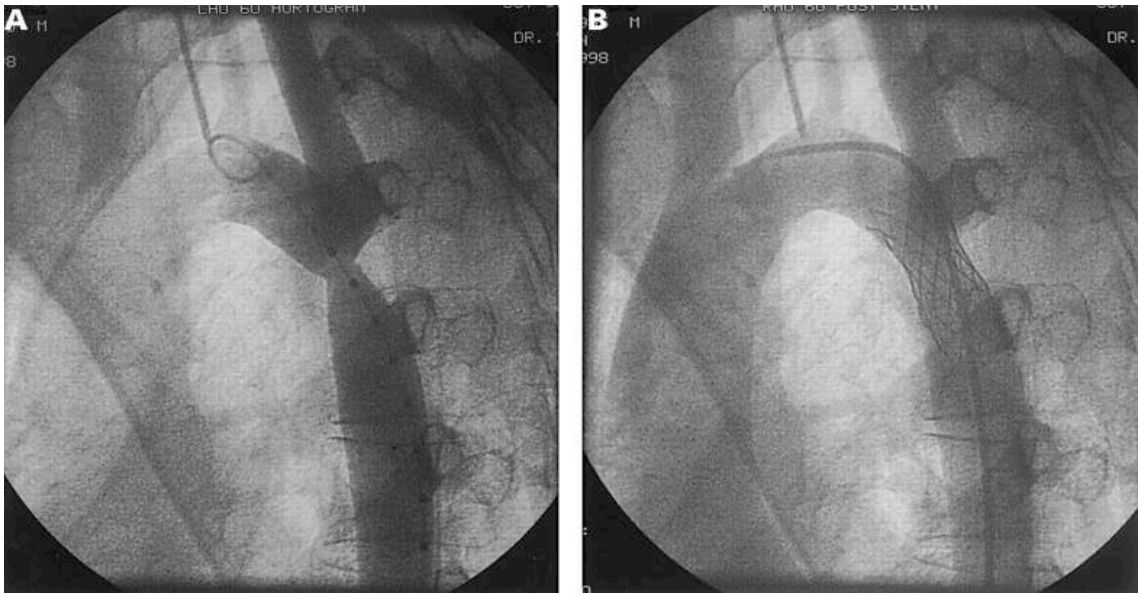


Figure 21. (A) Long axis aortogram using a 'marker' pigtail catheter showing discrete native coarctation in a patient who also had severe aortic valve stenosis. (B) Repeat aortogram following expansion of a Palmaz 4014 stent using an 18 mm 'Cristal' balloon. The stent is partially covering the origin of the left subclavian artery.

Antibiotics were given one hour before stent implantation and continued for 48 hours afterwards. A heparin bolus of 50-100 units/kg was injected intravenously following establishment of arterial access and continued as an infusion of 15-30 units/kg/hour for 48 hours after the end of the procedure, to maintain an activated clotting time of over 200 seconds. All the patients received an antiplatelet dose of aspirin (3-5 mg/kg/day) beginning on the day after the procedure and continuing for six months. In addition, four patients were fully anticoagulated with warfarin including the patient with the mechanical aortic valve, and the three patients at the start of the series.

Follow up investigations: All except one patient underwent evaluation with spiral computed tomography between 2 days and 46 months after stent implantation (median interval 7.5 months). The early scans were performed in the two patients proceeding to aortic valve replacement. Helical CT acquisition was performed during single breath holding with a 3 mm slice thickness and a pitch of 1.66 (Fig. 22A). Axial images were reconstructed at 2 mm increments and used to generate high quality multiplanar reformatted three dimensional images (Fig. 22 B). during acquisition, 150 ml of intravenous non-ionic contrast medium (Ultravist 240 mg/ml) was administered at a rate of 3 ms/sec.

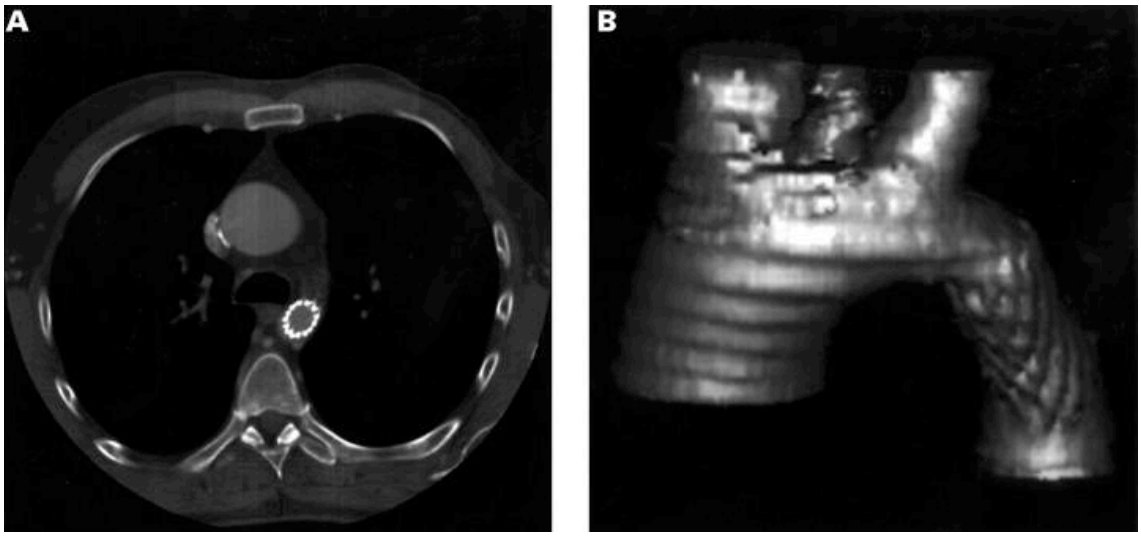


Figure 22. (A) Follow up spiral computed tomography (CT) with contrast showing stented aorta in cross section.(B) Axial three dimensional reconstruction of CT images in the same patient showing no evidence of aneurysm formation.

Seven patients underwent repeat cardiac catheterisation. The indications for second catheterisation were clinical evidence of recoarctation in one patient, continuing hypertension in four, and the presence of an aneurysm on computed tomography in one. The remaining patient, a 10 year old boy, underwent a second elective catheterisation a year after the initial stent procedure to dilate the stent further.

Statistics

Results are given as medians with ranges or as means with 95% confidence intervals (CI). Comparisons were made using the paired Student *t* test. A p value of < 0.05 was considered significant.

Results

Immediate results: Eighteen stents were implanted during 18 procedures in 17 patients (Table 6). The mean peak systolic pressure gradient fell from 26 mmHg (95% CI, 21 to 31 mmHg, range 12 to 55 mmHg) before to 5 mmHg (95% CI, 2 to 8 mm Hg, range 0 to 20 mmHg) after stent implantation ($p < 0.001$), and the mean minimum aortic diameter increased from 7 mm (95% CI, 6 to 8 mm, range 2 to 10 mm) before to 11.3 mm (95% CI, 10 to 12.6 mm, range 7 to 16 mm) after stent implantation ($p < 0.001$). The mean ratio of the expanded stent diameter to the transverse aortic arch diameter was 0.75 (95% CI, 0.67 to 0.83) and the mean ratio of the expanded stent diameter to the descending aorta diameter was 0.76 (95% CI, 0.7 to 0.82). The peak systolic gradients were > 20 mmHg under general anaesthesia in 13 patients (76%) before

Patient	Min diam	Arch diam	Ao at diaphragm	Stent min diam	Ratio stent to arch	Ratio stent to Ao at diaphragm	Systolic gradient pre-stent	Systolic gradient post stent	Stent redilate
1	6.4	11.3	12.0	11.9	1.05	0.99	40	0	Yes
2	10.1	20.0	22.0	12.8	0.64	0.58	12	0	
3	9.1	19.1	21.5	14.0	0.73	0.65	17	10	
4	7.4	16.0	14.4	13.6	0.85	0.94	13	0	
5	5.1	11.3	10.4	7.4	0.65	0.71	34	20	Yes
6	8.8	18.5	13.9	11.0	0.61	0.78	20	10	Yes
7	8.3	11.0	13.0	10.5	0.95	0.81	13	5	
8	5.3	11.4	8.8	7.0	0.60	0.8	20	0	Yes
9	7.0	18.4	16.2	13.2	0.72	0.81	20	0	
10	10.3	30.0	22.0	16.0	0.53	0.73	25	2	
11	7.9	22.4	16.2	13.3	0.59	0.82	31	0	
12	4.5	16.5	14.2	12.0	0.73	0.85	23	0	
13	4.3	10.0	10.0	7.4	0.74	0.74	30	2	Yes
14	2.0	16.0	12.0	10.0	0.63	0.83	55	10	Yes *
15	9.0	14.0	25.0	13.0	0.93	0.52	25	10	
16	5.0	11.0	12.0	7.0	0.64	0.58	30	8	
17	7.0	11.0	17.0	12.0	1.09	0.71	31	15	

Table 6. Aortic measurements and results of stent implantation,*second stent implanted.

stent implantation, and between 10 and 20 mmHg in the remainder. The median fluoroscopy time for the procedure was 17.5 minutes (range 12.4 to 39 minutes).

Complications: Procedure related complications occurred in five patients. The early complications included a groin haematoma in one, haemorrhage from the carotid arteriotomy site requiring further surgical repair in one, and stent migration during deployment in two. There were no other vascular complications at the site of arterial access. The late complication of a small aneurysm related to the stent occurred in one patient.

Stent migration during implantation occurred in two patients with recoarctation of the aorta after previous subclavian flap repair. In both, the narrowest segment of the aorta was just distal to the origin of the left common carotid artery beyond which the aorta widened at the site of subclavian flap repair site to 18 mm diameter in the first patient and to 35 mm diameter in the second. Palmaz P308 stents were used in both patients. In the first patient, the stent slipped during expansion using a 12 mm balloon and embolised to the abdominal aorta where it was expanded further to 16 mm diameter where it remained. A further P308 stent was then placed across the coarctation site, expanded using a 14 mm balloon and the proximal and distal ends further expanded using a 16 mm balloon. In the second patient, the stent slipped back over the balloon just after expansion. The balloon was re-inflated to 14 mm inside the stent, the assembly was readvanced across the coarctation site and the balloon expanded further to 16 mm (equivalent to the diameter of the transverse arch), after which the stent remained in position.

Formation of a small aneurysm was detected at angiography six months later in one patient (no. 14). This patient had a long segment coarctation of 2 mm diameter previously treated by a conduit bypass graft and had a systolic pressure gradient of 55 mmHg. A P4014 Palmaz stent was expanded to 12 mm with a good immediate angiographic result. Late angiography performed because of a residual systolic pressure gradient of 30 mm Hg, showed an aneurysm at the midpoint of the stent. At that time a further P5014 stent was implanted overlapping the initial stent in an attempt to prevent extension of the aneurysm. Serial computed tomography over the next two years has shown no increase in the size of the aneurysm.

Follow up results

Spiral computed tomography

Computed tomography was performed at least once during follow up in 16 patients after the initial procedure and apart from the one patient mentioned above, none had aneurysm formation. All the scans showed continued patency of the stent and of any head and neck vessels with origins partly covered by the stent (Fig. 23).

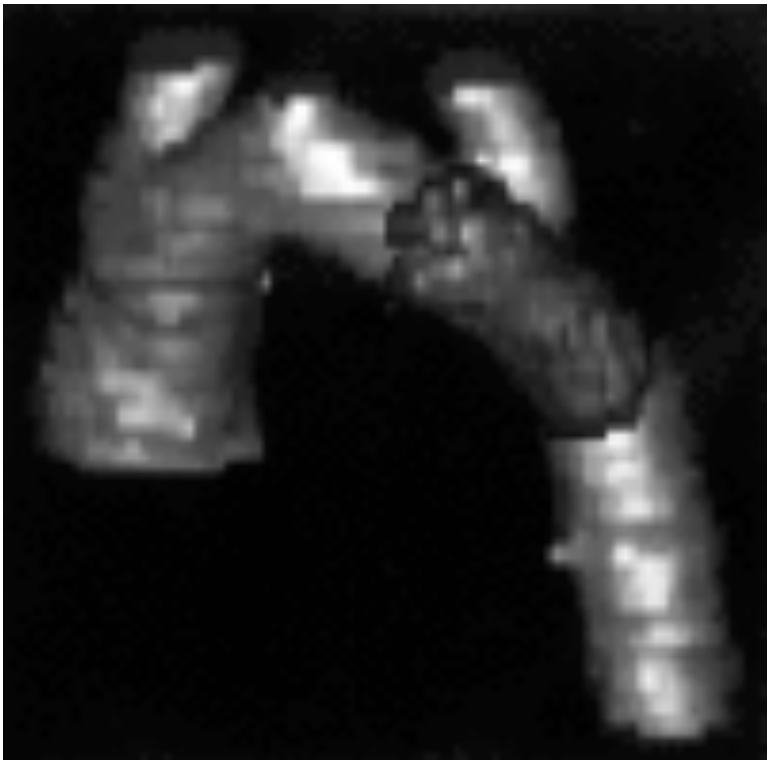


Figure 23. Three dimensional reconstruction of spiral computed tomography images with contrast taken nine months after stent implantation in the patient shown in Fig. 1. The stent has been outlined in a different shade of grey from the aorta. Note continued patency of the left subclavian artery.

Recatheterisation and stent redilatation

Recatheterisation was performed in seven patients after a median interval of 11.3 months (range 6 to 35 months) from the initial procedure. In five patients, further balloon dilatation was performed with reduction of residual peak systolic pressure gradients from a mean of 15 mm Hg to a mean of 2 mm Hg and three of these patients have since undergone spiral computed tomography with no evidence of aneurysm formation. In one patient, a gradient of only 6 mm Hg was found at recatheterisation and reintervention was not performed. The remaining patient, who had the aneurysm,

has had two recatheterisations, at 9 months and 17 months after the second stent implantation. On each occasion, the peak systolic gradient across the stented area was 35 mm Hg; however, as the aneurysm was still present, albeit small, no further intervention was performed.

Blood pressure

No patients had acute hypertensive crises immediately after stent implantation. At the most recent follow up, eight patients were nomotensive and were not receiving any treatment (including two patients who had previously been treated with antihypertensive drugs). One untreated patient had borderline systolic hypertension (152/62 mmHg). Eight patients were still on antihypertensive treatment which consisted of one drug in five patients and a combination of drugs in three. One of these patients still had borderline systolic and diastolic hypertension (150/95 mmHg).

Discussion

The choice of treatment of aortic coarctation and recoarctation is between balloon dilatation and surgery using several different techniques. Each type of treatment is associated with a variety of complications. While balloon dilatation may produce good results in around 60-75% of the patients (Bulbul et al., 1996), it is associated with a low but important incidence of aneurysm formation. On theoretical grounds, therefore, it was felt that stent implantation would avoid aneurysm formation. In our series, stent

implantation has been shown to be effective in acutely reducing the pressure gradient, but it was still associated with aneurysm formation, albeit with a lower incidence. In hypertensive patients, the upper limb blood pressures are brought under control more easily, although continued antihypertensive treatment is often required. Follow up computed tomography showed continued patency of the stents, and no new aneurysm formation was noted even after redilatation of the stents. In the rare clinical situation of aortic coarctation combined with aortic stenosis, treatment of the coarctation with stents may have an important role. In this, stent implantation avoids the operative hazards of treating both conditions surgically (Pethig et al., 1996) and makes subsequent aortic valve surgery more straightforward. We encountered a low incidence of complications at the level of vascular access. Patients who underwent a surgical approach from the carotid artery should have ultrasound angiography of the cutdown site at a later date.

We did not attempt to compare the results obtained with stent implantation with either surgery of balloon angioplasty techniques, in particular in the patients with aortic recoarctation. However, many of these patients had already undergone unsuccessful previous surgical or balloon angioplasty procedures.

Surgery in this situation may be technically more difficult, may often involve the use of patches or conduits, and runs a potential risk of causing compromise to the spinal blood supply. Surgical repair using synthetic patches is fraught with serious complications

such as a high incidence of aneurysm and late death from aneurysm rupture (Knyshov et al., 1996). While balloon dilatation may be considered to be better than surgery, there is a high proportion of cases (25%) with a suboptimal outcome as defined by a residual gradient or major complications (McCrindle et al., 1996). In that large series of 907 patients, these complications included death (0.7%), transmural aortic tear (0.7%) and stroke (0.6%).

The mechanism of successful balloon dilatation of coarctation involves tearing of the aortic intima and media. In vitro histological studies (Lock et al., 1982; Ho et al., 1988) and in vivo studies by intravascular ultrasound (Ino et al., 1998; Harrison et al., 1990) have confirmed this mechanism. However, it is impossible to control the extent of the tearing which may extend transmurally. In addition, no safe upper limit has been defined for the required balloon diameter in relation to any aortic diameter measurement. Thus there will inevitably be a risk of aneurysm formation with balloon dilatation. In contrast, during stent implantation it is not necessary to over-dilate the coarcted segment to produce a good and predictable result. In addition, the stent can buttress the aortic wall, thus preserving its integrity and preventing the extension of any tears that may be produced. However, in spite of this aneurysm formation was encountered in one patient who had an unusually long segment coarctation. It is

possible that this resulted from overdilatation of the narrow segment from 2 mm to 12 mm. In another study of stent implantation for aortic coarctation/recoarctation (Cheatham et al., 1998), the incidence of aneurysm formation was 13%. Following this complication in our series, we have modified our policy to adopt an approach of performing a staged dilatation. Thus the balloon is either not fully inflated to the diameter of the adjacent measured normal vessel at the time of stent implantation, or a smaller sized balloon is chosen. If necessary, a further dilatation is performed after six to 12 months in order to achieve complete expansion of the stent. In five of 17 patients in our study, redilatation of the stents was successfully achieved without any complications. If and when a significant aneurysm develops, a covered stent could be implanted. We are aware of covered stents having been used in adult patients with abdominal aortic aneurysms and thoracic aortic dissection.

Redilatation of stents in animal models of coarctation has produced conflicting results. Morrow et al. (1994) re-expanded stents in five animals and noted compression of the media beneath the struts but no evidence of dissection of the intima or media. However, Mendelsohn et al. (1996) encountered aortic rupture and death in two of seven animals at redilatation. To our knowledge, aortic rupture has not occurred during redilatation of the aortic stents in humans. Improvements in stent design including rounding of sharp edges or even the use of absorbable materials which might further lower the risk of such tramsmural damage during both dilatation and redilatation. The avoidance of

pre-dilatation with a balloon just before stent implantation may also reduce the risk of aortic damage.

Successful balloon dilatation of both native (Schrader et al., 1995) and recurrent coarctation (Witsenburg et al., 1993) of the aorta can bring upper limb hypertension under control in the medium term, even in adult patients. In our series, the patients were often hypertensive before stent implantation in spite of combinations of anti-hypertensive drugs. In the medium term, blood pressure has either normalized or has been easier to control with a more simplified drug regime. There is a theoretical concern that aortic stents may cause increased aortic wall impedance (Xu et al., 1997) and therefore systolic hypertension during exercise, but such a mechanism may occur in the post surgical aorta owing to scar formation or patch aortoplasty.

One further theoretical concern might be the compromise of blood flow to small side branches arising from the aorta, particularly those supplying the spinal cord. Continued patency of side branches in the coronary circulation has been demonstrated after stent implantation (Schatz et al., 1987) and here have been no reports of spinal cord damage after aortic stent implantation thus far.

Conclusion

Stent implantation for aortic recoarctation and native coarctation is successful in older children and adult patients and the acute results are encouraging. Upper limb blood pressure can be brought under improved control although some patients continue to require antihypertensive treatment. Short term follow up shows continued relief of stenosis with a low incidence of complications but longer follow up is necessary.

Aortopathy

Part 2: Combined interventional and surgical management of aortic stenosis and coarctation.

Introduction

Athough a bicuspid aortic valve is a common finding in association with coarctation of the aorta (Becker, Becker and Edwards, 1970), the combination of significant aortic stenosis and coarctation of the aorta appears to be much less common outside the setting of hypoplastic left heart syndrome. In children, aortic valve stenosis has been reported in 7% of a large group undergoing balloon angioplasty of native coarctation of the aorta (McCrindle et al., 1996). In adults, severe aortic valve stenosis has ben reported in 4% of those with aortic coarctation or following resection of coarctation (Turina et al., 1997). When this combination arises, the possible surgical options consist of either a two-staged surgical approach (Turina et al., 1997) or a one-stage surgical repair combining aortic valve replacement with the insertion of a Dacron graft from the ascending to the descending aorta (Bartoccioni et al., 1995; Thomka, Szedo and Arvay, 1997).

We report 2 patients,who underwent implantation of an endovascular stent for coarctation of the aorta as an initial procedure followed within 2 weeks by aortic valve replacement using pulmonary autografts (Gonzalez-Lavin et al., 1970). Spiral CT scanning was performed prior to the valve replacement to confirm the absence of aortic aneurysm following stent implantation.

Case histories

Patient 1: Clinical evidence of significant aortic valve disease was discovered incidentally in a normotensive 42 year old man during an accident and emergency attendance. A cross-sectional echocardiogram revealed left ventricular hypertrophy and a Doppler estimated gradient of 70 mmHg across the aortic valve together with a suspicion of aortic coarctation. Cardiac catheterization confirmed calcific aortic stenosis, additional discrete coarctation of the aorta with a peak systolic pressure gradient of 30 mmHg and normal coronary arteries. For 2-3 months prior to admission for surgery he began to experience dyspnoea on exertion.

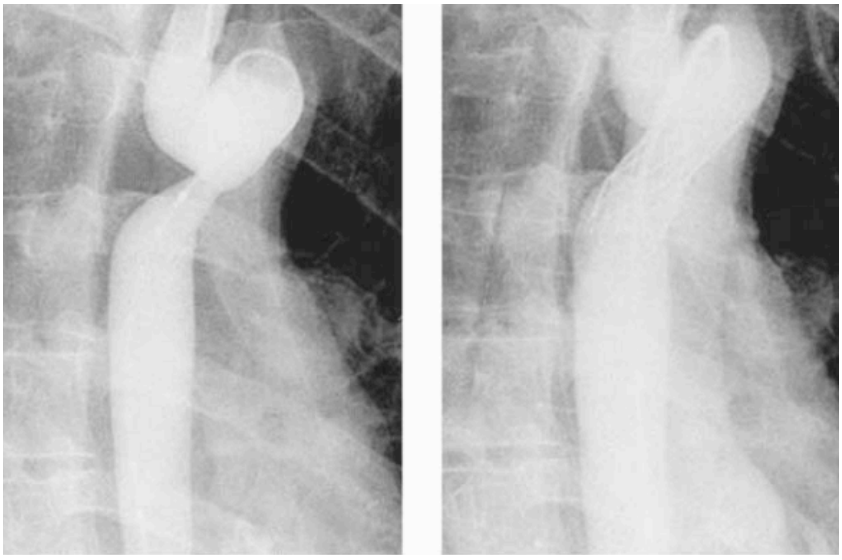
Patient 2: A 44 year old man was found to have a heart murmur in infancy but was not investigated and remained asymptomatic. During an employment medical, he was found to have borderline hypertension (BP 155/85 mmHg) and a loud murmur was heard. He was referred for echocardiography which showed the combination of moderate aortic stenosis (Doppler estimated systolic gradient of 60 mmHg and a tight coarctation of the aorta (Doppler estimated systolic gradient of 50 mmHg). Cardiac catheterization showed normal coronary arteries and confirmed a discrete coarctation of the aorta.

Procedures

Stent implantation: After obtaining written informed consent, the procedures were performed under general anaesthesia with percutaneous entry via the femoral arteries.

Systolic pressure gradients across the coarctation site were 25 mmHg and 30 mmHg and angiography revealed a discrete coarctation of the aorta in both patients with minimum diameters of 7 mm and 10 mm. The diameters of the adjacent aorta above and below the coarctation sites were 25 mm and 16 mm in the first patient and 17 mm and 20 mm respectively in the second patient.

Full anticoagulation with 100 units/kg of heparin and antibiotics (gentamicin and flucloxacillen) were administered prior to stent implantation. After dilating the site of femoral venous access, an 11 Fr. Mullins long trans-septal sheath (Cook Europe, Denmark) was advanced over an Amplatz Superstiff guidewire (Meditech, Watertown, Mass. USA) previously placed across the coarctation site. A 4014 ‘Palmaz’ iliac stent (Johnson and Johnson, Warren, NJ) was mounted and hand crimped onto an 18 mm Cristal angioplasty balloon (E Merck Inc., Montmorency, France) and advanced through the long sheath to the desired position. After check angiography, both the angiographic catheter and the sheath were withdrawn to uncover the stent and the balloon was inflated using an inflation device. Care was taken not to expand the stent fully to the diameter of the adjacent aorta. After stent deployment, simultaneous pressures proximal and distal to the stent were measured using the angiographic catheter and the delivery sheath, and a further aortogram was performed (Fig. 24). There were no residual gradients and the narrowest aortic diameters had increased to 13 mm and 16 mm respectively. At the conclusion of the procedure haemostasis was achieved by direct manual pressure. There were no complications in either patient.



A B

Figure 24. Aortogram (A) in a right anterior oblique projection showing a discrete coarctation of the aorta just distal to the left subclavian artery in patient 1 who also had severe calcific aortic stenosis. After stent implantation, (B) there is a substantial increase in the minimum vessel diameter with abolition of the pressure gradient.

Heparin infusion was continued for 48 hours following the procedure to maintain an activated clotting time of 200 seconds and antibiotics were continued over the same period. An anti-platelet dose of aspirin (3-5 mg/kg) was commenced on the day after the procedure for 6 months. Spiral CT scanning was performed at 3 and 6 days respectively after stent implantation, and this showed no evidence of aneurysm formation in either patient.

Aortic valve replacement: Both patients underwent aortic valve replacement using pulmonary autographs 7 and 15 days respectively after stent implantation within the aortic coarctation. The pulmonary roots were reconstructed using 24 mm pulmonary homografts. In the second patient the right coronary button disintegrated during the operation, and a short segment of the long saphenous vein was therefore harvested and anastomosed to the stump of the proximal right coronary artery with the proximal end of the graft being anastomosed to the ascending aorta. Both patients were weaned from cardiopulmonary bypass uneventfully. However the second patient had problems with needle point haemorrhage in the operating theatre and also developed a large pleural effusion several days after surgery which required drainage.

At the most recent follow-up visit (9 months after the valve replacement) both patients are well with normal arm blood pressure. Repeat spiral CT scanning has also been performed in both patients at 9 and 6 months respectively after surgery with no evidence of aortic aneurysm formation.

Discussion

The combination of significant aortic stenosis and coarctation of the aorta can present a significant challenge in the adult population. When valve replacement is performed first as part of a staged approach there is a potential for difficulty in re-establishing the patient's circulation in the face of persistent left heart obstruction. A single stage approach involving trans-pericardial bypass of the coarctation has evolved as it may be

difficult to reach the coarcted segment from the midline. When such an approach is employed, difficulty in weaning from cardiopulmonary bypass has been reported (Pethig et al., 1996). Therefore non surgical treatment of the coarctation could offer a significant advantage. Stent implantation has been successfully performed in older children and adults with both native and recurrent coarctation of the aorta (Bulbul et al., 1996). Although it should theoretically reduce the risk of transmural tears and aneurysm formation when compared with balloon angioplasty alone it does not abolish the risk of aneurysm formation entirely. Therefore careful evaluation by CT scanning is necessary before proceeding to cardiopulmonary bypass.

Conclusion

Two stage combined interventional and surgical management of aortic stenosis and native coarctation of the aorta was performed successfully in 2 patients. To our knowledge this approach has not been previously described. Both patients were easily weaned from cardiopulmonary bypass and remain well at latest follow-up. Neither patient has developed any evidence of aortic aneurysm formation related to the stent and both remain normotensive. While continued follow-up is necessary we believe this combined approach offers significant advantages over previous strategies for managing this condition.

Chapter 6

Balloon expandable stent implantation for superior vena caval obstruction following surgical repair of partial anomalous pulmonary venous drainage: medium term follow-up.

Introduction

Partial anomalous pulmonary venous drainage (PAPVD) accounts for 0.5% of congenital cardiac defects (Martinez-Jimenez et al., 2010). It most commonly involves the right upper pulmonary vein and usually coexists with a sinus venosus atrial septal defect (Oliver et al., 2002). Physiologically the effect is identical to any shunt at atrial level, the right heart will dilate producing breathlessness on exertion in adult life and some patients will go on to develop atrial arrhythmias and pulmonary hypertension (Webb and Gatzoulis, 2006). Surgical repair is usually performed by inserting a patch of autologous pericardium to direct flow from the pulmonary vein or veins across the atrial defect and into the left atrium (Gaynor et al., 1995). The caval to atrial junction may then be patch enlarged to prevent stenosis. The more superiorly the pulmonary vein enters the superior vena cava (SVC) the greater the chance of producing caval or pulmonary vein stenosis because of the smaller available SVC lumen (DeLeon et al., 1993). An alternative is to use the Warden technique (Warden et al., 1984) when the SVC is transected and oversewn above the anomalous pulmonary vein or veins and then coapted or baffled across the atrial septum to the left atrium (Fig. 25). Normal SVC-right atrial flow is reconstituted by anastomosis of the cephalad portion of the transected SVC to the right atrial appendage. Surgery is often delayed following diagnosis in smaller children to reduce the risk of venous obstruction.

Although the Warden technique should lessen the risk of obstruction to pulmonary venous return it does not completely remove the risk of superior vena caval obstruction (Tzifa et al., 2007).

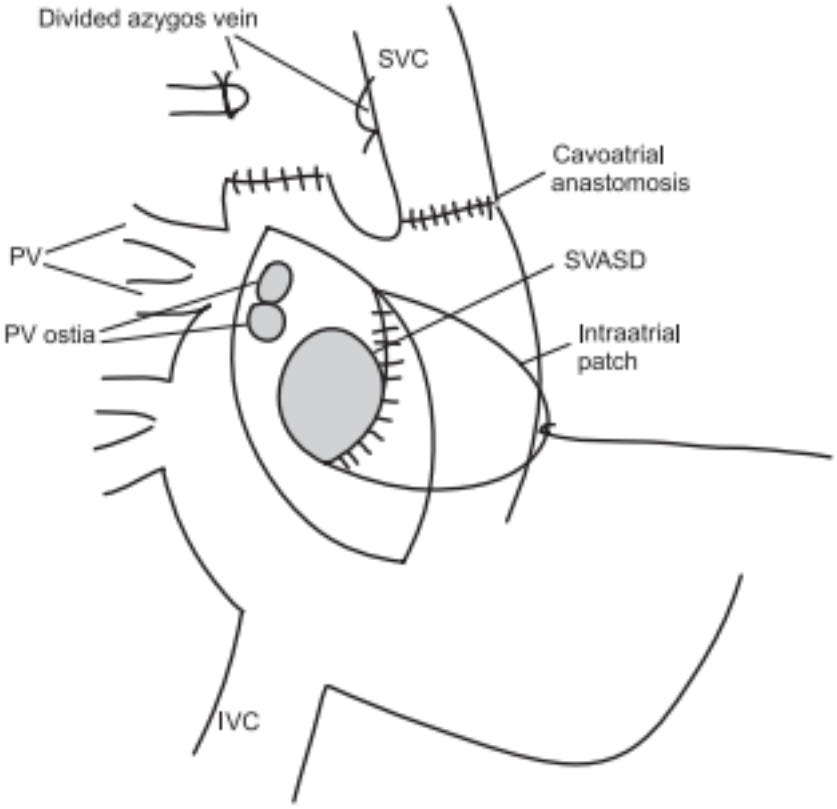


Figure 25. Diagram of Warden procedure for repair of partial anomalous pulmonary venous return from *Sogat V, Sagat M, Balazova E, Siman J. (2008) Outcomes after surgical repair of sinus venosus atrial septal defect in children. Bratislava Medical Journal,109, 215-219.*

Patients with SVC obstruction often present with headaches and facial puffiness especially in the morning, shortness of breath is a frequent finding however a number are asymptomatic and only diagnosed incidentally (Tzifa et al., 2007). On examination there might be evidence of SVC syndrome with upper body venous

congestion and facial oedema.

Three patients developed SVC obstruction following surgical repair of partial anomalous pulmonary venous drainage. The acute and medium term results of stent implantation are presented.

Patients and methods

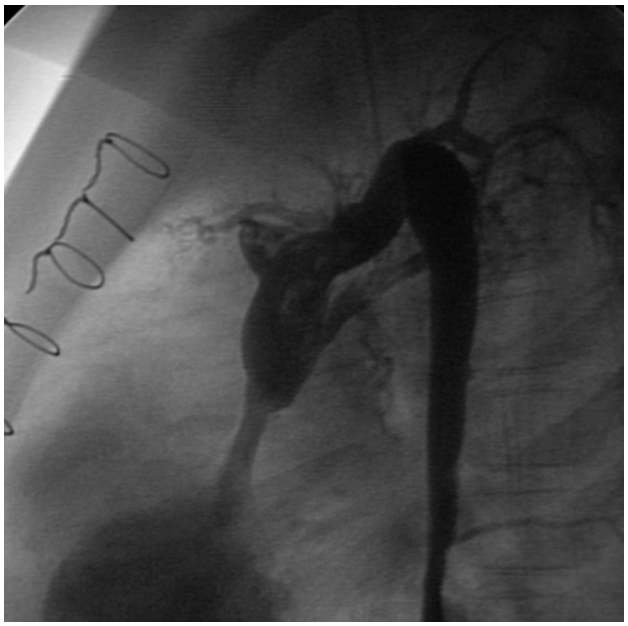
Patients: From the total congenital surgical database, 3 patients were identified over a 10 year period who presented with symptoms of headaches and also had echocardiographic evidence of SVC obstruction (Table 7), weights ranged from12.9-24.3 kg. Conventional repair had been performed in 2 patients and a Warden procedure in one.

Methods: All catheter procedures were performed under general anaesthesia with percutaneous entry into the right femoral vein. In one patient the right internal jugular vein was also entered for monitoring purposes. Pressures were measured above and below the stenoses and well as in the pulmonary arteries. Angiograms were performed in antero-posterior and lateral projections (Fig. 26). In the first patient a 10 mm Cordis OPTA balloon (Johnston and Johnston, Warren, NJ, USA) was placed across the stenosis and dilated to 5 atmospheres with recoil of stenosis. This patient then underwent stent implantation using a 39 mm Palmaz Genesis stent over an 8 mm Blue Max balloon (Boston Scientific, Mn, USA) which was further dilated to 12 mm using a

Cristal balloon (Balt, Montmorency, France). Care was taken to cover the narrowest portion of the SVC by implanting the stent using roadmaps from the lateral projection. Based on this experience, the other 2 patients went directly to stent implantation using 29 mm and 39 mm Palmaz Genesis stents over 12 mm Cordis OPTA balloons.

All procedures were performed uneventfully. Mean gradients fell from a median of 10 mmHg (range 7-17) to 0 mmHg (range 0-1 mmHg) with minimum diameters increasing from median of 4.6 mm (range 2.5-5) to 9.6 mm (range 7.6-12) (Table 1). Following stent implantation, angiograms were performed in the right pulmonary arteries to look for evidence of hold up of contrast in the territory of the right upper pulmonary vein on the laevophase and none was seen. There were no increases in pulmonary artery pressure and all patients reported a complete resolution of symptoms.

A



B

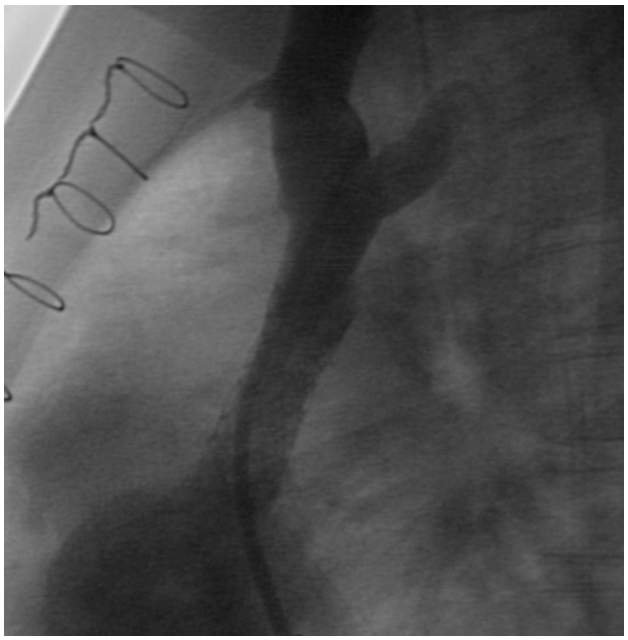
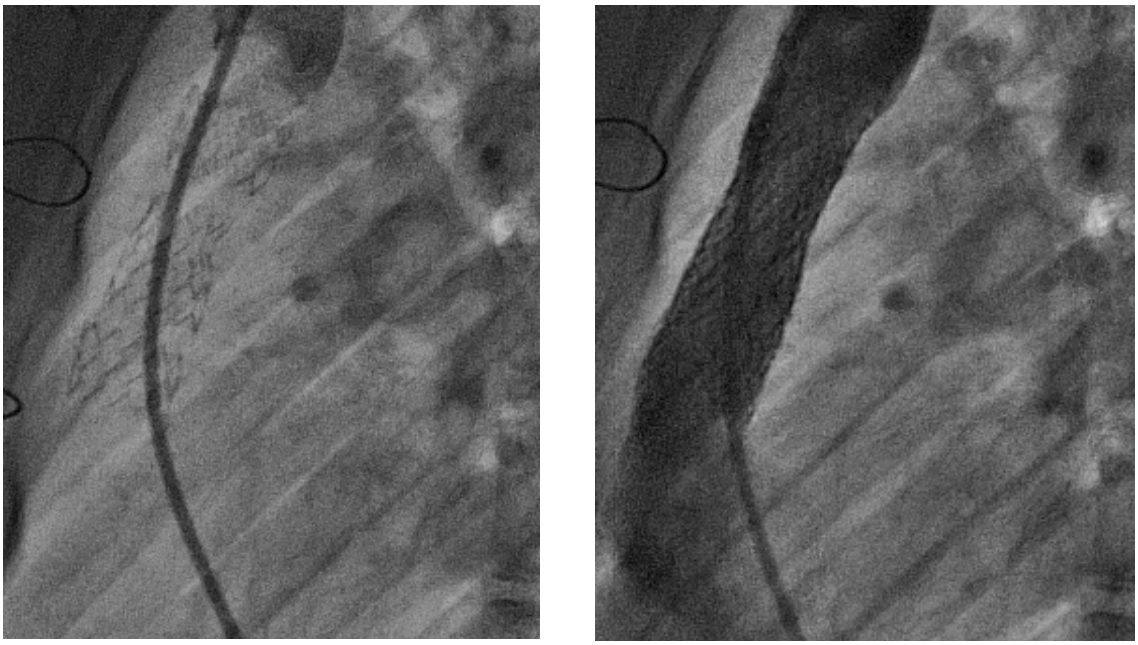


Figure 26. Lateral SVC angiogram before (A) and after (B) stent implantation in patient 2. The initial angiogram is via the azygous vein, following implantation of a 29 mm long Genesis stent the minimum diameter increased from to 10 mm. Note reduction in azygous run-off.

T**able 7**. Patient details and acute results of stent implantation.

Pt	Age surg	Age stent	Diam pre	Diam post	Grad pre	Grad post	Re-int	FU
1	7.7	8.3	5	12	10	0	N	10
2	3.2	3.7	2.5	7.6	7	1	Y	9.9
3	8.4	8.8	4.6	9.6	17	0	Y	9.1

Follow-up: The median duration of follow-up was 9.9 years (range 9.1-10). The first patient has had no further intervention, the most recent ECG shows sinus rhythm with a PR interval of 124 msec and echo shows a mean gradient of 2 mmHg across the SVC with no evidence of pulmonary hypertension. The second patient re-presented with headaches after 2.7 years and echocardiogram suggested narrowing at the lower end of the stent. At catheterization the lower end on the stent was narrowed to 8.5 mm compared to 11.5 mm superiorly. There was a pullback pressure gradient of 2-3 mmHg which was abolished with a single inflation of a 12 mm Cordis OPTA balloon. This patient has remained well with no further recurrence and the PR interval on latest ECG is 120 msec. The third patient had a further routine catheter procedure performed after 6.5 years. The original Palmaz Genesis stent was found to be fractured in 2 places (Fig. 27) and a further 2 overlapping Max LD stents (ev3 Endovascular, Plymouth MN, USA) were implanted uneventfully. A further cardiac catheter 2.6 years later showed continued evidence of normal SVC flow. ECG remains entirely normal.



A B

Figure 27. Lateral angiograms in the third patient 6.5 years after initial stent implantation (A) showing 2 stent fractures and (B) following implantation of 2 Max LD stents over 14 mm balloon with increase in minimum diameter from 9.3 to 10.7 mm .

Discussion:

The most common cause of superior vena caval obstruction in all ages is malignancy especially of bronchogenic origin (Rice, Rodriguez and Light, 2006). The second most common cause is the presence of an indwelling catheter and there appears to be an increasing frequency of SVC obstruction caused by the use of long term venous access (Funaki, 2006; Seelig et al., 1998) and pacemaker leads (Aryana et al., Chee, Bjarnason and Prasad, 2007).

In younger patients the pattern tends to be different. The largest reported series was of 63 patients (Tzifa et al., 2007) with median age 3.7 years (range 1 month to 42 years), 24 had previous atrial switch (Senning or Mustard) procedures for transposition of the great arteries, 12 had previous ECMO cannulation, 10 had previous PAPVD repair and 9 had long term central venous catheters.

For malignant SVC obstruction, endovascular stents have become the treatment of choice (NICE guidelines, 2004) Previously non malignant SVC obstruction was treated using surgical techniques particularly saphenous vein grafts with good long term patency (Kalra et al, 2003) however increasingly angioplasty and stents are gaining acceptance. There are a number of reports of successful relief of stenosis using angioplasty alone (Strecker et al, 2014; Sogat et al, 2008) however this technique does carry a not insignificant risk of causing SVC tears (Tzifa et al., 2007) and in our experience appeared to be ineffective because of vessel recoil although balloon sizes chosen were conservative.

The very first series of the use of balloon mounted stents in congenital heart disease from 1991 included one patient who had stenting of the SVC after repair of sinus venosus ASD (O'Laughlin et al., 1991). Stenting is now the treatment of choice for systemic venous baffle obstruction late after the atrial switch procedure (Bu'Lock et al., 1998) and has even been described (in combination with transeptal needle perforation) in a series of patients following atrial switch where the superior baffle has become

completely blocked (Ebeid et al., 2005). There are now very few patients having an atrial switch for simple transposition however with the development of the double switch procedure for congenitally corrected transposition of the great arteries (Reddy et al., 1997) there will continue to be some patients at risk of baffle obstruction.

There are a few case reports (Nicolae, Radford and Slaughter, 2006) and one series (mentioned above) of stenting for SVC narrowing after repair of partial anomalous pulmonary venous drainage albeit with limited follow-up.

After repair of partial anomalous pulmonary venous drainage there is already the potential for rhythm disturbances related to damage to the sinus node or to its blood supply. A series of 85 patients from Bratislava over a 13 year period revealed a 28% incidence of arrhythmias including junctional rhythm, sinus node dysfunction and atrial ectopic tachycardia (Sogat et al, 2008). On this background, placing a balloon or balloon expanded stent across this area might further raise the chance of dysrhythmia. There is one case report of sinus arrest after stent implantation for SVC syndrome (Tempelhof, Campbell and Ilkannoff, 2014) however this was in an 80 year old and there was complete recovery within 48 hours. None of the patients in our series had any PR prolongation on ECG but it is important to mention the possibility of damage to the sino-atrial node during the consent process.

There is also the potential for SVC rupture during percutaneous stent treatment with a reported total of 4 cases including 1 death and 1 immediate pericardiocentesis followed by open surgical repair (Samuels, Nyzio and Entwhistle, 2007). Therefore, as with all percutaneous techniques, it is important to proceed with caution and have covered stents immediately available in case of a significant tear producing haemodynamic compromise.

Conclusion

This small series of 3 patients with SVC obstruction after repair of partial anomalous pulmonary venous drainage shows effective obstruction relief using balloon expandable stent implantation with good medium term outcome albeit with the need for further intervention.

Chapter 7

Discussion and future direction

Discussion

The essential nature of congenital heart disease is the presence of a defect or defects in the macroscopic structure of the heart resulting from abnormal development thought to occur mostly within the first trimester of pregnancy (Neuman and Huhta, 2006). Around half of the approximately 8 per 1000 babies born with congenital heart disease (Van der Linde et al, 2011) will require treatment and this treatment has to take the form of a physical alteration to the structure of the heart and/or great vessels. Surgical treatment is now well established and outcomes continue to improve (Cunningham et al., 2013) both in terms of efficacy and safety however there is understandably a desire to provide treatment which minimizes the degree of disruption to the individual and their family. Even in the best hands cardiac surgery places a considerable catabolic load on the individual. This is particularly important in neonates and young infants (Costello et al., 2014) and may have implications for future neurological development (Levitt, 2003). Therefore less invasive endovascular techniques have gained popularity both to augment and replace cardiac surgery.

This thesis has explored how some obstructive congenital lesions can be treated using less invasive catheter methods with a particular emphasis on technique and materials. How have these treatments developed and what are the future directions?

Baffle obstruction after the atrial switch: percutaneous stent implantation has become the treatment of choice for baffle obstruction after an atrial switch procedure for transposition of the great arteries (Bu'Lock et al., 1998). However the number of adult patients being followed post atrial switch is starting to dwindle as it is now approximately 30 years since the arterial switch was introduced. The more recent double switch procedure (Hiramatsu, 2012) for congenitally corrected transposition should mean a small number of patients will continue to at risk of baffle obstruction. The only situation where balloon angioplasty alone, as described in this thesis, might still be considered would for the patient with pacing wires in an obstructed superior baffle limb and an unacceptable risk of lead extraction.

Cutting balloon angioplasty: The two main indications for this technique in congenital heart disease are pulmonary vein stenosis and small vessel pulmonary artery stenosis. In addition, cutting balloons are sometimes used to enlarge communications in the atrial septum. A case series from 2006 (Seale et al., 2006) reported 27 stenosed pulmonary veins treated during 12 procedures in 6 patients with some symptomatic relief but no change in the Doppler derived right ventricular pressure. The relief was only temporary with the longest time before a repeat procedure being only 6 months. Pulmonary vein stenosis remains a disappointing lesion to treat with high recurrence rates and similarly poor results from stent implantation (Tomita et al., 2003). The biggest series of stent implantation did show a lower risk of reintervention when larger stents

over 7 mm in diameter are implanted (Balasubramanian et al., 2012) but this is rarely possible in smaller children.

The use of cutting balloons for small vessel branch pulmonary artery stenosis is more encouraging. A study from 2002 of small vessel pulmonary artery stenosis resistant to conventional angioplasty during 4 catheter procedures showed significant increases in vessel diameter which persisted at follow-up catheter after a median interval of 14 months (Rhodes et al., 2002). This led to a multicentre randomised trial of cutting balloon therapy versus high pressure balloon therapy for resistant pulmonary stenoses (Bergesen et al., 2011). Seventy-three patients from 8 institutions were enrolled over a 4 year period. In these patients, 72 vessels responded to low-pressure balloon dilation alone and of the remaining 173 vessels, 107 were randomised to cutting balloon and 66 to high pressure balloon. Cutting balloon therapy was associated with greater percent increase in lumen diameter (85% versus 52%; P=0.004) in comparison to high pressure balloons with an equivalent safety profile.

Balloon dilation of aortic stenosis: The potential advantages of an antegrade approach for balloon angioplasty of the aortic valve in children are firstly to lessen the chances of arterial vascular damage and secondly to reduce the risk of aortic incompetence by performing the procedure in the direction of blood flow to optimise balloon stability. As the risk of arterial vascular damage is greater in infants, this age group might derive particular benefit. This is set against the increased technical difficulty of this approach

especially in smaller hearts and the risk of damaging the mitral valve. Since the paper describing this approach was published in 1997, the use of rapid right ventricular pacing to improve balloon stability has become widely accepted (Daehnert, 2004). Also newer low profile balloons requiring smaller introducing sheaths are available. Therefore there is no longer such a requirement to consider the antegrade approach to the aortic valve.

A numbers of centres continue to advocate surgery over a catheter approach to treat aortic stenosis in children and this is one of the few lesions where there have been direct comparisons between the 2 approaches. It is known that aortic regurgitation tends to progress after either balloon dilation or surgical valvotomy (Justo et al., 1996). A study from the Congenital Heart Surgeons Society(McCrindle et al., 2001) in the 1990s of 110 neonates with critical aortic stenosis showed that surgical and balloon valvotomy had similar outcomes. There was a greater likelihood of important aortic regurgitation with balloon valvotomy and of residual stenosis with surgery. To some extent the conclusions of these studies reflect authorship. A retrospective study going back 32 years from 2009 of 123 consecutive infants showed better freedom from re-intervention after surgery (Siddiqui et al., 2013). However a study from Munich in 188 patients over 17.5 years (Fratz et al., 2008) showed that around two thirds of patients remained free of surgery 10 years after catheter intervention. Therefore, as catheter intervention is able to significantly delay first surgery for aortic stenosis and as no surgical valve repair or replacement will last for a lifetime, catheter intervention does have a place in reducing the number of operations an individual with congenital aortic stenosis will require.

Aortic stenosis covers a broad spectrum of disease and at the severe end merges with hypoplastic left heart syndrome when the left ventricle is not capable of sustaining the circulation. A very poor outlook for prenatally diagnosed aortic stenosis led to the first attempted intrauterine dilation of the aortic valve in 2 fetuses in 1991 (Maxwell, Allan and Tynan, 1991). One died *in utero* but in the other the valve was successfully crossed and dilated, the fetus was delivered and a further balloon dilation performed. This child lived for 5 weeks before dying from persistent left ventricular dysfunction.

Although surgery for hypoplastic left heart syndrome subsequently became feasible, the possibility of successful fetal intervention became a driver to potentially alter the natural history of borderline hypoplastic left heart syndrome. It was felt that intervening on the valve *in utero* might prevent progression to endocardial fibrosis and ventricular hypoplasia and so increase the chances of a biventricular circulation. While there are some claims that this strategy is successful (Tworetzky et al., 2004) it is very difficult to predict which cases would have achieved a biventricular circulation in any case. At present, apart from a few centres in the US, this approach has not found widespread acceptance and is no longer attempted in the UK.

Apart from balloon dilation of the aortic valve, is catheter intervention possible elsewhere in the left ventricular outflow tract in children? Certainly balloon dilation of *supravalvar* aortic stenosis, which is due to the elastin aortopathy found in William's syndrome, is not to be recommended. The thickened vessel wall will not respond to

angioplasty and there is often coronary involvement with a degree of aortic valve leaflet adhesion to the narrowed sinotubular junction restricting diastolic filling of the coronary arteries (Stamm et al., 1997). Even sedation or anaesthesia for diagnostic cardiac cathterization carries a risk of sudden death (Burch et al., 2008).

The causes of *subvalvar* aortic stenosis are: a fibromuscular ridge extending to the anterior leaflet of the mitral valve (Kelly, Wulfsburg and Rowe, 1972), a tunnel like muscular narrowing (Maron et al., 1976), accessory mitral valve cords (MacLean, Kane and Culligan, 1963), a combination of these factors as well as hypertrophic obstructive cardiomyopathy (Wigle, Heimbecker and Gunton, 1962). Interestingly attempts have been made to use catheters to treat discrete subvalvar aortic stenosis caused by a fibromuscular ridge. A study in 1990 showed temporary relief of obstruction (Rao, Wilson and Chopra, 1990) and one long term study from a single centre showed persistent benefit in 77% of 76 patients over a 25 year period (De Lezo et al., 2011). In spite of these results, surgery remains the treatment of choice as the stenosis is often closely related to the valve and alters blood flow dynamics resulting in valvar incompetence which might be exacerbated by angioplasty. Left ventricular outflow tract obstruction caused by asymmetrical septal hypertrophy found in hypertrophic obstructive cardiomyopathy is treated by percutaneous alcohol septal ablation in adults (Sigwart, 1995) but not in children because of the risks of septal rupture, heart block and ventricular arrhythmias (Yetman and McCrindle, 2005).

Coarctation and recoarctation of the aorta: Stent implantation for coarctation of the aorta has become a firmly established treatment in older children and adults and is being extended to treat complex and more proximal arch obstruction (Holzer et al., 2008). The largest study of stent implantation was data from a prospective registry of 302 patients in 32 centres over a nine year period showing procedural success in 96% (defined by less than 20 mmHg upper to lower systolic limb pressure gradient) which fell to 77% after 1.5 years (Holzer et al., 2010). Complications such as dissection and aneurysm formation were very uncommon, but 32% of patients continued to require antihypertensive medication and around 20% of the patients continued to have systolic blood pressure over the 95th centile. Coarctation of the aorta is associated with abnormal vascular reactivity and there is some suggestion that the rigid stented portion of the aorta might exacerbate this leading to systolic hypertension on exercise in spite of adequate relief of stenosis (Chen et al., 2008). While this does occur there appears to be no difference in exercise induced hypertension between patients treated by surgery or stent implantation (de Caro, 2010).

Stent implantation for coarctation was also successful in a group of patients under 30 kg compared to older children (Mohan et al., 2009) but size of the patient does become a limiting factor when planning stent implantation due to the risk of vascular access damage and the maximum expandable stent diameter. Stents have been implanted in neonates as emergency bail out procedures when the risk of surgery was deemed too

high (Fink, Peuster and Hausdorf, 2000) but current available technology does not allow definitive treatment in infants and young children.

Balloon expandable stent implantation for superior vena caval obstruction: As mentioned above stent implantation is well established for systemic venous pathway obstruction after atrial switch. Obstruction after repair of partial anomalous pulmonary venous drainage is rare although there will probably be an increasing need for this technology to treat superior vena caval stenosis due to indwelling catheters. Where covered balloon expandable stents might have a place would be in the creation of non surgical bidirectional cavopulmonary connections (Levi et al., 2009).

Future directions

To some extent it could be argued that the last 10 years have been a period of consolidation rather than progress in the treatment of native and acquired stenoses in congenital heart disease. The one major development has been the balloon mounted percutaneous valve to treat conduit dysfunction (McElhinney et al., 2010) in right heart disease. Although principally designed to treat pulmonary incompetence, there usually exists a combination of both stenosis and incompetence which can be effectively treated by valve implantation.

A major feature of how the treatment of congenital heart disease is evolving is the much younger age at which most major cardiac surgical procedures are being performed. This

challenges catheter technology to find ways to effectively and safely treat smaller patients. A good example is tetralogy of Fallot, one of the commonest forms of congenital heart disease with a prevalence of 0.26 per 1000 livebirths (Ferencz et al., 1986). Although outcomes in terms of overall survival are good there is still debate on how to manage this condition in order to provide the best quality of life. Neonates with severe right ventricular outflow tract obstruction and a low birth weight can present a real management challenge. Previously insertion of an arterial to pulmonary artery shunt was used as palliation in this group until they were big enough to undergo complete repair however this palliation is far from simple. A study of 32 patients after modified Blalock-Taussig shunt insertion showed a 9% mortality (Dirks et al., 2013). Although not all suffering from tetralogy of Fallot, most of this group had biventricular hearts (n=21) and infants with hypoplastic left heart syndrome were excluded. Risk factors for an adverse outcome were lower body weight and bigger shunt size to body weight ratio. In addition, it is well known that pulmonary artery hypoplasia and distortion are common after Blalock-Tussig shunt palliation (Gladman et al., 1997).

To get around these problems, investigators have initially attempted balloon angioplasty of the right ventricular outflow tract (Qureshi et al., 1988: Sreeram et al., 1991) which can be effective if obstruction is mostly valvar but often fails and can precipitate severe hypercyanotic spells. The next step was to implant stents in the right ventricular ouflow tract, a small case series (Gibbs et al., 1997) showed promise but it has taken some time before further positive evidence has emerged (Stümper et al., 2013).

The problem is that this strategy makes the next stage of definitive surgical repair more difficult, often part of the stent is firmly embedded in the muscle of the right ventricular outflow tract and cannot be entirely removed. Also, if the original stent is lying across the pulmonary valve annulus extending into the main pulmonary artery then progression to severe pulmonary regurgitation will be accelerated.

Not only in tetralogy of Fallot but for many other congenital stenosis balloon angioplasty alone is often suboptimal. As mentioned above the problem with stents remains the maximum possible achievable diameter: for example in coarctation of the aorta a stent implanted in infancy would need to be dilated to 3 times implantation diameter to reach an adequate adult size. The two ways of dealing with this problem are bio-absorbable stents and a mechanical solution using stents which can be opened along their length during redilation.

Bio-absorbable stents are of two types either composed of polymers or of metal which corrodes so called bio-corrosion. Looking at bio-corrosion, the metals studied have been either iron or alloys consisting mostly of magnesium. Implantation of iron stents in the descending aorta of rabbits (Peuster et al., 2001) showed continued stent patency and the absence of inflammation thrombosis or neointima at follow up. There was considerable iron staining of the tissues but and no evidence of iron toxicity. As yet there are no reports of the use of iron stents in children and it may be that the low rate of metal degradation means that the advantages in a growing child may not be met. An

alternative is magnesium which if anything can degrade too quickly. Biotronik have developed the AMS stent which is 93% magnesium and 7% rare earth metals. The first study in man with coronary disease showed high rates of vessel restenosis due to the very rapid degradation of the stent, however this behaviour can be modified by polymer coating of the stent (Gray-Munro, Seguin and Strong, 2009).

The first use of an AMS stent in congenital heart disease was by Zartner (2007) who placed an AMS stent into the left pulmonary artery of a 1.7 kg preterm baby using a hybrid surgical cutdown. At 4 months the stent had completely degraded and the left lung remained well perfused. The child died of pneumonia one month later and autopsy showed continued vessel patency with a smooth endothelial surface. A magnesium stent was also used to treat severe long segment recoarctation of the aorta after surgical repair (Schranz et al., 2006). The coarctation reoccurred as the stent degraded and a further magnesium stent was implanted. In spite of the vessel remaining patent surgical repair was undertaken at the same time as closure of a ventricular septal defect.

Progress has also been made in the development of bio-absorbable polymer stents for coronary disease. The most common polymer is PLLA or Poly (L-lactic acid) which is readily hydrolysed and metabolised (Tamai et al., 2000). The difficulty with polymer stents in children is that they require more bulk to achieve the same radial strength as metal stents and therefore would require large introducing sheaths.

Others have opted for a mechanical solution using stents which either separate longitudinally or can be fractured allowing implantation of larger stents as the vessel grows. The growth stent consists of two stent halves connected by absorbable sutures. The stent halves have been demonstrated to separate with growth in animal studies (Ewert et al., 2004). Growth stents have also been used in humans in a study of 12 children aged 1-15 months with coarctation of the aorta, 5 underwent successful redilation and 6 successful late overstenting (Ewert et al., 2008). The Osypka baby stent is a breakable stent consisting of stainless steel with gold coating which is cut longitudinally and then reconnected using surgical sutures (Sigler et al., 2009). With growth, redilation allows the stent to be broken and if required further stents to be implanted within. As yet there are no reports of the use of this stent in man.

Finally there will need to be more interaction between surgeons and cardiologists to develop hybrid therapies to treat congenital stenoses. Already hybrid procedures exist to for stage one palliation of hypoplastic left heart syndrome (Galantowicz and Cheatham, 2005) and new hybrid catheter laboratories are being installed which conform to the standards required for cardiac surgery. At the very least the increasing complexity of cardiac surgery in very young children will drive the need for hybrid procedures to allow surgical access for the interventionalist (Mendelsohn et al.,1993).

Bibliography

ANJOS R., QURESHI S.A., ROSENTHAL E., MURDOCH I., HAYES A., PARSONS J., BAKER E.J., TYNAN M. (1992) Determinants of haemodynamic results of balloon dilation of aortic recoarctation. *American Journal of Cardiology,* 69, 665-671.

ARYANA A., SOBOTA K.D., ESTERBROOKS D.J., GELBMAN A.I. (2007) Superior vena cava syndrome induced by endocardial defibrillator and pacemaker leads. *American Journal of Cardiology,* 99, 1765-1767.

AYDOGAN U., DINDAR A., GURGAN L., CANTEZ T. (1995) Late development of dissecting aneurysm following balloon angioplasty of native aortic coarctation. *Catheterization and Cardiovascular Diagnosis,* 36, 226-229.

BALAJI S., OOMMEN R., REES P.G. (1991) Fatal aortic rupture during balloon dilation of recoarctation. *British Heart Journal,* 65,100-101.

BALASUBRAMANIAN S., MARSHALL A.C., GAUVREAU K., PENG L.F., NUGENT A.W., LOCK J.E., McELHINNEY D.B. (2012) Outcomes after stent implantation for the treatment of congenital and postoperative pulmonary vein stenosis in children. *Circulation: Cardiovascular Interventions,* 5, 109–111.

BARATH P., FISHBEIN M.C., VARI S., FORRESTER J.S. (1991) Cutting balloon: a novel approach to percutaneous angioplasty. *American Journal of Cardiology,* 68, 1249-1252.

BARTOCCIONI S., GIOMBOLINI C., FIASCHINI P., MARTINELLI G., FEDELI C., DI LAZZARO D., LANZILLO G., POSSATI G. (1995) Aortic coarctation, aortic valvar stenosis and coronary artery disease: combined one-stage surgical therapy operation. *Journal of Cardiac Surgery,* 10, 594-596.

BECKER A.E., BECKER M.J., EDWARDS J.E. (1970) Anomalies associated with coarctation of the aorta. Particular reference to infancy. *Circulation,* 41, 1075-1076.

BEEKMAN R.H., ROCCHINI A.P., ANDES A. (1991) Balloon valvuloplasty for critical aortic stenosis in the newborn: influence of new catheter technology. *Journal of the American College of Cardiology,* 17, 1172-1176.

BEEKMAN R.H., ROCCHINI A.P., GILLON J.H., MANCINI G.B.J. (1992) Haemodynamic determinants of the peak systolic left ventricular-aortic pressure gradients in children with valvar aortic stenosis. *American Journal of Cardiology,* 69, 813-815.

BEEKMAN R.H., ROCCHINI A.P., ROSENTHAL A. (1989) Therapeutic cardiac catheterization for pulmonary valve and pulmonary artery stenosis. *Cardiology Clinics,* 7, 331-340.

BERGERSEN L., GAUVREAU K., JUSTINO H., NUGENT A., ROME J., KREUTZER J., RHODES J., NYKANEN D., ZAHN E., LATSON L., MOORE P., LOCK J., JENKINS K. (2011) Randomized trial of cutting balloon compared with high-pressure angioplasty for the treatment of resistant pulmonary artery stenosis. *Circulation,* 124(22), 2388–2396.

BIGELOW W.G., LINDSAY W.K., GREENWOOD W.F. (1950) Hypothermia; its possible role in cardiac surgery: an investigation of factors governing survival in dogs at low body temperatures. *Annals of Surgery,* 132(5), 849-866.

BLALOCK A., HANLON C.R. (1950) The surgical treatment of complete transposition of the aorta and pulmonary artery. *Surgery Gynecology and Obstetrics,* 90(1), 1-15.

BLALOCK A., TAUSSIG H.B. (1945) The surgical treatment of malformations of the heart in which there is pulmonary stenosis or pulmonary atresia. *Journal of the American Medical Association,* 128(3),189-202.

BLUM U., LANGER M., SPILLNER G., MIALHE C., BEYERSDORF F., BUITRAGO-TELLEZ C., VOSHAGE G., DÜBER C., SCHLOSSER V., CRAGG A.H. (1996) Abdominal aortic aneuryms: preliminary technical and clinical results with transfemoral placement of endovascular self-expanding stent-grafts. *Radiology,* 198, 25-31.

BRAUNWALD N.S., COOPER T., MORROW A.G. (1960) Complete replacement of the mitral valve. Successful clinical application of a flexible polyurethane prosthesis. *The Journal of Thoracic and Cardiovascular Surgery*, 40, 1-11.

BROMBERG B.I., BEEKMAN R.H., ROCCHINI A.P., SNIDER A.R., BANK E.R., HEIDELBERGER K., ROSENTHAL A. (1989) Aortic aneurysm after patch aortoplasty repair of coarctation: a prospective analysis of prevalence, screening tests and risks. *Journal of the American College of Cardiology,* 14(3), 734-741.

BU'LOCK F.A., TOMETZKI A.J.P., KITCHINER D.J., ARNOLD R., PEART I., WALSH K.P. (1998) Balloon expandable stents for systemic venous pathway stenosis late after Mustard's operation. *Heart,* 79: 225–229.

BULBUL Z.R., BRUCKHEIMER E., LOVE J.C., FAHEY J.T., HELLENBRAND W.E. (1996) Implantation of balloon-expandable stents for coarctation of the aorta: implantation data and short-term results. *Catheterization and Cardiovascular Diagnosis,* 39(1), 36-42.

BURCH T.M., MCGOWAN F.X., KUSSMAN B.D., POWELL A.J., DINARDO J.A. (2008) Congenital supravalvular aortic stenosis and sudden death associated with anesthesia: what's the mystery? *Anesthesia and Analgesia,* 107, 1848-1854.

BURROWS P.E., BENSON L.N., WILLIAMS W.G., TRUSLER G.A., COLES J., SMALLHORN J.F., FREEDOM R.M. (1990) Iliofemoral arterial complications of balloon angioplasty for systemic obstructions in infants and children. *Circulation,* 82, 1697-1704.

CHATELAIN P., MEIER B., FRIEDLI B. (1991) Stenting of superior vena cava and inferior vena cava for symptomatic narrowing after repeated atrial surgery for D-transposition of the great vessels. *British Heart Journal,* 66(6),466-468.

CHEATHAM J., FLETCHER S., FOREMAN C., et al. (1998) Early experience using endovascular stents in children with coarctation of the aorta; promising results....but proceed with caution [abstract]. *Cardiology in theYoung,* 9 (suppl 1),11.

CHEE C.E., BJARNASON H., PRASAD A. (2007) Superior vena cava syndrome: an increasingly frequent complication of cardiac procedures. *Nature Clinical Practice Cardiovascular Medicine,* 4(4), 226-230.

CHEN S.S., DONALD A.E., STORRY C., HALCOX J.P., BONHOEFFER P., DEANFIELD J.E. (2008) Impact of aortic stenting on peripheral vascular function and daytime systolic blood pressure in adult coarctation. *Heart,* 94, 919–924.

COSTELLO C.L., GELLATLY M., DANIEL J., JUSTO R.N., WEIR K. (2014) Growth Restriction in Infants and Young Children with Congenital Heart Disease. *Congenital Heart Disease,* Nov 11. doi: 10.1111/chd.12231. [Epub ahead of print]

CRAFOORD C., NYHLIN G. (1945) Congenital coarctation of the aorta and its surgical management. *Journal of Thoracic Surgery,* 14, 347–361.

CUNNINGHAM D., FRANKLIN R., BRIDGEWATER B., DEANFIELD J. (2013) Investigation of mortality from Paediatric Cardiac Surgery in England 2009-12. *National Institute for Cardiovascular Outcomes Research.* Available from http://www.england.nhs.uk/wp-content/uploads/2013/04/finl-rep-mort-paed-card-surg-2009-12.pdf (last assessed 22/3/15).

DAEHNERT I., ROTZSCH C., WIENER M., SCHNEIDER P. (2004) Rapid right ventricular pacing is an alternative to adenosine in catheter interventional procedures for congenital heart disease. *Heart,* 90, 1047-1050.

DE CARO E., SPADONI I., CREPAZ C., SAITTA M., TROCCHIO G., CALEVO M.G., PONGIGLIONE G. (2010) Stenting of aortic coarctation and exercise-induced hypertension in the young. *Catheterization and Cardiovascular Interventions,* 75(2), 256-261.

DE LEZO J.S., ROMERO M., SEGURA J., PAN M., DE LEZO J.S., PAVLOVIC D., MAZUELOS F., DELGADO M., MESA D. (2011) Long-Term Outcome of Patients With Isolated Thin Discrete Subaortic Stenosis Treated by Balloon Dilation: a 25-Year Study. *Circulation,* 124, 1461-1468.

DeLEON S.Y., FREEMAN J.E., ILBAWI M.N., HUSAYNI T.S., QUINONES J.A., OW E.P., BELL T.J., PIFARRÉ R. (1993) Surgical techniques in partial anomalous pulmonary veins to the superior vena cava. *The Annals of Thoracic Surgery,* 55,1222-1226.

DIRKS V., PRÊTRE R., KNIRSCH W., VALSANGIACOMO BUECHEL E.R., SEIFERT B., SCHWEIGER M., HÜBLER M., DAVE H. (2013) Modified Blalock Taussig shunt: a not-so-simple palliative procedure. *European Journal of Cardiothoracic Surgery,* 44(6), 1096-1102.

DONTI A., BONVICINI M., GARGUILO G., FRASCAROLI G., PICCHIO F.M. (1995) Criteria for selection of balloon valvuloplasty for treatment of aortic stenosis in neonates. *Cardiology in the Young,* 5,31-35.

DOTTER C.T. (1969) Transluminally-placed coilspring endarterial tube grafts. Long-term patency in canine popliteal artery. *Investigative Radiology,* 4(5), 329-332.

DOTTER C.T., JUDKINS M.P. (1964) Transluminal treatment of arteriosclerotic obstruction. Description of a new technique and a preliminary report of its application *Circulation,* 30, 654–670.

EBEID M.R., GAYMES C.H., McMULLAN M.R., SHORES J.C., SMITH J.C., JORANSEN J.A. (2005) Catheter management of occluded superior baffle after atrial switch procedures for transposition of great vessels. *American Journal of Cardiology,* 95(6), 782– 786.

EDWARDS B.S., LUCAS R.V. Jr, LOCK J.E., EDWARDS J.E. (1985) Morphologic changes in the pulmonary arteries after percutaneous balloon angioplasty for branch pulmonary arterial stenosis. *Circulation,* 71, 195-201.

EWERT P., RIESENKAMPFF E., NEUSS M., KRETSCHMAR O., NAGDYMAN N., LANGE P.E. (2004) Novel growth stent for the permanent treatment of vessel stenosis in growing children: an experimental study. *Catheterization and Cardiovascular Interventions,* 62(4), 506-510.

EWERT P., PETERS B., NAGDYMAN N., MIERA O., KÜHNE T., BERGER F. (2008) Early and mid-term results with the Growth Stent--a possible concept for transcatheter treatment of aorticcoarctation from infancy to adulthood by stent implantation? *Catheterization and Cardiovascular Interventions,* 71(1), 120-126.

FERENCZ C., RUBIN J.D., MCCARTER R.J., BRENNER J.I., NEILL C.A., PERRY L.W., HEPNER S.I., DOWNING J.W. (1985) Congenital heart disease: prevalence at livebirth. The Baltimore-Washington Infant Study. *American Journal of Epidemiology,* 121(1), 31-36.

FINK C., PEUSTER M., HAUSDORF G. (2000) Endovascular stenting as an emergency treatment for neonatal coarctation. *Cardiology in the Young,* 10, 644-646.

FISCHER D.R., ETTEDGUI J.A., PARK S.C., SIEWERS R.D., DELNIDO P.J. (1990) Carotid artery approach for balloon dilatation of aortic valve stenosis in the neonate: a preliminary report. *Journal of the American College of Cardiology,* 15, 1633-1636.

FLETCHER S.E., NIHILL M.R., GRIFKA R.G., O'LAUGHLIN M.P., MULLINS C.E. (1995) Balloon angioplasty of native coarctation of the aorta: midterm follow-up and prognostic factors. *Journal of the American College of Cardiology,* 25, 730-734.

FOGELMAN R., NYKANEN D., SMALLHORN J.F., McCRINDLE B.W., FREEDOM R.M., BENSON L.N. (1995) Endovascular stents in the pulmonary circulation. Clinical impact on management and medium-term follow-up. *Circulation,* 92, 881-885.

FORSSMANN W. (1929) Die Sondierung des rechten Herzens [Probing of the right heart]. *Klinische Wochenschrift,* 8, 2085-2087.

FRATZ S., GILDEIN H.P., BALLING G., SEBENING W., GENZ T., EICKEN A., HESS J. (2008) Aortic Valvuloplasty in Pediatric Patients Substantially Postpones the Need for Aortic Valve Surgery: a Single-Center Experience of 188 Patients After up to 17.5 Years of Follow-Up. *Circulation,* 117(9), 1201-1206.

FUNAKI B. (2006) Superior Vena Cava Syndrome. *Seminars in Interventional Radiology,* 23(4), 361–365.

GALANTOWICZ M., CHEATHAM J.P. (2005) Lessons learned from the development of a new hybrid strategy for the management of hypoplastic left heart syndrome. *Pediatric Cardiology,* 26(3), 190-199.

GAYNOR J.W., BURCH M., DOLLERY C., SULLIVAN I.D., DEANFIELD J.E., ELLIOTT M.J. (1995) Repair of anomalous pulmonary venous connection to the superior vena cava. *The Annals of Thoracic Surgery,* 59, 1471-1475.

GEGGEL R.L., GAUVREAU K., LOCK J.E. (2001) Balloon Dilation Angioplasty of Peripheral Pulmonary Stenosis Associated With Williams Syndrome. *Circulation,* 103, 2165-2170.

GENTLES T.L., LOCK J.E., PERRY S.B. (1993) High pressure balloon angioplasty for branch pulmonary artery stenosis: early experience. *Journal of the American College of Cardiology,* 22(3), 867-72.

GIBBON J.H. (1954) Application of a mechanical heart and lung apparatus to cardiac surgery. *Minnesota Medicine,* 37(3), 171–185.

GIBBS J.L., UZUN O., BLACKBURN M.E.C., PARSONS J.M., DICKINSON D.F. (1997) Right ventricular outflow stent implantation: an alternative to palliative surgical relief of infundibular pulmonary stenosis. *Heart,* 77, 176-179.

GLADMAN G., MCCRINDLE B.W., WILLIAMS W.G., FREEDOM R.M., BENSON L.N. (1997) The modified Blalock-Taussig shunt: clinical impact and morbidity in Fallot's tetralogy in the current era. *The Journal of Thoracic and Cardiovascular Surgery,* 114, 25-30.

GONZALEZ-LAVIN L., GEENS M., SOMERVILLE J., ROSS D.N. (1970) Autologous pulmonary valve replacement of the diseased aortic valve. *Circulation,* 42, 781-785.

GRAY-MUNRO J.E, SEGUIN C., STRONG M., (2009) Influence of surface modification on the in vitro corrosion rate of magnesium alloy AZ31. *Journal of Biomedical Materials Research A,* 91(1), 221–230.

GREUNTZIG A.R. (1978) Transluminal dilatation of coronary artery stenosis (Letter to the Editor). *Lancet,* 1(8058), 263.

GROSS R.E., HUBBARD J.P. (1939) Surgical ligation of a patent ductus arteriosus. *Journal of the American Medical Association,* 112, 729-731.

HARKEN D.E. (1946) Foreign bodies in, and in relation to, the thoracic blood vessels and heart; techniques for approaching and removing foreign bodies from the chambers of the heart. *Surgery Gynecology and Obstetrics,* 83, 117-125.

HARKEN D.E., ELLIS L.B., WARE P.F., NORMAN L.R. (1948) The surgical treatment of mitral stenosis: I. Valvuloplasty. *The New England Journal of Medicine,* 239, 801–809.

HARRISON J.K., SHEIKH K.H., DAVIDSON C.J., KISSLO K.B., LEITHE M.E., HIMMELSTEIN S.I., KANTER R.J., BASHORE T.M. (1990) Balloon angioplasty of coarctation of the aorta evaluated by intravascular ultrasound imaging. *Journal of the American College of Cardiology*, 15(4), 906-909.

HAUSDORF G., SCHNEIDER M., SCHIRMIR K.R., SCHULZE-NEICK I., LANGE P.E. (1993) Anterograde balloon dilation of aortic stenosis in children. American Journal of *Cardiology,* 1993, 71, 460-462.

HAWKINS J.A., MINICH L., SHADDY R.E., TANI L.Y., STURTEVANT J.E., McGOUGH E.C. (1995) Aortic Valve Repair and Replacement After Balloon Aortic Valvuloplasty in Children. *Journal of the American College of Cardiology,* 25, Suppl 2, 124A.

Heart transplantation. (1967) *South African Medical Journal,* special issue. 41, 1257–1278.

HELLENBRAND W.E., ALLEN H.D., GOLINKO R.J., HAGLER D.J., LUTIN W., KAN J. (1990) Balloon angioplasty for aortic coarctation: results of the valvuloplasty and angioplasty of congenital anomalies registry. *American Journal of Cardiology,* 65, 793-797.

HIJAZI Z.M., FAHEY J.T., KLEINMAN C.S., HELLENBRAND W.E. (1991) Balloon angioplasty for recurrent coarctation of the aorta. Immediate and long term results. *Circulation,* 84,1150-1156.

HIRAMTSU T., MATSUMURA G., KONUMA T., YAMAZAKI K., KUROSAWA H., IMAI Y. (2012) Long-term prognosis of double-switch operation for congenitally corrected transposition of the great arteries. *European Journal of Cardiothoracic Surgery,* 42, 1004-1008.

HO S.Y., SOMERVILLE J., YIP W.C., ANDERSON R.H. (1988) Transluminal balloon dilatation of resected coarcted coarcted segments of thoracic aorta: histological study and clinical implications. *International Journal of Cardiology,* 19, 99-105.

HOLZER R., QURESHI S., GHASEMI A., VINCENT J., SIEVERT H., GRUENSTEIN D., WEBER H., ALDAY L., PEIRONE A., ZELLERS T., CHEATHAM J., SLACK M., ROME J. (2010) Stenting of aortic coarctation: acute, intermediate, and long-term results of a prospective multi-institutional registry--Congenital Cardiovascular Interventional Study Consortium (CCISC). *Catheterization and Cardiovascular Interventions,* 76(4), 553-563.

HOLZER R.J., CHISOLM J.L., HILL S.L., CHEATHAM J.P.(2008) Stenting complex aortic arch obstructions. *Catheterization and Cardiovascular Interventions,* 71(3), 375-382.

HOSKING M.C.K., THOMAIDIS C., HAMILTON R., BURROWS P.E., FREEDOM R.M., BENSON L.N. (1992) Clinical impact of balloon angioplasty for branch pulmonary arterial stenosis. *American Journal of Cardiology,* 69, 1467-1470.

HUGGON I.C., QURESHI S.A., BAKER E.J., TYNAN M. (1994) Effect of introducing balloon dilatation of native aortic coarctation on overall outcome in infants and children. *The American Journal of Cardiology,* 73, 799-807.

ING F.F., GRIFKA R.G., NIHILL M.R., MULLINS C.E. (1995) Repeat dilation of intravascular stents in congenital heart defects. *Circulation,* 92, 893-897.

INO T., KISHIRO M., OKUBO M., AKIMOTO K., NISHIMOTO K., YABUTA K., KAWASAKI S., HOSODA Y. (1998) Dilatation mechanism of balloon angioplasty in children: assessment by angiography and intravascular ultrasound. *Cardiovascular and Interventional Radiology,* 21,102-108.

JUSTO R.N., MCCRINDLE B.W., BENSON L.N., MD, WILLIAMS W.G., FREEDOM R.M., SMALLHORN J.F. (1996) Aortic valve regurgitation after surgical versus percutaneous balloon valvotomy for congenital aortic valve stenosis. *American Journal of Cardiology,* 77(15), 1332–1338.

KAEMMERER H., MEISNER H., HESS J., PERLOFF J.K. (2004) Surgical treatment of patent ductus arteriosus: a new historical perspective. *American Journal of Cardiology,* 94(9),1153-1154.

KALRA M., GLOVICZKI P., ANDREWS J.C., CHERRY K.C.Jr., BOWER T.C., PANNETON J.M., BJARNASON H., NOEL A.A., SCHLECK C., HARMSEN W.S., CANTON L.G., PAIROLERO P.C. (2003) Open surgical and endovascular treatment of superior vena cava syndrome caused by nonmalignant disease. *Journal of Vascular Surgery,* 38(2), 215-223.

KAN J.S., MARVIN W.J. Jr., BASS J.L., MUSTER A.J., MURPHY J. (1990) Balloon angioplasty-branch pulmonary artery stenosis: results from the Valvuloplasty and Angioplasty of Congenital Anomalies Registry. *American Journal of Cardiology,* 65, 798-801.

KAN J.S., WHITE R.I., MITCHELL S.E., GARDNER T.J. (1982) Percutaneous balloon valvuloplasty: a new method for treating congenital pulmonary valve stenosis. *The New England Journal of Medicine,* 307(9), 540-542.

KAULITZ R., STÜMPER O.F., GEUSKENS R., SREERAM N., ELZENGA N.J., CHAN C.K., BURNS J.E., GODMAN M.J., HESS J., SUTHERLAND G.R. (1990) Comparative values of the precordial and transesophageal approaches in the echocardiographic evaluation of atrial baffle function after an atrial correction procedure. *Journal of the American College of Cardiology,* 16(3), 686-694.

KEITH J.D., ROWE R.D., VLAD P. (1967) *Heart disease in infancy and childhood,* 2nd edn. New York: MacMillan Publishing Co, pp 252-254.

KELLY D.T., WULFSBERG E., ROWE R.D. (1972) Discrete subaortic stenosis. *Circulation,* 46, 309-322.

KNYSHOV G.V., SITAR L.L., GLAGOLA M.D., ATAMANYUK M.Y. (1996) Aortic aneurysms at the site of the repair of coarctation of the aorta: a review of 48 patients. *The Annals of Thoracic Surgery,* 61(3), 935-939.

KONSTANTINOV I.E. (2000) Robert H. Goetz: the surgeon who performed the first successful clinical coronary bypass operation. *Annals of Thoracic Surgery,* 69(6), 1966-1972.

KRON I.L., RHEUBAN K.S., JOOB A.W., JEDEKEN R., MENTZER R.M., CARPENTER M.A., NOLAN S.P. (1985) Baffle obstruction following the Mustard operation: cause and treatment. *The Annals of Thoracic Surgery,* 39(2),112-115.

LABABIDI Z., WU J.R., WALLS J.T. (1984) Percutaneous balloon aortic valvuloplasty: results in 23 patients. *The American Journal of Cardiology,* 53(1), 194-197.

LEVI D.S., DANON S., GORDON B., VIRDONE N., VINUELA F. Jr., SHAH S., CARMAN G., MOORE J.W. (2009) Creation of transcatheter aortopulmonary and cavopulmonary shunts using magnetic catheters: feasibility study in swine. *Pediatric Cardiology,* 30(4), 397-403.

LEVITT P. (2003) Structural and functional maturation of the developing primate brain. *The Journal of Pediatrics,* 143(4 Suppl), S35-45.

LEWIS F.J., TAUFIC M. (1953) Closure of atrial septal defects with the aid of hypothermia; experimental accomplishments and the report of one successful case. *Surgery,* 33(1), 52-59.

LEWIS, O. (1994). Stephen Hales and the measurement of blood pressure. *Journal of Human Hypertension*, 8 (12), 865–871.

LILLIHEI C.W., COHEN M., WARDEN H.E., VARCO R.L. (1955) The direct-vision intracardiac correction of congenital anomalies by controlled cross circulation; results in thirty-two patients with ventricular septal defects, tetralogy of Fallot, and atrioventricularis communis defects. *Surgery.* 38(1),11–29.

LOCK J.E., BASS J.L., CASTANEDA-ZUNIGA W., FUHRMAN B.P., RASHKIND W.J., LUCAS R.V. Jr. (1984) Dilation angioplasty of congenital or operative narrowings of venous channels. *Circulation,* 70(3), 457-464.

LOCK J.E., CASTANEDA-ZUNIGA W., BASS J.L., FOKER J.E., AMPLATZ K., ANDERSON R.W. (1982) Balloon dilatation of excised aortic coarctations. *Radiology,* 143(3), 689-691.

LOCK J.E., CASTANEDA-ZUNIGA W., FUHRMAN B.P., BASS J.L. (1983) Balloon dilation angiopasty of hypoplastic and stenotic pulmonary arteries. *Circulation,* 67, 962-967.

LOCK J.E., NIEMI T., EINZIG S., AMPLATZ K., BURKE B., BASS J.L. (1981) Transvenous angioplasty of experimental branch pulmonary artery stenoses in newborn lambs. *Circulation,* 64, 886-893.

MAASS D., ZOLLIKOFER C.L., LARGIADÈR F., SENNING A. (1984) Radiological follow-up of transluminally inserted vascular endoprostheses: an experimental study using expanding spirals. *Radiology,* 152(3), 659-663.

MACLEAN L.D., KANE D.J., CULLIGAN J.A. (1963) Subaortic stenosis due to accessory tissue on mitral valve. *The Journal of Thoracic and Cardiovascular Surgery,* 45, 382–387.

MARON B.J., REDWOOD D.R., ROBERTS W.C., HENRY W.L., MORROW A.G., EPSTEIN S.E. (1976) Tunnel subaortic stenosis: left ventricular outflow tract obstruction produced by fibromuscular tubular narrowing. *Circulation,* 54, 404-416.

MARTINEZ-JIMENEZ S., HEYNEMAN L.E., McADAMS H.P., JASINOWODOLINSKI D., ROSSI S.E., RESTREPO C.S., WASHINGTON L. (2010) Nonsurgical extracardiac vascular shunts in the thorax: clinical and imaging characteristics. *Radiographics,* 30(5), e41.

MAXWELL D., ALLAN L., TYNAN M.J. (1991) Balloon dilatation of the aortic valve in the fetus: a report of two cases. *British Heart Journal,* 65, 256-258.

MCCRINDLE B.W., BLACKSTONE E.H., WILLIAMS W.G., SITTIWANGKUL R., SPRAY T.L, AZAKIE A., JONAS R.A. (2001) Are outcomes of surgical versus transcatheter balloon valvotomy equivalent in neonatal critical aortic stenosis? *Circulation,* 104, I-152-I-158.

McCRINDLE B.W., for the Valvuloplasty and Angioplasty of Congenital Anomalies (VACA) Registry Investigators. (1996) Independent predictors of immediate results of percutaneous balloon aortic valvotomy in childhood. *American Journal of Cardiology,* 77, 286-293.

McCRINDLE B.W., JONES T.K., MORROW W.R., HAGLER D.J., LLOYD T.R., NOURI S., LATSON L.A. (1996) Acute results of native coarctation versus recurrent aortic obstruction are equivalent. *Journal of the American College of Cardiology,* 28, 1810-1817.

MCELHINNEY D.B., HELLENBRAND W.E., ZAHN E.M., JONES T.K., CHEATHAM J.P., LOCK J.E., VINCENT J.A. (2010) Short- and medium-term outcomes after transcatheter pulmonary valve placement in the expanded multicenter US melody valve trial. *Circulation,* 122(5), 507-516.

MENDELSOHN A.M., BOVE E.L,, LUPINETTI F.M,, CROWLEY D.C,, LLOYD T.R., FEDDERLY R.T., BEEKMAN R.H.3rd. (1993) Intraoperative and percutaneous stenting of congenital pulmonary artery and vein stenosis. *Circulation,* 88(5), II210-217.

MENDELSOHN A.M., DOROSTKAR P.C., MOOREHEAD C.P., LUPINETTI F.M., REYNOLDS P.I., LUDOMIRSKY A., LLOYD T.R., HEIDELBERGER K., BEEKMAN R.H. 3RD. (1996) Stent redilation in canine models of congenital heart disease: pulmonary artery stenosis and coarctation of the aorta. *Catheterization and Cardiovascular Diagnosis,* 38(4), 430-440.

MENDELSOHN A.M., LLOYD T.R., CROWLEY D.C., SANDHU S.K., KOCIS K.C., BEEKMAN R.H. 3rd. (1994) Late follow-up of balloon angioplasty in children with a native coarctation of the aorta. *American Journal of Cardiology,* 74, 696-700.

MOHAN U.R., DANON S., LEVI D., CONNOLLY D., MOORE J.W. (2009) Stent implantation for coarctation of the aorta in children <30 kg. JACC *Cardiovascular Interventions,* 2(9), 877-883.

MORROW W.R., SMITH V.C., EHLER W.J., VANDELLEN A.F., MULLINS C.E. (1994) Balloon angioplasty with stent implantation in experimental coarctation of the aorta. *Circulation,* 89(6), 2677-2683.

MULLINS C.E. (1998) History of Pediatric Interventional catheterization: Pediatric Therapeutic Cardiac Catheterizations. *Pediatric Cardiology,* 19, 3–7.

MULLINS C.E., LATSON L.A., NECHES W.H., COLVIN E.V., KAN J. (1990) Balloon dilation of miscellaneous lesions: results of Valvuloplasty and Angioplasty of Congenital Anomalies Registry. *American Journal of Cardiology,* 65(11), 802-803.

MUSTARD W.T., KEITH J.D., TRUSLER G.A., FOWLER R., KIDD L. (1964) The surgical management of transposition of the great vessels. *The Journal of Thoracic and Cardiovascular Surgery,* 48, 953-958.

NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE. (2004) Stent placement for vena caval obstruction. Available from: www.nice.org.uk/guidance/ipg79 IPG79 (accessed 10/3/15).

NEUMAN A., HUHTA J.C. (2006) First trimester screening for congenital heart disease. *Minerva Cardioangiologica,* 54, 337-354

NICOLAE M.I., RADFORD D.J., SLAUGHTER R.E. (2006) Stenting for superior caval vein stenosis after surgical repair of sinus venosus atrial septal defect. *Heart Lung and Circulation,* 15(6), 386-8.

NISHIMURA R.A., VONK G.D., RUMBERGER J.A., TAJIK A.J. (1992) Semiquantitation of aortic regurgitation by different Doppler echocardiographic techniques and comparison with ultrafast computed tomography. *American Heart Journal,* 124, 995-1001.

O'LAUGHLIN M.P., PERRY S.B., LOCK J.E., MULLINS C.E. (1991) Use of endovascular stents in congenital heart disease. *Circulation,* 83, 1923-1939.

O'LAUGHLIN M.P., SLACK M.C., GRIFKA R.G., PERRY S.B., LOCK J.E., MULLINS C.E. (1993) Implantation and intermediate-term follow-up of stents in congenital heart disease. *Circulation,* 88, 605-614.

OLIVER J.M., GALLEGO P., GONZALES A., DOMINGUEZ F.J., AROCA A., MESA J.M. (2002) Sinus venosus syndrome: atrial septal defect or anomalous venous connection? A multiplane transoesophageal approach. *Heart,* 88(6), 634–638.

PALMAZ J.C., RICHTER G.M., NOELDGE G., SCHATZ R.A., ROBISON P.D., GARDINER G.A., BECKER G.J., McLEAN G.K., DENNY D.F.Jr., LAMMER J. (1988) Intraluminal stents in atherosclerotic iliac artery stenosis: preliminary report of a multicentre study. *Radiology,* 168(3), 727-731.

PALMAZ J.C., SIBBITT R.R., REUTER S.R., TIO F.O., RICE W.J. (1985) Expandable intraluminal graft: a preliminary study. Work in progress. *Radiology,* 156(1), 73-77.

PARKS W.J., NGO T.D., PLAUTH W.H., BANK E.R., SHEPPARD S.K., PETTIGREW R.I., WILLIAMS W.H. (1995) Incidence of aneurysm formation after Dacron patch aortoplasty repair for coarctation of the aorta: long-term results and assessment utilizing magnetic resonance angiography with three-dimensional surface rendering. *Journal of the American College of Cardiology,* 26(1), 266-271.

PETHIG K., WAHLERS T., TAGER S., BORST H.G. (1996) Perioperative complications in combined aortic valve replacement and extraanatomic ascending-descending bypass. *The Annals of Thoracic Surgery,* 61(6), 1724-1726.

PEUSTER M., WOHLSEIN P., BRU M., EHLERDING M., K SEIDLER K., FINK C., BRAUER H., FISCHER A., AND HAUSDORF G. (2001) A novel approach to temporary stenting: degradable cardiovascular stents produced from corrodible metal - Results 6-18 months after implantation into New Zealand white rabbits, *Heart,* 86(5). 563-569.

PINZON J..L, BURROWS P.E., BENSON L.N., MOËS C.A., LIGHTFOOT N.E., WILLIAMS W.G., FREEDOM R.M. (1991) Repair of coarctation of the aorta in children: postoperative morphology. *Radiology,* 180(1), 199-203.

QURESHI S.A., KIRK C.R., LAMB R.K., ARNOLD R., WILKINSON J.L. (1988) Balloon dilatation of the pulmonary valve in the first year of life in patients with tetralogy of Fallot: a preliminary study. *British Heart Journal,* 60, 232-235.

RAO P.S., GALAL O., SMITH P.A., WILSON A.D. (1996) Five to nine-year follow-up results of balloon angioplasty of native aortic coarctation in infants and children. *Journal of the American College of Cardiology,* 27, 462-470.

RAO P.S., WILSON A.D., CHOPRA P.S. (1990) Balloon dilatation for discrete subaortic stenosis: immediate and intermediate-term results. *The Journal of Invasive Cardiology,* 2, 65–70.

RASHKIND W.J., MILLER W.W. (1966) Creation of an Atrial Septal Defect Without Thoracotomy: A Palliative Approach to Complete Transposition of the Great Arteries. *Journal of the American Medical Association,* 196(11), 991-992.

REDDY V.M., McELHINNEY D.B., SILVERMAN N.H., Hanley F.L. (1997) The double switch procedure for anatomical repair of congenially corrected transposition of the great arteries in infants and children. *European Heart Journal,* 18, 1470-1477.

REHN, L. (1897) Ueber penetrirende Herzwunden und Herznaht. *Archiv für Klinische Chirurgie,* 55, 315-329.

RHODES J.F., LANE G.K., MESIA C.I., MOORE J.D., NASMAN C.M., COWAN D.A., LATSON L.A. (2002) Cutting balloon angioplasty for children with small-vessel pulmonary artery stenoses. *Catheterization and Cardiovascular Interventions,* 55(1), 73-77.

RHODES L.A., COLAN S.D., PERRY S.B., JONAS R.A., SANDERS S.P. (1991) Predictors of survival in neonates with critical aortic stenosis. *Circulation,* 84, 2325-2335.

RICE T.W., RODRIGUEZ R.M., LIGHT R.W. (2006) The superior vena cava syndrome: clinical characteristics and evolving etiology. *Medicine (Baltimore),* 85, 37-42.

RING J.C., BASS J.L., MARVIN W., FUHRMAN B.P., Kulik T.J., Foker T.J., LOCK J.E. (1985) Management of congenital stenosis of a branch pulmonary artery with balloon dilation angioplasty. Report of 52 procedures. *The Journal of Thoracic and Cardiovascular Surgery,* 90(1), 35-44.

ROSENTHAL E., QURESHI S.A., TYNAN M. (1995) Stent implantation for aortic recoarctation. *American Heart Journal,* 129, 1220-1221.

ROTHMAN A., PERRY S.B., KEANE J.F., LOCK J.E. (1990) Early results and follow-up of balloon angioplasty for branch pulmonary artery stenoses. *Journal of the American College of Cardiology,* 15, 1109-1117.

RUBIO-ALVAREZ V., LIMON R., SONI J. (1953) Intracardiac valvulotomy by means of a catheter. *Archivos del Instituto de Cardiología de México,* 23, 183-192.

SAMUELS L.E., NYZIO J.B., ENTWHISTLE J.W. (2007) Superior vena cava rupture during balloon angioplasty and stent placement to relieve superior vena cava syndrome: a case report. *The Heart Surgery Forum,* 10(1), E78-80.

SANDOR G.S., OLLEY P.M., TRUSLER G.A., WILLIAMS W.G., ROWE R.D., MORCH J.E. (1980) Long term follow up of patients after congenital valvular aortic stenosis in children. *The Journal Of Thoracic And Cardiovascular Surgery,* 80, 171-176.

SCHATZ R.A., PALMAZ J.C., TIO F.O., GARCIA F., GARCIO O., REUTER S.R. (1987) Balloon-expandable intracoronary stents in the adult dog. *Circulation,* 76(2), 450-457.

SCHRÄDER R., BUSSMANN W.D., JACOBI V., KADEL C. (1995) Long-term effects of balloon coarctation angioplasty on arterial blood pressure in adolescents and adult patients. *Catheterization and Cardiovascular Diagnosis,* 36(3), 220-225.

SCHRANZ D., ZARTNER P., MICHEL-BEHNKE I., AKINTÜRK H. (2006) Bioabsorbable metal stents for percutaneous treatment of critical recoarctation of the aorta in a newborn. *Catheterization and Cardiovascular Interventions,* 67(5), 671-673.

SEALE A.N., DAUBENEY P.E.F., MAGEE A.G., RIGBY M.L. (2006) Pulmonary vein stenosis: initial experience with cutting balloon angioplasty. *Heart,* 92(6), 815-820.

SEELIG M.H., OLDENBURG W.A., KlLINGLER P.J., ODELL J.A. (1998) Superior vena cava syndrome caused by chronic hemodialysis catheters: Autologous reconstruction with a pericardial tube graft. *Journal of Vascular Surgery,* 28, 556-560.

SELDINGER S.I. (1953) Catheter Replacement of the Needle in Percutaneous Arteriography: A new technique. *Acta Radiologica,* 39(5), 368-376.

SELLORS T.H. (1948) Surgery for pulmonary stenosis: A case in which the pulmonary valve was successfully divided. *Lancet,* 1(6513), 988.

SEMB B.K., TJONNELAND S., STAKE G., AABYHOLM G. (1979) 'Balloon valvulotomy' of congenital pulmonary valve stenosis with tricuspid valve insufficiency. *Cardiovascular Radiology,* 2(4), 239-241.

SENNING A. (1959) Surgical correction of transposition of the great vessels. *Surgery,* 45, 966-980.

SERRUYS P.W., DE JAEGERE P., KIEMENEIJ F., et al. for the Benestent Study Group. (1994) A comparison of balloon-expandable-stent implantation with balloon angioplasty in patients with coronary artery disease. *New England Journal of Medicine,* 331, 489-495.

SIDDIQUI J., BRIZARD C.P., GALATI J.C., IYENGAR A.J., HUTCHINSON D., KONSTANTINOV I.E., WHEATON G.R., RAMSAY J.M., D'UDEKEM Y. (2013) Surgical valvotomy and repair for neonatal and infant congenital aortic stenosis achieves better results than interventional catheterization. *Journal of the American College of Cardiology,* 62(22), 2134-2140.

SIGLER M., SCHNEIDER K., MEISSLER M., KÖNIG K., SCHNEIDER M.B.E. (2009) Breakable stent for interventions in infants and neonates: an animal study and histopathological findings. *Heart,* 92, 245-248.

SIGWART U. (1995) Non-surgical myocardial reduction for hypertrophic obstructive cardiomyopathy. *Lancet,* 346, 211–214.

SIGWART U., PUEL J., MIRKOVITCH V., JOFFRE F., KAPPENBERGER L. (1987) Intravascular stents to prevent occlusion and restenosis after transluminal angioplasty. *New England Journal of Medicine,* 316, 701-706.

SOGAT V., SAGAT M., BALAZOVA E., SIMAN J. (2008) Outcomes after surgical repair of sinus venosus atrial septal defect in children. *Bratislava Medical Journal,* 109 (5), 215-219.

SONES F.M.Jr. (1959) Acquired heart disease: symposium on present and future of cineangiocardiography. *American Journal of Cardiology,* 3, 710.

SOUTTAR H.S. (1925) The surgical treatment of mitral stenosis. *British Medical Journal,* 2, 603-606.

SREERAM N., SALEEM M., JACKSON M., PEART I., MCKAY R., ARNOLD R., WALSH K. (1991) Results of balloon pulmonary valvuloplasty as a palliative procedure in tetralogy of Fallot. *Journal of the American College of Cardiology,* 18(1), 159-165.

STAMM C., LI J., HO S.Y., REDINGTON A.N., ANDERSON R.H. (1997) The aortic root in supravalvular aortic stenosis: the potential surgical relevance of morphologic findings. *Journal Of Thoracic And Cardiovascular Surgery,* 114(1), 16-24.

STANGER P., CASSIDY S.C., GIROD D.A., Kan J.S., LABABIDI Z., SHAPIRO S.R. (1990) Balloon pulmonary valvuloplasty: Results of the Valvuloplasty and Angioplasty of Congenital Anomalies Registry. *American Journal of Cardiology,* 65(11), 775–783.

STRECKER T., ZIMMERMANN I., HEINZ M., RÖSCH J., AGAIMY A., WEYAND M. (2014) Successful Venous Angioplasty of Superior Vena Cava Syndrome after Heart Transplantation. *Case Reports in Cardiology,* Article ID 490276, 3 pages.

STUMPER O., RAMCHANDANI B., NOONAN P., MEHTA C., BHOLE V., REINHARDT Z., DHILLON R., MILLER P.A., DE GIOVANNI J.V. (2013) Stenting of the right ventricular outflow tract, *Heart,* 99, 1603-1608.

TAMAI H., IGAKI K., KYO E., KOSUGA K., KAWASHIMA A., MATSUI S., KOMORI H., TSUJI T., MOTOHARA S., UEHATA H. (2000) Initial and 6-month results of biodegradable poly-l-lactic acid coronary stents in humans. *Circulation,* 102 (4), 399-404.

TEMPELHOF M., CAMPBELL J., ILKANNOFF L. (2014) Sinus Arrest Following Angioplasty and Stenting for Superior Vena Cava Syndrome. *Journal of Invasive Cardiology,* 26(2),:E21-E23.

THOMKA I., SZEDO F., ARVAY A. (1997) A repair of coarctation of the aorta in adults with simultaneous aortic-valve replacement and coronary artery bypass grafting. *The Thoracic and Cardiovascular Surgeon,* 45, 93-96.

TOMITA H., WATANABE K., YAZAKI S., KIMURA K., ONO Y., YAGIHARA T., ECHIGO S. (2003) Stent implantation and subsequent dilatation for pulmonary vein stenosis in paediatric patients: maximizing effectiveness. *Circulation Journal,* 67(3), 187-190.

TRUSLER G.A., WILLIAMS W.G., DUNCAN K.F., HESSLEIN P.S., BENSON L.N., FREEDOM R.M., IZUKAWA T., OLLEY P.M. (1987) Results with the Mustard operation in simple transposition of the great arteries 1963-1985. *Annals of Surgery,* 206 (3), 251-60.

TURINA J., HIPPENMEYER-ZINGG I., SCHONBECK M., TURINA M. (1997) Severe aortic valve diseases and aortic isthmus stenosis in adults. Incidence, clinical aspects and long-term results of surgical treatment. *Zeitschrift fur Kardiologie,* 1997, 676-683.

TWORETZKY W., WILKINS-HAUG L., JENNINGS R.W., VAN DER VELDE M., MARSHALL A.C., MARX G.R., COLAN S.D., BENSON C.B., LOCK J.E., PERRY S.B. (2004) Balloon dilation of severe aortic stenosis in the fetus: potential for prevention of hypoplastic left heart syndrome. *Circulation,* 110, 2125-2131.

TYNAN M., FINLEY J.P., FONTES V., HESS J., KAN J. (1990) Balloon angioplasty for the treatment of native coarctation: results of valvuloplasty and angioplasty of congenital anomalies registry. *American Journal of Cardiology,* 65(11), 790-792.

TZIFA A., MARSHALL A.C., McELHINNEY D.B., LOCK J.E., GEGGEL R.L. (2007) Endovascular Treatment for Superior Vena Cava Occlusion or Obstruction in a Pediatric and Young Adult Population: a 22-Year Experience. *Journal of the American College of Cardiology,* 49, 1003–1009.

UNTERBERG C., BUCHWALD A.B., BARATH P., SCHMIDT T., KREUZER H., WIEGAND V. (1993) Cutting balloon coronary angioplasty-initial clinical experience. *Clinical Cardiology,* 16, 660-664.

VAN DER LINDE D., KONINGS E.E.M., SLAGER M.A., WITSENBURG M., HELBING W.A., TAKKENBERG J.J.M., ROOS-HESSELINK J.W. (2011) Birth prevalence of congenital heart disease worldwide: a systematic review and meta-analysis. *Journal of the American College of Cardiology,* 58(21), 2241-2247.

VOGEL M., BENSON L.N., BURROWS P., SMALLHORN J.F., FREEDOM R.M. (1989) Balloon dilation of congenital aortic valve stenosis in infants and children: short term and intermediate results. *British Heart Journal,* 62,148-153.

WALDMAN J.D., WALDMAN J., JONES M.C. (1983) Failure of balloon dilatation in mid-cavity obstruction of the systemic venous atrium after the Mustard operation. *Paediatric Cardiology,* 4(2), 151-154.

WARDEN H.E., GUSTAFSON R.A., TARNAY T.J., NEAL W.A. (1984) An alternative method for repair of partial anomalous pulmonary venous connection to the superior vena cava. *The Annals of Thoracic Surgery,* 38, 601-605.

WEBB G., GATZOULIS M.A. (2006) Atrial septal defects in the adult: recent progress and overview. *Circulation,* 114, 1645-1653.

WELLS W.J., BLACKSTONE E. (2000) Intermediate outcome after Mustard and Senning procedures: a study by the Congenital Heart Surgeons Society. Seminars in Thoracic and Cardiovascular Surgery. *Pediatric Cardiac Surgical Annual,* 3, 186-197.

WIGLE E.D., HEIMBECKER R.O., GUNTON R.W. (1962) Idiopathic Ventricular Septal Hypertrophy Causing Muscular Subaortic Stenosis. *Circulation,* 26, 325-340.

WITSENBURG M., THE S.H., BOGERS A.J., HESS J. (1993) Balloon angioplasty for aortic recoarctation in children: initial and follow-up results and midterm effects on blood pressure. *British Heart Journal,* 70(2), 170-174.

XU J., SHIOTA T., OMOTO R., ZHOU X., KYO S., ISHII M., RICE M.J., SAHN D.J. (1997) Intravascular ultrasound assessment of regional aortic wall stiffness, distensibility and compliance in patients with coarctation of the aorta. *American Heart Journal,* 134(1), 93-98.

YETMAN A.T., MCCRINDLE B.W. (2005) Management of pediatric hypertrophic cardiomyopathy. *Current Opinion in Cardiology,* 20, 80-83.

ZARTNER P., BUETTNER M., SINGER H., SIGLER M. (2007) First biodegradable metal stent in a child with congenital heart disease: evaluation of macro and histopathology, *Catheterization and Cardiovascular Interventions,* 69(3), 443–446.

ZEEVI B., KEANE J.F., CASTANEDA A.R., PERRY S.B., LOCK J.E. (1989) Neonatal critical aortic stenosis: a comparison of surgical and balloon dilation therapy. *Circulation,* 80, 831-839.

ZIMMERMAN H.A., SCOTT R.W., BECKER N.O. (1950) Catheterization of the Left Side of the Heart in Man. *Circulation,* 1(3), 357-359.

Appendix: Published papers