A review: Percutaneous pulmonary artery stenosis therapy: state-of-the-art and look to the future

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Abstract

Stenosis, or narrowing, of the branches of the pulmonary artery is a type of CHD that, if left untreated, may lead to significant complications. Ideally, interventions to treat stenosis occur before significant complications or long-term sequelae take place, often within the first 2 years of life. Treatment depends on specifics of the condition, the presence of other malformations, and age of the child. Research and recent innovation to address these shortcomings have provided physicians with safer and more effective methods of treatment. This has further continued to push the ceiling of pulmonary arterial stenosis treatment available for patients. Despite continuous advancement in angioplasty – such as conventional and cutting balloon – and stenting, each treatment method is not without its unique limitations. New technological developments such as bioresorbable stents can accommodate patient growth and pulmonary artery stenosis treatment. As more than a decade has passed since the review by Bergersen and Lock, this article aims to provide a contemporary summary and investigation into the effectiveness of various therapeutic tools currently available, such as bare metal stents and potential innovations including bioresorbable stents.

History of the transcatheter approach

Surgical treatment of pulmonary artery stenosis has long been in practice, dating back to before the advent and establishment of simple balloon angioplasty in the early 1980s.[1–3] The obvious benefits of increasing diseased vessel diameter, improving pulmonary artery perfusion, and decreasing right ventricular pressure justify the popularity of the technique.[4] Simple angioplasty has continued to be the standard of treatment since its introduction, and provides the cornerstone for initial therapy with low complication rate and ability to treat effectively with minimal risk, as previously reviewed in Bergersen and Lock.[2] The development of improved guidewire platforms, advanced catheter techniques, lower-profile balloons, larger balloons, high-pressure balloons, and cutting balloons has made simple balloon angioplasty the preferred method of treatment for patients with more aggressively diseased vessels.

High-pressure balloons and cutting balloons offer an effective method of treatment for pulmonary artery stenosis, particularly in vessels resistant to low-pressure balloon dilation. As there is still a specific population of lesions that do not respond well to low- or high-pressure balloon angioplasty, cutting-balloon angioplasty has become the next step in therapeutic evolution. This technique uses a balloon with multiple microatherotomes – cutting blades – that are exposed to balloon inflation, allowing the interventionist to strategically make cuts into the lesion to increase the vessel diameter. This is an effective strategy, but they do still hold potential complications, which must be considered.

In the late 1980s, Mullins et al developed a method involving deployment of stents into the diseased vessel to increase the diameter of the vessel, while providing a rigid scaffold to maintain patency.[2,5] Bergersen and Lock[2] highlighted that stents are particularly effective in the treatment of large and compliant vessels, as well as vessels that might be compressed by adjacent structures. Stenting provides interventionists the technology to provide the patient's vessel with a rigid framework to avoid compression. Stents still have their limitations, which are reflected in the hesitation to use stents in some lesions such as the ones distal to the pulmonary arterial tree. Furthermore, the populations that are usually treated with pulmonary artery stenosis are children. In addition, during development, children undergo exponential growth of the pulmonary system. This includes vascular branching from the heart, which results in further hesitation when considering stent placement. These disadvantages to the use of existing stent technology provide an opportunity for breakthrough research.

General population involved in pulmonary arterial stenosis

Pulmonary artery stenosis is a congenital stenosis, or narrowing, of vessels from the right side of the heart, which lead to the lungs. Narrowing of the vessel can occur at numerous points throughout the pulmonary arterial tree. The location of the narrowing defines the degree of risk that it, and potential interventions, poses to the patient. Many patients born with CHD, specifically pulmonary artery stenosis, are treated at a young age depending on the severity of the condition and vascular obstruction. In addition, other findings such as elevated right ventricular or main pulmonary artery pressure, unbalanced lung perfusion, and systemic cyanosis may dictate therapy.[6]

As many high-risk individuals affected by pulmonary artery stenosis are neonates and children, there are many factors to be considered when determining the appropriate intervention to treat the disease. Most of the time, when a patient exhibits severe pulmonary artery stenosis, it is acceptable to intervene. This is because an increased pulmonary gradient compounded with decreased efficiency of circulation of blood from the heart leads to ventricular dysfunction, which may result in pulmonary hypertension and further vascular disease.[2]

Even with treatment being paramount, exponential growth in this patient population must be considered. Moreover, it is not merely an increase in size that must be considered, but morphologic change during this time. Dammann and Ferencz articulated this when they described thinning and expanding of pulmonary arteries in the early stages of life.[7] Future technology must address the dynamic development of the pulmonary arterial system in young patients.

Methods for treatment of pulmonary arterial stenosis

Surgery

Surgical intervention for pulmonary artery stenosis is the oldest treatment modality and predates the oldest modern transcatheter intervention, the simple balloon angioplasty, which was pioneered in 1982.[4] Today, surgical intervention is reserved for more complex diagnoses or in cases in which intervention is not possible. Surgical intervention presents significant procedural risks and uncertain benefits. Trant et al[8] reported branch pulmonary artery stenosis surgical success rates to be only 62%, acutely. The inherent risks associated with surgical intervention, including procedural complications, prolonged hospitalisation and recovery times, and high costs per procedure, make surgery less appealing than alternative therapies.[8] The favourable risks and safety profiles of catheter-based therapy, when compared with the benefits of a surgical approach, explain why physicians reserve treatment of pulmonary artery stenosis with surgery for situations in which additional anatomic corrections must be made as well.

Balloon angioplasty

Balloon angioplasty was the first intervention of its kind providing interventionists with a novel approach to a variety of diseases. With the advent of this technology, physicians have been able to treat patients with a minimally invasive technique that exhibits reduced recovery time and cost to the patient. Balloon dilations are performed by inflating the device in the narrowed vessel until the elimination of the waist, inferring that the vessel has been successfully expanded. The dismissal of the waist

corresponds to the tearing of the intima and media of the vessel wall, or a "therapeutic tear".[9] Inflation of balloon at high pressures has led to reported success rates of up to 72% in pulmonary angioplasties.[9]

Balloon angioplasty inherently contains a variety of positive attributes; however, it does present potential risks that should be considered. Dilation of the vessel with this method can lead to complications including excessive tearing of the arterial wall, hypotension, and aneurysm. Despite present risks, years of practice and effective complication management strategies, such as covered stents and vessel occlusion, have led to reported mortality rates of <1%[9] (Table 1). With complications rates being low, Holzer et al[10] specifically examined cases that underwent balloon angioplasty of the proximal pulmonary artery from 238 patients, concluding a 13.0% (31) adverse event rate with a major adverse events rate of 0.8%. This was further studied by Holzer et al[11] in a larger patient population, which concluded an adverse event rate of 22% in 931 patients undergoing balloon angioplasty with an inclusive balloon pressure range. Another aspect inspected was the incidence of adverse events in relation to the age of the patient; balloon angioplasty is often used to treat young children. Researchers found that the highest rate of adverse events occurs in the youngest patients. In addition, the chances of re-stenosis of the treated vessel can range from 10 to 42%. Despite the variable success rate, specifically on resistant pulmonary artery stenosis lesions, the lack of alternative therapeutic options has made balloon angioplasty the favoured method to treat pulmonary artery stenosis.

Cutting balloons

The introduction of the cutting balloon (Boston Scientific Inc., Natick, Massachusetts, United States of America) 10 years ago made it possible to treat lesions in the pulmonary artery that are resistant to balloon angioplasty alone. The blade feature of the low-pressure balloon allows for a greater precision therapeutic tear of the vessel, which significantly reduces the likelihood of re-stenosis.[9] A multi-centre investigational device exemption study that compared the use of cutting balloons and high-pressure balloon angioplasty for the treatment of resistant pulmonary artery stenosis found that both procedures exhibited nearly the same safety profiles.[12] The patients treated with cutting balloon exhibited a 3% rate of adverse events, compared with the high-pressure balloon, which was 2%, with some adverse events possibly correlated to non-device complications. In addition, treatment with a cutting balloon was exponentially more effective in increasing the lumen diameter of the treated vessels when compared with the high-pressure balloons treatment alone (85 versus 52%; $p = 0.004$).[12] Figure 1 shows cutting balloons prove to be more effective in addressing some limitations of simple balloon angioplasty, specifically in resistant vessels treated using low- or high-pressure balloon alone. Nevertheless, even through improved techniques, the challenge of treating vessels with obstructions caused by compression, kinking, or recoil has proved challenging with balloon angioplasty alone and remains reliant on stent technology (Fig 1).[1]

Bare metal stents

Bare metal stents have advanced the reach of interventional cardiology, allowing physicians to dilate vessels that were unable to be adequately treated with balloon angioplasty alone (Fig 2). They provide a rigid framework for vessels that tend to have

Table 1. Comparison of adverse events experienced during pulmonary artery stenosis intervention.[13-18]

	Gentles (1993)	Zeevi (1997)	Bush (2000)	Baker (2000)	Bergersen (2005)	Geggle (2001)
Event rates by procedure						
Complication	13.2% (7/53)	12.5% (4/32)			26.9% (28/104)	48.7% (19/39)
Death				0.8% (6/728)		
Pulmonary oedema		3.1% (1/32)	4.0% (3/75)		5.8% (6/104)	15.4% (6/39)
Pneumothorax		3.1% (1/32)				
Haemoptysis						
Arrhythmia	1.9% (1/53)				4.8% (5/104)	12.8% (5/39)
Hypotension	9.4% (5/53)				2.9% (5/104)	28.2% (11/39)
Access Complication		6.2% (2/32)				
Stroke						
Cardiac arrest					1.0% (3/104)	
Vessel complications by dilation						
PA vessel tear from dilation	1.4% (1/72)			2.3% (29/1286)	1.0% (2/203)	2.2% (3/134)
PA vessel tear from wire	2.8% (2/72)					
Aneurysm	4.2% (3/72)		0.7% (1/134)		3.4% (7/203)	17.9% (24/134)
Branch occlusion						
Stent for vessel trauma					4.9% (7/203)	

PA = pulmonary artery.

recoil characteristics secondary to external pressure and anatomic distortion.[9] This allows for suitable blood flow through the vessel, which can relieve stress on the right side of the heart and increase perfusion to developing lungs. The major risk associated with stents is growth restriction; stents remain at the implanted size as the surrounding vasculature grows with the developing child. Most patients treated for pulmonary artery stenosis undergo additional interventions in their youth to serially dilate implanted stents to accommodate somatic growth (Fig 2).

Since the introduction of stents, the variety of bare metal stents have increased significantly. They now include different cell configurations, are self- and balloon-expanding, and can be of variable size and shape to further accommodate the location of the lesion. The advancement of bare metal stents design and flexibility, along with the decreased profile within the vessel, allows for them to be placed in diverse locations within the pulmonary tree. A major advantage of many new stents is that they are self-expanding, which decreases the size of the catheter an interventionist must use in order to position the stent and treat the diagnosed vessel. Despite advancements, stent designs are still limited in expansion by re-dilation of the stent. In addition, there still is a possibility of stent fracture and/or loss of integrity and compression from external structures.

The continued development of stent design technology provides a wide breadth of options for treatment of pulmonary artery stenosis; however, the major shortcoming of stent technology is the fixed diameter of the stent in a growing patient. The re-intervention often required to accommodate growth in relation to adjacent vasculature is an aspect that is of great concern in paediatrics, as removal can only be conducted via surgery and expansion can incur risk. Covered stents are used in pulmonary

artery stenosis as a bailout technique to avoid emergent surgery in the event of vascular injury, which may compromise the vessel and result in unconfined bleeding into the chest. The development and advancement of stent technology provide a variety of treatment options for interventionists when considering pulmonary artery stenosis; however, gaps in technology are still present. This can be addressed through research and production of a stent that will provide the patient's vessel with a firm framework while allowing the vessel to grow and proceed with dynamic changes that occur in the early years of life.

In a study conducted in 2013, Takao et al researched the effectiveness of stent placement in young patients. The study investigated the indirect effect of somatic growth in the stented pulmonary artery diameter as compared with the collateral pulmonary artery diameter.[19] Most patients received a follow-up catheterisation 20 + 13.5 months after the first stent was placed. They observed that the stent had a decreased diameter of almost 10% at the pulmonary artery, whereas the non-stented collateral exhibited a 16% increase in diameter. Both distal and proximal pulmonary artery vessels from the stent location had similar growth. Comparable results were produced when patients underwent a second follow-up catheterisation months from the initial procedure. Takao et al displayed that stent placement encourages normal distal pulmonary artery growth in patients. Furthermore, the researchers made a critical observation that the younger and smaller – lower body surface area – a patient was at the time of the intervention, the greater the bilateral growth that the patient exhibited in pulmonary vessels.[19]

The study conducted by Takao et al[19] not only demonstrated the benefits of stent placement in younger patients, but also highlighted the prevalence of the re-intervention often required

for this patient population. In total, 66% of patients who took part in the study were required to have follow-up intervention to expand the stent that was initially placed. Most bare metal stents that are placed compel physicians to re-intervene later in order to expand the stent to accommodate somatic growth. In select cases, surgical intervention is needed to remove the stent if it is no longer adequate for the vessel diameter.

Stent fractures and safety

Along with growth concerns, mechanical stressors imparted by the local environment can compromise stent structural longevity. McElhinney et al described the repetitive cyclic stress placed on stents that causes fractures. In the examination of 166 stents, they found that 35 (21%) exhibited complete axial or complex fractures.[20] The resorting fractures caused haemodynamically significant vessel obstruction in 80% of cases.[20] Bergersen et al[21]

analysed nearly 4000 cases and determined four procedure-type risk categories that would aid in predicting the risk associated with congenital heart procedures.[21] Balloon angioplasty, stent placement, and stent re-dilation were placed in Risk Category 3 or 4, with Risk Category 4 being the highest risk associated with procedures; the odds of a level 4 or 5 adverse event increases exponentially in these specific risk categories. Despite the potential risks, treatment has been proven to be highly effective. In a review conducted by Holzer et al,[10] a total of 287 total stenoses in 245 patients from eight centres were analysed and exhibited a 99.3% success rate of the procedure. Among the 245 patients, there were 244 adverse events recorded in 32 patients (13.2%), with three (1.2%) being major adverse events. Holzer et al[10] specifically analysed cases that included the balloon and stenting of the proximal pulmonary artery from 48 patients, concluding a 10.4 % adverse event rate. A critical observation across multiple studies shows that there is a decreased adverse
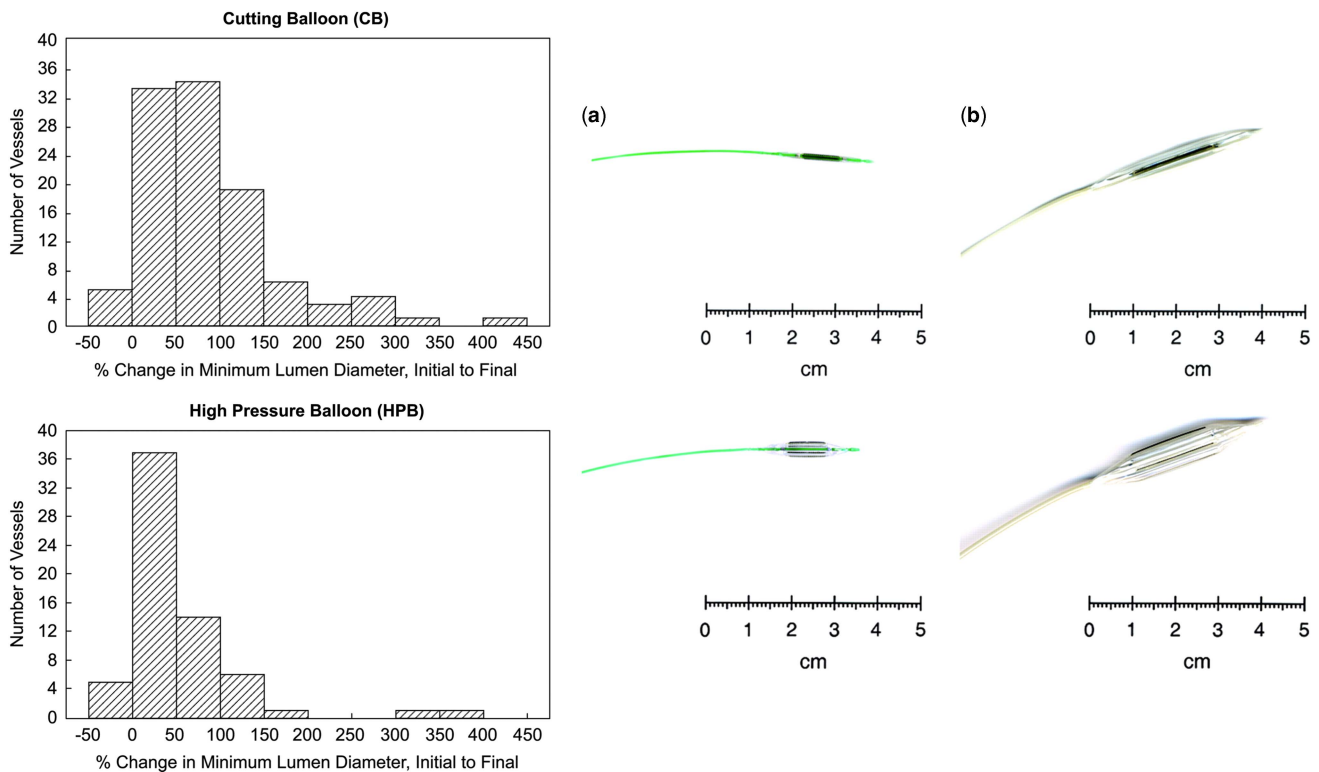
Figure 1. Cutting balloons (CB; Boston Scientific, Inc., Natick, Massachusetts, United States of America) are noncompliant balloons with atherotomes (microsurgical blades) mounted longitudinally on their outer surface. (*a*) The Flextome CB. (*b*) A magnified 2-cm-long peripheral CB device deflated and inflated (Bergersen et al[21]).
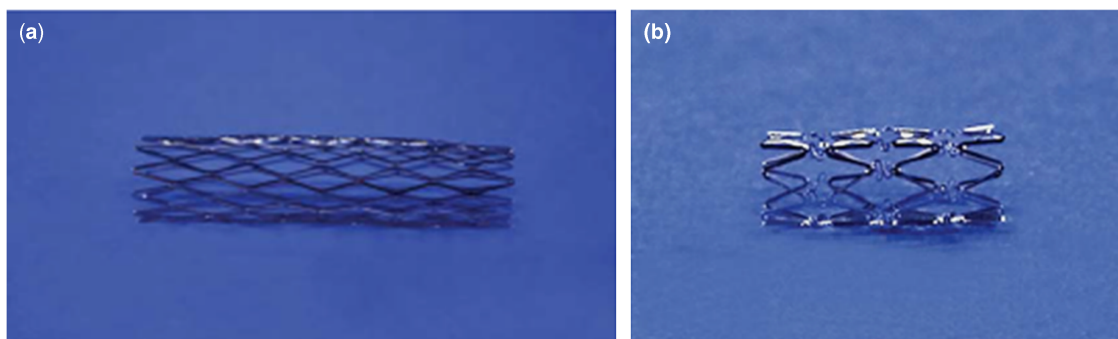
Figure 2. (*a*) Palmaz stent. (*b*) Genesis stent (Bergersen and Lock[2]). Common Bare Metal Stents.

Table 2. Adverse event (AE) by age: incidence of any AE in patients undergoing pulmonary artery balloon angioplasty and/or stent placement.

	Holzer et al[11]	Moore et al[16]
< 1 month	13/31 (38%)	1/3 (33%)
1 < 12 month	71/285 (25%)	10/39 (26.3%)
1 < 10 years	127/644 (20%)	16/175 (9.2%)
10 < 18 years	47/202 (23%)	
≥18 years	29/150 (19%)	5/29 (17.2%)

event rate as patients age (Table 2).[11,22] Ideally, younger patients could be treated with balloon angioplasty until they are older, whereupon bare metal stents could be placed with less risk and require less invasive procedures for serial stent re-dilation to accommodate for somatic growth. In patients with balloon angioplasty treatment-resistant lesions, advances in stent technology may provide an alternative, and hopefully superior, management strategy.
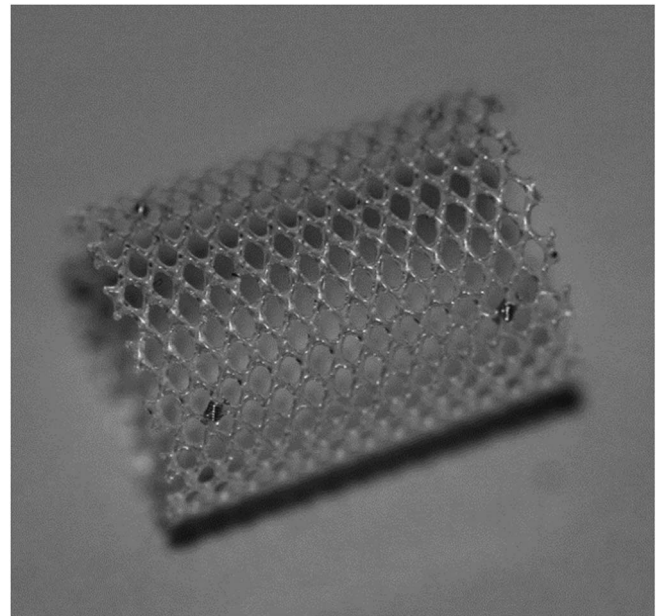
Re-intervention

The placement of bare metal stents is considered one of the most effective intervention methods to help the structural integrity of the treated vessel. However, despite short-term success, recent studies show that the rate of long-term effectiveness is far from ideal.[23] The rate of re-intervention was previously reported as high at 43%; other reports suggest that intervention for the initial procedure is approximately 11% by 18 months and upwards of 30% by three years.[23,24]

Re-intervention of post-stent placement is most commonly performed to increase the size of the stent as the patient grows. During the first 18 months of the patient's life, fetal pulmonary arteries grow rapidly, necessitating repeat intervention on a static stent. As technology develops, stent designs have made it possible for re-dilation up to 2 years after the placement of the stent in the vessel – allowing stents to expand with the somatic growth of the patient's vessel up to a certain point.[9] Ultra-high-pressure balloons have made it possible to expand placed stents with a higher success rate (91%). Maglione et al[25] reported that the median change exhibited in the vessel diameter was 36%, ranging from 7 to 220% of the original diameter, when the waist of the ultra-high-pressure balloon was eliminated.

Nevertheless, as reported by Bergersen and Lock, stents have limited ultimate expansion diameter. If potential expansion is insufficient, the stent will have to be surgically removed.[9] This dogma has been challenged over the past two decades, initially by "growth" stents and more recently by "unzipping" techniques.[26–29]

Bioresorbable stent

Currently, the development of bioresorbable stent technology is an important advancement for the paediatric population who require stent therapy.[30] Indeed, even before an ideal purpose-built paediatric device is available, paediatric interventionists have used existing bioresorbable stent for alternate indications in the paediatric population.[31–33] Re-intervention of older bare metal stents is usually conducted to increase the size of the stent as the patient grows, or less commonly to treat stent re-stenosis or fracture. Bioresorbable stents could provide a temporary scaffolding to increase vessel size

Figure 3. 480 Biomedical Inc. bioresorbable stent.[34]

and may obviate the need for re-intervention through serial dilation as they are able to grow with the patient. Research on older bare metal stents has concluded that re-intervention rates may be as high as 43%.[24] Decreasing the amount, or at least the level of intervention needed, may provide substantial direct benefit to the patient.[35]

Researchers are still investigating the ideal structural integrity of the bioresorbable stent to make it capable to hold up to the pressure within the vascular system. Ideally, the bioresorbable stent is designed to expand vessel stenosis and exhibit intended reabsorption over time. However, to what extent this design will compromise sufficient rigidity of the framework, and thus vessel lumen, remains to be seen. This programmed loss of structural integrity permits the patient's body to have time to heal the vessel, and allow continued vessel growth with the normal growth of the body.[6,35] During this gradual reabsorption, the foundational structural scaffold of the stent is still within the vessel, which provides the vessel the integral support it needs to prevent re-stenosis.[35] If further intervention is needed, interventionists can delay additional therapy until both the vessel and patient have grown and can accommodate larger available technology. This would avoid the conundrum of using permanent bare metal stents that cannot grow to adult size, even with balloon dilation, and may necessitate surgical removal from smaller-diameter vessels.

It seems reasonable to expect that the potential risks associated with the bioresorbable stent will be on par with other interventional methods to treat pulmonary artery stenosis. Bioresorbable stent technology resembles the previous and currently used stents to a great degree. As bioresorbable stents have inherited many characteristics from previous stents, it is very reasonable to assume that they will exhibit similar safety concerns. This is not to say that it might display risks unique to the bioresorbable characteristics of the stent. Bioresorbable stent technology risks could include inflammation-based constrictive remodelling, vascular biocompatibility, long-term stent failure, and in-stent stenosis.

Bioresorbable stenting is not a novel idea. Many physicians have used bioresorbable stents, which were designed for other uses, to help patients through various pulmonary artery stenosis. Zartner[31] published a case where a magnesium stent was used in a

female preterm baby born at the 26th week of gestation. In addition, in a case presented by Rodriguez et al a bioresorbable vascular scaffold, which is usually reserved for coronary intervention, was used to treat a 3-month-old child. They cited the off-label use of the device as it would allow for them to open the occluded vessel, while taking into account the growth of the pulmonary circulation.[32] Many positive aspects of bioresorbable stents can be seen in these cases (Fig 3).[31–33]

Currently, the paediatric bioresorbable stent closest to moving forward with a clinical trial is in the final phases of development and is being manufactured by 480 Biomedical Stent Inc. The stent and delivery system have been specifically designed for application in children with pulmonary artery stenosis. Unlike many technologies in paediatric interventional cardiology that were developed for adult diseases, including present balloon and stent technology, this will be a specific treatment for CHD in the growing child. Support from the National Institutes of Health (National Heart, Lung, and Blood Institute) was contracted to the sponsor after a call for submissions to bring this technology to the CHD population.[36] In this context, over the past four years, 480 Biomedical has partnered with the paediatric interventional community to design technology to meet the specifications required to treat children with pulmonary artery stenosis.

Having completed the technology development, the sponsor is in the final phases of proposing an early feasibility clinical trial to the Food and Drug Administration. The purpose-built paediatric bioresorbable stent is designed to support pulmonary artery anatomy affected by pulmonary artery stenosis for a minimum of 3 months, and then relieve its own structural integrity to conform to the somatic growth of the surrounding vessel over the next 6 months. With this unique ability, physicians would not have to intervene surgically to remove metal stents, but have the opportunity, if required, to re-dilate the growing vessel. Bioresorbable stents may ultimately replace the traditional methods of treatment and provide physicians a method of treatment that confidently treats pulmonary artery stenosis patient now, and as the patient grows. The first application of the stent hopes to be in the more proximal vessels, which allows for easier delivery and placement of the stent. With delivery methods suitable for children, the 480 Biomedical bioresorbable stent will be able to provide a much-needed innovative therapy for this specific population of pulmonary artery stenosis patients and could address the issue of growth in small patients.

Despite perceived risks, bioresorbable stents are an essential innovation necessary to breakthrough many of the limitations that hinder the progression of pulmonary artery stenosis care in the paediatric population. These stents will hopefully mitigate the risks that patients currently face throughout their care. They create an intervention that encompasses the cost-effective and decreased hospitalisation benefits of balloon angioplasty and stents, while also providing a safe, long-term solution. Bioresorbable stents will offer vessels the structural support of traditional stents, but will be able to grow with the patient's vasculature, and rapid somatic growth in the early years of life.

Summary

Even with the continuing improvement of current interventional technology involving balloon angioplasty, cutting balloons, and bare metal stenting of pulmonary artery stenosis, innovation needs to be made. The limitations that have been observed in current standards of practice have not only left a large population of patients unable to be effectively treated but have pushed physicians and researchers to elucidate what is needed to provide the best long-term care of patients with pulmonary artery stenosis. Surgery, balloon angioplasty, and cutting balloons have long been used to effectively increase the size of vessels, resolve pressure gradients, and relieve immediate danger for patients. Further, the advent of bare metal stents allowed interventionists the ability to place devices that would give diseased vessels a structural backbone so that they could be dilated more easily. However, with this rather effective method of treatment, patient growth has forced physicians to dilate the stents via further catheter interventions as much as possible or ultimately surgically remove the implanted stents. The promise of bioresorbable stents possibly holds the solution for many of the issues that plague physicians today when it comes to the treatment of pulmonary artery stenosis in this population. Bioresorbable stents are designed to initially provide a rigid framework for the vessel as it is dilated, allowing the vessel to grow. Thereafter, the stent will intentionally degrade, losing its integrity and permitting normal growth of the vessel with surrounding vasculature. Even though many of the benefits of this groundbreaking technology are evident, risks and uncertainties still exist, which require exploration in clinical trials. The innovation of bioresorbable stents as a treatment for pulmonary artery stenosis holds much hope as the key to a more effective intervention for young patients.

Conflicts of Interest. L.B. is a Consultant for 480 Biomedical Inc.

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