

Percutaneous pulmonary valve implantation

Implantación percutánea de válvula pulmonar

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Abstract

Development of right ventricular outflow tract (RVOT) dysfunction due to progressive pulmonary valve stenosis and insufficiency is not uncommon after surgical repair of congenital heart disease. Since the early 90s, bare metal stenting has been considered as an approach to prolong conduit longevity. The drawback of this approach is that it only treats pulmonary stenosis leaving behind severe pulmonary valve insufficiency.

Although surgical intervention in the RVOT is considered to have relatively low morbidity and mortality, it carries the inherent risks of surgery plus the known limitations in lifespan of the surgical implants such that subjects continue to require multiple open heart procedures. Percutaneous valve therapies have emerged in the last 10 years to decrease the need for open surgical procedures.

As a consequence there has been a major change in the treatment of RVOT dysfunction.

Author in this revision described major current transcatheter heart valves systems and also those trials involved with them: the Melody (Medtronic Inc., Minneapolis, MN) and the Edwards SAPIEN (Edwards Lifesciences, Irvine, CA).

Melody valve received Humanitarian Device Exemption from the FDA in 2010 and is commercially available in the United States. At present time percutaneous pulmonary valve implantation has been categorized as a Class II by the American Heart Association (level of evidence B).

Key words: congenital pulmonary stenosis, pulmonary valve insufficiency, pulmonary valve replacement surgery, percutaneous pulmonary valve implantation.

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INTRODUCTION

The development of right ventricular outflow tract (RVOT) dysfunction due to progressive pulmonary valve stenosis and insufficiency is not uncommon after surgical repair of congenital heart disease.¹ Therapeutic options have traditionally consisted of surgical implants in the form of homografts, valved conduits and bioprosthetic valves. Since the early 90s, when the main lesion is stenosis, bare metal stenting has been

considered as an approach to prolong conduit longevity.² The drawback of this approach is that it only treats pulmonary stenosis leaving behind severe pulmonary valve insufficiency. It is well known that chronic severe pulmonary valve insufficiency leads to progressive right heart failure, decreased exercise tolerance and life threatening arrhythmias.³⁻⁵

Although surgical intervention in the RVOT is considered to have relatively low morbidity and mortality,^{6,7} it carries the inherent risks of surgery plus the known limitations in lifespan of the surgical implants such that subjects continue to require multiple open-heart procedures.^{8,9} Percutaneous valve therapies have emerged in the last 10 years to decrease the need for open surgical procedures and prolong the lifespan of existing valve implants. As a consequence there has been a major change in the treatment of RVOT dysfunction. Currently, two transcatheter heart valves systems exist: the Melody (Medtronic Inc., Minnea-

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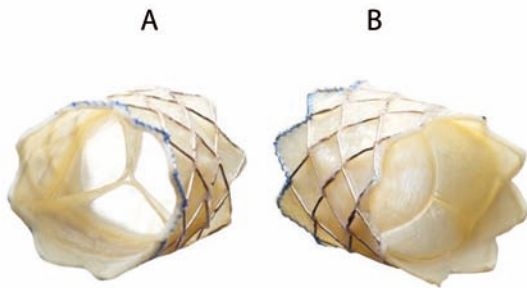


Figure 1. A and B. Photograph of the Melody Medtronic valve.



Figure 2. Photograph of the Ensemble delivery system.

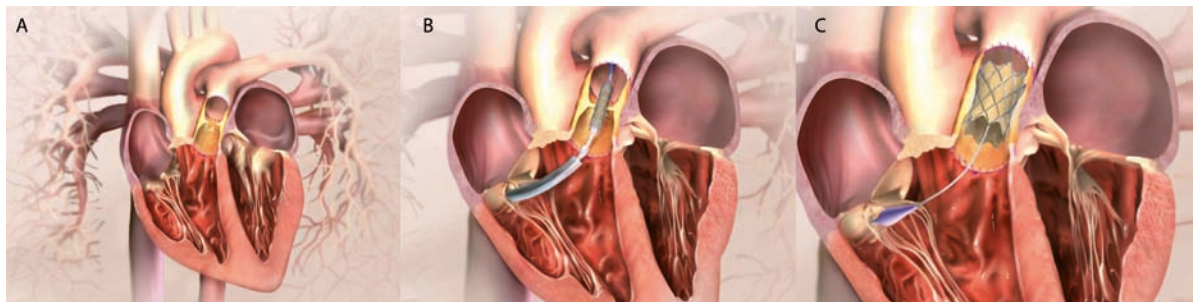


Figure 3. Illustration of the anatomic characteristics of a right ventricle to pulmonary artery conduit (A). The Melody valve is advanced into the conduit and the valve is exposed by retracting the sheath (B). Following implantation of the valve within the conduit (C), the delivery system is retracted back over the wire. Courtesy of Medtronic Inc., Minneapolis, MN.

polis, MN) and the Edwards SAPIEN (Edwards Lifesciences, Irvine, CA) valves. The Edwards SAPIEN valve in the pulmonary position has been studied as part of the COMPASSION (COngenital Multicenter Trial of Pulmonic VALve Regurgitation Studying the SAPIEN IntervENTIONal) clinical trial, whereas the Melody valve received Humanitarian Device Exemption from the FDA in 2010 and is commercially available in the United States.

Percutaneous pulmonary valve implantation has been categorized as a Class II AHA recommendation for conduits with moderate to severe stenosis or insufficiency provided the patient meets the inclusion/exclusion criteria for the available valve (Level of evidence B).¹⁰

MELODY PERCUTANEOUS PULMONARY VALVE

A. History and characteristics

Dr. Phillip Bonhoeffer implanted the first percutaneous pulmonary valve in the year 2000.^{11,12} This original design, conceived by Dr Bonhoeffer, was subsequently modified, and eventually resulted in what we now know as the Melody Valve-

TM, manufactured by Medtronic (Minneapolis, MN, USA), commercially available in the United States as a Humanitarian Use Device since March of 2010. This valve is a bovine jugular venous valve sewn into a platinum iridium balloon expandable stent (Figure 1A and 1B). The valve is mounted manually by the implanter on the Ensemble® Transcatheter Valve Delivery System, which consists of a balloon-in-balloon catheter with a retractable polytetrafluoroethylene (PTFE) sheath (Figure 2). The distal cup is large enough to front-load the stented valve after crimping. The delivery system has a 22 Fr crossing profile and comes in outer balloon sizes of 18, 20, and 22 mm (Figure 2). The valve is delivered in a similar fashion to conduit stents (Figure 3).

B. Indications

The Melody valve was the first percutaneous valve approved for human use in the United States by the Food and Drug Administration.¹³ Specifically, it is approved only for use in:

- dysfunctional conduits with either a mean gradient of 35 mmHg or
- at least moderate pulmonary valve insufficiency.

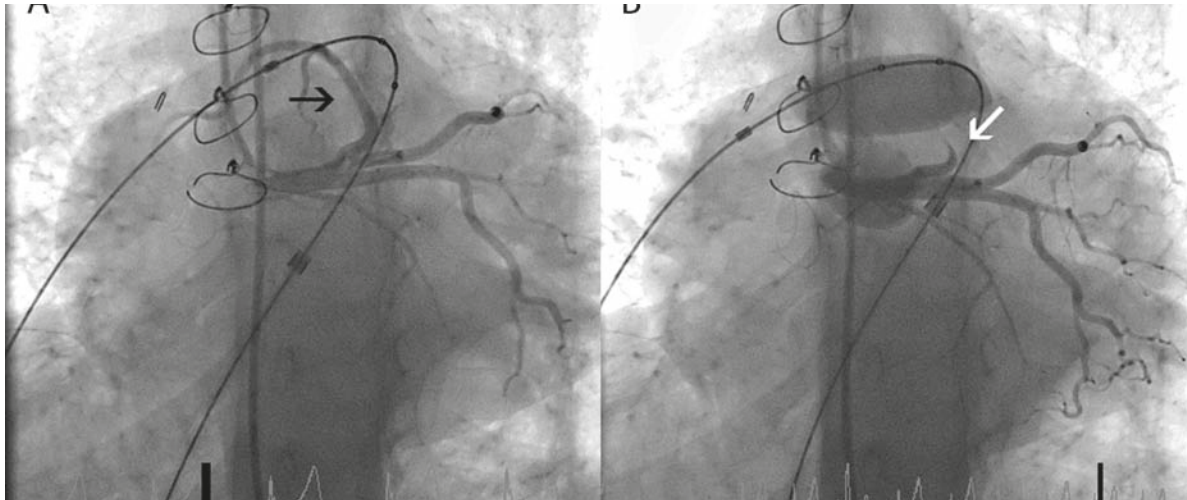


Figure 4. A. Image in AP/Caudal projection demonstrates a selective coronary angiography in a patient with Tetralogy of Fallot and a single left coronary artery with the right coronary crossing the right ventricular outflow tract (black arrow). **B.** During balloon dilation of the right ventricle to pulmonary artery conduit there is complete occlusion of flow (white arrow) by compression of the right coronary artery.

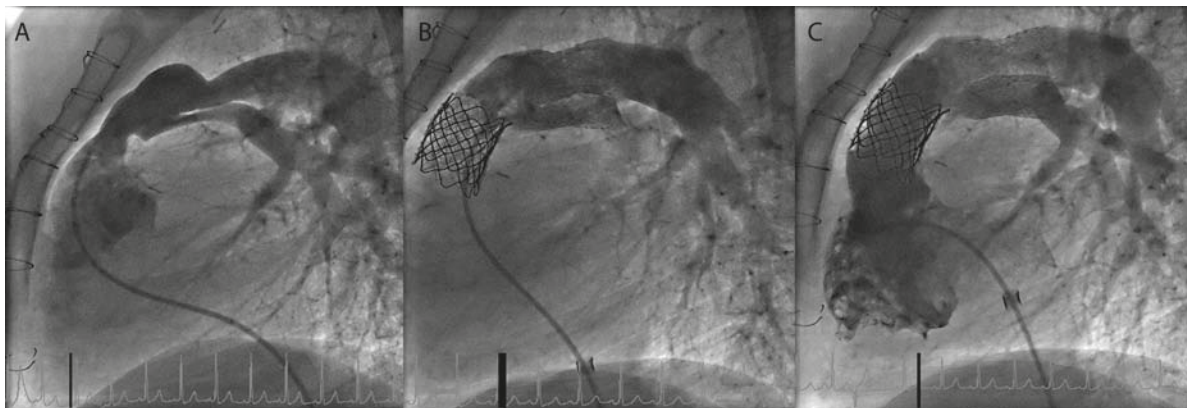


Figure 5. A. In lateral projection the right ventriculogram demonstrates a stenotic right ventricle to pulmonary artery conduit with additional stenosis at the proximal pulmonary arteries bilaterally. **B.** Following angioplasty and stenting of both branches in addition to stent implantation in the conduit and Melody valve implantation the pulmonary angiogram demonstrates no pulmonary valve insufficiency. **C.** The right ventriculogram following intervention demonstrates a widely patent right ventricle to pulmonary conduit as well as no residual stenosis in the proximal pulmonary arteries.

And:

- Original conduit implantation size has to have been at least 16 mm when implanted.

Although there are no specific contraindications, in the United States it is not recommended for implantation in the following:

- Aortic or mitral position, since preclinical bench testing of the Melody valve suggests that valve function and durability will be extremely limited when used in these locations.
- When patient's anatomy precludes introduction of the valve, if the venous anatomy cannot accommodate a 22-Fr size introducer, or if there is significant obstruction of the central veins.
- There are clinical or biological signs of infection including active endocarditis.

There is however increasing experience in the use of the valve in off-label applications,¹⁴⁻¹⁶ such as in tricuspid valve or other valve positions, inside bio-

prosthesis or outflow tract patches. For patients in whom venous access is limited, hybrid periventricular approach can be used. In addition, intraoperative implants can also be performed in young patients in whom the potential for late re-dilation of the valve stent gives an alternative which could accommodate to growth.

C. Implantation considerations

Similar to when stenting RVOT conduits, prior to deployment of a transcatheter pulmonary valve careful assessment of the coronary artery anatomy for the risk of coronary artery compression should be performed in all patients. Certain coronary anatomies are at increased risk of compression (anomalous left anterior descending from right coronary artery; single right coronary or single left coronary) (**Figure 4**). When the coronaries course in proximity of the conduit, selective coronary angio-



Figure 6. Photograph of the Edwards SAPIEN valve.

graphy with simultaneous conduit balloon dilation to the expected ending diameter must be performed (**Figure 4**) to evaluate for coronary compression at the time of conduit expansion. If compression or distortion is seen, the patient would be considered not a candidate for stent placement^{17,18} nor percutaneous pulmonary valve implantation.

In addition, restrictions with regards to diameter of balloon to expand the conduit do exist. To minimize the risk of conduit rupture, it is recommended not to use a balloon with a diameter greater than 110% of the nominal diameter (original implant size) of the conduit for pre-dilation of the intended site of deployment, or for deployment of the TPV.

The size and shape of the RVOT must be evaluated prior to PPV implantation. The RVOT will need to measure between 16 and 22 mm in diameter to accommodate the Melody Valve™. Morphologically, a straight or hour glass shaped conduit is more favorable for Melody Valve™ implantation than a divergent or pyramidal shape¹⁹. However the shape of the RVOT is rarely a limitation to proceed.

The major component of the procedure is the preparation of an adequate “landing zone”. This can be particularly challenging in patients in whom the predominant indication for pulmonary valve implantation is stenosis, as these conduits are commonly resistant to dilation. The RVOT is prepared using sequential angioplasties and stent implantations within the conduit, almost always with use of ultrahigh pressure balloons. Once the target diameter has been achieved implantation of the Melody Valve™ is a relatively simple component of the procedure.

D. Experience and results

Melody percutaneous pulmonary valve implantation is currently performed in over 170 centers worldwide, with more than 5,000 implants to date.

USA

In the United States, there have been 2 major studies carried out. One was the original Investigatio-

nal Device Exemption (IDE) study prior to approval 13. The second is the post market approval study, which is still on going. Among to initial 100 patients of the IDE study, the incidence of serious adverse events related to the device or procedure was 5.1%, including 4 four procedure-related events (homograft rupture, branch pulmonary artery rupture, supra-ventricular tachycardia, and coronary dissection) and one device-related SAE (stent fracture that necessitated repeat TPV placement). There was one death from intracranial hemorrhage after coronary artery dissection, and one valve was explanted after conduit rupture. The median peak right ventricular outflow tract gradient was 37 mm Hg before implantation and 12 mm Hg immediately after implantation. Before implantation, pulmonary regurgitation was moderate or severe in 92 patients (81%); no patient had more than mild pulmonary regurgitation early after implantation or during follow-up (1 year in 65 patients). Freedom from diagnosis of stent fracture was 77.8+/-4.3% at 14 months. Freedom from Melody valve dysfunction or reintervention was 93.5+/-2.4% at 1 year. A higher right ventricular outflow tract gradient at discharge ($P=0.003$) and younger age ($P<0.01$) were associated with shorter freedom from dysfunction.

Since this original study, experience has demonstrated that pre-stenting helps lower the chances of fracture and restenosis during follow up. A more aggressive approach to prepare an optimal “landing zone” for the valve will likely lead to improved long term results.

With regards to the post market approval study, it included 127 patients who were enrolled at 10 U.S. centers. There have been no deaths to date and a rate of 5.6 per 100 person-year significant adverse events, including stent fractures and endocarditis. Follow up data is still being collected for this study. As it is known for stents in cardiac conduits, there is a risk of stent restenosis and fracture. In a series of 123 patients who underwent Melody valve placement, Nordmeyer et al.²⁰ reported an incidence of 25% of stent fracture at a two-year-follow-up.

Radiographic assessment of the stent with chest radiography or fluoroscopy should be included in the routine post-procedural evaluation of patients who receive a percutaneous pulmonary valve. Stent fracture is typically associated to restenosis. If a stent fracture is detected, continued monitoring of the stent should be performed in conjunction with clinically appropriate hemodynamic assessment. In patients with stent fracture and significant associated RVOT obstruction or regurgitation, reintervention should be considered in accordance with usual clinical practice. The presence of a fracture may indicate the increased risk of re-

tenosis, but in the absence of a gradient, it is of little significance. If there is no loss of stent integrity, fractures are considered benign.

In the series of patients who underwent Melody valve implant as part of the US IDE trial, it was demonstrated²¹ that stent fractures were more likely in patients with severely obstructed right ventricular outflow tract conduits and when the Melody was directly behind the anterior chest wall and/or clearly compressed, whereas a valve implant site protected by a pre-stent or bioprosthetic valve was associated with lower risk of fracture and reintervention.

Since approval, the experience at Children's Hospital of Pittsburgh of UPMC includes 41 Melody ValveTM implantations, one intraoperative and the rest percutaneous. Review of the data demonstrates that on average, the conduits had narrowed by 33% of their original size by the time of implant. All but one patient required pre-stenting with one or more bare metal stents, which significantly expanded the conduits (**Figure 5**). Melody ValveTM implantation further expanded the area by an average of 10%. Intracardiac echocardiography was used to evaluate for paravalvular leaks whenever there was any regurgitation seen on post implantation angiograms. During follow up, there was one death unrelated to the procedure in an adult patient with diabetic end stage renal disease and severe biventricular dysfunction, who died from non-cardiac causes. The Melody Valve was functioning well. During follow up (up to 3 years) one valve was explanted due to endocarditis, and all others remain in place. There were 2 paravalvular leaks, one treated at the time of implantation with a second Melody valve implant. Another (which had been an intraoperative implantation in a small child) was managed medically. All patients have mild or less regurgitation during follow up, and gradients have been in mild to moderate range. Many of these patients are followed in the post market approval study.

European experience

The original experience by Dr Bonhoeffer I included 155 patients who underwent percutaneous pulmonary valve implantation between September 2000 and February 2007 with stenosis and/or regurgitation. There was significant reduction in right ventricular systolic pressure and right ventricular outflow tract gradient. Follow-up ranged from 0 to 83.7 months (median 28.4 months). Freedom from reoperation was 93%, 86%, 84%, and 70% at 10, 30, 50, and 70 months, respectively. Freedom from transcatheter reintervention was 95%, 87%, 73%, and 73% at 10, 30, 50, and 70 months, respectively. Survival at 83 months was

96.9%. On time-dependent analysis, the first series of 50 patients and patients with a residual gradient > 25 mm Hg were associated with a higher risk of reoperations, showing the effect of the learning curve on clinical outcome.

A prospective, observational, multi-centric survey by means of a web-based database registry of the Italian Society of Pediatric Cardiology²² reported 63 patients between October 2007 and October 2010 aged 11 to 65 years, who underwent Melody valve implantation due to pure stenosis (21 patients), pure regurgitation (12 patients), combined disease (30 patients). Implantation was performed in 61 subjects (97%). Pre-stenting was performed in 85%. Immediate results demonstrated no significant regurgitation, with a significant decrease in gradient. Early major complications occurred in 7 subjects (11%). One death occurred in the early post-operative period in a severely ill subject. At a median follow-up of 30 months (range 12-48 months), three patients died due to underlying disease. Major complications occurred in six patients during follow-up, which included arrhythmias, viral encephalitis, Melody valve endocarditis (2 pts) and major stent fractures requiring second valve implant (2 pts). Freedom from valve failure at latest follow-up was 81.4% ± 9%.

Other reports reflecting the world experience with the Melody valve implant indicate similar early results.¹⁶

Edwards SAPIEN Pulmonic Valve

Edwards SAPIENTM Pulmonic Valve (Edwards Lifesciences LLC, Irvine, CA) consists of three bovine pericardial leaflets hand-sewn to a tubular, slotted, stainless steel, balloon expandable stent (**Figure 6**). The leaflet pericardial tissue is processed with the same ThermafixTM anti-calcification treatment utilized in the Carpentier-Edwards PERIMOUNT MagnaTM surgical valves. There is a fabric sealing cuff covering the lower portion of the stent to facilitate a seal with the calcified conduit and prevent paravalvular leak. The valve is available in 23 and 26 mm diameter sizes with heights of 14.5 and 16 mm, respectively. A 29 mm diameter valve is also available for the aortic position. The valve requires a specific delivery system: the RetroflexTM I or II catheters (Edwards Lifesciences LLC, Irvine, CA.). These catheters consist of a balloon catheter and a deflectable guiding catheter, and require either 22 or 24 Fr hydrophilic sheaths for the 23 and 26 mm valves, respectively. A specialized manual crimping tool is used to symmetrically compress the valve onto a valvuloplasty balloon.

The first use of the Edwards SAPIEN^(™) valve in a human was reported by Garray et al.²³ in a 16-year-

old patient after a Ross procedure based on a compassionate use approved by the FDA. The first use of the Edwards Sapien valve in Europe was reported by Ewert et al. in 2010.²⁴ The new Edwards SAPIEN™ pulmonic valve reached European CE certification at the end of 2010, thus offering an attractive alternative for percutaneous valve implantation with extended sizes (23 and 26 mm).

The experience with the SAPIEN valve in the RVOT in the United States has been relatively small, as access to the valve is restricted in the US to the COMPASSION clinical trial and is limited to insertion within a pre-existing homograft. Results of phase 1 FDA approved COMPASSION trial using the SAPIEN valve demonstrated efficacy and safety in reducing RVOT pressure gradient and establishing pulmonary valve competence.²⁵ Thirty-six patients from 4 centers were recruited between April 2008 and May 2010. Successful valve deployment was achieved in 33 of 34 attempts (97.1%). Valve migration occurred in 3 patients, with 2 requiring surgical retrieval. Procedure complications also included pulmonary hemorrhage in 2, ventricular fibrillation in 1, and stent migration in one. Pullback gradient across the conduit decreased significantly. At 6-month follow-up, all patients were alive. The number of patients with New York Heart Association functional class I increased from 5 at baseline to 27 at follow-up. Pulmonary regurgitation was $\leq 2+$ in 97% of patients. Freedom from reintervention was 97% with 1 patient undergoing elective placement of a second valve due to conduit-induced distortion of the initial implant.

It is not clear whether this valve will demonstrate superior resistance from fracture relative to the Melody valve. The fact that the valve has been implanted in the aortic position in over 20,000 patients with excellent valve function reported at 2-year follow-up in large clinical trials is very encouraging.²⁵

A study on the experience in Germany²⁷ reviewed the results during a one year period using the Edwards SAPIEN™ pulmonic valve in 22 patients. Implantation was successful in 21 (10 received a 23 mm valve and 11 received a 26 mm one). Invasive data showed a significant decrease of right ventricular systolic pressure with reduction of RVOT gradient. There was a substantial reduction of pulmonary regurgitation from before (none/trivial $n = 0$, mild $n = 2$, moderate $n = 9$, severe $n = 11$) to after implant (none/trivial $n = 20$, mild $n = 1$). During the short-term follow-up of 5.7 months there was persistent favorable valve function.

In the meantime, further data assessing long-term functionality and durability of both valves are needed to evaluate their long-term outcome.

LIMITATIONS OF AVAILABLE PERCUTANEOUS VALVE IMPLANTS

Only approximately 15 percent of potential patients with RVOT dysfunction can accommodate the currently approved implantable valves.¹⁸ Many patients remain poor Melody Valve™ candidates due to their small physical size, limited vascular access, or the size and shape of their RVOT. At times, pre-stenting with bare-metal stents can be used as a way to “prime” the RVOT in patients with prior RVOT patch repair, permitting subsequent successful PPV implantation.²⁹ In patients with large and distensible RVOT conduits, a hybrid approach combining intra-operative PPV implantation with simultaneous conduit down-sizing has been undertaken with some success.³¹ Alternatively, Melody Valve™ implantation into the bilateral branch pulmonary arteries has been proposed as a minimally invasive, though still experimental, option in patients with large and insufficient conduits.³² These limitations have led some physicians to explore innovative techniques, including self expanding nitinol pulmonary valve stents.³⁰

CONCLUDING COMMENTS

The development of percutaneous pulmonary valve stents such as the Medtronic Melody Valve™ and the Edwards SAPIENTM pulmonic valve has revolutionized the treatment of RVOT dysfunction. The pulmonary stenosis and insufficiency that previously required an open-heart procedure, can now be safely and effectively treated with minimally invasive percutaneous techniques. Pulmonary valve stent technology continues to evolve with the goal of treating a larger percentage of patients with RVOT dysfunction with the percutaneous technique. The Edwards SAPIENTM transcatheter heart valve can be used in patients with larger RVOT conduits, as it is sized as large as 26 mm, and possibly up to 29 mm. Its use will likely increase significantly once it becomes widely available for use. Self-expanding nitinol pulmonary valve stents offer the potential of treating larger RVOT morphologies with a low-profile design, but are still under investigation.

RESUMEN

El desarrollo de disfunción del tracto de salida del ventrículo derecho (TSVD) debida a estenosis e insuficiencia progresivas no es infrecuente después de la reparación quirúrgica de cardiopatías congénitas. Las opciones terapéuticas han consistido tradicionalmente en implante quirúrgico de homoinjertos, conductos valvulados y prótesis valvulares biológicas. Desde principios de los años 90, cuando la lesión dominante era la estenosis, la angioplastia con *stents* desnudos ha sido considerada como posibilidad de prolongar

la duración del conducto. El problema de esta táctica es que solo trata la estenosis pulmonar, dejando insuficiencia valvular severa. Es bien sabido que la insuficiencia pulmonar valvular severa crónica conduce a insuficiencia cardíaca derecha progresiva, disminución de la tolerancia al ejercicio, y arritmias con riesgo de muerte. Las terapias con implante de válvulas percutáneas han aparecido en los últimos 10 años para disminuir la necesidad de procedimientos quirúrgicos abiertos y prolongar la vida útil de los implantes valvulados existentes. Como consecuencia, ha habido un cambio importante en el tratamiento de la disfunción del TSVD.

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