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Review

Transcatheter valve-in-valve therapy: What does the pediatric cardiologist need to know?

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ABSTRACT

Valve pathology is a significant component of pediatric cardiovascular disease. Outside the pediatric age group, patients are selecting bioprosthetic valve replacements to avoid the obligate anticoagulation associated with mechanical valves either because of the inability to take anticoagulation, pregnancy considerations, or preference. Bioprosthetic valves, however, inevitably degenerate. The standard treatment is a repeat operation that entails additional risk. Transcatheter valve therapy has rapidly emerged as an appealing alternative. In this manuscript, we discuss the progress in transcatheter valve-in-valve (VinV) procedures. This is essential knowledge for the practicing pediatric cardiologist as it may promote the application of bioprosthetic valves as a treatment option and management strategy.

1. Introduction

Cardiac valve dysfunction is a major cause of morbidity and mortality in the young. While valve repair is preferred, valve replacement is often required due to anatomic constraints. Unfortunately, the durability of surgically-implanted valves is limited with deterioration accelerated in the young and repeat operation associated with increased risk [1–4]. The prevalence of this problem is increasing in the middle-aged population due to the widespread use of bioprosthetic valves that obviate the need for long-term anticoagulation but are less robust than their mechanical counterparts. Recently, catheter-based valve technologies have emerged as a less-invasive strategy to treat failing bioprosthetic valves. In this review, we discuss the current state-of-the-art of these so-called "valve-in-valve" (VinV) procedures for each cardiac valve.

2. Aortic valve

Although more common in adults, aortic valve disease represents a significant portion of the overall burden of congenital heart disease (~5%) [5,6]. Many children with aortic stenosis can be treated with balloon valvotomy, but others require surgical aortic valve replacement (SAVR). In contrast, SAVR is the standard treatment for degenerative aortic valve disease in adults. Given their advanced age, many of these adult patients have significant comorbidities that enhance surgical risk. It is for these high-risk patients that transcatheter aortic valve implantation (TAVI) has been developed and tested.

In 2002, a team led by Dr. Alan Cribier performed the first TAVI in a human [7]. Two TAVI systems are now commercially available for clinical use: the balloon-mounted SAPIEN® valve (Edwards Lifesciences, Irvine, California) and the self-expanding CoreValve® (Medtronic Inc., Minneapolis, MN). The SAPIEN® valve consists of 3 leaflets made from bovine pericardium mounted within a stainless steel frame. Fig. 1 shows the SAPIEN® XT valve, a slightly modified version of the original SAPIEN® valve that will be discussed later in the review. The valve is deployed with balloon expansion during rapid pacing, which reduces cardiac output minimizing valve movement during deployment. The valve comes in 2 sizes (23 mm and 26 mm diameter) and can be delivered from 5 sites: femoral artery, left ventricular apex, directly from the aorta, axillary artery, or inferior/superior vena cava [8]. The Edwards SAPIEN® valve was evaluated in the Placement of Aortic Transcatheter Valve (PARTNER) trial — a randomized, prospective, multi-center trial with 2 cohorts. The PARTNER A cohort [9] included 699 high-risk patients (Society of Thoracic Surgeons surgical risk score of >10% or a surgeon assessed risk of mortality of >15%) assigned to TAVI or SAVR. The primary end-point was death from any cause at 1 year which was not significantly different between the 2 groups (24.2% TAVI vs 26.8% SAVR, $P = 0.44$) demonstrating the non-inferiority of TAVI in the studied population, and persisted at 2 years follow-up [10]. The PARTNER B cohort [11] included 358 patients deemed inoperable by 2 surgeons. These patients were assigned to TAVI or best medical therapy (including balloon aortic valvuloplasty). At one-year, the primary end-point of death from any cause occurred in 30.7% of the TAVI group compared to 50.7% of the standard therapy group ($P < 0.001$) demonstrating the superiority of TAVI. Based on these studies, the Food and Drug Administration (FDA) approved the device in 2011. The European SOURCE registry has recorded the real life experience with the Edwards

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SAPIEN® valve since 2007. Results thus far are consistent with the findings of the PARTNER trials [12–14].

Edwards has developed two newer versions of the SAPIEN® valve. The SAPIEN® XT valve has 4 important modifications. First, the leaflet shape was altered to improve durability and optimize stress distribution. Secondly, a larger size became available (29 mm), and thirdly, a cobalt-chromium frame improved radial strength. Finally, the valve could be loaded on the balloon while within the body, decreasing the profile and vascular access requirements. The XT device is being tested in the PARTNER II trial and followed in the SOURCE XT real-world European registry. The SAPIEN® 3 valve incorporates a fabric cuff to reduce paravalvular leaks and has a small profile allowing delivery transfemorally through 14–16 Fr. sheaths (original SAPIEN® valve required 22–24 Fr. sheaths). This device is being tested in the PARTNER III trial.

The CoreValve® revalving system is notably different from the SAPIEN® valve in many respects. The CoreValve® consists of 3 porcine pericardium leaflets mounted within a self-expanding nitinol cage (Fig. 1). It cannot be used transapically, has not been delivered via the vena cava, and is deployed more slowly than the Edwards valve allowing for some device repositioning. The largest diameter CoreValve® is 31 mm (SAPIEN® XT largest diameter is 29 mm) allowing for use in patients with larger aortic roots. The CoreValve® can also be used for valves that are not calcified [15] which may be particularly important for younger patients.

The CoreValve® was evaluated in the High Risk CoreValve® US Pivotal Trial [16] — a prospective, multi-center, randomized trial that included 795 patients with severe aortic stenosis (New York Heart Association class II or higher heart failure) considered to be at increased surgical risk as determined by 2 cardiac surgeons and 1 interventional cardiologist. The study participants were randomized to TAVI or SAVR. The primary endpoint was all-cause mortality at 1 year. The results showed a reduction in mortality with TAVR compared to SAVR (14.2% vs. 19.1%, $P < 0.001$ for noninferiority; $P = 0.04$ for superiority) with an absolute risk reduction of 4.9%. This led to FDA approval of the device in January 2014.

These landmark trials demonstrated the efficacy of TAVI in a subset of patients with native aortic valve stenosis but excluded patients with bioprosthetic aortic valve dysfunction. This group seemed well-suited for TAVI given the inherent increased risk of a repeat operation. Furthermore, the prevalence of bioprosthetic aortic valve dysfunction will increase over time. A study of 108,687 isolated aortic valve replacements from 1997 to 2006 showed a striking shift toward bioprosthetic valves (43.6% in 1997 vs. 78.4% in 2006) [17]. While modern bioprostheses have improved structural integrity, the major reason for this shift was unwillingness or inability of patients to take anticoagulation long-term. The issue of anticoagulation may be particularly relevant in some children who have difficulty with medications and dietary compliance. Additionally, young women can avoid anticoagulation during pregnancy. Given that young patients will be on anticoagulation for long periods of time, the lifetime risk of having a bleeding complication is likely increased compared to adults.

Despite improvements, biologic valves eventually fail and require treatment. At 15 years, the primary failure rate of a bioprosthetic aortic valve is ~26% in those <65 years old and ~9% in those >65 years old [18]. The durability is even worse in children [19]. Risk factors for valve degeneration are young age and kidney failure [20,21] with failure manifesting as stenosis or regurgitation. Stenosis is generally due to calcification, pannus formation, or thrombosis, while regurgitation is generally due to wear and tear, or infection.

From 2010 to 2012, numerous case reports and small case series were published demonstrating the short-term efficacy of aortic VinV procedures [22–25]. The Valve-in-Valve International Data (VIVID) Registry began in late 2010. The initial report was published in 2012 which included data from 202 patients [26]. The success rate was 93% with a 1 year survival of 86.8%. The 2% rate of stroke was similar to native valve TAVI. Of note, pacemaker implantation was less common (7.4% for VinV vs. ~15% for native valve) likely due to protection of surrounding structures by the valve sewing ring. Conversely, device malposition (15%) and coronary obstruction (3.5%) were more common in the VinV procedures.

The causes for increased malposition are unclear. In some situations, anatomical landmarks may be difficult to identify. Bioprosthetic leaflet calcification may be less severe if pannus formation is responsible for valve dysfunction. Some stented valves and all stentless valves are radiolucent making placement more challenging. However, given that most bioprosthetic valves are stented and radiopaque, landmarks in most procedures are easier to identify. Indeed, some aortic VinV procedures can be performed without the use of intravenous contrast. We suspect that most of the difficulty arises from the implant shifting during deployment

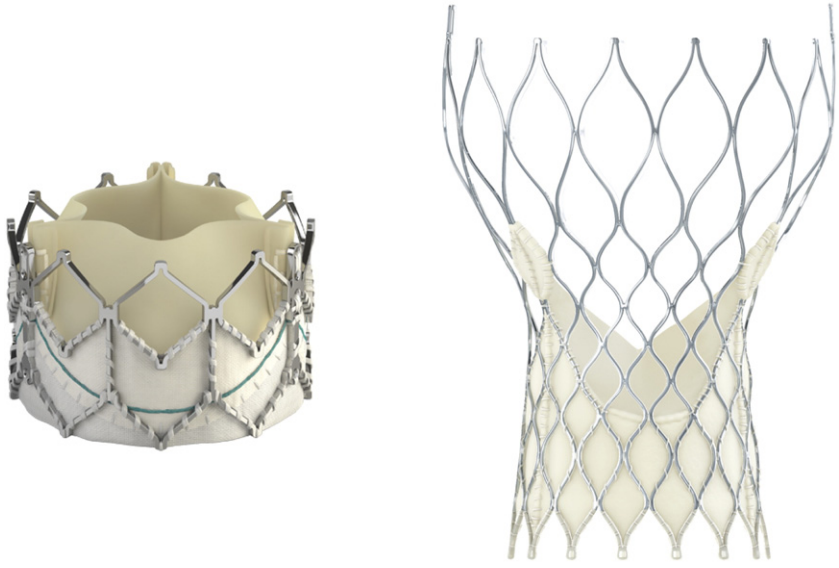

Fig. 1. SAPIEN® XT valve (Edwards Lifesciences, Irvine, California) and the CoreValve® (Medtronic Inc., Minneapolis, MN). The Edwards SAPIEN® XT valve is shown on the left. It consists of three bovine pericardium leaflets mounted within a cobalt–chromium frame. The Medtronic CoreValve® is shown on the right. It consists of three porcine leaflets mounted within a self-expanding nitinol cage.