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Chapter

Introductory Chapter: The Evolution of Complex Valve Pathology - The Surgeon's Perspective

Michael S. Firstenberg and Jennifer Hanna

1. Introduction

The management of aortic valve disease has undergone a dramatic transformation over the past 10 years. Without a doubt there has been significant developments in the diagnostic and management tools available to assess patients with aortic valve pathology. In addition to these tools are better and safer surgical techniques, especially with regards to anesthesia, myocardial protection, and peri-operative care, as well as the means in which patients can be risk-assessed to help guide decision-making. However, despite these advances, patients presenting with significant valvular disease are getting older and often will have substantial and more complex co-morbidities that place them at significant risk for challenging short- and long-term adverse outcomes. The goal of this text is to illustrate some of the challenges and controversies, with an emphasis on a surgical perspective, regarding the diagnosis and management of one of the most common forms of degenerative valve disease – aortic stenosis. While, by no means, is this a comprehensive review, it does provide a foundation and potential paradigm for how we evaluate, manage, and study valve disease both at a patient as well as a population level.

2. Background

Aortic stenosis is the most prevalent form of native valvular disease. Significant stenosis, as determined by the gradients across the valve and estimated orifice areas, are encountered in up to 2% of the population over 65 years old, 3% in those over 75 years old and 4% over 85 years old. Furthermore, over 100,000 people in the United States alone are diagnosed with severe aortic stenosis each year. Historically, the management of severe and critical aortic stenosis, especially in the context of symptoms such as chest pain, syncope, and shortness of breath, has focused on surgical intervention. However, the risks increase substantially with patients age and comorbidities [1].

Typically, severe or critical stenosis is manifested with the onset of symptoms such as shortness of breath. However, when patients start developing heart failure, chest pain, or syncope, their prognosis becomes worse than many cancers, including breast and colon. In fact, without intervention, the estimated survival in this population is less than 50% at two years [2].

3. Treatment options

It has been well established that the mortality difference between symptomatic aortic stenosis patients treated with surgery and those treated medically is one of the most striking mortality differences in all of medicine. In fact, it is argued that it is unethical to withhold therapy in symptomatic patients regardless of approach unless there are compelling contraindications. The percent survival of critical aortic stenosis patients is less than 20% at two years compared to a greater than 85% 4- to 5-year survival in those undergoing surgery [3]. A variety of tools have been developed over the years regarding risk assessment for surgery to aid in decision-making. One of the most commonly used is the Society of Thoracic Surgeons predicted risk of mortality calculator [4, 5]. Additional variables include a formal assessment of patient frailty, existing comorbidities and major organ system dysfunction, and technical or anatomical aspects of the procedure that may increase perioperative risks. Putting all of these variables together allows patients to be stratified as low, intermediate, high, and prohibitive risk. These tools are then used to help patients participate in shared decision-making regarding management options as guided by a Heart Team of cardiovascular specialists [6]. Historically, the options for treatment focused on surgery with a variety of biologic and mechanical valve choices – each with advantages and disadvantages, with trade-offs being either durability or the need for lifelong anticoagulation. The development over the past 10 to 15 years of catheter-based options, specifically transaortic valve replacement (TAVR) has resulted in a dramatic increase in therapies offered to patients who otherwise were prohibitive risk [7, 8]. Recent data has allowed for catheter-based therapies to be offered to lower risk populations [9]. However, despite the appeal of catheter-based therapies over conventional open-heart surgery, there are still many questions that need to be answered with regards to durability, paravalvular leaks, need for permanent pacemaker implantation, and the growing concerns surrounding both short- and long-term complications that are only slowly being definitively reported. Nevertheless, despite the evolving data and significant amount of industry-driven support stimulating the excitement over transcatheter therapies, combined with the significant costs associated with these based therapies, there are still concerns that surgery might still be the preferred approach for certain patients.

Some of the initial multi-center randomized trials that focused on high and extreme risk patients demonstrated a survival advantage which led to a considerable amount of enthusiasm regarding the potential for catheter-based valves as a viable option for patients who would otherwise die of complications related to their critical aortic stenosis. Following regulatory approval of these devices, additional studies in intermediate and lower risk patients were undertaken. While the selection criteria for intermediate risk patients was based upon their predicted risk of mortality, other significant comorbidities and baseline characteristics were considered in the decision-making. Again, despite the appeal of non-surgical options, the early data in the intermediate risk patient population demonstrated similar all-cause mortality and risk of disabling stroke of around 13 to 14% at two years [10]. These results suggested that catheter-based therapies were non-inferior to surgical approaches, and despite the similarities in outcomes, these findings have often been cited to imply that a non-surgical approach may be preferred by the patients and are even potentially superior with regards to both short- and long-term outcomes when compared to conventional surgery [11]. In fact, while surgery was associated with a period of recovery that impacted formal quality of life assessments, by six months, the objective assessment of quality of life was similar in the surgical and catheter-based patients. In addition, similar short- and long-term mortality and stroke risks were seen in low, intermediate, and higher risk patients, again illustrating that both approaches were similar with regards to patient outcomes. Nevertheless, there has been a significant appeal, for a variety of reasons, for trans-catheter therapies, and numerous studies have been undertaken to define which patient characteristics and comorbidities might be better suited for one therapy over the other. A review of 9500 intermediate risk patients enrolled in multiple studies showed no significant benefit of one therapy over another at one year [12]. Similar reviews were also performed in lower risk patients. Specifically looking at the mortality at two years in almost 3500 patients, there was no benefit to a trans-catheter approach over surgery, further emphasizing the concept of non-inferior outcomes [13]. In this meta-analysis, there were also similar outcomes with regards to procedure-related stroke. However, there was evidence of a potential 2-year survival advantage for patients undergoing surgery. This survival advantage was also seen in a meta-analysis of intermediate risk patients enrolled in 14 studies consisting of almost 4200 patients. All told, at three years, there appeared to be a significant survival advantage for the intermediate risk patients undergoing surgical aortic valve replacement when compared to trans-catheter therapies [14]. Despite these concerns regarding the long-term outcomes in patients undergoing catheter-based therapies, there have been several randomized multi-center studies exploring their potential role in lower risk patients. The early data has suggested non-inferior outcomes, although some suggest a potential small survival advantage in those undergoing catheter-based therapies with specific types of valves. However, these trials have been heavily criticized. For example, in the PARTNER-3 trial, there was some concern that, despite enrolling low risk patients only, some of the comorbidities and surgical procedures required for these patients implied an inherently much higher risk profile [15]. Furthermore, there was concern that many patients were excluded based upon anatomical considerations, and patient selection might have played a substantial role in reported outcomes favoring catheter-based therapies [16]. Other low risk trials validated some of the short-term outcome experiences that contributed to regulatory approval with low-risk patients. A fundamental consideration is that low risk is not synonymous with younger patients, and given some of the evolving concerns surrounding intermediate- and long-term survival differences, there are still substantial concerns about offering catheter-based therapies to patients who have a predicted life expectancy beyond several years. Unfortunately, this has not attenuated the astronomical growth of catheter-based therapies at the expense of surgery in a patient population that still, based upon best available evidence, might still benefit from a surgical approach.

The selection bias and concerns of the low-risk trials for TAVR have prompted investigators to report some of the real-world outcomes in similar patients. For example, registry data out of Israel looking at very low risk and low risk patients demonstrated a 10 to 15% two-year mortality, respectively [17]. These outcomes were substantially worse than similar two-year survival rates reported in contemporary surgical studies in which the reported mortality was almost half of those reported in similar TAVR patients [18]. It is unclear if patients are aware of the substantial risks of these procedures when they are making decisions or are being consented.

Clearly, there is still much to learn with regards to the risks, benefits, and patient selection for specific therapies used to treat aortic stenosis. Furthermore, as experiences evolve, especially with the rapid proliferation of transcatheter therapies, there are still many challenges and unanswered questions.

4. Evolving controversies

4.1 Stroke

There is a common misconception that trans-catheter therapies are inherently associated with fewer strokes. This is an observation that has not been demonstrated in many of the high-profile studies. Furthermore, there are growing concerns that the neurologic events that patients experience after trans-catheter therapies occur after the index hospitalization in which the procedure is performed. For example, one study exploring a Medicare database of over 44,000 patients suggested an 86% greater risk of ischemic stroke and a six-fold increase risk of hemorrhagic stroke after trans-catheter therapies when compared to conventional surgery, with many of the events occurring in subsequent readmissions to the hospital within the first year [19]. In fact, the 90-day readmission rate for neurologic events after TAVR was substantially higher than many other cardiac and non-cardiac procedures, including left ventricular assist device placement, cardiac catheterization, surgical aortic valve replacement, and coronary artery bypass procedures [20]. Clearly, the risk of neurologic events after catheter-based valvular interventions requires further objective review.

Such concerns have resulted in a substantial increase in the development and utilization of cerebral protection devices during TAVR. Despite the inherent appeal and considerable cost associated with these protection devices, definitive data demonstrating a clinical improvement and reduction in neurologic events is still lacking [21, 22]. Nevertheless, this is an area of tremendous research and development [23, 24].

4.2 Pacemaker rates

There is no doubt, as demonstrated in almost every major study of TAVR, that this procedure is associated with a much greater risk for needing a permanent pacemaker when compared to conventional surgery. While conduction abnormalities are not uncommon after valve surgery, there is growing concern that the need for a pacemaker after TAVR is neither trivial nor benign. Some large-scale studies suggest a four-fold increase in the need for permanent pacemaker after TAVR [25]. While the long-term consequences of needing a pacemaker are still unclear, especially since the short and long-term natural history of conduction problems after valve replacement is variable, there is evidence to suggest that the need for a pacemaker is associated with worse long-term survival in these patients [26]. Considering the growing emphasis on early discharge and the concern that some of the conduction abnormalities might be physiologically significant and not present until after the index hospitalization, the consequences of such events is still unclear [27].

4.3 Paravalvular leaks

Unlike surgical valve replacement in which the existing stenotic calcified valve is physically removed, TAVR inserts and expands against the existing valve. This fundamental difference in the two procedures can explain why TAVR is still associated with a significantly higher rate of paravalvular leaks – especially in those with eccentric valve pathology or bicuspid valves [28]. Again, the long-term significance of paravalvular leaks is incompletely defined, but without a doubt, those patients with at least moderate leaks have a much worse survival at 2 years than those with mild or less leaks. The PARTNER 2 study, as previously discussed above, demonstrated a 34% risk of mortality in patients with moderate to severe paravalvular leaks, when compared to the 13-14% risk in those with none, trace, or mild leaks [29]

4.4 Durability and cost

Durability and cost remain a considerable concern regarding catheter-based therapies. Although costs vary significantly depending on the intrinsic structure of a health-care system, conflicting evidence regarding the short- and long-term costs of different types of therapy for valvular disease exists. Without a doubt, a surgical valve is substantially less expensive than a catheter-based valve, but the overall costs of the hospitalization and short-term rehabilitation needs might be more. However, factoring in the needs for pacemakers, stroke management, and concomitant coronary disease, there is growing concern surrounding the real-world costs for catheter-based therapies – especially as an increasing number of patients with advanced comorbidities, age, and poor functional status are being treated prior to dying [30, 31].

4.5 Coronary artery interventions

Especially with patients who are older and have multiple comorbidities, the incidence of coronary artery disease further challenges clinical decision-making. Again, despite the appeal of catheter-based solutions to treat both obstructive coronary disease and aortic valve pathology, definitive data directing one therapeutic option over another is lacking. In fact, many of the initial studies exploring the outcomes of one approach over another specifically excluded concomitant coronary procedures or those patients with significant obstructive disease. Nevertheless, criticism of some of the more recent low risk trials is that the surgical patients had a much higher intrinsic risk profile because of the need for concomitant coronary revascularization. In addition, structural characteristics of artificial valves also raises concerns regarding difficulties in coronary access in patients with previous valve replacements (both surgical and TAVR) and further suggests the importance of complete revascularization at the time of definitive valve therapies. As mentioned, many studies specifically excluded patients with combined aortic stenosis and coronary artery disease, and current guidelines tend to favor surgery considering the limitations of the data [32, 33]. Preliminary data also suggests that patients undergoing coronary stenting prior to TAVR may have worse outcomes and increased need for re-interventions due to major adverse cardiac and cerebrovascular events [34, 35].

4.6 Repeat interventions

The area of aortic valve disease that probably is the most supportive of trans-catheter therapies is in patients that have had previous valve replacement, either with a previous surgical valve or a trans-catheter valve. Many patients underwent surgical replacement with a biologic valve, despite established guidelines and a potential survival advantage advocating the use of a mechanical valve under the promise that their next intervention would be a trans-catheter valve [36, 37]. While the appeal of this approach is undeniable and logical, the practical applications are still under considerable study. Conflicting data regarding the best approach for the management of a failing biologic valve is substantial. Even though repeat surgery is not without risks, many experienced centers can offer re-operative surgery with a risk profile similar to first-time valve replacement. Furthermore, there are concerns surrounding a reduction in the effective orifice areas and the risk for patient-prosthesis mismatch after placement of a TAVR inside of a previous surgical or trans-catheter valve.

4.7 Choice of valves

In the surgical era, the choice of valves consisted of tissue valves and mechanical valves. Mechanical valves required life-long anticoagulation and this was often unappealing to patients, despite studies demonstrating a long-term survival advantage. Tissue valves did not require long-term anticoagulation, but were associated with structural degeneration and the need for repeat interventions – often at significant risk as outlined above. Many different types of biologic valves exist – bovine, porcine, homographs, stentless, etc – and there is extensive literature generated over decades of experience regarding the advantages and disadvantages of each valve type. Much of the decision-making regarding the initial valve choice is now under debate with the development of catheter-based therapies that can be used for failing biologic valves. Since the concept (as mentioned above) of "valve-in-a-valve" has altered the natural history of the long-term outcomes associated with biologic valves, there is growing interest in their use in younger patients and in the use of those prosthetic valves with structural characteristics that might lend themselves to a more favorable scaffolding for future re-interventions. Concepts surrounding strut design and annular cracking (or fracking) to increase the annular size to allow for larger replacement valves are rapidly evolving areas of study [38]. Likewise, the choice of transcatheter valve design – annular, supra-annular, self- vs balloon-expanding -- and tissue characteristics are also areas of extensive clinical research and debate.

4.8 Indications for intervention

The guidelines for intervention on critical aortic stenosis have also been evolving to reflect the developments in therapy options. However, there is growing evidence to suggest that adverse, and potentially irreversible, structural changes in the myocardium occur prior to the development of symptoms. Even patients with very advanced disease can have minimal symptoms, and much research is being directed towards, as illustrated by the chapter on strain-rate assessment of valvular disease, more objective tools to assess the pathophysiologic consequences of valvular pathology. Tools such as cardiac magnetic resonance imaging, strain-rate, and stress-echocardiography are becoming more commonly used in complex clinical cases to help direct management decisions.

4.9 Other areas of debate

The list of potential controversial topics in the diagnosis and management of valvular disease is extensive and beyond the scope of a simple chapter or even text. Such areas only illustrate the complexity of valve disease and, especially in the context of newer options for therapy, how there are great opportunities to re-explore the options patients have for aortic valve interventions. Even the methods we have to guide therapies – such as the development of Heart Teams (similar to cancer tumor boards in which each patient's clinical characteristics and pathologies are reviewed to make an optimal decision based upon expertise and best available data) and "shared decision making" (a concept in which the patient plays a substantial role in deciding how they want to be treated after weighing the pros/cons of the options as presented to them) – continue to evolve [39].

DOI: http://dx.doi.org/10.5772/intechopen.95049

Other areas that only scratch the surface regarding the management of valve disease include:

- Endocarditis
    - Native vs prosthetic valve
    - Early vs late surgical vs medical management
    - Re-operative options in the setting of substance abuse
    - Indications for left-sided vs right-sided valves
- Aortic insufficiency
    - Timing of surgery
    - Role of catheter-based therapy
- Bicuspid valve disease
- Associated ascending aortic aneurysms and pathology
- Impact of previous cardiac surgery
- Special patient populations
    - End-stage renal disease – i.e. dialysis
    - Morbid obesity
    - Small/large aortic roots
    - Complex co-morbidities
    - "Younger" patients
    - Women of child-bearing age
    - Impact of other co-morbidities
        1. Frailty
        2. End-stage pathologies – i.e. liver, lung, cancers
        3. Age
- Role of anticoagulation/anti-platelet agents
    - Impact on short-term risk for stroke
    - Risk for tissue or valve degeneration/thickening

- Interventions in asymptomatic patients
- Impact of and options for concomitant cardiac pathologies
    - Atrial fibrillation
    - Obstructive coronary artery disease
    - Other valvular pathologies
        1. Mitral, tricuspid
    - Aortic aneurysms
- Evolving repair technologies
- Prosthetic tissue and structural options
    - Bovine vs porcine vs non-biologic
    - Anti-calcification treatments
    - Stented vs non-stented
    - Stent material

5. Conclusions

The list of topics that can be reviewed is endless, clearly beyond the scope of a single text, and only serves to illustrates the importance of having a solid foundation in the existing literature, guidelines, and technologies as we move forward with regards to how we objectively assess and manage patient with aortic valve pathology. While patient preferences clearly should have a role, it is imperative that patients and their families be provided with accurate and objective data that take their personal characteristics into consideration so that their decisions can be properly guided with the goal of optimizing their opportunities for an ideal short- and long-term outcome. Hopefully, texts such as this along with multi-disciplinary Heart Teams can help improve these short- and long-term outcomes in terms of quality and quantity of life for those patients with significant valvular pathology.

Conflict of interest

Dr Firstenberg serves as a heart valve repair and replacement educational consultant for Medtronic plc. Dr Hanna reports no conflicts of interest or relevant disclosures in the context of the material presented in this chapter.

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