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EDITORIAL COMMENT

Catheter-Based Intervention of the "Forgotten" Valve

Time to Reconsider Tricuspid Valve Intervention?*

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Functional tricuspid regurgitation (TR) is one of the most common valvular disorders seen among heart failure patients (1), and its presence is associated with a worse clinical prognosis (2,3). In the adult population, primary tricuspid valve disease is rare, and TR usually results from chronic underlying mitral valve conditions. The therapeutic approach to "functional TR" has historically been conservative and focused on treating the underlying mitral valve pathology first (4). Recent data suggest that medically treated TR continues to worsen over time and carries a worse prognosis among patients undergoing mitral valve surgery (5). In the last several years, a growing academic interest in the early diagnosis and therapy of the so-called "forgotten valve" is gaining momentum.

Many questions still remain unanswered regarding the proper treatment of patients with functional TR. In response to this unmet clinical need, several transcatheter-based technologies aimed to either repair or replace the tricuspid valve are under development. This large number of devices and technological approaches has resulted from the need to develop solutions to a condition with a high degree of anatomic variability and the technical desire to replicate proven surgical techniques.

The development of catheter-based therapies to treat functional TR faces multiple technical challenges. Functional TR involves, not only dilatation of the annulus, but also leaflet malcoaptation and myocardial dysfunction. Compared with the mitral valve, the tricuspid annulus is larger, noncircular, and displays less fibrous tissue support. The tricuspid annulus is semilunar and frequently gets deformed from its original shape as the disease progresses. Also, the tricuspid valve is a low-flow structure lacking structural support, thus making the anchoring of sutureless devices more challenging. The tricuspid leaflets are irregular in size and geometry, and the subvalvular apparatus is highly variable between patients. Finally, the AV node resides adjacent to the septal leaflet increasing its potential for injury.

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In this issue of *JACC: Basic to Translational Science*, the experimental data of the novel NaviGate catheter-based tricuspid valve replacement system (NaviGate Cardiac Structures, NCSI, Lake Forest, California) is presented (6). The NaviGate is a low-profile (~21-mm height), self-expandable, nitinol frame device including 3 equine leaflets and a conical configuration with the larger diameter toward the ventricle. The valve anchors to the tricuspid annulus using 12 radially arranged winglets on the atrial side and 12 radially arranged graspers on the ventricular side that grasp and penetrate the leaflets and subvalvular structures. In this study, the NaviGate valve was delivered using either the direct transatrial or transjugular approach and achieved high periprocedural device success (~100%) with the longest chronic animal surviving up to 210 days. Overall, valve frame stability and

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hemodynamics remained stable over time resulting in low transvalvular gradients. No cases of right ventricular outflow tract obstruction and no significant paravalvular leak were present in the majority of animals studied. Limited macroscopic findings demonstrated the structural integrity of the valve, proper tissue coverage, and lack of thrombus formation over time; the degree of device-induced injury on the subannular structures was not described in detail.

Despite the broad enthusiasm and substantial investment in the field, significant challenges exist in the transcatheter tricuspid valve replacement field. First, in the surgical field, valve repair is generally the preferred therapeutic approach compared with replacement due to poor long-term durability of the prosthetic valve in the tricuspid position. Second, due to the complex biomechanical behavior following ventricular contraction and annular deformation, long-term durability of the metallic frame and leaflet becomes a challenge. Third, due to the multiple design requirements, these devices still display high crossing profiles (above 32-F). Fourth, due to the presence of the atrioventricular (AV) node close to the tricuspid annulus, specific complex device orientation, fixation, and deployment techniques are usually required in order to avoid injury. Finally, the prothrombogenic profile of these devices is still unknown.

Transcatheter tricuspid valve replacement may have potential advantages over transcatheter valve repair in that a single device may be used regardless of the type of primary pathology and deliver reproducible and predictable elimination of TR. In fact, one of the challenges of the current transcatheter tricuspid repair systems is to achieve a sufficient reduction of the regurgitant volume in patients with torrential TR. However, significant device-related challenges including potential for AV node injury, high-thrombogenicity profile, and post-implantation right ventricular failure still exist for tricuspid replacement strategies. On the other hand, transcatheter tricuspid repair has been associated with a better safety profile and high procedural success rates without negatively impairing ventricular geometry and function. Considering the complexity of the tricuspid valve anatomy and pathological variations seen during the course of disease progression, it is unlikely that a single device concept will fulfill all the clinical and technical requirements to treat these complex patients. Thus, the interventional treatment of tricuspid valve disease will probably require a lesion-specific "toolbox" approach, potentially including percutaneous repair, replacement, and ventricular support.

The device tested in this study has the potential to address some of the technical and anatomic challenges of this field because of its low height profile and larger available size range. Also the valve has a low atrial footprint, which may potentially decrease the thrombogenicity risk. However, the long-term durability data of equine leaflets are still under investigation, and long-term animal data on the durability of the valve and interaction of the anchoring mechanism with the underlying tissue are still needed. As with other devices, the biggest translational challenge will be to adapt the technology to a lower profile delivery system for fully percutaneous use.

Due to the nature of the animal models and experimental settings, the experimental validation of these devices is challenging and encounters fundamental differences compared with the human environment. First, due to animal size considerations, only small (<40 mm) devices can be tested in typical animal models. Second, the tricuspid valve shape is different, inducing a high degree of valve deformation compared with in humans. Third, the ventricle is smaller and hyperdynamic, inducing higher stress to the implanted valve. Fourth, the surrounding tissue support is healthy and fragile. Fifth, the thrombogenic profile is different, and clot formation is not frequently seen in large animal models. Finally, patients presenting with severe TR who are high risk for surgery often have significant right ventricular dysfunction, as well as hepatic and renal dysfunction. Therefore, the clinical course is often determined, not only by a correct anatomic implantation and a well-functioning device, but by patient factors that are not present in the experimental setting. Then, as has occurred with other valve technologies, experimental findings have not been able to fully predict device performance in the clinical setting.

We congratulate the authors for sharing their experimental findings with the scientific community and would encourage others to do the same. Understanding the nature of the challenges is an important step forward in this complex, yet at the same time exciting field. However, as has happened with other innovative technologies in the past, regulatory agencies must be prepared to put into perspective the experimental findings based on the clinical needs and variations in human anatomy. The road to clinical success of transcatheter tricuspid therapies will be long and complex, and we need to ensure that lessons learned from early preclinical and clinical studies pave the way for future improvements and technological changes. Tricuspid regurgitation is no longer a "forgotten" condition, and exciting catheter-based technologies are already under development. It is

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still early to predict whether any of these technologies will have a major impact on long-term clinical outcomes. However, they have the potential to improve quality of life by reducing debilitating clinical symptoms such as lower extremity edema. Only if this is the case, transcatheter tricuspid intervention may play a major role in the treatment of this debilitating condition affecting millions of patients worldwide.

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