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REVIEW TOPIC OF THE WEEK

Bioprosthetic Valve Thrombosis

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ABSTRACT

Bioprosthetic valve (BPV) thrombosis is considered a relatively rare clinical entity. Yet a more recent analysis involving a more systematic echocardiographic follow-up, the advent of transcatheter heart valve (THV) technologies coupled with the highly sensitive nature of 4-dimensional computed tomographic imaging for detecting subclinical thrombi upon both surgically implanted and THVs, has generated enormous interest in this field, casting new light on both its true incidence and clinical relevance. Debate continues among clinicians as to both the clinical relevance of subclinical BPV thrombosis and the value of empirical oral anticoagulation following BPV implantation. Furthermore, currently no systematic, prospective data exist regarding the optimal treatment approach in THV recipients. The authors provide an overview of the clinical and subclinical spectrum of BPV thrombosis of surgical and THVs, outline its diagnostic challenges, summarize its pathophysiological basis, and discuss various therapeutic options that are emerging, particularly within the rapidly expanding field of THV implantation. (J Am Coll Cardiol 2017;69:2193–211) © 2017 by the American College of Cardiology Foundation.

Of the >110,000 valve replacements undertaken annually within the United States alone (1), there has been a gradual shift from mechanical to bioprosthetic valve (BPV) implantations; bioprostheses now account for nearly 80% of all surgical aortic valve replacements (SAVRs) within the United States (2). This stems largely from the changing demographics of valve recipients, who are now older, with higher surgical risk profiles, and who also harbor greater bleeding risk because of the need for lifelong oral anticoagulation (OAC) following valve replacement. Although BPVs are less thrombogenic than their mechanical counterparts, clinically apparent BPV thrombosis (BPVT) is a rare yet important clinical entity, known to occur at all 4 valve locations. Its incidence and clinical relevance have recently come under intense scrutiny within the context of ongoing evaluations of the performance and durability of transcatheter heart valves (THVs) and the advent of 4-dimensional (4D) computed tomography (CT) as a novel means of valve surveillance. This, coupled with the continuing debate regarding optimal antithrombotic regimens in both surgical and THV recipients, has reignited the focus on BPVT per se. Moreover, its true incidence is probably greater than previously thought, and its clinical relevance is likely to increase in conjunction with the rapidly expanding field of THV technologies. In this review, we summarize BPVT as a clinical and subclinical entity, outline its diagnostic challenges, provide an overview of its pathophysiological basis, and discuss various therapeutic options.

VALVE BIOPROSTHESES

SURGICAL BIOPROSTHESES. BPVs are derived from either human or animal tissue (3–5) (**Figure 1**).

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ABBREVIATIONS AND ACRONYMS

4D = 4-dimensional

ACT = activated clotting time

AF = atrial fibrillation

BPV = bioprosthetic valve

BPVT = bioprosthetic valve thrombosis

CT = computed tomography

DAPT = dual-antiplatelet therapy

HALT = hypoattenuated leaflet thickening

NOAC = novel oral anticoagulant agent

OAC = oral anticoagulation

PPM = prosthesis-patient mismatch

SAVR = surgical aortic valve replacement

TAVR = transcatheter aortic valve replacement

TEE = transesophageal echocardiography

THV = transcatheter heart valve

TTE = transthoracic echocardiography

Human tissue valves can be divided into 2 categories: allografts and autografts. Allografts are cadaveric valves that are cryopreserved in liquid nitrogen until use and implanted without a stent. Autografts are composed of the patient's own valve. The most common autograft is the Ross procedure, during which the patient's pulmonary valve is transplanted to the aortic position, and an allograft valve is placed in the pulmonary position (3). Clinical indications for human tissue valves are currently limited (i.e., women of childbearing age, endocarditis). On the contrary, animal tissue valves, known as xenografts, are the most widely used type of BPV, falling into 2 categories: stented and stentless valves, and can be either porcine or bovine. Valve leaflets are crosslinked with glutaraldehyde and mounted on a metallic or polymer supporting stent. Pericardial valves consist of sheets of bovine pericardium mounted inside or outside a supporting stent (4). Stentless BPVs tend to be hemodynamically superior compared with stented BPVs (5). Sutureless valves have recently emerged as an option to reduce cross-clamp and cardiopulmonary bypass duration, thereby improving surgical outcomes and facilitating minimally invasive approaches. These valves seem also especially suitable for patients with small aortic annuli, to optimize hemodynamic results (6).

THVs. Most THVs are stent-caged BPVs implanted using a catheter-based delivery system (**Figure 1**). First-generation devices have been the most widely used THVs in clinical practice to date. The SAPIEN valve (Edwards Lifesciences, Irvine, California) and its current iterations (SAPIEN XT and SAPIEN 3) consist of bovine pericardial leaflets sewed within a balloon-expandable cobalt-chromium stent, with the SAPIEN 3 THV being covered by a polymer skirt at the bottom of the stent frame aimed to reduce paravalvular leaks. The CoreValve, CoreValve Evolut R and CoreValve Evolut PRO (Medtronic, Minneapolis, Minnesota) are made of a self-expanding nitinol stent with porcine pericardial leaflets (7). Several manufacturers have developed newer generation devices, which are mainly nitinol-based self-expandable THVs, using either bovine or porcine pericardium (**Figure 1**). Of note, THV leaflets are thinner than surgical BPV leaflets (~0.25 mm vs. ~0.40 mm, respectively) (8).

More recently, several THV platforms have emerged for treating mitral regurgitation (9). Most of these valves consist of a stent frame made of nitinol and 3 leaflets of bovine or porcine pericardium sutured inside the stent frame. The most common mechanism of valve fixation consists of capturing the native mitral leaflets, in addition to radial force.

DIFFERENCES BETWEEN SURGICAL BPVs AND THVs

Fundamental differences between BPVs and THVs lie in their respective implantation techniques. Although manipulation of BPVs is avoided during SAVR, crimping the valve upon the delivery catheter is required for THV implantation, and this may translate into disrupted collagen fiber orientation on the valve surface (10,11). Although the clinical relevance of these findings remains unclear, over the medium to long term, these subtle surface alterations could serve as a nidus for calcification, structural valve deterioration, and subsequent thrombus formation. Moreover, the mounting of the valves within a rigid stent increases the amount of mechanical stress subjected upon the THV leaflets, compared with surgical BPVs, which have greater flexibility within the stent. The presence of native valve calcification may also lead to suboptimal deployment, and paravalvular leaks, which may also increase the risk for valve failure and thrombosis (5,12,13). However, the superior hemodynamic results currently demonstrated by THVs compared with surgical BPVs, with a much lower incidence of prosthesis-patient mismatch (PPM) (14), may nevertheless contribute to improved durability, but data on long-term THV outcomes are currently limited (5).

DEFINITION AND DIAGNOSIS OF BPVT

The diagnosis of BPVT remains challenging in clinical practice, in part because of a lack of general awareness of this condition, coupled with the lack of a universal definition, and thus is often confused or the term is used interchangeably with "valve deterioration." In published surgical reports, valve thrombosis is considered any thrombosis unrelated to infection, attached to or within close proximity of the valve per se, thus occluding the path of blood flow, interfering with valve function, or sufficiently large so as to warrant treatment (15). In contrast, structural valve deterioration includes dysfunction or deterioration of the prosthetic valve, exclusive of infection or thrombosis, as determined by reoperation, autopsy, or clinical investigation. This usually involves wear and tear, fracture, calcification, leaflet tear, stent creep, suture line disruption of valve components, and so forth. Nonstructural dysfunction