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Bioprosthetic Valve Thrombosis Versus Structural Failure

Clinical and Echocardiographic Predictors

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ABSTRACT

BACKGROUND Bioprosthetic valve thrombosis (BPVT) is considered uncommon; this may be related to the fact that it is often unrecognized. Recent data suggest that BPVT responds to vitamin K antagonists, emphasizing the need for reliable diagnosis.

OBJECTIVES This study sought to determine the diagnostic features of BPVT and to formulate a diagnostic model for BPVT.

METHODS Cases of BPVT occurring between 1997 and 2013 were identified from the Mayo Clinic pathology database. Patients with BPVT were matched 1:2 for age, sex, and prosthesis position with patients whose valves were explanted for structural failure. We formulated a diagnostic model for BPVT using multivariate linear logistic regression and receiver operating characteristic.

RESULTS Among 397 consecutive cases of explanted bioprostheses, there were 46 cases of BPVT (11.6%; aortic 29, mitral 9, tricuspid 7, pulmonary 1), mean age was 63 years, and 68% were male. Thirty (65%) cases occurred >12 months post-implantation; median bioprosthetic valve longevity was 24 months (cases) versus 108 months (controls) ($p < 0.001$). Independent predictors of BPVT were >50% increase in mean echo-Doppler gradient from baseline within 5 years (odds ratio [OR]: 12.7), paroxysmal atrial fibrillation (OR: 5.19), subtherapeutic international normalized ratio (OR: 7.37), increased cusp thickness (OR: 12.2), and abnormal cusp mobility (OR: 6.94). Presence of all 5 diagnostic features was predictive of BPVT with 76% sensitivity, 93% specificity, 85% positive predictive value, and 89% negative predictive value ($p < 0.001$).

CONCLUSIONS BPVT is not uncommon and can occur several years after surgery. A combination of clinical and echocardiographic features can reliably diagnose BPVT. (J Am Coll Cardiol 2015;66:2285–94)

The predominant mechanism of bioprosthetic valve (BPV) dysfunction is structural deterioration (1,2), and the risk of bioprosthetic valve thrombosis (BPVT) is considered very low. As a result, the American College of Cardiology/American Heart Association (ACC/AHA) and European Society of Cardiology (ESC) guidelines (3,4) do not recommend oral anticoagulation with vitamin K antagonists (VKAs) beyond 3 months for mitral, tricuspid, and pulmonary valve implantation. Furthermore, the guidelines are discordant for aortic BPVs, with aspirin preferred over VKA in the European guidelines and VKA recommended for 3 to 6 months in the ACC/AHA guidelines. The diagnosis of BPVT remains very challenging due to a general lack of awareness of its existence. Several case series have shown that BPVT can be effectively treated with VKA, avoiding the need for thrombolytic therapy and surgery (5–8).

We previously suggested that presence of an increased gradient >50% over baseline should raise

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ABBREVIATIONS AND ACRONYMS

AF = atrial fibrillation

BPV = bioprosthetic valve

BPVT = bioprosthetic valve thrombosis

INR = international normalized ratio

TEE = transesophageal echocardiogram

TTE = transthoracic echocardiogram

VKA = vitamin K antagonist

suspicion of BPVT (9), but direct comparison of echocardiographic characteristics of BPVT and degenerated BPV has not been performed. Thus, we set forth to delineate the clinical and echocardiographic characteristics of pathologically proven BPVT to help clinicians recognize BPVT and, with effective VKA therapy, potentially help patients avoid surgical intervention.

METHODS

PATIENT SELECTION AND CHARACTERISTICS. The Mayo Clinic Institutional Review Board approved the study protocol. The pathology and surgical databases were used to identify all BPVs explanted from adults (age ≥18 years). We reviewed the pathology reports of 397 patients whose prostheses were explanted within the study period, and BPVT was considered to be present whenever valve thrombosis was the main mechanism of BPV dysfunction (n = 46). We then matched BPVs that were explanted for structural valve failure to cases of BPVT (1 BPVT: 2 structural valve failures). The structural valve failure group was matched by age (±5 years), sex, and prosthesis position. To estimate the overall incidence of BPVT in our surgical practice, we also recorded the total numbers of BPV implantations performed at the Mayo Clinic during the same time interval. Our study objectives were to estimate the prevalence of BPVT as a reason for BPV explantation, identify clinical and echocardiographic characteristics of BPVT, and formulate a diagnostic model for BPVT.

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Clinical, echocardiographic, and surgical data at the time of initial BPV implantation, during follow-up, and at the time of BPV dysfunction and explantation were retrieved from the medical record. We classified atrial fibrillation (AF) into: paroxysmal AF (defined as history of AF lasting <7 days documented in clinical notes, electrocardiogram, or Holter monitoring), perioperative AF (defined as AF occurring within 1 month of valve surgery), and persistent AF (defined as AF >7 days duration that is being treated with VKA ± rate control therapy). We reviewed all international normalized ratio (INR) results obtained within the last 3 months prior to diagnosis of BPVT or explantation; patients were classified as having subtherapeutic INR if they had any INR <2.0.

ECHOCARDIOGRAPHY. Reports and digitally stored images of transthoracic echocardiogram (TTE) and transesophageal echocardiograms (TEE) were systematically reviewed. Baseline prosthetic gradients were obtained from the "fingerprint" echocardiogram performed early after surgical BPV implantation; when baseline data were unavailable because these prostheses were implanted elsewhere (n = 17), mean normal values from the published literature were used as surrogates for baseline post-implantation gradients (10,11). The images from the index echocardiogram (TTE = 94 and TEE = 108) at the time of diagnosis of BPV dysfunction were systematically reviewed (A.C.E). Two-dimensional (2D) morphology of the BPV was assessed using the following pre-defined parameters: cusp thickness, presence of abnormal cusp motion, possible intracardiac thrombus or spontaneous echocardiographic contrast, and presence of calcification. These 2D parameters were collected both for BPVT and structural valve failure. Increased cusp thickness was defined as thickness >2 mm or significantly thicker compared to "fingerprint" echocardiogram. An echocardiographer with experience in valvular disease and BPVT (S.V.P.) reviewed randomly selected studies in one-half of the entire cohort. Discordant interpretations were adjudicated after a third review by a senior echocardiographer (H.M.C). All reviewers were blinded to the interpretation of others and the etiology of BPV dysfunction.

STATISTICAL ANALYSIS. All statistical calculations were performed with the JMP version 10.0 software (SAS Institute Inc., Cary, North Carolina). Categorical variables were expressed as percentages whereas continuous variables were expressed as mean ± SD or median and interquartile range (IQR) for skewed data. Comparison of categorical variables was performed using the chi-square test or Fisher exact test, whereas comparison of continuous variables was performed with Student *t* test or Wilcoxon rank sum test, as appropriate. To identify clinical and echocardiographic predictors of BPVT, data from BPVT and matched structural valve failure were analyzed with multivariable logistic regression model. Receiver operating characteristic (ROC) curves were plotted and the corresponding areas under the curve (AUC) were compared by the method of DeLong et al. (12) to determine the best combination of these clinical and echocardiographic predictors that identified BPVT, providing optimal balance between sensitivity and specificity.

RESULTS

Baseline clinical characteristics of BPVT and structural valve failure groups are shown in **Table 1**. Between January 1997 and December 2013, a total of 397 adult patients underwent surgical explantation of a BPV at the Mayo Clinic. Excluded from analysis