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The porcine valve type predicts obstructive thrombosis beyond the first three postoperative months in bioprostheses in the aortic position

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ABSTRACT

Background: Obstructive thrombosis of bioprosthetic valves is considered rare but may have dramatic consequences for the individual patient including repeat valve replacement, thrombolysis, or long-term anticoagulation. Whether the risk of obstructive thrombosis is dependent on the type of bioprosthesis (porcine versus bovine pericardial) is uncertain.

Methods and results: Between 2007 and 2012 a total of 1751 patients received a single stented bioprosthesis in the aortic valve position, 749 (43%) were porcine and 1002 (57%) bovine. During a mean follow-up of 3.4 ± 1.9 years, obstructive thrombosis (identified by an increase in mean pressure gradient ≥ 20 mm Hg or a decrease in velocity ratio ≥ 0.05 and confirmed by either ECG-gated computer tomography, a return to baseline of stenosis parameters under treatment with a vitamin K antagonist, or histology in case of reoperation) was diagnosed in 17 patients with a porcine (2.3%) and none with a bovine valve ($p < 0.001$). The cumulative probability of developing an obstructive thrombosis was significantly higher in patients with a porcine valve ($p < 0.001$ log-rank test). Adjusting for differences in baseline variables and stratification by the estimated propensity score showed that strata with a high probability of receiving a bovine valve had the highest number of obstructive thrombosis in porcine valves. These findings were further confirmed in a Poisson model and a competing risk model including all-cause mortality. Treatment of obstructive thrombosis with a vitamin K antagonist was safe and effective in 15/17 patients.

Conclusion: The porcine valve type is an independent predictor of obstructive thrombosis in bioprostheses in the aortic position.

1. Introduction

Obstructive thrombosis of stented bioprostheses in the aortic valve position beyond the first three postoperative months is considered a rare complication and is often not clearly separated from other forms of thromboembolic complication in the literature [1–8]. Currently available stented bioprostheses are manufactured from either porcine aortic valves (e.g. Epic®, St. Jude Medical, St. Paul, Minnesota or Mosaic®, Medtronic, Minneapolis, Minnesota) or from bovine pericardium (e.g. Perimount Magna® or Perimount Magna Ease®, both Edwards Lifesciences, Irvine, California; Trifecta®, St. Jude Medical, St. Paul, Minnesota; or Mitroflow®, Sorin, Milano, Italy). Based on published case reports and case series in which the majority of bioprostheses with obstructive thrombosis were porcine [9–15] we hypothesized that the porcine valve type represents an independent predictor of obstructive thrombosis in bioprostheses in the aortic valve position.

The recommended treatment of obstructive thrombosis in patients with a bioprosthesis in the aortic position is repeat valve replacement or thrombolysis [16–19] mirrored in a number of case reports [12–14]. However, recommendations are based on data from mechanical valves and recently, treatment with a vitamin K antagonist has been described as safe and effective in case reports [11,20,15] and small case series [21,22].

In the present analysis we investigate the role of bioprosthesis type in the development of obstructive thrombosis and assess the efficacy

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of treatment with a vitamin K antagonist in this complication of bioprosthetic valve replacement.

2. Patients and methods

From our database we retrospectively identified all patients who received a single stented bioprosthesis in the aortic valve position between January 2007 and December 2012. Patients with double-valve, composite graft, stentless valve or interventional valve replacement were excluded. Patients with other concomitant surgeries (valve reconstruction, bypass graft, and/or closure of an atrial septal defect) or reoperation remained in the study. The current analysis includes 6 patients with obstructive thrombosis from a previous report [21]. Until the middle of the year 2009 patients routinely received three months of oral anticoagulation, followed by ASA 100 mg/d only due to clinical reasons (i.e. coronary heart disease). As of July 2009, patients were treated with ASA 100 mg/d except when oral anticoagulation was clinically indicated (i.e. atrial fibrillation). Before discharge all patients underwent detailed echocardiographic assessment of the prosthetic valve and ventricular function. After hospital discharge, patients were seen regularly by their treating physician and underwent echocardiography by their cardiologist and were referred for repeat evaluation only when symptoms developed or echocardiographic assessment revealed any abnormality. Starting April 2014, we contacted all patients and/or their relatives and treating physicians to obtain information on vital status and valve related events.

2.1. Echocardiography

Echocardiography (ie33, Philips, Netherlands, 5-MHz transducer) was performed preoperatively, at discharge, and during follow-up according to the guidelines for the clinical application of echocardiography [23,24,22]. Maximal jet velocity (V_1) within the valve was recorded by aligning the continuous wave (CW) beam parallel to the stenotic jet. The velocity curve was traced and mean pressure gradient (MPG) was calculated automatically using the simplified Bernoulli equation. In patients with atrial fibrillation MPG was calculated from a representative (average) beat. Maximal jet velocity (V_2) of the left ventricular outflow tract (LVOT) was measured by pulsed wave (PW) Doppler just below the aortic valve. In patients with atrial fibrillation simultaneous delineation of LVOT signal within the CW Doppler signal played a key role. Velocity ratio (VR) was calculated as $VR = V_2 / V_1$. LVOT area A_1 was calculated as $A_1 = \pi * r^2$. LVOT diameter ($DLVOT = 2 * r$) was measured in zoom modus in the two-dimensional parasternal long-axis view at mid-systole just below the aortic valve annulus by an inner-edge-to-inner-edge method. Postoperative aortic valve area was calculated from the continuity equation using the diameter of the implanted bioprosthesis to calculate the area of the LVOT multiplied by VR. In patients with high or increasing gradient and/or other suspicion of obstructive thrombosis transesophageal echocardiography was performed in mild sedation (ie33, Philips, Netherlands, multiplane 7-MHz transducer). Alternatively, we examined the valve prosthesis by ECG-gated multi-slice computed tomography (CT; Somatom Definition Flash Dual Source, Siemens, Germany).

2.2. Diagnosis of obstructive thrombosis

The diagnosis of obstructive thrombosis was established by an increase in mean pressure gradient of ≥ 20 mm Hg or a decrease in velocity ratio ≥ 0.05 compared to the postoperative assessment and had to be confirmed by transesophageal echo (TEE), contrast-enhanced ECG-gated computed tomography (CT), histology in case of explantation of the prosthetic valve, or by return of mean pressure gradient and velocity ratio to baseline under the treatment with a vitamin K antagonist.

2.3. Treatment

Clinically stable patients with obstructive thrombosis of their bioprosthetic aortic valve were started on UFH (PTT 60–80) and subsequently on a vitamin K antagonist (phenprocoumon) with a target INR between 2.5 and 3.5 and seen three months later for a clinical and echocardiographic and/or CT follow-up.

2.4. Statistics

Statistical analysis was performed using SPSS software (Version 19.0). Continuous variables are presented as mean ± standard deviation and categorical variables as percentages. Continuous variables were compared by the Student's t-test and categorical variables by the chi-square test or by the Fisher's exact test. Kaplan–Meier method was used to assess the cumulative probability of thrombosis with differences between groups checked by means of the log-rank test. A propensity score analysis was performed to examine if obstructive thrombosis depends on treatment (choice of porcine versus bovine bioprosthesis) or on factors that led to a certain treatment decision reflecting the conditional probability of receiving a porcine valve given an individual patient's covariates. Variables which were associated with valve type or valve thrombosis at $p < 0.1$ (e.g. age, serum creatinine, and others) in univariate analysis were included into the model. Stratification by the estimated propensity score was performed as recommended by Freemantle et al. [25]. To confirm results from propensity score analysis we calculated the expected number of patients with a bovine bioprosthesis who should develop an obstructive thrombosis based on the null hypothesis that the thrombosis rate is the same for both valve types using a Poisson-distribution approach [26]. Finally, to exclude a competing risk effect from a substantial mortality in our cohort the data was analyzed using cumulative incidence functions [27].

3. Results

Between January 2007 and December 2012, a total of 1751 patients received a single stented aortic bioprosthetic valve at our hospital, 508 (29%) in combination with bypass surgery, 45 (2.6%) with mitral anuloplasty and 46 (2.6%) with tricuspid anuloplasty. A porcine prosthesis was implanted in 748 patients (492 St. Jude Medical Epic, St. Jude Medical, St. Paul, Minnesota; 256 Medtronic Mosaic, Medtronic, Minneapolis, Minnesota), and 1003 patients received a bovine prosthesis (630 Carpentier-Edwards Perimount Magna, 358 Carpentier-Edwards Perimount Magna Ease, both Edwards Lifesciences, Irvine, California; 8 St. Jude Medical Trifecta, St. Jude Medical, St. Paul, Minnesota; and 7 Carbomedics Mitroflow, Sorin, Milano, Italy).

Patients with porcine valve prostheses were older, less likely female, had a higher serum creatinine and LV mass than patients with bovine valves. Despite a slightly larger prosthesis size postoperative mean pressure gradient was higher and aortic orifice area was smaller in patients with porcine valves. Baseline clinical, surgical, echocardiographic and postoperative parameters are presented in Table 1.

3.1. Obstructive thrombosis

Follow-up was complete for 1749 patients (99.9%). During 3.4 ± 1.9 years of follow-up 17 patients were diagnosed with obstructive thrombosis on average 379 ± 266 (median = 309) days postoperatively. All obstructive thromboses were observed in porcine prosthetic valves, none in bovine valves (chi-square statistic of 22.97, $p < 0.001$, Table 2) resulting in an incidence for obstructive thrombosis of 2.3% in porcine valve prostheses. A comparison of patients with and without thrombosis who received a porcine valve is provided in Table 3.

The cumulative probability of developing an obstructive thrombosis was significantly higher in patients who received a porcine valve ($p < 0.001$ by the log rank test, Fig. 1). Propensity score adjustment for