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A CYANOTIC PATIENT WITH PROSTHETIC TRICUSPID VALVE THROMBOSIS AND PRIMUM ATRIAL SEPTAL DEFECT

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A 30-year-old man with congenital heart disease (CHD) presented to a community emergency room with fever to 105 F. He was diagnosed in early childhood with heterotaxy syndrome and a partial atrioventricular canal (PAVC) defect with primum atrial septal defect (ASD), cleft mitral valve, left superior vena cava, and interrupted inferior vena cava. He underwent initial PAVC repair, ASD closure, and mitral valve repair at 13 years of age. Two weeks later, he developed postoperative tricuspid and mitral valve endocarditis with complete atrioventricular (AV) block, requiring emergent placement of bileaflet mechanical valves in the mitral and tricuspid positions as well as an epicardial pacemaker. He was subsequently anticoagulated with warfarin with a goal of INR >2.0 and followed at our facility from 1992-2004. At his last visit in 2004, at 27 years of age, he had mild tricuspid and mitral valve stenosis without perivalvular or prosthetic regurgitation and normal ventricular function. He was lost to follow-up over the next three years.

When he presented to the community hospital with fever, he was found to have methicillin-sensitive Staphylococcus aureus (MSSA) bacteremia. Transthoracic echocardiogram (TTE) and transesophageal echocardiogram (TEE) showed no valve vegetations, normal prosthetic valve function, and normal ventricular function. Bacterial endocarditis was not confirmed. However, an infectious disease specialist noted a fresh-appearing subungual splinter hemorrhage on his left great toe and recommended treatment for endocarditis. He was treated with oxacillin, gentamicin, and rifampin and discharged home three days later to complete a six-week course of intravenous (IV) antibiotics. Two weeks after discharge, he presented to his outpatient clinic complaining of blue lips, progressive exertional dyspnea, and fatigue since discharge. His oxygen saturation was 72% on room air. His INR was 1.8. He was readmitted to the local hospital where TTE revealed new ventricular septal dyskinesis and right ventricular dilatation without elevated tricuspid or mitral prosthetic valve gradients, but bubble study evidence of a primum ASD with predominant right-to-left shunting. Prompt transfer to our facility was initiated.

At the time of transfer, he was NYHA class II, complaining only of easy fatigability. His fever had resolved two weeks earlier. He never complained of chest pain, palpitations, shortness of breath, cough, orthopnea, dizziness, syncope, rash, or joint pain. He had no other medical problems and did not smoke, drink alcohol, or use intravenous drugs. His chest X-ray showed his epicardial pacemaker leads but was otherwise unremarkable.

Oxygen saturation was 80% via pulse oximetry on 5 L/min nonrebreather facemask. He had cyanotic but moist mucous membranes. Jugular venous pressure was elevated at 10 cm. Lungs were clear bilaterally. Cardiac exam revealed regular rate and rhythm, normal S1, split S2, but prosthetic valve clicks that sounded muffled and a soft I/VI diastolic murmur. He had a slightly enlarged liver at 3 cm below the costal margin without ascites. There was cyanosis of his nail beds but no clubbing, peripheral edema, splinter hemorrhages or Janeway lesions.

Initial labs revealed WBC 13.5 K/μL, hemoglobin 17.2 g/dL, hematocrit 51.3%, platelets 306/μL, BUN 18 mg/dL, creatinine 1.6 mg/dL, arterial pH 7.46, $PaCO_2$ 26 mmHg, PaO_2 39 mmHg, ESR 10 ms, normal liver enzymes, and a PTT of 31 sec despite a continuous heparin infusion. Given our concern about endocarditis, a TEE was performed and showed mildly depressed left ventricular function and normal prosthetic mitral valve function, but a primum ASD with right-to-left shunting, mobile echodensities on the inferior atrial septum and prosthetic tricuspid valve, and a mean prosthetic tricuspid valve gradient of 14 mmHg (Figures 1-3). We suspected prosthetic tricuspid valve thrombosis and endocarditis with primum ASD patch dehiscence, and so the patient went for emergent surgical repair.

Intraoperatively, a large dehiscence was noted of the primum ASD patch. His tricuspid prosthesis was encased in organized clot on a bed of fibrous ingrowths. Gram stain was negative. The previous tricuspid prosthesis was completely excised and annular remnant debrided. A 29 mm mechanical tricuspid valve was placed, a small hole in the previous VSD Dacron patch was repaired, and the large primum ASD was closed with Dacron. A new epicardial bipolar pacemaker was also implanted. Postoperative TEE revealed normal prosthetic valve function, mildly depressed ventricular function, and no residual septal defects. Final pathologic evaluation of the tricuspid valve revealed thrombus with a moderate amount of neutrophilic, focal, acute inflammatory and organized fibrin pannus. Special stains for bacteria, acid-fast bacteria, and fungi were negative, with no microscopic evidence of endocarditis. His blood cultures also remained negative. Despite these findings, the infectious disease team recommended the patient complete the remainder of his six-week course of antibiotics. There were no immediate postoperative complications, and he was discharged home six days later on IV antibiotics, aspirin, and warfarin, with a goal INR of 3 to 3.5. Ten days later, he was feeling well in NYHA functional class I and a saturation of 96% on room air. At two-year follow up, the patient continued to feel well with a normal capacity to exercise and continued full-time employment.

Discussion

Over the past three decades, surgical repair of AV canal defects has improved such that the operative mortality surrounding initial repair now approaches zero. However, up to 15% of these patients require reoperation for residual or recurrent lesions. Stulak and colleagues have reported long-term outcomes and natural history in patients with repaired PAVC defects.[1] Their cohort of 96 patients with PAVC, repaired at mean 6 years of age at the Mayo Clinic from 1962–

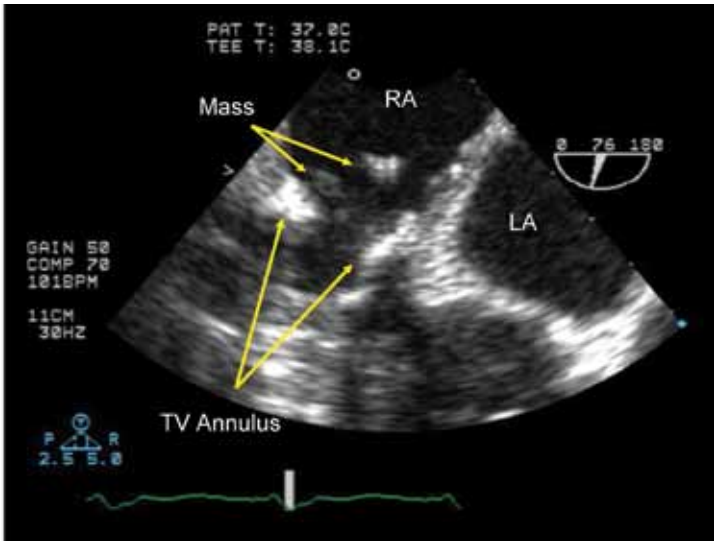

Figure 1. Transesophageal echocardiogram showing the mass seen on and around the tricuspid valve (TV) annulus. RA=right atrium, LA=left atrium.

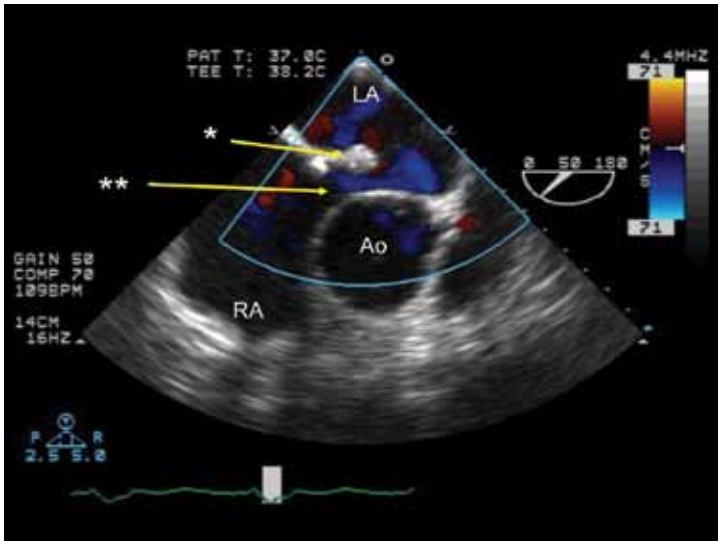

Figure 2. Transesophageal echocardiogram illustrating the primum ASD patch dehiscence (*) and the primum ASD (**) with right-to-left shunt. RA=right atrium, LA=left atrium, Ao=aorta.

2006, required reoperation on average 10 years after initial repair (range: 8 days to 48 years) at a median age of 26 years (range: 10 months to 71 years). The most common indications for reoperation were left AV valve regurgitation (67%), subaortic stenosis (25%), right AV valve regurgitation (22%), and residual ASD (11%). Postoperative mortality was as low as 2.6% in patients repaired in the last 25 years. Late mortality (17.7%) was attributed primarily to heart failure and arrhythmia. At 5-year follow-up, 91% were NYHA class I or II. Actuarial survival at 5, 10, 15, and 20 years was 84%, 77%, 75%, and 65%, respectively. Freedom from reoperation was 94% at 5 years and 84% at 10 years.[1] Right-sided valve disease requiring repair is relatively rare in patients with PAVC except when complicated by endocarditis, as in our case. There are limited data on outcomes of adult CHD patients who undergo tricuspid valve replacement.

The largest cohort of adult patients with CHD and tricuspid valve operation was reported in 1999 by Overgaard and colleagues. This cohort of 85 patients repaired between 1961 and 1995 in Toronto included 24% with primary ASD/VSD, 22% with Ebstein's anomaly, 27% younger than 18 years at the time of valve replacement (mean 27 years old), 27% with a morphologic tricuspid valve that was the systemic AV valve, and 62% with previous cardiac operation. The majority presented with fatigue (73%) and dyspnea (71%), with 3%, 41%, 45%, and 11% in NYHA classes I through IV, respectively.[2] Fifty-four percent underwent tricuspid valve repair and 46% underwent tricuspid valve replacement, with 54% using mechanical valves and 46% using bioprosthetic valves. Perioperative mortality was 5%, late mortality 8%, and survival at 5 and 10 years was 91% and 83%.[2] This cohort with CHD had lower perioperative mortality and better long-term survival than non-ACHD cohorts with tricuspid valve replacement previously reported in the literature.[2]

Prosthetic valve obstruction (PVO) is a rare but serious complication, occurring at a rate of 0.3 to 1.3% per patient year, with a mean time from implant to obstruction of 7.4 years, an average mortality rate of 10%, and a risk of recurrence of 8.1%.[3,4] Of the reported cases of prosthetic valve obstruction, 66% are mitral, 28% are aortic, 4% are combined mitral and aortic, and 1.5% are tricuspid.[4] However, when corrected for the frequency of valve replacement, there is a 20-fold higher risk of PVO in the tricuspid position relative to other locations.[3] Prosthetic valve thrombosis (PVT) is a more common entity, with a rate of 0.7 to 6% per patient year in mechanical valves, 10% occurring in the immediate postoperative period, 25% in the first

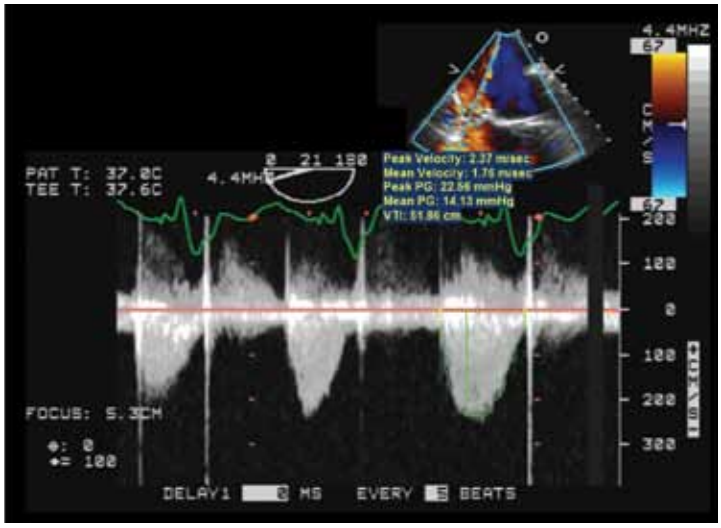

Figure 3. Doppler recordings of the obstructed tricuspid valve. Peak and mean gradients were 22 and 14 mmHg respectively.

postoperative year, 15% over the second and third postoperative years followed by a steady decline. Mechanical valve thrombosis is more common in bileaflet (60%) than tilting disc (35%) and ball-cage valves (5%).[4] Bioprosthetic valve thrombosis is much rarer, occurring almost exclusively in the early postoperative period when endothelialization of the suture zone is incomplete.[3]

The pathophysiology of prosthetic valve thrombosis is well explained by Virchow's triad. Appropriate endothelialization is dependent on the biocompatibility of prosthetic material with the native tissue at the suture line, which, if disturbed by host or environmental factors, fosters fibrin organization and clot deposition. Secondly, the interaction of patient hemodynamics, the prosthesis, and the native heart determines the turbulence of flow, amount of stasis, and propensity for thrombosis. Finally, if therapeutic anticoagulation is inadequate to overcome the patient's native coagulation cascade, thrombus is propagated.[3,5] More than half of patients with PVO are suboptimally anticoagulated.[4] Though inadequate anticoagulation may acutely cause fresh thrombus, recent research suggests that inadequate anticoagulation is also a major risk factor for fibrous

pannus formation and thus chronic valve obstruction. Studies have shown that fibrous pannus is present in 45 to 75% of surgical specimens removed for valve thrombosis or obstruction.[3-5]

Tricuspid prostheses are more prone to thrombosis and obstruction due to a combination of these factors. Suture lines in tricuspid valve replacement tend to be more prominent due to surgical efforts to avoid the conductive system, which increases the likelihood of over-endothelialization and pannus formation. Lower flow and more turbulent flow in the right heart predispose to stasis and clot formation.[3, 5] The propensity for thrombosis of tricuspid valves has led some experts to recommend long-term anticoagulation with a goal INR of 3 to 4, even in bioprosthetic valves.[6]

Classically, PVO presents with pulmonary edema in a left-sided prosthesis or lower extremity edema in a right-sided prosthesis. More often, partial obstruction manifests as mild dyspnea, systemic embolism, or fever. Laboratory studies generally show normal inflammatory markers, subtherapeutic anticoagulation profile, and elevated D-dimer and total protein due to consumption and fibrinolysis on the obstructed valve.[3] Diagnosis is based on clinical history, muffled prosthetic sounds on exam, fluoroscopy, and/or echocardiogram. While Doppler indices exist for diagnosing mitral prosthesis obstruction (mean gradient >8 mmHg, area <1.3 cm^2, peak E velocity >1.9 m/s, pressure half-time >130 sec) and for aortic prosthesis (mean >45 mmHg, dimensionless obstructive index <0.25), such criteria have not been well established for tricuspid valve obstruction.[7] Physicians generally use TEE to differentiate thrombus from fibrous pannus, which usually appears as an annular, immobile, highly echodense mass on the atrial side of the prosthesis. Invasive hemodynamic studies are rarely indicated for suspected PVO.[7]

Nonetheless, differentiating acute primary thrombosis from chronic fibrous tissue overgrowth and obstruction is challenging. Acute thrombus is associated with subtherapeutic anticoagulation and recent onset of symptoms (usually <7–14 days), whereas fibrous obstruction is more common in patients with proper anticoagulation, progressive deterioration in clinical status, progressive gradient increases over time, and more severe and complete restriction of valve motion.[8] A handheld "Thrombocheck" device has been evaluated as a means of early detection of valve obstruction by patients at home. By detecting acoustic changes in valve sound, it has a reported sensitivity of 90% and a specificity of 98%.[3, 5]

Optimal treatment for tricuspid valve thrombosis and obstruction remains controversial, as there are limited evidence-based data available on this rare condition. Currently, management is based primarily on case reports, anecdotal experience, clinician preference, and data derived from left-sided PVO. Strategies include optimization of anticoagulation, heparinization, fibrinolysis, or surgery. Left-sided PVO is managed aggressively with either an operation or fibrinolysis, as anticoagulant treatment is ineffective. ACC and AHA guidelines recommend surgery for all left-sided PVO except in patients with poor functional status (NYHA IV) in whom perioperative mortality is as high as 50%. For NYHA class I through III, surgical mortality is only 4.7%, while fibrinolysis has an efficacy of 82% but an embolic risk of 12 to 17% and a mortality rate of 10%.[4, 9] There is no difference in mortality rate in valve replacement (12%) versus declotting (13%), but declotting has a greater likelihood of rethrombosis.[4] Large (>5 mm) nonobstructive thrombi, especially mobile, pedunculated clots that do not respond to heparin, require surgical intervention as well. Small (<5 mm) nonobstructive thrombi can be managed with heparin infusion, warfarin optimization, or addition of low-dose aspirin for one week. If these methods fail, fibrinolysis is recommended.[10, 11]

Traditionally, right-sided PVO has been managed with fibrinolysis with acceptable efficacy and relatively few complications. However, the best fibrinolytic strategy has not been established. Rescue fibrinolysis with streptokinase (SK) or tissue plasminogen activator (tPA) over 60 or 90 minutes is preferable in patients with hemodynamic instability, whereas prolonged fibrinolysis with urokinase (UK) and heparin over 24 hours, SK over 10 hours, or tPA over 3 hours is preferable in hemodynamically stable patients.[8-14] Chronically obstructed valves are generally unresponsive to fibrinolysis and require surgical intervention.[9] Other novel approaches have been tried to relieve right-sided PVO, including adjunctive mechanical disruption with a temporary increase in cardiac pacing from 60 to 90–100 beats/minute. Aoyagi et al. reported success in a small series of patients with tricuspid bileaflet mechanical valve obstruction from 1992 to 2008. In cases where UK preceded mechanical disruption (by 96 to 144 hours), restoration of leaflet motion took 288 to 360 hours. When UK was given simultaneously with mechanical disruption, restoration of leaflet function took 240 hours. No hemorrhagic or clinically symptomatic pulmonary emboli were identified.[15]

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