Morphological changes in porcine bioprosthetic valves of a HeartMate left ventricular assist device

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NA Khan, J Butany, T Zhou, S Leong, V Rao, H Ross. Morphological changes in porcine bioprosthetic valves of a HeartMate left ventricular assist device. *Can J Cardiol* 2010;26(7):e270-e272.

A 27-year-old man who received a HeartMate (Thoratec Corporation, USA) left ventricular assist device for progressive heart failure as a bridge to orthotopic heart transplantation is described in the present report. The device failed (mechanical failure) after almost 19 months. The porcine bioprosthetic valves in the inflow and outflow cannulae showed hemorrhage, cusp tears and inflammatory cells, located largely on the inflow valve cusps. The role of the inflammatory cell reaction in the bioprosthetic valve is discussed.

Key Words: HeartMate; Inflammation; Left ventricular assist device; Porcine bioprosthetic valves

Over the past decade, ventricular assist devices (VADs) have played an increasing role in the management of end-stage heart failure. Clinically, a VAD can be used as a bridge to transplant, recovery or destination therapy (1). An important consideration in the long-term durability of these devices is the changes in the prosthetic valves within them. We report a patient who received a HeartMate (Thoratec Corporation, USA) left VAD (LVAD) for worsening heart failure. Examination of this device at explantation revealed significant pathological changes in the inflow and outflow porcine bioprosthetic valves (BHVs).

CASE PRESENTATION

A 27-year-old man presented with congestive heart failure secondary to idiopathic dilated cardiomyopathy. Echocardiography revealed severe, global, left ventricular systolic dysfunction with an ejection fraction of less than 10%, apical thrombus, moderately enlarged right ventricle, and mild mitral and tricuspid valve regurgitation. The patient became increasingly inotrope dependent and was referred for a HeartMate XVE LVAD as a bridge to cardiac transplantation. With the LVAD, the patient's cardiac function improved considerably. However, after 12 months of support, the patient developed clinical signs of inflow valve incompetence characterized by increasing pump flows, recurrence of mitral insufficiency on transthoracic echocardiography and intermittent aortic valve opening with left ventricular systole. After 18 months of support, the patient was admitted with LVAD malfunction secondary to driveline failure and was converted to pneumatic backup. One month later, the patient underwent an orthotopic heart transplant and was discharged on a standard regimen of immunosuppression.

Les modifications morphologiques des bioprothèses d'un dispositif d'assistance ventriculaire gauche de marque HeartMate

Le cas d'un homme de 27 ans à qui on avait implanté un dispositif d'assistance ventriculaire gauche de marque HeartMate (Thoracic Corporation, États-Unis) en raison d'une insuffisance cardiaque progressive dans l'attente d'une greffe cardiaque orthotopique est décrit dans le présent rapport. Le dispositif est tombé en panne (défaillance mécanique) au bout de près de 19 mois. Les bioprothèses porcines des canules de remplissage et d'éjection présentaient des hémorragies, des déchirures des valvules et des cellules inflammatoires, situées en grande partie dans les valvules de remplissage. Le rôle de la réaction des cellules inflammatoires dans la bioprothèse est abordé.

Pathology

The recipient's heart showed cardiomegaly, biventricular hypertrophy and dilation, and weighed 430 g. The ventricular myocardium showed interstitial fibrosis and muscle fibre hypertrophy, as well as patchy endocardial fibrosis, consistent with the diagnosis of dilated cardiomyopathy. The left ventricular apical endocardium showed significant fibrosis at the cannulation site, with pannus on the surface of the cannula. No significant apical thrombus was seen.

All components of the LVAD were examined in detail. The pump housing did not have any tissue adherent to it. The BHVs were explanted from the dacron fabric located inside the inflow and outflow conduits (Figure 1). There was no evidence of infection (ie, infective endocarditis) in either valve, as witnessed by a lack of vegetative growths on gross morphological examination. The inflow and outflow conduit BHVs showed hemorrhage at the base of the cusps. With respect to the inflow valve, one cusp showed fraying and a linear, longitudinal tear at the free margin (type I). The second cusp had a large fenestration-like tear at one lunular region (type III) along with another tear (type I) near the free margin. No cusp tears were present in the outflow valve. In addition, no pannus (host tissue overgrowth) was identified on any of the three cusps (inflow and outflow valve) or on the fabric covering the bioprosthesis sewing cuff.

Immunohistochemical analysis of the tissue sections did not reveal any signs of cuspal calcification (a negative von Kossa stain for calcium phosphate). However, the basal part of one cusp from the inflow valve showed a massive influx of mononuclear cells, predominately macrophages (CD45 mononuclear cells and CD68 macrophages; Dako Diagnostics, Canada) (Figure 2). Occasionally, plasma cells (CD138),

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Received for publication January 8, 2007. Accepted July 8, 2007

Figure 1 Gross pathology of inflow and outflow left ventricular assist device bioprosthetic valves. **A** Flow surface of inflow valve. **B** Nonflow surface of inflow valve. **C** Opened inflow valve. Three cusp tears can be seen in the inflow valve: one type I tear (black arrow) and two type III tears (open arrows). **D** Opened outflow valve. Significant focal hemorrhage at the base of the cusps (asterisks) is also seen. Reproduced with permission from reference 6

polymorphonuclear leukocytes and multinucleated giant cells (foreign body type) were also seen. The basal part of this cusp showed a large, loculated, cyst-like space with an exudate of fibrin, platelets and red blood cells (Figures 2A and 2B). The infiltrate of mononuclear cells was milder in the other two cusps and largely on the nonflow surface, and to a lesser extent, on the flow surface of all three cusps and the commissural regions.

DISCUSSION

We present a 27-year-old patient who underwent a HeartMate XVE LVAD implant for worsening heart failure, then underwent orthotopic heart transplantation 19 months later. One month before the transplantation, the patient was admitted because of LVAD malfunction. The significant findings in the BHVs of the device included focal hemorrhage, cusp tears and an inflammatory cell infiltrate, all contributing to cusp tissue failure.

Rose et al (2) demonstrated meaningful survival benefit to patients who were ineligible for a heart transplant but received an LVAD as treatment for end-stage heart failure (2). Despite improvements in outcome, the incidence of complications in LVAD recipients remains high and includes bleeding, infection, right heart failure, thromboembolism, renal dysfunction, neurological events and device failure (1). The management of device failure is dependent on the long-term goal of therapy. In patients destined for heart transplantation, electrical

failure of the device can be managed with pneumatic activation. Progressive inflow valve deterioration is common with the HeartMate device and can be managed with afterload reduction and switching the pump from automatic to fixed mode. Progressive valve regurgitation in a transplant candidate does not usually require device replacement. Patients receiving the HeartMate XVE for destination therapy should be considered for device replacement, especially if they are ineligible for transplantation.

In a report on 13 Novacor (World Heart Corporation, USA) devices, Moczar et al (3) showed that structural changes progress more rapidly in inflow than in outflow bioprosthetics. They also documented sparse macrophage deposition on the BHV, although the inflammatory response did not lead to significant bioprosthesis changes or device failure. In the present case, the inflow BHV showed significant pathology including an inflammatory cell infiltrate along with cusp tears and an insudate of fibrin, platelets and red blood cells at almost 19 months of support – the longest duration of VAD support in Canada. The inflammatory response was largely comprised of macrophages, and to a lesser extent, isolated plasma cells, polymorphonuclear leukocytes and giant cells. This chronic inflammatory cell infiltrate, in conjunction with other factors such as hemodynamic cusp injury, likely accelerated the pathological changes seen by weakening the underlying tissue and, over time, compromised the function of the LVAD. The resultant cusp tears can lead to valve regurgitation

Figure 2) Histological features of the HeartMate (Thoratec Corporation, USA) left ventricular assist device inflow valve. **A** and **B** Large cystic spaces (asterisks) in two different cusps of the inflow valve were found along with an exudate of fibrin, platelets and erythrocytes. **C** Magnification of inset box from figure **B** shows mononuclear inflammatory infiltrates consisting primarily of macrophages within valve tissues and along the surfaces. Immunohistochemical staining for monocytes and macrophages showed macrophage infiltrates in the base of the cusps (**D** and **E**) as well as on the nonflow surfaces of the cusps (**F**). The stain in figures **A** to **D** was hematoxylin and eosin; the stain in figures **E** and **F** was CD68 to stain for macrophages (arrows). Original magnifications: **A** $\times 1.6$; **B** $\times 2.5$; **C** $\times 20$; **D** $\times 20$; **E** $\times 40$; **F** $\times 40$. NF Nonflow surface. Reproduced with permission from reference 6

impairing the functional, beneficial reverse ventricular remodelling process (4) and/or necessitate urgent transplantation. Patients on HeartMate XVE destination therapy who deteriorate clinically should be examined for inflow valve-related device malfunction and considered for immediate device replacement.

The significant inflammatory reaction to the porcine BHVs in HeartMate VADs has not been documented before. The greater number of mononuclear cells on the nonflow surface is likely related to the lower shear forces on this surface because passing blood washes off the macrophages from the flow surface (5). The reason for the presence of mononuclear cells is uncertain. It is likely that clusters of these dead cells or their cell debris adherent to the valve cusp surface could provide a nidus for thrombus deposition or later calcification (5). Future studies, involving a larger number of inflow and outflow valve cases, are needed to fully assess the role of inflammation in the pathogenesis of cusp tissue lesions and valve dysfunction. To address this, our group is in the process of examining our series of implanted and explanted VADs (HeartMate, Novacor and Abiomed [Abiomed Inc, USA]).

CONCLUSION

The current report presented the novel case of a patient who underwent an LVAD implant for progressive heart failure, with mechanical device failure at 19 months. The BHVs in the inflow and outflow conduits showed hemorrhage, cusp tears and a significant mononuclear cell infiltrate resulting in clinical inflow valve regurgitation. Such issues are likely to become more prevalent as a greater diversity of cardiac patients are selected for long-term VAD support. Detailed

examination of the devices, including the removal of prosthetic valves from the conduits, is essential for their future development. The presence of mononuclear cells on the surfaces of the cusps may be associated with later tissue degeneration (pannus overgrowth and/or calcification).

CONFLICT OF INTEREST: None of the authors have any commercial association or sources of funding that may pose a potential conflict of interest in connection with this paper.

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