Bioprosthetic valve degeneration due to cholesterol deposition in a patient with a normal lipid profile

Leslie Price MD, Allan Sniderman MD, Attila Omerglu MD, Kevin Lachapelle MD

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Hypercholesterolemia has been identified as a risk factor for bioprosthetic valvular degeneration, and it has been suggested that statin therapy reduces this risk. The case of a 77-year-old man with low levels of low-density lipoprotein cholesterol (LDL-C) and apolipoprotein B who developed marked LDL-C crystal deposition and a severe foreign body giant cell reaction 21.5 years after aortic bioprosthetic replacement is reported. This observation confirms that cholesterol deposition contributes to bioprosthetic valve degeneration, but that this can occur even in patients with low levels of LDL-C. It suggests that the characteristics of the valve are more critical than the patient's level of LDL-C.

Key Words: Cholesterol; Degeneration; Prosthetic valve

The pathogenesis of bioprosthetic heart valve degeneration is not well understood. Calcification and mineralization occur in virtually all bioprosthetic valves, but they are especially pronounced in young adults (1). Two recent articles (2,3) have suggested that hypercholesterolemia is associated with bioprosthetic valvular degeneration and that treatment with statins may improve the longevity of the implanted valve. We report a case of bioprosthetic aortic valve degeneration with extensive cholesterol plaques on the free edges of the leaflets and commissures in a patient with low levels of low-density lipoprotein cholesterol (LDL-C) and apolipoprotein B.

CASE PRESENTATION

A 77-year-old man, who had undergone aortic valve replacement with a Carpentier-Edwards bioprosthetic valve (23) (Edwards LifeSciences, USA) for aortic stenosis, presented with acute pulmonary edema 21.5 years after surgery. The patient had a history of atrial fibrillation and gastric ulcers. A transthoracic echocardiogram revealed a mean aortic gradient of 36 mmHg, with at least moderate aortic insufficiency. His coronary angiogram was normal. The explanted valve had extensive raised yellowish plaques on the free margin of the leaflets and the commissures. The leaflets were also mildly calcified in these areas, and the free margins were curled and retracted, consistent with the diagnosis of combined stenosis and insufficiency. No tears or punched out lesions in the leaflets were noted.

Hematoxylin and eosin staining of the valve demonstrated extensive cholesterol crystal deposition on the surface of the valve leaflets (Figure 1). These deposits were surrounded by a foreign body giant cell reaction (Figure 2). Despite the marked accumulation of cholesterol on the leaflet margins, the patient had a very benign lipid profile, with low levels of LDL-C and apolipoprotein B, as shown in Table 1. These values were

Détérioration de bioprothèse valvulaire causée par des dépôts de cholestérol chez un patient normolipémique

L'hypercholestérolémie a été identifiée parmi les facteurs de risque de détérioration des bioprothèses valvulaires et selon certains, les statines pourraient réduire ce risque. On présente ici le cas d'un homme de 77 ans qui, malgré un taux de cholestérol LDL et d'apolipoprotéine B faible, a développé des dépôts notables de cristaux de LDL-C et une réaction de type cellulaire marquée à un corps étranger 21,5 ans après la pose d'une bioprothèse valvulaire aortique. Cette observation confirme que les dépôts de cholestérol contribuent à la détérioration des bioprothèses valvulaires, mais atteste également que ce phénomène peut se produire même chez les patients qui présentent des taux faibles de LDL-C et suggère que les caractéristiques de la valvule sont plus cruciales que le taux de LDL-C.

typical of all examinations reported since 1993. The patient received no calcium or vitamin D supplements. At the time of surgery, his serum calcium concentration was 2.16 mmol/L, with a normal albumin level, and his phosphorus concentration was 1.00 mmol/L. His serum creatinine was 96 µmol/L.

Types of bioprosthetic degeneration include cuspal tears (type I), crescentic tears at the bases of the sinus not involving the free margin (type II), irregular tears in the centre of the valve cusp (type III) and multiple small perforations (type IV) (1). Degeneration is thought to be related to a number of mechanisms: calcification and mineralization have been related to the pressure fixation of the valve, as well as the glutaraldehyde itself (4); the inflammatory reaction has been explained by the fact that the valve is a xenograft (5,6); and the ossification being the consequence of the action of osteopontin (7) in macrophages, which enter the valve leaflets.

The relationship between serum cholesterol level and bioprosthetic valve degeneration is controversial. Experimentally, the removal of lipids with solvents such as ethanol results in less cuspal calcification in experimental animals (8) and porcine aortic valve bioprostheses (9). In a retrospective cohort study, Farivar and Cohn (2) found that cholesterol ($P=0.035$), younger age ($P=0.014$) and coronary artery disease ($P=0.017$) were linked to calcification of first-generation aortic bioprosthetic valves. In their case-control analysis, the mean cholesterol level was significantly higher in individuals with valve explantation (4.89 mmol/L) than in those who did not need re-replacement (4.22 mmol/L, $P<0.0001$). Indeed, the OR for valve explantation and re-replacement was 3.9-fold higher in patients whose serum cholesterol levels were greater than 5.18 mmol/L. Nollert et al (3) found that in patients 57 years of age or younger, female sex ($P=0.001$), diabetes mellitus ($P=0.02$), smoking ($P=0.001$) and an increased cholesterol

McGill University Health Centre

Correspondence and reprints: Dr Kevin Lachapelle, McGill University Health Centre, 687 Ave Des Pins, Montreal, Quebec H3A 1A1.

Telephone 514-843-1519, fax 514-843-1602, e-mail kevin.lachapelle@muhc.mcgill.ca

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Figure 1) Hematoxylin and eosin stain of bioprosthetic leaflet, demonstrating cholesterol crystal deposition as empty finger-like projections with calcification and chronic inflammation (original magnification $\times 40$)

Figure 2) Hematoxylin and eosin stain of bioprosthetic leaflet in area of chronic inflammation demonstrating the formation of a foreign body giant cell reaction (original magnification $\times 400$)

level ($P=0.011$) were significantly associated with reoperation. Valve longevity was 8.42 years (range 7.06 to 9.79 years) for cholesterol levels 6.21 mmol/L or lower and 6.21 years (range 4.30 to 8.12 years) for cholesterol levels higher than 6.21 mmol/L (3). On the other hand, there was no relation between any of these parameters and valve dysfunction among patients older than 57 years of age. While both studies suggested a relationship between hypercholesterolemia and bioprosthetic degeneration, other confounding factors limited the validity of their conclusions (10).

The effect of statins on the progression of bioprosthetic valve degeneration remains unclear, but a recent retrospective study by Antonini-Canterin et al (11) suggested a beneficial effect. The OR for progression of prosthetic degeneration with statin treatment was 0.13 (95% CI 0.03 to 0.58), and the mean $\pm$ SD rate of decrease of effective orifice area was 0.031 ± 0.052 cm²/year for statin-treated individuals versus 0.100 ± 0.150 cm²/year for nontreated individuals ($P<0.001$) (11). This suggests that statin treatment may slow the progression of bioprosthetic degeneration. It is interesting that this was seen despite the presence of higher cholesterol levels in statin-treated individuals (11). It is also worth noting that the same arguments have been made with regard to the

TABLE 1

Patient lipid profiles before and after aortic valve replacement

Parameter	3/21/2005	12/20/2004	9/23/2004
Total cholesterol (mmol/L)	4.14	4.12	3.32
LDL-C (mmol/L)	2.63	1.22	1.93
HDL-C (mmol/L)	1.16	2.58	1.09
Triglycerides (mmol/L)	0.78	0.87	0.67
Apolipoprotein B (g/L)	0.75	—	0.54

HDL-C High-density lipoprotein cholesterol; LDL-C Low-density lipoprotein cholesterol

pathogenesis of aortic stenosis in native valves. Moreover, despite supporting data from retrospective studies, the first randomized control trial showed that atorvastatin, at the maximal dose, did not influence the rate of disease progression (12).

In summary, cholesterol deposition may play an important role in long-term bioprosthetic valvular degeneration even in individuals with normal lipid profiles. The deposition of LDL-C particles on the external surface of the valve leaflets initiates a chronic inflammatory reaction, which, over a long period of time, leads to calcification, scarring and leaflet dysfunction. However, the present case suggests that changes in the valve may be more critical than serum cholesterol levels in initiating this process.

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