Morphological findings in 192 surgically excised native mitral valves

Shaun W Leong BSc¹, Gursharan S Soor BSc¹, Jagdish Butany MBBS MS FRCPC^{1,3},
Jessica Henry BA¹, Molly Thangaroopan MD FRCPC², Richard L Leask PhD⁴

SW Leong, GS Soor, J Butany, J Henry, M Thangaroopan, RL Leask. Morphological findings in 192 surgically excised native mitral valves. *Can J Cardiol* 2006;22(12):1055-1061.

INTRODUCTION: Mitral valve disease (MVD) is a significant clinical problem that is becoming more common in the 21st century. The pathogenesis of MVD seems to be changing and is not well understood.

PATIENTS AND METHODS: The present study details the morphological findings in 192 native mitral valves excised over a one-year period at the Toronto General Hospital, Toronto, Ontario. The mean patient age was 59.7 ± 12.3 years at operation.

RESULTS: There were 106 men (55.2%) and 86 women (44.8%) in the present study. The most frequent changes in the surgically excised valvular leaflets were fibrosis (78.6%) and thickening (66.2%). Fusion (32.3%) and calcification (25.2%) were common changes at the commissures. Chordae tendineae most often showed evidence of thickening (47.9%) and fibrosis (37.0%). In total, 110 valves showed mitral incompetence (57.3%), 72 showed mitral stenosis (37.5%), and 10 showed a combination of stenosis and incompetence (5.2%).

CONCLUSIONS: In the present series, MVD was most frequently caused by postinflammatory (rheumatic) valve disease (RVD) (35.9%), followed by myxomatous degeneration (33.3%). Patients with RVD were usually female (66.7%), while those with myxomatous degeneration were more likely to be male (76.6%). RVD remains a significant problem even though the incidence of acute rheumatic fever with cardiac involvement has declined in Canada. This most likely reflects the current sociodemographic composition of the referral population.

Key Words: *Infective endocarditis; Mitral incompetence; Mitral stenosis; Mitral valve disease; Myxomatous degeneration; Rheumatic valve disease*

Mitral valve disease (MVD) affects 1% to 2% of the adult population, resulting in nearly 3000 deaths in the United States annually (1). The mitral valve apparatus consists of the leaflets, commissures, annulus, chordae tendineae, papillary muscles and the atrial and ventricular myocardium (2). The two leaflets, anterior and posterior, are connected to each other by the commissures. Although the anterior leaflet is longer (base to free margin), the posterior leaflet is wider (side to side) (2,3). The leaflets are supported by the chordae tendineae, which are attached to the papillary muscles. Histologically, the mitral valve consists of three layers (from atrial to ventricular

Observations morphologiques sur 192 valves mitrales naturelles, enlevées chirurgicalement

CONTEXTE : Les lésions de la valve mitrale (VM) constituent un problème clinique important, qui a pris de l'ampleur au cours du XXI^e siècle. La pathogenèse semble évoluer et on n'en comprend pas très bien les causes.

PATIENTS ET MÉTHODE : La présente étude donne une description morphologique détaillée de 192 valves mitrales naturelles, enlevées chirurgicalement, sur une période de un an, au Toronto General Hospital. L'âge moyen des patients était de $59,7 \pm 12,3$ ans au moment de l'opération.

RÉSULTATS : L'étude comptait 106 hommes (55,2 %) et 86 femmes (44,8 %). Les altérations les plus fréquentes étaient la fibrose (78,6 %) et l'épaississement (66,2 %) du tissu valvulaire. Autres observations courantes : la fusion (32,3 %) et la calcification (25,2 %) à la hauteur des commissures. Les cordons tendineux montraient le plus souvent des signes d'épaississement (47,9 %) ou de fibrose (37,0 %). Au total, 110 valves présentaient de l'insuffisance (57,3 %); 72, un rétrécissement mitral (37,5 %) et 10, de l'insuffisance et un rétrécissement (5,2 %).

CONCLUSIONS : Dans la présente série, les lésions de la VM étaient le plus souvent causées par une valvulopathie postinflammatoire (rhumatismale) (35,9 %) ou par une dégénérescence myxomateuse (33,3 %). La cardite rhumatismale s'observait généralement chez les femmes (66,7 %), tandis que la dégénérescence myxomateuse touchait surtout les hommes (76,6 %). La cardite rhumatismale reste une cause importante de valvulopathie mitrale, bien que la fréquence du rhumatisme articulaire aigu accompagné de lésions cardiaques ait diminué au Canada. Les observations recueillies reflètent sans doute la composition sociodémographique actuelle de la population dirigée.

surfaces): the atrialis (fibroelastic layer), the spongiosa (largely myxoid tissue) and the fibrosa (strong collagenous layer) (3).

A number of different processes can lead to MVD that can manifest as stenosis, incompetence or a combination of both. Mitral stenosis (MS) is most frequently postinflammatory and almost invariably due to rheumatic disease, an immune-mediated manifestation of streptococcal pharyngitis (3,4). Immune responses, resulting from streptococcal antigens produced during acute rheumatic fever, likely lead to a reaction in endocardial tissue, such as valvular tissue, which leads to progressive commissural fusion and leaflet scarring. Altered blood flow

¹Department of Pathology; ²Department of Cardiology, Toronto General Hospital; ³University of Toronto, Toronto, Ontario; ⁴McGill University, Montreal, Quebec

Correspondence: Dr Jagdish Butany, Department of Pathology E4-301, Toronto General Hospital, Toronto, Ontario M5G 2C4.

Telephone 416-340-3003, fax 416-340-4213, e-mail jagdish.butany@uhn.on.ca

Received for publication November 8, 2005. Accepted February 2, 2006

patterns then lead to ongoing and progressive damage of the mitral valve (3). Patients with MS often have a long, latent asymptomatic period of 10 to 20 years from the initial attack of rheumatic fever until the development of symptoms. Left-sided heart failure symptoms, such as dyspnea, orthopnea and paroxysmal nocturnal dyspnea, may develop as a result of elevated left atrial pressure caused by mechanical obstruction to filling of the left ventricle (5). Reduced forward cardiac output causes fatigue, and less frequently, symptoms of right-sided heart failure, hoarseness and hemoptysis may occur in end-stage severe MS. Although declining in the developed world, rheumatic fever is common in many parts of the developing world (3).

Myxomatous degeneration (MD) of the mitral leaflets, with or without mitral valve prolapse, is the most common cause of mitral incompetence (MI), and is the leading cause of valvular heart disease in the United States (6). MD may lead to marked leaflet redundancy and elongation of the chordal apparatus. This degenerative form of MVD is characterized histologically by fibroelastic inadequacy, collagen disorganization and accumulation of mucopolysaccharides or abnormal myxomatous material in the leaflets (6,7). Patients with MI are also often asymptomatic for long periods, sometimes experiencing palpitations and atypical chest pain. In some cases, the first presentation may be related to a serious complication such as embolic stroke, endocarditis or sudden cardiac death associated with high-risk mitral valve prolapse (3). In the presence of long-standing, significant MI, symptoms of left-sided heart failure will eventually ensue.

The present retrospective study was undertaken to assess the morphological changes in diseased native mitral valves, and to see the trends of MVD in our patient population. We describe the structural basis of MVD and evaluate gross and histological differences between valves explanted for postinflammatory (rheumatic) disease (RVD) and MD. We report the findings in 192 surgically excised mitral valves, which were explanted over a one-year period at the Toronto General Hospital (Toronto, Ontario) (referred to as 'the hospital' in the present paper) and were examined by one investigator with a significant interest in cardiovascular pathology (JB).

PATIENTS AND METHODS

A total of 192 surgically excised native mitral valves were seen at the hospital between January 2002 and December 2002 and were examined by one investigator (JB). All specimens were fixed in 10% formaldehyde solution and then examined in detail. All specimens were photographed on the inflow and outflow surfaces. Sections were taken from the leaflets and chordae tendineae, when available, and tissue was demineralized before sectioning when needed. Valves received intact were divided horizontally into two halves, with both halves being submitted for histology. In the case of valves received in pieces, longitudinal sections were taken of the leaflets and transverse sections of the commissural regions. Sections were taken from the most severely diseased regions. Sections from all valves were paraffin-embedded and stained with hematoxylin-eosin and Movat pentachrome stains. Additional stains for microorganisms (ie, Gram's stain for bacteria and Gomori methenamine-silver for fungi) were used when indicated.

For each valve, surgical pathology reports were examined for valvular dysfunction (MI, MS or combined MI and MS) and underlying causes of valve failure. Surgical pathology reports were constructed based on both gross and histological examination.

Morphological changes in leaflets, chordae tendineae and commissures were noted. Noteworthy morphological changes in leaflets included fibrosis (fibroelastic tissue deposits on valve surface) (8), thickening (determined semiquantitatively), calcification, inflammation, loss of scallops of the posterior leaflet and neovascularization. The chordae tendineae were also examined for fibrosis, thickening, calcification and neovascularization, as well as for fusion and rupture. Changes in the commissures, a feature nearly unique to RVD, included fusion, calcification, ulceration and neovascularization.

Valves were classified based on underlying pathology. Such pathologies were then classified as congenital, acquired or 'other' (nonvalvular). RVD was characterized by fibrous thickening, stiffening and calcification of the leaflets, loss of scallops of the posterior leaflet, and thickening and shortening of the chordae tendineae (in addition to the commissural changes listed above) (9). Histologically, RVD valves were characterized by chronic inflammatory cells, calcific nodules, and sometimes by thrombus deposition. Valves showing MD were characterized by gelatinous leaflets that were semitranslucent or opaque (10). The leaflet tissues were often redundant and hooded (defined as the visible, outward [toward the atrium] bulging of a segment of the anterior or posterior mitral leaflet). Chordae tendineae were often thinned and elongated. Histologically, MD was characterized by collagen and elastic fibre loss.

The morphological features of all 192 mitral valves were entered into a database, along with patients' clinical presentations, age and sex. Statistical analyses were performed using Minitab software, release 12 (Minitab Inc, USA). Two-sample t-tests were used to compare numerical data, and Fisher's exact tests were used to compare categorical data. All statistical tests were performed and considered significant if $P \leq 0.05$.

RESULTS

Patients and demographics

Over a one-year period, 192 native mitral valves were surgically excised at the hospital. The mean patient age was 59.7 ± 12.3 years at surgery, with a range of 17 to 83 years. Of the 192 patients, 151 (78.6%) were older than 50 years of age at operation. In all, 10 valves showed evidence of previous repair or operation (5.2%).

There were 106 men (55.2%) and 86 women (44.8%) in the present study. The mean ages of female and male patients were 61.1 ± 11.9 years and 58.5 ± 12.6 years at operation, respectively. There was no significant difference in age based on sex ($P = 0.15$).

Morphological findings

Leaflets: In total, 151 valves (78.6%) showed some degree of leaflet fibrosis, and 127 valves (66.1%) showed leaflet thickening. Leaflet calcification was present in 51 cases (26.6%), and neovascularization of the leaflets was seen in 35 cases (18.2%). The incidence of neovascularization among patients younger than 50 years of age at operation was significantly different from that among patients older than 50 years of age ($P = 0.004$). While 34.1% of patients ($n = 14$) younger than 50 years of age showed neovascularization of the leaflets, only 13.9% of patients ($n = 21$) older than 50 years of age had evidence of neovascularization.

Commissures: The most commonly reported morphological change of the commissures was fusion, present in 62 cases (32.3%). Calcification of the commissures was also fairly

common, present in 49 explanted valves (25.5%). Commissural region ulceration was noted in 31 cases (16.1%) and neovascularization in seven cases (3.6%).

Chordae tendineae: Of the 192 valves examined, 71 (37.0%) had chordae tendineae that showed fibrosis. Furthermore, 92 valves (47.9%) showed thickening of the chordae tendineae, and 24 valves (12.5%) showed calcification of the chordae tendineae. A total of 26 valves (13.5%) had apparently shortened chordae and 11 valves (5.7%) showed features of neovascularization of the chordae tendineae. A considerable proportion of cases ($n=72$, 37.5%) showed fusion of two or more chordae. A small proportion of explanted valves ($n=9$, 4.7%) had morphological evidence of ruptured chordae tendineae.

Valvular dysfunction

A total of 110 patients (57.3%) presented with MI, comprising the majority of the patient population, while 72 patients (37.5%) presented with MS. In addition, 10 patients (5.2%) presented with clinically documented combined MI and MS (Table 1). Overall, 32 patients (16.7%) presented with severe MI.

Among the 182 patients who presented with either MS or MI, men and women differed significantly in their dysfunction category ($P<0.001$). Among the 80 women in this group, the majority presented with MS ($n=47$, 58.8%) and the minority with MI ($n=33$, 41.2%). In contrast, the majority of the 102 men in this group presented with MI ($n=77$, 75.5%) and the minority presented with MS ($n=25$, 24.5%). Patients with combined MS and MI were 60.0% female ($n=6$) and 40.0% male ($n=4$).

All 192 valves were also classified based on the underlying pathology that caused the valve to fail (Table 2). A total of 167 valves failed (87.0%) due to acquired conditions, including RVD ($n=69$, 35.9% of total), MD ($n=64$, 33.3% of total), fibrosis of unknown cause ($n=15$, 7.8% of total), calcification ($n=7$, 3.6% of total; predominantly annular calcification), infective endocarditis ($n=7$, 3.6% of total), acquired changes of the chordae tendineae ($n=3$, 1.6% of total; including thickening, calcification and fusion), valve failure secondary to suspected drug use ($n=1$, 0.5% of total) or Libman-Sacks endocarditis ($n=1$, 0.5% of total). The mean age among patients with MVD due to calcification was 66.6 ± 5.8 years, significantly greater than the rest of the MVD group ($P=0.016$). Patients with infective endocarditis had a mean age of 45.9 ± 13.9 years at operation, significantly lower than the rest of the group ($P=0.036$). Furthermore, patients with infective endocarditis differed in sex distribution from the rest of the MVD group; there was only one woman among six men in this group. However, this difference was not statistically significant ($P=0.100$).

Meanwhile, eight valves (4.2%) showed congenital abnormalities, likely responsible for their failure, including congenital abnormalities of attachment of the chordae tendineae ($n=7$, 3.6% of total) and cleft leaflet ($n=1$, 0.5% of total). There were six men and one woman with abnormal chordal attachments ($P=0.100$).

Finally, 17 valves (8.9%) failed for nonvalvular reasons, primarily due to ischemic disease leading to valvular dysfunction. Patients with mitral valves explanted for nonvalvular reasons had a mean age of 66.9 ± 10.8 years at operation, significantly greater than the rest of the MVD group ($P=0.009$).

TABLE 1
Valvular dysfunction

	Men	Women	Total
MI	77	33	110
MS	25	47	72
MS + MI	4	6	10
Total	106	86	192

MI Mitral incompetence; MS Mitral stenosis

TABLE 2
Causes of valve failure

Cause of MVD	Men	Women	Male:female ratio	Mean age, years (mean $\pm$ SD)	n (% of total)
Acquired					
RVD	23	46	1:2	59.4 ± 11.8	69 (35.9)
MD	49	15	3.3:1	57.6 ± 11.9	64 (33.3)
Fibrosis	6	9	1:1.5	62.1 ± 16.0	15 (7.8)
Calcification (annular)	4	3	1.3:1	66.6 ± 5.8	7 (3.6)
Infective endocarditis	6	1	6:1	45.9 ± 13.9	7 (3.6)
CT disorder	0	3	0:3	69.0 ± 5.3	3 (1.6)
Drug use	1	0	1:0	61.0	1 (0.5)
LS endocarditis	0	1	0:1	49.0	1 (0.5)
Congenital					
CT disorder	6	1	6:1	64.0 ± 6.5	7 (3.6)
Cleft leaflet	0	1	0:1	51.0	1 (0.5)
Nonvalvular					
Ischemic disease	11	6	1.8:1	66.9 ± 10.8	17 (8.9)
Total	106	86	1.2:1	59.7 ± 12.3	192 (100)

CT Chordae tendineae; LS Libman-Sacks; MD Myxomatous degeneration; MVD Mitral valve disease; RVD Postinflammatory (rheumatic) valve disease

RVD

The mean age among 69 patients with RVD was 59.4 ± 11.8 years at operation. There were 46 women (66.7%) and 23 men (33.3%) in this subset. The majority of valves in this group showed MS ($n=62$, 89.9%), while a smaller proportion had a combination of MS and MI ($n=7$, 10.1%). In this group, no valves were explanted for MI alone.

Virtually all excised valves in this group showed leaflet fibrosis and thickening ($n=68$, 98.6%). Approximately one-half of the valves ($n=37$, 53.6%) in this subset showed significant leaflet calcification and a smaller proportion ($n=22$, 31.9%) showed evidence of neovascularization in the leaflets. Virtually every valve showed loss of scallops of the posterior leaflet, making the posterior leaflet a single sheet of thickened, shortened tissue. This feature was the most consistent feature in this group of valves.

The most frequent morphological change in the commissures was fusion ($n=55$, 79.7%), followed by calcification ($n=45$, 65.2%) and superficial ulceration ($n=29$, 42.0%). The majority of valves showed thickening ($n=57$, 82.6%), fibrosis ($n=37$, 53.6%) and fusion ($n=51$, 73.9%) of the chordae tendineae, while only one valve (1.4%) had a ruptured chorda tendinea.

The manifestations of postinflammatory changes were somewhat variable. The degree of commissural fusion varied from mild to severe, as did the degree of stenosis of the valve orifice (Figures 1 and 2). The posterior mitral leaflet showed loss of its scallops or subdivisions to variable degrees.

Figure 1 A to C A postinflammatory (rheumatic) mitral valve, excised from a 31-year-old man. **A** Flow surface. The specimen shows nodular calcification (black arrow), thickening and fibrosis of the leaflets. Two chordae tendineae have been pushed through the orifice (white arrow). **B** Nonflow surface. Shortening and fusion of the chordae tendineae can be seen (asterisks). **C** Transverse section through a commissure, showing ulceration (u), calcification (m), inflammation (i) and old hemorrhage (h) into this commissural region of the leaflets (hematoxylin and eosin stain, original magnification $\times 16$). **D** A postinflammatory (rheumatic) mitral valve, excised from a 43-year-old man. On the flow surface, the valve shows loss of scallops on the posterior leaflet (black arrowhead)

Figure 2 A postinflammatory (rheumatic) mitral valve, excised from a 56-year-old woman. **A** Flow surface. Mild commissural fusion can be seen (white arrows). **B** Nonflow surface. The specimen shows fibrosis and fusion of some of the chordae tendineae. No calcification is seen, and some chordae tendineae, especially from the posterior leaflet, appear virtually unremarkable (white arrowheads). A papillary muscle tip, with attached strips of chordae tendineae, is also seen. This mitral valve shows relatively mild changes compared with the usual gross findings in a rheumatic mitral valve as seen in Figure 1

MD

The mean age of the 64 patients with MD as the basis for valve failure was 57.6 ± 11.9 years at operation. There were 49 men (76.6%) and 15 women (23.4%) in this subset. The difference in sex distribution between patients with MD and those with RVD was significant ($P < 0.001$). All but one valve in this subset were dysfunctional due to MI ($n=63$, 98.4%). The remaining valve was dysfunctional due to a combination of MI and MS (1.6%). This valve also showed evidence of RVD, but the dominant mode of dysfunction was most likely related to MD.

The majority of valves in this subset showed leaflet fibrosis ($n=42$, 65.6%), while the minority showed leaflet thickening ($n=29$, 45.3%), leaflet calcification ($n=7$, 10.9%) and leaflet neovascularization ($n=4$, 6.3%) (Figure 3). Each of these changes was seen in a significantly greater proportion of RVD

Figure 3 A to C A myxomatous mitral valve, excised from a 63-year-old man. **A** Flow surface. The segments of the posterior leaflet show thickening, fibrosis, 'hooding' (asterisks) and myxomatous change. **B** Nonflow surface. One segment shows atypical chordal attachments, with the chordae attached to the basal regions of the free margin (white arrow). The cut edges have a thick, myxoid (edematous) appearance (red arrowhead). **C** Section through the posterior mitral leaflet, showing thickening and fibrosis (black arrowheads), myxomatous change (white asterisks) and elastosis (black arrows) of the leaflet (Movat pentachrome stain, original magnification $\times 16$). **D** Section through a myxomatous posterior mitral leaflet showing fibroelastic deficiency, excised from a 55-year-old man. (Movat pentachrome stain, original magnification $\times 25$). The higher magnification inset of the boxed area shows loss of elastic tissue and accumulation of mucopolysaccharides (area between the red arrows) (original magnification $\times 200$)

valves than MD valves ($P < 0.001$ for each change). Nearly all MD valves also showed fibroelastic inadequacy. MD valves showed few changes of the commissures. Only one MD valve (1.6%) showed fusion, calcification and ulceration of the commissures, and this was the valve that also showed features of RVD. Each type of change of the commissures was seen in a significantly greater proportion of RVD valves than MD valves ($P < 0.001$ for each change). However, in many MD valves, only a segment of the posterior leaflet of the valve was excised, and comment regarding these commissures was usually not possible.

Few MD valves showed morphological changes of the chordae tendineae. Thickening of the chordae tendineae was seen in 26.6% of cases ($n=17$), while mild fibrosis ($n=15$) and fusion of the proximal portions ($n=7$) were only seen in 23.4% and 10.9% of MD valves, respectively. RVD valves showed a greater proportion of each of these changes, compared with myxomatous valves ($P < 0.001$ for each change). A greater proportion of MD valves ($n=5$, 7.8%) showed rupture of one or more chordae tendineae compared with that of RVD valves ($n=1$, 1.6%), although this trend was not statistically significant ($P=0.088$).

Infective endocarditis

Evidence of infective endocarditis, with an acute inflammatory response, was found in seven valves (3.6%). As mentioned previously, groups of patients with infective endocarditis were younger and had a greater proportion of men than the rest of

Figure 4 A mitral valve from a 33-year-old woman, showing infective endocarditis. The flow (A) and nonflow (B) surfaces show evidence of pre-existing myxomatous change, infected vegetations (white arrows) and tissue destruction. C A section through the cusp showing extensive tissue destruction (black asterisk) (Movat pentachrome stain, original magnification $\times 16$). D This magnified section of the boxed area in C shows colonies of Gram-positive bacteria (black arrow) (Gram stain, original magnification $\times 200$)

the MVD group. Gram-positive microorganisms were found in four of the seven valves (57.1%), while no microorganisms were seen on special histological stains in the other three (42.9%). The majority of valves ($n=6$, 85.7%) with infective endocarditis showed significant tissue destruction or perforation. A high proportion of infected valves also showed thrombotic vegetations ($n=5$, 71.4%) and neovascularization ($n=4$, 57.1%). The majority of infected valves ($n=4$, 57.1%) showed no apparent underlying disease, while one valve (14.3%) showed evidence of pre-existing annular calcification, another (14.3%) showed evidence of pre-existing RVD and a third (14.3%) showed evidence of pre-existing MD (Figure 4).

Previous repair

There were 10 valves that showed evidence of previous repair, including six valves from women (60%) and four valves from men (40%). The mean age of patients who had previous repair was 53.8 ± 17.1 years at valve excision. Neither age nor sex distribution differed significantly from the rest of the MVD group. In two cases (20.0%), the repair was attempted and abandoned in favour of replacement during the same operation. In three cases (30.0%), the mitral valve had previously been repaired using an annuloplasty ring.

A total of five valves (50.0%) were previously repaired using sutures in the valve leaflets or commissures. Of these, four (80.0%) showed fibrosis and thickening around the suture sites. Previous repair was performed due to RVD in three of five valves (60.0%). The other two valves (40.0%) were repaired for congenital reasons, including valvular dysfunction related to an atrial septal defect and dysfunction related to the tetralogy of Fallot. The latter valve was excised 19 years after repair. This valve, in addition to the fibrosis at the repair site, showed a chorda tendinea made of synthetic material attached to help resuspend the valve to the papillary muscle tip (Figure 5). The artificial chorda showed circumferential fibrosis and thickening,

Figure 5 A mitral valve from a 37-year-old woman showing fibrosis and thickening. This mitral valve had been repaired 19 years before excision, for reasons related to the patient's tetralogy of Fallot. A A synthetic chorda tendinea can be seen, covered by significant circumferential fibrosis (white arrow). B Section through the posterior leaflet (Movat pentachrome stain, original magnification $\times 16$). The inset, polarized and magnified from the boxed area, shows the synthetic fabric of the suture (black arrow) and fibrosis surrounding the suture (original magnification $\times 200$)

making it difficult to distinguish it from the rest of the native chordae tendineae on gross examination.

Other pathologies

A total of 39 patients (20.3%) showed some form of aortic valve disease, five (12.8%) of whom had undergone a previous aortic valve replacement. A majority of patients with aortic valve disease ($n=27$, 69.2%) also had RVD. Coronary artery disease was common in the present study, existing in 14 cases (7.3%). Left atrial appendages were excised in 10 cases (5.2%). Furthermore, there were two cases (1.0%) of aortic aneurysms, two cases (1.0%) of Marfan's syndrome and two cases (1.0%) of cardiac muscle fibre hypertrophy (based on subaortic myectomy). A number of other pathologies were also found in isolated cases (data not shown).

DISCUSSION

Valvular heart disease is an increasingly common medical problem in the developed and developing worlds, affecting nearly 100,000 people in the United States annually (1,11). As such, a study of the pathology of explanted mitral valves is critical to understanding the treatment and prognosis of MVD. The aim of the present study was to assess morphological changes of surgically excised, diseased mitral valves in a contemporary population.

In our patient population, 57.3% of patients showed MI, 37.5% experienced MS, and 5.2% experienced combined MS and MI. These results differ somewhat from previous studies by Dare et al (12), Olson et al (4) and Hanson et al (13) (Table 3). MI was more frequent in our study than two previous studies (4,13), but it was similar in prevalence to the 1993 study by Dare et al (12). Our occurrence of MS (37.5%) was similar to that in the 1985 study by Hanson et al (13), in which MS accounted for 39% of cases. The incidence of combined MS and MI was lower in our study than each of the preceding studies, perhaps reflecting differences in classification of combined MS and MI, or that patients are now operated on earlier in the course of disease than they were in the past.

In the present study, the most frequent cause of MVD was RVD, present in 35.9% of cases. This finding is in contrast with that of previous studies, which state that MD has supplanted RVD as the most common underlying etiology of MVD today

TABLE 3
Mitral valve disease study comparison

	Hanson et al (1985) (13)	Olson et al (1987) (4)	Dare et al (1993) (12)	Present study
Patients with MI, n (%)	46 (46)	260 (37)	55 (58)	110 (57.3)
Patients with MS, n (%)	39 (39)	175 (25)	16 (17)	72 (37.5)
Patients with MI and MS, n (%)	15 (15)	277 (39)	24 (25)	10 (5.2)
Patients with RVD, n (%)	54 (54)	530 (74)	47 (49)	69 (35.9)
Patients with MD, n (%)	32 (32)	100 (14)	27 (28)	64 (33.3)

MD Myxomatous degeneration; MI Mitral incompetence; MS Mitral stenosis;
RVD Postinflammatory (rheumatic) valve disease

(3,6). The demographic composition of our referral base may account for the differences observed. Our study cohort was representative of the regional population demographics, with ethnic groups comprising over 47% of the sample population, a large proportion of whom emigrated from developing countries with a high prevalence of rheumatic disease. However, the incidence of RVD was lower in the present surgical series than in three previous series by Dare et al (12), Olson et al (4) and Hanson et al (13) (49%, 74%, and 54%, respectively). The lower incidence may represent a declining frequency of rheumatic disease in the developed world. One must keep in mind that the quoted studies are more than 10 years old. As in previous studies (3,4,12,14), there was a much higher proportion of women (67%) than men (33%) with RVD in the present study, with a ratio of 2:1. Nearly all RVD valves in the present study showed leaflet fibrosis and thickening, while many showed leaflet and commissural calcification, and chorda tendinea fusion, thickening and fibrosis. All such changes are likely hallmarks of RVD, as also reported in previous studies (3,13). The morphological manifestations of RVD appear to be changing. This may be related to fewer episodes of acute rheumatic fever, better medical management, earlier surgical intervention, or all three of these. The significant changes were in the chordae tendineae, with some showing changes in the commissural regions only, with the more 'central' chordae appearing relatively unremarkable.

MD was the second most frequent cause of MVD in the present study (33%). Although not the most common form of valvular disease, as reported in past literature (3), MD was found in a higher proportion of patients in the present study than in three previous surgical series by Olson et al (4), Dare et al (12) and Hanson et al (13) (14%, 28% and 32%, respectively). This finding may perhaps reflect the longer lifespan of patients in a contemporary population, because more patients have the potential to manifest age-related valvular degeneration (11). There was a much higher proportion of men with MD than women, in a ratio of 3.3:1, which is consistent with some previous studies (3,4,12). Interestingly, MD and RVD differ significantly in sex distribution, with RVD patients being primarily female, and MD patients being predominantly male. This finding may be related to immune-mediated disease (such as rheumatic disease) occurring more frequently in women (3). Notably, MD valves in this series still often showed leaflet fibrosis and thickening, superimposed on the myxomatous change. Such features are more commonly seen in RVD valves. For MD valves, this fibrosis was usually patchy and seen on the surface (flow and nonflow), rather than within the layers of the

leaflet tissue. Only one MD valve showed morphological changes of the commissures, consistent with previous literature (13), and this valve also showed evidence of mild RVD. Chordal rupture is a hallmark of advanced MD and MI (3,13), but it was only definitively noted in 7.8% of cases in the present study. This may be related to the chordal rupture having occurred recently and the typical changes not being grossly evident. The majority (55.6%) of chordal rupture cases were from the MD subset.

Overall, 8.9% of valves in the present study were explanted for failure related to nonvalvular causes, the most common being ischemic heart disease. Meanwhile, 3.6% of valves were explanted due to MVD related to annular calcification. Patients in both of these subsets were significantly older at operation than the rest of the MVD group. This is likely due to the increasing incidence of ischemic heart disease and annular calcification with age (3,15). In contrast, patients with MVD caused by infective endocarditis were significantly younger at operation than the rest of the MVD group. Patients in this group also differed in sex distribution from the rest of the group (85.7% men, 14.3% women). These findings are similar to those reported in some previous surgical series of excised mitral valves (4,12).

Study limitations

The present study is a retrospective, pathology-based study of explanted valves at our institution. Gross and histological findings of explanted valves were assessed qualitatively, and as such, some unavoidable human error may have been introduced into the study. Furthermore, the present study examined surgically excised, diseased mitral valves, and hence, a control group of normal explanted valves was neither feasible nor possible. In the present study, only significantly diseased valves that had been surgically explanted were available for examination. Mitral valve repair without valve excision may have been more common for some forms of MVD than others. Therefore, the incidences of some clinical causes of MVD may have varied somewhat from those reported in the present study.

CONCLUSIONS

The morphological findings in 192 diseased native mitral valves, excised over a one-year period, were described. Fibrosis and thickening were the most common morphological changes in the leaflets, and fusion and calcification were the most common changes at the commissures. Thickening, fusion and fibrosis were the most frequently observed changes in the chordae tendineae. A majority of dysfunctional valves showed evidence of MI (57.3%), followed by MS (37.5%) and combined MS and MI (5.2%). RVD (35.9%) and MD (33.3%) were the two common causes of MVD.

RVD valves were more likely to show morphological changes of the leaflets (fibrosis, thickening, calcification, neovascularization), commissures (fusion, calcification, ulceration) and chordae tendineae (fibrosis, thickening, fusion), compared with MD valves. RVD and MD valves differed significantly in sex distribution, with RVD patients being primarily female and MD patients being primarily male. The incidence of RVD in the current study was lower than in previous studies and the incidence of MD was higher, perhaps reflecting population-based temporal/epidemiological changes of MVD and an aging population.

REFERENCES

- Heart Disease and Stroke Statistics – 2005 Update. Dallas, Texas: American Heart Association, 2005:1-60. <www.americanheart.org/downloadable/heart/1105390918119HDSStats2005Update.pdf> (Version current at June 12, 2006).
- Edwards JE. Pathology of acquired valvular disease of the heart. *Semin Roentgenol* 1979;14:96-115.
- Virmani R, Burke A, Farb A, Atkinson JB. Pathology of Cardiac Valves. In: *Cardiovascular Pathology*, 2nd edn. Vol 40. Philadelphia: WB Saunders Company, 2001:231-79.
- Olson LJ, Subramanian R, Ackermann DM, Orszulak TA, Edwards WD. Surgical pathology of the mitral valve: A study of 712 cases spanning 21 years. *Mayo Clin Proc* 1987;62:22-34.
- Carabello BA, Crawford FA Jr. Valvular heart disease. *N Engl J Med* 1997;337:32-41.
- Bouknight DP, O'Rourke RA. Current management of mitral valve prolapse. *Am Fam Physician* 2000;61:3343-50, 3353-4.
- Pellerin D, Brecker S, Veyrat C. Degenerative mitral valve disease with emphasis on mitral valve prolapse. *Heart* 2002;88(Suppl 4):iv20-8.
- Silver M. Acquired disease of the valves and endocardium. In: Bloom S, Lie J, Silver MD, eds. *Diagnostic criteria for cardiovascular pathology: Acquired diseases*. Philadelphia: Lippincott-Raven Publishers, 1997:120-2.
- Lobo F, Walley V. Acquired disease of the valves and endocardium. In: Bloom S, Lie J, Silver M, eds. *Diagnostic criteria for cardiovascular pathology: Acquired diseases*. Philadelphia: Lippincott-Raven Publishers, 1997:145-6.
- Walley V. Acquired disease of the valves and endocardium. In: Bloom S, Lie J, Silver M, eds. *Diagnostic criteria for cardiovascular pathology: Acquired diseases*. Philadelphia: Lippincott-Raven Publishers, 1997:143-4.
- Butany J, Collins MJ, Demellawy DE, et al. Morphological and clinical findings in 247 surgically excised native aortic valves. *Can J Cardiol* 2005;21:747-55.
- Dare AJ, Harrity PJ, Tazelaar HD, Edwards WD, Mullany CJ. Evaluation of surgically excised mitral valves: Revised recommendations based on changing operative procedures in the 1990s. *Hum Pathol* 1993;24:1286-93.
- Hanson TP, Edwards BS, Edwards JE. Pathology of surgically excised mitral valves. One hundred consecutive cases. *Arch Pathol Lab Med* 1985;109:823-8.
- Segal BL. Valvular heart disease, Part 2. Mitral valve disease in older adults. *Geriatrics* 2003;58:26-31; quiz 32.
- Hanna IR, Wenger NK. Secondary prevention of coronary heart disease in elderly patients. *Am Fam Physician* 2005;71:2289-96.