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An analysis of autopsy findings in 108 patients who died after valve replacement

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Abstract. The pathological findings and the causes of death were reviewed in 108 patients who had received 142 heart valve prostheses (52 mechanical and 90 bioprostheses) at the National Cardiovascular Center in Osaka, Japan, from 1977 to 1991. Rheumatic heart disease was the major underlying disease (60.2%), and the age distribution at death ranged from 21 to 80-year-old. Survival duration after the surgery extended from 0 day to 9 years. Thirty-three patients (30.6%) died of perioperative complications such as myocardial haemorrhage and damage, or from heart failure which had been evident prior to the operation, a cause of death which predominated in patients who died within 1 week of surgery (15/17; 88.2%). Thirty-eight patients (35.2%) died of prostheses-related problems such as prosthetic valve failure (cuspal tears and calcifying destruction of the xenograft), thromboembolism, and prosthetic valve endocarditis. Endocarditis was frequent in patients who had survived longer than 1 year (25/33; 75.8%). None of the patients died of prostheses-related problems within 1 week. Non-infectious valve failure was more common in patients with bioprostheses than in those with mechanical valves; thromboembolism showed the opposite association. Prosthetic valve infective endocarditis was nearly equal in frequency in both types of valve.

Key words: Cardiac valve prostheses – Autopsy – Prosthetic valve failure – Prosthetic valve endocarditis

Introduction

Valve replacement is now the standard surgical therapy for cardiac valvular disease and great improvements in surgical techniques and newly-designed prosthetic valves have enhanced this therapeutic progress (Wheatly et al. 1987). The incidence of rheumatic heart disease (RHD) the most common underlying disease for cardiac valvular disease has been decreasing, nevertheless, potential candidates for valve replacement therapy are increasing because of application of newer diagnostic tools (Silver and Butany 1988). Furthermore, patients with cardiac disease now expect an improvement in the quality of their life and expect valvular replacement. However, nearly 10% of the patients with valve replacement die in the early or late post-operative state in our hospital and the reasons for this are clearly important. The National Cardiovascular Center, Osaka, Japan was founded by the Japanese government in 1977 as highly-specialized hospital for cardiovascular diseases including cardiac surgery. This provides us with a golden opportunity to examine a large series of deceased patients who had received valve replacement therapy. In this study, we took advantage of having both autopsy and clinical data of the pre- and post-operative state of the patients, and attempted an analysis of prognostic indicators after valve replacement.

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Patients and methods

Of 1900 consecutive autopsies performed over a 15 year period between 1977 and 1991 at the National Cardiovascular Center, 108 patients had a total of 142 implanted prosthetic heart valves in place at the time of death. They comprised 62 males and 46 females whose ages ranged from 21 to 80 years (mean: 55.4 years) (Table 1).

The hearts with prostheses and other organs were carefully examined grossly and microscopically and were photographed. Histological sections were taken from the cusps of bioprostheses and the periannular textile tissue of the mechanical valve, and were stained with haematoxylin-eosin, Masson's trichrome, elastic van Gieson, Gram stain and Brenn and Brown's stain when necessary. Bacterial cultures were done when infective endocarditis (IE) was suspected.

The cause of death was determined in each patient from autopsy findings and clinical data. Among patients with repeated valve replacement deaths were considered to have been caused by disorders of the removed prosthetic valves at the time of re-operation and not by the operative complication, as all these patients died within 1 week and the operation did not affect survival. The duration of survival in re-operated patients was counted from the day of the first replacement.

Table 1. Profiles of 108 patients

	Survival duration	No. of Patients	Age (yr) Mean (range)	Gender M/F	Sites of valve replacement		
					MV/TV	AV/PV	Multiple
Early deaths	<1 week	17	52.2(21–74)	4/13	8	6	3
	<1 months	32	56.2(31–76)	18/14	14	7	11
Late deaths	<1 year	26	54.3(28–80)	18/ 8	12/1	6	7
	≧1 year	33	57.4(29–79)	22/11	12	9/11	11
Total		108	55.4(21–80)	62/46	46/1 (8)	28/1 (3)	32 (8)

MV, mitral valve; TV, tricuspid valve; AV, aortic valve; PV, pulmonary valve; MV/TV, AV/PV indicates numbers of the patients with single valve replacement at each site; ( ) shows numbers of the patients with repeated valve replacement

Table 2. Types of 142 cardiac valvular prostheses implanted in 108 autopsy cases

	AV(PV)	MV(TV)	Subtotal	Total
Mechanical valve				52
Björk-Shiley	21	12	33	
Starr-Edwards	0	2	2	
Omni Carbon	1	3	4	
St Jude medical	8	5	13	
Bioprosthesis				90
Hancock	2	12	14	
Carpentier-Edwards	3(1)	6(9)	19	
Ionescou-Shiley	18(1)	34(2)	55	
Mitroflow	0	2	2	

AV, aortic valve; PV, pulmonary valve; MV, mitral valve; TV, tricuspid valve

Results

The underlying diseases that led to the valve replacement were RHD in 65 patients (60.2%), IE in 11 (10.2%), mitral valve prolapse in 10 (9.3% and congenital aortic bicuspid valve in 5 (4.6%). Other diagnoses such as Marfan's syndrome, congenital heart disease with atrioventricular valve regurgitation, and atherosclerotic aortic stenosis accounted for the remaining cases. The sites of replaced valves were shown in Table 1, and multiple valves (two or three) were replaced in 32 patients. The implanted prosthetic valves were replaced because of prosthetic valve failure in 13 patients, and for prosthetic valve endocarditis in 6 patients. The models of implanted prosthetic valves used are listed in Table 2. There were 52 mechanical valves and 90 bioprosthetic valves. Björk-Shiley (tilting disk) valves were implanted in more than half of the cases of mechanical valves. The most common type of tissue valves utilized in our institute were Ionescu-Shiley pericardial xenografts.

The survival duration after the first valve replacement operation was distributed from 0 day to 9 years. Thus, the patients were subgrouped according to the length of the survival after the valve replacement, and their causes of deaths were analysed. Patients were divided into two groups according to survival duration; early and late deaths. The early death group consisted of patients who died within 1 month, and this group was

Table 3. Cause of death after operation of valve replacement

Cause of death	Early death				Late death				Total
	<1 week		<1 month		<1 year		≥1 year		
Perioperative	15		10		8				33
Operation related haemorrhage		4		3		1			8
Myocardial necrosis/rupture		10				1			11
Cardiac failure→MOF		1		7		6			14
Valve related			7		6		25		38
PVF						1		12	13
Thromboembolism				5				4	9
PVE				2		5		9	16
Other complications	2		15		12		8		37
Infection/sepsis		2		13		11		4	30
Others (DA/CRF, etc)				2		1		4	7
	17		32		26		33		108

MOF, multiple organ failure; PVF, prosthetic valve failure; PVE, prosthetic valve endocarditis; DA, dissecting aneurysm; CRF, chronic renal failure

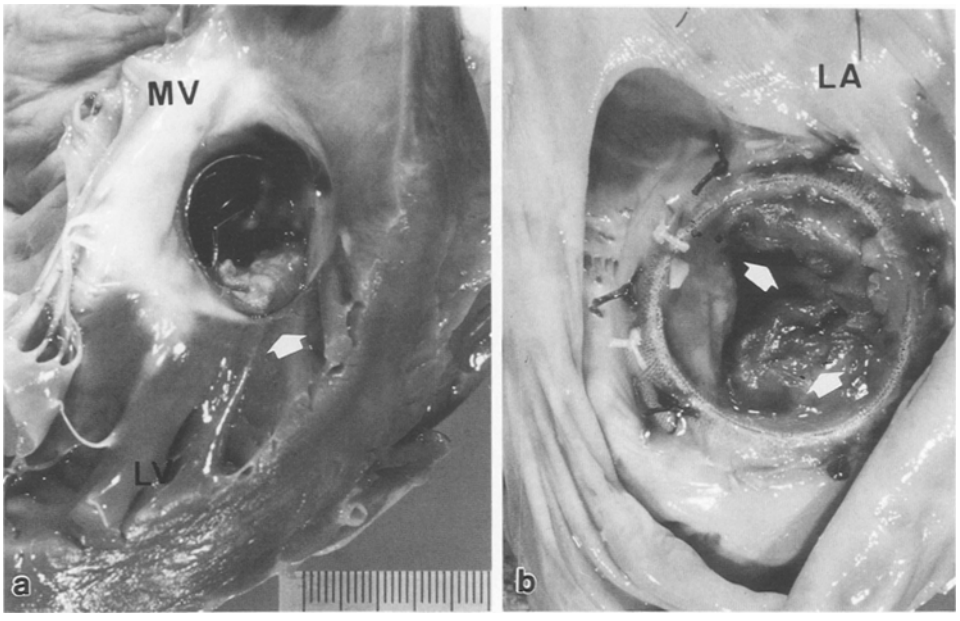

Fig. 1a. A photograph shows a huge vegetation (*arrow*) of the Bjork-Shiley aortic valve restricting disk motion. (MV, mitral valve; LV, left ventricle). **b** A photograph showing a vegetation of xenograft cusps (*arrows*) of Ionescu-Shiley valve at the mitral portion. (LA, left atrium)

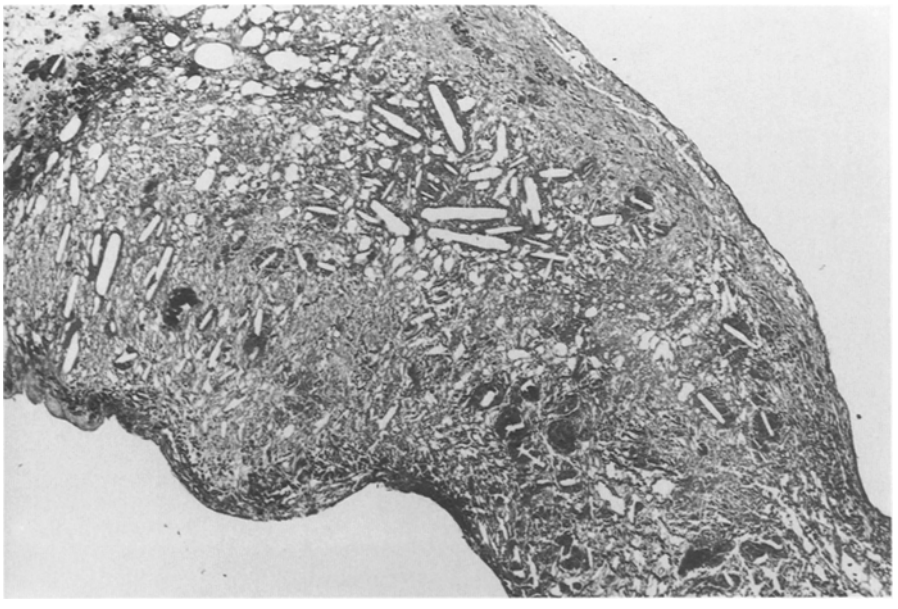

Fig. 2. A photomicrograph shows empty spaces found to be cholesterol crystals in the degenerative xenograft. (H & E, ×110)

further divided into two subgroups; cases dying within 1 week and cases dying from 1 week to 1 months. Late death group consisted of cases surviving longer than 1 month after the operation, and this group was further divided into two subgroups; cases surviving up to 1 year and those surviving longer than 1 year after surgery. The number of patients in each group and their causes of deaths are shown in Table 3.

Of 49 patients classified into early death group, 17 (34.7%) died of perioperative complications such as perioperative haemorrhage, myocardial damage and cardiac rupture; only 7 (14.2%) died of valve-related problems. Among the patients who died within 1 week, 14 out of 17 (82.3%) died of perioperative complications, 1 of heart failure which had existed prior to surgery and none of valve-related problems.

Among 59 patients in the late death group, only 2 patients (3.4%) died of perioperative complications and 31 (52.5%) of valve-related problems. Six patients died of persistent heart failure that existed prior to operation. In 33 patients who survived longer than 1 year, 25 patients (75.8%) died of prostheses-related problems, comprising 12 patients with prosthetic valve failure (PVF), 4 with thromboembolism and 9 cases of prosthetic valve endocarditis (PVE).

Table 4 compares valve-related problems as causes of death between mechanical and bioprosthetic valves. PVF caused by non-infectious valve tears and perforations occurred mostly in bioprostheses. In contrast, non-infectious thromboembolism was observed more frequently in mechanical valves, although anticoagulant therapy had been given. Two of the patients with me-

Table 4. Three valve-related principal causes of death in different types of valve prostheses

	Mechanical valve ($n=13$)	Bioprosthesis ($n=25$)
PVF	1(7.7%)	12(48.0%)
Thrombo-embolism	6(46.2%)	3(12.0%)
PVE	6(46.2%)	10(40.0%)

PVF, prosthetic valve failure; PVE, prosthetic valve endocarditis

chanical valves had isolated mural thrombi in the left atrium, which did not directly extend to the valves. Four thromboembolic cases with mechanical valves had thrombi located at the mitral valve site. PVE were of nearly equal incidence in both types. Huge vegetations on prosthetic valves were observed to disturb the motion of cusps and disks (Fig. 1 a, b).

The cusp tears occurred predominantly in the para-stent post or para-valve ring regions. The tears were usually vertical along the stent posts. The histological characteristics observed in bioprosthetic valve cusps demonstrating PVF was primary tissue failure such as dissection and fragmentation of the collagen bundles of the xenograft. There were scattered empty spaces between degenerative collagen bundles compatible with cholesterol crystals (Fig. 2). Homogeneously eosinophilic fluid was insudated in the space of separated collagen bundles of the cusps. Granular or nodular cuspal calcification was seen near the stent post or at the edges of the torn cusps. Fine granular calcification was observed in the xenograft cusps 120 days after implantation and chronic inflammatory cells lined the surface of tissue valves (Fig. 3). Mononuclear cells and giant cells sometimes infiltrated the deeper layers of the valves. Pin-hole-sized perforations of cusps were seen where there was no apparent sign of infection. Two cases of tissue valves showed mild pannus which consisted of hyalinized collagen tissue at the valve ring. The pannus of these cases seemed not inhibit valve motion because it did not extend to the prosthetic cusps.

Active PVE was observed in 16 patients. Large vegetations were found on the cusps of prosthetic valves (Fig. 1 a, b) and ring abscess were sometimes seen. In 5 patients with repeated valve replacement due to IE, recurrence of IE seemed to have occurred secondary to ring abscess which were not completely removed by the operation. The pathognomonic micro-organisms were detected in some cases, and *Staphylococcus aureus, Streptococcus viridans, Candida albicans* were identified by blood culture (Fig. 4). It is considered that large infected vegetations were the sources of multiple and systemic septic embolization and subsequently caused pyogenic arteritis (Fig. 6) and mycotic aneurysm, and secondary infarcts and/or haemorrhage. Eleven patients

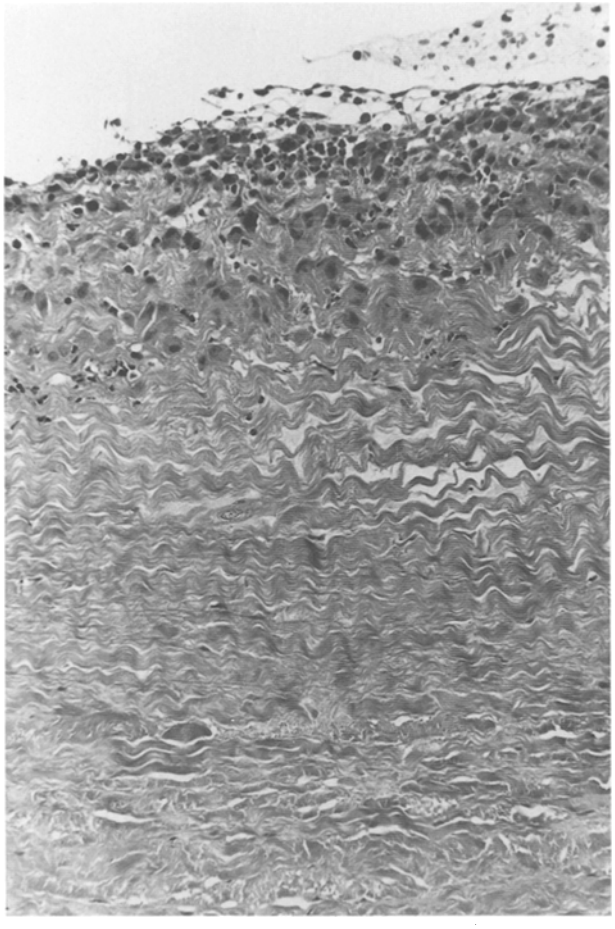

Fig. 3. Microscopically, small round cells and macrophages accumulate along the lining surface of xenograft. The middle layers of collagen bundles are separated. (H & E, ×200)

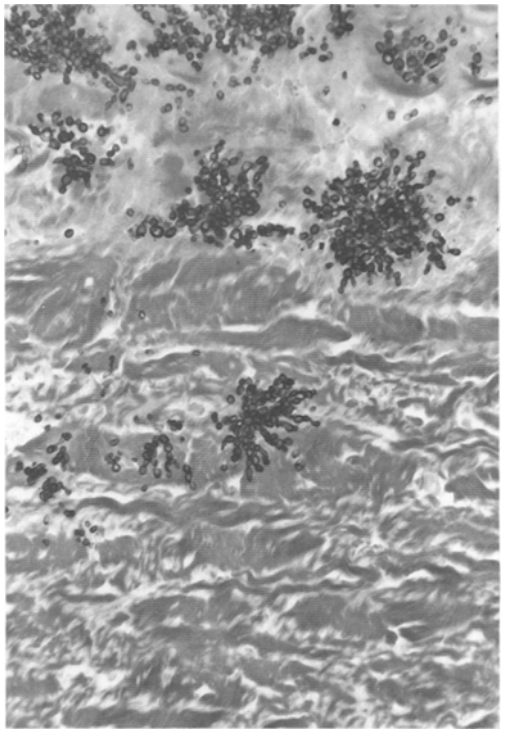

Fig. 4. Colonies of *Candida albicans* invading the xenograft were observed in the cusp of the mitral portion. (Grocott's fungal stain, ×300)

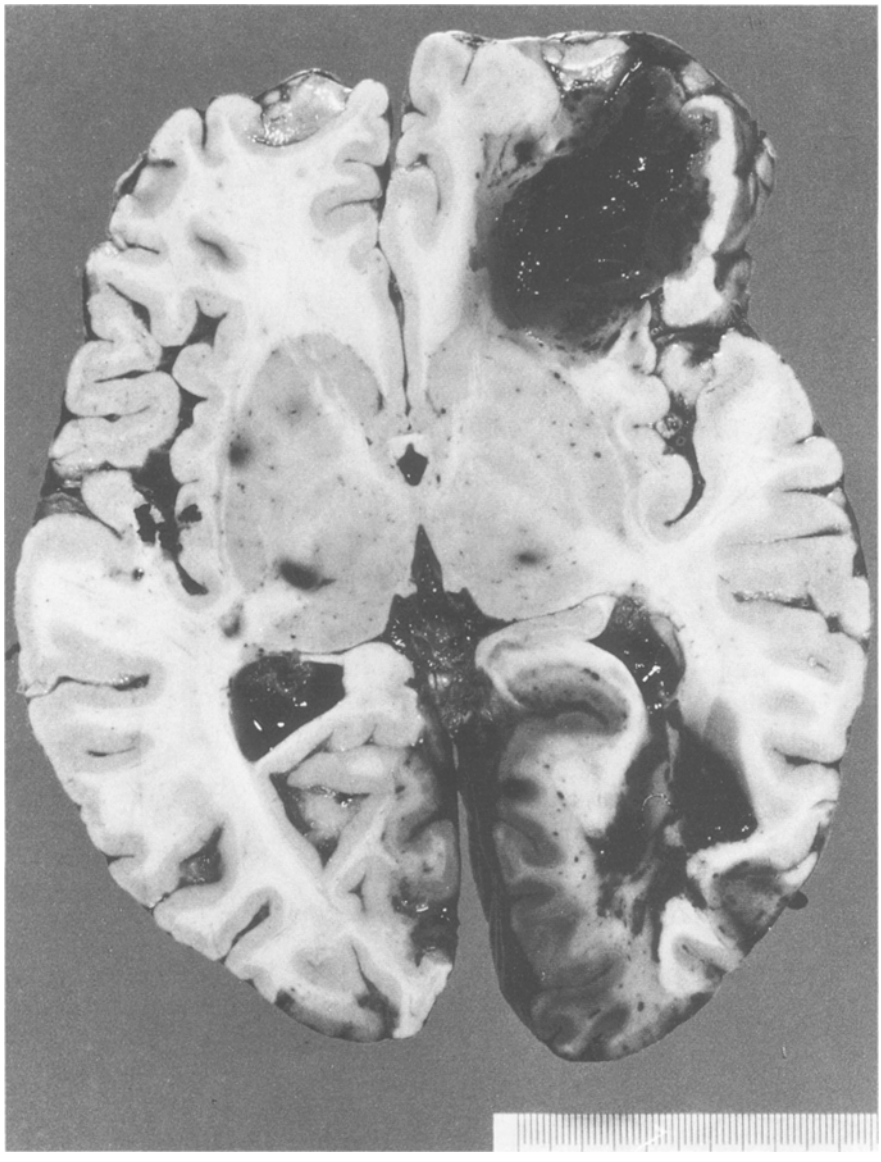

Fig. 5. Massive haemorrhagic infarcts in the frontal and posterior lobes of right hemisphere of brain secondary to prosthetic valve endocarditis.

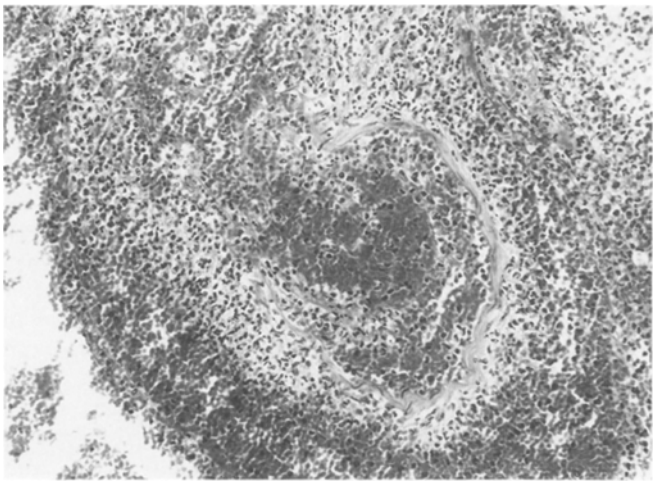

Fig. 6. A photomicrograph of pyogenic arteritis of a small cerebral artery causing cerebral haemorrhage. The arterial wall is destroyed by a purulent infiltrate. (H & E, ×75)

with PVE showed fatal haemorrhage or haemorrhagic infarcts in the brain parenchyma (Fig. 5).

Pathological changes elsewhere included chronic congestion of the liver in 15 cases and "cardiac cirrhosis" of the liver in 14 cases. Pulmonary findings included organizing bronchopneumonia and pulmonary thromboembolism (46 and 7 cases, respectively). One case showed multiple systemic embolism causing severe skeletal myonecrosis.

Discussion

We examined as surgical specimens all the native cardiac valves removed grossly as well as microscopically, and found that major underlying diseases which had led to the valve replacement was RHD. In 96 autopsy cases described by Zeien and Klatt (1990), the underlying diseases requiring valve replacement were RHD in 58% and IE in 22%. In our series, RHD was of similar inci-

dence (60.2%) but IE at 10.2% was less frequent. Among 13 patients whose valves demonstrated the findings of IE, 7 died of recurrence of IE (53.5%) and IE at surgery is clearly an important predictor for prognosis after valve replacement.

Unfortunately, we have 17 (15.7%) early post-operative deaths, with many patients dying within 1 week. Nearly 80% of them were women, although men dominanted all other groups. Their causes of death were mostly perioperative episodes such as massive haemorrhage or myocardial damage and most of these cases had been operated on in the early period of our series. We believe that this number can be reduced by improvement in evaluation of cardiac function and operative technique. In contrast, late deaths were not directly related to the operation but most often occurred secondary to prostheses-related problems, such as PVF, non-infectious thromboembolism and PVE. It is well-known that the choice of prosthetic valve is the most important predictor for late complications. Rose (1986), in his study of autopsy series, found that structural failures of bioprosthetic valves were more frequent whereas mechanical valves showed thrombosis and infection more commonly. Zeien and Klatt (1990) reported that infection occurred with equal incidence in both groups (8%) and that the incidence of structural failure was similar (18% for mechanical vs 17% for bioprostheses). They also reported that thrombosis rates for mechanical valves was triple that of bioprostheses (23% vs 8%). The study of Schoen and Hobson (1985) showed IE was equally frequent with mechanical valves and bioprostheses.

In the present study, PVF was much less common in mechanical valves than in bioprosthetic valves (7.7% vs 48%) in the 38 prosthesis-related deaths of our series. In contrast, non-infectious thromboembolism was nearly four times as common in mechanical implants (46% vs 12%) despite anticoagulant therapy. It is said that thromboembolic complications diminish in number after mechanical valves have been in place for 12 months because of a gradual coating of both surfaces of the cloth sewing ring by connective tissue (Edmunds 1982). In our series, however, thrombosis and/or thromboembolic complications occurred in early death in 5 cases and in 4 late deaths. One thromboembolic complication occurred 6 years after operation.

In general, thromboemboli arise more often from mitral prosthetic valve than aortic (Edmunds 1982), a finding probably related to the larger size of the left atrium in mitral valve disease. Four instances of thromboembolic complication were from the prosthetic mitral valve and the left atrium.

PVE occurred with nearly equal incidence in both mechanical and bioprosthetic groups (46% vs 40%). Vegetations on mechanical valves are formed at the base of the annulus and often disturb cusp motion. Thirteen patients (17.6%) had repeated valve replacement and almost 70% of patients with re-implanted valves had their prostheses replaced because of PVF; others were replaced because of PVE.

Our present study showed a relatively high frequency of use of bioprosthetic valves when compared with mechanical valves as newly designed bioprosthetic valves have been used frequently in our hospital during 1970's. In that period, bioprostheses made of porcine valves or bovine pericardium were said to be superior to non-tissue mechanical valves in terms of haemodynamic function (Gabby et al. 1984) and thrombus formation (Gonzalez-Lavin et al. 1984). Every artificial cardiac valve has advantages and disadvantages (Black et al. 1987), but bioprostheses have a relatively high rate of valve failure for several years after implantation because of progressive degenerative in xenografts. In this study, the shortest implantation duration for a bioprosthesis causing PVF was 120 days. Tears in xenograft cusps may be the result of a concentration of cusp stress at the alignment stitch (Butany et al. 1992), however, some pathological damage occurs in any type of bioprosthesis (Ferrans et al. 1987) due in part to the fact that for the purposes of decreasing antigenicity and sterility, bioprostheses are treated with glutaraldehyde before implantation. The collagen bundles are adversely affected and degenerate, bringing about loss of mobility of the cusps due to fixation (Ferrans et al. 1978; Schoen and Hobson 1985). The glutaraldehyde-treated tissue is denucleated and eosinophilic and the effects of time-dependent degeneration added to these changes and morphological degeneration reduce the effective duration of the valve. The initial mineralization of bioprosthetic cusps takes place in areas that sustain the highest mechanical stress (Nistal et al. 1988) Schoen et al. (1987) have suggested that stretching of cuspal tissue due to collagen bundle loosening in an Ionescu-Shiley valve may cause regurgitation.

It is believed that structural failure is relatively rare in mechanical valves. However, fracture of the Björk-Shiley valves is documented as a cause of mechanical valve failure (Lindblom et al. 1986) and Zeien and Klatt (1990) have described an autopsy case of disk embolism from the Björk-Shiley valve to the abdominal aorta and the heart.

Schoen and Hobson (1985) have reported that the histology of IE of mechanical valves and those of bioprostheses were different. Endocarditis of mechanical valves generally involved the surrounding tissues and frequently caused ring abscess. Infection of the bioprostheses often resulted in calcification in vegetations and frequently caused cuspal necrosis and destruction. The most severe complication in our experience was cerebral stroke in the form of haemorrhagic infarction due to infective emboli, and/or haemorrhage due to rupture of pyogenic arteritis and mycotic aneurysm (Masuda et al. 1992). Cases of cerebral stroke from PVE almost always showed evidence of multiple organ failure. Large vegetations were detected after attacks of embolic stroke in 3 patients with PVE. Valve replacement and subsequent anticoagulant therapy may enhance haemorrhagic transformation of the ischaemic insults produced by septic emboli. Thus indications for replacement surgery for PVE should be carefully evaluated in acute phase, and it is better to wait until extensive antimicrobial treatment has been completed.

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