One Thousand Carpentier-Edwards Pericardial Valves in the Aortic Position: What has Changed in the Past 20 years, and What are the Effects on Hospital Complications?

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Background and aim of the study: **Over the past 20 years, both the typical age and co-morbidity of patients referred for aortic valve replacement (AVR) have increased. In order to assess the effect of these changes on hospital complications, an evaluation was conducted of patient characteristics within this time period.**

Methods: **This retrospective study included 1,000 consecutive patients who underwent AVR with a pericardial valve. Concomitant coronary artery bypass grafting (CABG) was performed in 610 cases. Among 25 preoperative and five perioperative factors, and eight hospital complications, the changes in incidence that occurred during the periods 1986-1991, 1992-1996, 1997-2001, and 2002-2006, were investigated. Predictive factors for non-cardiac hospital complications required further exploration, as these were the only complications to increase significantly with time; however, this type of complication is less lethal.**

Results: **Significant increases were identified in age, and in the incidence of non-cardiac co-morbidity, previous CABG and preoperative congestive heart failure (p mostly <0.0001). Among hospital complications, only non-cardiac problems showed a significant increase. The independent predictors included previous CABG (p = 0.004), concomitant CABG (p = 0.006), renal impairment (p = 0.008), conduction defects (p = 0.010), previous pacemaker implantation (p = 0.014), chronic obstructive lung disease (p = 0.015), and concomitant carotid artery surgery (p = 0.032).**

Conclusion: **During the past 20 years, patients referred for AVR have become older and have more co-morbidity. However, the incidence only of non-cardiac hospital complications was increased. Previous and concomitant surgery, as well as non-cardiac co-morbidity, are important predictors that must be taken into account at referral, but should not contraindicate AVR.**

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The Carpentier-Edwards Perimount pericardial device has been used in the present authors' department for aortic valve replacement (AVR) since December 1986. The device has no sutures, and is used in patients with symptomatic aortic valve disease, who are aged over 65 years or who have an otherwise limited life expectancy. As the latter population comprises only 2% of all patients, the number of implanted pericardial valves provides an adequate reflection of the number of elderly patients requiring AVR. Among elderly patients, aortic valve disease is a frequent occurrence, for which AVR represents the only successful long-term treatment (1). Whilst monitoring the number of AVRs correlates well with the changes in referral practice, the effect on hospital complications during the past 20 years should also be monitored. However, very few reports have documented these changes over an extended time. Among a series of patients reported in 1994, the proportion aged over 70 years increased from 11% in 1978 to 54% in 1986 (2). Thus, a contemporary report is warranted. In several recently published reports (3-5), a considerable number of very elderly patients needing AVR were included, and consequently predictive factors for hospital complications need to be identified. This becomes increasingly important as systematic differences exist among cardiologists with regards to their advice for AVR in elderly patients, and in the way that such advice is influenced by the patients' age and co-morbidity. There is, therefore, a need to identify the best treatment for elderly patients, according to their clinical profile (6).

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Clinical material and methods

Patients

The patient cohort in this retrospective study comprised 1,000 patients who had undergone AVR with a pericardial valve. Coronary artery bypass grafting (CABG) was carried out in 610 of the patients. All data relating to preoperative factors and hospital complications were extracted from the patient files. Those patients who received a bioprosthesis in the mitral position, or who received a mechanical valve, were excluded from the study.

Preoperative and perioperative factors

Preoperative non-cardiac factors included age, gender, diabetes, carcinoma treated with a curative intent, impaired renal function (plasma creatinine >1.4 mg%) and pulmonary function (values <70% of expected), transient ischemic attack and cerebrovascular accident (CVA), hypertension (blood pressure >140/90 mm Hg), and carotid artery disease (stenosis of >40% on duplex-Doppler).

Preoperative cardiac factors included left ventricular function (ejection fraction (EF) and an ultrasonographic description), left ventricular hypertrophy, myocardial infarction, episode of pulmonary edema, coronary artery disease (including the number of affected vessels), previous percutaneous transluminal coronary angiography (PTCA) and CABG, atrial fibrillation (AF), conduction defects, implantation of a pacemaker, ventricular arrhythmias, NYHA functional class, and the need for digitalis. Preoperative valvular factors included the type of valve disease (stenosis versus regurgitation), previous valve replacement, and endocarditis.

Perioperative factors included associated procedures (CABG, with the number of bypasses, procedure on the aortic root or ascending aorta, on the mitral valve ring and the carotid artery), cross-clamp times for both the valve and for the total operation, and a need for urgent valve replacement.

Hospital events

Hospital events included valve-related events (endocarditis, thromboembolism, bleeding), other cardiac complications (AF, ventricular arrhythmia, congestive heart failure (CHF)), and non-cardiac complications such as pulmonary (infection and atelectasis), renal, surgical (wound infection, need for re-intervention, pneumothorax, subcutaneous emphysema) and others (urinary tract infection, fever of unknown origin, temporary disorientation, etc.), as well as mortality.

For the first 500 patients, all non-cardiac events were included in the long-term follow up.

Statistical analysis

Statistical analyses were performed for all preoperative and perioperative factors using Fischer's exact, Pearsons' chi-square (univariate) and logistic regression (multivariate) analyses.

Results

The significant changes in preoperative patient characteristics between 1986 and 2006 are listed in Table I. The absolute numbers of patients who underwent surgery increased considerably, from 80 between 1986 and 1991, to 365 between 2002 and 2006. The percentage of octogenarians has also increased considerably, though the mean age increment was limited, from 72.5 ± 5.4 years to 76.0 ± 5.2 years (p = NS). Neither was the male:female gender ratio altered over this time period (p = 0.67).

Non-cardiac co-morbidity was increased significantly, the only exception being previously treated carcinoma (p = 0.27). Among cardiac factors, only a period of preoperative CHF (pulmonary edema) and previously performed CABG had increased. Preoperative heart failure had become more prominent in patients aged over 80 years (53/186) than in younger patients (163/820, p = 0.008). The mean EF for the four episodes

Table I: Changes in preoperative patient characteristics between 1986 and 2006.

Factor	Time interval				p-value
	1986-1991	1992-1996	1997-2001	2002-2006	
Octogenarian	5/80 (6.3)	20/216 (9.3)	68/345 (19.7)	93/365 (25.5)	<0.0001
Diabetes mellitus	13/80 (16.3)	14/216 (6.5)	40/344 (11.6)	82/362 (22.7)	<0.0001
COPD	8/80 (10.0)	14/216 (6.5)	88/328 (26.8)	125/343 (36.4)	<0.0001
Renal impairment	1/80 (1.3)	2/216 (0.9)	42/341 (12.3)	64/362 (17.7)	<0.0001
Carotid artery disease	2/80 (2.5)	10/216 (4.6)	84/339 (24.8)	142/350 (40.1)	<0.0001
CHF	10/80 (12.5)	28/216 (13.0)	76/341 (22.3)	102/360 (28.3)	<0.0001
Previous CABG	1/80 (1.3)	10/216 (4.6)	39/345 (11.3)	31/356 (8.7)	0.004
Digitalis use	25/63 (39.7)	40/173 (23.1)	54/322 (16.8)	33/349 (9.4)	<0.0001

Values in parentheses are percentages.
CABG: Coronary artery bypass grafting; CHF: Congestive heart failure; COPD: Chronic obstructive pulmonary disease.

Table II: Changes in occurrence of hospital complications between 1986 and 2006.

Complication	Time interval				p-value
	1986-1991 (n = 80)	1992-1996 (n = 216)	1997-2001 (n = 345)	2002-2006 (n = 365)	
Non-cardiac	19 (23.8)	39 (18.0)	112 (32.5)	110 (30.0)	0.001
Mortality	6 (7.5)	6 (2.8)	12 (3.5)	13 (3.6)	0.279
AF	32 (40.0)	71 (32.9)	132 (38.3)	146 (40.0)	0.365
VA	2 (2.5)	10 (4.6)	11 (3.2)	14 (3.8)	0.781
Bleeding	2 (2.5)	3 (1.4)	8 (2.3)	7 (1.9)	0.861
CHF	2 (2.5)	7 (3.2)	13 (3.8)	12 (3.3)	0.946
TE	2 (2.5)	5 (2.3)	10 (2.9)	10 (2.7)	0.979

Values in parentheses are percentages.
AF: Atrial fibrillation; CHF: Congestive heart failure; TE: Thromboembolism; VA: Ventricular arrhythmia.

varied between 59.6 ± 14.7% and 63.5 ± 16.8% (p >0.10). Other preoperative cardiac co-morbidity (presence of coronary artery disease, p = 0.56; conduction defects, p = 0.31; pacemaker implantation, p = 0.46; AF, p = 0.09, ventricular arrhythmia, p = 0.70; previously implanted aortic valve, p = 0.29 or endocarditis, p = 0.91) also had not increased significantly. Among the valvular factors, only the presence of valve regurgitation was decreased (p = 0.0001). Although the use of digitalis had decreased significantly, it was still used more frequently in patients with AF (76/103 versus 75/652; p <0.0001).

Among all hospital complications, only non-cardiac complications had increased during the 20-year time span (see Table II); these included surgical (n = 140), pulmonary (n = 57), renal (n = 53) and other (n = 60) problems. Although these complications were less fatal (mortality of 20/280; 7.1%), they occurred much more frequently than cardiac complications. A single cause was identified among four patients with fatal non-cardiac hospital complications, while two or more complications were identified in the remaining 16 patients. Pulmonary complications were fatal in 10 patients; on seven occasions in combination with other factors, and on three occasions as the sole event. Postoperative impairment of renal failure was fatal in eight patients, but always in combination with other complications.

The incidence of cardiac hospital complications had not increased during the 20-year period. Among patients, 37 had ventricular arrhythmias (five mortalities; 13.5%), 27 had thromboembolism (four mortalities; 14.8%), 20 had bleeding (five mortalities; 25.0%), and 34 had CHF (13 mortalities; 38.2%). The total hospital mortality over the 20-year span was 3.7%. None of the 22 patients who underwent concomitant carotid artery surgery suffered from a stroke during their hospital stay.

As the occurrence of non-cardiac complications had increased over the 20-year period, these were subjected to further analysis. Those factors which had a significant effect on these complications in univariate and multivariate analyses are listed in Table III. Previous and concomitant surgery, as well as non-cardiac co-morbidity played an important role. A more detailed analysis of the separate categories of non-cardiac complications showed that postoperative renal impairment, preoperative decrease in renal function (23/109, p <0.0001), concomitant carotid artery surgery (5/22, p = 0.001), previous CABG (9/81, p = 0.011) and concomitant CABG (39/610, p = 0.047) each had an effect. Among postoperative pulmonary complications, only preoperative chronic obstructive pulmonary disease (COPD) had any effect (21/235, p = 0.010). Among surgical problems, a previously performed CABG also had an adverse effect (17/81, p = 0.044). For the remaining in-hospital problems, urinary tract infection, fever of unknown origin and temporary disorientation, preoperative decrease of renal function (13/109, p = 0.006) and concomitant CABG (44/610, p = 0.037) had adverse effects.

Those factors without effect on hospital non-cardiac complications are listed in Table IV, where the denominator indicates numbers of patients with a factor, and the numerator the patient fraction with the complication.

Follow up

Long-term follow up for the first 500 patients yielded a total of 2,202 patient-years. In total, 481 patients left hospital alive. During follow up, one or more non-cardiac events occurred in 200 patients, and only two preoperative factors had any significant effect on the occurrence of long-term non-cardiac events (i.e. previously treated tumor, and re-replacement of the aortic valve). Among 53 patients with a previously treated

Table III: Predictors for non-cardiac hospital complications.

Predictor	No. of patients	p-value (univariate)	p-value (multivariate)	Odds ratio	95% CI
Previous CABG	34/81	0.016	0.004	2.1	(1.3-3.5)
Concomitant CABG	191/610	0.009	0.006	1.5	(1.1-2.1)
Renal impairment	48/109	0.001	0.008	1.9	(1.2-3.0)
Conduction defect	98/270	0.002	0.010	1.5	(1.1-2.1)
Pacemaker implant	17/33	0.028	0.014	2.6	(1.2-5.7)
COPD	84/235	0.008	0.015	1.5	(1.1-2.1)
Carotid artery surgery	12/22	0.043	0.032	2.6	(1.1-6.4)
Previous AVR	9/23	0.001	NS		
CAD	197/622	0.004	NS		
Age >80 years	68/186	0.018	NS		
AF	70/197	0.025	NS		

AF: Atrial fibrillation; CABG: Coronary artery bypass grafting; CAD: Coronary artery disease; CHF: Congestive heart failure; COPD: Chronic obstructive pulmonary disease; NS: Not significant.

tumor, 28 had a non-cardiac event (p = 0.045) of which 17 were fatal, due mostly to metastases. Among 15 patients with a reoperation of the aortic valve, 12 had a non-cardiac event (p = 0.003) of which nine were fatal, for a variety of reasons.

Postoperative fatal progression of preoperative renal and pulmonary disease was rare: renal failure was observed in only six of the 481 patients (two due to sepsis, two due to dehydration), and fatal exacerbation of COPD was recorded in only four patients.

Table IV: Factors without an effect on non-cardiac hospital complications.

Preoperative factor	No. of patients	p-value
Carotid artery disease	77/238	0.11
Myocardial infarction	53/151	0.16
Diabetes	51/149	0.19
Pulmonary edema	70/216	0.32
Cross-clamp time > 75 min	30/88	0.49
PTCA	15/41	0.58
Male gender	152/530	0.63
Carcinoma	33/104	0.68
Aortic valve regurgitation	32/123	0.74
Use of digitalis	48/152	0.76
Cerebrovascular accident	28/108	0.78
Ventricular arrhythmia	20/74	0.84
Procedure on ascending aorta	16/61	0.91
Hypertension	180/654	0.91
Ejection fraction <50%	41/155	0.95
Endocarditis	5/17	0.98
Procedure on mitral ring	4/13	0.98
Need for urgent surgery	7/25	0.98

PTCA: Percutaneous transluminal coronary angiography.

Discussion

Among the present patient series, no increase in valve-related and other cardiac hospital complications, including highly lethal heart failure (7-10), were recorded during the 20-year period between 1986 and 2006. Non-cardiac hospital complications were the only events with a documented increase, and these therefore formed the main focus of the present investigation. Such problems had a relative low mortality (20/280; 7.1%), thereby confirming an older report which stated that "…associated arterial and extra-cardiac pathology does not significantly increase the mortality." (11).

Although the mean age of patients undergoing AVR has increased during the past 20 years, this was more evident from the increase in the percentage of patients aged over 80 than from the increase in median age, which was already over 70 years at the start of the study. The present patient population was relatively old, but comparable to that in some older series (7,9). In other patient series in which a pericardial valve was implanted, the mean age was considerably younger and below 70 years (8). In a large series which also included mechanical devices, the mean age was even lower, though this was related to the recommendation of using bioprostheses in patients aged over 70 years (12). In addition, some surgeons leave the choice of prosthesis to the patients, even if their age is above 80 years (13).

The preoperative non-cardiac co-morbidity was also found to increase with time: significantly more patients with diabetes, carotid artery disease and decreased renal and pulmonary function were operated on in the present series. The nature of the preoperative risk factor may differ in some series of elderly patients, with a higher rate of renal dysfunction and lower rate of pulmonary dysfunction (3). Taken togeth-

er, however, the incidence of preoperative co-morbidity remains high in most series (>50%), especially in the elderly (11). This is most likely the reason why postoperative non-cardiac complications in the present series had increased (from 18.0-23.8% during the first 10 years to 30.0-32.5% in the latter 10 years): a decreased preoperative organ function reserve in aged patients may be held responsible for the decreased physiological margin, and this may push such patients more easily into complications. This effect was clear among those present patients with preoperative impaired renal function and COPD.

The increase in mean age is probably the reason why the number of preoperative CABGs had also increased. Coronary artery disease is more prevalent among the elderly, and there is also an association with aortic valve degeneration. Both factors make it more likely that a second - and even a third - heart operation becomes necessary. These patients experience more pain, which can hamper respiratory rehabilitation and hence cause more pulmonary problems. The complication rate in the elderly may rise to 82%, with a high hospital mortality (14). In the present series, a two-fold increase in non-cardiac hospital complications was observed among patients with a previously performed CABG. The reason for this may be the embolization of loose atheromatous material during the manipulation of old venous grafts. In spite of a high age, increased co-morbidity and previously performed CABG in the present patients, the mortality of 3.7% was rather low compared to that in other series, which reported values of between 5.4% and 15% (3,5,7,9,10,12,15-17). Among the present patients, hospital mortality remained constant over time.

A concomitant CABG was performed in 61% of the present patients, which was a much higher proportion than in other series that cited values of between 20 and 40% (7-10,15). In elderly patients, although coronary artery disease is more likely to develop, the risk for early mortality when adding a CABG to AVR is low (18). In the present series, concomitant CABG led to a 1.5-fold increase in non-cardiac complications. Debate persists regarding the benefit of adding CABG to AVR in patients with aortic valve and coronary artery disease; however, concomitant CABG seems not to be a predictor of poor outcome, and the treatment of even moderate stenosis of a left anterior descending artery is beneficial (19).

The role of an implanted pacemaker for non-cardiac complications seemed limited. Previously, pacemaker implantation has been identified as a predictor for early postoperative death (20), but not among the present patients, where only three fatalities occurred among 33 patients with a previously inserted pacemaker, and two of these deaths were pulmonary in nature.

An increase was found in preoperative episodes of CHF in the present patients, although this may have been related to their increased age, as well as to a tendency for delayed referral, especially among older patients (4). Remarkably, the use of digitalis had fallen during the same time span. During the study period, angiotensin-converting enzyme inhibitors and angiotensin receptor-blocking agents had become available, and these are effective in reducing the symptoms of CHF and prolonging life. The latter effect might add to the number of aortic valve patients with heart failure, referred for AVR. Although the use of digitalis has been reduced, it is still used in many patients with AF.

Carotid artery surgery was performed simultaneously with AVR in 22 patients of the current series. This combination is considered safe (21) and, in a previous report, no increase in postoperative stroke was documented (22). To date, no report has been made on the effect of carotid artery surgery on non-cardiac hospital complications, which seem to be of lesser importance than stroke within the hospital, as the latter is more lethal and, in the case of survival, more debilitating. It must also be taken into account that surgery of the carotid artery leads to a 2.6-fold increase in non-cardiac complications (for previous and concomitant CABG, this factor is 2.1- and 1.5-fold). These complications are, for the large part, renal in nature. It is most likely that the presence of coronary and carotid artery disease are indicators of a more widespread presence of atheromatosis. This can result in a susceptibility to any postoperative impairment of renal function in case of renal artery involvement. The use of preoperative duplex-Doppler is crucial for selecting the correct operative procedure.

In previous reports made by the present authors, which included the first 500 patients of the current series, risk factors for long-term mortality were a need for urgent AVR, age over 80 years, preoperative myocardial infarction, previously treated carcinoma, and a preoperative need for digitalis (4). For long-term thromboembolism, the risk factors were preoperative CVA, hospital thromboembolism, and hypertension (22). For long-term CHF, the factors were preoperative conduction defects, chronic postoperative AF, and coronary artery disease (23). Among the first 500 patients of the current series, only two factors have had any effect on the occurrence of long-term non-cardiac events. Although patients with a previously treated carcinoma suffer more from metastasis, this is to be expected when the time interval between treatment of the malignancy and heart surgery is less than five years (24).

Patients who undergo reoperation of the aortic valve also have a greater risk for the occurrence of non-cardiac disease, although there are no specific patterns of postoperative events. For the other risk factors, no increase in non-cardiac disease was found, and the fatal progression of renal failure or COPD was rare.

In conclusion, among the present patient group no increase was identified in early mortality after AVR, in spite of increasing age and co-morbidity. However, an increase was found in non-cardiac hospital complications, which were less fatal. Although the risk for AVR in the elderly is considered higher, the outcome remains favorable. Its seems that age and co-morbidity are less important than the severity of heart disease when determining the risk profile in those patients eligible for AVR. The severity of the heart disease is influenced by the duration of the valve disease. The postponement of AVR to a point where a need develops for urgent surgery carries a high risk for mortality, and is much more important than age and preoperative co-morbidity.

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