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Predictors of long-term survival after valve replacement for chronic aortic regurgitation

Is M-mode echocardiography sufficient?

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Aims The clinical importance of pre-operative and follow-up echocardiographic studies in patients operated on for chronic severe aortic valve regurgitation is still a matter of debate. The prognostic significance of M-mode echocardiography has never been directly compared with clinical and angiographic data.

Methods and Results Univariate and multivariate analyses of cumulative survival were performed for clinical, echocardiographic and angiographic data of 125 patients operated on between 1975 and 1983, and followed for 13·3 ± 6·4 years. Ten and 20 year survival rates were 77% and 48%, respectively. Age, NYHA class, angiographic volumes, ejection fraction, as well as M-mode echocardiographic end-systolic dimension and shortening fraction were the main pre-operative prognostic parameters for long-term survival. In a multivariate analysis the angiographic end-systolic volume index, age and pre-operative NYHA class were independent pre-operative prognostic variables of long-term survival. A postoperative reduction in end-diastolic dimension of >20% predicted a significantly better late survival (74% vs 44% after 20 years, $P<0{\cdot}001$).

Conclusions Age, pre-operative NYHA class and left ventricular systolic function are the main determinants of long-term survival after valve replacement for chronic aortic regurgitation. Despite a slightly lower predictive value of echocardiography when compared to angiography, it appeared sufficient for everyday clinical decision making for valve replacement. Echocardiography within 6 months postoperatively is able to detect recovery of left ventricular function, and enables additional risk-stratification, regardless of pre-operative findings.
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Key Words: Aortic regurgitaton, echocardiography, prognosis, valves, valve replacement, angiography.

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Introduction

Chronic aortic regurgitation is a slowly progressive disease with a long asymptomatic period and rapid deterioration when symptoms develop[1–6]. It is generally accepted that valve replacement is mandatory in symptomatic patients with severe chronic aortic regurgitation[5]. Despite some controversies, there is a general consensus that valve replacement for chronic severe aortic regurgitation should be performed even in asymptomatic or mildly symptomatic patients before a considerable decrease in systolic function and severe enlargement of the left ventricle ensue[5,7,8]. The surgical results are poor when valve replacement is postponed until symptoms are severe or myocardial dysfunction is marked[9–12]. The best predictive parameter for postoperative outcome is still a matter of debate. However, the influence of pre-operative parameters on the true 'long-term' prognosis is scarcely known because most reports are based on relatively short follow-up (<5 years)[10,11,13–17]. During the last 20 years, beside symptoms and quantitative angiography, the prognostic value of echocardiography has been of particular interest because this non-invasive method is an ideal clinical tool for diagnosis and monitoring of chronic aortic regurgitation.

Surprisingly, the predictive value of echocardiography and the 'standard' invasive method of quantitative angiography have never been properly compared. In this study, we compared the predictive value of

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Table 1 Baseline characteristics of the study population (n=125)

Variable	Means ± SD	Range
Age (years)	44·3 ± 13	18–73
Gender (male/female)	109/16	
Heart rate (beats . min^{-1})	74·1 ± 16·6	45–142
NYHA class	2·26 ± 0·75	
I/II/III/IV	17/65/37/6	
Sinus rhythm	92%	
CI (l . min^{-1} . m^2)	3·09 ± 0·72	1·7–5
EDP (mmHg)	18·9 ± 10·9	5–65
LV angiography		
EDVI (ml . m^2)	217·28 ± 67·02	114–503
ESVI (ml . m^2)	101·8 ± 51·2	25–354
EF (%)	54·8 ± 10·6	30–78
AR (%)	60·2 ± 13·1	45–84
LV echocardiography		
EDD (cm)	7·86 ± 1·02	5·5–10·5
EDVI (ml . m^2)	187 ± 54	77–355
ESD (cm)	5·43 ± 1·02	3·19–7·74
ESVI (ml . m^2)	82 ± 37	27–183
Sh (%)	31·12 ± 8·17	12–51
PWT (cm)	1·1 ± 0·2	0·8–1·6
EDD/2*PWT index	3·52 ± 0·73	1·8–6·6

CI=cardiac index; EDP=end-diastolic pressure; LV=left ventricle; EDVI=end-diastolic volume index; ESVI=end-systolic volume index; EF=ejection fraction; AR=aortic regurgitant fraction; EDD=end-diastolic diameter; ESD=end-systolic diameter; Sh=shortening fraction; PWT=posterior wall thickness; SD=standard deviation.

pre-operative M-mode echocardiography and quantitative left ventricular angiography for long-term outcome after valve replacement for chronic aortic regurgitation. Besides pre-operative echocardiography, the prognostic value of early postoperative echocardiography was also evaluated.

Patients and Methods

We studied 125 patients who underwent aortic valve replacement for chronic aortic regurgitation between 1975 and 1983. All patients underwent pre-operative clinical assessment, cardiac catheterization, quantitative left ventricular angiography, and M-mode echocardiography. The patient population represents 90% (125/139) of all available patients at our institution. Patients with acute endocarditis, coronary artery disease, more than a trivial aortic stenosis (aortic valve opening area <1·5 cm^2) or mitral valve disease were excluded. Patients reported here were part of a larger study about predictive parameters of survival after extended follow-up after valve replacement in chronic aortic regurgitation[18]. The main characteristics of the patients are presented in Table 1. The age of the patients at the time of operation ranged from 18 to 73 years (mean 44 ± 13 years), 109 (87%) were male and 16 female. Symptoms and functional impairment, according to the New York Heart Association (NYHA), were assessed at the time of operation regardless of previous symptoms or history. Mean NYHA class was 2·3 ± 0·8: 14% of patients were in class I, 52% in class II and 30% in class III.

Cardiac catheterization and angiography

All patients underwent right and left heart catheterization and cineangiography. Coronary arteriography was performed in all patients older than 45 years or in the presence of angina pectoris. The angiographic left ventricular end-diastolic volume index, end-systolic volume index and left ventricular ejection fraction were calculated by the area–length method from monoplane and, since the end of 1976 from biplane cineangiograms. The severity of valve regurgitation was estimated by angiography.

Echocardiography

Echocardiographic recordings were obtained by a 2·2 MHz single beam transducer (Cardiovisor, Organon Teknika), with simultaneous recording of the ECG and phonocardiogram. All recordings and measurements were performed by two experienced physicians (R.J. and J.T.). Only high quality echocardiography tracings were accepted. The end-diastolic dimension was measured at the peak of the R-wave in the ECG, and the end-systolic dimension at the beginning of the second sound on the phonocardiogram. The majority of the patients (n=85) also underwent early postoperative (3–6 months after valve replacement), and a minority (n=35) late postoperative (mean 3·3 years, range 1–10 years) echocardiography at our institution. These 85 patients are representative of the entire collective with respect to pre-operative characteristics and postoperative survival (10 years survival 81% vs 78% in patients who survived the first 6 months but did not have postoperative echocardiography). The postoperative changes of the left ventricular end-systolic dimension and end-diastolic dimension, respectively, are expressed as a percentage of the pre-operative value. The echocardiographic left ventricular volume was calculated using the Teichholz formula ($volume=(7.0/(2.4+D)) \times D^3$; D means echocardiographic left ventricular dimension) and corrected for the body surface area[19]. Correlation between echocardiographic and angiographic left ventricular volumes was relatively good, especially for only moderately increased volumes (correlation coefficient r=0·67, Fig. 1). Correlation was less than optimal in patients with very large ventricles, mainly due to considerable under-estimation of the left ventricular volume by echocardiography in some patients (Fig. 1).

Surgical procedures

Different mechanical (n=78, 62%) and biological (n=47, 38%) prostheses were used. The Björk–Shiley valve

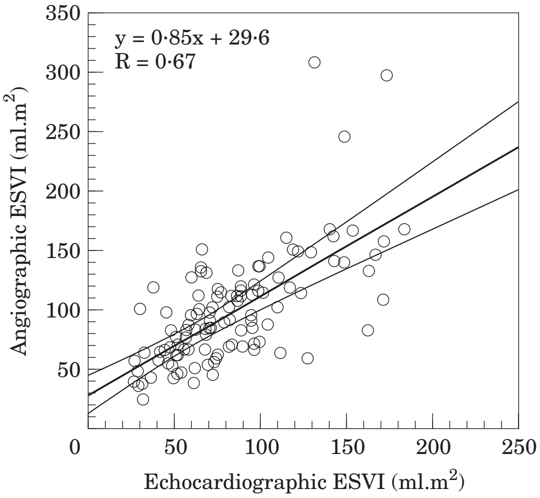

Figure 1 **Correlation of angiographic and echocardiographic volume. The echocardiographic volume was calculated using the Teichholz formula corrected for body surface area. ESVI=end-systolic volume index.**

(n=72, 58%) was the most frequently implanted mechanical prosthesis and the Carpentier–Edwards (n=35, 28%) was the most frequently implanted bioprosthesis. In 22 cases, additional surgical procedures were necessary because of aneurysmatic dilatation of the ascending aorta. Different types of intra-operative myocardial protection were used between 1975 and 1978; after 1978 hypothermic potassium cardioplegia and pericardial irrigation became the standard method of myocardial protection[18].

Follow-up

After surgery, all patients were seen at least once in our outpatient clinic. Additional information was obtained with standardized questionnaires mailed to patients and their physicians. Causes of death and cardiac complications were obtained from medical reports, death certificates, and telephone contact with physicians. These data were classified according to recommended guidelines[20]. All deaths related to heart failure, rhythm disturbancies, reoperations, prosthesis and prosthesis-related treatment as well as all sudden and otherwise unexplained deaths were classified as cardiac. The mean follow-up was 13·3 ± 6·4 years (1662 patients-years), 17·4 years in surviving and 8·3 in deceased patients. Follow-up was incomplete in eight patients lost 28–172 months (mean 105) after valve replacement.

Statistical analysis

Statistical evaluations and all calculations were performed with StatView 4.5 software (Abacus Concepts, Inc). Continuous data are presented with 1 standard deviation (± SD). Survival was calculated according to the Kaplan–Meier method, the survival curves were compared with the log rank test (Mantel–Cox), $P<0{\cdot}05$ was considered as statistically significant. Patients who underwent reoperation during follow-up were retained in the statistical calculation. Univariate analysis of general and cardiac survival was performed separately for each pre-operative clinical, angiographic and echocardiographic parameter. Multivariate analysis was applied stepwise using the Cox proportional hazard model to all significant parameters in the univariate analysis. The relationship between angiographic and echocardiographic volumetric data was evaluated by correlation analysis and presented as the linear correlation. The pre-operative and postoperative echocardiographic values were compared by Student's t-test for paired samples.

Results

Survival

Operative mortality (<30 days after surgery) was 3·9% (5/125). During follow-up 49 patients died, operative death included. Thirty six patients (73%) died of cardiac causes; heart failure (n=14) and sudden death (n=9) were the most frequent causes of cardiac death. Other cardiac deaths included stroke (n=5), endocarditis (n=2), arrhythmias (n=2), aortic dissection (n=2), coronary artery disease (n=1), and reoperation (n=1). Cumulative general and cardiac survival is shown in Fig. 2. Survival rate at 5, 10, 15 and 20 years was 88%, 77%, 65%, 48%, respectively. The mortality rate remained almost stationary during the entire follow-up (2·5%/pat-year). During follow-up, 38 patients underwent reoperation, mainly (68%) due to the degeneration of bioprostheses. At the end of follow-up, 80% of the surviving patients were in NYHA classes I or II.

Pre-operative survival parameters

The prognostic significance of different clinical, angiographic and echocardiographic pre-operative parameters on long-term survival is summarized in Table 2. Univariate analysis was performed separately for general and cardiac survival. Older age at operation, higher NYHA class, higher angiographic end-systolic volume index and end-diastolic volume index, lower ejection fraction, higher echocardiographic end-systolic dimension and end-systolic volume index and in part lower shortening fraction (%Sh) and end-diastolic dimension/2*PWT (PWT: posterior wall thickness) were negative predictors of long-term survival in the univariate analysis. The results of the analysis for general and cardiac survival were very similar. Predictive value of all angiographic and echocardiographic parameters was higher when the data were analysed as continues than as nominal values (Table 2). In a multivariate stepwise

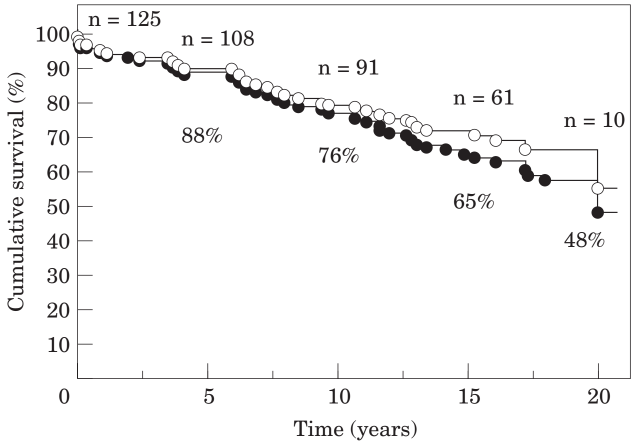

Figure 2 **Cumulative general and cardiac survival. The number of patients under study and survival rates at 5, 10, 15 and 20 years are indicated. ○=cardiac survival; ●=general survival.**

analysis age, pre-operative NYHA class and angiographic end-systolic volume index were independent predictive parameters for long-term cardiac survival (Table 3).

Early postoperative echocardiography

The course of left ventricular dimension assessed by echocardiography is shown in Fig. 3. The echocardiographic pre-operative end-diastolic dimension decreased significantly in the early postoperative (3 to 6 months) follow-up (7·8 ± 1·0 to 6·1 ± 1·0 cm, P<0·0001) and did not change significantly later on (6·1 ± 1·0 to 6·1 ± 1·4 cm, ns). Similarly, the echocardiographic-end-systolic dimension decreased early postoperation (5·4 ± 1·0 to 4·3 ± 1·2 cm, P<0·0001) and remained unchanged during the late follow-up (4·3 ± 1·2 to 4·2 ± 1·5 cm, ns). Surviving patients had a progressive decrease in left ventricular dimensions during follow-up: 25% and 42% at <6 months and 3·3 years, respectively. The reduction in postoperative cardiac dimensions was smaller in those patients who died from cardiac causes compared to surviving patients (16·6% vs 23·7%, P<0·05). The posterior wall thickness (1·1 ± 0·2 cm) and

Table 2 ***Univariate analysis of prognostic parameters for general and cardiac survival***

	General survival		Cardiac survival	
	Pre-op	Early post-op	Pre-op	Early post-op
NYHA class	0·004		0·01	
I/II vs III/IV	0·001		0·01	
Angiography				
EDVI	0·003		0·01	
<200 vs >200 ml . m^2	0·004		0·004	
ESVI	0·0002		0·001	
<120 vs >120 ml . m^2	0·01		0·004	
EF	0·02		0·007	
≥55 vs <55%	0·07		0·01	
Echocardiography				
EDD	0·2	0·01	0·01	0·002
<75 vs ≥75 mm	0·3	0·02	0·02	0·03
ESD	0·03	0·001	0·01	0·0003
<55 vs ≥55 mm	0·09	0·02	0·07	0·04
Sh (%)	0·06	0·007	0·04	0·01
≤25 vs >25%	0·01	0·03	0·02	0·02
EDVI	0·1	0·03	0·1	0·001
ESVI	0·04	0·003	0·03	0·002

EDVI=end-diastolic volume index; ESVI=end-systolic volume index; EF=ejection fraction; EDD=end-diastolic diameter; ESD=end-systolic diameter; Sh %=shortening fraction.

Table 3 Independent predictors of cardiac survival on long-term follow-up in multivariate, stepwise analysis

Parameter	*P*	Exp (Coef)
Age	<0·0001	1·054
NYHA	0·05	1·226
ESVI	0·0008	1·01

Exp (Coef)=exponential coefficient; ESVI=end-systolic volume index.

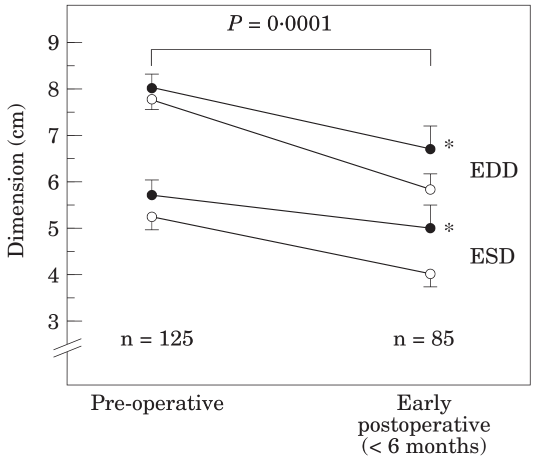

Figure 3 **The course of echocardiographic systolic (ESD) and diastolic dimension (EDD) from pre-operative to early postoperative (<6 months). ○=surviving patients; ●=cardiovascular deaths. Mean values and 1 standard deviation (SD) are shown, statistical significance is indicated for all groups of data; *=significant difference between cardiac death and surviving patients (*P*<0·0001).**

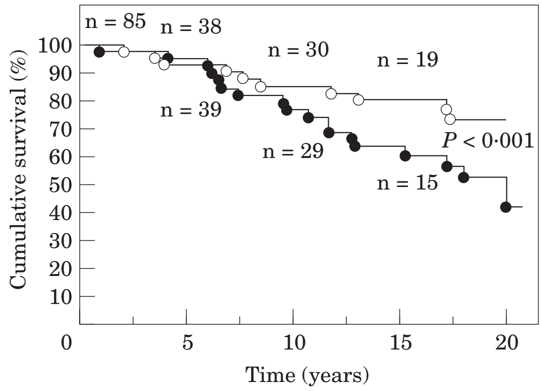

Figure 4 **Cumulative survival of 85 patients with postoperative echocardiographic examination. Patients are divided according to the reduction of the postoperative end-diastolic dimension (EDD) in relation to the preoperative value. ○=early postoperative reduction of EDD >20%; ●=the reduction of EDD <20%. Significance for trend was evaluated by log rank test in Mantel–Cox analysis.**

%Sh (31 ± 9%) did not significantly change during the follow-up.

Patients whose left ventricular diastolic and systolic dimensions were reduced early postoperation had a better long-term survival. In the univariate analysis of early postoperative echocardiographic left ventricular parameters for long-term survival (Table 2) higher end-systolic dimension, end-systolic volume index, end-diastolic dimension and lower %Sh were statistically significantly related to a less successful late survival. Early postoperative echocardiographic findings (3 to 6 months after valve replacement) had a significantly higher prognostic influence on long-term outcome than pre-operative echocardiographic data. The highest prognostic significance was end-systolic volume index, end-diastolic volume index and end-systolic dimension (Table 2). Patients with an early postoperative reduction of the end-diastolic dimension >20% have a significantly better cardiac and general survival (at 20 years: 74% vs 44% in those with a reduction <20%, P<0·001 for trend) (Figs 4 and 5). During the later follow-up, death due to heart failure and sudden death were registered mainly in patients with an early postoperative reduction of end-diastolic dimension <20%.

Discussion

In severe chronic aortic regurgitation, symptoms and left ventricular systolic function are the main predictors of early and late outcome after valve replacement[11–14,21]. Today, very low operative mortality and good long-term survival make valve replacement for severe aortic regurgitation mandatory even in mildly symptomatic or asymptomatic patients before left ventricular systolic function decreases and systolic dimensions are greatly enlarged[5,8,18,22]. Quantitative left ventricular angiography and echocardiography are standard, generally accepted methods for assessment of left ventricular function in chronic aortic regurgitation and of utmost importance for optimal timing of valve replacement[22]. Interestingly, despite more than 25 years experience with echocardiography and angiography, the predictive value of both methods for outcome after valve replacement in aortic regurgitation has not been directly compared.

In our study, we compared the predictive value of pre-operative echocardiographic and angiographic data for extended outcome after aortic valve replacement in chronic aortic regurgitation. Low operative mortality and good long-term survival in the study compared favourably with published reports[1,23–25]. Heart failure and sudden death were the main causes of postoperative death even at prolonged follow-up. Data presented here are representative of the experience in our institution on valve replacement for chronic aortic regurgitation in the late 1970s and early 1980s[18]. More than 90% of all consecutive patients with aortic regurgitation, who underwent valve replacement during that period, were included and neither the outcome nor the predictive value of different pre-operative clinical, haemodynamic or angiographic parameters in this study differed essentially from the entire group of patients[18]. Availability of high quality echocardiograms, conducted

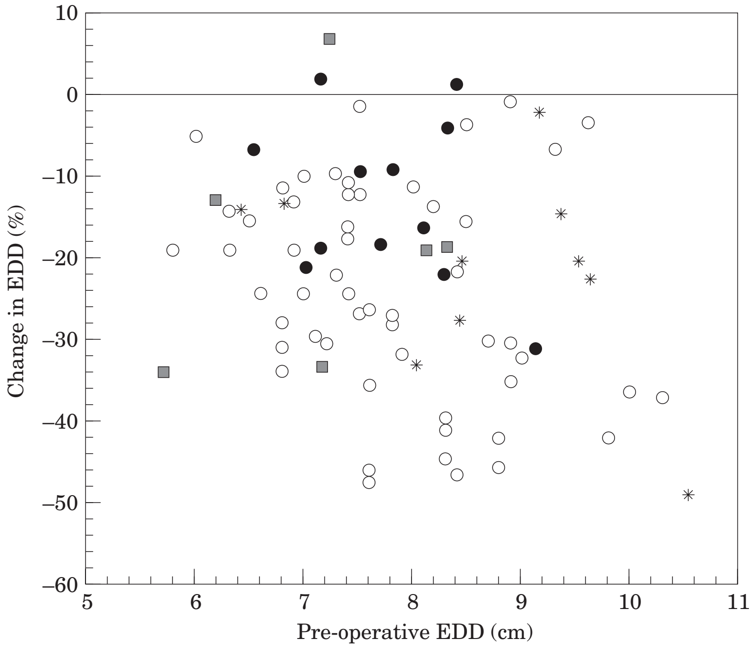

Figure 5 **Changes in end-diastolic dimension (EDD) are represented as a function of the pre-operative EDD value. ○ = surviving patients; ● = patients who died during the follow-up (sudden cardiac death or heart failure); * = other cardiovascular death: arrhythmia, endocarditis, reoperation, stroke, myocardial infarction; □ = non-cardiac death.**

in a prospective manner, was the only criterion for inclusion of the patients in the study.

Study limitations

Some caution is necessary in the interpretation of cine-angiographic studies and in particular echocardiograms performed 20 years earlier. Quantitative angiography was performed by the area length method, mostly from biplane left ventricular angiograms, which even today are considered to be the gold standard for volumetric calculations. Hence, these data must be considered as representative. In the 1970s and early 1980s only M-mode echocardiography was available. Hence, only the short axis of the left ventricle could be obtained for volumetric calculations. Measurements of left ventricular dimensions with M-mode were less than optimal when compared to 2D-echocardiography supported measurements used today, but still satisfactory. The correlation of our non-simultaneously performed angiographic and echocardiographic volumetric data is fair but, as expected, the variation is considerable in patients with very large left ventricles[26]. Different formulas for the calculation of M-mode echocardiographic volume have never been validated in chronic aortic regurgitation where the enlargement of the ventricle is more ellipsoid than spherical. As shown in this study, the Teichholz formula achieves an acceptable correlation between echocardiography and angiography in moderately enlarged left ventricles, but considerable under-estimation of the volume with echocardiography, however, is seen in some patients with very large ventricles. The calculation of left ventricular volumes from M-mode data is not necessary because these do not improve the predictive value of echocardiography and are today obsolete.

Prognostic value of pre-operative echocardiography and angiography

The systolic volume or dimension, respectively, and systolic function expressed as ejection fraction and shortening of left ventricular dimensions had, beside age and symptoms, the highest singular predictive value of different angiographic and echocardiographic parameters. This confirms many previous reports based on much shorter postoperative follow-up[8,10–13,15,21,23,27–29]. The angiographic and echocardiographic systolic volumes and dimensions are better predictors of postoperative outcome than those obtained at diastole[12,18,21]. For daily clinical practice, M-mode echocardiographic dimensions seem to be sufficient for determination of left ventricular function. Indeed, more sophisticated volume calculations do not increase the predictive value of echocardiography. In the univariate analysis, angiographic parameters had higher predictive value than M-mode echocardiographic parameters and that is why in multivariate stepwise analysis angiographic parameters override those of echocardiography.

The prognostic importance of pre-operative left ventricular function for postoperative survival became really evident and increased continuously with extension of follow-up. Some controversies concerning the prognostic value of pre-operative echocardiography can be resolved by this long-term follow-up. In patients with severely enlarged left ventricular dimensions and decreased function, an insufficient reduction in size and an insufficient increase in function was uniformly seen by all authors[22]. A reduced survival of patients with pre-operative severely enlarged left ventricles was found only in studies with a relatively high operative and early postoperative mortality[10,11,22]. Today, improved surgical techniques and intra- and peri-operative management of these patients allow excellent survival without excess early mortality, even in patients with pre-operatively severely impaired myocardial function[1,17,23,30,31]. In our study, patients who survived the operation but did not achieve a sufficient improvement of myocardial function remained exposed to a high risk of cardiac death and their long-term prognosis was less favourable. Cardiac death remains the main cause of attrition even 20 years after valve replacement; the proportion of patients dying of non-cardiac or strictly prosthesis-related causes was relatively low.

Prognostic value of early postoperative echocardiography

Early postoperative echocardiography was an important predictor of late outcome, which enabled further prognostic differentiation of the patients. Within the first weeks and months of valve replacement, considerable reduction of left ventricular size and improvement of myocardial function ensue[15,32,33]. Later on, only minor changes in myocardial function occur. A marked decrease of left ventricular diastolic dimensions (>20% of pre-operative value) was associated with a significantly better long-term survival, even in patients with pre-operative severely enlarged ventricles. Elimination of volume overload by valve replacement leads to considerable improvement of systolic function in chronic aortic regurgitation in a great majority of patients[15,16,27,32]. Rearrangement of myofibrils without intrinsic myocyte damage occurs in enlarged but otherwise 'normal' left ventricles without contractility deficit under severe chronic volume overload[34]. As our data demonstrate, especially in patients with insufficient early postoperative reduction of left ventricular size, heart failure or sudden death occurred late after valve replacement. Sufficient contractile function can be maintained over years even in patients with severely reduced myocardial function, and that is why only after very long follow-up can statistically significant differences in survival patterns be demonstrated. Echocardiography within 6 months of operation is able to detect recovery of left ventricular function, thus enabling additional risk-stratification of patients, regardless of pre-operative findings. Whether treatment with ACE inhibitors early after valve replacement can improve late outcome is unknown, although pre-operatively a 15–20% reduction of left ventricular dimensions has been described after 12 months therapy with quinapril[35]. None of our patients was treated with ACE inhibitors early postoperatively because these drugs were not available in the 1970s and early 1980s. At the end of the study, in the late 1990s, only 22% of our patients were on ACE inhibitors.

Summary and prospects for future handling

Pre-operative systolic left ventricular function, as assessed by left ventricular angiography and/or echocardiography is, besides age and symptoms, a major prognostic factor of late outcome after valve replacement in chronic aortic regurgitation. The prognostic value of pre-operative quantitative, biplane left ventricular angiography is superior to M-mode echocardiography. However, this disadvantage of echocardiography is more than offset by its non-invasive nature and the possibility of repeated monitoring of myocardial function. The good prognostic value of early postoperative changes in left ventricular dimensions considerably increases the clinical importance of echocardiographic monitoring in these patients. Thus, in severe chronic aortic regurgitation, serial monitoring of left ventricular dimensions and function is mandatory before and after valve replacement. Increasing systolic dimensions and decreasing contractility herald an impaired spontaneous course and should initiate aortic valve replacement. In uncomplicated cases, echocardiography gives sufficient information for operative decision making and quantitative left ventricular angiography is not needed. Within 6 months of valve replacement left ventricular dimensions become smaller in most patients. Persistence of severely increased left ventricular size is associated with impaired late postoperative survival. Future trials will have to show whether intensive medical treatment (i.e. ACE inhibitors) can improve long-term survival in patients who are at high risk. Other possible treatment options in patients with an unfavourable course are heart transplantation (when heart failure occurs) or ICD application (when severe rhythm problems arise).

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