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Left ventricular systolic and diastolic function in aortic stenosis

Prognostic value after valve replacement and underlying mechanisms

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Aims The aims of the study were to examine the prognostic value of pre-operative left ventricular systolic and diastolic function on early, and late mortality after valve replacement for aortic stenosis, and to identify possible underlying mechanisms.

Methods and Results Ninety-one prospectively recruited consecutive patients with a mean age of 61 years underwent valve replacement for aortic stenosis with concomitant coronary artery bypass grafting in 32 and a minimum postoperative observation period of 5·4 years. There were six early (≤30 days postoperatively) and 19 late deaths, and 18 deaths from specific causes (cardiac and prosthetic valve related). Early mortality occurred exclusively among patients with a combined subnormal left ventricular systolic function (subnormal ejection fraction or peak ejection rate, or supranormal time-to-peak ejection — duration of systole ratio) and a subnormal fast filling fraction. In Cox regression models on crude mortality and specific deaths, a subnormal ejection fraction and a fast filling fraction of ≤45% were the only independent risk factors. Patients with none of these risk factors had normal sex- and age-specific survival, those with any one factor had an early, and those with both factors a massive early and a late excess mortality, with 5-year crude survival of 92%, 77%, and 50%, respectively ($P<0·0001$). Systolic wall stress was without prognostic value. Further analyses indicated that impairment of left ventricular function occurred with increasing muscle mass over two phases: (1) diastolic dysfunction characterized by a pattern of severe relative concentric hypertrophy; (2) the addition of systolic dysfunction characterized by a more dilated, less concentric chamber geometry. Coronary artery disease seemed to provoke the latter development sooner.

Conclusions Impaired systolic and diastolic left ventricular function, irrespective of afterload, were decisive independent pre-operative risk factors for early as well as late mortality after aortic valve replacement for aortic stenosis. The adverse influence of concentric hypertrophy was the main underlying mechanism. Operative intervention, before impairment of diastolic and systolic function, should be advocated.

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Key Words: Aortic stenosis, valve replacement, ventricular function, hypertrophy, afterload, prognosis.

Introduction

In recent reports, despite some consensus to operate as soon as symptoms appear, more than 70% of patients with aortic stenosis from large U.S. and European centres had functional class III or IV symptomatology prior to valve replacement[1–4]. A conservative and reticent attitude has been advocated due to fear of 'prosthetic valve disease'[5,6] and due to the concept of afterload mismatch[6,7]. The latter suggests that there is a relationship between impaired left ventricular systolic function and significantly increased wall stress, which is believed to be reversible by raising the outflow obstruction[6]. Early operation has been supported by observations that patients with a favourable pre-operative risk profile may achieve sex- and age-specific normal long-term survival after valve replacement[8]. In addition, they probably also have a normal incidence

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rate of dominant prosthetic valve complications, anticoagulant-related haemorrhage and thromboembolism, as indicated by a normal stroke rate[9,10]. Patients with a high-risk profile suffer significant excess mortality[8] and stroke rate[9,10]. Furthermore, it has been shown that more than half of patients with aortic stenosis and clinical left ventricular (congestive) failure had normal systolic function[11]. A cardiac death mode late after valve replacement has been linked to abnormal diastolic function due to residual hypertrophy[12]. Whereas left ventricular systolic function has been studied extensively, the prognostic value of pre-operative impaired diastolic function on long- term survival after valve replacement has not been examined previously.

The aim of the present study was primarily to examine the prognostic influence of a complete profile of left ventricular systolic and diastolic performance indices on long-term results after valve replacement for aortic stenosis. By including indices of loading, geometry, and the degree of hypertrophy of the left ventricle in our test battery we wanted to identify possible underlying mechanisms as well.

Materials and methods

The study population comprised 91 prospectively enrolled patients who underwent valve replacement for aortic stenosis with or without concomitant coronary artery disease during August 1988 to October 1990. There were 54 men and 37 women, with a mean age of 61 years (range 22–82 years). Other heart disease, as well as diagnostic investigation with heart catheterization at other hospitals, served as exclusion criteria. None of the patients had significant aortic regurgitation[13].

Pre-operative investigation programme

Transthoracic echocardiography, including Doppler examination using standard equipment and methods[14], and left-sided heart catheterization via the femoral artery according to standard criteria[15] with biplane coronary arteriography and aortic root angiography, were performed in all 91 patients. Left ventriculography and measurements of ventricular pressures and peak-to-peak aortic valve gradients could not be done in nine patients, in whom the catheter could not be passed retrogradely to the ventricle. In order to have a reliable and reproducible estimate of left ventricular diastolic function in particular, all patients finally underwent ECG gated radionuclide left ventriculography. The method as well as its reliability and accuracy have been described in detail previously[16–18].

Definitions and calculations of variables

In 82 patients, using both measurements, there was a highly significant correlation between the peak-to-peak (invasive) aortic valve gradient and the peak instantaneous Doppler aortic valve gradient: peak–peak gradient = 24 + 0·69 Doppler gradient ($r = 0{\cdot}68$; $P < 0{\cdot}0001$). The above formula was used to estimate peak–peak gradients in the nine patients with no measured value; left ventricular peak systolic pressure was subsequently calculated in these nine patients as estimated peak–peak gradient plus peak aortic systolic pressure measured during catheterization. Coronary artery disease was defined as a luminal diameter reduction of at least 50% in a major epicardial vessel or first branch.

From the echocardiographic M-mode tracings, the following variables were measured[19]: left ventricular end-diastolic and end-systolic diameter (EDD; ESD), end-diastolic and end-systolic posterior free wall thickness (PWthED; PWthES), and interventricular septum wall thickness (SWthEd; SWthES). End-diastolic and end-systolic radius-wall thickness ratio (RThED; RThES) were calculated as EDD/(PWthED+SWthED) and ESD/(PWthES+SWthES), respectively, and muscle mass index (LVMMi) as $1{\cdot}04[(EDD+PWthED+SWthED)^3 - EDD^3] - 14$, divided by body surface area[20]. Diastolic and systolic wall stress were estimated as RThED × end-diastolic pressure × 1333 and RThES peak systolic pressure × 1333 ($dyn \cdot cm^{-2}$), respectively[21].

The left ventricular function indices derived from the radionuclide study were calculated as previously described in detail[18]. Ejection fraction (%), peak ejection rate (normalized for end-diastolic volume; $EDV \cdot s^{-1}$), and time (from ejection start) to peak ejection–duration of systole ratio, were calculated as systolic function indices, while the peak filling rate in the first half of diastole ($EDV \cdot s^{-1}$), time (from end-systole) to peak filling (in the second half of diastole if the peak filling rate here was greater than in first half)–duration of diastole ratio, fast filling fraction (filling in the first half of diastole as a percent of total filling volume), and late filling fraction (filling volume during the PQ interval of the ECG, atrial contraction, as a percent of total filling volume) were used as diastolic function indices. Left ventricular end-diastolic volume was finally calculated using the monoplane area–length method on the end-diastolic contour normalized for body surface area ($ml \cdot m^{-2}$). Subnormal or supranormal (as appropriate) levels of left ventricular function indices were drawn from a reference population, as described in Appendix 1. Subnormal systolic function was defined as the presence of a subnormal ejection fraction, a subnormal peak ejection rate, or a supranormal time to peak ejection–duration of systole ratio. Subnormal diastolic function was defined as the subnormal peak filling rate, the subnormal fast filling fraction, the supranormal late filling fraction, or the supranormal time to peak filling–duration of diastole ratio.

Operation

Standard techniques as described elsewhere[8,9], including general hypothermia (30 °C) and topical

cardiac cooling were employed in all 91 patients, using Bretschneider's crystalloid cardioplegia[9,22] in 73 (mean 1088 ml at 3 °C) and St. Thomas hyperkalemic cardioplegia[9] in 18 (mean 1718 ml at 3 °C). Mean aortic cross clamp time was 76 min (range 47–132 min). A standard St. Jude disc valve was implanted in 82 patients, a Starr-Edwards Silastic ball valve in eight, while one patient received a St. Jude Bioimplant (Liotta) stented xenograft. All except the latter patient received life-long warfarin treatment. Concomitant coronary artery bypass grafting was done in 32 patients who received from one to five, mean 1·9 distal anastomoses.

Follow-up

The patients of the present study have been attending serial follow-up investigations in our outpatient clinic for other study purposes. They were, in addition seen annually for normal standard clinical check-ups at the cardiological outpatient clinic. A complete follow-up was performed from 25 March to 3 April 1996, involving telephone contact to the patients who were still alive, and to the general practitioner and local hospital of the patients who had died. A total of 25 patients had died; death certificates were available in all and autopsy reports in eight. The minimum observation period from the operation was 5·4 years (maximum 7·7) with a total of 515 accumulated patient-years.

Statistical analysis

All tests were performed using the BMDP Dynamic release 7·0 software package[23]. Univariate comparisons between groups were performed using a standard Pearson chi-square test, a chi-square test for linear trend, a non-paired t-test, or a one-way analysis of variance as appropriate. Linear relations were checked with standard least-squares linear regression analysis. Cumulative survival was estimated with Kaplan and Meier's product-limit method and differences between curves checked with the log-rank test. The hazard rate of all patients was estimated, to identify a reasonable cut-off point for deaths related to the operation (early high risk phase) as opposed to a subsequent phase with low and relatively constant risk. The observed cumulative survival of identified risk groups were each compared with the survival of a general Danish background population selectively matched for age and sex using the method described by Lee[24] and the annually published national life-tables. Multivariate analysis of mortality was performed using logistic regression analysis[9,23] on deaths within a fixed time period after the operation (early deaths and 5-year deaths) and a Cox regression analysis[9,23,25] on death as a time-related response. The latter test were performed both on the late low risk phase and on total observation across both risk phases, here employing a model for time-interrelated covariates[23,25,26]. Cumulative survival and hazard rates are given with ± one standard error, while quantitative data are given with ± one standard deviation. The level of statistical significance was chosen as 0·05; ns, not significant.

Table 1 Causes of early and late deaths

	Early	Late
Specific		
Low output/congestive heart failure	3	7
Myocardial infarct	1	1
Arrhythmia	0	2
Prosthetic valve related†	0	4
Unspecific		
Postoperative bleeding‡	2	0
Other#	0	5
Total	6	19

†cerebral embolism, 1; endocarditis, 3; ‡4 days after re-sternotomy for infected sternum in one; #cancer, 4; cerebral thrombosis, 1 (autopsy verified).

Results

There were six deaths within 30 days of the operation (early deaths) and 19 late deaths (Table 1); 18 deaths were classified as specific (cardiac or prosthetic-valve related) and seven as unspecific. Within 5 years of the operation, there were 20 deaths (5-year deaths). Figure 1 depicts the long-term cumulative survival and the hazard rate of all 91 patients. The hazard rate was $2{\cdot}3 \pm 0{\cdot}9 \,.\, 10^{-3} \,.\, \text{day}^{-1}$ during the first month, and dropped to 0·8 ± 0·4 in the second, 0·6 ± 0·1 in the third, and 0 in the fourth month; it averaged 0·1 ± 0·05 during the second to 12 month. It was consequently reasonable to choose day 30 as a cut-off point between the early high-risk phase and the late low-risk phase.

Table 2 gives the pre-operative profile of the patients in relation to status at end of study. Patients who died were older, those who died a specific death had worse functional classification, more coronary artery disease, more impairment of both left ventricular systolic and diastolic function, lower aortic valve gradient, lower peak systolic pressure, and higher end diastolic volume.

Risk models for early deaths and 5 year deaths

All variables of Table 2, in addition to type and amount of cardioplegia, prosthetic valve type and size, aortic cross clamp time, and surgeon were entered into the multivariate analyses. Insufficient grafting was defined at two levels and also entered into the tests: one where coronary disease, for a variety of reasons (distal disease of small right coronary or circumflex arteries

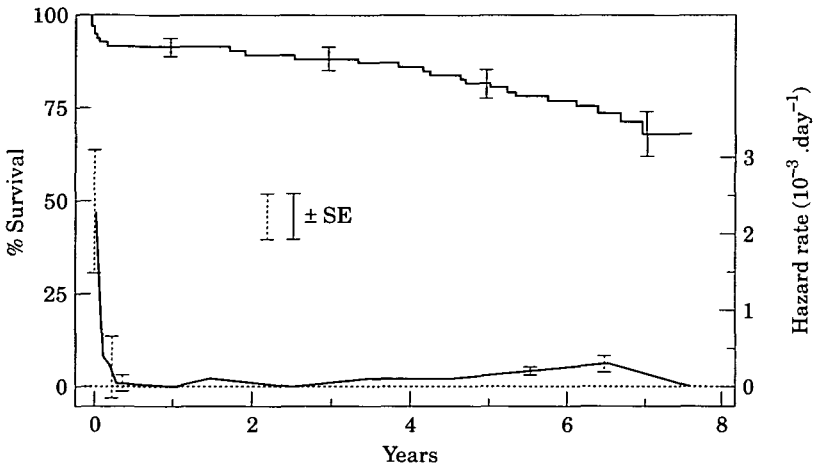

Figure 1 **Cumulative survival and hazard rate (curve at bottom) of all 91 patients. One-, 3-, and 5-year survivals ± one standard error (SE) were 91 ± 3%, 88 ± 3%, and 81 ± 4%, respectively.**

Table 2 Pre-operative risk profile in relation to status at end of study

	Alive (n=66)	Unspecific deaths¶ (n=7)	Specific deaths¶ (n=18)
Male gender	55%	86%	67%
Age (years)	59 ± 13‡*	66 ± 12	66 ± 10§*
Functional class†*			
II	35%‡*	29%	-6%#**
III	56%	71%	61%
IV	9%	0	33%
Coronary artery disease			
1–2 vessel	24%	14%	50%#*
3 vessel — left main stem	12%	14%	17%
Bypass grafting	32%	28%	50%
Coronary disease — no bypass grafting	5%	0	17%#*
Aortic valve peak to peak gradient (mmHg)	86 ± 26	91 ± 21	73 ± 24#*
LV end-diastolic pressure[$]	24 ± 10[$]	26 ± 11	24 ± 10
LV peak systolic pressure (mmHg)†**	215 ± 26	233 ± 22‖**	197 ± 31§*#**
LV end-diastolic radius–wall thickness ratio	1·83 ± 0·37‡*	1·82 ± 0·18	1·98 ± 0·38#*
LV end-systolic radius–wall thickness ratio	0·90 ± 0·29	0·76 ± 0·09‖**	1·10 ± 0·36§*#*
LV diastolic wall stress (10^3 . dyn . cm^{-2})[$]	62 ± 31[$]	64 ± 28	66 ± 42
LV systolic wall stress (10^3 . dyn . cm^{-2})	256 ± 71	238 ± 26‖*	286 ± 67
LV muscle mass index (g . m^{-2})	197 ± 63	185 ± 41	219 ± 81
LV end-diastolic volume index (ml . m^{-2})	84 ± 31	78 ± 29	103 ± 33§*#**
LV ejection fraction (%)†***	62 ± 15‡**	64 ± 11‖**	47 ± 16§***#***
LV peak ejection rate (EDV . s^{-1})†*	3·35 ± 0·99	4·07 ± 1·29‖*	2·76 ± 0·92§*#**
LV time to peak ejection–duration of systole ratio	0·55 ± 0·14	0·53 ± 0·11	0·58 ± 0·11
LV peak filling rate (EDV . s^{-1})†*	2·99 ± 0·99‡*	3·09 ± 0·84	2·35 ± 0·64§**#**
LV time to peak filling–duration of diastole ratio	0·41 ± 0·22	0·46 ± 0·21	0·50 ± 0·21
LV fast filling fraction (%)†*	62 ± 12‡*	57 ± 17	52 ± 16§*#*
LV late filling fraction (%)†*	34 ± 19‡**	37 ± 17	50 ± 18§**#**

Data are mean ± standard deviation or % of patients. LV=left ventricular. See text for definitions and calculations. ¶see Table 1; †overall test of the three groups; ‡test of alive group vs both deaths groups joined; ‖test of unspecific vs specific deaths groups; §test of alive vs specific deaths groups; #test of specific deaths vs alive and unspecific deaths groups joined; [$]missing in nine patients; ***P<0·001; **P<0·01; *P<0·5.

to technically non-graftable disease), did not result in bypass grafting (n=6), and the other where patients who underwent bypass grafting also had a diseased vessel area (left anterior descending, circumflex, right) that was not revascularized. The variables, with prognostic value in early or late risk phases using univariate testing, are shown in Table 3; some variables changed the prognostic influence between phases. Note the very strong influence of a subnormal systolic function and a fast filling fraction on early mortality, and of a subnormal ejection fraction and a fast filling fraction of ≤45% (low subnormal; see Appendix 1) on late mortality.

Table 3 Univariate predictors of early and late mortality†

			Early mortality‡		Overall survival#		Late survival§	
		n	%	*P*	5-year ± SE	*P*	5-year ± SE	*P*
Age	≤70 years	69	5·8		86 ± 4		91 ± 4	
				ns		0·05		0·04
	>70 years	22	9·1		68 ± 10		75 ± 10	
Functional class	II	26	3·8		96 ± 4		100	
				ns		0·04		0·04
	III–IV	65	7·7		75 ± 5		82 ± 5	
Coronary artery disease	no	53	5·7		89 ± 4		94 ± 3	
				ns		0·05		0·04
	yes	38	7·9		71 ± 7		77 ± 7	
Aortic valve peak to peak gradient	≥50 mmHg	86	7·0		83 ± 4		89 ± 4	
				ns		ns		0·008
	<50 mmHg	5	0		60 ± 21		60 ± 21	
LV ejection fraction	≥61%	54	1·9		89 ± 4		92 ± 4	
				0·03		0·0009		0·01
	<61%	37	13·5		68 ± 8		78 ± 7	
LV systolic function	normal‖	47	0		91 ± 4		91 ± 4	
				0·009		0·004		0·05
	subnormal‖	44	13·6		70 ± 7		82 ± 6	
LV fast filling fraction	normal‖	52	0		87 ± 5		87 ± 5	
				0·003		0·05		ns
	subnormal‖	39	15·4	74 ± 7		88 ± 6		
LV fast filling fraction	>45%	74	4·1		86 ± 4		90 ± 4	
				0·04		0·001		0·009
	≤45%	17	17·6		59 ± 12		71 ± 12	
LV late filling fraction	normal‖	47	0		93 ± 4		93 ± 4	
				0·009		0·004		0·05
	supranormal‖	44	13·6		70 ± 7		80 ± 6	
LV diastolic function	normal	36	0		92 ± 5		92 ± 5	
				0·03	ns		ns	
	subnormal	55	11·1		75 ± 6		86 ± 5	

†all deaths irrespective of cause (Table 1); ‡deaths within 30 days after the operation; #percent cumulative survival (all deaths included); §percent cumulative survival with early deaths excluded; ‖see text for definition of normal versus subnormal or supranormal; SE=standard error. Other abbreviations as in Table 2.

Table 4 Logistic regression model for early death†

Risk factors	b	*P*
z_1=subnormal LV fast filling fraction	10·1	0·006
z_2=subnormal LV systolic function	9·8	0·01

Risk factor present	none	z_2	z_1	both
Number of patients	33	19	14	25
Death rate***	0	0	0	24%

†death within 30 days of the operation (Table 1). b=regression coefficient; z_1, z_2=value of 1 in test if risk level present and of 0 if not. ***P<0·001. Other abbreviations as in Table 2.

Insufficient grafting and aortic cross-clamp time had no influence.

The final logistic regression model for early mortality is shown in Table 4. A subnormal fast filling fraction and a subnormal systolic function were independent risk factors, but deaths were grouped only when both were present; this interaction explains the very high regression coefficients and inordinately large estimate of relative risk (exp[regression coefficient]). Age (P<0·01) was the only independent risk factor for all 5-year deaths, and ejection fraction (P<0·01; inverse relation) for specific 5-year deaths. The logistic regression model for late 5-year deaths (early deaths excluded) included the end-diastolic radius–wall thickness ratio of ≥2·0 (P<0·0001), age (P<0·01), the end-systolic radius–wall thickness ratio of ≤1·0 (P<0·01), and coronary disease (P<0·05) as independent risk factors; the model for late specific 5-year deaths identified the end-diastolic radius–wall thickness ratio of ≥2·0 (P<0·01) and the peak filling rate (P<0·05; inverse relation).

Risk models for deaths as a time-related event

The Cox analyses included the same battery of potential predictor variables as the logistic regression analyses. Four risk models were made: one for all deaths, one for all specific deaths, one for late (≥30 days) deaths, and one for late specific deaths. None of the variables that changed prognostic influence between the hazard phases entered the final models. A subnormal ejection fraction

Table 5 Cox regression models for crude mortality (all deaths†) and specific mortality (all specific deaths†)

Risk factors	Crude mortality		Specific deaths	
	b	*P*	b	*P*
z_1=LV ejection fraction <61%	1·13	0·008	1 62	0·002
z_2=LV fast filling fraction ≤45%	0·98	0·03	1·07	0·03

†see Table 1. z_1, z_2=value of 1 if risk level was present and 0 if not; b=regression coefficient. Other abbreviations as in Table 2.

(<61%) and a fast filling fraction of ≤45% were identified as independent risk factors in all four models. The models, including both hazard phases for all deaths and for all specific deaths, are shown in Table 5. Figure 2 depicts the risk stratification of the model for all deaths: group A, patients with none of the two risk factors; group B, patients with either a subnormal ejection fraction or a fast filling fraction of ≤45%; and group C, patients with both risk factors. Data from patients with an isolated subnormal ejection fraction and those with an isolated fast filling fraction of ≤45% were combined since their death rates did not differ. The survival of background populations, selectively matched for sex and age to each of the resulting three risk groups, are also shown in Fig. 2. Note that survival in patients with neither risk factor did not differ from that of their background population; patients with either risk factor had excess mortality in the early phase, while those with both risk factors had a pronounced early excess mortality and tendencies for late excess mortality as well.

Prognostic influence of left ventricular function — possible mechanisms

The main result of the analyses of prognosis was that reduced systolic and reduced diastolic left ventricular function were both decisive factors. We consequently performed the following stratification: 27 patients with pre-operative normal ventricular function (group 1), 20 with isolated diastolic dysfunction (group 2), nine with isolated systolic dysfunction (group 3), and 35 with both systolic and diastolic dysfunction (group 4). Figures 3–5 show pertinent variables in relation to these groups. The left ventricular volume index rose across the groups from group 1 to group 4, as did radius–wall thickness ratio, with the exception that group 2, with isolated diastolic dysfunction, had the lowest ratio. The muscle mass index showed a steady increase across the groups. Systolic wall stress was highest in groups 3 and 4, primarily due to a shift in the end systolic radius–wall thickness ratio towards an eccentric type hypertrophy, and dilated chamber geometry, since peak systolic pressure was lowest in groups 3 and 4. End-diastolic pressure and diastolic wall stress did not differ among the four groups, although both conditions tended to be highest in the group with biphasic ventricular impairment. Figure 5 indicates that high age, coronary disease, and functional classes III and IV were especially prevalent in groups 3 and 4.

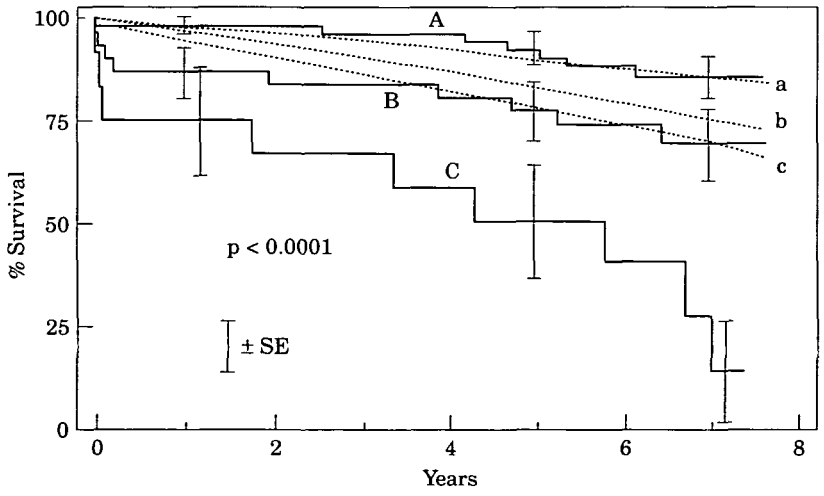

Figure 2 **Cumulative survival of risk group A (patients with neither risk factor: left ventricular ejection fraction <61% and fast filling fraction ≤45%, n=49), group B (patients with one of the two risk factors; n=30), and group C (patients with both risk factors; n=12) together with survival of their selectively age- and sex-matched background populations (a, b, and c, respectively, with mean ages of 57 ± 14, 65 ± 8, and 69 ± 10 years, respectively; *P*<0·01). The 5-year survival ± one standard error (SE) was 92 ± 4% in group A, 77 ± 7% in group B, and 50 ± 14% in group C. See Table 7.**

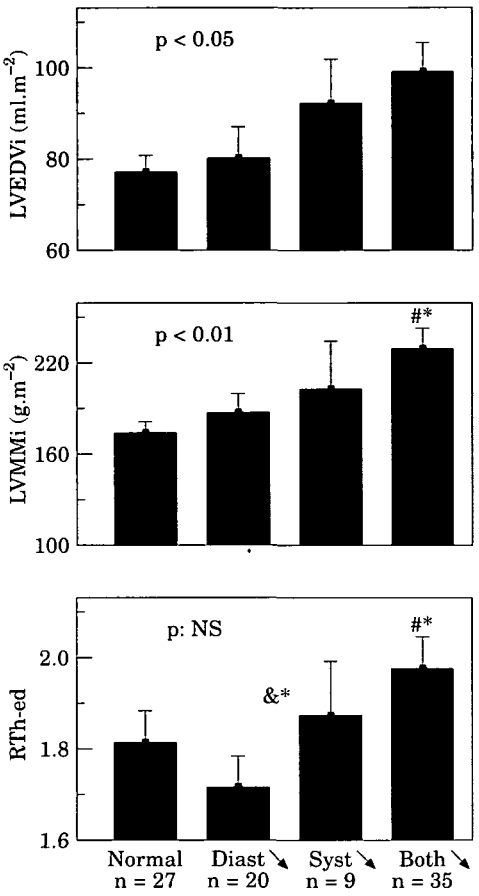

Figure 3 **Left ventricular end-diastolic volume index (LVEDVi), muscle mass index (LVMMi) and chamber radius to wall thickness ratio in end-diastole (RTh-ed) in relation to patients with normal left ventricular function, those with isolated impairment of diastolic function, those with isolated impairment of systolic function, and those with impairment of both diastolic and systolic function (see text for definitions). Mean values ± standard error of the mean (flags) are shown. #'Both' group vs the other three groups combined. & 'normal' plus 'Diast' groups vs 'Syst' plus 'Both' groups. *$P<0.05$.**

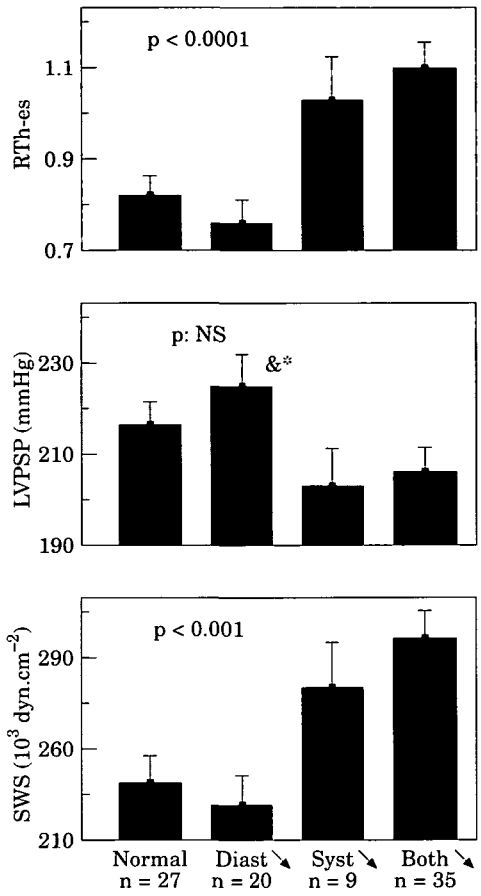

Figure 4 **Left ventricular chamber radius to wall thickness at end-systole (RTh-es), peak systolic pressure (LVPSP), and (peak) systolic wall stress (SWS) in relation to the same four groups as in Fig. 4. Other abbreviations as in Fig. 4.**

To test the influence of wall stress further, systolic wall stress strata of $\leq 200 \cdot 10^3 \cdot \text{dyn} \cdot \text{cm}^{-2}$ (approximate normal level with present method of calculation), of $201–300 \cdot 10^3 \cdot \text{dyn} \cdot \text{cm}^{-2}$, and of $>300 \cdot 10^3 \cdot \text{dyn} \cdot \text{cm}^{-2}$ were compared in each of the four groups in Figures 3–5. There were no differences between the wall stress strata in any of the four groups as regards functional class or coronary disease. Groups 1 and 2 patients, divided into the above three wall stress strata, had 5-year freedoms from specific death of 88 ± 8% (n=18), 100% (n=23), and 100% (n=6), respectively (ns); the figures in groups 3 and 4 were 100% (n=5), 68 ± 11% (n=22), and 82 ± 9% (n=17), respectively (ns). Systolic wall stress thus seemed to be without clinical or prognostic significance.

To analyse the relative impact of coronary artery disease and wall stress more directly, the following correlations were calculated for all 91 patients, for the 53 without coronary disease, and for the 38 with: systolic wall stress with ejection fraction, r= − 0·45 ($P<0·001$), r= − 0·26 (ns), and r= − 0·56 ($P<0·001$), respectively; systolic wall stress with late filling fraction, r=0·41 ($P<0·001$), r=0·30 ($P<0·05$), and r=0·47 ($P<0·001$), respectively; muscle mass index with ejection fraction, r= − 0·56 ($P<0·001$), r= − 0·59 ($P<0·001$), and r= − 0·48 ($P<0·001$), respectively; and muscle mass index with late filling fraction, r=0·38 ($P<0·001$), r=0·51 ($P<0·001$), and r=0·20 (ns), respectively. Patients with coronary artery disease had a higher systolic wall stress (279 ± 76 vs 248 ± 60 . 10^3 . dyn . cm^{-2}, $P<0·05$) despite lower peak systolic pressure (205 ± 29 vs 219 ± 29 mmHg $P<0·05$) than those without, primarily due to less relative hypertrophy (radius–wall thickness ratio, end-systolic: of 1·1 ± 0·4 vs 0·9 ± 0·2, $P<0·01$; end-diastolic of 2·0 ± 0·4 vs 1·8 ± 0·3, $P<0·05$). Coronary artery disease thus seemed to be related to impaired left ventricular function at a lesser degree of relative hypertrophy with higher wall stress, while absolute degree of hypertrophy was a main factor in patients without coronary disease.

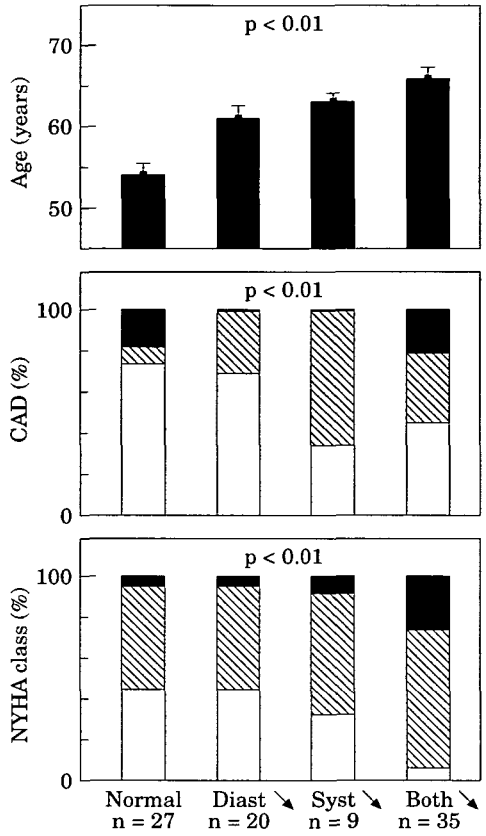

Figure 5 **Age (mean ± standard error of the mean), and prevalences (percent of patients) of coronary artery disease (CAD) and of New York Heart Association's (NYHA) functional classes I (n=0), II, III, and IV, in relation to the same four groups as in Figs 4 and 5. ■=three vessel or left main stem CAD, NYHA class IV; ▨=1–2 vessel CAD, NYHA III; □=no CAD, NYHA class II.**

Discussion

Results after aortic valve replacement in the current era are relatively homogeneous, with 5-year crude survival, as in the present study, of around 80%[1–4]. Generally, more than 70% of patients have symptoms corresponding to functional classes III–IV and the average age is 60–65 years[1–4]. With advanced functional deterioration identified as a risk factor for early postoperative mortality[3,27,28], and age from normal epidemiological reasons having a strong influence on late mortality[1,8,9], such results will probably not change if the pre-operative risk profile of patients remain static.

We have previously shown that pre-operative left ventricular failure, defined as an episode of pulmonary vascular congestion or oedema, was the strongest predictor of death early after aortic valve replacement[27], and among the strongest risk factors for late mortality[1,8]. However, clinical left ventricular failure is not necessarily caused by impaired systolic function. Dineen and Brent[11] showed that 60% of patients with aortic stenosis and congestive failure had a normal ejection fraction. They concluded that diastolic dysfunction was responsible[11]. Theoretically, systolic as well as diastolic left ventricular dysfunction should both be operational for the prognosis to be accurate.

Systolic function indices have been studied extensively, and ejection fraction has long been considered a poor prognostic factor[29–31]. This has been explained by afterload mismatch[6]: with a strong inverse relationship between systolic wall stress of the left ventricle and ejection fraction, reduced ejection fraction is related to excessively high wall stress due to insufficient hypertrophy and not to irreversibly impaired contractility. With reduction of wall stress, which is indeed the primary effect of valve replacement, ejection fraction should return to normal, which has also been observed in several studies[30–32]. Advocating the still stated view, that irreversible damage to left ventricular function rarely develops in aortic stenosis[5], such results do not exactly promote early operative intervention.

However, the above prognostic studies stem from an early era with high mortalities[29–31]. Current era studies, including the present one, have on the contrary, identified ejection fraction as an important risk factor[3,28]. It has, furthermore, been shown that the early improved ejection fraction, upon re-study, on average 41 months postoperatively, had returned to the pre-operatively subnormal starting point in half the patients[32]. The early improvement may thus be related to reduced myocardial oxygen demand brought about by afterload reduction[33], despite irreversible myocardial damage[9,34]. Furthermore, the very strong inverse relationship between systolic wall stress and ejection fraction with correlation coefficients as high as 0·96[35], which is the basis of the concept of afterload mismatch, has been difficult to reproduce[36,37], as was also the case in the present study. Finally, a main result of the present study was that wall stress had no clinical significance or prognostic influence, nor had it any modulating influence on prognosis. Virtually any combination of high or low ejection fraction and wall stress with congestive heart failure were observed in the present as well as in other studies[11,37].

The present study is, to our knowledge, the first to establish that impairment of both systolic and diastolic left ventricular function have independent and strong prognostic influence on both early and late mortality after aortic valve replacement. A glance at the pre-operative haemodynamic profile in relation to patient status at end-of-study gave a clue as to the relevant factors. Patients who died a specific death generally had reduced systolic function pre-operatively, although their wall stress was not higher than that of patients who were alive. Most importantly, patients who died a specific death had subnormal diastolic function with a lower peak filling rate, with peak filling tending to occur late in diastole, and with a subnormal fast filling fraction in the first half of diastole, compensated for by supranormal filling during atrial contraction. Early mortality, furthermore, only occurred among patients with both a subnormal systolic function and a subnormal fast filling

fraction. The Cox regression analysis of crude mortality and of specific deaths, of the early and late hazard phase together and of the isolated late phase, gave a most consistent result: a subnormal ejection fraction and a (very) low fast filling fraction ($\leq$45%) were the two most decisive independent risk factors, with a relative risk increase of 3·1 and 2·7 (exp[regression coefficient]; Table 5), respectively, for crude mortality across both risk phases. The risk stratification of the latter Cox model showed that patients with both a normal ejection fraction and a normal or only slightly reduced fast filling fraction had normal sex- and age-specific long-term survival at least up to 8 years after valve replacement, while those with any one of the two risk factors suffered an early excess mortality, and those with both risk factors a pronounced excess mortality. The risk stratifications of the risk models should be underlined as a main result of the present study: they indicate the potential gain in survival of operating at a prognostically beneficial point of time in the pathophysiological evolution of aortic stenosis, as opposed to 'late' intervention.

The stratification of our patients into those with normal systolic and diastolic left ventricular function, those with isolated diastolic dysfunction, those with isolated systolic dysfunction and those with biphasic dysfunction gave some insight into possible underlying mechanisms. Muscle mass index rose progressively across these four groups, indicating the influence of hypertrophy in the derangement of both systolic and diastolic left ventricular function. These developments were probably, to some degree, related to irreversible myocardial damage, given the prognostic influence of systolic and diastolic dysfunction in the present paper. Others have related impaired systolic[36,37] and diastolic[38,39] left ventricular function to the degree of hypertrophy in aortic stenosis. The left ventricular chamber size increased across the four left ventricular function groups, from those with normal to those with biphasic impaired function, towards a less concentric more eccentric chamber geometry and wall hypertrophy pattern in the end-stage of aortic stenosis with the poorest prognosis. An important modification was observed: patients with isolated derangement of diastolic function had the lowest radius–wall thickness ratio. These patients also had the lowest systolic wall stress, despite a high peak systolic pressure; as end-diastolic pressure and wall stress were not higher than in the other three groups, these findings considered together indicate that a severe relative concentric hypertrophy pattern, in its own right, was an important factor in compromising early diastolic filling and postoperative prognosis. The latter was underscored by the identification of a very low end-systolic radius–wall thickness ratio ($\leq$1·0) as a risk factor for late 5-year death.

The change from the group with isolated reduction of diastolic function to the small group with isolated systolic dysfunction accords well with results of Lavine *et al.*[40] and Murakami *et al.*[41]. The second of their two groups had the most pronounced degree of hypertrophy and a larger ventricular chamber, but filling had returned to a pattern resembling the bi-modal filling of a normal ventricle, but now with chronically increased filling pressures (pulmonary capillary wedge or left atrial pressure) and prolonged relaxation[40,41]. The latter was not discovered with our radionuclide method. It seems there is a third and worse phase, as indicated by our group with both systolic and diastolic dysfunction and the highest muscle mass index.

Coronary artery disease was obviously an important modifying factor in the pathophysiology of aortic stenosis. The 'classical' inverse correlation between systolic wall stress and ejection fraction was strong in patients with coronary disease but not in those without. Patients with coronary artery disease had higher wall stress despite lower peak systolic pressure than those without, and the explanation was found in a less concentric hypertrophic, more dilated chamber geometry. Coronary disease has been related to a lesser absolute degree of hypertrophy in aortic stenosis[42,43]; this could be regarded as insufficient hypertrophy as patients with mild hypertrophy (and those with severe hypertrophy but no coronary disease) had poorer long-term survival than those with hypertrophy of intermediary degrees[43]. Coronary artery disease is especially prevalent in patients with isolated systolic and in those with biphasic ventricular impairment. From this it seems that coronary artery disease unmasked the pathological influence of hypertrophy at a lower relative degree of concentric hypertrophy. In patients without coronary disease, on the other hand, the absolute degree of hypertrophy was a decisive factor: it correlated strongly and inversely with ejection fraction and directly with late filling fraction.

The classical distinction between compensated and appropriate hypertrophy, when left ventricular wall stress is kept normal and systolic function preserved, and of insufficient hypertrophy, when wall stress rises and systolic function deteriorates (afterload mismatch)[2], seems to be without clinical and practical significance. From the present results, it seems that increasing left ventricular hypertrophy in absolute terms decompensates the left ventricle, first in a uniphasic mode, then biphasically as an end-stage phenomenon. Impairment of early diastolic filling seems to be a first occurrence, related to a geometric pattern of severe relative concentric hypertrophy. Coronary artery disease seems to be an important modifying factor in unmasking the pathological influence of hypertrophy at a lower level of the relative concentric hypertrophy pattern. Impaired systolic and diastolic function were both identified as decisive and strong independent risk factors for early as well as late mortality after valve replacement. To improve the overall long-term prognosis after valve replacement for aortic stenosis, early operative intervention, before left ventricular diastolic and systolic function deteriorates, should be advocated.

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Appendix 1

Subnormal and supranormal levels of the left ventricular function indices

Using multivariate analysis in a reference population of healthy individuals aged 20–70 years, we have previously shown that the left ventricular diastolic function indices at rest were related to age[18]. The following lower or upper 95% confidence intervals of the reference population were used to identify patients with sub- or supranormal levels of the function indices. These subnormal or supranormal (as appropriate) levels were: ejection fraction<61%; peak ejection rate <2·29 EDV . s^{-1}; time to peak ejection-duration of systole ratio >0·67; peak filling rate <2·86 EDV . s^{-1} (age ≤49) or <2·00 EDV . s^{-1} (age ≥50); time to peak filling-duration of diastole ratio >0·41 (age ≤49) or >0·55 (age ≥50); fast filling fraction <69% (age ≤49) or <55% (age ≥50); Late (PQ) filling fraction >23% (age ≤49) or >32% (age ≥50); and end-diastolic volume index >89 ml . m^{-2}[18].