Br Heart J 1989;62:372–8

Inaccuracies in using aortic valve gradients alone to grade severity of aortic stenosis

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SUMMARY The severity of aortic stenosis is an important determinant of prognosis in patients with symptoms who do not undergo valve replacement. To assess the pitfalls of using valve gradients alone 636 patients with aortic stenosis in whom the aortic valve area had been calculated by the Gorlin formula were studied. The correlation between valve area and aortic gradients was poor. No gradient was found that was both sensitive and specific for aortic stenosis. The maximum predictive accuracy was 81% for a mean gradient of 30 mm Hg and 80% for a peak gradient of 30 mm Hg. A mean gradient of 50 mm Hg or a peak gradient of 60 mm Hg were specific with a 90% or more positive predictive value. It proved difficult, however, to find a lower limit with a 90% negative predictive value. Patients with severe aortic stenosis and low gradients (peak or mean gradient of <30 mm Hg) had small ventricles (on both angiographic and echocardiographic data) with good ejection fractions and so were unlikely to be detected subjectively. In comparison patients with mild aortic stenosis and low gradients tended to have more aortic regurgitation but have similar degrees of left ventricular hypertrophy on echocardiographic or electrocardiographic criteria.

The aortic valve area should be measured in all patients with the suspicion of severe aortic stenosis with a mean gradient of <50 mm Hg (50% of patients in this study) or a peak gradient of <60 mm Hg (47% of patients in this study).

The severity of aortic stenosis, as assessed by valve area, is an important determinant of prognosis in patients with symptoms who do not undergo valve replacement.[1] The widespread use of aortic valve gradients alone, either derived invasively or by Doppler echocardiography, is likely to be an inaccurate way of assessing the severity because it ignores cardiac output. This inaccuracy is increased by the fall in cardiac output as aortic stenosis progresses.[2–4] Furthermore, patients with low cardiac outputs have a very poor short term prognosis if the valve is not replaced.[5]

We studied the inaccuracy of both mean and peak aortic valve gradients alone in predicting aortic valve area and the values of valve gradient at which valve area must be calculated to ensure accurate assessment of the severity of aortic stenosis.

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Accepted for publication 23 May 1989

Patients and methods

METHODS

Over a 10 year period 636 consecutive patients with a precatherisation diagnosis of aortic stenosis were studied at St Thomas' Hospital. Patients were catheterised if they had symptoms or if the clinical diagnosis of severe aortic stenosis was made. Because Doppler assessment of the gradient or valve area was not available (or in its development phase), no attempt was made to grade the severity on the basis of the echocardiogram. All patients underwent full left and right heart catheterisation. All had an aortic valve gradient >10 mm Hg. Patients with mitral stenosis or $>$ grade I mitral regurgitation were excluded from the study. Cardiac output was calculated by indocyanine green dye dilution. Dye was injected in the pulmonary artery and measurement was made with an earpiece densitometer and dye curve analysis was performed by a Nihon Kohden cardiac output computer.[6] This was verified by the fore-'n-aft triangle method.[7] The mean of three measurements was calculated.

Angiographic volumes were measured by planimetry from the right anterior oblique angiogram.[8] Intracardiac distances were calibrated by moving the angio table a known distance and using the tip of the pigtail catheter in the left ventricle as the reference point. Extrasystolic or post-extrasystolic beats were excluded and angiographic stroke volume and cardiac output were then calculated by planimetry. The aortic valve gradient was measured by withdrawal of a fluid filled catheter across the valve. In atrial fibrillation simultaneous measurements were obtained with twin lumen catheters and the transseptal approach was used when the aortic valve could not be crossed retrogradely. Peak to peak gradients were measured directly and the mean gradient was measured by computerised planimetric integration, averaged over a minimum of five beats. The systolic ejection period was calculated in the standard manner. The aortic valve area was then calculated with the classic Gorlin formula[9] based on the green dye cardiac output, unless there was grade 3 or 4 aortic regurgitation, when the angiographic cardiac output was used.

$$\text{Aortic valve area (cm}^2\text{)} = \frac{\text{valve flow (ml/min)}}{44{\cdot}5 \text{ mean valve gradient}}$$

Electrocardiographic left ventricular hypertrophy was defined as being present if the sum of the S wave in lead V1 and the R wave in lead V5 or V6 was >35 mm.[10]

One operator performed and reported 90% of the echocardiograms. The M mode was guided by cross sectional images, using the ATL 300 or the Hewlett-Packard 7702A machines. The echocardiographic dimensions of the wall and cavity were measured just below the tips of the mitral valve leaflets in the parasternal view. Wall dimensions were measured at the end of diastole.

STATISTICAL ANALYSIS

Log plots of mean and peak gradients were plotted against the aortic valve area to determine the correlation coefficient. We used logarithmic plots because the relation is not linear. Because of the possibility that lack of correlation was a function of aortic regurgitation this was repeated with the patients divided into subgroups by angiographic grade of aortic regurgitation. Severe aortic stenosis was defined as a valve area of $\leqslant 0{\cdot}9$ cm^2 and the sensitivity, specificity, and diagnostic accuracy were calculated for the range of values of aortic valve gradients. Both these functions were performed on the University of London computer by the Statistical Analysis System. Student's t test was used to compare continuous variables and χ^2 was used for proportions.

Table 1 *Patient details*

Variable	*Result*
Sex	29% female
Mean (SD) age	58 (11) yr
Mean valve area	0·94 (0·71) cm^2
Peak gradient	60·3 (35) mm Hg
Mean gradient	50·6 (25) mm Hg
Mean EF	57 (15)%
Mean CI	3·3 (1·6) l/min/m^2
Mean LVEDI	95·1 (45) ml/m^2

EF, angiographic ejection fraction; CI, cardiac index; LVEDI, angiographic left ventricular volume index.

Results

Table 1 summarises the patient details. The aortic valve area was calculated in all patients and the peak gradient was available in 597 patients. The patient population studied had a range of severity of aortic stenosis with a mean aortic valve area of 0·94 cm^2. Table 2 shows the details of the patients' symptoms. Nearly all the patients had symptoms (94%)—with chest pain in 58% and syncope in 23%. The patients with severe aortic stenosis were significantly more likely to have symptoms and specifically more likely to have chest pain or syncope than those patients with mild aortic stenosis. Figures 1 and 2 show the plots of aortic valve area against mean and peak gradients and figs 3 and 4 show the log plots. There is a wide degree of scatter and this is reflected in the poor correlation seen with r values of $-0{\cdot}71$ and $-0{\cdot}70$ for mean and peak gradients respectively calculated by linear regression from the logarithmic plots. There was little difference when the patients were subdivided according to grade of aortic regurgitation (table 3). When there was no aortic regurgitation the r value reached $-0{\cdot}78$ for the mean gradient.

Table 4 examines the effect of age on the correlation. There was little difference between the various age groups except in the patients aged >70 in whom the correlation was much poorer (0·53 for mean gradients and 0·43 for peak gradients).

Tables 5 and 6 show the sensitivity and specificity of aortic valve gradients from 20 to 100 mm Hg for peak gradients and mean gradients respectively. The maximum predictive accuracy is 81% for a mean

Table 2 *Patients' symptoms in relation to severity of aortic stenosis*

Symptoms	*Severe stenosis*	*Mild stenosis*
None	15/443 (3%)	25/217 (12%)
Chest pain	274/443 (62%)*	108/217 (50%)*
Syncope	129/443 (29%)*	27/217 (12%)*

*$p < 0{\cdot}01$.

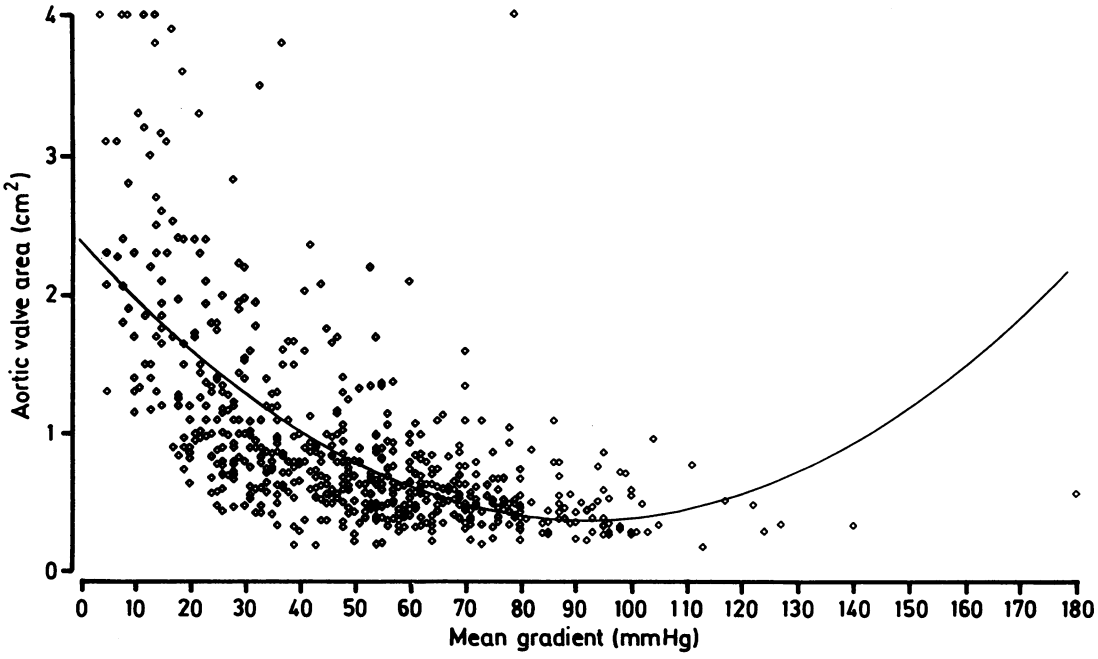

Fig 1 *A plot of aortic valve area against mean gradient gave a quadratic regression line.*

gradient of 30 mm Hg and 80% for a peak gradient of 30 mm Hg.

We hoped to establish a range of highly specific or sensitive gradients for clinical use—the upper limit with a 90% positive predictive value and the lower limit with a 90% negative predictive value. A peak gradient of 60 mm Hg and a mean gradient of 50 mm Hg were used as the upper limits. It proved

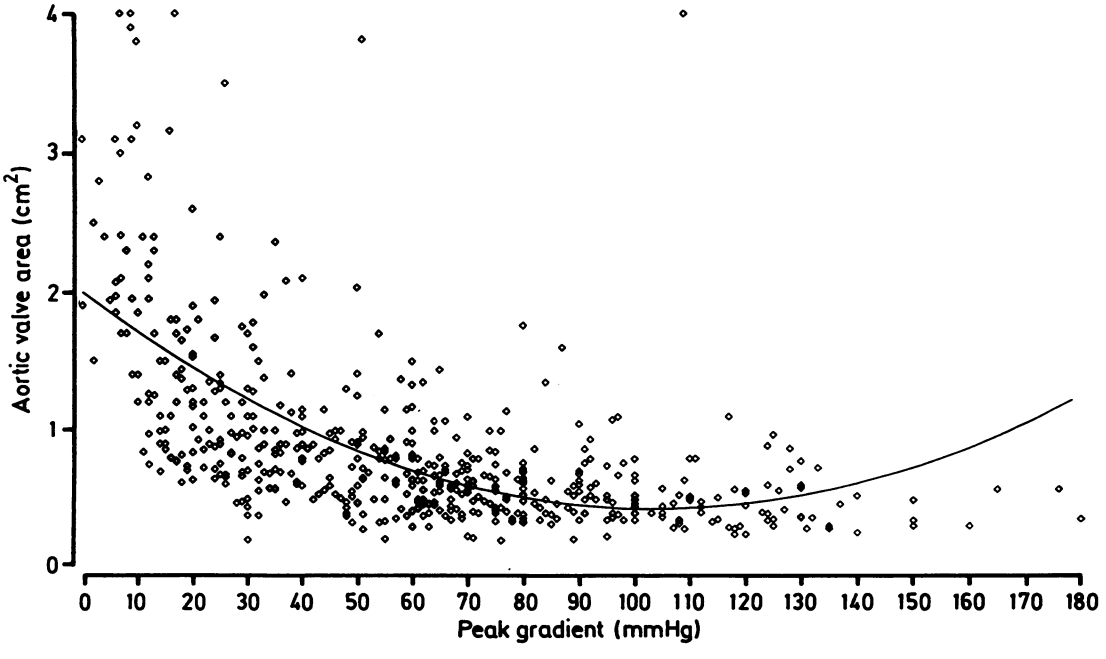

Fig 2 *A plot of aortic valve area against peak gradient gave a quadratic regression line.*

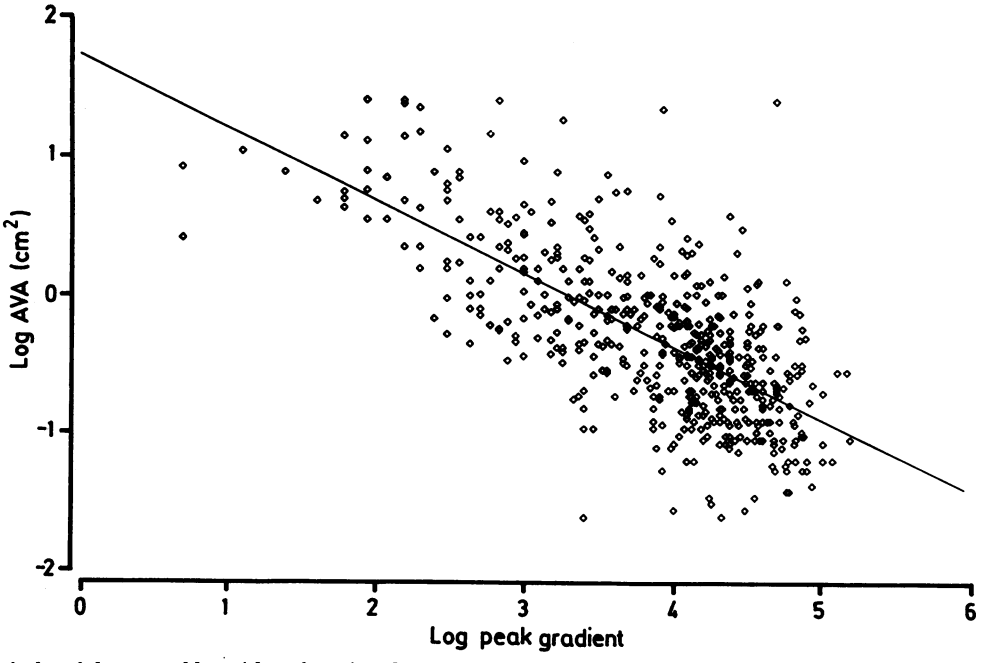

Fig 3 *A plot of the natural logarithm of aortic valve area against the peak aortic valve gradient gave a linear regression line.*

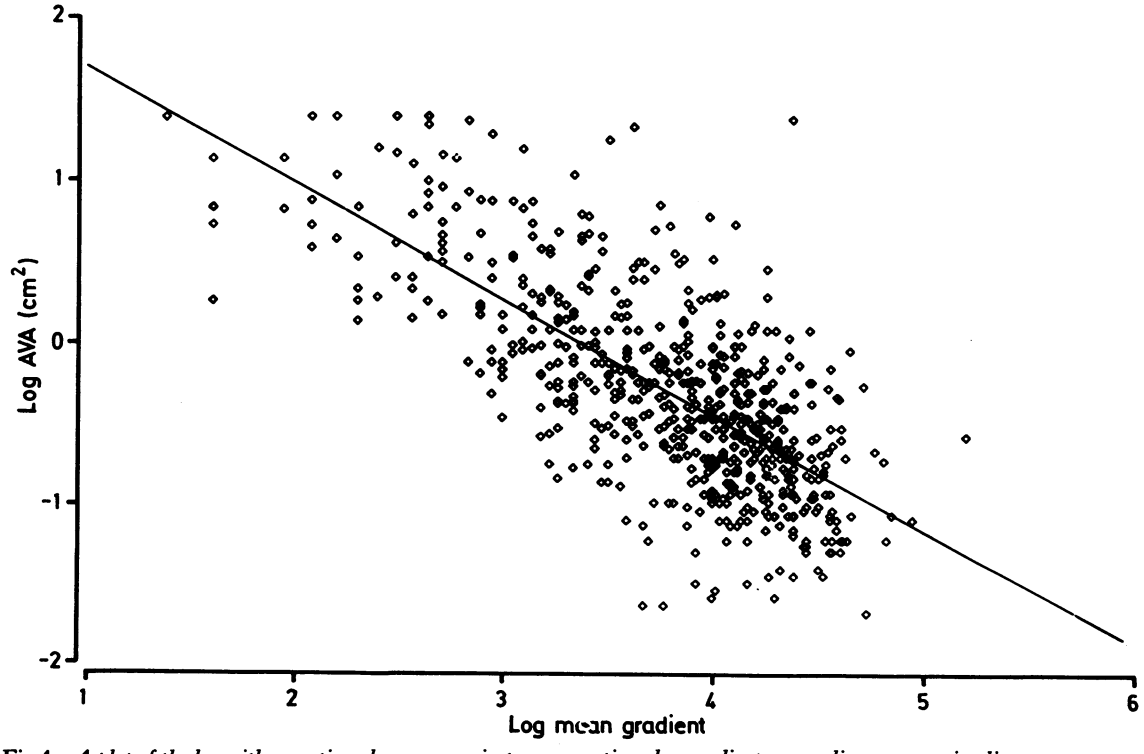

Fig 4 *A plot of the logarithm aortic valve area against mean aortic valve gradient gave a linear regression line.*

Table 3 *Correlation coefficients for the logarithmic plots of mean and peak gradients and valve area by angiographic grade of aortic regurgitation*

Grade AR	Aortic valve gradient		Number*
	Peak	Mean	
0	−0·73	−0·78	72
1	−0·63	−0·68	270
2	−0·68	−0·66	189
3	−0·69	−0·69	97
4	−0·63	−0·68	7
All	−0·70	−0·71	636

AR, angiographic grade of aortic regurgitation.
*Number of patients with that grade of aortic regurgitation.

Table 4 *Correlation coefficients for the logarithmic plots of mean and peak gradients and valve area by age group of patients*

Age (yr)	Aortic valve gradient		Number
	Peak	Mean	
<40	0·64	0·64	47
40–49	0·76	0·76	87
50–59	0·69	0·70	176
60–69	0·72	0·73	262
>70	0·53	0·53	88

difficult to define a lower limit that correctly classified a reasonable number of patients, so we used both 20 mm Hg and 30 mm Hg for the mean and peak gradients. With these criteria 12% of patients with a mean gradient <20 mm Hg and 18% of patients with a peak gradient of <20 mm Hg would be misclassified as having mild aortic stenosis. The figures increased to 23% and 30% respectively when a lower limit of 30 mm Hg was used. These patients were looked at in more detail (see table 7). As expected, these patients with low gradients and severe stenosis had low cardiac indices and usually had little or no aortic regurgitation, but their ejection fractions were normal with normal end diastolic volume indices. The ejection fractions were in fact better than in those patients with mean or peak gradients <20 mm Hg and mild stenosis but the misclassified patients had significantly smaller ventricles by angiographic or echocardiographic estimation ($p < 0·05$). The patients with severe stenosis had less aortic regurgitation. There was no significant difference in left ventricular hypertrophy when determined by either echocardiographic wall dimensions or on electrocardiographic criteria, though there was a trend for patients with mild aortic stenosis to have more electrocardiographic left ven-

Table 5 *Power of peak aortic valve gradients to predict severe aortic stenosis (aortic valve area <0·9 cm²) in 569 patients*

Gradient (mm Hg)	Specificity (%)	Sensitivity (%)	Predictive value		Accuracy (%)	Number of patients*
			+ve (%)	−ve (%)		
< 20						89
> 20	42	96	79	82	80	56
> 30	59	89	83	70	80	55
> 40	72	81	86	62	78	38
> 50	78	74	88	57	76	58
> 60	88	64	92	51	71	69
> 70	92	48	93	44	71	60
> 80	95	34	93	38	53	29
> 90	96	27	94	37	48	41
>100	98	18	96	34	42	74

*Patients with gradients ⩾10 mm Hg.

Table 6 *Power of mean aortic valve gradients to predict severe aortic stenosis (aortic valve area <0·9 cm²) in 636 patients*

Gradient (mm Hg)	Specificity (%)	Sensitivity (%)	Predictive value		Accuracy (%)	Number of patients*
			+ve (%)	−ve (%)		
< 20						77
> 20	33	98	75	88	77	82
> 30	60	92	83	77	81	79
> 40	73	80	86	63	77	83
> 50	84	66	90	54	72	101
> 60	93	46	93	45	61	81
> 70	97	30	95	40	51	67
> 80	99	15	97	36	42	26
> 90	100	9	98	34	38	27
>100	100	3	100	33	34	13

*Number of patients with gradients ⩾10 mm Hg.

Table 7 *Details of patients misclassified when gradients with a 90% predictive accuracy were used*

Gradient	*Number*	*CI (l/min/m²)*	*AR > 1*	*EF (cm³/m²)*	*EDVI*	*LVED (cm)*	*Septum (cm)*	*PW (cm)*	*LVH (%)*
All:									
Mild	217/660	4·6	72%	58%	116	6·0	1·27	1·14	45
Severe	443/660	2·7**	35%**	57%	86**	5·3	1·38*	1·20**	50
Mean < 20 mm Hg:									
Mild	68/ 77 (78%)	4·1	50/ 68 (73%)	53%	126	6·5	1·22	1·03	48
Severe	9/ 77 (12%)	2·4**	2/ 9 (22%)**	58%	81*	5·5	1·30	1·12	50
Mean > 50 mm Hg:									
Mild	31/315 (10%)	5·9	29/ 31 (94%)	61%	118	5·7	1·39	1·20	47
Severe	284/315 (90%)	2·8**	109/284 (39%)**	58%	83**	5·14*	1·42	1·26	53
Mean < 30 mm Hg:									
Mild	123/159 (77%)	4·1	81/123 (67%)	55%	118	6·3	1·22	1·09	45
Severe	36/159 (23%)	2·2**	6/ 36 (17%)**	57%	85**	5·3**	1·30	1·12	23*
Peak < 20 mm Hg:									
Mild	73/ 89 (82%)	4·3	56/ 73 (77%)	56%	118	6·3	1·25	1·13	43
Severe	16/ 89 (18%)	2·3**	1/ 16 (6%)**	62%	80*	4·9**	1·18	1·07	20
Peak > 60 mm Hg:									
Mild	20/273 (7%)	5·7	16/ 20 (80%)	63%	110	5·4	1·38	1·18	50
Severe	253/273 (93%)	2·8**	100/253 (40%)**	57%	83**	5·1	1·42	1·26	52
Peak < 30 mm Hg:									
Mild	102/145	4·2	74/102 (73%)	57%	116	6·1	1·26	1·13	44
Severe	43/145 (%)	2·3**	7/ 35 (14%)**	58%	84*	5·2**	1·27	1·12	29

This table shows in detail the patients who would be misclassified if gradients alone were used to grade the severity of aortic stenosis. The gradients used are the minimum gradient that had a >90% positive predictive value for severe aortic stenosis and the maximum gradient that had a >90% positive predictive value for mild aortic stenosis for both mean and peak gradients. Because no single gradient gave a predictive accuracy of >90% for mild aortic stenosis we used two gradients (20 mm Hg and 30 mm Hg).

CI, cardiac index; AR > 1 = number of patients with greater than angiographic grade 1 aortic regurgitation; EF, angiographic ejection fraction; EDVI, angiographic end diastolic volume index; mild, aortic valve area >0·9 cm²; severe, aortic valve area ≤0·9 cm².

*p < 0·05 and **p < 0·01 for comparisons between mild and severe stenosis.

tricular hypertrophy. This difference was significant for mean gradients of <30 mm Hg. At <30 mm Hg, the peak gradient is more likely to underestimate severity. Body surface area was the same in the two groups.

The higher gradients were more useful because they gave a much lower level of misclassification (10% for a mean gradient of >50 mm Hg and 7% with a peak gradient of >60 mm Hg). Furthermore, most (94% and 78%) of these patients had >grade 1 aortic regurgitation. The ejection fraction was similar to that in patients with severe aortic stenosis but again these patients had significantly smaller ventricles and there was no difference in echocardiographic wall dimensions or electrocardiographic left ventricular hypertrophy.

Of the patients studied 36% and 38% respectively had intermediate gradients that were neither sensitive or specific enough to be used on their own (peak from 20–60 mm Hg, mean from 20–50 mm Hg).

Discussion

An objective measure of the severity of aortic stenosis is important as it is on this basis that the decision for aortic valve replacement is made. If the valve area is accepted as the best measure available then this study shows the inadequacy of using aortic valve gradients alone. Haemodynamic studies of prognosis in severe aortic stenosis have been limited because the effectiveness of aortic valve replacement was demonstrated before modern haemodynamic methods were available.[11–13] The recent study by Turina and colleagues in patients who refused operation showed that prognosis was best predicted by the valve area.[1] Patients with symptoms and a valve area of <0·9 cm² had a poor prognosis while those with a larger valve area with or without symptoms had a good prognosis. Symptom free patients did not have the same poor prognosis; this result is further supported by the study by Kelly and colleagues who found no difference in mortality (excluding the perioperative period) between unoperated patients without symptoms and patients with similar valve areas who had undergone valve replacement.[14] The importance of the cardiac output was shown by Matthews and colleagues who found that patients with poor left ventricular function and low cardiac output were more likely to die while awaiting valve replacement.[5] Furthermore, because serial haemodynamic studies showed that as aortic valve disease progresses the cardiac output falls, the use of the gradient alone will

underestimate the degree of progression.[2-4] It may be argued that cardiac output is included because even where the valve area is not formally calculated, the decision to operate is also based on the subjective angiographic, echocardiographic, or clinical appearance and is not based on the gradient alone. This study showed that in patients with low gradients those with severe aortic stenosis had similar (or slightly better) ejection fractions and significantly smaller ventricles than those with mild aortic stenosis. These patients would be very difficult to identify on the subjective appearance of the echocardiogram or angiogram and would only be identified if the cardiac output was formally measured. The traditional clues of echocardiographic or electrocardiographic left ventricular hypertrophy would not be helpful because there is no significant difference between patients with severe and mild stenosis and low gradients. The patients with high gradients and mild aortic stenosis nearly all had grade 2 or more aortic regurgitation with large ventricles with good ejection fractions and would be less difficult to identify. In any case, the combination of stenosis and regurgitation in these patients may be sufficient to recommend operation.

It seems illogical to mix objective and subjective measurements when objective evidence can be obtained easily, either invasively or non-invasively. Doppler measurement of the aortic valve area by either the Gorlin formula or a continuity equation correlated closely with invasive measurements.[15-17] Doppler gradients alone, however, are poor predictors of valve area; the study by Danielsen and colleagues produced very similar correlations to our study.[18]

We suggest the following guidelines for calculating valve areas if a selective policy is envisaged. An upper limit of a mean gradient of 50 mm Hg or a peak gradient of 60 mm Hg will have a low false positive rate for severe aortic stenosis and most of these patients will have clinically significant aortic regurgitation. We cannot, however, stake an effective lower limit because false negative rates were high for gradients of 20 or 30 mm Hg, especially where the peak gradient was used. These patients would be difficult to identify if the valve area is not calculated because they have relatively small ventricles with good ejection fractions. We therefore recommend that the aortic valve area should be calculated in all patients with symptoms and aortic stenosis with a mean gradient of <50 mm Hg (50% of patients in this study) or a peak gradient of <60 mm Hg (47% of patients in this study), particularly if there is no aortic regurgitation.

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