Pulmonary hypertension and sudden death in aortic stenosis¹

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SUMMARY Sudden death is now an infrequent occurrence in severe aortic stenosis. However, an impressive increase in pulmonary arteriolar resistance has been found in some patients with end-stage aortic stenosis dying suddenly or deteriorating suddenly after catheterisation. Pulmonary hypertension does not seem to cause sudden death, but, in conjunction with decreased cardiac output, a critical reduction in aortic orifice area, and left ventricular failure, pulmonary hypertension identifies a population at significant risk. The rare finding of severe pulmonary hypertension in aortic stenosis should be considered an important marker for sudden death and in association with left ventricular failure may indicate an urgent need for valve replacement, regardless of the apparent clinical condition of the patient. In a small number of subjects catheterised postoperatively, increased pulmonary arteriolar resistance lessened rapidly.

Sudden death in patients with severe aortic stenosis is a well-recognised event which was estimated in older reports to occur in 5 to 15 per cent of patients (Mitchell *et al.*, 1954; Takeda *et al.*, 1963; Friedberg, 1966; Campbell, 1968). With present clinical recognition and diagnostic catheterisation, patients are usually referred earlier for aortic valve replacement, and sudden death is rare.

Within 24 hours of cardiac catheterisation, 4 patients with critical aortic stenosis died suddenly with heart failure and cardiogenic shock. In all, pronounced left ventricular failure and severe pulmonary hypertension with increased pulmonary arteriolar resistance were found. Three others deteriorated suddenly after study and underwent successful emergency aortic valve replacement. Review of the haemodynamics in 3 other patients with critical aortic stenosis who died suddenly while awaiting elective valve replacement indicated a similar pattern. With this knowledge 5 additional subjects identified by similar haemodynamics after catheterisation were subjected to immediate aortic valve replacement, with survival. The Smeloff-Cutter aortic prosthesis was used in all operated

patients. These 15 patients are termed the subject group. Clinical and haemodynamic data concerning the subject group are listed in Tables 1 and 2.

Methods and subjects

In order to investigate this problem, the records of 72 patients with critical aortic stenosis identified over a 5-year period were reviewed.

Haemodynamic data were determined in standard fashion by right heart catheterisation and by measurement of transaortic gradients by trans-septal left ventricular catheterisation and central aortic catheterisation. Contrast injections were limited to the coronaries and aortic root alone because of the risk of transseptal left ventricular angiography (Braunwald *et al.*, 1964). Consequently, left ventricular injections for assessment of mitral regurgitation were not performed. Patients with more than minor angiographic evidence of aortic regurgitation were excluded. The clinical deterioration of patients after catheterisation could not be related to arrhythmias, the trauma of a prolonged procedure, or acute myocardial infarction.

Statistical analysis was applied using a negative t test to identify whether within the population separate subsets of individuals were present. Frequency histograms and distribution curves of the

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Table 1 Sudden death in aortic stenosis: clinical and haemodynamic findings

Case no.	Age (y)	LA	PA	Ao	LV	CI	AVA	PAR	Coronaries	Comment
1	59	20*	78/30 (51)	78/45	190/23	1.4	0.24	992	Normal	Died of cardiogenic shock 3 h after study awaiting operation
2	57	35	113/50 (70)	106/60	273/41	1.1	0.13	1528	Normal	Died in lift 48 h after study on way to operation
3	49	20	73/27 (44)	110/52	264/26	3.2	0.41	304	Ostial right coronary artery block	Died suddenly 6 weeks after study awaiting operation
4	61	15	42/20 (31)	120/67	222/21	2.4	0.50	280	60% mid-right coronary artery block	Died suddenly 1 mth after study awaiting operation
5	60	17	56/31 (48)	135/80	204/28	1.6	0.28	864	80% prox. left anterior descending coronary artery block	Died 2 h after study on way to operation
6	49	20*	45/24 (30)	115/50	220/25	2.1	0.28	221	Not done	Died in ante-room awaiting operation
7	54	31	70/35 (52)	98/65	295/36	2.0	0.20	437	Not done	Died suddenly 4 h after study

*PA wedge pressure.

LA, left atrial mean; PA, pulmonary artery; Ao, aortic pressure; LV, left ventricle; CI, cardiac index (l/m^2); AVA, aortic valve area; PAR, pulmonary arteriolar resistance ($dynes\ cm\ s^{-4}$).

entire population were generated by a computer and compared with those patients dying or suddenly deteriorating (Fig.).

Results

The haemodynamic profile of the 72 patients is presented in Table 3. The normal value for the cardiac index was greater than $2.7\ l/m^2$, the value for left ventricular filling pressure was 14 mmHg or

less, and for the critical reduction in aortic valve area it was assumed to be $0.5\ cm^2$ or less (Gorlin *et al.*, 1955). The normal value for pulmonary arteriolar resistance was less than $160\ dynes\ cm\ s^{-5}$. As expected, in those dying suddenly or deteriorating after study, mean cardiac index and valve area were significantly reduced and left heart filling pressure was high. Though mean pulmonary artery pressure and resistance were somewhat raised for the entire population, in subjects dying suddenly or needing

Table 2 Aortic stenosis with pulmonary hypertension: clinical and haemodynamic findings in 8 patients who underwent emergency valve surgery

Case no.	Age (y)	LA	PA	Ao	LV	CI	AVA	PAR	Coronaries	Comment
8	56	17	100/51 (72)	98/72	205/22	3.1	0.52	648	Normal	Severe congestive heart failure before surgery; died of myocarditis 4 mth after aortic valve replacement
9	63	33	67/33 (49)	143/100	225/38	2.4	0.40	376	Normal	Severe congestive heart failure; IHSS on postop. cath.
10	61	17	42/19 (30)	80/53	171/24	1.3	0.18	482	Not done	Cardiogenic shock preop.; acute myocardial infarct 18 mth postop.
11	51	31	65/30 (44)	90/64	160/40	1.5	0.30	484	Not done	Shock after study; minor congestive heart failure postop.
12	60	28	90/35 (49)	110/68	208/32	3.1	0.53	226	Not done	Severe congestive heart failure preop.; died 5 y postop. of cerebral haemorrhage
13	57	35	112/57 (68)	87/61	190/32	2.3	0.33	587	Normal	Severe congestive heart failure preop.; minor congestive heart failure postop.
14	60	31	72/32 (46)	86/68	145/25	0.98	0.15	769	Normal	Diagnosis unsuspected until study; now asymptomatic
15	67	23	97/47 (65)	92/64	141/27	1.6	0.44	1159	Complete obstruction of left anterior descending coronary artery and right coronary artery	Valve replacement, double coronary bypass and left ventricular aneurysm resection

LA, left atrial mean; PA, pulmonary artery; Ao, aortic pressure; LV, left ventricle; CI, cardiac index; AVA, aortic valve area; PAR, pulmonary arteriolar resistance ($dynes\ cm\ s^{-4}$); AVR, aortic valve replacement; IHSS, idiopathic hypertrophic subaortic stenosis; AMI, acute myocardial infarct.

Fig. Statistical analysis of haemodynamic indices in patients with aortic stenosis. Patients dying suddenly or deteriorating suddenly are compared with those who were clinically stable.

emergency surgery because of a deterioration in their clinical state the mean value was raised to 47 mmHg.

Statistical analysis indicated that with sudden death or deterioration there was a significant relation to lowered cardiac index and valve area and to increased left heart filling pressures (Table 4). However, when pulmonary arteriolar resistance was analysed, statistical correlation with death or deterioration increased by one order of magnitude. Patients dying suddenly or deteriorating suddenly had a higher pulmonary arteriolar resistance than

the remaining population, averaging 591 dynes as compared with 130 dynes in the stable population (Fig.). Pronounced reduction in pulmonary arteriolar resistance occurred in 3 patients restudied soon after operation (Table 5). Additionally, the cardiac index rose and left ventricular filling pressure dropped, as did left atrial mean pressure and pulmonary artery pressure.

Reversal of the ventriculoatrial gradient was found in 13 of the 15 patients in the subject group (Tables 1 and 2). However, premature closure of the mitral valve was not felt to be the cause (Basu

Table 3 Aortic stenosis: haemodynamic values* in 72 patients

CI	0.98	2.6	4.0	l/min
AVA	0.15	0.46	0.9	cm ²
LVEDP	8	21.2	47	mmHg
PAP	11	27	72	mmHg
PAR	13	218.9	1528	dynes cm s ⁻²

*Range and mean values.

et al., 1978) since all subjects were in sinus rhythm and echocardiographic study of the mitral valve in 8 showed normal closing times. The 'reversed gradient' was felt to be the result primarily of the forceful increase in atrial contraction in end-diastole.

Discussion

Patients with aortic stenosis and congestive heart failure admittedly have a poor prognosis. In the subject group, 7 of 15 patients had severe heart failure and 5 had cardiogenic shock, occurring after catheterisation in 4 and before study in 1 patient who survived operation. In the clinically stable group, over 50 per cent had congestive failure but were well controlled medically.

Sudden death from aortic stenosis has been well correlated with left ventricular failure, and with the duration of delay between catheterisation and the time of operation (Matthews *et al.*, 1974), but neither the pathophysiological mechanisms responsible for sudden death in aortic stenosis nor the pre-mortem haemodynamics are known. Data from this study suggest that resting pulmonary hypertension caused by increased precapillary resistance may occur as a late and near-terminal manifestation of aortic stenosis and, in combination with left ventricular failure, may formidably influence prognosis. The effect of this added resistance is to

Table 4 Population identity: P values relating to sudden death or deterioration; statistical relation between haemodynamic events

AVA	= 0.001
CI	= 0.001
LVED	= 0.002
PAR	≪ 0.001

increase right ventricular overload, compromising the cardiac output of an already afterloaded left ventricle. Such afterloads in series may identify a population at greater risk for sudden death. The data do not, however, prove that abnormal pulmonary vascular resistance causes death, but suggest that, together with left ventricular failure, it may be a marker for sudden death or deterioration in marginally compensated patients.

Pulmonary hypertension in disease of the left ventricle is not uncommon at rest and with exercise, and mortality, as reported by Trell (1973), increases significantly with increasing levels of pulmonary artery pressure. In prior haemodynamic studies, pulmonary hypertension in aortic stenosis has been attributed to left ventricular failure alone without precapillary vascular obstruction (Kirsch *et al.*, 1970; Trell, 1973; Matthews *et al.*, 1974). In contrast, we find that there may be pronounced pulmonary vasoconstriction in severe aortic stenosis, not unlike that seen in long-standing mitral stenosis (Gorlin *et al.*, 1951) and perhaps serving the same physiological purpose of averting pulmonary oedema at the expense of right ventricular function (Wood, 1954). Additional causes of pulmonary hypertension (Walston *et al.*, 1973) were not apparent clinically but cannot be excluded since pulmonary function studies and arterial blood gases were not uniformly performed. However, there was no history of pulmonary disease in the subject population. Arterial oxygen tensions at the time of cardiac catheterisation were mildly reduced in 3 of the subject population. Mitral stenosis was excluded by left heart catheterisation, though mitral regurgitation

Table 5 Pre- and postoperative haemodynamics after emergency aortic valve replacement

Case no.	LA	PA	Ao	LV	CI	AVA	PAR
13							
Preop.	35	112/57 (68)	87/61	190/32	2.3	0.33	587
Postop. 1 mth	8	40/19 (23)	148/84	172/10	3.3	1.4	184
14							
Preop.	31	72/32 (46)	86/68	145/25	0.98	0.15	769
Postop. 1 wk	8	42/18 (25)	83/58	103/10	2.6	1.4	309
15							
Preop.	23	97/47 (65)	92/64	141/27	1.6	0.44	1159
Postop. 10 dy	12	58/29 (36)	103/56	110/17	2.3	1.56	492

was not assessed angiographically.

One might properly ask why severe pulmonary hypertension and increased precapillary vascular obstruction have not previously been recognised in aortic stenosis. First, since the development of mathematical criteria for orifice area (Gorlin *et al.*, 1955), critical reduction in this index has been the primary indication for surgery in symptomatic patients. Secondly, abnormal pulmonary vascular resistance and pulmonary hypertension have seldom been reported or sought (Smith *et al.*, 1954; Pirincci *et al.*, 1961; Kirsch *et al.*, 1970; Lee *et al.*, 1970; Trell, 1973; Matthews *et al.*, 1974), and analysis of the dynamics of the pulmonary circulation has not been considered a useful criterion for assessing diseases of left ventricular outflow.

All patients clearly showed haemodynamic findings of severe aortic valvular stenosis, and operation was warranted by these criteria alone. Only the timing of the operation was in question. Fifty-seven stable patients underwent elective replacement of the aortic valve. Of these, 7 had pulmonary hypertension (mean pulmonary artery pressure 39 mmHg; mean pulmonary arteriolar resistance 222 dynes). Their pressures and resistances, though increased, were significantly lower than in the unstable group. Therefore, not all patients with pulmonary hypertension may need emergency surgery. However, the magnitude of pulmonary resistance changes may be useful in choosing candidates for urgent operation.

Our experience suggests an arbitrary cutoff point where a critical rise in pulmonary arteriolar resistance exists and where urgent surgery should be considered. Ten patients with pulmonary arteriolar resistances over 350 dynes suddenly died or became seriously ill. Using this arbitrary cutoff value, 4 subjects died but 6 survived emergency operation.

Clinically terminal patients with aortic stenosis need no haemodynamic studies to confirm the severity of their disease. However, we emphasise that of the 7 patients who died (Table 1), 3 were stable enough to be discharged for elective surgery and 1 died suddenly and unexpectedly while awaiting hospital discharge. Of the 8 patients who underwent emergency valve replacement (Table 2), 4 were in congestive failure and 2 were in cardiogenic shock. Of these patients, 5 would not have been selected for urgent surgery had not the relation of abnormal pulmonary vascular resistance to sudden death been known.

We, therefore, believe that severe pulmonary hypertension caused by increased precapillary resistance may exist as a late physiological manifestation of severe aortic stenosis either in patients who appear stable or who are critically ill. In conjunction with severe left ventricular failure, this

finding relates to sudden death or sudden clinical deterioration. Rapid and successful surgical intervention may prevent death in these patients. The data suggest that patients with assumed end-stage disease can survive operation and improve haemodynamically.

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