Natural history of valvular aortic stenosis[1]

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Fifteen adult patients (ages 32 to 59 years) with significant valvular aortic stenosis in whom the severity of obstruction was documented by haemodynamic measurement and in whom the natural history was not inter- rupted by operation were followed for up to 11·7 years, or until death. The overall prognosis was poor, two-thirds of the group being dead at last follow-up. The percentage mortality, corrected for the number of patients followed, was 36 per cent at 3 years, and 52 per cent at 5 years; of those who were followed for 10 years, 90 per cent had died. The age at the onset of symptoms was not related to duration of survival, there was no clear relation between the type of symptom and survival, and haemodynamic parameters could not be correlated with symptoms or survival. Patients with a combination of symptoms tended to have the worst prognosis. Three patients were asymptomatic, one of whom died suddenly. These data provide a basis for predicting the natural history of isolated valvular aortic stenosis in adult patients, and indicate that significant obstruction together with symptoms portends an extremely poor prognosis.

The development of effective prosthetic devices for replacement of the aortic valve has underscored the need for greater understanding of the natural history of patients with valvular aortic stenosis. Though there is considerable information regarding the clinical features of this disease (Wood, 1958; Mit- chell *et al.*, 1954; Bergeron *et al.*, 1954; Kumpe and Bean, 1948; Anderson, 1961; Takeda, Warren, and Holzman, 1963; Campbell, 1968) and retrospective analyses of necropsy data have been useful (Mitchell *et al.*, 1954; Bergeron *et al.*, 1954; Kumpe and Bean, 1948; Anderson, 1961; Campbell, 1968), little is known of the natural history of patients in whom the haemodynamic severity of obstruction has been documented. Thus, in clinical studies in which left heart catheterizations were performed, the natural history frequently was interrupted by operation (Hohn *et al.*, 1965; Abelmann and Ellis, 1959; Baker and Somerville, 1959; Morrow, Austen, and Braun- wald, 1963). Other studies have included patients with associated mitral valve disease (Mitchell *et al.*, 1954; Kumpe and Bean, 1948), other forms of left ventricular outflow tract obstruction (Hohn *et al.*, 1965; Baker and Somerville, 1959; Campbell, 1968), or they have included patients in whom aortic

stenosis was not clearly differentiated from coexist- ing predominant aortic regurgitation (Wood, 1958; Mitchell *et al.*, 1954; Kumpe and Bean, 1948; Hohn *et al.*, 1965; Abelman and Ellis, 1959).

The present study was undertaken to evaluate the natural history of valvular aortic stenosis in adult patients in whom the degree of obstruction was documented by left heart catheterization. Since many of these patients were studied before the ad- vent of aortic valve prostheses, their follow-up has provided an unusual opportunity to document the fate of patients with this disease in whom the clinical course was not interrupted by operation.

Methods

Among the first 500 adult patients (over 25 years of age) with aortic valve disease admitted to the National Heart Institute after 1954, 102 had isolated valvular stenosis and 20 were not operated upon. Fifteen of these patients had haemodynamically significant obstruction and form the basis for the present report. Excluded from con- sideration were patients with aortic regurgitation characterized by a diastolic murmur of greater than 1/6 intensity, a pulse pressure of more than 60 mmHg, or significant aortic regurgitation by cineangiography. Also excluded were patients with haemodynamic and cine- angiographic evidence of mitral or tricuspid valve disease, supra- or subaortic stenosis, or idiopathic hypertrophic subaortic stenosis. Significant obstruction was defined as a left ventricular to brachial artery peak systolic pressure

gradient $\geq$ 50 mmHg and/or an aortic valve area index less than 0·7 cm²/m² BSA (Braunwald and Morrow, 1963). Left ventricular hypertrophy on the electrocardiogram was identified as SV1 + RV5–6 > 35 mV.

Each patient was followed for at least two years, or until death. Surgical treatment was not undertaken for a variety of reasons. Some patients refused operation, in some of the earlier patients operation was deferred because of the relatively high risk of the operative procedure, and in several patients the symptoms were not considered sufficiently disabling to warrant operation. The long follow-up was obtained from clinic notes, by letter, or by telephone conversation with the patient, his physician, or relatives.

Results

The clinical, haemodynamic, and follow-up data in all patients are summarized in the Table. The patients ranged in age from 32 to 59 years at the time of their initial haemodynamic evaluation. Twelve of the 15 patients were men.

Ten of the 15 patients were dead by the end of the follow-up period. In each, death was thought to be due to progressive cardiovascular deterioration, or it was unexpected. In 4 of the 10 patients who died, necropsy was performed and confirmed the presence of severe calcific aortic stenosis. At necropsy, Case 7 had no demonstrable coronary artery disease, Cases 6 and 8 had slight to moderate coronary artery disease, and Case 13 had severe coronary artery disease. The haemodynamic data, including the left ventricular peak systolic and end-diastolic pressures, the left ventricular to systemic arterial pressure gradients, the aortic valve orifice area indices, and the cardiac indices in the 10 patients who died were similar to those in the 5 patients who were alive at the end of the follow-up period (Fig. 1). The yearly percentage mortality is shown in Fig. 2. The time scale represents years after the onset of symptoms, or in the case of the asymptomatic patients, the years after initial haemodynamic evaluation, and the percentage mortality is corrected for the number of patients followed for that time. Of those followed for 2 years, mortality was 15 per cent; for 3 years, 36 per cent; for 5 years, 52 per cent; and for 10 years, 90 per cent.

The age at onset of symptoms averaged 47 years but encompassed a wide range. The duration of survival after onset of symptoms did not appear to be related to patient age. The average life expectancy after onset of symptoms or study in those patients

TABLE *Clinical and haemodynamic findings in patients with aortic stenosis*

Case No.	Sex	Duration of symptoms			NYHA	Electrocardiogram	Haemodynamic study				
		Angina	Syncope	Congestive heart failure			LV-BA gradient (mmHg)	LVS/ED (mmHg)	CI	VOA (cm²)	VOA/ m² BSA
1	M	1 yr	—	—	II	LVH	51	180/12	—	—	—
2	M	—	—	—	I	LVH LVS	90	220/20	2·4	0·64	0·33
3	M	1 yr	—	—	II	LVH LVS	32	164/9	2·2	0·88	0·46
4	F	4 yr	—	4 yr	II	Digitalis effect	45	180/10	3·1	0·74	0·45
5	M	—	—	—	I	LVH LVS	50	170/12	2·7	0·91	0·50
6	M	—	—	1 yr	III	LVH LVS	30	170/8	2·2	0·75	0·43
7	M	—	1 mth	—	II	LVH	35	15/18	3·7	1·2	0·63
8	F	3 yr	—	3 yr	III	LVS	90	172/26	6·5	0·94	0·60
9	M	1 yr	1 yr	—	II	LVH	30	190/8	2·3	0·91	0·50
10	M	—	—	—	I	LVH LVS	70	176/6	—	—	—
11	F	1 yr	—	—	II	Digitalis effect	30	190/12	2·9	0·70	0·42
12	M	10 yr	—	10 yr	III	LVH LVS	44	153/29	1·7	0·63	0·32
13	M	—	—	1 yr	III	LVH LVS	83	196/13	2·4	0·64	0·30
14	M	10 yr	—	10 yr	II	LVH LVS	36	180/12	1·9	0·48	0·26
15	M	15 mth	2 mth	—	II	LVH LVS	85	205/5	—	—	—

LVH, left ventricular hypertrophy; LVS, left ventricular 'strain'; BA, brachial artery; LVS/ED, left ventricular systolic and end-diastolic pressures; CI, cardiac index; VOA, valve orifice area.
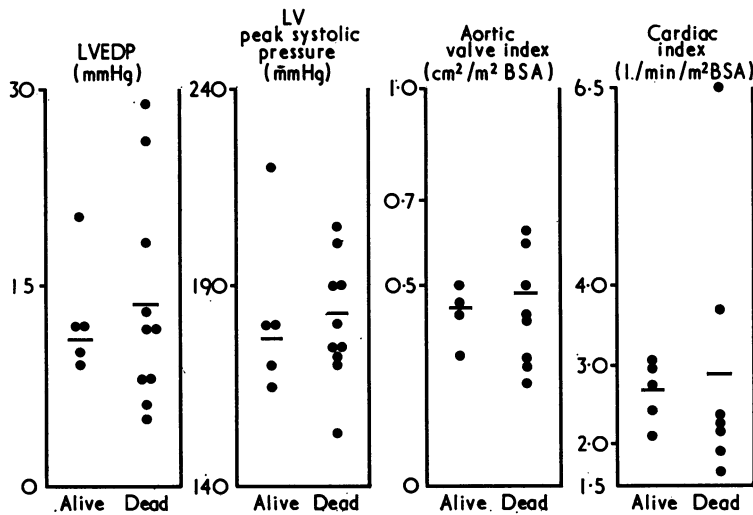
FIG. 1 *Haemodynamic features in patients with significant valvular aortic stenosis related to survival. No apparent differences in any of these measurements distinguish survivors from non-survivors.*

Follow-up

Age at onset of symptoms	Age at study	Age at last follow-up	Duration of history or follow-up	Status
56	57	61	5 7/12	Alive
51	51	56	5 11/12	Alive
40	41	45	5 9/12	Alive
39	43	47	8	Alive
49	49	51	2 1/11	Alive
56	57	58	2 2/12	Dead
47	47	47	6/12	Dead
29	32	32	3 1/12	Dead
52	53	56	4 2/12	Dead
45	45	46	1 7/12	Dead
58	59	62	3 2/12	Dead
47	57	11	11	Dead
54	55	56	2 8/12	Dead
43	53	54	10 6/12	Dead
44	46	52	6 6/12	Dead

who died was 4·8 years (range 6 months to 11 years).

Twelve of the 15 patients (80%) had symptoms, 8 of the patients being in functional Class II (NYHA) and 4 in Class III when first seen. Three patients (20%) were in functional Class I (Table). Of these latter 3 patients, 2 remained without symptoms at last follow-up, 2 years and 6 years after study, but the third patient died suddenly 19 months after study despite the fact that he had remained asymptomatic.

When first evaluated, 9 of the 15 patients (60%) had noted angina pectoris for periods of 1 to 10 years; in 7 of these 9, angina had been present for 4 years or less. Left ventricular failure, manifested by dyspnoea on exertion, paroxysmal nocturnal dyspnoea, orthopnoea, pulmonary oedema, or peripheral oedema had been present in 6 patients (40%), with a duration of from 1 to 10 years. Syncopal attacks had occurred in 3 patients (20%) from 1 to 12 months before initial evaluation.

The incidence of angina pectoris was similar in the patients who were alive at last follow-up and in those who died. Six of the 9 patients with angina died; however, 5 of these had histories longer than 5 years, and 2 greater than 10 years. Five of the 6 patients with heart failure died (83%), the average life expectancy after the onset of symptoms of failure being 7·3 years. Of the 3 patients with syncope, 2 had associated angina pectoris, and all died. Survival after the first syncopal episode varied from 6 months to 6 years. Four of 6 patients with congestive
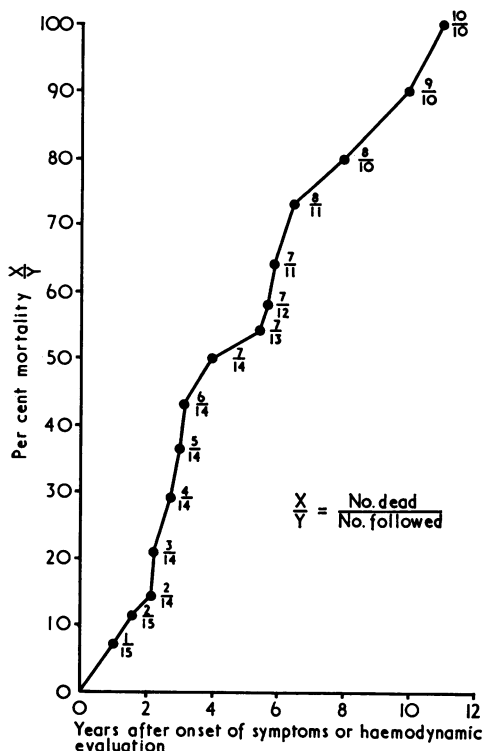
Per cent mortality $\frac{X}{Y}$

100 — 90 — 80 — 70 — 60 — 50 — 40 — 30 — 20 — 10 — 0

$\frac{10}{10}$ $\frac{9}{10}$ $\frac{8}{10}$ $\frac{8}{11}$ $\frac{7}{11}$ $\frac{7}{12}$ $\frac{7}{13}$ $\frac{7}{14}$ $\frac{6}{14}$ $\frac{5}{14}$ $\frac{4}{14}$ $\frac{3}{14}$ $\frac{2}{14}$ $\frac{2}{15}$ $\frac{1}{15}$

$$\frac{X}{Y} = \frac{\text{No. dead}}{\text{No. followed}}$$

0 2 4 6 8 10 12
Years after onset of symptoms or haemodynamic evaluation

FIG. 2 *The yearly percentage mortality in patients with significant valvular aortic stenosis after the onset of symptoms, or from the time of cardiac catheterization, corrected for the number of patients followed.*

heart failure had associated angina pectoris, and 3 of these 4 died. Thus, only 1 of 6 patients with angina pectoris associated with either congestive failure or with syncope has survived.

All 5 patients who were survivors at last follow-up were initially in Class I or II; 90 per cent of those who died were in Class II or III at the time of initial evaluation, though several of these patients subsequently deteriorated to Class III or IV.

On the initial electrocardiogram, sinus rhythm was present in all patients, and left ventricular hypertrophy was present in 12 (Table). A left ventricular 'strain' pattern and a QRS-T vector angle of greater than 90° were present in 10 patients. Left axis deviation was present in 4 patients. In 2 patients, the only electrocardiographic abnormalities were ST segment and T wave changes suggesting digitalis effect. Both of these patients were in Class II and though one continued to exhibit only minor ST segment and T wave abnormalities 4 years subsequently, the other patient had evidence of left ven-

tricular hypertrophy on an electrocardiogram taken 1 year later. The latter patient subsequently died. There was no obvious correlation between the praecordial electrocardiographic voltage and the peak left ventricular systolic pressure or the left ventricular to brachial arterial systolic pressure gradient. No correlation was noted between the amplitude of the praecordial electrocardiographic voltage and survival.

Discussion

Little information is available regarding patients with severe aortic stenosis evaluated by cardiac catheterization who were not subjected to operation. Wood (1958) followed 64 patients with significant aortic stenosis treated medically; 18 of the 32 who were followed for 7 years were known to have died, yielding a *minimum* mortality of 28 per cent. However, Harken *et al.* (1958) reported that 49 of 54 patients (91%) who were advised to have cardiac operation and refused were dead within 6 months. Because many patients in earlier investigations did not have haemodynamic studies, and because of considerable variability in patient selection present in previous reports, an effort was made to confine the present analysis to patients with significant, isolated valvular aortic stenosis. The precise haemodynamic criteria for 'significant' aortic stenosis have varied. Braunwald and Morrow (1963) and Hancock and Fleming (1960) considered a valve orifice index of less than $0.7 \text{ cm}^2/\text{m}^2/\text{BSA}$ to indicate significant obstruction. Wood (1958) considered a valve orifice area of less than 0.75 cm^2 to constitute severe obstruction, whereas others have suggested that 0.5 cm^2 indicates severe narrowing (Conn and Horwitz, 1971). In the present study, the Braunwald and Morrow criterion was used, though no patient had an aortic valve orifice index of greater than $0.63 \text{ cm}^2/\text{m}^2/\text{BSA}$. Therefore, the degree of stenosis was not haemodynamically 'severe' by some criteria, but these data nevertheless provide a basis for understanding the natural history of patients with significant aortic stenosis that was documented by haemodynamic study. It seems clear that given the currently favourable atmosphere concerning aortic valve replacement, many of these patients would now have operations, and it is unlikely that information of this nature will be available in the future.

No patient in our series had a normal electrocardiogram: however, 2 patients had only minimal ST-T abnormalities associated with digitalis administration. Isolated instances of a normal electrocardiogram in the presence of severe aortic stenosis have been reported (Bergeron *et al.*, 1954; Forker *et al.*, 1970; Sanders and Friedlich, 1964). The re-

maining patients had electrocardiographic evidence of left ventricular hypertrophy and/or strain, the usual electrocardiographic findings in the adult patients with significant aortic stenosis (Wood, 1958; Bergeron *et al.*, 1954).

The three cardinal symptoms of aortic stenosis-angina pectoris, syncope, and congestive heart failure have been considered indicative of the presence of severe obstruction (Wood, 1958; Hohn *et al.*, 1965; Baker and Somerville, 1959; Hancock and Fleming, 1960) and to constitute ominous prognostic signs (Wood, 1958; Takeda *et al.*, 1963; Abelmann and Ellis, 1959; Braunwald and Morrow, 1963). Angina pectoris has been reported to occur in from 39 to 70 per cent of symptomatic patients with aortic stenosis (Wood, 1958; Anderson, 1961; Takeda *et al.*, 1963; Hohn *et al.*, 1965; Hancock and Fleming, 1960), its frequency tending to increase with age (Hohn *et al.*, 1965; Hancock and Fleming, 1960). Hancock and Fleming (1960) noted, however, that angina pectoris might occur in patients having various levels of left ventricular systolic pressure and aortic valve areas, and considered alone it proved the least reliable predictor of imminent death in the present small series. Some of our patients were noted to have coronary artery disease at necropsy, and many patients were in the age group at risk from coronary artery disease. Unfortunately, a number of the patients in the present series were studied before the era of routine coronary arteriography; whether or not coronary artery disease was present and its influence on their course is therefore unknown. However, the fact that duration of survival usually was short after the onset of symptoms, and did not appear to be influenced by the age at onset of symptoms, tends to support the view that aortic stenosis rather than possible associated coronary artery disease was the predominant factor responsible for the high mortality rate.

The onset of left ventricular failure generally has been considered to be a grave prognostic sign in patients with aortic stenosis (Anderson, 1961; Baker and Somerville, 1959; Hancock and Fleming, 1960). On the other hand, Hohn *et al.* (1965) suggested that while the onset of failure is ominous, it is not incompatible with prolonged survival provided the patient is on an optimum medical regimen. Though the mortality was high, several patients in the present group survived for many years after the onset of symptoms of left ventricular failure.

Previous studies have suggested that the onset of syncope carries a poor prognosis (Wood, 1958; Hohn *et al.*, 1965), though the duration of syncopal spells may vary considerably (Mitchell *et al.*, 1954; Baker and Somerville, 1959). All of our patients with syncope died, but 2 had associated angina pectoris.

Furthermore, when angina pectoris was associated with left ventricular failure the prognosis was extremely poor. Finally, while much emphasis has been placed on the onset of symptoms, it was disturbing that 1 of 3 patients without symptoms died suddenly.

It now seems apparent that surgical intervention improves the immediate prognosis of symptomatic adult patients with significant aortic stenosis documented at cardiac catheterization (Ross and Braunwald, 1968). However, the role of operation in the management of patients with moderate to severe aortic stenosis who are without symptoms will require further objective prospective studies.

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