Left Heart Haemodynamics at Rest and During Exercise in Patients with Mitral Stenosis

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Transseptal and retrograde catheterization of the right and left heart (Cournand and Ranges, 1941; Seldinger, 1953; Ross, 1959) provided methods of studying human cardiac haemodynamics on a large scale, which was particularly necessary in view of the widening scope of the surgical treatment of mitral stenosis and other valve defects. In such cases, measurement of left heart pressures and pressure gradients are particularly important.

Increased experience with cardiac catheterization drew attention to the fact that apart from the mechanical obstruction by the stenosed mitral valve, the so-called myocardial factor might also play a role. This assumption of a left ventricular myocardial defect is supported by the following observations made in patients with mitral stenosis: low cardiac output both at rest and during exercise (Harvey *et al.*, 1955), its increase after administration of digitalis (Ferrer *et al.*, 1952), signs of cardiac failure with low cardiac output with normal pulmonary capillary venous pressure (Fleming and Wood, 1959), and increased left ventricular diastolic pressure (Feigenbaum *et al.*, 1966). In such cases, surgical dilatation of the mitral valve cannot bring about the expected improvement; the operation may be even contraindicated because the increased post-operative load on the left ventricle may cause deterioration. Study of this problem has shown that catheterization, at rest, of patients with rheumatic mitral stenosis is inadequate for assessing the cardiac state. It does not take into account the haemodynamics during activity and when performing various types of work. Such conditions may be simulated by subjecting the patient to physical exercise during catheterization. The response to exercise helps to estimate the degree of mitral stenosis on the basis of increased

pressures proximal to the mitral valve and increased left atrioventricular pressure gradients with increased flow; in addition, physical exercise may also help to uncover further disturbances resulting from pathological conditions of the myocardium.

SUBJECTS AND METHODS

Our series comprised 11 patients and 6 controls. The control group consisted of 6 patients without left heart disease, apical systolic murmurs, and suspected pulmonary embolism. An exception was the man (H.B.) examined for a systolic murmur in the apical region. He had a slightly increased pulmonary capillary venous pressure both at rest and during exercise and a raised pulmonary arterial pressure during exercise, together with a small gradient between the capillary venous and the left ventricular end-diastolic pressures, indicating a haemodynamically insignificant mitral stenosis. Since all the other findings were normal, the patient was included in the control group.

The 11 patients comprising the experimental group had pure or dominant mitral stenosis without other valve lesions of haemodynamic significance. An exception was the patient (B.J.) who had tight mitral stenosis and mitral regurgitation (grade 2/3) demonstrated by angiocardiology. All patients had normal systemic blood pressures.

The investigations were carried out in the morning, in the fasting state, without premedication. First, a single- or double-lumen catheter was inserted through the cubital vein into the pulmonary artery (in three control subjects, into the pulmonary periphery); in the others, another catheter was inserted transseptally into the left atrium and a third catheter was passed retrogradely, using the Seldinger technique, from the femoral artery into the left ventricle. The subjects were allowed to rest for 15–20 minutes; afterwards intracardiac pressures were measured and the cardiac output was measured by the Fick method. The subjects then exercised in the supine position using an ELEMA Schönander bicycle ergometer usually at a load of 250

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kpm./min.; if unable to sustain such a load, at 150–200 kpm./min. (Tables I and II). Pressures were recorded throughout the exercise. For the calculations, the pressures measured in the 4th minute of exercise were used. The cardiac output was determined between the 4th and 7th minute of exercise using the Fick method.

Statham electromanometers and the direct-writing Cardirex (Siemens) apparatus were used to obtain the following pressures: pulmonary arterial, left atrial, or pulmonary capillary venous (pulmonary wedge-pressure), and left ventricular; in the course of the examination, the aortic pressure was measured by retrograde catheterization to exclude aortic stenosis. Mean pressures were obtained by electric integration. The phlebostatic plane was situated 5 cm. below Louis' angle. The cardiac output was measured by the Fick method by collecting expired air into a Douglas bag; the O_2 and CO_2 concentrations were determined by a Zeiss (Jena) interferometer. Blood samples from the pulmonary artery and the left atrium or the left ventricle were withdrawn simultaneously in the middle of the collection period. Oxygen saturation of blood was measured by a Kipp (Delft) haemoreflectometer, and haemoglobin was determined by photometry. After exercise, a majority of the patients was subjected to left heart angiocardiology in order to exclude valvular regurgitation or shunt, and to identify the mitral valve lesion.

Pulmonary vascular resistance (PVR) was calculated and expressed in units from the formula:

$$PVR = \frac{\bar{P}_{PA} - \bar{P}_{LA}(\bar{P}_{cv}) \text{ mm. Hg}}{CO \text{ in litres/min.}}$$

where $\bar{P}_{PA}$, $\bar{P}_{LA}$, and $\bar{P}_{cv}$ are the mean pressures in pulmonary artery, left atrium, and wedge positions, respectively, and CO the cardiac output.

FIG. 1.—The mean left atrial pressure ($\bar{P}_{LA}$)—cardiac index (CI) ratio at rest and during exercise in patients with mitral stenosis.

Mitral valve area was calculated from the Gorlin formula (Gorlin and Gorlin, 1951).

RESULTS

Values of the parameters investigated both at rest and during exercise in individual control subjects and patients are presented in Tables I and II.

It is apparent from Table II that patients with mitral stenosis had conspicuous pulmonary hypertension both at rest and during exercise. Pulmonary arterial pressure increased both in control subjects and in patients with mitral stenosis; however, the pulmonary arterial pressure increased during exercise in control subjects on the average by 43.2 per cent, while in patients with mitral stenosis it increased on the average by 79.5 per cent. This increase in pulmonary arterial pressure was a consequence of a high resting left atrial pressure as shown in Table II. Seven patients had resting mean left atrial pressures higher than 20 mm. Hg, indicating that the majority of patients had haemodynamically significant mitral stenosis. During exercise, the mean left atrial pressures increased on the average by 63 per cent of the initial values ($p < 0.001$) while the increases of the left atrial or of the pulmonary capillary venous pressures in control subjects were not significant. From Fig. 1 it is apparent that the increase in left atrial pressure was very steep in relation to the increased blood flow.

The left ventricular end-diastolic pressure in 4 control subjects at rest and in 3 during exercise did

FIG. 2.—The mean left ventricular end-diastolic pressure ($\bar{P}_{LVED}$)—cardiac index (CI) ratio at rest and during exercise in patients with mitral stenosis.

TABLE
HAEMODYNAMIC DATA IN CONTROL

Initials, age, and sex	Diagnosis	Work (kpm./min.)	Mean pulm. art. pressure (mm. Hg)		Mean left atrial pressure (mean pulm. capill. venous) (mm. Hg)		Mean left ventric. end-diast. pressure (mm. Hg)	
			Rest	Exercise	Rest	Exercise	Rest	Exercise
H.B. 26 M	Mitral stenosis grade 1/6	250	18.8	25.5	14.9	15.6	4.9	9.4
S.F. 41 M	Syst. murmur	250	10.2	18.0	2.2	7.2	6.5	9.7
K.V. 22 M	Syst. murmur	400	7.4	12.5	3.1	—	—	—
S.V. 40 M	Haemoptysis	250	18.1	20.5	9.1	9.4	11.4	10.9
K.E. 35 F	Syst. murmur	250	14.5	19.8	0.3	5.2	2.2	—
K.V. 35 F	Syst. murmur	200	10.0	16.8	1.9	1.8	—	—
$\bar{x}$			13.16	18.85	4.86	7.75	6.25	10.0
SD			4.7	4.68	5.86	3.7	3.87	0.79
$\bar{d}$			+5.68		+2.883		+2.56	
Probability			<0.001		NS		NS	

TABLE
HAEMODYNAMIC DATA IN PATIENTS WITH

Initials, age, and sex	Grade of stenosis	Mitral valve area (cm./m. ²)	Work (kpm./min.)	Mean pulm. art. pressure (mm. Hg)		Mean left atrial pressure (mm. Hg)		Mean left ventric. end-diastolic pressure (mm. Hg)		Mean left atrial pressure minus mean left ventric. end-diast. pressure (mm. Hg)	
				Rest	Exercise	Rest	Exercise	Rest	Exercise	Rest	Exercise
K.E. 35 F	3/6	0.5	250	30.8	63.0	22.2	29.9	1.0	7.2	21.2	22.7
P.V. 34 M	5/6	0.4	150	40.5	62.9	25.4	30.5	5.4	5.5	20.0	25.0
H.L. 38 F	4/6	—	250	13.1	48.5	—	—	3.4	15.9	—	—
P.L. 39 M	5/6	0.5	250	34.3	64.5	22.8	41.0	12.4	13.0	10.4	28.0
B.J. 42 M	2/6*	0.9	250	21.2	33.0	17.8	32.4	14.0	17.8	3.8	14.6
K.M. 49 F	2/6	1.2	250	26.8	54.5	20.3	39.0	10.3	24.3	10.0	14.7
F.A. 52 M	4/6	1.3	250	20.0	39.0	10.4	22.8	5.0	13.2	5.4	9.6
F.L. 38 M	4/6	0.5	250	50.5	62.0	27.0	40.5	14.0	16.7	13.0	23.8
C.A. 52 F	5/6	0.8	250	23.5	47.0	15.6	30.3	—	11.1	—	19.2
H.M. 53 F	4/6	1.3	250	32.8	42.1	22.2	39.8	15.0	—	7.2	—
S.K. 38 M	3/6	0.3	250	52.5	116.0	25.5	34.4	4.8	2.3	20.2	32.1
$\bar{x}$				31.45	57.50	20.87	34.06	8.53	12.7	12.3	21.1
SD				12.48	22.20	5.06	5.97	5.16	6.5	6.6	7.2
$\bar{d}$				+26.05		+13.19		+5.06		+8.31	
Probability				<0.001		<0.001		<0.05		<0.001	

* This patient had grade 2/3 incompetence as well.

not exceed 12 mm. Hg, which is the upper limit of normal (Braunwald *et al.*, 1961; Samet *et al.*, 1965). End-diastolic pressure in the left ventricle increased during exercise on the average by 49 per cent ($p < 0.05$). Only the patient (S.K.) with tight mitral stenosis (mitral valve area, 0.32 cm.²/m.²) had a lower left ventricular end-diastolic pressure during exercise. In 3 patients, end-diastolic pressures increased during exercise by more than 10 mm. Hg. The highest increase was in a woman (patient K.M.) (mitral valve area, 1.25 cm.²/m.²) who also had the highest left ventricular end-diastolic pressure (24.3 mm. Hg) of the whole group. The gradient between the left atrial and the left ventricular end-diastolic pressures measured at rest in patients who had left ventricular end-diastolic pressures higher than 12 mm. Hg averaged 8.6 mm. Hg (3.8–13.0); on the other hand, in patients who had left ventri-

cular end-diastolic pressure higher than 12 mm. Hg, the corresponding gradient measured during exercise averaged 18.1 mm. Hg (9.6–28.0). Fig. 2 shows that in 2 patients the increase in left ventricular end-diastolic pressure concurred, with a slight increase of the cardiac index during exercise. The gradient between the left atrial and left ventricular end-diastolic pressures at rest averaged 12.3 $\pm$ 6.6 mm. Hg. During exercise the gradient increased by 8.31 $\pm$ 5.2 mm. Hg on the average, reaching a mean value of 21.1 $\pm$ 7.2 mm. Hg during exercise for the whole group.

The heart rate increased during exercise both in controls and in patients; in the controls it was slightly higher both at rest and during exercise, but the differences were not significant. The mean oxygen consumption of the patients, both at rest and during exercise, was lower than that of the

I

GROUP BEFORE AND AFTER EXERCISE

Heart rate/min.		O ₂ consumption (ml./min./m. ²)		A-V O ₂ diff. (vol. %)		Cardiac index (l./min./m. ²)		Stroke index (ml./min./m. ²)		Pulm. vasc. resist. (units)	
Rest	Exercise	Rest	Exercise	Rest	Exercise	Rest	Exercise	Rest	Exercise	Rest	Exercise
105	126	179	662	4.0	6.7	4.45	5.5	42	44	0.49	1.00
84	100	213	554	4.4	6.8	2.75	5.1	36	51	1.65	1.32
60	84	383	1054	4.7	8.75	3.7	5.47	62	65	0.81	0.43
60	102	305	692	4.4	6.6	3.86	5.85	64	57	1.30	1.06
102	148	190	713	4.2	7.2	3.08	6.73	30	45	3.27	1.48
96	126	306	736	5.6	9.45	3.49	5.0	37	40	1.49	1.92
84.5 20.29 +29.83 <0.025	114.3 23.16	262.6 81.1 +423.5 <0.01	686.1 226.8	4.55 0.56 +3.01 <0.001	7.56 1.19	3.55 0.59 +1.05 <0.001	5.60 0.62	45.16 14.37 +5.16 <0.05	50.33 9.35	1.5 0.96 -0.28 NS	1.2 0.5

II

MITRAL STENOSIS, BEFORE AND AFTER EXERCISE

Heart rate/min.		O ₂ consumption (ml./min./m. ²)		A-V O ₂ diff. (vol. %)		Cardiac index (l./min./m. ²)		Stroke index (ml./min./m. ²)		Pulm. vasc. resist. (units)	
Rest	Exercise	Rest	Exercise	Rest	Exercise	Rest	Exercise	Rest	Exercise	Rest	Exercise
78	108	184	758	5.4	9.65	1.95	4.48	25	42	2.50	4.20
96	102	133	239	6.3	9.6	1.70	2.50	20	25	4.86	8.0
60	114	205	738	7.4	11.3	1.83	4.28	30	38	—	—
64	90	116	197	6.0	8.1	1.95	2.45	30	27	2.60	4.30
69	102	104	340	7.2	9.8	1.45	3.48	21	34	1.24	0.09
96	144	280	616	4.4	9.1	4.25	4.50	44	31	1.02	2.22
66	78	326	660	7.2	11.8	2.50	3.10	38	40	2.14	2.90
72	102	333	702	9.4	10.7	1.95	3.59	27	35	6.60	4.50
72	114	313	741	7.9	11.0	2.40	4.09	33	36	1.29	2.28
78	108	233	481	6.45	9.95	2.13	2.86	27	26	2.94	0.47
60	96	129	268	7.9	13.0	1.64	2.02	27	21	8.50	20.0
73.7 12.59 +28.81 <0.001	105.1 16.62	214.1 88.1 +300.1 <0.001	521.8 222.6	6.86 1.36 +3.48 <0.001	10.3 1.65	2.16 0.76 +1.23 <0.001	3.39 0.87	29.27 7.05 +3.0 NS	32.54 5.16	3.37 2.5 +1.53 NS	4.89 5.77

controls, but again the differences were not significant. The arteriovenous difference was significantly higher ($p < 0.001$) in the patients both at rest and during exercise. The increase in arteriovenous difference during exercise was higher in the patients (+50.2%) than in the controls (+44.2%).

Patients with mitral stenosis had significantly lower cardiac index as well as stroke index both at rest and during exercise compared with the controls (see Table III). Exercise, however, influenced each index differently. The increase in cardiac index above the initial values was practically identical in the control group (+58%) and in the patients with mitral stenosis (+57%), whereas only the control group showed a significant ($p < 0.05$) increase in stroke index. In 4 of the patients with mitral stenosis a decrease in stroke index during

exercise was observed; the increase in this group averaged only 3.2 ml./m.² (in controls +5.17 ml./m.²), and was not statistically significant. A decreased stroke index was also observed in 1 control subject.

Table III shows that the mean pulmonary vascular resistance both at rest and during exercise was higher in the patient group; the differences, however, are not statistically significant. While the mean pulmonary vascular resistance during exercise in the control subjects fell slightly (from 1.5 U. to 1.2 U.), in the patients it increased (from 3.37 U. to 4.89 U.). The change, however, is statistically not significant because of a wide scatter in the results. During exercise, the PVR increased by more than 10 per cent in 7 patients but decreased in 3. The patient S.K. developed severe pulmonary

TABLE
COMPARISON OF MEAN

	Mean pulm. art. pressure (mm. Hg)		Mean left atrial pressure (mean pulm. capill. venous) (mm. Hg)		Mean left ventric. end-diast. pressure (mm. Hg)	
	Rest	Exercise	Rest	Exercise	Rest	Exercise
Controls	13.16	18.85	4.86	7.75	6.25	10.0
Mitral stenosis	31.45	57.50	20.87	34.06	8.53	12.7
Probability	< 0.001	< 0.001	< 0.001	< 0.001	NS	NS

hypertension during exercise because of an enormous increase of the PVR (from 8.5 U. to 20.0 U.).

DISCUSSION

When it was customary to subject patients with mitral stenosis to right heart catheterization before undertaking planned commissurotomy, several authors pointed out that the reason for the haemodynamic disturbance in such patients was not confined to a mechanical obstacle impeding the blood inflow into the left ventricle (Ferrer *et al.*, 1952; Harvey *et al.*, 1955; Fleming and Wood, 1959). Hence it followed that even a successful dilatation of the mitral valve would not suffice to restore completely normal cardiac function. Post-operative follow-up revealed a certain percentage of patients in whom the operation did not bring about the expected improvement (Harvey *et al.*, 1955; Bergy and Bruce, 1955; Donald *et al.*, 1957; Samet *et al.*, 1959; Basu and Gupta, 1962). In some patients failure to improve correlated with post-operative dilatation of the left ventricle (Soloff and Zatuchni, 1954; Gary, 1956).

A low cardiac output is the main haemodynamic disturbance accompanying mitral stenosis, as shown by our findings which agree with those of other authors (Ferrer *et al.*, 1952; Harvey *et al.*, 1955; Rowe *et al.*, 1960; Bruce *et al.*, 1961; Morbelli, Mascaretti, and Regalia, 1964; Frank, Levinson, and Hellems, 1965; Feigenbaum *et al.*, 1966). The basic cause is a mechanical obstacle impeding good left ventricular diastolic filling.

When the stenosis has been relieved, the rate of flow through the atrioventricular orifice suddenly increases and so a substantially increased load is put on the left ventricle. Physical exercise is the most satisfactory means for bringing about a sudden and substantial increase of blood flow through the left heart and for obtaining information on how the left ventricle will react to the load.

Subjects without cardiopulmonary disturbances react to physical exercise by an instantaneous rise in cardiac output, proportional to the magnitude of the effort and to the oxygen consumption (Levy,

Tabakin, and Hanson, 1961; Morbelli *et al.*, 1964; Widimský *et al.*, 1965; Levinson, Pacifico, and Frank, 1966; Feigenbaum *et al.*, 1966). In acute and chronic cardiac failure, the cardiac output during exercise either does not increase at all or increases only very slightly (Besterman, 1954; Barger *et al.*, 1961; Harvey *et al.*, 1962).

In patients with mitral stenosis, neither the resting cardiac output nor the increase with exercise reaches the normal values (Morbelli *et al.*, 1964; Frank *et al.*, 1965; Feigenbaum *et al.*, 1966).

Our results agree with these findings. Furthermore, the percentage increase in cardiac index during exercise was similar in those with mitral stenosis and in the controls. The oxygen consumption during exercise rose higher in the control subjects (by 161% on the average) than in the patients with mitral stenosis (by 143% on the average). It is interesting that the oxygen consumption was lower both at rest and during exercise in our patients with mitral stenosis, in agreement with data published by Cronin and MacIntosh (1962).

Furthermore, the increase in cardiac output during exercise in patients with mitral stenosis was achieved in a different way. Healthy subjects increase cardiac output by accelerating heart rate and increasing stroke volume (Mitchell, 1963; Levinson *et al.*, 1966), as has been shown in our control group; in our group of patients, however, a distinct increase in stroke volume by more than 10 per cent was seen in only 5 patients, i.e. in less than a half of the group. On the other hand, in two patients the stroke volume fell by more than 10 per cent. The inability of patients with mitral stenosis to increase stroke volume during exercise or under myocardial stimulation has also been observed by Bruce *et al.* (1961). In healthy subjects, on the other hand, a reduced stroke volume occurs only with prolonged severe exercise (Saltin and Sternberg, 1964).

These haemodynamic changes cannot be ascribed to myocardial insufficiency alone. Mitral stenosis creates a mechanical obstacle to left ventricular inflow, particularly when tachycardia is present, as is apparent from the increase in both left ventricular

III

VALUES IN BOTH GROUPS

Heart rate/min.		O ₂ consumption (ml./min./m. ²)		A-V O ₂ diff. (vol. %)		Cardiac index (l./min./m. ²)		Stroke index (ml./min./m. ²)		Pulm. vasc. resist. (units)	
Rest	Exercise	Rest	Exercise	Rest	Exercise	Rest	Exercise	Rest	Exercise	Rest	Exercise
84.5 73.7	114.3 105.1	262.2 214.1	686.1 521.8	4.55 6.86	7.56 10.3	3.55 2.16	5.60 3.39	45.16 29.27	50.33 32.54	1.5 3.37	1.2 4.89
NS	NS	NS	NS	<0.001	<0.001	<0.001	<0.001	<0.05	<0.001	NS	NS

pressure and pressure gradient (Björk and Malmström, 1959; Silverman *et al.*, 1961). A sudden increase in left atrial pressure and in end-diastolic atrioventricular pressure gradient during exercise, compared with the control subjects, was also observed, in agreement with published data (Litwak *et al.*, 1957; Samet *et al.*, 1959; Frank *et al.*, 1965). Hence it follows that a shortening of the diastolic filling period during exercise leads to an increase in the left atrioventricular pressure gradient, indicating an obstructed forward flow into the left ventricle. Although in mitral stenosis the left ventricle is not overloaded by an increased diastolic volume, either at rest or during exercise, the left ventricular end-diastolic pressure in our patients exceeded the normal upper limit of 12 mm. Hg in 4 patients at rest and in 6 patients during exercise. The left ventricular end-diastolic pressure during exercise exceeded 15 mm. Hg in 4 patients; the highest value was 24.3 mm. Hg (patient K.M.). Feigenbaum *et al.* (1966) reported similar findings though the physical load on their patients was substantially lower, which is apparent from the smaller increase in oxygen consumption and cardiac output during exercise. On the other hand, neither Gorlin *et al.* (1965) nor Frank *et al.* (1965) observed such high values of left ventricular diastolic pressure during exercise.

It is still debatable, however, whether an increase in left ventricular end-diastolic pressure is an accurate sign of left heart failure (Braunwald and Ross, 1963), since no correlation has been found between the end-diastolic pressure and the blood volume in the left ventricle in patients with mitral stenosis. The diastolic left ventricular volume in patients with mitral stenosis did not differ from that in the controls (Folse and Braunwald, 1962; Bristow *et al.*, 1964; Gorlin *et al.*, 1964). Dye dilution techniques, commonly used for estimating end-diastolic blood volume, give excessively high results (Bartle and Sanmarco, 1966; Carleton, Bowyer, and Graettinger, 1966). We may conclude that the resting end-diastolic volume in the left ventricle is not increased in mitral stenosis. In healthy subjects the diastolic volume in the left

ventricle diminishes during exercise (Wilson, 1962; Mitchell, 1963), and this tendency seems to occur also in patients with mitral stenosis (Gorlin *et al.*, 1965).

If, therefore, the left ventricular end-diastolic volume in mitral stenosis is not increased at rest or during exercise while the diastolic pressure rises, then the pressure-volume ratio must have been changed as a result of altered properties of the left ventricular wall. The same phenomenon occurs in left ventricular hypertrophy accompanying aortic stenosis (Braunwald and Ross, 1963; Gorlin *et al.*, 1964). In mitral stenosis, however, left ventricular hypertrophy has never been clinically observed (except a single report of Malara, Andreone, and De Giorgi, 1960) and the left ventricular wall is thin. Acute rheumatic disease affects the myocardium by diffuse disintegration of myofibrils which heal by connective tissue replacement closely resembling fibrotic changes in ischaemic heart disease (Clawson, 1940; Murphy, 1959). In the chronic state, similar changes occur in the left ventricle impairing myocardial function.

Our results justify the assumption that some patients with haemodynamically significant mitral stenosis exhibit initial signs of left ventricular failure. For a more accurate evaluation of left ventricular function in such patients, a precise determination of left ventricular blood volume is indicated.

CONCLUSION

Eleven patients with pure or dominant mitral stenosis and 6 control subjects were investigated by combined right and left heart catheterization at rest and during exercise. Left atrial and pulmonary artery pressures were significantly increased in patients during exercise, reaching high values. The left atrioventricular end-diastolic pressure gradient was considerably raised. Low cardiac index and stroke index, and decrease of the stroke index during exercise in the patients compared with the control

subjects, and increased left ventricular end-diastolic pressure in 4 patients at rest and in 6 during exercise represent, in our opinion, early signs of left ventricular failure. Possible causes of this insufficiency are discussed.

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