Hæmodynamic Effects of Exercise in Pulmonary Stenosis

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Patients with pulmonary stenosis and an intact ventricular septum often lead normal active lives with no disability, and the condition of patients with right ventricular pressures of up to 100 mm. Hg may not deteriorate over many years (Tinker *et al.*, 1965). However, patients with severe stenosis may have serious impairment of effort tolerance and develop heart failure. There have been few detailed studies of the way in which the right ventricle responds to the increased load of exercise in this condition. Satisfactory intraventricular pressure tracings are often unobtainable with an end-hole catheter because of frequent ectopic beats, but this difficulty can be overcome by means of a double-lumen catheter. Using this method, Johnson (1962) compared the response to exercise in pre- and post-operative cases and more recently Lewis *et al.* (1964) have reported exercise studies in 13 unoperated patients.

In this paper the effect of exercise in 18 patients with pulmonary stenosis and an intact ventricular septum are reported.

SUBJECTS AND METHODS

Eighteen patients with pulmonary stenosis were studied: 11 women and 7 men, whose ages ranged from 15 to 51 years (Table). They were divided into mild, moderate, and severe according to the height of the right ventricular (RV) systolic pressure (Wood, 1956). There were 4 patients with mild stenosis (RV pressure below 50 mm. Hg), 7 with moderate (RV pressure between 50 and 100 mm. Hg), and 7 with severe stenosis (RV pressure greater than 100 mm. Hg).

The stenosis was valvular in all patients except 2 with a subvalvular diaphragm. Two patients had previously undergone pulmonary valvotomy. Seven had an arterial saturation of less than 94 per cent, both at rest and during exercise, but the level did not fall more than 1 per cent from rest to exercise. Injection of dye into the right atrium and right ventricle in these 7 patients

and in the remainder of the series revealed no evidence of a right-to-left shunt. It was considered that in all instances the ventricular septum was intact and that probably some patients with a low arterial oxygen saturation had an intermittent right-to-left shunt through a patent foramen ovale.

Cardiac catheterization using a double-lumen catheter was performed in the usual way from an antecubital vein. Brachial arterial pressures were measured through an indwelling Cournand needle. Cardiac outputs were estimated by the Fick method, blood gases were analysed on the Van Slyke-Neill apparatus, and expired air was collected in a Tissot spirometer and analysed on the Haldane apparatus. Cardiac outputs were estimated at rest and during the 4th to 6th minutes of steady state exercise on a cycle ergometer. All rest and exercise studies were carried out with the patients supine. In each case the work load had been previously determined and was adjusted so that the patient was able to perform steady state exercise without undue distress. This exercise led to an oxygen consumption of between 1.9 and 3.6 times the resting level, an average exercise oxygen consumption for the whole group of 2.7 times the resting value. One patient (Case 11, Table) was unable to tolerate the mouthpiece for the collection of expired air, but was included in the series because she performed steady state exercise for 5 minutes and then pedalled as fast as possible against an increased load for 30 seconds, blood samples and pressures being taken towards the end of this period. The patient with the highest RV pressure (Case 18, Table) was unable to exercise with the mouthpiece in position.

Analysis of Pressure Traces. The pulmonary arterial wave form was so distorted in the majority of cases that the systolic ejection period could not be measured. A fairly accurate estimation of the ejection period, however, can be obtained by drawing a line across the ventricular pressure curve at the level of the mean pulmonary arterial pressure and then measuring the time interval between the two points at which this line crosses the ventricular pressure curve. This was the method used to estimate ejection time in this study.

The time interval between the point at which the ventricular pressure rose steeply at the beginning of

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systole to the point at which it levelled out in diastole could be accurately measured and was named the V_t period. This is the time from the beginning of isovolumetric contraction to the end of the isovolumetric relaxation phase. The point at which systole ended could not be defined and hence the actual duration of systole could not be measured; it should, however, correspond closely with V_t , and this interval was used to compare the duration of systole in different patients and in the same patients at rest and during exercise.

The rate of flow through the pulmonary valve changes throughout the ejection period, but the mean ejection rate per beat was calculated by dividing stroke volume by the ejection period.

The right ventricular peak systolic and end-diastolic pressures varied considerably with respiration in many instances, and the averages over at least 3 respiratory cycles were calculated.

The systolic pressure in the brachial artery was taken as the peak systolic left ventricular pressure, and the left ventricular end-diastolic pressures were assumed to be normal: 7.7 mm. Hg at rest and 10.3 mm. Hg during exercise (Dexter *et al.*, 1951). The left ventricular systolic ejection time was measured from the brachial arterial trace (Levine *et al.*, 1962).

RESULTS

The haemodynamic data are recorded in the Table.

Cardiac Output. The resting cardiac output was below 3.0 l./min. m^{-2} in one girl aged 16 years with

mild stenosis and in 2 with severe stenosis. The average outputs in the mild, moderate, and severe groups were 4.2, 3.7, and 3.2 l./min. m^{-2} at rest and 5.5, 6.7, and 4.2 l./min. m^{-2} during exercise. The arteriovenous oxygen (avO_2) differences in mild, moderate, and severe cases were 3.88, 4.62, and 5.33 vol. per cent at rest, and 7.24, 7.60, and 10.18 vol. per cent during exercise.

When the adequacy of the output on exercise in relation to oxygen consumption was assessed by the criteria suggested by Bishop, Donald, and Wade (1955), the response was impaired in only 4 patients, all with severe stenosis (Fig. 1), 2 showed grade I impairment, one grade II, and one grade III. In this last patient (Case 17, Table) the cardiac output fell slightly on exertion in spite of a 94 per cent rise in oxygen consumption associated with an increase in avO_2 difference from 7.57 to 15.94 vol. per cent. One other (a 16-year-old post-operative patient with residual mild stenosis) showed a fall in output from rest to exercise, but his resting output was abnormally high, probably due to emotional factors.

The patient with the highest right ventricular pressure at rest (Case 18, Table) showed an increase in avO_2 difference from 6.25 to 11.15 vol. per cent on exercise; this was almost certainly associated with impairment in the output response, but the exercise cardiac output could not be measured.

FIG. 1.—Cardiac output during exercise in patients with pulmonary stenosis, using the method of assessment suggested by Bishop *et al.* (1955). The normal values lie between the top and third lines; grades I–III are grades of impairment.

TABLE
HÆMODYNAMIC DATA AT REST AND DURING

Case No., sex, and age (yr.)	Body surface area (m. ²)	Rest and exercise	O ₂ consumption (l./min.m. ²)	Arteriovenous oxygen difference (vol. %)	Cardiac output (l./min.m. ²)	Heart rate/min.	Stroke volume (ml.m. ²)
1 F 30	1.53	Rest	138	3.9	3.6	75	47.3
		Exercise	418	6.59	5.7	102	55.7
2 M 16	1.51	Rest	215	3.91	5.5	84	65.4
		Exercise	400	8.06	5.0	98	50.7
3 F 39	1.51	Rest	123	2.46	5.0	102	49.2
		Exercise	393	7.13	5.5	123	44.7
4 F 16	1.41	Rest	147	5.25	2.8	68	41.2
		Exercise	400	7.18	5.6	96	58
5 M 15	1.49	Rest	189	5.21	3.6	57	63.8
		Exercise	465	7.79	6.0	93	64.4
6 F 26	1.54	Rest	183	4.6	4.0	78	51.1
		Exercise	398	7.47	5.3	126	42.3
7 M 18	1.88	Rest	150	4.18	3.6	87	41.3
		Exercise	541	6.39	8.5	132	64
8 M 46	1.52	Rest	191	5.25	3.5	63	57.7
		Exercise	654	9.4	7.0	99	70.3
9 M 16	1.33	Rest	174	4.17	4.2	92	45.6
		Exercise	449	7.23	6.2	104	59.9
10 F 22	1.71	Rest	141	4.33	3.3	72	45.2
		Exercise	453	6.40	7.1	116	61.5
11 F 26	1.78	Rest	4.61	8.40	10.62	66	100
		Exercise	177	4.19	4.2	150	47
12 M 51	1.7	Rest	488	9.66	5.1	122	41.5
		Exercise	132	3.9	3.4	70	48.4
13 F 37	1.74	Rest	329	6.32	5.2	90	57.9
		Exercise	156	4.69	3.3	74	45
14 F 39	1.66	Rest	448	8.52	5.2	98	53.2
		Exercise	131	4.88	2.7	69	38.8
15 F 25	1.71	Rest	329	9.76	3.4	108	31.2
		Exercise	203	5.64	3.6	64	56.4
16 M 21	1.67	Rest	453	9.87	4.5	90	50.3
		Exercise	160	7.57	2.1	96	22.1
17 F 25	1.7	Rest	309	15.94	1.9	116	16.7
		Exercise	189	6.25	3.02	98	30.8
18 F 36	1.5	Rest		11.15		110

FIG. 2.—Heart rate at rest and during exercise in patients with pulmonary stenosis.

EXERCISE IN 18 PATIENTS WITH PULMONARY STENOSIS

Pressures (mm. Hg)			Total pulmonary resistance (dynes/sec./cm. ²)	Brachial artery mean pressure (mm. Hg)	RV systolic ejection period (sec.)	V _t (sec.)	RV systolic ejection rate (ml./sec.m. ²)	Ventilatory volume (l./min.m. ²)	Arterial O ₂ % sat.
RV systolic	RV end-diastolic	PA mean							
28	2.0	10	147	79	0.34	0.48	139.2	4.8	92
39	3.0	12	114	88	0.30	0.36	185.7	13.2	91
37 (153)*	4.0	12	116	86	0.30	0.40	218.0	7.7	90
45	6.0	14	149	90	0.26	0.36	194.8	12.7	94
42	2.5	16	169	102	0.24	0.44	205.0	4.6	87
63	5.0	23	222	—	0.20	0.32	223.5	12.3	95
46	2.5	8	162	70	0.34	0.44	121.2	5.4	92
58	4.5	7	71	71	0.31	0.36	187.2	11.3	94
55	4.0	7	103	67	0.34	0.38	187.6	6.0	91
69	6.0	10	90	83	0.29	0.32	222.0	12.2	92
59	4.0	13	170	87	0.44	0.48	116.2	7.9	93
70	5.0	23	225	95	0.33	0.40	128.3	13.9	92
73	7.0	12	142	100	0.32	0.34	129.2	6.2	93
124	10.0	16	81	102	0.27	0.32	237.1	17.5	92
74	4.5	11	160	110	0.35	0.42	164.9	5.5	92
130	4.5	16	120	—	0.29	0.34	242.5	17.7	94
75 (180)*	4.5	13	178	81	0.34	0.44	134.2	5.7	94
94	6.0	16	155	82	0.28	0.34	214.0	13.7	94
88	7.0	13	187	90	0.38	0.46	119.0	5.4	95
134	9.0	13	86	93	0.30	0.38	205.1	16.4	95
65	6.0	15	—	102	0.32	0.40	—	—	95
82	4.5	16	—	104	0.28	0.36	—	—	94
101	—	20	—	127	—	—	—	—	96
105	3.0	13	145	94	0.35	0.48	134.3	7.0	90
119	5.0	19	177	108	0.30	0.36	138.3	17.8	89
110	5.0	9	122	94	0.44	0.48	110.0	4.8	95
146	5.0	13	115	—	0.32	0.38	181.0	13.9	95
134	5.5	12	174	77	0.38	0.46	118.4	6.0	87
162	8.5	10	93	94	0.34	0.40	156.4	15.0	87
149	4.0	6	105	75	0.39	0.44	99.7	6.0	92
188	6.0	9	125	85	0.33	0.36	94.6	14.3	95
148	7.0	6	80	84	0.51	0.56	110.6	10.2	90
153	8.0	6	64	95	0.40	0.44	125.9	24.0	89
178	14.0	6	—	104	0.45	0.44	49.1	6.9	91
189	19.0	8	—	116	—	—	—	13.0	94
208	6.0	9	118	74	0.46	0.46	67	10.7	98
225	8.0	14	—	—	—	—	—	—	98

* Pressures in brackets are pre-operative values.

Heart Rate. The heart rate is plotted against oxygen consumption in Fig. 2; the rate of rise on exercise is roughly the same in all cases.

There is a wide variation in heart rate at rest and during exercise in normal subjects, and it is difficult to lay down criteria of a normal rate response to effort. Harvey *et al.* (1962) found that the change in heart rate gave no indication of ventricular function in their study of the response of the abnormal heart to exercise, though they found a trend towards higher rates in patients with heart disease. Sancetta and Kleinerman (1957) found no difference in the heart rate on exercise between normal subjects and patients with aortic stenosis.

Stroke Volume. The average stroke volumes at rest in mild, moderate, and severe cases were 50.8, 50.8, and 43.0 ml.m.², and on exercise 52.3, 60.4, and 41.5 ml.m.², respectively. The changes in stroke volume with exercise are shown in Fig. 3. In 4 of the patients with severe stenosis, the stroke volume fell on exercise: these were the 4 who

showed an impaired cardiac output response to exercise. The stroke volume fell on exercise also in one patient with moderate and 2 with mild stenosis.

Normal subjects usually have an unchanged or raised stroke volume on exercise, but a fall is not necessarily abnormal; Donald, Bishop, and Wade (1955) reported that the stroke volume might fall in normal subjects exercising in the supine position.

Right Ventricular Dynamics. The systolic pressure in the right ventricle rose on exercise in all patients, but there was no definite relation between the increase and the severity of the stenosis (Fig. 4). The relation between the increase in right ventricular pressure and the amount of exertion is illustrated by Case 11; the right ventricular pressure increased from 65 to 82 mm. Hg on steady state exercise and then increased to 101 mm. Hg on severe exertion.

In Fig. 5, right ventricular systolic minus end-diastolic pressure is plotted against systolic ejection

FIG. 3.—Stroke volume at rest and during exercise in patients with pulmonary stenosis.

rate at rest and during exercise. Three main points emerge from this graph and from the calculation of ejection rate:

1. As might be predicted, for a given rise in ejection rate, the increase in right ventricular pressure is greater in patients with more severe stenosis.

2. The systolic ejection rate, particularly on exercise, is usually least in patients with the most severe stenosis. The average systolic ejection rates

for mild, moderate, and severe cases were 170.9, 141.5, and 98.4 ml./sec.m.² at rest, and 197.8, 208.2, and 139.2 ml./sec.m.² during exercise. Levine *et al.* (1962) showed that in normal subjects the systolic ejection rate increased with exercise irrespective of what happened to stroke volume; an increase in systolic ejection rate on exercise occurred in only 2 of their patients with aortic stenosis and in none with aortic stenosis and left ventricular failure. Patients with congestive heart failure (Levine *et al.*,

FIG. 4.—Right ventricular systolic pressure at rest and during exercise in patients with pulmonary stenosis.

FIG. 5.—Right intraventricular pressure and systolic ejection rate at rest and during exercise in patients with pulmonary stenosis.

1963) and coronary arterial disease (Messer *et al.*, 1963) showed little or no increase in ejection rate on exercise, and Yurchak *et al.* (1964) reported that systolic ejection rate increased less in hypertensive patients than in normals.

3. One patient with severe stenosis showed a considerable increase in right ventricular pressure in spite of a slight fall in ejection rate. This could be explained by contraction of the outflow tract on exertion causing a greater degree of effective stenosis. Another patient with mild stenosis showed the same phenomenon, but his cardiac output and stroke volume were greater at rest than during exercise, and probably his resting ejection rate was not measured under basal conditions.

The right ventricular systolic ejection period was longer in patients with more severe stenosis. The average ejection times for mild, moderate, and severe cases were 0.31, 0.36, and 0.43 sec. at rest and 0.27, 0.29, and 0.34 sec. during exercise. The average resting left ventricular systolic ejection time for the whole group was 0.28 sec., with no difference between groups with different grades of stenosis; this is slightly longer than the 0.26 sec. reported by Levine *et al.* (1962) for 26 "control" subjects. The average V_t (RV) for mild, moderate, and severe cases were 0.44, 0.42, and 0.48 sec. at rest and 0.35, 0.35, and 0.39 sec. during exercise. Assuming the resting V_t to be normal for the left ventricle (0.39 sec.: Wiggers, 1962), it appears that the duration of systole, as gauged from V_t , is

appreciably longer for the right than for the left ventricle in pulmonary stenosis, particularly in severe stenosis.

In the presence of pulmonary stenosis, the ratio between kinetic and pressure work is considerably greater for the right than for the left ventricle. The total work of either ventricle (pressure plus kinetic work) can be derived from the ventricular pressure and output and so the relative work of the two ventricles may be assessed by comparing the intraventricular pressures (Burton, 1962). The relation between right and left intraventricular (systolic minus end-diastolic) pressures at rest and during exercise is shown in Fig. 6. The data of Lewis *et al.* (1964) are incorporated in Fig. 6 and show the general pattern. In the majority of patients with moderate stenosis, right ventricular work increased more than, but did not exceed, left ventricular work on exercise. The mechanical work of the heart, however, constitutes only a small fraction of the total load, the greater part is the energy cost of maintaining tension in the heart muscle (Burton, 1962). Sarnoff and Braunwald (1962) concluded from experimental studies that the "Tension Time Index" (TTI) was the principal, if not the sole, determinant of myocardial oxygen utilization. TTI is the product of mean systolic pressure, duration of systole, and heart rate; it does not take into account any increase in tension in the ventricular wall associated with ventricular dilatation. The relative TTI of the left and right ventricles in pulmonary stenosis, therefore, depends on the intraventricular pressure and duration of systole. In a patient with similar left and right ventricular pressures, the ventricular work is equal, but the TTI is appreciably greater for the right ventricle because of the longer duration of systole. The oxygen consumption of the right ventricle is greater and its efficiency less.

The right ventricular end-diastolic pressure was increased to 14 mm. Hg in one patient (Case 17, Table); she was the only one with a cardiothoracic ratio greater than normal. Excluding this patient, the average RV end-diastolic pressures for mild, moderate, and severe cases were 2.8, 5.2, and 5.1 mm. Hg at rest, and 4.6, 6.9, and 6.9 mm. Hg during exercise. Harvey *et al.* (1962) regard 5 mm. Hg as the upper limit of the right ventricular end-diastolic pressure on exertion. The left ventricular end-diastolic pressure is normally greater than the right, because its greater mass renders it less distensible; in congenital pulmonary stenosis a right ventricular end-diastolic pressure above normal would be expected physiologically and need not be a manifestation of right ventricular failure.

The cardiac output measured by the Fick method

FIG. 6.—Right and left intraventricular pressures at rest and during exercise in patients with pulmonary stenosis, showing the relation between right and left ventricular work. The data of Lewis *et al.* (1964) are shown as interrupted lines.

was the left ventricular output, and in the assessment of right ventricular dynamics this has been taken to be the same as the output from the right ventricle. However, the 7 patients with arterial oxygen saturations of 87–94 per cent at rest and on exercise probably had a small right-to-left shunt through a patent foramen ovale and consequently a slightly greater output from the left than from the right ventricle. The lowest oxygen saturations (87–90%) occurring both at rest and during exercise, were in 3 patients with severe stenosis, and if the true right ventricular output could have been measured in these patients the haemodynamic changes observed in severe stenosis would have been more striking.

Pulmonary Circulation. The pulmonary arterial pressures were normal at rest and increased slightly or remained unchanged on exertion. One patient

showed a rise in mean pressure of 10 mm. Hg on exercise, otherwise the rise was within normal limits—less than 8 mm. Hg (Harvey *et al.*, 1962). In 5 patients total pulmonary arterial resistance increased on exercise; in the remainder it fell.

There was no difference in the behaviour of the pulmonary circuit between mild, moderate, and severe cases.

Systemic Circulation. The brachial arterial mean pressure remained the same or increased on exertion in all patients. Systemic resistance increased on exercise in 2: one with severe stenosis and the other a post-operative patient whose resting output was raised probably due to emotional factors.

There was no difference in the behaviour of the systemic circuit between mild, moderate, and severe cases.

Ventilatory Volume. The average rates of oxygen removal (ml. oxygen per litre of ventilation, Baldwin, Cournand, and Richards (1948)) for mild, moderate, and severe cases were 41.2, 44.4, and 41.4 at rest, and 48.6, 51.0, and 41.4 during exercise. The resting figures are within the normal limits quoted by Baldwin *et al.* (1948). The lower values during exercise in severe cases imply a state of hyperventilation.

DISCUSSION

These results demonstrate that, as a group, patients with severe pulmonary stenosis (RV pressure > 100 mm. Hg) have an abnormal haemodynamic response to exercise. Compared with mild and moderate cases the cardiac output and stroke volume were less at rest and during exercise, and the ventilatory volume per unit oxygen consumption during exercise was greater. Stroke volume decreased from rest to exercise, and the cardiac output in relation to oxygen consumption was subnormal during exercise. The right ventricular systolic ejection time was greater and the ejection rate less in severe than in mild and moderate cases.

Apart from one patient with severe stenosis and an end-diastolic pressure of 14 mm. Hg, the end-diastolic pressures were raised to similar levels in moderate and severe cases both at rest and during exercise. Using the normal left ventricle as a standard, the raised right ventricular end-diastolic pressure was no greater than might be expected in a thick-walled right ventricle. The end-diastolic pressures in the patients reported by Lewis *et al.* (1964) were slightly greater than in ours, but they found no difference in this respect between those with a normal or subnormal output response to effort. Johnson (1962) suggested that the two main factors responsible for the diminished cardiac output on exercise were the prolongation of right ventricular ejection, decreasing diastolic filling time, and an increased right ventricular filling resistance. This increased filling resistance should be manifested by a considerably raised end-diastolic pressure; our results indicate that an impaired output response may occur with no such rise.

Although, as a group, patients with severe stenosis showed abnormalities not seen in the mild and moderate cases, all the patients in the series who had a resting RV pressure of up to 134 mm. Hg (apart from one man aged 51 with a pressure of 105 mm. Hg) showed a normal cardiac output response to effort. In other respects also the mild and moderate cases behaved similarly, though we had only one patient with an RV pressure in the 76–100 mm. Hg range. Four patients studied by Lewis

et al. (1964) with RV pressures between 74–88 mm. Hg had abnormal cardiac output responses, but 2 others in this range and a third with a pressure of 112 mm. Hg had normal responses. Johnson (1962) investigated 17 patients before valvotomy whose resting RV pressures ranged from 65–193 mm. Hg; 8 had an impaired cardiac output on exercise, but he did not record the right ventricular pressures in these patients. Age may play some part in the exercise response of our patients; the average ages of those with severe stenosis who had an impaired response were from 21–51 years (average 32.8 years) and the ages of moderate and severe cases with a normal response were from 15–37 years (average 25.7 years).

It has been suggested on theoretical grounds and from follow-up studies of individual patients seen over a number of years (Tinker *et al.*, 1965) that in the presence of pulmonary stenosis the right ventricle can tolerate, for an indefinite period, work loads approaching those normally borne by the left ventricle. The results reported here are of single exercise studies with only a moderate work load and may not be a true reflection of how the heart responds to the normal, often more strenuous, exertions of everyday life. When the degree of pulmonary stenosis is such that the pressure in the two ventricles is the same at rest, the work performed by the two ventricles is the same, but it appears that during exercise right ventricular work usually increases a little more than that of the left ventricle. However, the duration of systole is greater in the right than in the left ventricle in these cases, and it is probable that the increased energy required to maintain tension leads to a greater load on the right ventricle at all times.

SUMMARY

The haemodynamic effects of exercise were studied in 18 patients with pulmonary stenosis and an intact ventricular septum. Four patients had mild stenosis (RV pressure below 50 mm. Hg), 7 had moderate (RV pressure between 50 and 100 mm. Hg), and 7 had severe stenosis (RV pressure greater than 100 mm. Hg).

Five of the 7 patients with severe stenosis (and probably a sixth whose actual output could not be measured) had an impaired cardiac output response to effort. All patients with mild or moderate stenosis had a normal output response.

As a group, patients with severe stenosis had a lower cardiac output and stroke volume at rest and on exercise and a greater ventilatory equivalent on exercise than mild or moderate cases. Right ventricular ejection time was greater and ejection rate less in severe cases at rest and during exercise.

When the left and right ventricular pressures are similar at rest, the work performed by the two ventricles is the same at rest, but right ventricular work is usually a little greater during exercise. Because of the prolongation of right ventricular systole, however, the load on the right ventricle is greater than on the left at rest and during exercise.

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REFERENCES

- Baldwin, E. de F., Cournand, A., and Richards, D. W. (1948). Pulmonary insufficiency. I. Physiological classification, clinical methods of analysis, standard values in normal subjects. *Medicine (Baltimore)*, **27**, 243.
- Bishop, J. M., Donald, K. W., and Wade, O. L. (1955). Changes in the oxygen content of hepatic venous blood during exercise in patients with rheumatic heart disease. *J. clin. Invest.*, **34**, 1114.
- Burton, A. C. (1962). Physical units and concepts useful in cardiovascular research. In *Cardiovascular Functions*, ed. A. A. Luisada, p. 53. McGraw-Hill Book Company, New York.
- Dexter, L., Whittenberger, J. L., Haynes, F. W., Goodale, W. T., Gorlin, R., and Sawyer, C. G. (1951). Effect of exercise on circulatory dynamics of normal individuals. *J. appl. Physiol.*, **3**, 439.
- Donald, K. W., Bishop, J. M., and Wade, O. L. (1955). Changes in the oxygen content of axillary venous blood during leg exercise in patients with rheumatic heart disease. *Clin. Sci.*, **14**, 531.
- Harvey, R. M., Smith, W. M., Parker, J. O., and Ferrer, M. I. (1962). The response of the abnormal heart to exercise. *Circulation*, **26**, 341.
- Johnson, A. M. (1962). Impaired exercise response and other residua of pulmonary stenosis after valvotomy. *Brit. Heart J.*, **24**, 375.
- Levine, H. J., Messer, J. V., Neill, W. A., and Gorlin, R. (1963). The effect of exercise on cardiac performance in human subjects with congestive heart failure. *Amer. Heart J.*, **66**, 731.
- , Neill, W. A., Wagman, R. J., Krasnow, N., and Gorlin, R. (1962). The effect of exercise on mean left ventricular ejection rate in man. *J. clin. Invest.*, **41**, 1050.
- Lewis, J. M., Montero, A. C., Kinard, S. A., Dennis, E. W., and Alexander, J. K. (1964). Hemodynamic response to exercise in isolated pulmonic stenosis. *Circulation*, **29**, 854.
- Messer, J. V., Levine, H. J., Wagman, R. J., and Gorlin, R. (1963). Effect of exercise on cardiac performance in human subjects with coronary artery disease. *Circulation*, **28**, 404.
- Sancetta, S. M., and Kleinerman, J. (1957). Effect of mild, steady state exercise on total pulmonary resistance of normal subjects and those with isolated aortic valvular lesions. *Amer. Heart J.*, **53**, 404.
- Sarnoff, S. J., and Braunwald, E. (1962). Hemodynamic determinants of myocardial oxygen consumption. In *Cardiovascular Functions*, ed. A. A. Luisada, p. 24. McGraw-Hill Book Company, New York.
- Tinker, J., Howitt, G., Markman, P., and Wade, E. G. (1965). The natural history of isolated pulmonary stenosis. *Brit. Heart J.*, **27**, 151.
- Wiggers, C. J. (1962). The heart as a pump. In *Cardiovascular Functions*, ed. A. A. Luisada, p. 71. McGraw-Hill Book Company, New York.
- Wood, P. (1956). *Diseases of the Heart and Circulation*, 2nd ed. Eyre and Spottiswoode, London.
- Yurchak, P. M., Hood, W. B., Rolett, E. L., Hickler, R. B., and Gorlin, R. (1964). Effect of systemic hypertension on mean left ventricular ejection rate. *Amer. J. med. Sci.*, **247**, 42.