Original Article

Clinical Studies on the Right Ventricular Function

AKIRA SAKAI

*The 3rd Division, Department of Internal Medicine, Kyoto University, Kyoto
(Director: Prof. M. Maekawa)*

NUMEROUS investigations have been reported on the ventricular function studied by the experimental cardiac catheterization in man¹⁻⁴⁾. There are extreme difficulties, however, in estimating cardiac functions from hemodynamic values obtained in clinical routine cardiac catheterization, which offers only incomplete and limited information. In this respect, it is useful in understanding cardiac functions, to find out what kind of hemodynamic rules are dominating in each case.

The direction and the extent to which the heart exerts its own adaptation mechanisms in facing the various conditions should be shown in order to evaluate its performance. One of the adaptation mechanisms originally belonging to the heart is STARLING's law⁵⁾⁶⁾, that is, the heart makes more forceful contraction against an augmented inflow, an increased end-diastolic fiber length. Another adaptation mechanism is homeometric autoregulation⁷⁾, in which several beats after the ventricle increases its contractility, the ventricle maintains the original end-diastolic pressure and fiber length. In addition to these autoregulations, the ventricle is regulated by nervous and humoral influences⁸⁾. These various regulations should be taken into consideration in an estimation of clinical hemodynamic data.

In order to study the right ventricular function, the hemodynamic values obtained in patients with mitral stenosis will be presented

and analysed in this report. Since hemodynamic values in each case merely represent hemodynamic status of some specific time of the course, it should be extremely important to evaluate them in consideration of the history, clinical course and the nature of the etiological diseases in each case.

METHODS AND MATERIALS

Fifty-three patients with mitral stenosis, 33 females and 20 males, ranging from 18 to 70 years in age, with an average of 34 years, were studied, and the diagnostic data of the right heart catheterization carefully reviewed.

The cardiac catheterization studies were carried out in the usual manner⁹⁾ via an antecubital vein. The zero level for the recorded pressure was referred to mid-point between LOUIS's angle and the back of the patients in supine position. All pressure recordings were made with a Satham P24D transducer and with a cathode-ray photographic recording system. The paper speed was usually 75 millimeter per second. Each pressure measurement was averaged during at least two respiratory cycles. Mean pressures were obtained by electronic integration. The oxygen content of the blood was determined by the method of VANSLYKE and NEIL¹⁰⁾, and the expired air collected in the DOUGLAS bag was analysed by the modified HALDANE apparatus. The cardiac output was then calculated by FICK's principle¹¹⁾, and the stroke volume was obtained by dividing the cardiac output by the ventricular rate.

The mean values of right ventricular minute work, right ventricular stroke work, and pulmonary

(Received for Publication, May 6, 1965)

arteriolar resistance were calculated according to the following formulae⁹⁾¹²⁾:

$$\text{RVMW} = (\text{PAm} - \text{RVed}) \times \text{CI} \times \frac{13.6 \times 1.050}{10^6}$$

$$\text{RVSW} = (\text{PAm} - \text{RVed}) \times \text{SI} \times \frac{13.6 \times 1.050}{10^2}$$

$$\text{PAR} = \frac{(\text{PAm} - \text{PCm}) \times 1332}{\text{CI}/60}$$

Where RVMW = right ventricular minute work in Kg.M./min./M². B.S.A.; RVSW = right ventricular stroke work in Gr.M./beat/M². B.S.A.; PAR = pulmonary arteriolar resistance in dyne. sec. cm⁻⁵; PAm = mean pulmonary artery pressure in mmHg; PCm = mean pulmonary wedge pressure in mmHg; RVed = right ventricular end-diastolic pressure in mmHg; CI = cardiac index in L./min./M². B.S.A.; SI = stroke index in ml./beat/M². B.S.A.; B.S.A. = body surface area in M².

RESULTS

Fifty-three patients with mitral stenosis were classified into three groups according to the cardiac indices.

Group A, B, and C consisted of the cases with a low ($1.5 < \text{CI} < 2.5$), a borderline ($2.5 < \text{CI} < 3.0$), and a normal ($3.0 < \text{CI} < 5.2$) cardiac output, with averages of cardiac indices, 2.12, 2.75, and 3.85 L./min./M². B.S.A., respectively. The average values for each pressure measurement and calculated data are shown in Table I.

TABLE I GROUPING AND HEMODYNAMIC DATA

	Group A	Group B	Group C
Number of cases	16	16	21
PCm mmHg	24.6	22.0	20.6
PAs mmHg	60.9	59.5	48.8
PAd mmHg	27.6	24.3	21.5
PAm mmHg	39.2	36.6	31.7
RVed mmHg	11.1	9.3	7.1
CI L/min/M ² BSA	2.12	2.75	3.85
SI ml/beat/M ² BSA	27.2	33.6	40.9
RVMW Kg.M/min/M ² BSA	0.78	1.05	1.39
RVSW Gr.M/beat/M ² BSA	10.0	12.1	14.7
PAR Dyn.sec.cm ⁻⁵ /M ² BSA	555	428	249

Each number represents an average value in a Group

Abbreviations. PCm: Mean pulmonary capillary pressure measured by pulmonary artery wedge pressure. PAs, PAd, PAm: Systolic, diastolic, mean pulmonary artery pressure, respectively. RVed: Right ventricular end-diastolic pressure. CI, SI: Cardiac and stroke index. RVMW, RVSW: Right ventricular minute and stroke work. PAR: Pulmonary arteriolar resistance.

The functional capacity of the heart was estimated by appraising the patient's ability to

perform physical activity, according to the classification by the Criteria Committee of the New York Heart Association (NYHA)¹³⁾ and its modification: Class II is subdivided into two groups, Class IIa and Class IIb. Class IIa includes the patients corresponding to those in Class II of the NYHA criteria who have never experienced cardiac decompensation. Class IIb includes those who basically belong to Class II of the NYHA criteria but who have once slipped into Class III.

The distribution of cardiac indices in each Class is illustrated in Fig. 1 and summarized in Table II. Group A consisted of ten cases of Class IIb and six cases of Class III, Group B consisted of eight of Class IIa, seven of Class IIb and one of Class III, and Group C consisted of two of Class I, fourteen of Class IIa, four of Class IIb and two of Class III. Group A did not include patients in Class I and IIa, and

TABLE II CLASSIFICATION OF THE PHYSICAL CAPACITY OF THE HEART

Cardiac Index	Group A 1.5-2.5	Group B 2.5-3.0	Group C 3.0-5.2	Total
Class I	0	0	7	2
Class IIa	0	8	14	22
Class IIb	10	7	3	20
Class III	6	1	2	9
Class IV	0	0	0	0
Total	16	16	21	53

Fig. 1. Relation between cardiac index and functional capacity of the heart represented by classification of New York Heart Association.

Fig. 2. Relation between right ventricular end-diastolic pressure (RVed) and systolic pulmonary artery pressure (PAs). Dark, half-dark and light spots represent the cases belonging to Group A, B, and C, respectively.

Fig. 3. Relation between right ventricular end-diastolic pressure (RVed) and diastolic pulmonary artery pressure (PAd).

Class IV-patients were not found in this series. In addition, atrial fibrillation was found in 13 patients in Group A, 8 in Group B and 11 in Group C⁽¹⁴⁾⁽¹⁵⁾ (Fig. 1).

It was found that when cardiac output (index) was low, the right ventricular end-diastolic and pulmonary artery pressures as well as pulmonary arteriolar resistance were high, the external right ventricular work in a minute or in a stroke was low, and the physical capacity of the heart deteriorated. In brief, the cases in Group A (low cardiac output) declined much more to right ventricular failure.

Relations of right ventricular end-diastolic pressure (RVed) to the pulmonary artery pressures are shown in Fig. 2, 3, 4 and 5. As a whole, RVed increased proportionally to the elevation of pulmonary artery pressures, having sample correlation co-efficients of 0.517, 0.575, 0.665 and 0.496 ($P < 0.01$), systolic (PAs), dias-

Fig. 4. Relation between right ventricular end-diastolic pressure (RVed) and mean pulmonary artery pressure (PAm). Symbols with horizontal line represent the cases with mean pulmonary artery pressure of 50 mmHg or more.

Fig. 5. Relation between right ventricular end-diastolic pressure (RVed) and pulmonary artery pulse pressure (PApp).

tolic (PAD), mean pulmonary artery pressure (PAm) and pulmonary artery pulse pressure (PApp), respectively.

Consequently, it can be said that the cases with the elevation of RVed in general also showed high pulmonary pressures. There were some exceptions, however, the cases with the high RVed associated with the low pulmonary artery pressures. These cases were found in Group A (low cardiac output).

In addition, all the cases with pulmonary hypertension of 50 mmHg or more in mean, showed the electrocardiogram consistent with right ventricular hypertrophy¹⁴⁾¹⁵⁾.

Relationships between RVed and cardiac index, and stroke index are shown in Fig. 6 or 7.

RVed revealed an inverse correlation with cardiac index and stroke index, having sample correlation co-efficients of minus 0.675 and minus 0.516, respectively ($P < 0.01$).

Fig. 6. Relation between right ventricular end-diastolic pressure (RVed) and cardiac index (CI). Symbols with horizontal line represent the cases with mean pulmonary artery pressure of 50 mmHg or more.

Fig. 7. Relation between right ventricular end-diastolic pressure (RVed) and stroke index (SI).

Fig. 8. Relation between right ventricular end-diastolic pressure (RVed) and right ventricular minute work (RVMW). See Discussion about the line "S".

Fig. 9. Relation between right ventricular end-diastolic pressure (RVed) and right ventricular stroke work (RVSW).

Subsequently, the high RVed in general was found in the cases with low cardiac and stroke indices.

Relationships between RVed and right ventricular minute work (RVMW) and stroke work (RVSW) are shown in Fig. 8 and 9.

There was no significant correlation between RVed and RVMW, and RVSW. The area above 10 mmHg of RVed in Fig. 8 and 9 was occupied by the cases with low cardiac output in its lower half, and by those with marked pulmonary hypertension in its upper half. When the cases with severe pulmonary hypertension were omitted, however, the RVMW and RVSW had a tendency to an inverse correlation with RVed. In addition, they seemed to show a positive correlation, when the cases with low cardiac output were omitted.

Relation between RVed and pulmonary arteriolar resistance (PAR) is shown in Fig. 10.

PAR correlated positively to RVed, with a sample correlation co-efficient of 0.400 ($P < 0.01$). All the cases with the high RVed above 10 mmHg, revealed PAR above the upper limit of normal ($250 \text{ dyne} \cdot \text{sec} \cdot \text{cm}^{-5}$), except one case which belonged to Group A. When RVed was below 8 mmHg, PAR was within the normal limit.

Fig. 10. Relation between right ventricular end-diastolic pressure (RVed) and pulmonary arteriolar resistance (PAR).

Fig. 11. Relation between cardiac index (CI) and mean pulmonary artery pressure (PAm). Vertical lines divide the spots into Group A, B and C. Horizontal lines divide them into three groups, that is, those with markedly, moderately and slightly elevated or normal pulmonary artery pressure.

Fig. 12. Relation between diastolic pulmonary artery pressure (PAd) and mean pulmonary arterial wedge pressure (PCm).

Correlation between mean pulmonary artery pressure (PAm) and cardiac index is shown in

Fig. 11.

Cardiac index appeared to correlate inversely with PAm, having a sample correlation coefficient of minus 0.563 ($p < 0.01$), when the cases with severe pulmonary hypertension above 50 mmHg in mean were excluded.

Relation between pulmonary artery diastolic pressure (PAd) and mean pulmonary artery wedge pressure (PCm) is shown in Fig. 12.

Fig. 13. Relation between pulmonary arteriolar resistance (PAR) and diastolic pulmonary artery pressure (PAd).

Fig. 14. Relation between right ventricular minute work (RVMW) and diastolic pulmonary artery pressure (PAd).

Fig. 15. Relation between pulmonary arteriolar resistance (PAR) and right ventricular minute work (RVMW).

There was a good correlation ($r=0.754$, $P<0.01$). When PCm was elevated to 25 mmHg or more, PAd tended to exhibit a disproportionate elevation in comparison with an elevation of PCm as previously described¹⁶⁾¹⁷⁾.

PAd demonstrated considerable correlations with pulmonary arteriolar resistance (PAR) and right ventricular minute work (RVMW), as shown in Fig. 13 and 14; $r=0.850$, and $r=0.630$ ($P<0.01$), respectively. In Fig. 15, no significant correlation was present between PAR and RVMW as a whole. The cases in Group A (dark spot) and Group B (half-dark spot) occupied the left side of the scattergram, and the cases in Group C (light) the lower half of it.

Consequently at any level of PAd, the cases with low cardiac index (Group A and B) exhibited more increased PAR and less augmented RVMW than those normal cardiac index (Group C).

DISCUSSION

All the fifty-three patients in this series were diagnosed as having mitral valvular disease with predominant lesion of stenosis on the basis of clinical and right heart catheterization findings. In no cases was a regurgitation wave¹⁸⁾ found in the pulmonary artery wedge pressure

tracings, which has well been known to represent the left atrial pressure¹⁹⁾²⁰⁾. Although the pulmonary artery wedge pressure itself provides only partial information as to the degree of mitral obstruction, it does influence the pulmonary artery pressure and the performance of the right ventricle, as far as the mitral stenosis itself blocks pulmonary circuit. It is believed that as far as the wedge pressure tracings reveal no regurgitation pattern, actual mitral regurgitation²¹⁾, if any, would not influence the right heart hemodynamics.

A long standing elevation of left atrial pressure resulting from an increased resistance offered by the mitral block induces a rise in the pulmonary venous and capillary pressures. The pulmonary artery pressure for a given blood flow through the pulmonary artery is considered as a function of the pulmonary capillary pressure and the pulmonary arteriolar resistance.

The changes in pulmonary artery pressure due to the elevation of pulmonary artery wedge pressure have been investigated by the author's colleagues. They revealed a fairly good correlation between pulmonary artery wedge pressures, pulmonary artery pressures, including systolic, diastolic and mean, in normal subjects and patients with mitral valvular disease¹⁶⁾. They also suggested the importance of the pulmonary artery diastolic pressures¹⁷⁾. They studied 160 cases with mitral valvular disease, in 128 of which pulmonary artery wedge pressure and pulmonary artery diastolic pressures were almost identical in a range of five millimeter mercury. However, in those cases with pulmonary artery wedge pressures of 25 mmHg or more, the pulmonary artery diastolic pressures tended to become higher by 5 mmHg or more than the wedge pressures (Fig. 16). Such cases showed markedly elevated pulmonary arteriolar resistance²²⁾ (Fig. 17). In some cases pulmonary biopsy was performed during commissurotomy, and histological findings were studied and compared with the hemodynamic values. Thickening of the vessel walls of the pulmonary arteries and arterioles was most characteristic. The ratio of the wall thickness to the diameter (W/D) was used as an index to represent the grade of the

Fig. 16. Relationship between diastolic pulmonary artery pressure (PAd) and mean pulmonary arterial wedge pressure (PCm) in mitral valve disease.

PAd = PCm $\pm$ 5 mmHg: 56 cases (75.7%)
 PAd > PCm + 5 mmHg: 15 cases (20.3%)
 PAd < PCm - 5 mmHg: 3 cases (4.0%)

Fig. 17. Relationship between pulmonary arteriolar resistance (PAR) and diastolic pulmonary artery pressure (PAd).

Symbols with dot in circle represent the cases with diastolic pulmonary artery pressure higher by 5 mmHg or more than pulmonary arterial wedge pressure.

Fig. 18. Relationships of diastolic pulmonary artery pressure (PAd) to the ratio of wall thickness to diameter (W/D) in the pulmonary muscular arteries (left) and in the pulmonary arterioles (right).

Fig. 19. Relationships of pulmonary arteriolar resistance (PAR) to the wall-diameter ratio (W/D) in the pulmonary muscular arteries (left) and in the pulmonary arterioles (right).

thickening of the vessels. Correlation was noted between W/D and the pulmonary artery diastolic pressures. The cases in which the pulmonary artery diastolic pressure was disproportionately elevated in comparison with pulmonary artery wedge pressure, showed a high value in W/D (Fig. 18). Relation between W/D and PAR is shown in Fig. 19.

As a result, the discrepancy between pulmonary artery diastolic pressure and pulmonary artery wedge pressure may indicate an increase in PAR due to morphological changes in pulmonary arteries and arterioles, either reversible or irreversible.

Thus, the elevation of pulmonary artery wedge pressure of sufficiently long duration, in connection with the resulting increased pulmonary arteriolar resistance, induces a rise in pulmonary artery pressure. Facing these changes in the pulmonary circulation, the right ventricle must exert more effort to maintain its normal output. This in turn may lead to a greater elevation of pulmonary artery and right ventric-

ular systolic pressure, which imposes a more severe load on the ventricle.

In the detailed description of the hemodynamics of the ventricle, the end-diastolic volume and tension are considered to be two of the most important factors in the performance of the heart. However, a direct measurement of these factors in clinical and routine examinations is not possible yet, although they have been measured in research studies²³⁻²⁷. Accordingly, the ventricular end-diastolic pressure has been used as a guide to the end-diastolic volume and tension. There are, however, some limitations in its use, because profound alteration can be caused by a number of factors, such as the functional status of the ventricle, ventricular end-diastolic compliance, intrapleural pressure²⁸, etc. It is extremely difficult to measure the compliance of the ventricle exactly, which is one of the most dominant determinants of the pressure-volume relationship.

At any given end-diastolic compliance, changes in the end-diastolic pressure may mirror

changes in the volume proportionally at a level of the moderately elevated pressure, but when the end-diastolic pressure is normal or only slightly elevated, this variable is relatively insensitive as an index of the end-diastolic volume or in the assessment of the ventricular function²⁹⁾. Besides, it has been reported that in the cases with a ventricular hypertrophy the end-diastolic pressure may be strikingly elevated without concomitant increase in the end-diastolic volume²⁵⁾.

The mitral block itself brings about a sustained decrease in cardiac output, and the left atrial and pulmonary congestion. The heart must always exert all the adaptive mechanisms to meet an increased work load or to maintain its normal cardiac output in the presence of the mitral block and its resulting hemodynamic changes. Above all, the ability of the right heart to meet the systolic load must mainly depend upon its contractility.

Recently, the contractility of the ventricle has been shown to be represented by the maximal rate of ventricular pressure development. It has been shown that the maximal rate of rise in ventricular pressure has a linear correlation to peak systolic pressure chronically developed by the ventricle³⁰⁾.

As shown in Fig. 2, there is a good correlation between RVed and PAs. This finding suggests that RVed may have a close relation to the contractility, and that elevated pulmonary artery systolic pressure may reflect a development of ventricular hypertrophy. It has been shown that in the cases with hypertrophy and normal end-diastolic volume, the end-diastolic pressure may be strikingly elevated²⁴⁾. It has also been revealed that RVed pressure well above the normal range may be associated with marked ventricular hypertrophy in the absence of the other evidences of heart failure³¹⁾³²⁾. It is demonstrated in this study that although the pulmonary artery pressure is elevated proportionately to an increase in RVed, forward flow through the pulmonary arteries is not increased in relation to the elevation of the pressures. Namely, the cardiac index correlates inversely to RVed as shown in Fig. 8. The stroke index does the same (Fig. 8). In other words, the higher the right ventricular end-

diastolic pressure is, the more the cardiac output is diminished. This statement seems to be apparently paradoxical to the original concept of STARLING's law. It is obvious, however, that the cardiac output itself is determined originally by the mitral block, and the right ventricle must act against the block to increase the output. The right ventricle adjusts to higher PAR by elevating RVed. But the energy loss in the pulmonary circuit is so great that the output is still small in relation to the amount of effort that the right ventricle must perform. Thus the ventricle must exert its performance at the expense of the high RVed under chronically diminished output, according to the grade of the severity of the forward load. These energy-losses of the right ventricular performance must be shown in the ventricular function curves.

As shown in Figs. 8 and 9, RVMW and RVSW reveal no significant correlation with RVed pressure, but when the cases with severe pulmonary hypertension are excluded, the work appears to correlate inversely with RVed. The individual spots in Figs. 8 and 9 merely indicate a hemodynamic status in steady state which has been achieved by the right ventricle to meet the altered conditions. It is assumed, therefore, that when one takes RVed-RV-work-relationship beat-to-beat of the ventricle to meet the increased work, the work-pressure curves may represent STARLING's law.

Many studies have been done to examine and to illustrate STARLING's curves, and it has been shown that a ventricle exhibits many different ventricular function curves³²⁾. Among them, McMICKEL suggested that there are series of the curves, and illustrated three representative curves, that is, hypertrophic, normodynamic and hypodynamic. As shown in Figs. 8 and 9, when an imaginary line marked "S" is drawn in such a way that the spots representing the cases with pulmonary hypertension above 50 mmHg in mean are above the line and those with low cardiac output are below the line, it is easy to understand that the cases above the line exert greater external work under the relatively lower RVed and those below the line do lesser work under the higher RVed.

From the other point of view, each spot

above the line may represent a point on the ascending limb of its own ventricular function curve with a normal or steeper slope, and each one below the line a point either on the ascending or descending limb of its own ventricular function curve with easier slope.

Consequently, the suggested line may divide the cases into two groups, that is, compensating group with hypertrophic heart and decompensating group with hypodynamic heart.

The measurable hemodynamic expressions of decompensation of the heart are high ventricular end-diastolic pressure and reduced cardiac output. And they do characterize decompensation collectively, but each may exist alone under conditions without any evidence of decompensation³¹⁾³²⁾³⁵⁾. It should be added that decompensation not apparent at rest, may become manifest on exercise, which brings on a further elevation of RVed without any adequate increase in cardiac output or even with a fall in it³⁶⁾³⁷⁾. The suggested line mentioned above, is obtained only by imagination and its exact position in the RVed-RV-work relation is not yet determined. It may be determined by generalization of individual ventricular function relationship. It is concluded that low right ventricular work under high ventricular end-diastolic pressure is the most characteristic feature of right ventricular decompensation, and that it may be much more important to determine whether the heart can not exert an augmented work in spite of an elevation of right ventricular end-diastolic pressure against an increased burden on the heart.

SUMMARY AND CONCLUSION

1) The hemodynamic values of fifty-three patients with mitral stenosis were analysed, in respect to the right ventricular function.

2) The functional capacity of the heart was more deteriorated, when the cardiac index was lower.

3) Right ventricular end-diastolic pressure showed significant correlations with pulmonary artery pressures, and significant inverse correlations with cardiac and stroke indices.

4) The decrease in cardiac index occurred concomitantly with the elevation of right ventricular end-diastolic pressures and pulmonary

artery pressures, and with the decrease in right ventricular work in a minute or a stroke.

5) Right ventricular work had no significant correlation with right ventricular end-diastolic pressure or cardiac index.

6) An imaginary line was presented in the right ventricular work-end-diastolic pressure relation, and it was suggested that the line may divide the cases into two groups; a group with compensated and hyperdynamic heart, and the other with decompensated and hypodynamic heart.

7) Relation between pulmonary artery wedge pressure and pulmonary artery diastolic pressure was reviewed, and the clinical significance of the pulmonary artery diastolic pressure was discussed.

Acknowledgement

The author wishes to express his sincere gratitude to Professor M. Maekawa for his helpful criticism and suggestion, and also Assistant Professor S. Hayase and Dr. Y. Nohara for their kind advice. The author also wishes to acknowledge his indebtedness to Dr. Y. Ogata, Dr. T. Ohta, Dr. C. Kawai, Dr. R. Kusukawa, Dr. A. Wakabayashi, and other coworkers in the cardiac catheterization team of the Third Clinic of Internal Medicine.

REFERENCES

- 1) Gleason, W. L. and Braunwald, E., Studies on the first derivative of the ventricular pressure pulse in man. *J. Clin. Invest.* **41**: 80, 1962.
- 2) Ferrer, I., Conroy, R. J. and Harvey, R. M., Some effects of digoxin upon the heart and circulation in man. *Circulation* **21**: 372, 1960.
- 3) Doyle, J. T., Wilson, J. S., Estes, E. H. and Warren, J. V., The effect of intravenous infusions of physiologic saline solution on pulmonary arterial and pulmonary pressure in man, *J. Clin. Invest.* **30**: 345, 1951.
- 4) Schnabel, T. J., Jr., Elisch, H., Thomasson, B. and Werkö, L., The effect of experimentally induced hypervolemia on cardiac function in normal subjects and the patients with mitral stenosis. *J. Clin. Invest.* **38**: 117, 1959.
- 5) Starling, E. H., Linacre lecture on law of the heart. Longman, Green & Co., London, 1918.
- 6) Pickerling, S. G., Starling and the concept of heart failure. *Circulation* **21**: 3, 1960.
- 7) Sarnoff, S. J., Michel, J. H., Gilmore, J. P. and Remenonyder, J. P., Homeometric autoregulation in the heart. *Circulation Res.* **8**: 1077, 1960.
- 8) Mitchell, J. M., Linden, R. J. and Sarnoff, S. J., Influence of cardiac sympathetic and vagal nerve stimulation on the relation between left ventricular diastolic pressure and myocardial segment length. *Circulation Res.* **8**: 1100, 1960.
- 9) Luisada, A. A. and Liu, C. K., Intracardiac phenomena in right and left heart catheterization. 2nd Ed. Grune & Stratton, New York & London, 1958.

- 10) Peters, J. P. and Van Slyke, D. D., Quantitative clinical chemistry. Vol. II, Methods, The Williams and Wilkins Co., Baltimore.
- 11) Fick, A., Über die Messung des Blutquantums in der Herzventrikeln. Sitzungsab. phy. med. Gesell. zu Würzburg, July 1870, p. 16.
- 12) Murphy, G. W., Schreiner, B. F., Blearkley, P. L. and Yu, P. N., Left ventricular performance following digitalization in patients with and without heart failure. *Circulation* **30**: 358, 1964.
- 13) Kossman, C. E., et. al., Diseases of the heart and blood vessels. 'Nomenclature and criteria for diagnosis' by The Criteria Committee of the New York Heart Association. p. 110. Little, Brown, Boston, 1964.
- 14) Tounce, J. R., The electrocardiogram in mitral stenosis. *Brit. Heart J.* **14**: 185, 1952.
- 15) Fraser, H.R.L. and Turner, R., Electrocardiography in mitral valvular disease. *Brit. Heart J.* **17**: 459, 1955.
- 16) Maekawa, M., Ogata, Y., Sakai, M., Kawai, C., Hashida, E., Morita, Y., Ota, T., Masuda, K., Wakabayashi, A., Kawamura, H., Torii, H. and Hayashi, K., Studies on pulmonary circulation. Part II. Pulmonary capillary and pulmonary arterial pressures, and findings of biopsy of the lung in mitral valvular disease. Presented at the 24th Annual Meeting of the Japanese Circulation Society, 1960. *Abstr. in Jap. Circ. J.* **24**: 1212, 1960.
- 17) Maekawa, M., Kawai, C., Kusukawa, R., Ota, T., Wakabayashi, A., Hayashi, K., Kawamura, K., Torii, H., Matsubara, H. and Sakai, A., Studies on the pulmonary circulation. Part III. 1) Clinical significance of the pulmonary diastolic pressure. Presented at 26th Annual Meeting of the Japanese Circulation Society, 1962. *Abstr. in Jap. Circ. J.* **26**: 887, 1962.
- 18) Liu, C. K. and Bendezu, J. A., Left atrial and ventricular pulses in mitral valve disease and in subjects with normal mitral valve. *Am. J. Cardiol.* **1**: 68, 1962.
- 19) Werkö, L., Vanauskas, E., Elisch, H. and Lagerlöff, H., Sennig, A. and Thomasson, B., Further evidence that the pulmonary capillary venous pressure pulse in man reflects cyclic changes in the left atrium. *Circulation Res.* **1**: 337, 1953.
- 20) Luchinger, P. C., Selpp, H. W. Jr. and Patel, D. J., Relation of pulmonary artery wedge pressure to left atrial pressure in man. *Circulation Res.* **11**: 315, 1962.
- 21) Ankeney, J. L., Fishman, A. P. and Feritts, H. W., Jr., An analysis of normal and abnormal left atrial pulse in man. *Circulation Res.* **4**: 95, 1956.
- 22) Dexter, L., Dow, J. W., Haynes, F. W., Whittenberger, J. L., Ferris, B. G., Goodale, W. T. and Hellemes, H. K., The studies of the pulmonary circulation in man at rest. Normal variations and the interrelations between increased pulmonary arterial pressure and high pulmonary, 'capillary' pressures. *J. Clin. Invest.* **29**: 602, 1950.
- 23) Chapman, C. B., Baker, O., Reynolds, J. and Bonte, F. J., Use of biplane cinefluorography for measurement of ventricular volume. *Circulation* **18**: 1105, 1958.
- 24) Dodge, H. T., Sandler, H., Ballew, D. W. and Lord, J. D., The use of biplane angiocardiology for the measurement of left ventricular volume in man, *Am. Heart J.* **60**: 762, 1962.
- 25) False, R. and Braunwald, E., A method for the determination of the fraction of left ventricular volume ejected per beat and of the ventricular end-diastolic and residual volumes. *Circulation* **25**: 674, 1962.
- 26) Lewis, M. L., Giuntini, C., Donato, L., Harvey, R. M. and Cournand, A., Quantitative radiocardiography. III. Results and validation of the theory and methods. *Circulation* **26**: 189, 1962.
- 27) Aygen, M. M. and Braunwald, E., Studies on Starling's law of the heart. VIII. Mechanical properties of human myocardium in vivo. *Circulation* **26**: 516, 1962.
- 28) Cournand, A., Montrey, H. L., Werkö, L. and Richard, D. W., Jr., Physiological studies of the effects of intermittent positive pressure breathing on cardiac output in man. *Am. J. Physiol.* **152**: 162, 1948.
- 29) Eraunwald, E. and Ross, J., Jr., The ventricular end-diastolic pressure. Appraisal of its value in the recognition of ventricular failure in man. *Am. J. Med.* **34**: 147, 1963.
- 30) Gleason, W. L. and Braunwald, E., Studies on the first derivative of the ventricular pressure pulse in man. *J. Clin. Invest.* **41**: 80, 1962.
- 31) McCord, M. C., Komesu, S. and Blount, S. G., Jr., The characteristics of the right atrial pressure wave associated with right ventricular hypertrophy. *Am. Heart J.* **45**: 706, 1953.
- 32) Musser, B. G., Bougas, J. and Goldberg, H., Left heart catheterization. II. With particular reference to mitral and aortic valvular disease. *Am. Heart J.* **52**: 567, 1956.
- 33) Sarnoff, S. J. and Braunwald, E., Ventricular function. Starling's law of the heart studied by means of simultaneous right and left ventricular function curves in the dog. *Circulation* **9**: 706, 1954.
- 35) Katz, L. N., Feinberg, H. and Shaffer, A. B., Hemodynamic aspects of congestive heart failure. *Circulation* **21**: 13, 1960.
- 36) Hickam, J. B. and Cargill, H. B., Effect of exercise on cardiac output and pulmonary arterial pressure in normal persons and in patients with cardiovascular disease and pulmonary emphysema. *J. Clin. Invest.* **27**: 10, 1948.
- 37) Lewis, B. M., Haussay, H. E. J., Haynes, F. W. and Dexter, L., The dynamics of both right and left ventricles at rest and during exercise in patients with heart failure. *Circulation Res.* **1**: 312, 1953.