President’s Lecture

ON SOME POINTS OF THE CONGESTIVE HEART FAILURE

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The pathophysiology and treatment of congestive heart failure is always a new problem for cardiologists, although abundant studies and clinical trials were carried out in the past. For example, the causes underlying the reduction of myocardial contractility are not clearly and precisely elucidated by morphological basis alone, but are to be considered from the changes in the myocardial metabolism resulting in altered substrate utilization and proton production (pH). Furthermore vasodilator therapy for the intractable heart failure is recently introduced to determine its efficacy and exact indication.

This paper presents the results recently obtained by us on pathological, experimental and clinical investigations in the congestive heart failure, although they are fragmentary to the huge problems in congestive heart failure.

I. CLINICO-PATHOLOGICAL STUDY

The clinico-pathological studies were carried out in autopsy cases succumbed to congestive heart failure by following three procedures, in order to clarify the interrelation between morphological findings and cardiac death. First, the grade of myocardial fibrosis was compared with that of chronic congestive change in lung or liver to find whether there was a difference among underlying causes of congestive heart failure. Second, the quantitation of myocardial fiber diameter and interstitial tissue in right and left ventricle of valvular heart diseases was performed. Third, the worst laboratory data before death were examined in correlation with the pathological findings.

1) Myocardial fibrosis and pulmonary or hepatic congestion.

The autopsy cases examined were 27 valvular heart diseases (mitral 9, aortic 8 and combined 9) and 13 myocardial infarctions. In addition, 15 cases of myocardial infarction in another series died from shock or serious arrhythmias were also examined to compare with those died from congestive heart failure.

Myocardial fibrosis was classified slight, moderate and marked according to the grade of myocardial loss and interstitial fibrosis. The chronic congestion of lung was classified slight, moderate and marked by the grade of fibrous thickening in alveolar septa, widening of capillary basement membrane and wall-thickening as well as narrowing of lumen in pulmonary arteries and arterioles. The 3 grades of chronic congestion of liver was determined by the grade of dilatation of the central vein, centrilobular necrosis, connective tissue formation and fibrous retraction. Furthermore, the areas of myocardial necrosis and fibrosis in three representative cross sections (apical, middle and basal one thirds) of left ventricle in the cases with myocardial infarction were measured by point counting method and expressed as mean percentage of three cross sections.

Some differences were observed in relation of myocardial fibrosis to pulmonary and/or hepatic congestion among the underlying causes (Fig. 1). The grade of chronic congestion in lung and liver was rather marked than that of myocardial fibrosis in combined mitral valvular heart diseases, whereas myocardial infarctions had an opposite relationship i.e. myocardial fibrosis was rather marked than chronic congestive findings of both organs. On the other hand, the cases with aortic valvular heart diseases showed myocardial fibrosis approximately parallel to the grade of chronic congestive pathological findings in lung and liver.

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to the cause of death, that are death groups from congestive heart failure, arrhythmias and shock. The former two groups had significantly larger areas of myocardial fibrosis than the shock group, whereas shock group had significantly larger necrotic areas of myocardium than the former 2 groups (Fig. 2-b).

2) The quantitation of myocardial fiber diameter and interstitial tissue.

The quantitation of myocardial fiber diameter (MFD) and interstitial tissue (IT) of left and right ventricular free wall (LV and RV) were performed in 25 succumbed cases from congestive heart failure due to valvular heart diseases (mitral 9, aortic 7 and combined 9) by the method of Fuster et. al1 with some modification. One hundred myocardial fiber diameters were measured at the shortest length on the level of nuclei and were averaged. The averaged MFDs of left and right ventricle in age-matched normal control hearts were 15.5 ± 1.3 and 13.9 ± 1.1 x 10^{-3} mm (mean ± SD). The averaged MFDs of left and right ventricles in three groups of valvular heart diseases were all significantly (p < 0.01 ~ 0.02) larger than that of normal control. The averaged MFDs of left ventricle were 18.8 ± 3.3, 24.0 ± 3.4, and 20.0 ± 2.9 in mitral (M), aortic (A) and combined (C) valvular heart diseases respectively and those of right ventricle were 18.5 ± 2.0, 19.0 ± 1.0 and 18.0 ± 2.2 in M, A and C respectively. The areas of IT in left ventricle were significantly (p < 0.01 ~ 0.05) larger than that of normal control (36.7 ± 4.9%), i.e. 45.1 ± 5.6, 41.5 ± 4.9 and 46.9 ± 4.0% in M, A and C respectively, whereas that of right ventricle in three groups did not show any significant difference from that of normal control (46.9 ± 3.0%). Furthermore, the MFDs and the areas of IT of left ventricles in three groups showed a significant negative correlation (r = −0.40, p < 0.05), although those of right ventricles did not. The averaged myocardial fiber diameters of left or right ventricle and their respective standard deviations in each case had significant positive correlation (r = 0.70, p < 0.001 for LV, r = 0.57, p < 0.01 for RV), indicating that the averaged MFD becomes the larger, the more marked dispersion exists in diameters of individual myocardial fiber.

Moderate to marked chronic pulmonary congestion was found on histological examination more frequently (p < 0.05) in cases with IT area of left ventricle exceeding 40% along with MFD of right ventricle greater than 17.5 x 10^{-3} mm,

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3) Interrelation between the worst laboratory data before death and pathological findings.

In this report, the worst values of blood chemistry in several days to a few weeks before death were chosen to correlate with pathological findings. There was a significant negative correlation between the level of serum sodium and the averaged myocardial fiber diameter of right ventricle ($r = -0.55, p < 0.01$) (Fig. 3). The cases with serum sodium less than 132 mEq/L had more frequently ($p < 0.01$) the area of right ventricular IT less than 45%, in comparison to the cases with serum sodium over 132 mEq/L. The cases with marked chronic pulmonary congestion showed more frequently ($p < 0.01$) the level of serum sodium less than 135 mEq/L before death. It may be said from these data that the cases with low serum sodium level before death are likely to have increased myocardial fiber diameter along with decreased area of interstitial tissue in right ventricle and to develop marked pulmonary congestion. Furthermore the serum potassium levels before death showed a significant negative correlation with the areas of left ventricular interstitial tissue indicating that the cases with the lower serum potassium level had the larger left ventricular interstitial tissues (Fig. 4-a). On the other hand, the levels of serum total proteins had a significant positive correlation with the areas of right ventricular interstitial tissues, showing that the cases with the lower total protein level before death had the smaller areas of interstitial tissue in right ventricle (Fig. 4-b).

Summary: The results of the clinico-pathological study on congestive heart failure are summarized as follows.

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1) The death from congestive heart failure in myocardial infarction was explained mainly by gross loss of myocardium and increased myocardial fibrosis. On the other hand, the myocardial loss and fibrosis in valvular heart diseases were relatively slight in general and other factors such as defective valvular function resulting in hemodynamic, biochemical and hormonal derangement had to be also considered to explain the death from congestive heart failure.

2) The abnormal low levels of serum total protein, sodium and potassium before death in valvular heart diseases correlated with the increase of interstitial tissue in left ventricle and the increase of myocardial fiber diameter along with the decrease of interstitial tissue in right ventricle. The cases with the combination of these pathological findings showed moderate to marked chronic pulmonary congestion. This fact suggests that marked pulmonary congestion may be induced by breaching out of normal balance in contractile force of right and left ventricle.

II. EXPERIMENTAL STUDY

1) Turnover rates and synthesis of cardiac
Fig. 5. Incorporation rates of glycine-2-\(^{14}\)C into myocardial DNA, RNAs and proteins in rabbits with aortic coarctation.

\[\uparrow: \text{increase} \quad \downarrow: \text{decrease} \quad \sim: \text{unchanged} \quad \ast: p < 0.02 \text{ or } 0.05 \quad \ast\ast: p < 0.01 \quad \ast\ast\ast: p < 0.001\]

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Fig. 6. Incorporation rates of 1-lysine-\(^{3}\)H into myosin B and soluble protein in left ventricle of rabbits with aortic coarctation.

Fig. 7. Incorporation rates of 1-lysine-\(^{3}\)H into various structural proteins of left ventricle in rabbits with aortic coarctation.

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structural proteins in normal and aortic coarcted rabbit heart.

It is well known that the long-standing overload on the heart results in cardiac hypertrophy and then gradually in heart failure. The protein synthesis and nucleic acid metabolism during the course of this events have been studied on aortic constriction in animals by many investigators, including Meerson et al.\textsuperscript{2}

We have previously\textsuperscript{3} reported the changes of incorporation rates in various subcellular protein fractions and nucleic acids in left ventricle of rabbit with aortic coarctation using glycine-\textsuperscript{14}C (Fig. 5). It was to be noted that the incorporation rate of glycine-\textsuperscript{14}C into contractile protein did not show any significant difference from normal control value at 3 to 5 months after aortic constriction, when the lungs showed histologically the findings of chronic congestion i.e. left ventricular failure, although the incorporation rate into mRNA increased significantly again at this time as shown in figure 5. It was suggested from these results that left ventricular failure might be induced by some regulatory disturbances in synthesis of contractile protein on the steps following mRNA.

Then the incorporation rates into various fractions of contractile protein in 6 normal and 25 hypertrophied rabbit hearts with aortic constriction three-fourths of original circumference were investigated by using l-lysine-\textsuperscript{3}H (100 µCi/Kg). Rabbits were killed 24 hours after the intravenous injection of l-lysine-\textsuperscript{3}H and myosin B were prepared from left and right ventricle, atria and skeletal muscle. Left ventricular myosin B were fractionated to native tropomyosin, heavy and light chain of myosin, actinin (10s-actinin + α-actinin) and actin by the method of Ebashi and Sugita\textsuperscript{4} combined with preparative block gel electrophoresis. The details of method will be published elsewhere\textsuperscript{5} The protein content, specific activities and lysine content of each fractions were measured by Lowry’s method, liquid scintillation spectrometer model SL-31 and automatic amino acid analyser JIC-6AH respectively. The rabbits with aortic coarctation were sacrificed 3 days, 7 days, 1 month and 5 months after operation and the same procedures were carried out.

The order of incorporation rates (mean ±

| TABLE I EFFECTS OF PULMONARY ARTERY CONSTRICTION ON THE HEMODYNAMICS AND METABOLISM IN LEFT VENTRICLE |
|-------------------------------------------------|-----------------|-----------------|-----------------|-----------------|
| No. | before | 10 min | 20 min | 5 min |
| RVSP (mmHg) | 15 | 29.6 ± 2.5 | 62.7 ± 5.3** | 63.1 ± 6.8** | 33.2 ± 3.2 |
| RVEDP (mmHg) | 15 | 2.4 ± 0.3 | 5.9 ± 0.6** | 5.9 ± 0.5** | 3.0 ± 0.3 |
| LVSP (mmHg) | 15 | 126.5 ± 5.3 | 117.5 ± 8.1 | 115.6 ± 4.1 | 123.1 ± 5.3 |
| LVEDP (mmHg) | 15 | 6.5 ± 0.9 | 7.5 ± 1.3 | 8.2 ± 1.4 | 7.0 ± 0.6 |
| $LVmax dp/dt_{dp}$ (sec$^{-2}$) | 15 | 833.2 ± 60.5 | 691.5 ± 57.1 | 701.0 ± 73.8 | 791.1 ± 57.7 |
| $AoF$ (L/min) | 14 | 1.1 ± 0.1 | 0.9 ± 0.1 | 0.8 ± 0.1* | 1.0 ± 0.1 |
| $CBF$ (ml/min) | 9 | 35.8 ± 2.3 | 30.7 ± 3.5 | 29.8 ± 1.9 | 32.8 ± 2.2 |
| $LVW$ (kgm/min/m$^2$) | 14 | 1.6 ± 0.1 | 1.2 ± 0.2* | 1.0 ± 0.1* | 1.4 ± 0.04 |
| $\Delta G$ (mg/dl) | 13 | 5.0 ± 1.3 | 5.2 ± 1.7 | 5.3 ± 1.6 | 6.2 ± 1.3 |
| $\Delta L$ (mg/dl) | 13 | 7.3 ± 1.3 | 7.4 ± 1.0 | 8.4 ± 1.2 | 8.7 ± 1.1 |
| $\Delta P$ (mg/dl) | 13 | 0.56 ± 0.12 | 0.46 ± 0.13 | 0.58 ± 0.13 | 0.60 ± 0.14 |
| $\Delta FFA$ (mEq/l) | 9 | 0.12 ± 0.03 | 0.08 ± 0.02* | 0.06 ± 0.01** | 0.07 ± 0.01 |
| $\Delta G \times CBF$ (mg/min) | 8 | 1.65 ± 0.65 | 0.92 ± 0.29 | 1.37 ± 0.46 | 1.56 ± 0.47 |
| $\Delta L \times CBF$ (mg/min) | 8 | 2.43 ± 0.61 | 2.56 ± 0.73 | 2.33 ± 0.46 | 2.47 ± 0.39 |
| $\Delta P \times CBF$ (mg/min) | 8 | 0.14 ± 0.04 | 0.09 ± 0.06 | 0.11 ± 0.04 | 0.14 ± 0.03 |
| $\Delta FFA \times CBF$ (μEq/min) | 5 | 3.16 ± 0.79 | 1.96 ± 1.04 | 1.48 ± 0.57 | 2.08 ± 0.37 |

(Mean ± SEM) RV: right ventricle LV: left ventricle SP: systolic pressure EDP: end-diastolic pressure AoF: aortic flow CBF: blood flow in left coronary circunflex branch LVW: left ventricular work G: glucose L: lactate p: pyruvate FFA: free fatty acid $\Delta$: coronary arterio-venous difference *: P < 0.05 **P < 0.001
SEM, cpm/mg) of 1-lysine-3H into myosin B in normal rabbit was left ventricular (431.0 ± 39.3), right ventricular (334.0 ± 20.1), atrial (255.9 ± 43.8) and skeletal (131.3 ± 25.0) myosin B, indicating that cardiac myosin B turned over more rapidly than that of skeletal muscle.

The relative turnover rates of cardiac structural proteins in normal rabbits were calculated after being corrected by lysine content, when turnover rate of actin was 1.0. The order was: native tropomyosin (2.7), actinin (2.5), heavy chain of myosin (2.0), light chain of myosin (1.7), soluble protein (1.6) and actin (1.0). There were some differences in cardiac muscle from the skeletal muscle, in which the order of relative turnover rates were: troponin (6.5), soluble protein (3.7), tropomyosin (3.3), α-actinin (3), myosin (2.5), 10s actin (1.7) and actin (1.6). As to cardiac structural proteins, Zak reported recently that the order of turnover rate in rats was myosin heavy chain > α-actin = tropomyosin > myosin light chain > actin. It is difficult to explain the difference between his and our results. It may be due to the difference of species or of analytical methods.

The incorporation rates of 1-lysine-3H into left ventricular proteins after aortic coarctation were shown in Figure 6. The ratio of heart weight to body weight became as twice as the control in 5 months. The incorporation rate into myosin B of left ventricle increased at 3 days and reached to the peak at 7 days and returned to control level at 1 month after aortic coarctation and remained at the same level thereafter, while the incorporation rate into soluble protein did
Fig. 10. Two types of aortic coarctation in open chest dogs. Type A is usual aortic coarctation. Type B has aorto-left coronary circumflex branch bypass. Left ventricular pressure by catheter via left atrial appendage and aortic pressure are measured. Pulmonary blood flow as cardiac output and blood flow in circumflex branch of left coronary artery as representative of coronary blood flow are measured by magnetic flow meter. Coronary venous blood are drawn through catheter in coronary sinus.
LV: left ventricle  CX: circumflex branch of left coronary artery
PA: pulmonary artery

Fig. 11. Changes of left ventricular systolic pressure, end-diastolic pressure, cardiac index and left ventricular work after the aortic coarctation with (○) and without (●) aorto-left coronary circumflex branch bypass.
LVSP: left ventricular systolic pressure
LVEDP: left ventricular end-diastolic pressure
CI: cardiac index
LVW: left ventricular work
*: denotes p value of changes as compared with control

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not return to control level by 1 month after initial rise and showed a tendency to increase again at 5 months. The skeletal muscle did not show any change in incorporation rate during the whole course.

The incorporation rates of radioactive lysine into each fraction of myosin B increased to the peak on the 7th day after operation and returned to control level at 1 month. The rate of light chain labeling was increased relative to that of heavy chain. This result was coincident with Zak’s report. It was noteworthy that the incorporation rate into native tropomyosin was extraordinary higher than that of other fractions (Fig. 7). The reason and meaning of this finding are not clear in this study and need to be investigated further. Furthermore, lungs of rabbits with aortic coarctation in this study did not show chronic congestion in pathological findings even after 5 months in contrast with the previous study.

This difference was probably due to the grade of aortic coarctation, i.e. three-fourths of original circumference in this study instead of two-thirds in the previous study. The difference in the grade of aortic stenosis could also explain the difference in two studies on the incorporation rates into contractile protein at 1 month and 5 months. Therefore the changes in incorporation rates of each contractile protein fraction at the stage of heart failure which may reflect the changes in synthetic process of each contractile protein fraction, remained to be investigated in the future.

2) Substrate utilization of canine left ventricle with acute pulmonary and aortic constriction.

It has been reported previously in our coronary sinus catheterization study in man that there was a significant negative correlation (r =
Fig. 13. Changes of carbohydrate and free fatty acid uptake in left ventricle after aortic coarctation with (○) and without (●) aorto-left coronary circumflex branch bypass.

\[ \Delta G: \text{coronary arterio-venous difference of glucose} \]
\[ \Delta L: \text{coronary arterio-venous difference of lactate} \]
\[ \Delta P: \text{coronary arterio-venous difference of pyruvate} \]
\[ \Delta \text{NEFA: coronary arterio-venous difference of free fatty acid} \]

CBF: coronary blood flow in left circumflex branch

* denotes the same as in Fig. 11.

\[ \text{Mean±SEM} \]  
\[ **P<0.02: \text{Significant to before} \]

\[-0.62, p<0.01, n=20\] between the myocardial oxygen extraction ratio of free fatty acid (FFA)\textsuperscript{8} in left ventricle and the level of pulmonary wedge pressure (PCm) in cases with mitral stenosis, whereas that of carbohydrate (glucose, lactate and pyruvate) tended to increase with the increment of PCm. Furthermore, in left heart overloaded cases there was a slight but significant negative correlation \( r = -0.34, p<0.05, n=40 \) between the myocardial oxygen extraction ratio of FFA in left ventricle and the level of PCm, and a significant positive correlation \( r = 0.54, p<0.025, n=21 \) between the myocardial oxygen extraction ratio of carbohydrate and the level of PCm was observed in cases with PCm exceeding 12 mmHg. \textsuperscript{10} These facts suggested that the left ventricle utilized less FFA and relatively more carbohydrate when the right ventricle was overloaded or the left ventricle fell to failure.

Then experimental study was carried out in open chest dogs to ascertain these facts in two methods, namely by acute constriction of pulmonary and aortic artery root.

\textit{a) Acute constriction of the pulmonary artery.}

The details of method and results were reported elsewhere.\textsuperscript{11}

Effects of main pulmonary artery constriction 20 minutes long by 75% of the cross sectional area on the left ventricular hemodynamics and metabolism were as follows (Table I).

The left ventricular end-diastolic pressure tended to increase slightly. The aortic flow measured by magnetic flow meter (Model 26 MF Nihon Koden Co.) decreased significantly by 20 minutes after constriction and the blood flow in circumflex branch of left coronary artery showed a tendency to decrease. The left ventricular work decreased significantly at 10 and 20 minutes after constriction. The coronary arterio-venous difference of FFA showed a significant reduction during constriction and this reduction sustained 5 minutes after release of banding. The coronary arterio-venous differences of glucose and lactate seemed to increase very slightly. There was a significant negative correlation \( r = -0.79, p<0.01, n=20 \) between the uptake (coronary arterio-venous difference times coronary blood flow in left circumflex branch) of FFA and that of carbohydrate (glucose, lactate and pyruvate). The hearts of sham-operated dogs

Fig.14. Interrelationship between left ventricular end-diastolic volume and stroke volume or mVcf. The left upper figure shows type A, in which left ventricular end-diastolic volume increases with increase of stroke volume and mVcf. The left lower figure shows type B, in which left ventricular end-diastolic volume increases with increase of stroke volume, while mVcf is almost constant. The right figure shows the relationship of cardiothoracic ratios with the two types.

A.K. □ MSi + Ai

CTR 69%

Fig.15. Interrelationship between the RR interval \( r" \) just before the preceding RR interval \( r' \) of Ecg and left ventricular stroke volume or mVcf in type A. The left lower figure indicates a negative correlation between \( r" \) and left ventricular stroke volume or mVcf. The right figure indicates a positive correlation between the \( (r'-r") \) and left ventricular stroke volume.
did not show any significant hemodynamic and metabolic changes during the whole course.

The interrelations between coronary arteriovenous difference of FFA and left ventricular end-diastolic pressure or max dp/dt/IIP are shown in Figures 8 and 9, in which the average values of before, at 20 minutes after constriction and at 5 minutes after release of banding and sham-operated groups are compared. It was clearly shown that the myocardial uptake of FFA decreased in accordance with the increase in end-diastolic pressure or decrease in max dp/dt/IIP of left ventricle and these changes of myocardial FFA uptake did not return to control level at 5 minutes after release of banding, indicating retarded metabolic repair.

b) Acute constriction of the aorta.

Effects of aortic constriction 20 minutes long on the left ventricular hemodynamics and metabolism were investigated in two types of aortic coarctation with (type B) and without (type A) aorto-left coronary circumflex branch bypass (Fig. 10-A, B). Type B resembled more likely to clinical valvular aortic stenosis concerning the coronary hemodynamics, because one vessel of coronary arteries stented from distal portion of aortic stenosis.

The systolic and end-diastolic pressure of left ventricle increased significantly to approximately the same level in two types of coarctation (Fig. 11). On the other hand, the cardiac index tended to decrease and the decrease in type B was more marked, although the difference in type A and B was statistically not significant. Then the left ventricular work tended to increase in both types, and the increase in type B was less marked as compared with type A, but the difference was not significant (Fig. 11).

The aortic systolic pressure decreased in both types and the magnitude of reduction in type B was significantly greater than in type A. The aortic diastolic pressure decreased significantly in type B, while that in type A remained almost unchanged. The blood flow in circumflex branch
of left coronary artery tended to increase in both types (Fig. 12).

As to the substrate utilization in left ventricle with aortic coarctation, the myocardial uptake of carbohydrate (glucose, lactate and pyruvate) increased in type B coarctation and this increment at 20 minutes after coarctation was statistically significant, while the increase of myocardial carbohydrate uptake in type A was less marked. (Fig. 13). The myocardial uptake of FFA in type A tended to increase and contrarily that in type B tended to decrease (Fig. 13).

Thus the type B aortic coarctation, which is more similar to clinical valvular aortic stenosis, showed somewhat different hemodynamic changes as compared with simple aortic coarctation (type A), that were more marked reduction in coronary perfusion pressure, probably more marked reduction in cardiac index, while the rise in left ventricular end-diastolic pressure was comparable to type A. Furthermore the left ventricle in type A and B showed different responses in substrate utilization and the left ventricle in type B utilized more carbohydrate and slightly less FFA than that in normal control as fuel.

Summary of experimental studies are as follows.

1) Relative turnover rates of cardiac structural proteins in normal rabbit were determined. 
2) Cardiac native tropomyosin seemed to be metabolically more active than other cardiac structural proteins at 7 days after aortic constriction in rabbits.
3) In dogs, the acute constriction of pulmonary artery or of aorta with and without aorto-left coronary circumflex branch bypass induced the elevation in left ventricular end-diastolic pressure. The myocardial uptake of FFA decreased or tended to decrease at that time in the cases of pulmonary constriction and aortic coarctation with aorto-coronary bypass.

The rise of left ventricular end-diastolic pressure in these cases was difficult to determine whether it was due to left heart failure or due to the change of left ventricular compliance, since the rise of end-diastolic pressure was not so marked. Therefore the change of substrate utilization in left ventricle might not necessarily be regarded as the result of left heart failure alone. Further study was needed to ascertain the failing left ventricle utilizes less FFA and relatively more carbohydrate as fuel.
III. CLINICAL STUDY

1) Echocardiographic study on valvular heart diseases with atrial fibrillation.

Cases with atrial fibrillation are suitable clinical models to investigate the relation of myocardial contractility with the Frank-Starling's law of heart, since the heart pumps the blood at variable end-diastolic volumes along with constant myocardial contractility proper to that heart at least during echocardiographic study.

Thirteen atrial fibrillation cases of mitral and combined valvular heart diseases were studied by M-mode echocardiography (Model OIA Toshiba Co. and 2.25 MHz transducer focused at 7.5 cm). Left ventricular end-diastolic volume (Pombo's method\textsuperscript{12}), stroke volume and mean velocity of fiber shortening corrected for end-diastolic diameter (mVcf) were calculated per beat. End-diastolic volumes more than 300 ml were corrected by Gibson's method\textsuperscript{13}.

There were two types of atrial fibrillation, i.e. a type, in which stroke volume and mVcf increased with the increase of left ventricular end-diastolic volume (type A) and the other type, in which mVcf remained almost unchanged when the left ventricular end-diastolic volume increased (type B). It was observed that hearts...
Fig. 19. The interrelationship between serum digitoxin concentration and albumin level. Fig. 19 a, b and c show the data in cases receiving digitoxin 0.05, 0.075 and 0.1 mg daily respectively. These figures show the levels of serum albumin necessary to maintain the serum digitoxin concentration over than 10 ng/ml decrease in accordance with the increase of maintenance dose of digitoxin.

Fig. 20. a) The interrelationship between [Na\(^+\)-Cl\(^-\)] and [base excess +42] in blood of cases with congestive heart failure before discharge or death. ○: improved  ●: intractable heart failure  †: dead  
b) The relation of base excess in blood with the prognosis of congestive heart failure. white: survived  black: dead

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blood volume in left ventricle. The hearts of type B had a gross residual blood volume so that the abbreviation of diastole in some extent, say 0.5 second, might not influence the end-diastolic volume due to rapid filling resulting in an unchanged stroke volume.

2) Serum digitalis concentration in outpatients.

Serum digoxin and digitoxin concentration were measured by radioimmunoassay kit (Clinical Assay Co.) in 145 outpatients receiving maintenance dose, ranging from 0.05 to 0.15 mg for digoxin and from 0.125 to 0.375 mg for digitoxin.

The average maintenance doses in 59 digitoxin cases did not differ definitely among various age groups, however the average serum digitoxin concentration in cases exceeding 65 years of age was 25.3 ng/ml and higher (p < 0.02) than that in cases under 45 years of age (17.3 ng/ml), when only the cases maintained with 0.1 mg digitoxin were considered. On the other hand, in 86 digoxin cases the maintenance doses in cases under 60 years of age were frequently (p < 0.05) larger than those in cases over 60 years of age, although average serum digoxin concentration of cases with maintenance dose 0.25 mg was higher (p < 0.02) in patients over 45 years of age (1.07 ng/ml) than in patients under 45 years of age (0.53 ng/ml). These results coincided with other reports published previously.

The variances of serum digitalis concentration from day to day was 13.8% for digoxin and 24.4% for digitoxin, when they were calculated from the measurements more than twice in different days on the same cases receiving fixed maintenance dose.

Current concept indicates that digitoxin is metabolized in liver and changes in part to digoxin. Then the blood of outpatients were analyzed both for digitoxin and digoxin concentration irrespective of digitalis preparation administered, and result was shown in Figure 18.

In cases receiving digitoxin, the serum level of digitoxin concentration increased with that of digoxin resulting in a significant positive correlation (r = 0.66, p < 0.001), while in cases receiving digoxin, the serum digoxin concentration increased along with the increment of administered dose without any significant serum digitoxin concentration. This results suggested that digoxin administered exerts the inotropic effect on the heart as additive action of digitoxin and digoxin, according to their concentration in blood.

Digitoxin absorbed from digestive organs moves in blood mostly as bounded form with albumin, while digoxin moves mostly as free form. It was observed also in our present study that the serum concentration of digitoxin and of albumin in blood had a significant positive correlation (r = 0.43, p < 0.01), although there was no correlation in the case of digoxin. It will be presumed from these results that the serum concentration of digitoxin may be determined not only by administered dose but also by the level of serum albumin. Then the serum concentration of digitoxin were examined according to various administered doses, i.e. 0.05, 0.075 and 0.1 mg daily (Fig. 19). In the 0.05 mg group (Fig. 19-a), the level of serum albumin exceeding 4.5 g/dl was necessary to maintain the serum digitoxin concentration more than 10 ng/ml, which is generally considered as effective level at least. This necessary level of serum albumin lowered to 4.0 g/dl or less when the administered doses increased to 0.075 mg and to 0.1 mg, as shown in Fig. 19-b and c.

3) Clinical laboratory data and prognosis of congestive heart failure.

In previous study we have noticed that congestive heart failure cases with serum sodium less than 130 mEq/L or serum chloride under 95 mEq/L died afterwards significant more frequently than the cases exceeding these values. The cases with blood urea nitrogen more than 30 mg/dl, icterus index over 20, serum total protein under 6.0 g/dl or serum albumin under 3.0 g/dl died significant more frequently than the cases without these values.

In the present study 86 cases with congestive heart failure were examined on the level of sGOT, sGPT and data of Astrup method. Cases consisted of 50 valvular heart diseases, 20 ischemic heart diseases, 6 cardiomyopathies, 3 hypertensive heart diseases, 3 chronic cor pulmonales, 2 congenital heart diseases and 2 miscellaneous. Male were 49 and female were 37 and age was ranging from 22 to 81 years.

There was a significant positive correlation (r = 0.945, p < 0.001) between the worst values...
of sGOT and sGPT (RF units) before death and the regression line (sGOT = 2.8 x sGPT - 26.4) was steeper than that of liver cirrhosis (sGOT = 1.6 x sGPT + 12.5). The 27 cases with sGOT: sGPT ratio more than 2.5 consisted of 17 cases of poor risk, i.e. dead or intractable heart failure, while the 50 cases with the ratio under 2.5 included of only 18 such cases. The difference between 2 groups was significant (p < 0.025).

The acid-base balance in blood is influenced by the changes of serum electrolytes and blood gases and it is necessary to consider these 2 factors when the acid-base balance changes.

According to G. Rooth, the equation: Base Excess +42 = Na+ - Cl- is valid if the concentration of the residual anions is not increased as it in the following clinical conditions: ketosis in diabetes mellitus and starvation, increased lactate level in blood due to insufficient oxygen supply to the tissues, salicylate or methylalcohol intoxication and kidney insufficiency. Then the relation of [Na+ - Cl-] with [base excess + 42] in the blood before death or at discharge was examined in cases with congestive heart failure. As shown in Figure 20-a, there were many cases plotted in right lower part of the 45 degree line and these cases were presumed in a state of metabolic alkalosis induced by use of diuretics. It was noteworthy that the cases with base excess over ±3.5 mEq/L died afterwards more frequently (p < 0.01) than the cases with base excess less than ±3.5 mEq/L (Fig. 20-b).

The serum chloride level in survived cases had a significant negative correlation with the level of base excess indicating a regression line: [BE] = -0.41 x [Cl-] + 42.3 (r = -0.48, p < 0.01) (Fig. 21). This fact was easy to understand, because both base excess and chloride were major components of anions in the blood. On the other hand, the dead cases in the left lower part detached from the regression line in Figure 21 were supposed to have large negative base excess resulted from lactate production due to deficient oxygen supply to the tissues. The dead cases in the left upper part of the regression line were presumed to die from the extreme meta-
bolic alkalosis by excessive use of diuretics, on which we as clinicians had to reflect on ourselves.

There was a significant positive correlation between PCO$_2$ and base excess in the survived cases as shown in Figure 22. The cases located outside the square surrounded by values of PCO$_2$ 30, 50 mmHg and of base excess $\pm$ 3.5 mEq/L in blood consisted of significantly more dead and intractable heart failure cases than the cases in the square area ($p < 0.01$) (Fig. 22-a, b).

Moreover the cases located outside the square area surrounded by values of blood pH 7.35, 7.50 and of base excess $\pm$ 3.5 mEq/L or of blood PCO$_2$ 30 and 50 mmHg consisted of significantly ($p < 0.01$) more dead and intractable cases than those in the square area (Fig. 23 and 24).

4) Vasodilators in chronic congestive heart failure.

Many investigations have been reported about the effectiveness of vasodilator therapy on the intractable heart failure. The prerequisites of vasodilators to treat chronic congestive failure are effective by oral route and able to long term use. Chatterjee and Parmley$^{16}$ indicated the standard to apply various vasodilators, that are nitroglycerine, isosorbide dinitrate, hydralazine and phenoxibenzamine, according to the level of cardiac index and left ventricular end-diastolic pressure.

Then the acute effects of isosorbide dinitrate and nifedipine were investigated in a few cases of congestive heart failure. Isosorbide dinitrate 10 mg or nifedipine 20 mg were administered orally or sublingually. Isosorbide dinitrate tended to decrease cardiac output, pulmonary and systemic vascular resistances. Nifedipine tended to increase cardiac output and to decrease systemic vascular resistance without change of pulmonary vascular resistance.

Our experiences with isosorbide dinitrate and nifedipine in the relatively long term oral administration to the chronic congestive heart failure were shown in Table II. Isosorbide dinitrate 15 to 20 mg or nifedipine 20 to 40 mg daily were added to the conventional therapy. The favorable effects were not always obtained. Following were two unfavorable examples in our experiences of vasodilator therapy.

Case I: 64 years of age, female case with congestive heart failure due to combined valvular heart disease and atrial fibrillation. She was in a
TABLE II  EFFECTS OF ORAL USE OF ISOSORBIDE DINITRATE AND NIFEDIPINE ON THE CHRONIC CONGESTIVE HEART FAILURES

<table>
<thead>
<tr>
<th></th>
<th>No. of cases</th>
<th>daily dose</th>
<th>favorable</th>
<th>unchanged</th>
<th>worse</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isosorbide dinitrate</td>
<td>12</td>
<td>15 ~ 20 mg</td>
<td>4</td>
<td>5</td>
<td>3</td>
</tr>
<tr>
<td>nifedipine</td>
<td>14</td>
<td>20 ~ 40 mg</td>
<td>7</td>
<td>3</td>
<td>4</td>
</tr>
</tbody>
</table>

Fig.25. The time course of clinical state in a female congestive heart failure case, 64 years of age, with combined valvular heart disease and atrial fibrillation. Note the increase of edema and body weight after initial short time diuresis by addition of isosorbide dinitrate 15 mg daily to the previous therapy.

state of so-called intractable heart failure in spite of combined use with deslanoside, furosemide and spironolacton. Then she was administered additionally isosorbide dinitrate (ISDN) 15 mg daily. After initial favorable diuretic response within a few days, her body weight, edema and hepatic congestion increased markedly and fell in a critical state, although she did not complain any augmented dyspnea. Diuresis was again obtained on the discontinuation of isosorbide dinitrate and on the medication of acetazolamide and she got better to discharge (Fig. 25).

Case 2: 65 years of age, female case with rheumatic aortic regurgitation. She was maintained in compensated state with digoxin, hydroflumethiazide and hydralazine. However she gained pretibial pitting edema and slight liver enlargement although her blood pressure stabilized, since she was given nifedipine 30 mg per day additionally in order to reduce the blood pressure (Fig. 26).

The clinical study was summarized as follows:

1) The working point on the Frank-Starling's curve was able to presume in cases with atrial fibrillation by using echo-cardiography.

2) In the cases maintained with digitoxin, the serum concentration of digoxin increased with that of digitoxin. The serum concentration of digitoxin were influenced not only by dose given but also the level of serum albumin.

3) The prognosis of congestive heart failure cases with sGOT: sGPT ratio over 2.5 were unfavorable. The values within ± 3.5 mEq/L in
base excess, from 30 to 50 mmHg in PCO₂ and from 7.35 to 7.50 in blood pH were favorable targets in managing the chronic congestive heart failure.

4) Vasodilators which dilate mainly capacitance vessels may exaggerate the system congestion in some cases, although they are useful to alleviate the pulmonary congestion. Therefore they should be administered with careful clinical observations.

CONCLUDING REMARKS

The elucidation of pathogenesis in the congestive heart failure is important as to find a improved remedy to treat. This purpose is achieved not only by morphological and functional but also biochemical study. Biochemical events in heart as well as in whole body are underlying bases for morphological and functional events. So the biochemical fundamental investigations on the heart have to be carried out vigorously. The present study was performed from such view points. The results obtained were very fragmentary as mentioned at the end of each chapter and I am now hoping eagerly the successors to proceed the investigations in biochemical areas.

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