Studies on the Serum Electrophoretic Patterns in Cardiac Diseases (II)
Significance of Variation in Serum Protein Fraction
of Cardiac Patients in Decompensation

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There have been numbers of excellent reports on the pathophysiology of cardiac decompensation.

The cardial symptoms consist of cardiac enlargement, dyspnea and edema, caused by the impairment of the liver, kidneys, lungs, brain and other various organs due to the rise of venous pressure.

It has been taken into consideration that the congestion of those organs might cause a considerable influence on the protein metabolism. Until the invention of Tiselius' electrophoretic analysis the variation of serum protein has been studied by a primitive method and the data were comparatively insufficient in number.

For example, Posner and Teleman, reported albuminuria in the decompensated stage. Rowntree, Winton and Race observed albuminuria in association with renal venous pressure. Chavez reported the dysfunction of the liver in association with cardiac failure Bland et al, reported the increased erythrocyte sedimentation rate in connection with cardiac decompensation.

Since after the invention of electrophoretic analysis, the serum protein fraction in cardiac decompensation has been actively investigated by the following workers; Wurmann, Evans, Tomita, Wachi, Wada, etc.

14) Yamada, Ueda, Oji, etc.

Although these investigators have observed the decrease of albumin and increase of r globulin, it seems that no one has done precise analytical study on the significance of variation in serum protein fraction in correlation with various function's tests. The author, to verify this correlation, has summed the following findings such as venous pressure, liver function's tests, hepatomegaly and red cell sedimentation rate, renal function's tests, cardiac catheterization's test, and inflammatory symptoms. Results are as follows.

MATERIALS AND METHOD

Patients admitted to the Third Division of Department of Medicine, Kyoto University were the objects of this study. They were confirmed to be cardiac patients in failures examined by various functional studies and some were confirmed by postmortem examinations.

The following methods were applied.

1) Serum protein fraction; The measurement was done by the large sized Tiselius' apparatus of H. T.—A type made by Hitachi Co., Ltd. The method & condition of the measurement were the same as those reported in the previous article.

2) Measurement of venous pressure; In a lying position on the back, the No. 18 gage needle was inserted into the antecubital vein which was placed 4cm below the level of anterior chest wall, and the needle was connected to the tube where 3.8%
citrate sodium solution has been filled. Then the venous pressure was measured.

4) Brom sulphalein test (BSP test): 5% Brom sulphalein solution was injected into the arm vein in a dose of 0.1 cc per kg of body weight. After 30 minutes a blood specimen was obtained from the vein of the other arm. There after serum was separated and 10% NaOH solution was added to the serum to reveal the color. This color was compared with the color of the standard solutions (Daiichi Seiyaku Co., Ltd.) and quantitative measurement was done. The value expressed in % at 30 minutes indicates the retention of brom sulphalein.

5) Serum cobalt reaction: Measured according to Inoue & Kumo’s method for liver function study.

6) Serum cadmium reaction: Measured according to the Inoue’s modified method for liver function study.

7) Erythrocyte sedimentation rate: Measured according to Westergen’s method.

8) In cases whose liver edge was palpated below the costal margin at the midsternal line, the size of the enlargement was expressed by finger breadth.

9) Renal plasma flow: Intravenous infusion or single intravenous injection was given in a fasting condition in early morning. Effective renal plasma flow was measured with para-amino-hippuric acid.

10) Pulmonary capillary pressure: Wedge pressures in diastole and systole were measured by a manometer and the average pressures were recorded.

By inserting a catheter into pulmonary arteriole after passing through the cubital vein, superior vena cava, right atrium, right ventricle and pulmonary artery, the systolic and diastolic pressures were measured by a manometer and the average pressures were recorded.

RESULTS

The correlation between serum protein fraction patterns and the various laboratory & clinical findings were checked on 204 cases of cardio-circulatory diseases in compensation. This study, however, does not include the cases having had frequent decompensation resulting in organic changes of the liver or combining other serious diseases which might give a false influence on the protein fraction’s pattern.

1) Normal value

As reported in the previous article, the normal range is shown in Table I.

<table>
<thead>
<tr>
<th>T. P.</th>
<th>Al</th>
<th>α-Gl</th>
<th>β-Gl</th>
<th>γ-Gl</th>
<th>A/G</th>
</tr>
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<tbody>
<tr>
<td>8.15</td>
<td>4.96</td>
<td>0.60</td>
<td>1.16</td>
<td>1.70</td>
<td>1.78</td>
</tr>
<tr>
<td>7.21</td>
<td>4.29</td>
<td>0.32</td>
<td>0.71</td>
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2) Relationship between venous pressure and albumin or γ-globulin:

As shown in Fig. 1, a counter correlation was often observed, i.e. a correlation between the decrease of albumin and the rise of venous pressure. No correlation between γ-globulin and venous pressure, as seen in Fig. 2.

![Fig. 1. Relationship between Serum Albumin and Venous Pressure in Heart Failure 102 Cases.](image)

3) Relationship between albumin, γ-globulin and BSP test:

As shown in Fig. 3 and Table II, there was observed in 75% a correlation between albumin and BSP values (Dye retention at

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Fig. 2. Relationship between Serum γ-Globulin and Venous Pressure in Heart Failure 101 Cases.

Fig. 3. Relationship between Serum Albumin and Bromsulphalein Test in Heart Failure 101 Cases.

30 minutes. No correlation was observed between γ-globulin and BSP value, as shown in Fig. 4.

4) Relationship between albumin, γ-globulin and serum cobalt reaction (Modified method by Inoue and Kumo): No correlation was observed between albumin and serum cobalt reaction.

5) Relationship between albumin, γ-globulin and serum cadmium reaction (modified by Inoue): No correlation seen.

6) Relationship between albumin, γ-glob-
Fig. 5. Relationship between Serum γ-Globulin and Cobalt Reaction (Inoue-Kumo) in Heart Failure 110 Cases.

Fig. 6. Relationship between Serum γ-Globulin and Cadmium Reaction (Inoue) in Heart Failure 108 Cases.

Fig. 7. Relationship between Serum Albumin and Erythrocyte Sedimentation Rate in Heart Failure 186 Cases.

Fig. 8. Relationship between Serum γ-Globulin and Erythrocyte Sedimentation Rate in Heart Failure 186 Cases.

γ-Globulin and erythrocyte's sedimentation rate:
As shown in Fig. 7 and 8, no correlation was observed between them. Moreover the

erythrocyte's sedimentation rate was occasionally within normal limits in cases having a marked decrease of albumin or marked increase of γ-globulin.

7) Relationship between albumin, γ-globulin and hepatomegaly:

The size of the liver was measured by the finger breadth on palpation below the

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Fig. 9. Relationship between Serum Albumin and Liver Enlargement in Heart Failure 92 Cases.

Fig. 10. Relationship between Serum γ-Globulin and Liver Enlargement in Heart Failure 92 Cases.

Fig. 11. Relationship between Serum Albumin and Liver Enlargement in Heart Failure (Below 20 Year Age) 22 Cases.

Fig. 12. Relationship between Serum γ-Globulin and Liver Enlargement in Heart Failure (Below 20 Year Age) 22 Cases.

lowest costal margin at the right midclavicular line. As shown in Fig. 9 and 10, no correlation was observed. However, in the group of younger ages than 20 years, as shown in Fig. 11 and 12, there was a correlation between albumin and hepatomegaly but no correlation between γ-globulin and hepatomegaly.

8) Relationship between albumin, γ-globulin and eff. RPF:
A parallel correlation was observed between albumin and eff. RPF, as shown in Fig. 13, but no correlation between γ-globulin and eff. RPF as shown in Fig. 14.

9) Relationship between albumin, γ-globulin and pulmonary capillary pressure:
A slight correlation was observed, as shown in Fig. 15, between albumin and pulmonary capillary pressure, but no correlation, as seen in Fig. 16, between γ-globulin and pulmonary capillary pressure.

10) Relationship between albumin, γ-globulin and inflammatory signs (leukocytosis of more 9,000 per cmm with the shifting of nuclei to the left, i.e. stab cells more than 10% and temperature more than 37.5°C etc. When two of these three signs are combined,
the inflammatory process in classified to be one plus):
The cases were divided into the following four groups: the groups of albumin more than and less than 4.29 g/dl, the groups of positive and negative inflammatory signs.

It was noted that there was no correlation between albumin content and inflammatory signs. However, 7-globulin content was correlated with inflammatory signs in 75% of the cases, as shown in Table III, when the cases were divided into two groups: the groups of 7-globulin more than and less than 1.70 g/dl.

**Table III** Relationship between Inflammation Symptons (Fever, Leukocytosis, Non-filament Leukocytose) and 7-Globulin

<table>
<thead>
<tr>
<th>7-Gl.</th>
<th>g/dl</th>
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<tr>
<td>-</td>
<td>26</td>
</tr>
<tr>
<td>+</td>
<td>8</td>
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(+ Cases with more than one of the following Temperature, 37.5°C, Leukocytose 9000, Nonfilament Leukocytose 10%)

(-) Cases not included in the above.

**Discussion**

Congestive heart failure is the manifestation of the terminal stage of heart diseases due to lowering of the cardiac function. This status is due to the increase of venous pressure, thus causing congestion of the various organs resulting in hepatic and renal failure and pulmonary congestion etc. It has been observed by many scholars that organic changes influence protein metabolism resulting in the decrease of albumin and increase of 7-globulin in the protein fractions. The author, therefore, sought a correlation between renal, hepatic and pulmonary functions and the changes in protein metabolism and studied the cause of the changes in protein metabolism. The changes of venous pressure are well correlated with the changes of albumin and not at all correlated with 7-globulin.

It is presumed, therefore, the decrease of albumin ensues to the increase of venous pressure. The author also checked the correlation between liver functions tests and albumin and 7-globulin. As shown in Table II, serum albumin and BSP retention’s value at 30 minutes are correlated in 73% of the cases, and 7-globulin is not at all correlated, as shown in Fig. 4.

On the other hand, it has been clarified by the works of Maekawa, Kusunoki, Nose, etc., that BSP dye is generally combined to albumin.

The author also observed by the Tislius’ apparatus that BSP dye is combined to albumin fraction.

Hosoda also observed a correlation between albumin and BSP retention’s value. Oda states regarding the elimination of BSP dye in the human body that BSP dye is combined with serum albumin but the dye is absorbed into the liver cells, for the liver cells are much stronger in the combining power than albumin is, so that BSP is finally excreted through the bile duct.

In case of hepato-cellular damage, the absorption mechanism is hampered, there,
BSP dye retention's value becomes elevated at the time of liver damage. The increase of venous pressure ensues dilatation of central hepatic vein and its surrounding capillary veins with flattening of hepatic cells, followed by a decrease of hepatic blood flow and lack oxygen supply to liver cells\(^{30}\). On the other hand, there are various studies regarding the site of albumin production, and it is nowadays agreed by some investigators that albumin is produced in the liver, e.g. Emmrich et al\(^{31}\) who resected 2/3 of the liver and studied serum protein fraction and histological picture, by Miller et al\(^{32}\) who gave lysin EC\(^{14}\) as a tracer, to the post hepatectomy rats.

Miyoshi\(^{30}\) also assumed the production of serum albumin in the liver. From those researches, the author can assume that the cause of decreased serum albumin in decompensated stage is due chiefly to the decreased production of albumin in the liver secondary to the hepatic dysfunction due to oligemia in the liver resulting from a rise in hepatic venous pressure.

Maekawa et al\(^{36}\) have studied any relationship between serum cobalt and cadmium reaction's tests and albumin or \(\gamma\)-globulin, and found in cardiac patients that there was some correlation between cobalt reaction and \(\gamma\)-globulin and between cadmium reaction and \(\gamma\)-globulin. The author also found some correlation between cobalt reaction and \(\gamma\)-globulin, but no correlation between cobalt reaction and albumin and between cadmium reaction and albumin or \(\gamma\)-globulin, as were the same as the results obtained by Maekawa et al. Fujita\(^{35}\) states that cobalt reaction is in connection with interstitium of the liver. Numa\(^{26}\) also pointed a correlation between cobalt reaction with its shifting to the right and \(\gamma\)-globulin. The author assumes, from those data, that a marked increase of \(\gamma\)-globulin seen in a decompensated stage is in part due to some degree of organic change of hepatic interstitium resulted from continuous stagnation of blood in hepatic vein.

Since Biernuchi\(^{37}\) first invented sedimentation rate test, there have been numbers of studies on its essential attitude and its relationship with serum protein fraction. There are, however, different opinions; e.g. some investigators observed a correlation with \(\gamma\)-globulin, and others observed a correlation with fibrinogen\(^{38}\), albumin\(^{30}\), \(\alpha\)-globulin\(^{40}\) or combination of each protein fraction\(^{42}\) etc. On the other hand, Bland et al\(^{30}\) observed an increase of E.S.R. in patients with congestive heart failure. The author too attempted but failed to find any parallel correlation between E.S.R. and albumin or \(\gamma\)-globulin, as seen in Fig. 7 and 8.

Correlation between albumin or \(\gamma\)-globulin and hepatomegaly:

During decompensation stage hepatomegaly develops as a result of congestion of hepatic venous system and cellular edema caused by the increase of venous pressure. The author, therefore, studied and was unable to find any parallel correlation between albumin or \(\gamma\)-globulin and hepatomegaly. However, there is a correlation between hepatomegaly and the decrease of albumin, due to hepatocellular dysfunction caused by increased venous pressure.

Correlation between albumin or \(\gamma\)-globulin and renal plasma flow:

Since many years ago it has been known that the impairment of renal function exists in cases of cardiac decompensation which presents albuminuria, oliguria and edema etc, and this knowledge has been rapidly increased since after the appearance of renal clearance method. Mokotoff\(^{45}\) reported about impairment of renal function in congestive heart failure. Shiota et al\(^{38}\) studied renal plasma flow before and after the administration of digitalis, and observed the increase of renal plasma flow when cardiac decompensation has been improved. Maekawa et al\(^{40}\) reported a parallel correlation between venous pressure and Natrium clearance. The author has made a research on the correlation between renal plasma flow and serum albumin or \(\gamma\)-globulin.
and found a parallel correlation between renal plasma flow and albumin, but no correlation between renal plasma flow and $\gamma$-globulin. This correlation, the author assumes, is in connection with venous pressure.

Relationship between albumin or $\gamma$-globulin and pulmonary capillary pressure:

The author found that pulmonary capillary pressure has a slight correlation with albumin and no correlation with $\gamma$-globulin. Shiota et al observed a parallel correlation between pulmonary capillary pressure and renal plasma flow. The author, as described above, confirmed that renal plasma flow was correlated with albumin in connection with venous pressure.

Relationship between albumin or $\gamma$-globulin and inflammatory signs (fever, leukocytosis and shifting of nuclei to the left):

No correlation was found between albumin and the inflammatory signs. However, a correlation between $\gamma$-globulin and inflammatory signs was found in 75% of the cases. This is the author's finding that the inflammatory process has much more influence on the increase of $\gamma$-globulin than hepatic damage does. This fact has been overlooked so far and it has been presumed that the increase of $\gamma$-globulin in cardiac decompensation is due to hepatic damage.

Conclusion

204 patients in cardiac decompensation have been studied by the author regarding serum protein fraction, and a comparative study has been made on the protein fraction in connection with venous pressure, liver functions, hepatomegaly, erythrocytes sedimentation rate, renal plasma flow, pulmonary capillary pressure, inflammatory signs (leukocytosis, shifting of nuclei to the left, fever) etc. The study revealed that the decrease of albumin was correlated with venous pressure, B.S.P. retentions value, hepatomegaly, renal plasma flow and pulmonary capillary pressure etc. On the other hand, the increase of $\gamma$-globulin was well correlated with inflammatory signs and slightly correlated with serum cobalt reaction and not at all correlated with other clinical & laboratory results.

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REFERENCES