pulmonary circulation may be determined by intrapulmonary air pressure.

(5) There are many cases of cor pulmonale in which a physiological abnormality rather than the morphological changes of pulmonary vascular bed is the determinant of the pulmonary hypertension. Disability of the heart in these cases can be relieved by the treatment. Therapeutic efforts are directed not only at the treatment of the heart failure, but also toward the elimination the results of pulmonary dysfunction.

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We are greatly indebted to Dr. F. Amako, the Head at Yoku- fukai Hospital for the aged, Professor K. Yamakawa, at the Department of Internal Medicine of Juntendo Medical College, Dr. S. Hinohara, at the Department of Internal Medicine of St. Luke's International Hospital, Assistant Prof. S. Osu, at the Department of Pathology of Tokyo University, Assistant Prof. A. Yamanaka, at the Department of Pathology of Juntendo Medical College, Dr. T. Shimamine, at the Department of Pathology of Tohomon General Hospital, Dr. Z. Ishimi, at the Cardiac Department of Tohomon General Hospital and the staffs in these Hospitals and Institutes who cooperated with us. Also the authors wish to thank Drs. M. Ikeda, S. Yoshida, K. Kuramoto, Y. Fukusima, H. Murao, S. Kira and T. Shosawa for their friendly suggestion and cooperation.

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tor in the regulation of the pulmonary circulation.

3. Clinical Aspect of Digitalis Treatment in Congestive Heart Failure
Due to Acquired Heart Disease.

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DIGITALIS HAS BEEN IN USE AS THE DRUG OF FIRST CHOICE IN THE TREATMENT OF CONGESTIVE HEART FAILURE, PARTICULARLY IN THE CASES OF ACQUIRED HEART DISEASE. NOT INFREQUENTLY, HOWEVER, DO WE ENCOUNTER INSTANCES IN WHICH DIGITALIS FAIL TO BRING ABOUT DESIRED EFFECT WHEN THESE PATIENTS ARE IN NEED OF FULL DIGITALIZATION. IN THE USE OF DIGITALIS, IT IS DESIRABLE TO KNOW IN ADVANCE WHETHER DIGITALIS TREATMENT, ESPECIALLY RAPID DIGITALIZATION COULD BE CARRIED OUT SUCCESSFULLY, TO AVOID UNNECESSARY MEDICATION WHICH MIGHT HAVE TO BE CHANGED DUE TO INEFFECTIVENESS, OR HAZARD CAUSED BY THE OVERDOSAGE OF DIGITALIS. SINCE IT MIGHT NOT BE EASY TO KNOW WHICH THERAPEUTIC BENEFITS WILL BE OBTAINED BY THE ADMINISTRATION OF DIGITALIS, OBSERVATIONS ON THE PATIENT'S RESPONSES TO RAPID DIGITALIZATION WOULD PROVIDE THE USEFUL INFORMATION AS TO WHETHER THE DIGITALIS TREATMENT IS GOING ON SUCCESSFULLY. THE PRESENT PAPER IS TO REPORT OF CLINICAL TRIAL ON THE DEMONSTRATION OF IMMEDIATE EFFECT OF STROPHANTHINE TO OBTAIN THERAPEUTIC GUIDE OR TO FORECAST THE EFFICIENCY OF RAPID DIGITALIZATION.

METHOD

TO INVESTIGATE THERAPEUTIC EFFICIENCY OF DIGI-

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talix, a preliminary administration of strophanthine was tried before digitalization. To predict the effect of digitalis, strophanthine G 0.075 mg. was intravenously injected and observed for 30 minutes hemodynamic changes including cardiac rate, blood pressure and cardiac output, the latter was measured by means of electric conductivity method.

An experimental course of therapy consisted of an initial injection of strophanthine G (Uabani) followed by Lanatoside C (Digilanogen C) for a method of rapid digitalization. Dosage of 0.4 mg. of Digilanogen C every six hours would be expected to offer clinical effect.

During a period of 24 to 36 hours of digitalization and subsequent one or two days, the following estimations were made, i.e., hemodynamic changes, serum electrolytes and urinary excretion of electrolytes and also catecholamines.

Cardiac output was determined by precordial counting upon intravenous administration of iodinated Iö serum (RISA). These estimations were carried out pre- and post-digitalization. Urinary electrolytes and catecholamine were determined every 6 hours during rapid digitalization period, and daily in the ensuing course of therapy. A flamephotometer was employed for quantitative sodium and potassium determinations while adrenaline and noradrenaline were separately determined by Euler et Flodin’s method.

RESULTS AND COMMENT

Strophanthine Test: Single injection of strophanthine G (Uabani) 0.075 mg. was tried to 7 patients who were devoid of cardiovascular abnormality and 28 patients with cardiac disease. Of this 20, there were 10 mitral insufficiency cases, 9 mitral stenosis and 1 aortic insufficiency. The others known were, coronary sclerosis 1, hypertensive heart disease 3, high output failure 2 and two cases of congenital heart disease.

Hemodynamic parameters including cardiac output, venous pressure, cardiac rate and blood pressure are presented in Table I.

As illustrated Figures 1 and 2, three types of pattern are demonstrable on the alteration of cardiac output. In type I, cardiac output was either kept in normal range or fairly often reduced even to an extent of 60 percent of the control level. Of 14 cases of this type, three showed increased cardiac output but never reached 20 percent increase.

This type involved mitral stenosis 6, mitral insufficiency 1, high output failure 2, aortic insufficiency 1, Ebstein’s disease 1, and control subjects 3. In type II, all of eleven cases including mitral insufficiency 4, mitral stenosis 2, pulmonary stenosis 1 and control subjects 4 were shown to have increased cardiac output from 120 to 140 percent. In type III, increased output was as much as more than 40 percent compared with the previous level. Of the 10 patients of this type included mitral insufficiency 5, hypertensive decompensation 3, mitral stenosis 1 and coronary sclerosis 1. It was found that stroke volume of these three types demonstrated the same tendency comparing with cardiac output patterns. Cardiac rate diminished in type III, but not significantly. In no other types does the author find changes in cardiac rate.

Primary actions of strophanthine are like the

<table>
<thead>
<tr>
<th>Type</th>
<th>Cardiac Output</th>
<th>Stroke Volume</th>
<th>Venous Pressure</th>
<th>Cardiac Rate</th>
<th>Blood Pressure</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>before</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Type I</td>
<td>2.6-8.3</td>
<td>30.2-105.3</td>
<td>56-190</td>
<td>56-96</td>
<td>100-170</td>
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<tr>
<td></td>
<td>4.66</td>
<td>64.0</td>
<td>129</td>
<td>77</td>
<td>126.5</td>
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<tr>
<td></td>
<td>2.5-7.3</td>
<td>27.1-108</td>
<td>55-185</td>
<td>60-94</td>
<td>108-166</td>
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<tr>
<td></td>
<td>3.78</td>
<td>49.0</td>
<td>127</td>
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<td>127.7</td>
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<td>Type II</td>
<td>2.35-5.2</td>
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<td>62-220</td>
<td>56-79</td>
<td>108-146</td>
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<tr>
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<td>3.85</td>
<td>56.6</td>
<td>141</td>
<td>68</td>
<td>124.4</td>
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<td>2.80-6.65</td>
<td>40.2-60.0</td>
<td>65-206</td>
<td>54-72</td>
<td>110-145</td>
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<td>4.46</td>
<td>65.6</td>
<td>136</td>
<td>68</td>
<td>133</td>
</tr>
<tr>
<td>Type III</td>
<td>2.35-3.75</td>
<td>19.5-51.6</td>
<td>56-215</td>
<td>90-44</td>
<td>94-156</td>
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<td>3.06</td>
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<td>139</td>
<td>75</td>
<td>129</td>
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<td></td>
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<td>29.8-85.5</td>
<td>50-200</td>
<td>80-46</td>
<td>102-170</td>
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<tr>
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<td>5.02</td>
<td>69.7</td>
<td>121</td>
<td>72</td>
<td>139.5</td>
</tr>
</tbody>
</table>

*Japanese Circulation Journal Vol. 28, March 1964*
similar cardiac glycosides to slow the heart, to increase strength of contractility. Elevation of the arterial pressure and development of the ectopic rhythm which may arise are the additional effects of glycoside\(^5\). With regard to strophantnine administration, the inotropic action is most noteworthy, not necessarily associated with the chronotropic action\(^2\)\(^5\), due to the fact, as we have observed, that reduction of cardiac rate is neither remarkable during a period of 30 minute observation nor found to be accompanied by increased cardiac output.

There was definite increased output to be seen in all patients of type III who showed the signs of the left heart failure; yet, those patients who showed no signs of the left heart failure mostly classifiable to type I failed to demonstrate increased cardiac output but marked diminution.

This fact does suggest inotropic effect of single strophantnine administration serving a therapeutic indication for an ensuing rapid digitalization. It is our interest to note that there occurred a significant difference in the inotropic response when compared between the cases of mitral insufficiency and mitral stenosis, which may be interpreted as presenting existence of the left sided failure in mitral insufficiency (Fig. 2).

**Natriuresis and cardiac output**: Urinary excretion of electrolytes has been observed in a course of rapid digitalization. It was found that there are four different patterns of natriuresis. In the Figure 3, a case of woman, 49 years of age with rheumatic mitral insufficiency showed disappearance of pulse deficit, fall of venous pressure and remarkable increase of urinary flow.

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with simultaneous high sodium and potassium excretion, or high Na/K ratio with digitalis regimen. This pattern should be regarded as Type I, because of its striking therapeutic effectiveness.

As shown in the right panel of the Figure 3, a case of 35 year old man with rheumatic mitral insufficiency associated with tricuspid stenosis and complicated with pericarditis exhibited hardly any sign of changes in urinary sodium or potassium or Na/K ratio despite pronounced diuresis. Full effect of digitalis is lacking in this instance and this is referred as Type III natriuresis.

However, type II had noticeably rapid increase of Na/K ratio along with heightened excretion but shortly came down to the previous low level regardless of increased urinary volume (the left panel of Fig. 4).

This is a minimum effective type. There is another pattern which is type 0, in this type urinary excretion of sodium was kept definitely high before the treatment but remained almost unchanged or even reduced during digitalization. (the right panel of Fig. 4)

In order to investigate the inotropic action of a long termed digitalization with natriuresis, seventeen cardiac patients listed in the Figure 5 were subjected to the precordial determination of cardiac output before and after digitalization. It was found that 6 out of 17 cardiacs demonstrated significantly increased cardiac output, more than 20 percent. Speaking of the natriuresis patterns, two of these six were of type 0, another two of type I and one was of type III and remaining one did not undergo the measurement of urinary electrolyte excretion. Eleven out of 17 patients have shown minimum variation in cardiac output; of these eleven, three were of type II, five of type III, and of the remaining two, one was type 0 and the other was type I. Most of them were the patients suffering from
Fig. 4. Influences of rapid digitalization (within 24 to 48 hours) on urinary flow, urinary excretion of Na, K and Na/K.
left: case of transient effect, Y. G. 60 male H. D.
right: case of ineffectiveness with much diuresis before digitalization, Y. K. 61 male H. D.

either mitral stenosis or pericarditis. Assuming a glycosid acts directly on the renal tubules
as its action on the myocardial fibrils one would expect a higher sodium excretion with an increased cardiac output.

With the patients of type I, unusually increased urinary sodium has been found with accompaniment of increased cardiac output during rapid digitalization. All but one of both types II & III with minimum or transient increase in urinary excretion were not associated with increased cardiac output.

On the other hand, with the patients of type 0, inotropic action was often remarkable though natriuretic effect was absent.

It is suggested that inotropic effect of digitals often appears with natriuresis but the former may be seen regardless of an amount of sodium and water excreted. No convincing evidence could be found that cardiac glycoside acts
directly on the renal tubules to exert influence on the transportation of electrolytes. Primary action of digitalis is apparently of inotropic in character and natriuretic action would be the secondary\(^{12}\).

The author and his colleagues\(^{12}\) have investigated the urinary catecholamine in congestive heart failure and reported that both adrenaline and noradrenaline have often been found to be increased in an order of class I, II and III, class IV showing the level rather lower than that of class III. The level of urinary catecholamine output varied according to the clinical condition which would take a turn for better or worse. The fact has lead us to further studies. During a period of digitalis therapy urinary catecholamine has been determined daily and hourly, hourly examination was made every five or six hours in course of rapid digitalization.

The figure 6 illustrates clinical improvement together with marked natriuresis of type I in a case of 60 year old man with rheumatic mitral stenoinufficiency following digitalization regimen. Urinary catecholamine especially of adrenaline showed a sharp increase in a course of rapid digitalization and gradual fall during a period of maintenance dose of digitalis. Rapid increase in urinary adrenaline is more clearly demonstrable in Figure 7 by six hour urine determination. Urinary noradrenaline remains unchanged.

![Graph](image)

**Fig. 6.** Daily variation of urinary excretion of active catechols during the period of digitalization. effective case: Y. Y. 60, male M S I

![Graph](image)

**Fig. 7.** Urinary excretion of active catechols observed every 5 to 6 hours during the period of rapid digitalization. effective case: Y. Y. 60, male M S I

On the contrary, Figure 8 and 9 illustrates a case of 23 year old female with rheumatic mitral stenoinufficiency who was intractable to digitalis therapy showing a low level of natriuresis, type III. Although urinary output of catecholamine was higher than the normal level, daily determination of catecholamine fluctuated from day to day showing inconsistent tendency and six hour urinary catecholamine and adrenaline remain unchanged.

![Graph](image)

**Fig. 8.** Daily variation of urinary excretion of active catechols during the period of digitalization. ineffective case: F. S. 23, female M S
DIGITALIS TREATMENT IN GLOMESTIVE HEART FAILURE DUE TO ACQUIRED HEART DISEASE

Fig. 9. Urinary excretion of active catechols observed every 5 hours during the period of rapid digitalization.

ineffective case: F. S. 23, female M S

It was found that analysis of urinary catecholamine and adrenaline/noradrenaline ratio of 15 patients has revealed a fact that these values have been increased when digitalis was found to be effective, whereas these were unchanged or reduced when it was ineffective. As shown in Figure 10, the patients with marked natriuresis of type I demonstrated reduced daily adrenaline elimination, rapid but transient increase in six hour urinary adrenaline, the high urinary adrenaline/noradrenaline ratio as well as relatively lower level of the urinary concentration of adrenaline. The same can be said of the patients with type 0 except adrenaline/noradrenaline ratio which is slightly low. The patients with low natriuresis of type II show less significant changes of both daily and hourly determinations of catecholamine and consistent or otherwise diminishing adrenaline/noradrenaline ratio. In those of type III, there is no more than minimum transient increase in urinary adrenaline soon followed by diminution even to zero and death bound to occur always.

It is suggested that there are certain close relations between therapeutic effect of digitalis and urinary catecholamine output. Sarnoff drew conclusion from his experimental studies: if the effective catecholamine stimulus remains constant, the contraction of the ventricle varies directionally with its endodiastolic pressure and fiber length: if the endodiastolic pressure and fiber length remain constant, the contraction of the ventricle varies directionally with the effective catecholamine stimulus. He has emphasized the importance of catecholamine in myocardial contraction but his finding refers to noradrenaline. Urinary catecholamine is stated to reflect

<table>
<thead>
<tr>
<th>Case</th>
<th>Therapeutic Effect</th>
<th>$A$/day</th>
<th>$A$/hour</th>
<th>$A$/NA</th>
<th>Natriuresis</th>
<th>$A$/Urine</th>
</tr>
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<tbody>
<tr>
<td>Y Y</td>
<td>(+)</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
<td>Type I</td>
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<tr>
<td>W S</td>
<td>(+)</td>
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<tr>
<td>E O</td>
<td>(+)</td>
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<td>T M</td>
<td>(+)</td>
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<td>Y K</td>
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<tr>
<td>M S</td>
<td>(+)</td>
<td>↑</td>
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Fig. 10. Summarized data of daily and hourly variations of urinary adrenaline, Adrenaline/Noradrenaline, Natriuresis and adrenaline concentration in the cardiac patients treated with digitalis.

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the circulating catecholamine level or the production of catecholamine\(^{16}\). Since urinary recovery of the exogenous catecholamine is no more than 5 percent and circulating catecholamine, on the other hand, is taken up by the heart, spleen and some glandular tissue\(^{15}\), it might not be exactly correct to assume that urinary output of catecholamine permits to draw inference on the endogenous catecholamine, but this hypothesis would be practically useful for the present. In digitalis effective case with marked natriuresis of type I, urinary excretion of catecholamine is increased by the first injection of the cardiac glycoside and gradually reduced day by day. Increase in catecholamine chiefly depends on the increment of adrenaline as indicated by adrenaline/noradrenaline ratio. (Fig. 11) In case of natriuresis of type II the excretion of catecholamine indicates no consistent tendency. In case of minimal natriuresis of type III variations of urinary catecholamine are of minimum, the urinary adrenaline/noradrenaline ratio remains unchanged or reduced, death would occur with early diminution of urinary catecholamine. It strongly suggests that catecholamines and particularly adrenaline play an important role in pharmacodynamic action of cardiac glycoside.

Raab\(^{19}\) reported a significant increase of epinephrine in the heart muscle of persons who had died after a fresh myocardial infarction, of patients in congestive heart failure and of patients with renal uremia. Pakkarine\(^{17}\) make the assumption of a limited and temporary adrenal medullary overactivity in a minority of instances (\(\frac{1}{4}\)) in cardiac failure, but he added the lowest excretion in patients with most severe cardiac failure.

Author precisely stated that in congestive heart failure urinary excretion of catecholamine was over the normal range: highest in class III, and fairly lower in class IV.

![Fig. 11. Urinary Adrenaline/Noradrenaline before and after digitalization.](image)

![Fig. 12. T. H. 35, male MI, TI, & Pericarditis.](image)

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The most severe cardiac failure (class IV) are often refractory to the digitalis therapy. Inference would be made that the adrenal medulla is incapable of supplying the sufficient amount of catecholamine, especially adrenaline to the myocardium in the most severe cardiac failure. With the view to suppressing the secretion of catecholamine reserpine has been tried to the patients treated with the digitalis.

As shown in Figure 12, not only reduction in urinary flow, natriuresis and urinary Na/K ratio, but also increase in the body weight as well as rise in the venous pressure were seen during a period of administration of reserpine and clinical improvement began to appear after discontinuance of the drug.

The trials of reserpine were made to six cardiacs which include severe and mild cases, three of each. It has been demonstrated that reserpine exerts the definite influence on the advanced patients and lesser with milder cases.

**SUMMARY AND CONCLUSION**

1. An initial single injection of strophanthine G made it possible to appreciate the therapeutic efficiency of the ensuing digitalis regimen. Increase in cardiac output of more than 140 per cent following the single injection of strophanthine is a reasonable proof to show a remarkable efficacy of digitalization, and therapeutic benefit would be expected when cardiac output became below 120 per cent or even reduced.

2. Cardiac patients who underwent a course of digitalis therapy may be classifiable into four types of natriuretic patterns. These patterns usually accord with the increase of cardiac output except for the patients with the relatively high level of urinary sodium prior to the medication.

3. When the patients were successfully treated with digitalis, urinary output of adrenaline was increased in the first few days and reduced, while urinary adrenaline/noradrenaline ratio was high. However, when digitalis failed to improve the clinical condition, no significant variation of urinary adrenline to be observed: at time, even a noticeable reduction would be found when urinary adrenaline/noradrenaline ratio was low.

4. It is assumed from these results that there seemed to be intimate relation existing between the digitalis effectiveness and the adrenal medullary hormone.

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