The Acute Effect of Aminophylline on Left Ventricular Function in Patients with Heart Failure

Clinical Studies on the Cardiac Performance by Means of Left Heart Catheterization

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Numerous investigators1)-12) have been interested in the pharmacological and therapeutic action of aminophylline (theophylline ethylenediamine). In frog's and excised mammalian heart, it is shown that this drug increases the rate and force of cardiac contraction. In excised papillary muscle of cat, it also produces an increase of systolic tension. In addition to these effects, there is direct evidence of dilatation of the coronary vessels. It stimulates the central nervous system and dilates the peripheral vessels.

However, there is no papers reporting the action of this drug to the human failing heart in particular reference to the left ventricular function.

In this clinical investigation, we performed the simultaneous left and right cardiac catheterization13)-15) in patients with heart disease, and observed the hemodynamic changes induced by this drug, revealing what is the most important action of this drug in diseased human heart, and what mechanism underlies in this condition.

Materials and Methods

A total of 10 patients treated as hospitalized or as out-patients at the Second Department of Internal Medicine, Tokyo University Hospital, have been studied. As listed in Table I, they were 5 cases of mitral stenosis, 3 cases of hypertensive heart disease, 1 case of aortic and mitral regurgitation and 1 case of mitral stenosis and regurgitation. The functional capacity of these patients ranged from grade II to III according to the Classification of the New York Heart Association.

Studies were carried out in the fasting, steady state without premedication. Under local anesthesia the right heart catheter was introduced into the pulmonary artery. The transseptal Brockenbrough's catheter was inserted into the left ventricle.
from the right femoral vein. Blood pressure was measured with Statham P 23 B or Nihonkohden strain-gauge transducer, and recorded with Nihonkohden’s pen-recorder at a paper speed of 50 mm. per sec.

Determination of cardiac output was made by the direct Fick’s method. Oxygen consumption was measured by Benedict Roth’s respirometer and blood samples from the pulmonary artery and left ventricle were analyzed by the method of Van Slyke and Neill for oxygen content.

The left ventricular volume was measured by the radioisotope dilution method by external cardiac monitoring modified after Fisle and Braunwald. One hundred and twenty µc. of I¹³¹ hippuran was injected instantaneously into the left ventricle through the left heart catheter, and the dilution process of the radioactivity in the left ventricle was counted by scintillation detector, which was focused over the left ventricle. Calculation of left ventricular end-diastolic volume and endsystolic volume was made by the method of Donato et al. modified by us. Circumferential shortening rate (CSR, cm./sec.) which indicates the contracting speed of left ventricle (and can be regarded as an indicator of left ventricular contractility), was calculated by the following formula; CSR=2π(rₑₑₑ₅ₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑₑ европа

The left ventricular minute (LVMW) and stroke work (LVSW), left ventricular systolic mean force (F), and total peripheral vascular resistance (TPVR) were calculated by the following:

\[
\text{LVMW, Kg.M./min.M.}² = \text{CI} \times 1.055 \times (\text{BAmp-LVEDP}) \times 13.6/1000
\]
\[
\text{CI} = \text{cardiac index, L./min.}
\]
\[
\text{BAmp} = \text{mean brachial artery pressure, mm.Hg}
\]
\[
\text{LVEDP} = \text{left ventricular end-diastolic pressure, mm.Hg}
\]
\[
\text{LVSW}, \text{Gm.M./min.M.}² = (\text{LVMW/Heart Rate}) \times 1000
\]
\[
\text{F, dyne} = 4\pi r_m^2 \times \text{left ventricular systolic pressure, mm.Hg} \times 1332
\]
\[
\text{TPVR, dyne-sec.cm.-}^5 \times \text{M.}² = (\text{BAmp/CI}) \times 1332
\]
\[
\text{CI} = \text{cardiac index, ml./sec.M.}²
\]

These measurements were repeated about 20 min. after the 5 min. infusion of 250 mg. of theophylline ethylenediamine diluted with 20 ml. normal saline into the pulmonary artery through the right heart catheter.

Results

In Table I the results obtained before and after injection of aminophylline for each patient are shown.

The hemodynamic observations in the resting state varied from patient
to patient. Three of 10 cases had lower cardiac index than 3 L./min./M.² Seven had lower left end-diastolic pressure than 9 mm.Hg. Left ventricular end-diastolic volume in 9 cases averaged 209±85 ml./M.², and all except 2 cases had larger volume than 150 ml./M.²

In Fig. 1 to 4, are illustrated average changes in heart rate, cardiac

![Graphs showing changes in heart rate, cardiac index, stroke index, and mean blood pressure before and after aminophylline administration.](image)

Fig. 1. Average changes before and after aminophylline administration.

HR: heart rate
CI: cardiac index
SI: stroke index
MBP: mean blood pressure

![Graphs showing changes in total peripheral vascular resistance, end-diastolic pressure, left ventricular forward fraction, and end-diastolic volume before and after aminophylline administration.](image)

Fig. 2. Average changes before and after aminophylline administration.

TPVR: total peripheral vascular resistance
EDP: end-diastolic pressure
LVFF: left ventricular forward fraction
EDV: end-diastolic volume
Table I. Hemodynamic

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<th>Case</th>
<th>Age</th>
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<th>Disease</th>
<th>BSA (M²)</th>
<th>HR (L/min/M²)</th>
<th>CI (ml/min/M²)</th>
<th>SI (ml/sec/cm²)</th>
<th>BP (mmHg) S</th>
<th>D</th>
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<th>TPVR (dyne sec/cm²)</th>
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BSA = body surface area; HR = heart rate; CI = cardiac index; SI = stroke index; BP = blood pressure, mean (M); TPVR = total peripheral vascular resistance; LV = left ventricular pressure, EDV = end-diastolic volume; ESV = end-systolic volume; MSER = mean systolic ejection rate; shortening rate; F = left ventricular mean force; TTI = tension time index.

Injection of aminophylline produced a significant increase in cardiac index, stroke index, mean blood pressure, total peripheral vascular resistance, end-diastolic pressure, left ventricular forward fraction, end-diastolic and end-systolic volume, circumferential shortening rate, left ventricular mean force, mean systolic ejection rate, left ventricular minute and stroke work, and tension-time index.
Effects of Aminophylline

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<th>LA (mm.Hg)</th>
<th>LV (mm.Hg)</th>
<th>EDV (ml/M²)</th>
<th>ESR (ml/sec)</th>
<th>LVWW (Kg/M²)</th>
<th>LVSW (Gm/M²)</th>
<th>CSR (cm/sec)</th>
<th>F × 10³ (dyne)</th>
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pressure, systolic (S), diastolic (D), mean (M); PA=pulmonary pressure, systolic (S); LA=left atrial systolic (S), end-diastolic (EDP); LVFF=left ventricular foward fraction, or stroke volume/EDV; LVW=left ventricular minute work; LVSW=left ventricular stroke work; CSR=circumferential index by 14.6±4.2% (S.D.), (P<0.01). Heart rate also increased by 7.3 ±8.1% (P<0.05), and stroke index increased by 5.5±11.5% (P<0.4) on an average. Stroke index increased or remained unchanged in 8 of 10 cases, and only 2 cases revealed a decrease in stroke index.

Mean arterial blood pressure diminished by 10.7±0.4% (P<0.01) so that calculated peripheral vascular resistance decreased by 14.5±9.1% (P<0.01).
Pulmonary systolic pressure, systolic blood pressure, left atrial mean pressure and left ventricular systolic pressure revealed no significant changes, although pulmonary systolic pressure increased markedly in 2 cases (H.F. and Y.K.) with pulmonary hypertension. Forward fraction of left ventricular volume increased by $33.9 \pm 18.8\%$ ($P<0.01$), while left ventricular end-diastolic

![Bar charts](image)

**Fig. 3.** Average changes before and after aminophylline.

ESV: end-systolic volume  
CSR: circumferential shortening rate  
F: force  
MSER: mean systolic ejection rate

![Bar charts](image)

**Fig. 4.** Average changes before and after aminophylline.

LVW: left ventricular work  
LVSW: left ventricular stroke work  
TTI: tension time index
Fig. 5. Relationship between end-diastolic pressure and end-diastolic volume before and after aminophylline.

Fig. 6. Relationship between EDV and SI before and after aminophylline.

Fig. 7. Relationship between circumferential shortening rate and left ventricular force.
and end-systolic volume decreased significantly by 15.8 ± 10.6% (P < 0.01) and 17.3 ± 7.4% (P < 0.01) respectively. In all except a case of F.A. with aortic regurgitation EDP and EDV decreased simultaneously as illustrated in Fig. 5. The relationship between stroke index and EDV is shown in Fig. 6, revealing that stroke index increased or unchanged except in 1 case in spite of the decrease in EDV. Left ventricular work per min. and per stroke revealed no significant changes. Circumferential shortening rate increased markedly by 47.2 ± 24.6% (P < 0.01), although left ventricular mean force fell by 13.0 ± 10.9% (P < 0.01) as seen in Fig. 7. No significant change was found in mean systolic ejection rate and tension-time index.

**DISCUSSION**

Aminophylline has been shown in dogs and men to induce arteriolar dilatation in both pulmonary and systemic circulation. In our results, the systemic mean blood pressure showed a significant decrease while cardiac output increased markedly. Therefore, the calculated peripheral resistance decreased. This decrease in peripheral resistance might cause a decrease in venous return because of an increase in peripheral blood pooling and reduce ventricular filling pressure and overload imposed to the failing heart, resulting in improvement of myocardial performance by the Starling’s mechanism. However, Fowell et al. and Parker et al. suggest the consistency and magnitude of the increase in cardiac output seems out of proportion to what one would expect on the basis of vasodilatation alone.

**Left ventricular volume:** Although there may be overestimation of left ventricular volume in our method comparing with cineangiographic method, the values of left ventricular volume in our cases are significantly increased in comparison with normal values except 2 cases. In case F.A. with mild aortic and mitral regurgitation, left ventricular volume was calculated according with non-regurgitation cases.

After aminophylline injection, stroke volume showed no significant change, whereas both ESV and EDV decreased significantly. This is attributed to the positive inotropic effect of this drug, because the same or larger volume can be ejected from smaller EDV. Except one case in whom EDV and stroke index decreased simultaneously, EDV decreased always in association with an increase or no change in stroke index.

This result is due mainly to the increased left ventricular contractility of myocardium. In other words, the Starling’s curve of myocardial function was considered to be shifted into another one.

Gorlin et al. showed that in supine exercise, left ventricular ESV de-
creased significantly, but changes of ESV were divided into 3 groups: increased, unchanged and reduced EDV, and heart rate, circumferential shortening rate and left ventricular oxygen consumption increased significantly. The hemodynamic change induced by the injection of aminophylline resemble the third group.

In dog experiment Chapman et al.\textsuperscript{29} showed that both EDV and ESV decreased during exercise. Therefore, except for the mild increase in heart rate, the reaction to the injection of aminophylline is the same as the reaction to exercise in which both EDV and ESV decreased and heart rate increased.

\textbf{EDV and EDP:} Jones\textsuperscript{30} and Dodge\textsuperscript{31} pointed out that there was no parallelism between EDV and EDP. Braunwald\textsuperscript{32} pointed out that EDV is better index for left ventricular function than EDP, and emphasized the necessity of measuring left ventricular volume. Our results (Fig. 3) revealed also that EDV did not always change in combination with EDP. This unparalleled change was seen in case F.A. In these clinical experiments the decrease in EDV and EDP is considered due chiefly to the improvement of myocardial contractility, but it is partly attributed to the increase in heart rate, causing shortening of left ventricular filling period.

\textbf{Myocardial Effects:} Our results show that aminophylline has positive chronotropic and inotropic effect on heart. Many investigators\textsuperscript{1)-10} have pointed out that aminophylline has a direct action of inotropism on heart. In frog's heart and in mammalian heart,\textsuperscript{11} it increases the rate and force of cardiac contraction. In excised papillary muscle of cat it produces an increase of systolic tension. In the present study, the CSR, a parameter suggesting the myocardial contractility, showed a significant increase after the injection of aminophylline. This finding indicates a strong positive inotropic effect. The effect was also demonstrated by other investigators. They showed that it strengthens myocardial contraction as measured by myocardial force transducers\textsuperscript{83} and increases the concentration of grucose-6-phosphate in heart muscle,\textsuperscript{34} as do many of the known inotropic agents. However, this marked increase in CSR was not parallel to the increase in heart rate and blood pressure, excluding the possibility that this change is attributed to Bowditch's effect (response to the increase of heart rate)\textsuperscript{35} and Anrep's effect (response to the increase of blood pressure).\textsuperscript{36} The blood pressure did not change, and the increase in heart rate (8\%) is unproportionately small comparing to the increase in CSR (47\%). Gorlin et al.\textsuperscript{28} reported that CSR increased by 38\% with an increase in heart rate by 48\% and Sonnenblick\textsuperscript{37} showed that \(\frac{df}{dt}\) increased by 42\% with an increase in heart rate by 50\%.

It is interesting to note that there may be some differences between MSER and CSR in showing the myocardial contractility, because MSER did
not change in spite of the marked increase in CSR.

A decrease in left ventricular force was observed in spite of an increase in CSR. In other words, left ventricle could contract much more rapidly with less force. This effect is due partly to the peripheral vasodilatation or a decrease in peripheral vascular resistance, and partly to accentuation of myocardial contractility.

TTI: It was demonstrated that both ventricular size and pressure have been considered as the determinants of myocardial oxygen consumption in isolated dog-heart preparation.\textsuperscript{38, 39} If heart size is constant, TTI correlates well with myocardial oxygen consumption.\textsuperscript{40}

In our experiments the left ventricular end-diastolic and end-systolic volume decreased significantly, but TTI did not change markedly. This fact suggests an increased oxygen consumption of the heart by the action of aminophylline. It was previously shown by one of the authors that myocardial oxygen consumption increased by the injection of this drug using coronary sinus catheterization in man.\textsuperscript{41}

For these reasons, it is concluded that aminophylline decreases the left ventricular volume or heart size by stimulating the myocardium and results in an increase in the oxygen consumption of the heart.

**SUMMARY**

In 10 patients with acquired valvular or hypertensive heart diseases, the acute effects of aminophylline (theophylline ethylenediamine) were studied by the combined left and right cardiac catheterization, calculating the left ventricular volume and circumferential shortening rate using external monitoring of radioisotope dilution. Aminophylline produced a significant increase in cardiac output, left ventricular forward fraction and circumferential shortening rate, and a significant decrease in left ventricular end-diastolic pressure, end-diastolic and end-systolic volume, left ventricular mean force and total peripheral vascular resistance. These results indicate that aminophylline improve the function of failing heart by the stimulation of myocardium and resultant increase in myocardial contractility together with its vasodilating action on peripheral vessels.

**REFERENCES**