Experimental Study on Vasodilator Therapy and Its Clinical Application

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To evaluate the effects of vasodilator therapy, the quantitative relationships between peripheral resistance, LVEDP, coronary circulation and cardiac output were analyzed by using 23 isolated coronary perfused canine heart which afterload, preload, coronary blood flow and heart rate are able to regulate independently. Peripheral resistance was decreased incrementally to lower mean arterial pressure from 107–97 mmHg to 48–22 mmHg keeping preload and heart rate at constant level. A decrease in mean arterial blood pressure to 72 (physiologically coronary perfused heart) and 68 mmHg (coronary stenosed model) increased cardiac output, respectively. However, myocardial oxygen consumption in each group decreased under 5.5 ml/min/100g LV which suggested myocardial ischemia worsen and further decrease in blood pressure lowered cardiac output.

LVEDP also decreased incrementally from 18–20 mmHg to 5 mmHg keeping afterload at 100 mmHg of mean arterial blood pressure constantly. A decrease in LVEDP from 20 to 14 mmHg reduced stroke work index in normal heart but increased slightly in failing heart. Further lowering in LVEDP resulted decreasing in stroke work index in both group. Thus modest and adequate reduction in preload and afterload has beneficial effects to cardiac function. In contrast, further decrease will worsen myocardial perfusion and cardiac function.

RECENT years, vasodilators were used for treatment to patients with heart failure due to myocardial infarction and other cardiac disease.^{1–3}

However, there have reported conflicting experimental and clinical data concerning the effects of vasodilator therapy and is still in controversy.^{4–5} Afterload reduction will result in increasing cardiac output, on the other hand, coronary blood flow will be reduced by reduction of coronary perfusion pressure and worsen a myocardial ischemia.

Also preload reduction which will be induced by venodilators may result the reduction of myocardial oxygen consumption and cardiac output will increase due to recover from myocardial

ischemia. However, decreasing in preload will have a possibility to affect a cardiac output by left ward shift of Frank-Starling curve.^{7–10} The clinical effects of vasodilator therapy will depend on sum of those conflicting effects. Thus we analyzed the relationships between the afterload, preload, cardiac output and coronary circulation in normal and ischemic heart to evaluate the potentially deleterious effect and beneficial effect of vasodilator therapy. We studied those relationships by 23 canine isolated coronary perfused hearts in which a afterload, preload, coronary perfusion and heart rate could be regulate independently to clarify the primary effect of each factor on cardiac output.^{11–14}

Key Words:

Afterload reducing
Preload reducing
Isolated canine heart

METHOD

Two support and one donor dogs were used in each experiment. Three dogs were anesthetized

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Fig.1. experimental arrangement: see text

Rp = resistance component (total peripheral resistance),
 C = capacitance component (total arterial compliance),
 Rc = resistance component (characteristic impedance),
 AoF = aortic flow, AoP = aortic pressure, LVP = left
 ventricular pressure, Cor.F = coronary blood flow, PP
 = coronary perfusion pressure.

ed by sodium pentobarbital 25–30 mg/kg intravenously injection. A donor dog was intubated tracheal cannula for artificial respiration by Harvard respirator and thoracotomy was performed. A Gregg's cannula was inserted into aortic root via brachiocephalic artery and coronary perfusion was kept by Langendorff technique by support dog's arterial blood which was withdrawn from femoral artery of a support dog through a Harvard peristaltic pump. Then the heart was excised under ventricular fibrillating condition which was induced by electrical stimulus. The Gregg's cannula was inserted into left main coronary artery and was fixed. A physical device which was simulated to canine aortic input impedance and was able to change incrementally a part of peripheral resistance was attached to the aortic ostium. A overflow system reservoir was connected to the left atrium to regulate left ventricular enddiastolic pressure (LVEDP) by changing the height of reservoir in which warmed saline was filled. A heart rate was also controlled by atrial electrical pacing. The coronary perfused arterial blood was sampled frequently to check pH, PaCO₂, PaO₂ and was kept physiological range by means of blood transfusion, O₂ inhalation and infusion of bicarbonate

and saline to support dog. A warmbath, air buffer, microfilter, strain gauge pressure transducer (Toyo Sokki: MPU-0.5), and electromagnetic flow probe (Nihon Kohden-MF46) was set into the coronary circuit. Coronary venous blood was sampled from drain tube which was inserted into right chamber to back to the femoral vein of support dog through a warmbath and microfilter.

Left ventricular pressure was measured by a glass cannula inserting into left ventricular cavity through apex and connected to strain gauge pressure transducer (Toyo Sokki MPU-0.5). Aortic pressure and aortic flow was also measured by strain gauge pressure transducer (Toyo Sokki MPU-0.5) and electromagnetic flow probe (Nihon Kohden MF46) which was set the physical device of aortic input impedance. Left coronary blood flow and perfusion pressure, left ventricular pressure, aortic pressure and flow were recorded by a direct pen recorder (Sanei Sokki 8s Rectigraph) and by a magnetic tape data recorder (Sony Magnetic Inc Type 3915). We also set two servosystem to regulate coronary perfusion and afterload level as described later. Heparin was used to prevent a blood coagulation (1000u bolus injection first, then 5000u each

Fig. 2. The relationship between the peripheral resistance and aortic blood pressure, ejection time, cardiac output and myocardial oxygen consumption. Aops = mean systolic aortic pressure, Ej Time = ejection time, CO = cardiac output, MVO = myocardial oxygen consumption, R_p = peripheral resistance.

subsequent hour) (Fig. 1).

EXPERIMENTAL PROTOCOL

After the preparation was established, the heart was defibrillated by DC current and we wait 30–60 min. for stabilizing the hemodynamics i.e. LVP maintained at 100 mmHg when peripheral resistance $10 \times 10^3 \text{ dyne} \cdot \text{sec} \cdot \text{cm}^{-5}$ and LVEDP 4–8 mmHg, then following experimental procedures were performed.

Procedure 1. Afterload reduction: The peripheral resistance was decreased incrementally from $20 \times 10^3 \text{ dynes} \cdot \text{sec} \cdot \text{cm}^{-5}$ to $1 \times 10^3 \text{ dynes} \cdot \text{sec} \cdot \text{cm}^{-5}$ as following condition.

- i) coronary blood flow was kept constant at 80 ml/min/100g. (constant flow perfusion)
- ii) coronary perfusion pressure was kept at same level of mean aortic pressure regarding as a physiological perfusion. ($PP = \overline{AoP}$)
- iii) coronary perfusion pressure was adjusted at 30 mmHg below the mean aortic pressure regard-

Fig. 3. The relationship between the mean arterial pressure and cardiac output (left panel) and regional myocardial shortening rate (right panel), CO = cardiac output, AoP = mean aortic pressure.

ing that 90% of stenosis will exist at main left coronary trunk^{15,16} ($PP = \overline{AoP} - 30$)

iv) left circumflex coronary artery was stenosed at proximal portion till the flow reduced 50% of control level and coronary perfusion pressure was adjusted at same level of mean arterial pressure. Regional contraction was measured by microsonosensor which was set in the endocardium of each region (LCX St)

Procedure 2. Preload reduction: As a afterload, mean aortic pressure was kept at constant level of 100 mmHg by infusion of saline into the physical device and LVEDP was reduced from 20 mmHg to 5 mmHg incrementally in condition of physiological coronary perfusion and in LCX St till the coronary blood flow reduced to 30% of control level.

RESULTS

Afterload reduction: The relationship between the peripheral resistance, cardiac output, aortic pressure and myocardial oxygen consumption were shown in Fig. 2. In constant flow perfusion, decreasing in peripheral resistance increased in cardiac output and lowered mean aortic pressure. Decreasing in peripheral resistance from $10 \times 10^3 \text{ dyne} \cdot \text{sec} \cdot \text{cm}^{-5}$ to $4 \times 10^3 \text{ dyne} \cdot \text{sec} \cdot \text{cm}^{-5}$ in physiological coronary perfusion ($PP = \overline{AoP}$) and to $6 \times 10^3 \text{ dyne} \cdot \text{sec} \cdot \text{cm}^{-5}$, increased in cardiac output from 837 ± 19 and $658 \pm 104 \text{ ml/min}$ to 1438 ± 119 and $1078 \pm 126 \text{ ml/min}$, respectively, then lowered gradually. Mean aortic pressure and myocardial oxygen consumption was also lowered in both perfusion.

Fig. 4. The relationship between the left ventricular end-diastolic pressure and cardiac work. LVEDP = left ventricular end-diastolic pressure.

In LCX St group, lowering peripheral resistance increased in cardiac output and increased in shortening rate at none stenotic area. However, shortening rate at stenotic area worsened in spite of increasing in cardiac output (Fig. 3).

Preload reduction: The relationship between the cardiac work and left ventricular enddiastolic pressure in normal and LCX St heart was shown in Fig. 4. In normal heart increased LVEDP resulted increasing in left ventricular work, on the other hand, in LCX St group moderate increase in LVEDP resulted increasing in cardiac work, however, further elevation of LVEDP resulted in no change or slight decreasing in cardiac work, and suggest the existing of a descending limb of Frank-Starling curve.

DISCUSSION

Because regulation system in cardiac performance is so complex and change in one factor will induce change in another factors and we only know the overall effect of those changes and it is difficult to analyze the pure effect of each factor separately. We developed a new experimental preparation to evaluate a effects of vasodilator therapy or effects of preload and afterload on

Relationship between the Afterload and Cardiac Output

Fig. 5. The relationship between the peripheral resistance and % change in cardiac output (left panel) and schematic drawing of left ventricular pressure-volume relation.

Rp = peripheral resistance, CO = cardiac output, LVP = left ventricular pressure, LVV = left ventricular volume.

Fig. 6. The relationship between the peripheral resistance and cardiac output and myocardial oxygen consumption, $\dot{MVO}_2$ = myocardial oxygen consumption.

cardiac performance in which the coronary blood flow, peripheral resistance, left ventricular end-diastolic pressure and heart rate could be controlled independently.¹¹⁻¹⁴ By such kind of preparation, we are able to know the primary or pure effects of afterload or preload on cardiac performance. We showed in this study that afterload reduction will increase in cardiac output in relatively lower level of peripheral resistance then decreased. The rate of increase in cardiac output showed a tendency of greater in ischemic heart than physiological or constant flow heart as shown in Fig. 5. The mechanism of increasing in cardiac output will be explained by this figure (right panel) in which left ventricular pressure-volume relationships of various afterload level in constant preload was shown. Suga & Sagawa¹⁷ reported that the line which was connected the shoulder of pressure-volume curve (end systolic point) will be linear and the gradient of this line correlate to cardiac contractility. As shown this figure, increment of cardiac output by reduction of afterload will be larger in failing heart than normal heart because gradient of linear line in normal heart is more steeper than failing heart. Our results clearly showed this relationship and we expect to increase in cardiac output by a little decreasing in

afterload level in failing heart. However, the oxygen concentration level in coronary sinus blood showed under 5 ml/min/100g which suggest the myocardium will be in under perfusion or myocardial hypoxic state even the level of peripheral resistance in which cardiac output increased maximum (Fig. 6). In this experiment, we observed only short period of afterload reduction. If we continue more longer time, the cardiac output may decrease due to underperfusion of cardiac muscle. To confirm this relationship further, we observed segmental shortening rate of regional myocardium in partial stenosis of left circumflex coronary artery in stead of regional myocardial oxygen consumption. In this experiment, segmental shortening worse by reduction of peripheral resistance in spite of increasing in cardiac output and also increasing in shortening rate at normal segment. This fact means that ischemic segment will be affected earlier before cardiac output become to lowering in afterload reduction. This relationships told us to take care for protecting myocardium from ischemia due to under perfusion and it is dangerous to take only cardiac output as a index for determining the level of afterload when we apply a vasodilator therapy to patients with heart failure due to ischemic heart disease.

Preload reducing therapy also was expected to be useful for heart failure in clinical case^{1,3,4,18}. However, the direct effect of preload reduction on cardiac function in failing heart is not clear. Our study showed that in normal heart, increasing in LVEDP resulted increasing in stroke work as well known of Frank-Starling effect, on the other hand, in heart with partial stenosis, increasing in LVEDP at higher level resulted decreasing in stroke work showing a similar curve to so called descending limb of Frank-Starling curve. Gregger, Monroe¹⁹ also reported such a relationship by in vitro experiment and they assumed that those phenomenon will be induced by increasing in afterload. As our experiment was performed under constant afterload, so this assumption was denoted. We assumed to explain this phenomenon as follows. The increased LVEDP augment myocardial oxygen consumption and uneven distribution of myocardial blood flow especially underperfusion in subendocardial layer. Those change will reduce the contractility and shift to the lowered contractility curve of Frank-Starling (from b-4 to d-5, e-6, f-7, and g-8).

Those results suggested that the decreasing of preload also will be effective for treatment of heart failure by ischemic heart disease.

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