Experimental Study of Afterload-reducing Therapy
The Effects of the Reduction of Systemic Vascular Resistance on Cardiac Output, Aortic Pressure and Coronary Circulation in Isolated, Ejecting Canine Hearts

SHOGEN ISOYAMA, M.D., YUKIO MARUYAMA, M.D., YOSHIRO KOIWA, M.D., NOBUMASA ISHIDE, M.D., SHIGENORI KITAOKA, M.D., KENJI TAMAKI, M.D., SHOICHI SATO, M.D., YOSHI SHIMIZU, PH.D., EIJI INO-OKA, M.D., AND TAMOTSU TAKISHIMA, M.D.

SUMMARY The relationship between cardiac output (CO) and peripheral resistance (Rp) was examined under the following conditions for coronary perfusion: constant coronary flow perfusion; perfusion with a pressure equal to mean aortic pressure (AoP perfusion); and perfusion with a pressure equal to the mean AoP - 30 mm Hg (AoP - 30 mm Hg perfusion). We also examined the coronary pressure-flow relationship. For these studies, we used paced, isolated, ejecting canine hearts, which were loaded by a hydraulic system that simulated the input impedance of a dog's systemic arterial tree.

The CO in the constant coronary flow perfusion continued to increase with the reduction of Rp. The CO in the AoP perfusion became maximal at a slightly subphysiologic Rp, or at an average mean AoP of 65 mm Hg. This mean AoP was closely associated with the lower limit of the autoregulation of coronary blood flow. In the AoP - 30 mm Hg perfusion, the mean AoP at which CO became maximal was 72 mm Hg and the corresponding coronary perfusion pressure appeared to be lower than the lower limit of the perfusion pressure range for coronary flow autoregulation. The Rp value at that point was slightly higher than the physiologic range.

We conclude that when coronary perfusion pressure changes with mean AoP, and when left ventricular end-diastolic pressure is fixed, there is a clear optimal Rp at which CO becomes maximal, and this optimal Rp is higher if coronary perfusion pressure is biased from mean AoP to a significant degree.

BENEFICIAL EFFECTS have been reported in afterload-reducing therapy for the treatment of congestive heart failure. They are achieved from alterations in ventricular systolic loading and ventricular filling pressure through the use of peripheral vasodilator drugs. Reduced systemic vascular resistance (SVR) improves left ventricular systolic loading, and it can both raise the cardiac output (CO) and lower the myocardial oxygen needs in severe congestive heart failure due to ischemic or nonischemic heart disease. However, afterload-reducing therapy may not always be beneficial, especially when the aortic pressure (AoP) is reduced to the extent of causing a deficit of coronary flow relative to the metabolic need.

It is possible to produce beneficial hemodynamic effects with little or no change in mean arterial pressure (MAP). MAP is related to CO and SVR by the formula MAP = CO × SVR (assuming right atrial pressure is negligible). Thus, if the percent increase in CO produced by afterload-reducing therapy is of the same magnitude as the decrease in the SVR, there may be little or no change in MAP. Chatterjee et al. observed unloading of the ventricle in terms of the reduction of SVR without a decrease in MAP. Therefore, it is important to examine how the reduction of SVR alters AoP and CO and to determine the minimal safe level of AoP for coronary circulation.

The purpose of this study was to determine experimentally how far SVR or AoP can be reduced so as to achieve maximal CO without coronary ischemia. We also examined the effect of the alteration of SVR on coronary circulation and gaseous metabolism. For this purpose, we used paced, isolated, ejecting canine hearts, which were loaded by a hydraulic system that simulated the input impedance of a dog's systemic arterial tree and that could be perfused independently of the systemic circulation.

Methods
Preparation
Eight adult mongrel dogs, 15-22 kg (18.7 ± 0.9 kg, mean ± SEM), were anesthetized intravenously with sodium pentobarbital (25-30 mg/kg) and thoracotomized bilaterally in the third intercostal space. This was performed under intermittent positive-pressure ventilation with a Harvard respirator and by means of an endotracheal tube. A modified Gregg cannula (3.0-3.5 mm i.d.; 5-6.5 mm o.d.; neck angle approximately 120°) was introduced from the right carotid artery into the ascending aorta and secured at the brachiocephalic artery. Then, we ligated the left carotid and subclavian arteries and the descending aorta. We started to perfuse the heart by peristaltic pump (Harvard pump, type 1215) with arterial blood from the femoral artery of a support dog that was anesthetized with sodium pentobarbital (25-30 mg/kg). Then, the heart was isolated and fibrillated by
alternating current. The perfusion pressure (PP) was measured from the side arm of the perfusion line and maintained between 70 and 100 mm Hg during the following procedure: After the pericardium was removed, the proximal portions (about 1 cm long) of the right and left coronary arteries were isolated from the surrounding tissues. The right coronary artery was ligated proximally and cannulated distally in less than a minute and perfused by another peristaltic pump. The modified Gregg cannula was put forward from the ascending aorta into the ostium of the left coronary artery and carefully secured at a site proximal to the origin of the septal artery so as not to disturb its perfusion. Thus, the left coronary arterial cannulation was performed without interrupting its flow. Finally, for the measurement of coronary sinus blood oxygen tension \( (P_{O_2}) \), a glass cannula was embedded into the coronary sinus and secured. The experimental setup is shown in figure 1.

The aortic root was connected to an adaptor for the hydraulic loading system at a site about 1.5 cm distal from the aortic valve. The loading system consisted of two hydraulic resistors, \( R_C \) and \( R_p \), a capacitance \( C \), and an inertial \( L \), representing, respectively, the characteristic impedance, the peripheral vascular resistance, the total arterial compliance and the inertia of the blood.  

A wide cannula was inserted into the left atrium through the pulmonary vein and connected to a large reservoir filled with saline. The heart was then electrically defibrillated. The ejected saline was pumped back into the reservoir, where it was maintained at 37 ± 0.5°C. The left ventricular end-diastolic pressure (LVEDP) was controlled by adjusting the height of the reservoir. The right and left coronary blood flows were monitored electromagnetically. We also measured the right and left coronary PPs from the side arms of the perfusion line. The mean right coronary blood flow was set at a constant value (19 ± 0.7 ml/min) such that the mean right coronary PP would be 70–100 mm Hg. We opened the right atrium and induced a complete atrioventricular block by injecting 1–2 ml of formaldehyde into the atrioventricular nodal region. The heart rate was kept constant by electrical bipolar stimulation of the atrioventricular junction, using a pulse generator (110–140 beats/min). Finally, an epicardial electrode was sutured at the surface of the left ventricle for ECG recording.

Arterial blood was obtained from the side arm of the perfusion line, and the \( P_{O_2} \), \( P_{CO_2} \) and pH of each support dog were monitored by frequent blood gas determinations. The \( P_{O_2} \) was always held above 75 mm Hg by \( O_2 \) inhalation. The pH and the \( P_{CO_2} \) were also maintained within their physiologic ranges. Sodium bicarbonate was added at frequent intervals to correct for any change in pH. The perfusing blood temperature was maintained at 37 ± 0.5°C by a thermostatic system. The central venous and arterial blood pressures of the support dog were continually observed and maintained within their physiologic ranges. Coagulation was prevented with heparin (30,000 U initial injection; 5000 U every hour thereafter).

Two support dogs were used for each experiment: one to support the heart during the surgical preparation period and/or the priming of the hydraulic loading system and the other to support the heart during the experiment.

**Hydraulic System of the Aortic Input Impedance of the Dog**

We used a hydraulic system of the aortic input impedance of the dog that was first described by Westerhof et al.  and further developed in our laboratory. Details of its structure and hydraulic characteristics have been described.  Briefly, this system consists of four components, arrayed in series. The inertial component is a simple conduit pipe (15

---

**Figure 1. Layout of the experimental setup.** The isolated canine heart is loaded with a hydraulic system of the input impedance of the arterial system of the dog. \( L \) is the inertial component, representing the inertia of the blood; \( R_C \) is the resistance component, representing the characteristic impedance; \( C \) is the capacitance component, representing the total arterial compliance; and \( R_p \) is the resistance component, representing the total peripheral resistance. The instantaneous aortic flow (AoF), aortic pressure (AoP) and left ventricular pressure (LVP) were measured. The coronary sinus (CS) blood was obtained from the CS cannula. Cor.F = coronary flow.
mm i.d.), with an adjustable length to give the desired inertial value. In this study, it was kept constant at 10 dyn-sec²-cm⁻³. The characteristic resistance component was made of tightly packed capillary tubes 0.29 ± 0.01 mm in diameter and 75 mm long. The characteristic resistance was fixed at 0.2 × 10⁴ dyn-sec-cm⁻³. The capacitance component is a compression chamber filled with air (Windkessel) and the air volume was fixed at 200 ml; i.e. capacitance = 2.0 × 10⁻⁴ dyn⁻¹-cm⁵. The Rp component has the same structure as the characteristic resistance component, but the available number of capillaries can be changed in a stepwise fashion. The hydraulic impedance properties of each component and the total system were determined with static flow and oscillatory flow.

Measurements and Calculations

Left ventricular pressure (LVP) was measured by a stiff polyethylene cannula penetrated through the apex of the left ventricle and connected to a strain-gauge pressure transducer (Toyo Sokki, MPU 0.5). The frequency response of this total system, evaluated by the pop method, indicated a resonant frequency of 163 Hz and a damping factor of 0.198. The gain increased by 10% and the phase shifted by 5° at about 50 Hz. As AoP, the lateral pressure was measured at the inlet of the hydraulic system by the similar transducer system. The right and left coronary PPs were also measured as described above. The middle of the left ventricular cavity was taken as the reference level for pressure measurements. Aortic flow (AoF) was measured with an extracorporeal-type probe (12 mm i.d.) attached at the inlet of the hydraulic impedance system and connected to a square-wave electromagnetic flowmeter (Nihon Kohden, MF 46). The frequency response of this system, evaluated electrically by imposing an electrical signal on the electrodes, was 3 db down at 50 Hz. The flow signal was calibrated by the bucket and stopwatch method with steady flows. The mean right and left coronary flows were continuously measured by an electromagnetic flowmeter with an extracorporeal-type probe (3 mm i.d.). They were calibrated by the same method, and the errors were within ± 5% for the range of values used in the experiment. We determined the CO by collecting the fluid ejected by the left ventricle over 30 seconds.

The data were recorded on a direct-writing system (Sanei Sokki, 8s Rectigraph) and on a magnetic analog tape (Sony Magnescale Inc., UFR-71460). The first time derivative (dP/dt) of LVP was obtained by an analog differentiator, and the dP/dt/common peak developed isovolumic pressure (mm Hg/sec/mm Hg) was measured. The cardiac work per minute (CW) was calculated as the product of the CO and the mean AoP during ejection.

The Po₂, PcO₂ and the pH of the blood sample were determined with an Astrup apparatus (Radiometer, BMS-Mk 2 and PHM 72-Mk Digital Acid-base Analyzer).

Measurements were not taken until the fluctua-
tions of the CO₂, the peak LVP and the mean PP for control values of Rp, LVEDP and mean left coronary flow reduced to ± 5% of the mean value over a 10-minute period. This stability was observed usually about 20 minutes after defibrillation.

The values of the measured variables were expressed as mean ± SEM and the significance of the difference between mean values was determined by using an analysis of variance technique.

Experimental Protocol

Hemodynamic changes were studied in eight hearts; the coronary sinus blood Po₂ was measured in four hearts. The Rp was changed in a stepwise fashion under the following conditions for coronary perfusion: (1) constant coronary flow perfusion, i.e., the mean left coronary flow was kept constant; (2) AoP perfusion, i.e., we attempted to make the left coronary PP follow the mean AoP as closely as possible by adjusting the mean PP once every minute, as the mean AoP and the mean PP gradually changed after the initial step change in mean PP over a 2–3-minute period; (3) AoP – 30 mm Hg perfusion, i.e., we attempted to make the mean PP follow the mean AoP minus 30 mm Hg as closely as possible by the same way as described above. For a given Rp, we first obtained the data in the AoP perfusion, then, the data in the AoP – 30 mm Hg perfusion, and finally, the data in the constant coronary flow perfusion. We obtained the data in both the AoP perfusion and the AoP – 30 mm Hg perfusion when we could verify that the mean PPs were set at the respective desired levels during a 3-minute period, and obtained the data in the constant coronary flow perfusion 3 minutes after the time when the mean left coronary flow was set at the constant level.

In four of the eight hearts, we obtained the hemodynamic data under the three conditions for coronary perfusion; in two hearts, we did the same measurement except in the constant coronary flow perfusion. In the other two hearts, only the data in the constant coronary flow perfusion were obtained.

In five of the six hearts that were studied in AoP perfusion, a hemodynamic steady state was not observed at 20 × 10⁴ dyn-sec-cm⁻³ of Rp. When the mean PP increased to be equal to the mean AoP, the mean AoP progressively increased. On the other hand, at 1 × 10⁴ dyn-sec-cm⁻³ of Rp, the AoP progressively decreased after the mean PP was reduced. For these reasons, the mean PP could not be precisely equal to the mean AoP in the case of all six hearts. The data in these cases were obtained 2 minutes after the third check and setting of the mean PP.

Throughout each study, the LVEDP was kept at a constant value of 4–8 mm Hg. With this value of LVEDP and at Rp of 10 × 10⁴ dyn-sec-cm⁻³, the mean AoP and the mean PP of 100 mm Hg were obtained. We attempted to maintain the LVEDP within ± 0.2 mm Hg of the desired level in each study. However, it decreased by approximately 1 mm Hg when the Rp was reduced from the control value to the experi-
mental value. Therefore, we had to reset the LVEDP at the desired level by adjusting the height of the reservoir. Thus, the actual variations of the LVEDP were within ± 0.3 mm Hg of the desired level.

All measurements were performed in 80 minutes or less. Sixty minutes after the beginning of the measurements, the CO for the same values of LVEDP, Rp and mean left coronary flow decreased by 6 ± 2.6%.

At the conclusion of each experiment, the weight of the left ventricle with septum was determined. The mean weight was 108 ± 9.3 g (range 84–148 g). In the three hearts, coronary angiography, performed at a PP of 100 mm Hg, proved that the left anterior descending, circumflex and septal arteries were perfused normally. The pressure drop due to the modified Gregg cannula was below 4 mm Hg at the flow rate of 100 ml/min.

Results

Figure 2 shows an example of simultaneous tracings of mean left coronary flow, PP and AoP with a constant Rp of $6 \times 10^6$ dyn-sec-cm$^{-5}$, while the perfusing condition was changed from a constant coronary flow perfusion to AoP perfusion and finally to AoP = 30 mm Hg perfusion. At the left side, the mean left coronary flow was set at the control level (100 ml/min). We then increased the mean PP (arrow A) to a level that we predicted the AoP would eventually reach. Over the next 1 minute, the mean AoP did rise gradually but not quite as high as we expected. Therefore, we lowered the mean PP (arrow B) as the mean AoP slowly increased. One minute after the second setting (arrow C), the mean PP and the mean AoP were rechecked. At this point, both pressures were equal to each other (80 mm Hg), so we did not have to change the mean PP. After confirming that the mean PP was equal to the mean AoP for a 3-minute period, we measured hemodynamics in the AoP perfusion and obtained the coronary sinus blood. After this data acquisition, we lowered the mean PP in order to set it to the same level as the mean AoP = 30 mm Hg (arrow D). As a result, the mean AoF decreased slightly. One minute later, we could observe that the mean PP was set at the desired level, i.e., mean AoP = 80 mm Hg, mean PP = 50 mm Hg (arrow E). We obtained the data in the AoP = 30 mm Hg perfusion 3 minutes after the point marked by arrow D. Finally, we reset the mean left coronary flow at the control level (arrow F) and 3 minutes later obtained the data with the constant coronary flow perfusion. After this measurement Rp was changed to a new value and a similar set of procedures was repeated.

Figure 3 shows representative tracings when the mean PP was equal to the mean AoP. The peak LVP, the AoP and the mean left coronary flow decreased when the Rp was decreased from $8 \times 10^6$ to $2 \times 10^6$ dyn-sec-cm$^{-5}$; however, the CO simultaneously increased from 1000 to 2400 ml/min. When the Rp was further reduced to $1 \times 10^6$ dyn-sec-cm$^{-5}$, the mean PP and the mean left coronary flow decreased to 22 mm Hg and 10 ml/min, respectively; the CO also decreased to 1260 ml/min.

Figure 4 shows the hemodynamic data of the six hearts in which the mean left coronary flow was kept

![Figure 2](https://example.com/figure2.png)

**Figure 2.** Simultaneous tracings of pressures and flows at $6 \times 10^6$ dyn-sec-cm$^{-5}$ of peripheral resistance (Rp) under the three perfusing conditions. LVP = left ventricular pressure; AoP = aortic pressure; AoF = aortic flow; l.Cor.F = mean left coronary blood flow; PP = left coronary perfusion pressure; r.Cor.F = mean right coronary blood flow; AoF = mean aortic flow.
constant at 82 ± 3.0 ml/min. The peak LVP decreased from 115 ± 7 to 66 ± 6 mm Hg (p < 0.01) and the mean AoP from 93 ± 5 to 25 ± 2 mm Hg (p < 0.01) as the Rp was reduced from 10 × 10³ to 1 × 10³ dyn-sec-cm⁻⁴. At the same time, the CO increased from 818 ± 40 to 1976 ± 121 ml/min (p < 0.01). However, the dP/dt/CPIP was not significantly changed. The CW was maximal with Rp between 4 × 10³ and 6 × 10³ dyn-sec-cm⁻⁴, although the peaking of CW was not very prominent. Additionally, the mean PP was not changed significantly with the reduction of Rp.

Figure 5A shows the hemodynamic data in the AoP perfusion. The CO increased from 846 ± 59 to 1512 ± 122 ml/min when the Rp was reduced from 10 × 10³ to 4 × 10³ dyn-sec-cm⁻⁴ (p < 0.01). It again decreased to 1030 ± 79 ml/min when the Rp was further reduced to 1 × 10³ dyn-sec-cm⁻⁴. The mean AoP correspondingly decreased from 100 ± 5 to 68 ± 6 mm Hg and then to 16 ± 1 mm Hg (p < 0.01). During the reduction of Rp from 10 × 10³ to 4 × 10³ dyn-sec-cm⁻⁴, the dP/dt/CPIP was not changed significantly; however, the change was significant at 1 × 10³ dyn-sec-cm⁻⁴ of Rp (from 47.5 ± 8.0 to 24.4 ± 3.8 sec⁻¹; p < 0.05).

The mean left coronary flow decreased from 121 ± 22 to 71 ± 20 ml/min when the Rp was reduced from 10 × 10³ to 2 × 10³ dyn-sec-cm⁻⁴ (NS). When Rp was reduced to 1 × 10³ dyn-sec-cm⁻⁴, the mean left coronary flow decreased to 19 ± 3 ml/min (p < 0.01), and CO decreased despite the reduction of Rp.

Figure 5B shows the hemodynamic data in the AoP – 30 mm Hg perfusion. The CO increased from 655 ± 85 to 1015 ± 121 ml/min as the Rp was reduced from 10 × 10³ to 6 × 10³ dyn-sec-cm⁻⁴ (NS). Compared with the value at 20 × 10³ dyn-sec-cm⁻⁴ of Rp, the CO at 6 × 10³ dyn-sec-cm⁻⁴ of Rp significantly increased (423 ± 51 vs 1015 ± 121 ml/min; p < 0.01). The CO decreased again, to 566 ± 199 ml/min at 4 × 10³ dyn-sec-cm⁻⁴ of Rp. The mean AoP decreased from 93 ± 4 to 37 ± 11 mm Hg (p < 0.01) when the Rp was reduced from 10 × 10³ to 4 × 10³ dyn-sec-cm⁻⁴; and the dP/dt/CPIP also decreased, from 50.8 ± 9.3 to 24.2 ± 5.3 sec⁻¹ (p < 0.05).

The mean left coronary flow did not change
Figure 5. Hemodynamic data for six hearts in (A) the aortic pressure (AoP) perfusion and (B) AoP - 30 mm Hg perfusion. Abbreviations and symbols are as in figure 4.

significantly with the reduction of Rp from $10 \times 10^5$ to $6 \times 10^5$ dyn-sec-cm$^{-5}$; however, it did decrease significantly, from $82 \pm 12$ to $22 \pm 9$ ml/min, with a further reduction of Rp to $4 \times 10^5$ dyn-sec-cm$^{-5}$ of Rp ($p < 0.05$). The mean left coronary flows in both the AoP perfusion and the AoP - 30 mm Hg perfusion were not significantly changed in the respective ranges of Rp at which the CO could increase by the reduction of Rp.

Figure 6 shows the relationship between the Rp and the CO under the three perfusing conditions. The maximum value of CO in the AoP perfusion was obtained at $4 \times 10^5$ dyn-sec-cm$^{-5}$ of Rp and it decreased when Rp was lowered to $1 \times 10^5$ dyn-sec-cm$^{-5}$. At this value of Rp, the CO in the AoP perfusion was smaller than that in the constant coronary flow perfusion ($p < 0.01$). The maximum value of CO in the AoP - 30 mm Hg perfusion was obtained with Rp at $6 \times 10^5$ dyn-sec-cm$^{-5}$; when the Rp was set at $4 \times 10^5$ dyn-sec-cm$^{-5}$, the CO in the AoP - 30 mm Hg perfusion was smaller than that in the AoP perfusion ($p < 0.01$).

Figure 7 shows the relationship between the mean AoP and the CO in the three perfusing conditions. The CO in the constant coronary flow perfusion increased in a roughly linear fashion with a decrease in the mean AoP. In the AoP perfusion, the CO also increased almost linearly, with a decrease in the mean AoP from $116 \pm 13$ to $68 \pm 6$ mm Hg, but the curve shifted downward and to the left with further decreases in mean AoP. In addition, the CO in the AoP - 30 mm Hg perfusion increased with a decrease in the mean AoP from $106 \pm 5$ to $72 \pm 7$ mm Hg, and it decreased for lower values of mean AoP.

Figure 8 shows the relationship between the mean PP and the mean left coronary flow as a percentage of the control value at $10 \times 10^5$ dyn-sec-cm$^{-5}$ of Rp. The mean left coronary flow in the AoP perfusion was gradually decreased by $21.7 \pm 6.2\%$ as the mean PP decreased from $99 \pm 4$ to $67 \pm 4$ mm Hg; then, it decreased more abruptly by $60.7 \pm 4.3\%$ as the mean...
Figure 7. Relationship between mean aortic pressure (AoP) and cardiac output (CO) for six hearts. PP = mean perfusion pressure.

PP decreased from 67 ± 4 to 20 ± 2 mm Hg. The slopes for these ranges of mean PP were 0.425 and 1.075 (percentage/mm Hg) respectively, calculated from all points of the six hearts in those respective ranges of mean PP by using linear regression analysis by least squares. These slope values were significantly different from each other (p < 0.01). In contrast, the mean left coronary flow in the AoP - 30 mm Hg perfusion decreased in a linear fashion (r = 0.805, p < 0.05) with a decrease in the mean PP ranging from 74 ± 6 to 28 ± 11 mm Hg.

Figure 9 shows the coronary sinus blood Po2 in four hearts. In the constant coronary flow perfusion, the coronary sinus Po2 increased from 26.8 ± 2.5 to 34.0 ± 2.3 mm Hg when the Rp was reduced from 10 x 10^6 to 1 x 10^6 dyn-sec-cm⁻². On the other hand, the coronary sinus Po2 in the AoP perfusion decreased from 31.7 ± 3.4 to 21.0 ± 1.5 mm Hg as the Rp was reduced from 10 x 10^6 to 1 x 10^6 dyn-sec-cm⁻², but these changes were not statistically significant. At this value of Rp, the coronary sinus Po2 in the AoP perfusion was lower than that in the constant coronary flow perfusion (p < 0.05). At 4 x 10^6 dyn-sec-cm⁻² of Rp, the coronary sinus Po2 in the AoP - 30 mm Hg was also lower than that in the AoP perfusion (i.e. 14.8 ± 3.9 vs 29.5 ± 2.9 mm Hg; p < 0.05).

Discussion

Experimental Model

The ventricular pump performance is markedly influenced by the alteration of not only the mean component of the input impedance of an arterial system, i.e., resistance, but also the pulsatile component, i.e., compliance. Therefore, we used a hydraulic system consisting of resistive and pulsatile components.

We set the control value of Rp in our dog experiment at 10 x 10^6 dyn-sec-cm⁻², which was approximately twice as high as that of a normal dog because we considered that the value of Rp in human patients with congestive heart failure is approximately twice as high as it is in subjects without congestive heart failure.

However, although it has been reported that aortic compliance is reduced in human patients with congestive heart failure and that vasodilator drugs increase aortic compliance, the extent to which they alter the compliance is not clear. Therefore, we kept the compliance of the hydraulic system within the normal range.

We attempted to make mean coronary PP equal to mean AoP to simulate approximately the physiologic coronary PP and to make mean coronary PP equal to mean AoP - 30 mm Hg to simulate very crudely a pathologic condition such as coronary stenosis of the left common coronary artery.

The Rp - CO and the Mean AoP - CO Relationships

Many studies about the relationship between the left ventricular load and the CO are not adequate, for various reasons. Elzinga and Westerhof reported the relationship between the Rp and the CO in isolated, ejecting cat heart preparations. However, the coronary artery was perfused by the AoP that was developed by the left ventricle in their preparation;
Therefore, the range of the Rp reduction was limited to the physiologic range, so they could not examine the relationship between the coronary and systemic circulations in the values of Rp lower than those of the physiologic range. Weber et al.20 examined the relationship between the LVP during ejection and stroke volume. However, in their study, the coronary perfusing condition was held constant and its effect on the hemodynamic state was not examined. Beneken et al.21 studied the AoP–CO relationship in the open-chest dog in which the left ventricle was loaded by a Starling resistor. They did not examine the coronary hemodynamics at the time when the mean AoP–CO relationship was obtained, nor did they examine the relationship under restricted coronary perfusions.

Little information is available concerning the SVR–CO relationship for the value of SVR lower than those of the physiologic range, and no information concerning the coronary hemodynamics when the SVR or the mean AoP is reduced. Nevertheless, it is important to consider the systemic and coronary hemodynamic changes over a wide range of values of SVR in order to fully appreciate the beneficial effects of afterload-reducing therapy for congestive heart failure.

In our study, the CO continued to increase with the reduction of Rp when the mean left coronary blood flow was kept constant. The maximum value of CO in the AoP perfusion was obtained at a value of Rp that was smaller than the lower limit of the physiologic range. (According to the reports of Westerhof et al.,3 Abel28 and Pouleur et al.,29 we considered that the physiologic range of Rp values was between $4.5 \times 10^4$ and $5.5 \times 10^4$ dyn-sec-cm$^{-4}$. In contrast, the maximum value of CO in the AoP – 30 mm Hg perfusion was obtained at a value of Rp that was slightly greater than the upper limit of the physiologic Rp range.

We found that the mean AoP–CO relationship was roughly linear when the mean left coronary blood flow was kept constant. In the other two perfusing conditions, CO increased with reduction of Rp in a roughly linear fashion up to a certain point, and thereafter declined. Thus, our findings concerning the mean AoP–CO relationship in the AoP perfusion are similar to those reported by Beneken et al.21 Furthermore, in our study, the mean AoP value that produced the maximum CO depended upon the perfusing condition.

Beneken et al.21 have reported that high mean left atrial pressure tends to shift the mean AoP–CO relationship upward and to the right. Although we kept the LVEDP constant in this study and did not directly measure its effect on either the mean AoP–CO or Rp–CO relationships, we suppose that in the higher LVEDP, the mean AoP–CO relationship (fig. 7) would tend to shift upward and to the right, while the Rp–CO relationship (fig. 6) would tend to shift upward and to the left. Accordingly, the mean AoP that produces the maximum CO in the higher LVEDP may be somewhat higher and the Rp for the maximum CO may be somewhat lower than those presently reported.

Coronary Circulation

It has been reported that the flow rate increment diminishes relative to the pressure increment over a certain range of mean PP.24, 25 Although the range shifts with loading conditions,26 it is usually 60–130 mm Hg of mean coronary PP for either a canine heart perfused with blood from an anesthetized support dog26 or for an open-chest dog.25 On the other hand, Wyatt et al.25 reported that the relationship between the mean coronary PP and the mean left coronary blood flow was rectilinear in cannulated canine hearts.

In our study, using isolated hearts, we could also observe the autoregulation of the mean left coronary blood flow, just as in the case of the open-chest dog.25 That is, the relationship between the mean coronary PP and the left coronary blood flow in the AoP perfusion was curvilinear; and, below 70 mm Hg of mean coronary perfusion pressure, the mean left coronary blood flow decreased abruptly, with decrease in the mean coronary PP. However, the extent of the autoregulation in our experiment was not as remarkable as it was in the open-chest dog.25 Moreover, in our study, we did not observe the autoregulation of the mean left coronary blood flow in the AoP – 30 mm Hg perfusion, since the relationship was rectilinear for the range of mean coronary PP values that we used in our experiment. However, if the range of mean coronary

\[ \text{CO and coronary flow in afterload reduction} / \text{Isoyama et al.} \]

\[ 497 \]

\[ \text{Figure 9. Changes in the coronary sinus oxygen tension} \]
\[ (\text{PcsO}_2) \text{ for four hearts under the three perfusing conditions.} \]
\[ \text{Cor F = coronary flow; PP = mean perfusion pressure; AoP = mean aortic pressure; Rp = peripheral resistance.} \]
PP over which autoregulation of mean left coronary blood flow occurs shifts with loading condition, this may be explained as follows: The lower limit of the range in the AoP – 30 mm Hg perfusion may be considered to be higher than the mean coronary PP value which was studied in our experiment, because the mean AoP in the AoP – 30 mm Hg perfusion was higher than it was in the AoP perfusion by 30 mm Hg for the same value of mean coronary PP (fig. 8).

The CO in the AoP perfusion was maximal at the lower limit of the autoregulatory range of mean left coronary blood flow. This finding supports the hypothesis of Beneken et al.21 However, it must be qualified, because the CO in the AoP – 30 mm Hg perfusion could have been increased by the reduction of Rp and it was maximal at a mean coronary PP value that was lower than those of the autoregulatory range.

The coronary sinus Po2 in the constant coronary flow perfusion had a tendency to increase with the reduction of Rp. In both the AoP perfusion and the AoP – 30 mm Hg perfusion, the CO could be increased by the reduction of Rp without a significant change in the coronary sinus Po2. Therefore, we do not consider that myocardial tissue is hypoxic in the range of Rp over which CO can increase with the reduction of Rp.

Clinical Implications

In our preparation, the pericardium was removed and the right ventricle was emptied. Therefore, the results of our study only indicate the relationship between SVR and left ventricular function under three perfusing conditions at constant heart rate and LVEDP, excluding the effects of the pericardium, the right ventricle, and of neurohumoral factors that admittedly have influence on cardiac performance. However, the results of our experiment may still have important clinical implications for afterload-reducing therapy.

In the clinical situation, the CO would be increased when the SVR is reduced up to a certain level. However, the coronary blood flow would become a limiting factor when SVR is reduced under the level, and the CO would accordingly decrease. In addition, in the case of coronary artery disease, we have to consider that the coronary blood flow would be very sensitive to the decrement of AoP, because the actual coronary PP would be lower than that of the autoregulation in the coronary vascular bed. According to the data by Beneken et al.,21 decrease in LVEDP elevates the Rp at which the maximum CO is obtained and therefore, if vasodilator therapy in patients decreases the preload (LVEDP) as well as the afterload pressure, the optimum mean AoP or Rp might be less clear than in the present study.

In conclusion, the CO continued to increase with the reduction of Rp if the mean left coronary blood flow did not significantly decrease. When the perfusing condition was adjusted to simulate the physiologic condition, the mean AoP that produced the maximum CO was closely associated with the lower limit of the autoregulatory range of coronary blood flow. In contrast, when the perfusing condition was adjusted to simulate a pathologic condition such as coronary stenosis of the left common coronary artery, the mean AoP value that produced the maximum CO became lower than the autoregulatory range.

Acknowledgment

We are grateful to P. Cantor and S. Omori for their assistance in the preparation of this paper.

References

Results of Long-term Vasodilator Therapy in Patients with Refractory Congestive Heart Failure

WARREN F. WALSH, M.B., AND BARRY H. GREENBERG, M.D.

SUMMARY The long-term effects of vasodilator therapy with oral hydralazine and long-acting nitrates were studied in 34 patients with refractory heart failure. Seven patients who had marginal hemodynamic improvement despite optimal hydralazine therapy were not maintained on vasodilators, and eight who had a favorable hemodynamic response subsequently discontinued hydralazine therapy because of side effects. Of these 15 patients, four (27%) died and 11 remained in New York Heart Association functional class III or IV at a mean follow-up of 10 ± 2 months (SEM). The 19 patients who received chronic therapy for 8 ± 2 months were divided into nine late responders (47%), who improved to functional class I or II, and 10 late nonresponders (53%), who remained in functional class III or IV. Only one of the nine late responders (11%) died, compared with seven of the 10 late nonresponders (70%) (p < 0.01). The actuarially determined survival at 1 year was 100% for late responders and 13 ± 12% for late nonresponders (p < 0.001).

No clinical variable could distinguish late responders from late nonresponders. Hemodynamic variables measured before vasodilator therapy showed that late responders had lower mean right atrial pressure (8 ± 1 vs 17 ± 3 mm Hg, p < 0.01) and lower mean pulmonary artery wedge pressure (20 ± 2 vs 30 ± 2 mm Hg, p < 0.005), higher stroke volume index (27 ± 2 vs 20 ± 1 ml/m², p < 0.005) and higher stroke work index (32 ± 4 vs 19 ± 2 g-m/m², p < 0.01) than late nonresponders. There were no significant differences in the acute response to vasodilators between the two groups.

We conclude that (1) a substantial portion of patients with refractory congestive heart failure either do not have a beneficial response to vasodilator therapy or discontinue it because of side effects; (2) about half of the patients who are maintained on chronic vasodilator therapy (or about one-fourth of the patients in whom therapy is initiated) had sustained clinical benefit; and (3) the initial hemodynamics, but not the clinical variables, are predictive of late mortality and late clinical response. Patients with evidence of more severe left ventricular dysfunction have an unfavorable course.

VASODILATOR drugs improve cardiac performance in patients with chronic congestive heart failure.1-11 Hydralazine, whose predominant effect is arteriolar vasodilatation, has been shown to increase cardiac output in these patients.2, 4, 9-11 When hydralazine is combined with long-acting nitrates, left ventricular filling pressure is also reduced.9, 10 Although combined vasodilator therapy acutely improves hemodynamics, the long-term results of such therapy are uncertain in patients with chronic heart failure, who have a poor prognosis.12-14 We undertook this study to examine the long-term clinical effects of vasodilator therapy with hydralazine and nitrates in patients with chronic refractory congestive heart failure and to determine whether the initial clinical or hemodynamic variables are predictive of the late response.

Methods

Patient Population

The study population consisted of 34 consecutive patients admitted to our institution for management of congestive heart failure who met the following criteria: (1) congestive heart failure refractory to conventional medical therapy with digitalis and diuretics; (2) New York Heart Association (NYHA) functional class III or IV; (3) absence of primary valvular heart disease, prosthetic valve malfunction or any other surgically correctable lesion; and (4) no change in clinical course during the preceding 3 months. All patients had multiple previous hospital admissions for treatment of
Experimental study of afterload-reducing therapy: the effects of the reduction of systemic vascular resistance on cardiac output, aortic pressure and coronary circulation in isolated, ejecting canine hearts.
S Isoyama, Y Maruyama, Y Koiwa, N Ishide, S Kitaoka, K Tamaki, S Sato, Y Shimizu, E Ino-Oka and T Takishima

Circulation. 1981;64:490-499
doi: 10.1161/01.CIR.64.3.490

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1981 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/64/3/490

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation is online at:
http://circ.ahajournals.org/subscriptions/