Effect of Carvedilol on Venous Return: A Mechanism of Reduction in Blood Pressure

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ABSTRACT—We studied the effect of carvedilol, a $\beta$-blocker with a potent $\alpha$-blocking activity, on venous return in anesthetized dogs. Though 3 $\mu$g/kg of carvedilol caused a slight increase in blood pressure and total peripheral resistance, these changes disappeared by further doses of the agent. On the other hand, each dose of carvedilol (3–100 $\mu$g/kg) decreased venous return significantly and dose-dependently. These results indicate that the hypotensive effect of carvedilol mainly depends on the decrease in venous return rather than arterial vasodilation.

Carvedilol is a noncardioselective $\beta$-adrenoceptor blocking agent without partial agonist activity (1). This agent produces a decrease in blood pressure with a reduction in total peripheral resistance attributable to its vasodilating activity (1, 2). In our previous report (3), the contribution of the potent $\alpha$-blocking activity of carvedilol to the reduction in blood pressure was strongly suggested. However, the changes in blood pressure were not proportional to those in total peripheral resistance (3). Therefore, we thought that the decrease in venous return should be taken into consideration.

Thus, we examined the effect of carvedilol on venous return in an experimental model with constant input with which changes in the volume of capacitance vessels can be observed (4).

Experiments were performed on 6 mongrel dogs of either sex weighing 9.6 ± 0.6 kg. Animals were anesthetized with a mixture of $\alpha$-chloralose (45 mg/ml) and urethane (450 mg/ml) given intravenously (1 ml/kg) after premedication with morphine hydrochloride (1.5 mg/kg) subcutaneously, and then the animals received continuous injection of the mixture at the rate of 0.5 ml/kg/hr.

A tracheal cannula was inserted and artificial respiration started with room air supplemented with oxygen. The tidal volume and the respiratory rate were adjusted under an end-expiratory pressure of 4 cmH2O to keep $Po_2$, $Pco_2$ and pH at 100–150, 30–40 and 7.4 ± 0.05, respectively. The arterial blood sample was drawn through a pig-tail catheter, the tip being located above the aortic valve. A cannula was inserted into the aortic arch via the left femoral artery, and the blood pressure was monitored by the use of a pressure transducer (Statham P50, CA, U.S.A.). The left femoral vein was also cannulated as a route for heparin injection.

After a midsternal incision was made, the azygos vein and internal mammalian arteries were ligated and cut. A cannula for constant blood supply from a reservoir was inserted into the right atrium through a small incision in the pericardium after the dog had been given sodium heparin (500 U/kg, i.v.). Glass
cannulae were inserted into the superior and inferior venae cavae, and blood from these cannulae was led to the venous reservoir of about 1200 ml, 40 cm beneath the heart. Electromagnetic flow probes (6 and 4 mm in diameter for the inferior vena cava and superior vena cava, respectively) connected to a flow meter (MFV-2100, Nihon Kohden, Tokyo, Japan) were set between glass cannula and the reservoir to measure flows of the respective vena. The reservoir containing about 900 ml of fresh whole blood obtained from a donor dog (15 - 22 kg) prior to the operation was set in a bath maintained at 38°C. The blood in the reservoir was pumped into the cannulated right atrium by a pulsatile blood pump (Harvard Apparatus, 1421, MA, U.S.A). A simplified diagram of the experiment is shown in Fig. 1. The pulse rate was initially adjusted to the spontaneous beat of the heart, and the input volume was adjusted to maintain the systemic blood pressure in the physiological range. The pulse rate and the input volume were kept constant throughout the experiment.

The hydrostatic pressure at the bottom of the reservoir was measured by a pressure transducer, and the changes were transformed into the changes in blood volume. Calibration was conducted by adding the blood to the reservoir. To standardize the changes in blood volume, they were divided by the body weight of the preparation. The heart rate was measured by a cardiotachometer (San-ei, 1321, Tokyo, Japan) which was triggered by blood pressure pulse. Recordings were made on charts by two rectilinear polygraphs (Graph-tec, WR 3001 and WR 3101, Tokyo, Japan). Additional heparin (100 U/kg) was administered every one hour. The blood oozing from the wound into the thoracic cavity was pumped into the reservoir by a peristaltic pump (LKB, Sweden). Throughout the experiments, all animals were handled in a humane way in accordance with recognized guidelines on animal experimentation.

Carvedilol was obtained from Daiichi Seiyaku Co., Ltd, and it was dissolved in a mixture of dimethylsulfoxide (2.4%), acetic acid (0.24%) and glucose (5%). Comparisons of date from the control values were made by paired Student's t-test and considered to be significant when \( P < 0.05 \).

After about a 1-hr stabilization period, all hemodynamic parameters became stable. Because total venous outflow (sum of the outflow from superior and inferior venae cavae) as well as the input to the right atrium was stable at this point, we considered the input to the atrium as equal to the cardiac output and total peripheral resistance was calculated by
Carvedilol (in a volume of 0.01 ml/kg) and vehicle (the same volume) were administered into the reservoir. The vehicle had no effect on any of the examined parameters. As shown in Fig. 1B, administration of carvedilol caused transient increases in heart rate, venous outflow and volume of venous return. On the other hand, a transient decrease was observed in blood pressure. The transient increases in heart rate and venous outflow represent the reflex tachycardia with reflex translocation of blood from capacitance vessels induced by the arterial hypoten spline effect of carvedilol. Thereafter, though detectable changes were not observed in venous outflow, the volume of venous return decreased gradually, and the steady state was achieved after 30–50 min of administration. Therefore, all data for comparison were taken after the establishment of a steady state of venous return.

As summarized in Fig. 2, cumulative administration of carvedilol (3–100 μg/kg) caused a dose-dependent decrease in heart rate, although this did not reach a significant level. Carvedilol at 3 μg/kg increased blood pressure slightly; however, the increase disappeared by further doses of the drug (10, 30 and 100 μg/kg).

Over the same dose range (3–100 μg/kg), carvedilol had caused sustained and dose-dependent decreases in blood pressure by about 4–26 mmHg in our previous study (3). Total peripheral resistance, calculated from cardiac output and mean blood pressure, was increased by 3 μg/kg of carvedilol, but returned to the control value when the dose was increased. Though the venous outflow of the inferior and superior venae cavae, i.e., the total venous outflow, showed no significant change by cumulative administration of carvedilol (data not shown), the volume of the venous return decreased dose-dependently and significantly. The maximum reduction of the venous return (36.6 ± 5.4 ml/kg) was observed by 100 μg/kg of carvedilol.

This study clearly and directly showed a decrease in venous return underlying the hypoten spline effect of carvedilol. This finding is consistent with our previous findings that the decrease in blood pressure correlated well to that in cardiac output, whatever the changes in total peripheral resistance were (3). The decrease in venous return indicates pooling of blood in the venous side of the animals because no decrease was observed in total peripheral resistance. Assuming that the volume of circulating blood is 800 ml in a dog of 10 kg, about 560 ml of blood (70%) is in the capacitance vessels (5). Therefore, pooling of 36 ml/kg of blood (the maximum decrease in venous return by 100 μg/kg of carvedilol) corresponds to an increase in the volume of capacitance vessels by about 60%. The spleen may play a role in blood pooling and a possible contribution of pulmonary circulation is not excluded in our preparation. We did not examine further mechanisms of reduction of venous return; however, a potent α-blocking activity of carvedilol may play an important
role, for α-adrenergic stimulants are known to cause venoconstriction (6). In fact, prazosin was demonstrated to reduce the venous return in our previous study using the same preparation as that of the present study (7). However, a possible contribution of β-blocking activity which would result in the constriction of the splanchnic sphincter (8) can not be ruled out. Hashimoto et al. (9) reported in pithed spontaneously hypertensive rats that the α-blocking activity of carvedilol plays a major role in reducing blood pressure. Thus, the importance of reduction of venous return in carvedilol-induced depressor response is evident. As the α-blocking activity of carvedilol is 3.8 times less potent than the β-blocking activity in dogs (3), predominant β-blocking activity would cause only a slight increase in total peripheral resistance. In addition, a decrease in heart rate would result in increased stroke volume. This, together with slightly increased total peripheral resistance, might have prevented the blood pressure from falling still further in our preparation. In this preparation, changes in venous return are difficult to detect as changes in venous outflow when the changes in venous return occurred over an extended period of time. As \( \Delta \text{venous return} = \Delta \text{venous outflow} \times t \) (time), barely detectable small changes in venous outflow can amount to a rather large changes in venous return, when \( t \) is large.

In conclusion, the reduction in blood pressure by carvedilol mainly depends on its ability to pool blood in capacitance vessels and a resultant reduction of the venous return rather than the decrease in peripheral vascular resistance.

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