DIFFERENTIAL EFFECTS OF NITROGLYCERIN, TRIMETAZIDINE, VERAPAMIL AND SK&F 24260 ON VENOUS RETURN AS REVEALED BY THE OPEN-LOOP METHOD IN THE DOG

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Abstract—To obtain detailed information concerning the effects of different vasodilators on venous return, experiments were carried out on 28 dogs by the use of the open-loop method. Blood from the superior and inferior venae cavae was drained at the level of the tricuspid valve into a reservoir, from which blood was pumped into the right atrium at a constant flow rate. Changes in reservoir volume reflected a total blood shift from the experimental dog and indicated changes in venous return. Drugs were administered into the ascending aorta. Nitroglycerin (1-10 µg/kg) decreased systemic blood pressure, total peripheral resistance and venous return but scarcely altered heart rate. Trimetazidine (0.3-3 mg/kg) decreased systemic blood pressure, total peripheral resistance, venous return and heart rate. Verapamil (10-100 µg/kg) decreased systemic blood pressure, total peripheral resistance and heart rate, and increased venous return. SK&F 24260 (1-10 µg/kg) decreased systemic blood pressure, total peripheral resistance, venous return and heart rate. Only high doses (10-30 µg/kg) of SK&F 24260 reduced heart rate. Rigorous measurements of systemic output showed that nitroglycerin (10 µg/kg), trimetazidine (3 mg/kg), verapamil (100 µg/kg), SK&F 24260 (10 µg/kg) produced no change in this parameter. SK&F 24260 increased venous return even when sino-aortic baroreceptor reflex was eliminated, ruling out reflex venoconstriction as a possible cause of the increased venous return. The results suggest the following: [1] Vasodilators like SK&F 24260 and verapamil increase venous return by decreasing arterial and/or venous resistance. [2] If the effect which increases venous capacitance prevails over the effect which decreases arterial and/or venous resistance, venous return is reduced as is the case of nitroglycerin and trimetazidine.

Nitroglycerin reduces the left ventricular end-diastolic pressure and volume (1-4), and such is considered to be one of mechanisms responsible for the antianginal action of nitroglycerin (1, 2, 4-6). The reduction in these 2 parameters is thought to be due mainly to a decrease in venous return (3, 4). Thus, it was of interest to investigate the effect on venous return of other vasodilators used for prevention of attacks of angina pectoris. In previous studies (7, 8) we demonstrated that some of vasodilators increased venous return whereas others decreased it. However, in those studies we measured venous return by noncannulating-type flow probes of electromagnetic flow meters placed at the superior and the inferior vena cava in anesthetized open-chest dogs and did not control cardiac input (the closed-loop method). Thus, it was hardly discernible whether the observed change in venous return by a certain vasodilator would be due to its effect on vasculature or on the heart. Most
vasodilators affect heart rate (9) and myocardial contractility (10, 11). Indeed, in the previous studies right atrial pressure was measured as an index of contractility of the heart, and some knowledge of the effect on myocardial contractility was acquired. The present study was designed to obtain more detailed information on the effects of vasodilators on venous return and to gain insight into the related vascular mechanisms. For this purpose, we utilized the open-loop method in dogs in which venous outflow from the superior and the inferior vena cava was drained at a fixed hydrostatic pressure to a blood reservoir and thus, cardiac input (venous return to the heart) was controlled. Furthermore, to minimize the effect on the heart, drugs were injected into the ascending aorta. By using the open-loop method, we have recently gained some insight into the role of vascular α- and β-adrenergic receptors in changes related to venous return produced by sympathomimetic amines (12). In the present study in addition to nitroglycerin, 3 vasodilators, i.e., verapamil, trimetazidine, and 3,5-dicarbethoxy-2,6-dimethyl-4-(2-trifluoromethyl-phenyl)-1,4-dihydropyridine (SK&F 24260) (13, 14) were used, since in the previous studies (7, 8) a full analysis of the findings with these vasodilators was not made. Nitroglycerin served as a reference drug. To estimate the contribution of the sympathetic reflex to the change in venous return, the effect of removal of the baroreceptor reflex of the sino-aortic origin was investigated in some experiments.

MATERIALS AND METHODS

Twenty-eight young, healthy mongrel dogs were anesthetized with sodium pentobarbital initially at a dose of 30 mg/kg, i.v., and hourly at maintenance doses of 4–6 mg/kg, s.c. Under positive pressure respiration of 18 breaths/min with a tidal volume of 20 ml/kg by the aid of a dog respirator (Harvard Apparatus, Model 607), the chest was opened by a midsternal incision. The vagus and phrenic nerves were cut bilaterally. Intra- and extracorporeal circulation is shown schematically in Fig. 1. Details of the preparation were described previously (12). After the azygos vein had been ligated, the heart was kept in position within the pericardial cradle. After the animal had been given sodium heparin (500 units/kg, i.v.), cannulae were placed in the superior and the inferior vena cava. Blood from the cannulae was led through Y-tubing and a cannulating-type flow probe of an electromagnetic flow meter (Nihon Kohden, MF-46) to a relay reservoir. Thus, the flow probe measured venous return. The level of the relay reservoir was adjusted at the level of the tricuspid valve to maintain central venous pressure equal to the hydrostatic level of the tricuspid valve. The blood from the relay reservoir was drained into another 1.5 liter reservoir maintained at 39°C by a water jacket. The 1.5 liter reservoir had been primed with about 1 liter of fresh whole blood from donor dogs. The blood in the reservoir was pumped into the cannulated right atrium by a peristaltic pump (Harvard Apparatus, Model 1215) to provide cardiac input. Cardiac input was adjusted initially so as to maintain systemic blood pressure in a physiological range, and kept constant throughout the experiment. Thus, a change in blood volume in the reservoir was a total blood shift from the experimental dog, being measured as a change in hydrostatic pressure of the reservoir by
the use of a pressure transducer (Nihon Kohden, LPU-0.1). Cardiac input was monitored by a cannulating-type probe of the electromagnetic flow meter. In Series 1 and 2 experiments systemic output was monitored by a noncannulating-type flow probe fitting the ascending aorta. However, for accurate measurements of systemic output, in Series 3 experiments, 2 cannulating-type flow probes were used. One was placed in the descending thoracic aorta and the other in the brachiocephalic artery. The left subclavian artery was ligated. Phasic systemic blood pressure was measured at the left femoral artery by a pressure transducer (Nihon Kohden, MPU-0.5). The mean right atrial pressure was measured by another pressure transducer (Nihon Kohden, LPU-0.1). The zero base line reference for right atrial pressure was set to the hydrostatic level of the tricuspid valve. Heart rate was measured by a cardiotachometer (San-ei, Biophysigraph type 2130), which was triggered by R waves of lead II ECG. Recordings were made on charts by 2 rectilinear recorders (San-ei, Rectiholy 8S and Rectiholiz 8S). Not all of the 6 cardiohemodynamic parameters were successfully measured in each dog.

Tyrode solution was transfused at rates of 40–60 ml/hr in order to prevent the negative balance of body fluid during the experiment. The blood oozing from the wound into the thoracic cavity was continuously pumped up into the reservoir by the use of a peristaltic pump (Harvard Apparatus, Model 607).

In Series 2 experiments the carotid sinuses were denervated bilaterally in the following way: the carotid sinus nerves were carefully dissected free on both sides and severed surgically, and furthermore a minute amount of 50% saponated cresol solution was applied to the carotid sinuses to secure complete degeneration of the nerves. When changes in systemic blood pressure caused by bilateral occlusion of the common carotid arteries

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**Fig. 1.** Schematic representation of the open-loop preparation and the recording system. AO, aorta; IVC, inferior vena cava; SVC, superior vena cava; PA, pulmonary artery; PV, pulmonary vein; SBP, systemic blood pressure; SOP, systemic output; CIP, cardiac input; VR, venous return; RV, reservoir volume; RAP, right atrial pressure; HR, heart rate; PT, pressure transducer; FP, probe of electromagnetic flow meter; PP, peristaltic pump; I, point of drug injection; 1, relay reservoir as an adjuster of central venous pressure; 2, reservoir. Arrows indicate directions of blood flow.
were smaller than 10% of control values, the carotid sinus denervation was taken to be virtually complete. Aortic baroreceptor reflex was eliminated by bilateral vagotomy.

The drugs used in the present study were nitroglycerin (Nippon Kayaku), trimetazidine dihydrochloride (Inabata), verapamil hydrochloride (Knoll), and 3,5-dicarbethoxy-2,6-dimethyl-4-(2-trifluoromethylphenyl)-1,4-dihydropyridine (SK&F 24260, Smith Kline & French). Nitroglycerin was dissolved in distilled water at a concentration of 1 mg/ml. SK & F 24260 was first dissolved in Tween 80 (Wako) at a concentration of 20 mg/ml. Other drugs were dissolved in 0.9% saline. All drug solutions were diluted with saline to the desired concentrations. Drug solutions in a volume of 1 ml were injected into the ascending aorta (for 10 sec). Drugs were given into the ascending aorta to minimize their cardiac effect. Doses of drugs except nitroglycerin and SK&F 24260 refer to their salts. In Series 1 experiments, 10 of 19 dogs were given one drug and the remaining 9 dogs were given 2 of the 4 drugs. In these experiments, a drug was administered when the effect of the preceding dose had virtually disappeared; intervals of drug administration spanned from 5 to 40 min, and the order of drug administration was randomized. Most experiments ran about 5 hours.

Values of cardiohemodynamic responses to the 4 vasodilators refer to peak responses. When responses were biphasic, a peak increase and a peak decrease were measured and plotted individually. All values are expressed in terms of mean ± S.E.; n being the number of experiments, i.e., animals. Statistical significance of the difference between mean values was analyzed with Student's t-test and expressed by p values.

RESULTS

Table 1 shows the mean body weight of dogs used and control values of 4 cardiohemodynamic parameters in 3 series of experiments.

Effects of 4 vasodilators on cardiohemodynamics (Series 1 experiments)

Nitroglycerin: In all 7 dogs, nitroglycerin (1-10 μg/kg) injected into the ascending aorta caused dose-dependent decreases in systolic and diastolic blood pressure and in reservoir volume. However, it should be noted that a transient increase in reservoir volume always preceded the decrease (Fig. 2). The half duration of the decrease in reservoir volume, that is the period from the onset of decrease to the point of half recovery from a peak decrease, was

| Experimental Series | No. of dogs | Body weight (kg) | Systolic blood pressure (mm Hg) | Diastolic blood pressure (mm Hg) | Cardiac input (ml/kg per min) | Heart rate (beats/min) |
|---------------------|-------------|------------------|---------------------------------|---------------------------------|-------------------------------|------------------------|
| 1                   | 19          | 12.6 ± 1.8       | 129 ± 19                        | 66 ± 16                         | 55.3 ± 6.8                    | 182 ± 24               |
| 2                   | 4           | 13.2 ± 1.7       | 116 ± 19                        | 58 ± 17                         | 54.0 ± 5.0                    | 205 ± 13               |
| 3                   | 7           | 11.4 ± 1.3       | 115 ± 25                        | 71 ± 18                         | 62.6 ± 8.2                    | 181 ± 40               |

Values are expressed by mean ± S.E. *Values are expressed by mean ± S.D.
Trimetazidine: In all 7 dogs, single bolus injections of trimetazidine (0.3–3 mg/kg) into the ascending aorta decreased both systolic and diastolic blood pressure and reservoir volume. The peak decreases in reservoir volume attained with 1 and 3 mg/kg of trimetazidine

2.5±0.3 min (n=6) at 3 µg/kg and 3.4±0.6 min (n=7) at 10 µg/kg. In all doses, right atrial pressure remained virtually unchanged (p>0.05; n=5 at 1 and 3 µg/kg, n=6 at 10 µg/kg). In lower doses, heart rate was scarcely affected but at a dose of 10 µg/kg it was increased slightly. The results obtained with nitroglycerin are summarized in Fig. 3.
were 1.2±0.5 ml/kg (n=6) and 3.2±0.6 ml/kg (n=7), respectively, and the half duration of the decrease at 1 and 3 mg/kg was 6.6±1.2 min (n=6) and 8.0±1.5 min (n=7), respectively. However, at a dose of 1 mg/kg in 3 of and at a dose of 3 mg/kg in 4 of the 7 animals, reservoir volume was initially increased. Trimetazidine increased right atrial pressure and decreased heart rate in a dose-dependent manner. Figure 4 shows a typical experiment with trimetazidine, and results are summarized in Fig. 5.

**Verapamil:** In all 8 dogs, verapamil (10–100 μg/kg) injected into the ascending aorta produced dose-dependent decreases in systolic and diastolic blood pressure. These doses of verapamil increased reservoir volume in a dose-dependent manner in all the dogs examined.
However, with the high dose (100 μg/kg), a long-lasting decrease in reservoir volume followed an initial clear increase in 2 of the 8 dogs (Fig. 6). Right atrial pressure was increased significantly (p<0.05; n=8) only at the high dose (100 μg/kg). Heart rate was decreased in a dose-dependent manner. The results obtained with verapamil are summarized in Fig. 7.

**SK&F 24260:** Single bolus injections of SK&F 24260 (1–10 μg/kg) into the ascending aorta of 6 dogs caused dose-dependent falls of both systolic and diastolic blood pressure. With this dose range, reservoir volume increased monophasically and in a dose-dependent manner. However, with a further increase in doses to 30 μg/kg, an increase in reservoir
volume was followed by a long-lasting decrease in 2 of the 3 dogs examined. In doses of 1–10 μg/kg right atrial pressure was unchanged (p > 0.1; n=5 at 1 and 10 μg/kg, n=6 at 3 μg/kg), but at 30 μg/kg right atrial pressure increased in 2 of the 3 dogs examined. Heart rate increased slightly at a dose of 1 μg/kg but decreased in doses above 3 μg/kg. However, a decrease in heart rate in response to 30 μg/kg of SK&F 24260 did not exceed about 10% of the control. The results obtained with SK&F 24260 are summarized in Fig. 8.

Absence of modification of the effects of SK&F 24260 by bilateral carotid sinus denervation (Series 2 experiments): To determine the extent to which baroreceptor reflex triggered by hypotension caused by SK&F 24260 might contribute to an increase in reservoir volume, the effects of SK&F 24260 were examined in 4 vagotomized dogs in which bilateral carotid sinus denervation was performed acutely. The values obtained in this series of experiments were compared with those obtained from the 6 dogs in which the carotid sinus nerves were left intact. In the 4 dogs in which the carotid sinuses were bilaterally denervated, systolic and diastolic blood pressure and heart rate were clearly higher than those of intact dogs (Series 1 experiments); 175±17 mm Hg, 76±8 mm Hg, and 215±6 beats/min (n=4) as against 140±9 mm Hg, 67±4 mm Hg, and 175±9 beats/min (n=6) in the intact dogs. After the carotid sinus denervation, reservoir volume tended to increase transiently (Fig. 9). In the dogs in which the carotid sinuses were denervated, SK&F 24260 (1–30 μg/kg) decreased both systolic and diastolic blood pressure and heart rate, and increased reservoir volume.
but scarcely altered right atrial pressure (Fig. 9). These changes were not significantly different from those obtained from the intact dogs at each dose ($p > 0.1$).

**Effects of 4 vasodilators on systemic output and total peripheral resistance (Series 3 experiments):** To determine whether the 4 vasodilators might affect systemic output and whether the change in systemic output, if any, caused by these drugs might result in change in reservoir volume, the effects on systemic output were precisely measured in 5 dogs. Blood flow through the descending thoracic aorta and the brachiocephalic artery was measured individually by the use of 2 cannulating-type flow probes, after the left subclavian artery had been ligated. The blood flow through these 2 arteries for 3 min was measured planimetrically from the areas circumscribed by a base line and a tracing of the blood flow on the chart. Systemic output for 3 min was obtained by summation of blood volume measured as above. Total peripheral resistance was calculated as follows: $\text{TPR} = \text{mean systemic blood pressure}/\text{systemic output} (\text{mm Hg} \cdot \text{min}/l)$. Mean systemic blood pressure was measured at 3 min after drug injection. The dose of drugs used was as follows: 10 $\mu$g/kg of nitroglycerin, 3 mg/kg of trimetazidine, 100 $\mu$g/kg of verapamil and 10 $\mu$g/kg of SK&F 24260. These 4 vasodilators produced almost the same cardiohemodynamic changes as described in the section of Series 1 experiments.

Changes in systemic output induced by nitroglycerin, trimetazidine, verapamil and SK&F 24260 were $0.1 \pm 0.1$ (n=5), $0.1 \pm 0.2$ (n=5), $0.4 \pm 0.6$ (n=5) and $0.4 \pm 0.4$ (n=5) ml/kg for 3 min, respectively and all were insignificant ($p > 0.3$ against pre-drug values for each drug). Table 2 shows changes in total peripheral resistance caused by these 4

| Drug            | Dose (µg/kg) | No. of dogs | Total peripheral resistance (mm Hg·min/l) | Before injection | After injection |
|-----------------|--------------|-------------|------------------------------------------|------------------|----------------|
| Nitroglycerin   | 10           | 5           | 135±14                                   | 106±6*           |
| Trimetazidine   | 3*           | 5           | 124±13                                   | 98±16*           |
| Verapamil       | 100**        | 5           | 117±15                                   | 76±6*            |
| SK&F 24260      | 10           | 5           | 137±15                                   | 82±5*            |

Values are expressed by mean±S.E. *Significantly smaller than before injection ($p<0.05$). **mg/kg.
vasodilators. Total peripheral resistance was decreased significantly by these 4 drugs ($p<0.05$; $n=5$).

**DISCUSSION**

In the present study venous return was measured by the flow probe set in the outflow circuit from the experimental dog. However, since the flow meter was not sensitive enough to measure small changes in venous return produced by drugs, peak changes in blood volume in the 1.5 liter blood reservoir were taken to indicate peak changes in venous return. Thus, in the following discussion, an increase or a decrease in the reservoir volume will indicate an increase or a decrease in venous return.

In the present study, the 4 vasodilators investigated, *i.e.*, nitroglycerin, trimetazidine, verapamil and SK&F 24260, all caused a fall of systemic blood pressure. However, their effects on venous return were different; venous return was decreased by nitroglycerin and trimetazidine, whereas it was increased by verapamil and SK&F 24260. The present results on nitroglycerin, trimetazidine and SK&F 24260 are in agreement with those obtained in the closed-loop preparation to which these drugs were administered i.v. (refer to 7 for nitroglycerin; 8 for trimetazidine and SK&F 24260), although in the present experiments the drugs were injected into the ascending aorta. Thus, the question arises why one group of vasodilators decreases venous return whereas the other increases it. Since systemic output was not changed by these drugs (Series 3 experiments), the change in venous return is by no means explained by a change in systemic output. There are 3 possible causes of the increased venous return by verapamil and SK&F 24260. The first possibility is that the fall of systemic blood pressure in response to verapamil or SK&F 24260 might trigger the reflex venoconstriction, and this in turn might squeeze out blood from the systemic venous bed to the extracorporeal reservoir. This possibility, however, can be ruled out by the results of Series 2 experiments; elimination of baroreceptor reflex of sino-aortic origin failed to modify the increased venous return in response to injection of SK&F 24260. Although a similar analysis was not performed on the effect of verapamil, the reflex may also not be responsible for the increased venous return seen with this drug. The second possibility is that an increase in venous return resulted from a decrease in arterial resistance. Guyton (15) has described that a decrease in total peripheral resistance allows for rapid flow of blood from the arterial to the venous side and results in an increase in venous return. Alternatively, a decrease in arterial resistance may allow translocation of blood from the arterial to the venous side and finally to the extracorporeal reservoir. Such a possibility has been proposed by Emerson (16) and Emerson et al. (17) to interpret the increased venous return by vasodilators like bradykinin and prostaglandin E$_1$. The results of Series 3 experiments clearly indicate that total peripheral resistance was definitely decreased by injection of SK&F 24260 and verapamil into the ascending aorta. The third possibility is a decrease in venous resistance as was proposed by Green (18, 19) to interpret the increased venous return in response to isoproterenol. However, venous resistance was not measured in the present experiments.
Unlike SK&F 24260 and verapamil, nitroglycerin and timetazidine injected into the ascending aorta decreased both total peripheral resistance and venous return. Since in the preceding paragraph we conjectured that the increased venous return by vasodilators would be due to decreases in total peripheral resistance and/or venous resistance, we should answer the question why venous return was reduced by nitroglycerin and trimetazidine despite the decreased total peripheral resistance and/or venous resistance by the 2 drugs. Although sodium nitrate and nitroglycerin dilate both venous and arterial beds, their actions are more prominent on the former (20–22). This has been confirmed by experiments on isolated veins and arteries (23). Thus, the decreased venous return by nitroglycerin can be explained in such a way that volume of blood transferred from the arterial to the venous side by the decreased peripheral resistance is surpassed by the pooling capacity of the venous bed by an increase in venous capacitance, i.e. venodilatation. Alternatively, the increase in venous return due to the decreased venous resistance would be masked by the increased venous capacitance. The increase in venous return alone by SK&F 24260 can be well understood if one takes into account of the finding by Fielden et al. (14) and by Johnston (24) that SK&F 24260 dilates preferentially precapillary sphincter vessels to reduce resistance but does little to capacitance vessels. Although the decreased venous return was a main feature of the effect of nitroglycerin, a transient but overt increase preceded the decrease. Thus, its possible cause should be inferred. The reflex venoconstriction triggered by hypotension may contribute to this increase. In spite of this possibility, it is tempting to consider that the initial increase may reflect rapid transfer of blood from the arterial to the venous side and finally to the extracorporeal reservoir due to a decrease in arterial resistance before nitroglycerin reaches the venous side to increase its capacitance. Although no information is available about whether trimetazidine dilates preferentially capacitance over resistance vessels, the present results suggest that a decrease in venous return by this drug is due probably to venous pooling, and its more prominent action on the venous rather than on the arterial bed. The initial increase in venous return by this drug can also be interpreted as in the case of nitroglycerin.

When verapamil was given intravenously to the closed-loop preparation it produced apparent decreases in venous return and cardiac output with clear indications of cardiodepressant action; an increase in right atrial pressure and a decrease in heart rate (7). In the present experiments in which verapamil was injected into the ascending aorta in order to minimize the cardiac effect, venous return was increased. Thus, the decreased venous return and cardiac output as observed in the closed-loop preparation can be ascribed to the pooling of blood in the heart and lung vasculature due to the decreased force of contraction rather than to an increase in venous capacitance. Verapamil decreases force of contraction of mammalian myocardium (10, 11, 25) and also causes relaxation of vein strips contracted by acetylcholine or noradrenaline (26). SK&F 24260 is also a drug which reduces force of contraction of mammalian myocardium (27). In the present study, after high doses of verapamil and SK&F 24260, an increase in venous return was followed by a long-lasting decrease and the decrease was accompanied by reduction of heart rate and elevation of right
atrial pressure. Thus, the decrease in venous return may partly be attributable to a decrease in systemic output caused by the cardiodepressant action of the 2 drugs. Therefore, it appears that the decrease in arterial and/or venous resistance results in an increase in venous return unless systemic output is reduced and an increase in venous capacitance is marked. Indeed, data are available that vasodilators or hypotensive drugs like isoproterenol (12, 18, 19, 28), salbutamol (29), acetylcholine (30), nifedipine (7), dilazep and diltiazem (8) increase venous return. In contrast, vasoconstrictors like angiotensin, vasopressin (31) and methoxamine (12) decrease it.

Finally the implication of the effects on venous return of these vasodilators in their antianginal action should be considered. Since trimetazidine reduced venous return, this would contribute to its antianginal action through the reduced preload of the heart as is the case with nitroglycerin. In contrast to trimetazidine, the antianginal effect of verapamil has no relation to its effect on venous return.

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