Role of the Peripheral Vasculature in Changes in Venous Return Caused by Isoproterenol, Norepinephrine, and Methoxamine in Anesthetized Dogs

YUTAKA IMAI, KEISUKE SATOH, AND NORIO TAIKA

SUMMARY We studied effects on venous return of α- and β-adrenergic agonists in anesthetized dogs. Blood from the superior and inferior vena cavae (venous return) was drained at the level of the tricuspid valve into a reservoir, from which blood was pumped into the right atrium at a constant rate. Isoproterenol infused into the ascending aorta or the right atrium increased the venous return and heart rate and decreased systemic blood pressure. The increase in venous return produced by isoproterenol given into the right atrium was not significantly different from that produced by isoproterenol administered into the ascending aorta, although the increase in heart rate was more marked with the latter route of administration. Norepinephrine infused into the ascending aorta increased the systemic blood pressure, venous return, and heart rate. Methoxamine infused into the ascending aorta increased the systemic blood pressure and decreased the venous return but produced no change in heart rate. Isoproterenol increased the venous return even when the sinoaortic baroreceptor reflex was eliminated. Propranolol abolished the increase in venous return caused by isoproterenol and reversed the increase in venous return caused by norepinephrine. The results suggest that a decrease in venous resistance mediated through a β-adrenergic mechanism is important in increasing venous return, whereas an increase in venous resistance mediated through an α-adrenergic mechanism is responsible for a decrease in venous return.

REFLEX augmentation of sympathetic tone by carotid sinus hypotension1-3 or stimulation of the lumbar sympathetic nerves4 causes an increase in venous return which has been attributed to an increase in venous tone.1-5 Intravenous injection of epinephrine or norepinephrine also increases venous return,5-7 and this also has been attributed to an increase in venous tone or to a decrease in venous capacitance.6,7 Kaiser et al.6 observed, in dogs on cardiopulmonary bypass, that isoproterenol, epinephrine, and phenylephrine all increase venous return. They interpreted the increased venous return induced by epinephrine and phenylephrine as being due to venoconstriction mediated by α-adrenergic stimulation and the increase in venous return caused by isoproterenol as also due to venoconstriction mediated by venous β-adrenergic receptors. Green8 also observed that isoproterenol increased venous return in dogs on right heart bypass. However, as opposed to the explanation given by Kaiser et al.,6 Green suggested that the increase in venous return caused by isoproterenol resulted in large part from dilation of venous resistance vessels. In view of the present state of our knowledge of vascular mechanisms and adrenergic receptors involved in changes in venous return induced by sympathomimetic amines, we designed the present experiments. For this purpose, we used the open-loop method in which the cardiac input was held constant, and examined the effects on the cardiohemodynamics of three sympathomimetic amines, isoproterenol which is a relatively pure β-adrenergic stimulant,9 methoxamine, a relatively pure α-adrenergic stimulant,9 and norepinephrine, which has both α- and β-adrenergic effects.9 We also investigated how the actions of these three sympathomimetic amines would be modified by elimination of the baroceptor reflex, by β-adrenergic receptor blockade by propranolol, or by reduction of vascular tone by a vasodilator drug, SK&F 24260.10

Methods

Experiments were performed on 40 young, healthy mongrel dogs of both sexes, weighing 10–15 kg (mean ± SE = 12.3 ± 0.3). The animals initially were anesthetized with sodium pentobarbital (30 mg/kg, iv) and then received hourly doses of 4–6 mg/kg, sc. Positive pressure ventilation was initiated at 18 breaths/min with a tidal volume of 20 ml/kg (Harvard Apparatus, model 607) and a mid-sternal incision was made. The vagus and phrenic nerves were cut bilaterally. The azygos vein was ligated and the heart suspended in pericardial cradle. A schema of intra- and extracorporeal circulation is shown in Figure 1. After the dog had been

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flow probe placed between the pump and the right output was monitored by a noncannulating probe of an electromagnetic flow meter. The cardiac input was monitored by another and the relay reservoir to measure the venous return, which was kept adjusted initially to maintain the systemic blood pressure in a physiological range and was kept constant throughout the experiment. Thus, a change in blood volume in the second reservoir had been primed with about 1 liter rounded by a water jacket maintained at 39°C. The level of the relay reservoir was maintained at the level of the tricuspid valve. The blood from the relay reservoir was drained into another 1.5-liter reservoir (second reservoir) surrounded by a water jacket maintained at 39°C. The second reservoir had been primed with about 1 liter of fresh whole blood from donor dogs. The blood in the second reservoir was pumped into the cannulated right atrium by a peristaltic pump (Harvard Apparatus, model 1215). The cardiac input was adjusted initially to maintain the systemic blood pressure in a physiological range and was kept constant throughout the experiment. Thus, a change in blood volume in the second reservoir reflected a total blood shift from the experimental dog, and was measured as a change in hydrostatic pressure of the second reservoir by a pressure transducer (Nihon Kohden, MPU-0.1). A cannulating probe of an electromagnetic flow meter (Nihon Kohden, MF-46) was placed between the Y-tubing and the relay reservoir to measure the venous return. The cardiac input was monitored by another flow probe placed between the pump and the right atrium. In experiments of series 1–4, the systemic output was monitored by a noncannulating probe of the ascending aorta. However, for accurate measurements of the systemic output, in series 5 experiments, two cannulating flow probes were used; one was placed in the descending thoracic aorta and the other in the brachiocephalic artery. Blood flow through the brachiocephalic artery was secured in such a way that, after ligation of the left subclavian artery, blood from the proximal stump of the cut subclavian artery was led to the distal stump of the cut brachiocephalic artery through the flow probe. The phasic systemic blood pressure was measured in the left femoral artery by a pressure transducer (Nihon Kohden, LPU-0.5). The mean right atrial pressure was measured by another pressure transducer (Nihon Kohden, LPU-0.1). The zero base line reference for the right atrial pressure was set equal to the hydrostatic level of the tricuspid valve. The heart rate was measured by a cardiotachometer (San-ei, Biophysiograph type 2130) which was triggered by the R waves of a lead II ECG. Recordings were made on charts by two rectilinear polygraphs (San-ei, Rectiholy 88 and Rectiholiz 8S). Not all of the seven cardiohemodynamic parameters were successfully measured in each dog.

Tyrode's solution was transfused at rates of 40–60 ml/hr to maintain a stable hemodynamic state by preventing the negative balance of body fluid during the experiment. The blood oozing from the wound into the thoracic cavity was pumped into the second reservoir by a peristaltic pump (Harvard Apparatus, model 607). In series 3 experiments, bilateral carotid sinus denervation was performed as follows. The upper cervical region was incised in the midline, and the internal, external, and common carotid arteries were exposed on both sides. The carotid sinus nerves were carefully dissected free on both sides and severed surgically, and a minute amount of cresol solution was applied to the carotid sinus to ensure complete destruction of the nerves. Bilateral denervation of the carotid sinuses was judged to be virtually complete when elevation of the systemic blood pressure on bilateral occlusion of the common carotid arteries was nearly abolished. The aortic baroceptor reflex was eliminated by the bilateral vagotomy.

The drugs used included l-isoproterenol hydrochloride (Nikkken Kagaku), l-norepinephrine (Fluka), dl-methoxamine hydrochloride (Nihonshinyaku), dl-propranolol hydrochloride (ICI), and l,4-dihydro-2,6-dimethyl-4-(2-trifluoromethylphenyl)-3,5-pyridinedicarboxylic acid diethyl ester (SK&F 24260, Smith Kline & French Laboratories). Norepinephrine was dissolved in 0.01 N HCl. SK&F 24260 was dissolved in Tween 80 (Wako) at a concentration of 20 mg/ml. All other drugs were dissolved in 0.9% saline. All drug solutions were diluted with 0.9% saline to the desired concentrations. Solutions of the three sympathomimetic amines were infused at a rate of 1 ml/min for 3 minutes into the ascending aorta to minimize their cardiac effects.
Effects of Isoproterenol

Isoproterenol was infused at rates of 0.03, 0.1, and 3 \( \mu \)g/kg per min for 3 minutes into the right atrium or the ascending aorta in 11 dogs. Results of a typical experiment are depicted in Figure 2, and summarized results are presented in Figure 3. When infused into the ascending aorta, isoproterenol produced increases in systolic and diastolic blood pressure and in reservoir volume and heart rate in a dose-dependent manner, but no significant change in right atrial pressure. When isoproterenol was infused into the right atrium, the diastolic blood pressure and the right atrial pressure were decreased, and the reservoir volume and the heart rate were increased in a dose-dependent manner, whereas the systolic blood pressure remained virtually unchanged. The increase in heart rate produced by the three doses of isoproterenol given into the right atrium clearly was greater than that caused by corresponding doses of isoproterenol administered into the ascending aorta (Fig. 3, \( P < 0.01 \) in all doses). However, the increase in reservoir volume produced by the three doses of isoproterenol infused into the right atrium was not significantly different from that produced by corresponding doses of isoproterenol infused into the ascending aorta (Fig. 3, \( P > 0.8 \)).

Effects of Norepinephrine

Norepinephrine was infused at rates of 0.3, 1, and 3 \( \mu \)g/kg per min for 3 minutes into the ascending aorta in 13 dogs. In 12 of the 13 dogs, norepinephrine caused dose-dependent increases in systolic and diastolic blood pressure and in reservoir volume (Fig. 4). The right atrial pressure decreased and the heart rate increased only with higher doses of norepinephrine (1 and 3 \( \mu \)g/kg per min for 3 minutes) (Fig. 4). However, in one of the 13 dogs, the reservoir volume decreased at all doses of norepinephrine, although the other cardiohemodynamic parameters responded in a way similar to those of the other 12 dogs. Close inspection of the change in reservoir volume revealed that the volume decreased initially in four of the 12 dogs.

Effects of Methoxamine

Methoxamine was infused at rates of 10, 30, and 100 \( \mu \)g/kg per min for 3 minutes into the ascending aorta in six dogs. Data are summarized in Figure 5. The pattern of response of the systemic blood pressure to methoxamine was similar to that for norepinephrine. However, unlike norepinephrine, methoxamine decreased the reservoir volume and increased the right atrial pressure. The heart rate was not affected by methoxamine.

Series 2: The Effects of Isoproterenol before and after Bilateral Carotid Sinus Denervation

To determine to what extent the baroreceptor reflex triggered by isoproterenol-induced hypotension might be involved in the cardiohemodynamic effects of isoproterenol, the effects of isoproterenol were studied before and after bilateral carotid sinus denervation in five vagotomized dogs. Since both vagi had been severed, carotid sinus denervation
was sufficient to eliminate the baroreceptor reflex. After carotid sinus denervation, the mean systemic blood pressure increased by 24 ± 10 mm Hg and the heart rate by 12 ± 4 beats/min. However, changes in cardiohemodynamic parameters in response to isoproterenol were not different before and after this intervention (P > 0.3).

Series 3: Modification of the Effects of Isoproterenol and Norepinephrine by Propranolol

The effects of norepinephrine on cardiohemodynamics were determined in five vagotomized dogs before and after propranolol in doses which just abolished the effects of isoproterenol (0.1 µg/kg per min for 3 minutes). After a single dose of propranolol, 0.3 mg/kg, systolic blood pressure remained almost unchanged, but diastolic blood pressure increased by 8 ± 1 mm Hg and right atrial pressure by 16 ± 6 mm Hg. With this dose, the reservoir volume decreased by 5.9 ± 1.2 ml/kg and heart rate by 26 ± 6 beats/min. Figure 6 shows results of one of such experiments. Of the changes produced by propranolol, 0.3 mg/kg, the decrease in reservoir volume was most marked and of such a long dura-

Figure 2 Cardiohemodynamic effects of isoproterenol infused into the right atrium or into the ascending aorta. Periods of infusion (3 minutes) are indicated by horizontal solid lines, under which infusion rates are given. Abbreviations except for ΔRV are the same as in Figure 1. ΔRV is a change in volume of the second reservoir.

Figure 3 Dose-response curves for cardiohemodynamic parameters to isoproterenol infused at rates of 0.03, 0.1, and 0.3 µg/kg per min for 3 minutes into the ascending aorta (left panel) or into the right atrium (right panel). ○ = change in systolic blood pressure (n = 10-11); ● = change in diastolic blood pressure (n = 10-11); □ = change in right atrial pressure (n = 5); ▲ = change in heart rate (n = 10-11). Each symbol represents the mean ± SE. * P < 0.05, ** P < 0.01, and *** P < 0.001 compared to values obtained when corresponding doses were infused into the ascending aorta.

Figure 4 Dose-response curves for cardiohemodynamic parameters to norepinephrine infused at rates of 0.3, 1, and 3 µg/kg per min for 3 minutes into the ascending aorta. ○ = Change in systolic blood pressure (n = 12-13); ● = change in diastolic blood pressure (n = 12-13); □ = change in reservoir volume (n = 12-13); ▲ = change in right atrial pressure (n = 8-10); ▲ = change in heart rate (n = 12-13). Otherwise, the same as in Figure 3.
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FIGURE 5

Dose-response curves for cardiohemodynamic parameters to methoxamine infused at rates of 10, 30, and 100 µg/kg per min for 3 minutes into the ascending aorta. O = Change in systolic blood pressure (n = 6); ● = change in diastolic blood pressure (n = 6); ○ = change in reservoir volume (n = 6); □ = change in right atrial pressure (n = 5); ▲ = change in heart rate (n = 5-6). Otherwise, the same as in Figure 3.

Figure 5 Dose-response curves for cardiohemodynamic parameters to methoxamine infused at rates of 10, 30, and 100 µg/kg per min for 3 minutes into the ascending aorta. O = Change in systolic blood pressure (n = 6); ● = change in diastolic blood pressure (n = 6); ○ = change in reservoir volume (n = 6); □ = change in right atrial pressure (n = 5); ▲ = change in heart rate (n = 5-6). Otherwise, the same as in Figure 3.

dition that the volume hardly began to return toward the initial volume. For complete abolition of the cardiohemodynamic effects of isoproterenol, 0.1 µg/kg per min for 3 minutes, three successive injections of propranolol, 0.3 mg/kg, were needed. Since after such treatment the reservoir volume remained decreased and was off scale on the charts, the zero line was shifted as shown by an arrow in Figure 6. After β-adrenergic receptor blockade had been confirmed, as above, norepinephrine was infused into the ascending aorta at a rate of 3 µg/kg per min for 3 minutes. Rather than increasing reservoir volume, norepinephrine induced a decrease, and right atrial pressure was increased. The changes resembled those produced by methoxamine, except that norepinephrine increased heart rate. Figure 7 summarizes the results obtained with norepinephrine (1 µg/kg per min for 3 minutes) before and after propranolol. In this figure, increases in systolic and diastolic blood pressure and heart rate induced by norepinephrine appear to be greater after propranolol, but these changes were not statistically significant (P > 0.1). Only the changes in reservoir volume caused by norepinephrine were significantly different before and after propranolol (P < 0.05).

Series 4: Modification of the Effects of Methoxamine by a Vasodilator Drug, SK&F 24260

Five vagotomized dogs were examined to see whether the cardiohemodynamic effects of methoxamine were different when vascular tone was reduced by vasodilator drugs. For this purpose, SK&F 24260 was chosen because it is a long-acting and potent hypotensive drug having rather little cardiodepressant action.\(^\text{11,12}\) In the five dogs that received a single injection of SK&F 24260 (30 µg/kg), the systolic and diastolic blood pressures clearly were lower than those of untreated dogs (series 1 experiments), 74 ± 9 and 33 ± 6 mm Hg as against 133 ± 12 and 63 ± 9 mm Hg in the untreated dogs. After SK&F 24260, the reservoir volume tended to decrease for a long period after the initial increase. In the dogs given SK&F 24260, methoxamine (100 µg/kg per min for 3 minutes) increased venous return, although other changes were not significantly different from those obtained from the untreated dogs (P > 0.05) (Fig. 8). The increase in reservoir volume is in contrast to the decrease obtained in the untreated dogs (P < 0.01).

Series 5: Effects of Three Sympathomimetic Amines on the Systemic Output and Total Peripheral Resistance

To determine whether the three sympathomimetic amines might affect the systemic output and whether the change in systemic output, if any, caused by these drugs might result in change in venous return, the effects on systemic output were

Figure 6 Cardiohemodynamic effects of isoproterenol (0.1 µg/kg per min for 3 minutes) and norepinephrine (3 µg/kg per min for 3 minutes) and their modification by propranolol (0.9 mg/kg). The zero base line reference is reset at an arrow. Abbreviations are the same as in Figure 1.
studied in eight dogs. Blood flow through the descending thoracic aorta and the brachiocephalic artery was measured individually by the use of two cannulating flow probes, after the left subclavian artery had been ligated. The systemic output for 3 minutes was determined in the following way. The blood volume passing for 3 minutes through each of these two vessels was measured planimetrically from blood flow tracings on the chart. The blood volume thus obtained was summed and divided by the body weight of the animal. This yielded the systemic output for 3 minutes in terms of liters/kg. Such measurements were made for 3 minutes just before and during infusion of the three sympathomimetic amines to obtain control values and those during drug action. The systemic output used for calculation of total peripheral resistance (TPR) was obtained by dividing the values determined as above by 3 minutes. TPR was calculated as follows: TPR = mean systemic blood pressure/systemic output (mm Hg min/liter). Isoproterenol (0.3 μg/kg per min), norepinephrine (1 μg/kg per min), and methoxamine (100 μg/kg per min) were infused for 3 minutes into the ascending aorta. These three sympathomimetic amines produced almost the same cardiohemodynamic changes as they did in series 1 experiments. With infusion of these three sympathomimetic amines, the systemic output remained virtually unchanged (Table 2). The total peripheral resistance was definitely decreased by isoproterenol (P < 0.05), whereas it was increased by norepinephrine (P < 0.05) and methoxamine (P < 0.05) (Table 3).

**Discussion**

In the present experiments which used the open-loop method, infusion of isoproterenol into the ascending aorta increased venous return, i.e., blood volume of the reservoir from which blood was pumped at a constant rate into the cannulated right atrium. The present results are consistent with those obtained by Kaiser et al. in dogs on cardiopulmonary bypass and by Green in dogs on right heart bypass with intravenous infusion of isoproterenol. Several possible causes of the increased venous return induced by isoproterenol can be considered: (1) an increase in systemic output in spite of the controlled cardiac input, (2) "squeezing out" of blood from the systemic venous bed by reflex venoconstriction triggered by hypotension in response to isoproterenol, (3) "squeezing out" of blood from the systemic venous bed by venoconstriction in its direct response to isoproterenol, (4) translocation of blood from the arterial to the venous side and finally to the blood reservoir owing to a decrease in resistance of the peripheral arterial bed, and (5) shift of blood from the capillary and venous beds to the blood reservoir owing to a decrease in venous resistance.

The first possibility arises from the finding that isoproterenol increased the heart rate to some extent although it was infused into the ascending aorta to minimize the cardiac effect. The increase in heart rate reflects a stimulant action on the
heart. This cardiomodulator effect might cause an increase in the systemic output by mobilization of blood from capacitance in the heart and lung vasculature despite the controlled cardiac input. However, the possibility appears to be ruled out by the finding obtained in series 5 experiments in which the systemic output was measured with the flow probe. In these experiments, the systemic output was not changed during infusion of isoproterenol into the ascending aorta. However, doubt still remains as to whether the flowmeters used to measure the systemic output of the order of about 0.6 liter/min might not detect a change in blood flow as small as 20 ml for 3 minutes. Nevertheless, the circumstantial evidence obtained from series 1 experiments can rule out the possibility that the increased venous return caused by isoproterenol might result from the increased systemic output. In series 1 experiments, the increase in reservoir volume caused by infusion of isoproterenol into the ascending aorta was not significantly different from that obtained with infusion of isoproterenol into the right atrium, although the increase in heart rate was more marked in the latter case. The cardiomodal action of isoproterenol should be more marked when it is administered into the right atrium than when it is given into the ascending aorta. This finding is enough to rule out a possible increase in cardiac output induced by the cardiomodal action of isoproterenol which might lead to an increased venous return.

The second possibility, that the increased venous return might be due to reflex venoconstriction resulting from hypotension, can be ruled out by the results of the series 2 experiments. Elimination of the baroreceptor reflex of sinoaortic origin failed to modify the increased venous return induced by infusion of isoproterenol into the ascending aorta.

The third possibility, that the increased venous return might be due to venoconstriction as a direct response of the systemic venous bed, has been suggested by Kaiser et al. Here an action of adrenergic receptors involved in venoconstriction should be inferred. Available data indicate that veins have both α- and β-adrenergic receptors. Kaiser et al. speculated that venoconstriction responsible for the increased venous return might be mediated through β-adrenergic receptors. However, in vivo experiments on the cutaneous veins of the dog and on various venous beds have demonstrated that isoproterenol causes venodilation by stimulation of β-adrenergic receptors. In vitro experiments on isolated veins have also shown that isoproterenol causes relaxation when the veins have some initial tone. Thus, it is difficult to assume that the increased venous return caused by isoproterenol is due to venoconstriction mediated through β-adrenergic receptors. It is also known that isoproterenol in large doses causes constriction of isolated veins by stimulating α-adrenergic receptors. Thus, it is possible that the increased venous return induced by isoproterenol might result from venoconstriction mediated through α-adrenergic receptors. However, this possibility can be ruled out by the following findings obtained in the present experiments: (1) isoproterenol in low doses produces a dose-dependent increase in venous return (series 1 experiments); (2) the increased venous return induced by isoproterenol was abolished almost completely by the β-receptor blocking dose of propranolol (series 3 experiments); (3) the α-adrenergic stimulant, methoxamine, as well as norepinephrine in the presence of β-adrenergic receptor blockade (propanolol), caused a decrease in venous return when vascular tone was maintained (series 1 and 3 experiments). Guimaraes and Osswald have also demonstrated that isoproterenol never stimulates α-adrenergic receptors to cause constriction of several autoperfused veins in the dog.

The fourth possibility is that the decrease in arterial resistance might result in translocation of blood from the arterial to the venous side and finally to the extracorporeal reservoir. This possibility has been proposed by Emerson to interpret the increased venous return induced by vasodilator agents like bradykinin and prostaglandin E1. As the results from series 5 experiments clearly indicate, total peripheral resistance was definitely decreased by infusion of isoproterenol into the ascending aorta. However, norepinephrine also increased venous return although it increased total peripheral resistance. Thus, a change in venous return cannot be interpreted as being induced by a change in arterial resistance.

The fifth possibility appears the most plausible, i.e., that an increase in venous return caused by isoproterenol may be a result of decreased venous resistance. Guyton et al. calculated that a given change in venous resistance affects venous return about 8 times as much as the same change in arterial resistance. Although in the conceptual framework of Guyton et al. it is unclear what venous segments mainly behave as venous resistance, venous sphincters may be responsible. For example, such sphincters in the hepatic vein are thought to control the blood volume in the splanchic bed. Stimulation of β-adrenergic receptors by isoproterenol may dilate such sphincters to cause a shift of blood from the systemic venous bed to the
extracorporeal reservoir. Green has suggested that the hepatic sphincter would play an important role in the increased venous return induced by isoproterenol. The decrease in venous resistance also may lead to the increased venous return by translocation of blood from the capillary to the venous side and by a shift of the body fluid from the extravascular to the vascular space due to the decreased capillary hydrostatic pressure.

Infusion of the α-adrenergic stimulant, methoxamine, into the ascending aorta decreased venous return. Veins contract through stimulation of α-adrenergic receptors. Thus, it can be expected that methoxamine causes venoconstriction (a decrease in venous capacitance) and leads to the increased venous return. However, a decrease in capacitance of veins needs not be associated with an increase in venous return at constant right atrial pressure. Moreover, the observed change in venous return was opposite to that which is expected. Therefore, the decrease in venous return should be ascribed to elevation of venous resistance. The decrease in venous return in response to methoxamine, however, presupposes the presence of vascular tone. In dogs in which vascular tone was greatly reduced, favoring an increase in venous return to constant right atrial pressure.

In conclusion, three sympathomimetic amines, when infused into the ascending aorta, changed venous return, probably by the following mechanisms: (1) isoproterenol increased venous return mainly by a decrease in venous resistance through stimulation of β-adrenergic receptors; (2) methoxamine, an α-adrenergic stimulant, decreased venous return mainly by increasing venous resistance through stimulation of α-adrenergic receptors, although it may have acted to increase venous return through a decrease in venous capacitance; (3) norepinephrine, which has stimulant actions on both α- and β-adrenergic receptors, increased venous return probably by reduction of venous resistance and capacitance; β-adrenergic receptors are mainly responsible for the former change and α-adrenergic receptors for the latter.

Addendum

Just after submission of the manuscript, a pertinent paper by Green appeared (JF Green: Mechanism of action of isoproterenol on venous return. Am J Physiol 232: H152-156, 1977). In that paper, Green demonstrated that isoproterenol increases venous return mainly by dilating the hepatic sphincter through a β-adrenergic mechanism.

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Effects of Hypertension and Its Reversal on Aortic Metabolism in the Rat

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SUMMARY The relationship between aortic metabolism and hypertension was examined in spontaneously hypertensive rats (SHR) and in the normotensive Wistar-Kyoto (WKY) strain of rats. Comparative studies between age-matched animals of both strains showed in the SHR, enhanced activities of the aortic enzymes, N-acetyl β-glucosaminidase (NAGA) and acid phosphatase, which are associated with lysosomes. Similar increases were shown for aortic 5'-nucleotidase activity. Antihypertensive drug treatment of 30-week-old SHR for 17 weeks effectively lowered blood pressure and reduced the activity of aortic NAGA and acid phosphatase in the SHR to control levels. 5'-Nucleotidase activity remained significantly elevated, and aortic collagen and elastin concentrations were unaffected by antihypertensive drug treatment. Hypertension was produced in WKY rats by doxycorticosterone treatment for either 4 or 7 weeks and then was reversed by discontinuing treatment and maintaining the pretreated animals on a low-salt diet for up to 11 weeks. At the end of the treatment period, aortic enzymatic activity was increased significantly, as were heart and aortic weights. Following the reversal of hypertension, the activity of the lysosomal enzymes was decreased significantly, but 5'-nucleotidase activity remained elevated. Collagen and elastin concentrations were not affected by mineralocorticoid treatment, but the total amount of connective tissue protein was increased and remained elevated following the reversal of hypertension, paralleling the changes in aortic weight. The studies indicate that etiologically different forms of hypertension result in characteristic changes in aortic metabolism which are not completely reversed by subsequent blood pressure reduction.

HYPERTENSION is known to be an important risk factor for atherosclerosis in man, but the biochemical basis for this relationship has not yet been established. Changes in the vascular endothelium of hypertensive animals may lead to increased vascular permeability and smooth muscle cell proliferation, thereby contributing to the development of atherosclerotic lesions.1-3 Wolinsky et al.4 have

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