Quantitative Contribution of Systemic Vascular Autoregulation in Acute Hypertension in Conscious Dogs

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Abstract

Experiments were performed in nine conscious dogs to quantitate the contribution of systemic vascular autoregulation to the increases in total peripheral resistance (TPR) and mean arterial pressure (MAP) produced by angiotensin II (ANG II), arginine vasopressin (AVP), and norepinephrine (NE). We hypothesized that if autoregulatory vasoconstriction is significant, then the increase in TPR produced by vasoconstrictor infusion will be greater when MAP is controlled at hypertensive values than when the increase in pressure is prevented by controlling MAP at the animal's normotensive value. Each drug was infused at a dose sufficient to increase MAP by 50%. Then, a constant rate of vasoconstrictor infusion was maintained while MAP was controlled at hypertensive or normotensive levels for 15-min periods using a gravity reservoir connected to the left common carotid artery. During AVP infusion, TPR was significantly greater when MAP was controlled at hypertensive than at normotensive values. This autoregulatory-mediated vasoconstriction accounted for approximately three-fourths of the increase in MAP produced by AVP. No significant autoregulatory component was identified for the increases in TPR and MAP produced by ANG II or NE. We conclude that systemic vascular autoregulation is a powerful physiological property that contributes to the hemodynamic response to pressor doses of AVP.

Introduction

An increased total peripheral resistance is the cardinal hemodynamic disorder in most experimental and clinical forms of hypertension. Investigations concerning the etiology of the increased total peripheral resistance have dealt mainly with the participation of the autonomic nervous system, the renin-angiotensin-system, and arginine vasopressin. Autoregulation of blood flow has also been implicated in the genesis of the increased total peripheral resistance in hypertension (1). Recent work demonstrates that autoregulation and the neurohumoral pressor systems are not mutually exclusive, and that autoregulation may interact with neurohumoral vasoconstrictor stimuli to amplify increases in vascular resistance and arterial pressure (2–5).

The idea that autoregulation of blood flow contributes to the development of hypertension was originally put forth for volume-dependent hypertension by Borst and Borst-DeGeus (6) and Ledingham and Cohen (7). They postulated that hypertension develops as a sequence of hemodynamic events initiated by sodium and water retention, which causes an increase in extracellular fluid volume, and thus blood volume. This increase in blood volume results in an increase in cardiac output via the Frank-Starling mechanism. The increase in cardiac output leads to an increase in blood pressure and perfusion of tissues in excess of metabolic demands. This rise in blood pressure is thought to trigger an increase in vascular resistance through mechanisms that are presumably similar to those involved in normal short-term autoregulation of peripheral blood flow. Because essentially all tissues of the body can demonstrate autoregulatory behavior, this scheme is now termed the whole body autoregulatory theory of hypertension (8). Although autoregulation of blood flow is a well substantiated property of most vascular beds, a universal role for autoregulation in hypertension was controversial for many years because not all forms of hypertension have an elevation of cardiac output as an initial event (1, 9). Recent work, however, demonstrates that an initial increase in cardiac output is not a prerequisite for the participation of autoregulation in hypertension. In this revised scheme of the autoregulatory theory of hypertension, an increase in arterial pressure (independent of the mechanism) is sufficient to elicit autoregulatory-mediated vasoconstriction in regional vasculatures (3–5, 10) and in the total systemic circulation (2).

Previous studies have evaluated whole body autoregulation during hypertension in conscious animals in the absence of competition from major reflex responses (2, 11). Although studies in areflexic animals demonstrate the capacity of the systemic circulation to autoregulate its blood flow during increases in arterial pressure, they have not determined if local autoregulatory processes are of sufficient magnitude to be manifest when allowed to interact and compete with reflex pressure regulating mechanisms in an intact animal. Thus, the exact quantitative importance of total systemic vascular autoregulation in hypertension remains unknown.

The major goal of the present study was to determine whether autoregulation-induced vasoconstriction contributes to the increases in total peripheral resistance and arterial pressure produced by the intravenous infusion of pressor doses of angiotensin II, norepinephrine, or vasopressin in conscious dogs with intact reflexes. We hypothesized that if autoregulatory vasoconstriction is significant, then the increase in total peripheral resistance produced by vasoconstrictor infusion will be greater when mean arterial pressure is maintained at a hypertensive value than when the systemic circulation is protected from the increased pressure by controlling mean arterial pressure at the animal's normotensive value.

Previously we demonstrated that autoregulation accounted for a major portion of the vasoconstrictor and pressor responses to these vasoactive hormones in ganglionic blocked

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Received for publication 4 April 1989 and in revised form 22 August 1989.

J. Clin. Invest.

0021-9738/89/12/1900/06 $2.00
Volume 84, December 1989, 1900–1905

dogs (2). We predicted that baroreflex responses would compete with autoregulatory responses during vasoconstrictor infusion in dogs with intact reflexes, resulting in a lower efficiency of autoregulation than that previously found in ganglionic blocked dogs. We postulated, however, that autoregulatory mechanisms would predominate over competing reflex responses if whole body autoregulation is a major component of the integrated cardiovascular response to acute vasoconstrictor-induced hypertension. Our data indicate that pressure-mediated increases in total peripheral resistance contribute significantly to the pressor effects of vasopressin, but not norepinephrine or angiotensin II, in dogs with intact reflexes.

Methods

Animal preparation. Nine mongrel dogs of either sex, weighing 15–23 kg, were used in these experiments. The dogs were maintained and used in accordance with the recommendations in the *Guide for the Care and Use of Laboratory Animals,* prepared by the Institute of Laboratory Animal Resources, National Research Council, U. S. Department of Health, Education and Welfare (National Institutes of Health publication No. 85-23, 1985). All dogs were in good general health, and were free of heartworms and intestinal parasites. The animals underwent repeated training sessions for 2–4 wk. In these sessions, the dogs became familiar with the experimental environment and learned to lie quietly and unrestrained in the right lateral recumbent position for 2–3 h.

Surgery for chronic instrumentation was performed under pentobarbital sodium anesthesia (30 mg/kg i.v.) and sterile conditions. The dogs were instrumented for evaluation of systemic pressure-flow relationships, as described previously (2, 12). An electromagnetic flow probe was implanted around the root of the aorta for measurement of cardiac output. Catheters (0.040 in. i.d. × 0.085 in. o.d.) were implanted in the superior vena cava and descending aorta for measurement of central venous and arterial blood pressures, respectively. A large bore catheter ($^1/_8$ in. i.d. × $^3/_{16}$ in. o.d.) was implanted in the left common carotid artery to provide a low resistance conduit for controlling arterial pressure with a reservoir bottle (2, 12–14). All catheters were made from Silastic tubing (Dow-Corning Corp., Midland, MI). The implanted devices were tunnelled subcutaneously and exteriorized on the lateral aspect of the neck. The animals received Combiotic (Pfizer Inc., New York) just before surgery and for 3–5 d thereafter. The catheters were flushed daily and filled with sterile saline containing 1,000 U/ml heparin and 100,000 U/ml penicillin G.

Hemodynamic measurements. Arterial and central venous pressures were measured with strain gauge transducers (model P23Db; Gould-Statham, Oxnard, CA); zero pressure reference was taken at heart level. Heart rate was measured using a cardiotachometer (Sensormedics, Anaheim, CA) that was triggered by the pulsatile arterial pressure signal. The flow signal from the aortic flow probe was transduced with an electromagnetic sinewave flowmeter (model BL-610; Biotronex, Kensington, MD). Zero flow baseline was taken as flow in the aorta at end-diastole (15), and was monitored with an oscilloscope. The pressure and flow signals were amplified and the mean signals were recorded through low-pass filters with a time constant of 1.2 s. All variables were recorded on a polygraph (model R-611; Sensormedics). Total peripheral resistance was calculated as the quotient of arterial driving pressure (arterial minus central venous pressure) and cardiac output.

Experimental protocol. Experiments began 10–12 d after surgery. Each dog was studied in the conscious state while lying at rest on its right side. Systemic vascular autoregulatory capacity was evaluated using a conventional method for controlling arterial pressure with a gravity reservoir while measuring cardiac output (13, 14, 16–18), that we have adapted for use in conscious dogs (2, 12). The pressure control system consisted of a siliconized glass reservoir bottle (10 cm diam) that was connected to a 250-cm length of tubing (¼ in. i.d. × ⅜ in. o.d.). The top of the reservoir was open to the atmosphere. The sterilized reservoir bottle and tubing system was filled with 3 ml/kg of sterile saline, and then connected to the left common carotid artery catheter after intravenous administration of 400 U/kg heparin to the animal. With this gravity reservoir system, mean arterial blood pressure could be controlled at any value less than the animal's prevailing pressure by lowering the bottle.

To obtain baseline hemodynamic measurements before initiating reservoir bottle control of arterial pressure, the bottle was set at a height equivalent to a pressure greater than the animal's control arterial pressure, causing saline to descend in the tubing to a height dictated by the prevailing arterial pressure. Quiet conditions were established in the laboratory and 10–15 min of stable recordings were obtained for all variables.

After the stabilization period, acute vasoconstrictor-induced hypertension was produced as previously described (2). An intravenous infusion of angiotensin II (Bachem Co., Torrance, CA), arginine vasopressin (Pitressin; Parke-Davis Co., Morris Plains, NJ), or norepinephrine (Levophed; Winthrop-Breon, New York, NY) was started using a variable speed syringe-drive pump, and the rate of infusion was adjusted over a 10–20-min period until arterial pressure was increased by ~ 50% above control. Then, while maintaining the rate of infusion of the vasoconstrictor constant, arterial pressure was controlled at a hypertensive pressure by lowering the reservoir bottle to a height equivalent to a pressure a few millimeters of mercury below the prevailing hypertensive pressure so that a small volume of blood entered the reservoir. This state of controlled hypertension was maintained for 15 min, and steady-state hemodynamic measurements were made during the last 2–3 min of this hypertensive period. After recording the volume of blood in the reservoir bottle, and while continuing the same rate of infusion of the pressor agent, arterial pressure was decreased to the animal's normotensive control value by lowering the height of the reservoir bottle. This state of controlled normotension was maintained for 15 min, and steady-state hemodynamic measurements were obtained during the last 2–3 min of this period. After recording the reservoir volume, the infusion of the pressor agent was stopped, and the reservoir bottle was raised to return the animal's shed blood. 20–45 min was allowed for the cardiovascular variables to return to their initial, control values. The experiment was then repeated using the same drug. Usually, at least 2 d of study were obtained with each drug in each dog. The order of administration of the three pressor agents was randomized, and the studies were performed every other day (i.e., 48 h intervened between experiments).

Analysis of data. Repeated measures were averaged so that each dog was represented only once for each drug studied. Paired *t* tests were used to analyze for possible differences in hemodynamic variables between (*a*) baseline values before and after agonist infusion, and (*b*) reservoir bottle control of arterial pressure at hypertensive vs. normotensive values during the infusion of the vasoconstrictor agents. Differences were considered significant if the computed probability was ≤ 0.05.

The efficiency of systemic vascular autoregulation was calculated as the closed-loop gain (Gc) of the cardiac output control system (2, 12), according to the following equation: $Gc = 1 - \{[(Q_H - Q_N)/Q_N]/[(P_H - P_N)/P_N]\}$, where Q_N and P_N are the cardiac output and arterial driving pressure, respectively, when arterial pressure was controlled at the animal's normotensive value, and Q_H and P_H are the cardiac output and arterial driving pressure during controlled hypertension. Gc values greater than zero indicate net autoregulatory behavior, with perfect autoregulation denoted by a Gc equal to one. An isoresistance system in which cardiac output changes proportionally with changes in perfusion pressure is characterized by a Gc value of zero. Negative Gc values are indicative of a non-autoregulating system in which an imposed increase in arterial pressure is accompanied by a decrease in total peripheral resistance due to active vasodilation or passive distension of the vessels. The Gc values were calculated for each pair of measurements during controlled hypertension and controlled normotension. The Gc values from repeated measures were averaged in each dog. A *t* test was performed to determine if the Gc values were different from zero.

Results

Table I summarizes the baseline hemodynamic data before (control) and after administration of the three vasoconstrictor agents. All three groups had comparable control baseline values. The average doses of agonists required to increase mean arterial pressure by ~ 50% were 11.8±1.1 ng/min per kg for angiotensin II, 24.5±3.7 ng/min per kg for arginine vasopressin, and 348.3±49.0 ng/min per kg for norepinephrine. All three agents increased arterial pressure by increasing total peripheral resistance. Cardiac output was not significantly altered by angiotensin II or norepinephrine, but was decreased by vasopressin. Heart rate was decreased by angiotensin II and vasopressin, but not by norepinephrine. All three drugs caused central venous pressure to increase.

While maintaining a constant infusion of the vasoconstrictor agent, mean arterial pressure was then controlled with a gravity reservoir at hypertensive or normotensive values. The average values of mean arterial pressure, central venous pressure, heart rate, cardiac output, total peripheral resistance, and reservoir blood volume during controlled hypertension and controlled normotension are summarized in Fig. 1. Lowering mean arterial pressure to the animal's normotensive value during infusion of all three vasoconstrictor agents caused central venous pressure to decrease and heart rate to increase. During angiotensin II and norepinephrine administration, cardiac output decreased proportionally with the decrease in arterial driving pressure, such that total peripheral resistance was not different between the states of controlled hypertension and controlled normotension with these two drugs. With vasopressin infusion, however, cardiac output was maintained relatively constant in the face of changes in perfusion pressure, and total peripheral resistance was significantly greater during controlled hypertension than when the vasculature was protected from hypertension by controlling arterial pressure at the animal's normotensive pressure. Thus a portion of the increase in total peripheral resistance during vasopressin administration is attributed to pressure-mediated vasoconstriction (i.e., autoregulation). As shown in the bottom panel of Fig. 1, a significant increase in reservoir bottle volume was required to maintain the state of controlled normotension with all three drugs studied.

Table I. Effect of Vasoconstrictor Agents on Baseline Hemodynamic Variables

	MAP	CVP	CO	TPR	HR
	mmHg		*liters/min*	*mmHg·l⁻¹·min*	*bpm*
ANG II group (n = 8)					
Control	94±3	2±1	2.2±0.4	52±1	70±5
After ANG II	141±5*	4±1*	1.8±0.3	101±2*	64±5*
AVP Group (n = 9)					
Control	93±3	2±0.5	2.1±0.4	59±1	70±3
After AVP	139±5*	5±1*	1.3±0.2*	148±3*	50±4*
NE Group (n = 7)					
Control	93±3	1±1	2.1±0.5	60±1	65±4
After NE	135±4*	5±1*	2.2±0.6	80±2*	68±4

Values are means±SE. MAP, mean arterial pressure; CVP, central venous pressure; CO, cardiac output; TPR, total peripheral resistance; HR, heart rate; ANG II, angiotensin II; AVP, vasopressin; NE, norepinephrine; * $P < 0.05$ vs. control.

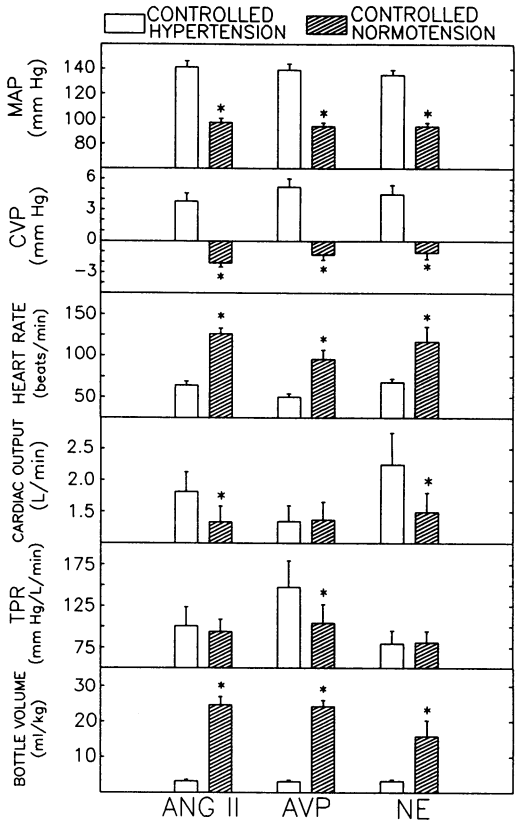

Figure 1. Hemodynamic variables recorded during infusion of equipressor doses of angiotensin II (ANG II), arginine vasopressin (AVP), or norepinephrine (NE), while mean arterial blood pressure (MAP) was controlled with a gravity reservoir bottle at either a hypertensive or a normotensive value. During AVP administration, cardiac output (CO) was maintained relatively constant and total peripheral resistance was significantly greater during controlled hypertension than during controlled normotension. Data are mean values±SE. *$P < 0.05$ between controlled hypertension and controlled normotension. CVP, central venous pressure.

The percent changes in steady-state arterial driving pressure and cardiac output between controlled normotension and controlled hypertension during the constant infusion of angiotensin II, vasopressin, and norepinephrine are shown in Fig. 2. The pressure-flow changes are compared with that of an isoresistance system, in which driving pressure and flow change proportionally, and to a perfectly autoregulating system, in which flow is independent of changes in perfusion pressure. The average pressure-flow relationship for vasopressin lies to the right of that for an isoresistance system. Thus vasopressin-mediated increases in arterial pressure are accompanied by an increase in total peripheral resistance, with resultant systemic vascular autoregulation. Systemic vascular autoregulation was not found during angiotensin II or norepinephrine infusion.

The efficiency of systemic vascular autoregulation, calculated as the closed-loop gain of the cardiac output control system, is shown in Fig. 3. The gains for angiotensin II (Gc = −0.16±0.90) and norepinephrine (Gc = −0.40±0.30) were not significantly different from a gain of zero, indicating that there was no significant steady-state whole body autoregulation during administration of these two drugs. Significant systemic vascular autoregulation occurred with vasopressin infusion, however, as evidenced by the positive Gc values that

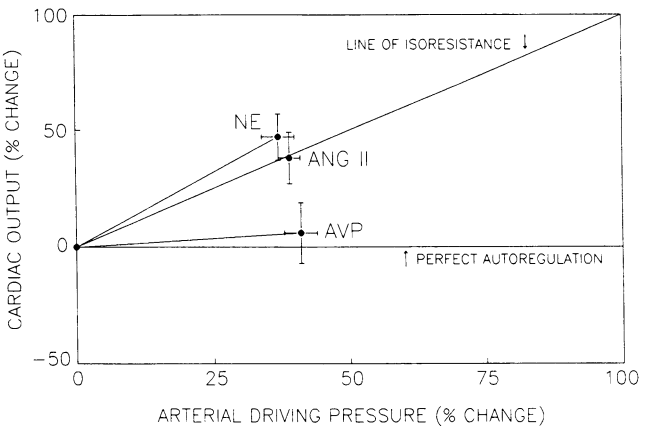

Figure 2. Percent changes in steady-state arterial driving pressure and cardiac output between controlled normotension and controlled hypertension during the infusion of pressor doses of norepinephrine (NE), angiotensin II (ANG II), and vasopressin (AVP). Systemic vascular autoregulation was found with AVP only. During ANG II and NE administration, the systemic circulation behaved as an isoresistance system.

averaged 0.77±0.33. The Gc also represents the fraction of the increase in arterial driving pressure that is due to autoregulation (2). Thus, on the average, 77% of the increase in arterial driving pressure produced by arginine vasopressin is attributed to autoregulation, and the remaining 23% is attributed to the primary vasoconstrictor effects of vasopressin.

Discussion

The major goal of this study was to quantitate the contribution of systemic vascular autoregulation to the increases in total peripheral resistance and arterial pressure produced by the intravenous infusion of pressor doses of angiotensin II, arginine vasopressin, and norepinephrine, three agents with putative roles in the development of hypertension. Systemic vascular autoregulation refers to the maintenance of a relatively constant cardiac output during changes in mean arterial driving pressure. Thus systemic vascular autoregulation is characterized by an increase in total peripheral resistance when arterial pressure is increased. For total peripheral resistance to increase in response to an increase in systemic arterial pressure, local autoregulatory vasoconstrictor mechanisms must be of sufficient magnitude to overcome both reflex vasodilation and the passive increase in vascular caliber that occurs because of the elastic properties of blood vessels (2, 16). Previous studies in conscious animals have demonstrated that systemic vascular autoregulation has the capacity to be manifest during hypertension when competition from reflex alterations are blocked (2, 11). In the present study, we evaluated systemic vascular autoregulation in conscious dogs with intact reflexes in an effort to determine the physiologic significance of autoregulation; i.e., to determine if systemic vascular autoregulation is powerful enough to be manifest in an intact animal as part of the integrated cardiovascular response to a pressor stimulus.

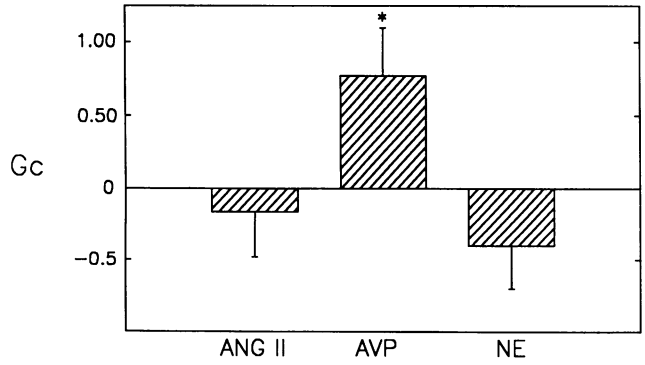

Figure 3. Average closed-loop gain of systemic vascular autoregulation (Gc) during infusion of angiotensin II (ANG II), vasopressin (AVP), or norepinephrine (NE). Significant systemic vascular autoregulation occurred only during the administration of AVP. (*$P < 0.05$ vs. Gc = 0.)

It seems reasonable to assume that the contribution from autoregulation will depend on both the degree to which pressure increases and on the efficiency of autoregulation. We used equipressor doses of the agonists so that differences in the Gc values would reflect differences in the efficiency of autoregulation between the three drugs. The values of total peripheral resistance during the administration of vasopressin were greater when arterial pressure was controlled at hypertensive than at normotensive values. These findings indicate that a pressure-mediated increase in total peripheral resistance occurred in response to the increase in blood pressure, with resultant amplification of the direct constrictor effects of vasopressin. The extent to which autoregulation amplified the direct effects of vasopressin was substantial; the autoregulatory gain averaged 0.77, indicating that approximately three-fourths of the pressor response to vasopressin was attributed to autoregulation.

The marked autoregulation that occurred with vasopressin infusion is contrary to what would be expected based on data regarding vasopressin and baroreflex interactions. Sensitization of the baroreceptors by vasopressin (19) should result in greater baroreflex-mediated vasodilation, and thus greater opposition to autoregulatory vasoconstriction, than that expected with equipressor doses of either norepinephrine or angiotensin II. Instead, only vasopressin was associated with a higher total peripheral resistance during controlled hypertension compared to controlled normotension. Furthermore, the efficiency of autoregulation during vasopressin infusion in dogs with intact baroreceptor reflexes is the same magnitude as that previously found in ganglionic blocked dogs (2). In their theoretical modeling analysis of vasopressin's vascular and reflex effects, Cowley and Barber (20) also noted that some mechanism apparently exists whereby the reflex buffering of arterial resistance during vasopressin infusion is attenuated so that total peripheral resistance rises to a higher level than would be predicted if the baroreceptors were attempting to offset the rise in resistance. It is possible that the mechanism of attenuation of this proposed baroreflex buffering may be related to vasopressin's apparent enhancement of the gain of systemic vascular autoregulation.

Another property of vasopressin is its potent constrictor effects in skeletal muscle and skin (21, 22). Autoregulation of blood flow is absent or weak in resting skeletal muscle (23), and the cutaneous circulation is generally described as a passive vascular bed (24). Because systemic vascular autoregulation results from the net autoregulatory contribution of all of the regional vascular beds, redistribution of blood flow from

non-autoregulating to autoregulating organs may contribute to the magnitude of autoregulation observed with vasopressin.

A number of studies have shown that the effectiveness of autoregulation is enhanced when tissues operate near their nutritive limit (12, 14, 23, 25); only vasopressin caused a significant decrease in baseline cardiac output (Table I), which would bring tissues closer to this limit. This may be another reason for finding a greater contribution of autoregulation in the hemodynamic response to vasopressin compared to angiotensin II or norepinephrine.

No significant autoregulatory component of the increase in total peripheral resistance was found during the infusion of angiotensin II or norepinephrine in dogs with intact reflexes. In our previous study in ganglionic blocked dogs, autoregulation accounted for a major portion of the pressor response to both angiotensin II (34%) and norepinephrine (62%) (2). Thus the absence of autoregulation during infusion of angiotensin II or norepinephrine in the present study does not indicate the absence of pressure-mediated contraction of vascular smooth muscle; rather, it indicates that net vasoconstriction did not predominate over the passive and reflex vasodilatory responses elicited by pressor doses of these two drugs.

Studies by Meininger and colleagues have demonstrated significant autoregulation in the intestinal and hindquarters circulations during acute infusions of angiotensin II and phenylephrine (5) and during acute renovascular hypertension (3, 4) in anesthetized rats. In those studies, the regional circulations were protected at lower pressures while the systemic arterial pressure remained at hypertensive levels. Thus arterial baroreceptor reflexes would not be competing with local autoregulatory behavior in their experiments. The results of the present study suggest that even if autoregulation is manifest in some vascular beds during angiotensin II or norepinephrine infusion, the sum of the regional autoregulatory contributions was not sufficient to result in total systemic vascular autoregulation.

In most tissues and organs, autoregulatory vascular adjustments are typically completed over a 1–3-min time course. Previous studies have emphasized, however, that long-term observation of flow changes during changes in perfusion pressure are necessary for whole body autoregulation to become evident (12, 13). We did not evaluate the transient flow responses to changes in perfusion pressure because we already knew that the capacity for steady-state autoregulation existed for all three drugs, and the purpose of this study was to determine if this autoregulatory capacity was powerful enough to compete with intrinsic reflex responses. In addition, the initial events were highly variable both within and between dogs and thus revealed little interpretable information. 15 min was adequate time for steady-state systemic vascular autoregulation to be manifest with all three drugs in ganglionic blocked dogs (2), and for vasopressin in dogs with intact reflexes. In contrast, autoregulation did not occur within 15 min during angiotensin II or norepinephrine infusion in dogs with intact reflexes, though it is possible that a longer period of time may be necessary for systemic vascular autoregulation to be manifest under these conditions.

In conclusion, our data indicate that when blood pressure is elevated by vasopressin, a major portion of the increased pressure is due to an autoregulatory-mediated increase in total peripheral resistance. These findings demonstrate the power of autoregulation as a physiological property and support the contention that there are important interactions between local autoregulatory and neurohumoral pressure regulating mechanisms. In addition, the results have important implications for the role of autoregulation in the genesis or maintenance of any type of hypertension that may involve vasopressin, such as the deoxycorticosterone acetate (DOCA)-salt model (10, 26–28) and experimental renovascular hypertension (29).

Acknowledgments

The authors thank Marianne Miller for her expert secretarial assistance.

This work was supported by National Institutes of Health Research grant HL-32899 and grants from the American Heart Association, Ohio Affiliate, Columbus, OH. P. M. Stein and K. A. Kostrzewski were supported by National Institutes of Health Hypertension Training Program grant HL-07357. S. L. Britton is the recipient of a Research Career Development Award (HL-01515) from the National Institutes of Health.

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