Effect of Intravertebral Angiotensin II on Cardiac Output and Its Distribution in Conscious Dogs

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Intravertebral infusion of angiotensin II (Ang II) increases mean arterial pressure (MAP), but the contribution of cardiac output (CO) and total peripheral resistance (TPR) to this increase is unclear. In the present study, the effects of Ang II infusion on CO and regional blood flow was determined by the microsphere technique in eight conscious, chronically catheterized dogs. Ang II was infused into both vertebral arteries at 0.33 and 1.0 ng/kg/min, and intravenously at 0.66, 2.0, and 5.0 ng/kg/min. Intravertebral infusion of Ang II at 0.33 ng/kg/min increased MAP by increasing CO without changing TPR or peripheral plasma Ang II concentration. MAP also was increased with intravertebral infusion of Ang II at 1.0 ng/kg/min, but this resulted from small increases in both CO and TPR. In contrast, intravenous infusion of Ang II at 2.0 and 5.0 ng/kg/min increased MAP by increasing TPR in association with a decrease in CO. The increase in CO with intravertebral infusion of Ang II at 0.33 ng/kg/min was distributed primarily to the muscles, kidneys, heart, and brain. Intravenous infusion of Ang II at 5.0 ng/kg/min and, to a lesser extent, 2.0 ng/kg/min decreased blood flow to the skin, splanchnic region, and kidneys. These data indicate that the increase in MAP produced by a low intravertebral dose of Ang II results from an increase in CO, which is distributed primarily to the muscle, kidney, heart, and brain. In contrast, the increase in MAP produced by a higher intravertebral dose of Ang II results from increases in CO and TPR. This latter action is apparently due to a peripheral action of Ang II to increase resistance in the skin, splanchnic, and renal circulations. (Circulation Research 1988;63:702–711)

Angiotensin II (Ang II) is a potent pressor peptide that plays an important role in the regulation of arterial pressure. Ang II increases blood pressure by a variety of mechanisms including direct vasoconstriction, stimulation of aldosterone secretion, stimulation of renal sodium and water reabsorption, facilitation of norepinephrine release and inhibition of its reuptake at sympathetic synapses, and several actions on the central nervous system. A central action of Ang II to increase arterial pressure has been demonstrated by intravertebral, intracarotid and intraventricular administration of the peptide in a variety of species including the dog, cat, rabbit, rat, and human. The most thoroughly studied of these is the pressor response to intravertebral infusion in the dog. It has been established that this response is mediated via receptors in the area postrema, a circumventricular organ in the medulla oblongata. There is also evidence that this central effect constitutes a significant component of the overall pressor response to systemically administered Ang II. For example, early studies in dogs indicated that 35–50% of the total pressor action of Ang II is centrally mediated. More recent studies by Fuji and Vatner in conscious, sinoaortic denervated dogs with β-adrenergic and ganglionic blockade are consistent with this.

Despite the obvious physiological significance these data suggest for the intravertebral component of the Ang II pressor response, the contributions of cardiac output (CO) and total peripheral resistance (TPR) in sustaining the elevated levels of arterial pressure are unclear. Scroop and Lowe concluded that intravertebral infusion of Ang II increases CO via withdrawal of parasympathetic tone to the heart. On the other hand, Ferrario et al concluded that intravertebral Ang II elevates TPR by increasing sympathetic activity. Furthermore, intravertebral Ang II may have different effects on resistance and blood flow in different vascular beds. For example,
recordings of sympathetic nerve activity have shown that splanchnic and cardiac nerve activity are either increased or unchanged by intravertebral Ang II while renal nerve activity is decreased.17-18 The present studies were designed to further investigate the mechanisms by which intravertebral Ang II increases arterial blood pressure and influences blood flow to different vascular beds. This was accomplished by determining CO and its regional distribution in response to intravertebral infusion of Ang II in healthy, chronically instrumented conscious dogs.

Materials and Methods

Experiments were performed in eight mongrel (seven female, one male) dogs with an average body weight of 21 ± 1.1 kg. The dogs were housed separately in a large vivarium where they were allowed free access to water and fed at 1:00 PM daily a diet of Purina dry chow containing approximately 80 meq Na.

Animal Preparation

Two separate, sterile surgical procedures were performed under sodium pentobarbital anesthesia. During the first procedure, indwelling catheters were placed in the low abdominal aorta and vena cava via the femoral vessels, and a left thoracotomy was performed for the placement of right and left atrial catheters. Following 7–10 days of recovery, a small nonocclusive catheter was placed in each vertebral artery through an incision along the inferior margin of the sternocleidomastoid muscle at the base of the neck. The vertebral catheters were formed of 0.04 i.d. by 0.07 o.d. Tygon Microbore Tubing (Norton Plastics, Akron, Ohio) and implanted according to the method of Herd and Barger.19 All catheters were tunneled subcutaneously to the suprascapular region. The dogs received 600,000 units of penicillin G with 0.75 g of dihydrostreptomycin at surgery and once daily for the following 5 days. The catheters were protected in the pocket of a nylon jacket worn by the dog (Alice King Chatham Medical Arts, Los Angeles, California) and were flushed with saline and filled with heparin (1,000 IU/ml), after withdrawal of the deadspace, every second day to maintain patency.

A second group of four dogs, with an average body weight of 24.1 ±0.4 kg, was prepared in a similar manner except that during the left thoracotomy an electromagnetic flow probe, lined with Dacron, was placed around the ascending aorta. At conclusion of the studies, the ascending aorta with attached flow probe was removed. The probe
was then calibrated against isotonic saline in a reservoir perfusion system.

**Microsphere Flow Methods**

Blood flow determinations were performed with 15-μm plastic microspheres according to the procedures described by Heymann et al. 20 For each flow determination, approximately one million spheres labeled with either 51Cr, 54Mn, 57Co, 59Zn, 85Sr, 95Nb, 113Sn, 114In, or 153Gd were placed aseptically into specially designed injection vials connected to the left atrial catheter. The microspheres were injected by flushing the injection vial with 10 ml sterile saline over a 15-20-second period. CO was simultaneously determined by diverting the arterial catheter from the pressure transducer to a small roller pump and, beginning at the start of the microsphere injection, collecting arterial blood into preweighed counting vials. Blood collection continued for four 30-second periods at a flow rate of 8.9 ± 1.4 ml/min. The total counts injected were calculated from preinjection and postinjection counts of the injection vial, and CO was calculated as the product of the pump flow rate and the total counts injected divided by the counts recovered in the blood. 20

**Experimental Protocol**

On two successive experimental days the dogs were brought to the laboratory where they stood in a nylon sling (Alice King Chatham Medical Arts, Los Angeles, California). Blood pressure transducers (Micro Switch PC136, Freeport, Illinois) were mounted on the sling frame and positioned in the horizontal plane of the tricuspid valve. 21 Mean arterial (MAP), mean left and mean right atrial pressures, and heart rate (HR) were continuously recorded on a Model 7 Grass recorder (Quincy, Massachusetts).

On each of the two experimental days, an isotonic saline control infusion and two or three infusions of [Ile5]Ang II (Peninsula Labs, Belmont, California; >98% purity) dissolved in isotonic saline were made. Ang II was infused into both vertebral arteries at doses of 0.33 and 1.0 ng/kg/min per artery. The intravenous Ang II doses were 0.66, 2.0, and 5.0 ng/kg/min. Since the intravertebral infusions were delivered bilaterally, the comparative intravenous Ang II doses were chosen as the sum of the intravertebral doses and by assumption of the worst case of no brain clearance, that is, 0.66 and 2.0 ng/kg/min. All infusions were delivered at a total rate of 0.5 ml/min (i.e., 0.25 ml/min per vertebral artery). The order in which these eight treatments were administered and the application of the different microspheres were randomized.

Each infusion was begun only at basal blood pressure and heart rate and was generally continued

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**FIGURE 2.** Effect of intravertebral saline (open bars), intravertebral angiotensin II (solid bars), and intravenous angiotensin II (hatched bars) on plasma angiotensin II concentration (pAngII), cardiac output (CO) determined electromagnetically, and mean arterial pressure (MAP). Intravertebral doses of 0.33 and 1.0 ng/kg/min were delivered bilaterally, so that the intravenous doses were actually 0.66 and 2.0 ng/kg/min. *Significant change from saline control infusion (n=4).
for 10–15 minutes, but was always continued until a steady state was achieved. Then the microsphere injection protocol described above was performed to determine cardiac output and blood flow to the different vascular beds. Data was accepted only when blood pressure and heart rate were equal immediately before and after the microsphere injections.

**Compartmental Flow Analysis**

On the day after the experiments were completed, the dogs were killed by rapid intravenous injection of sodium pentobarbital. The ears, nose, feet, tail, fat, omentum, mesentery, vertebral column, and great vessels of the trunk were not sampled. Muscle and bone were sampled unilaterally from the right side, opposite the left thoracotomy and left femoral catheters. Otherwise, all tissues were sampled in total. For structures that were sampled unilaterally, weights and flows are presented as twice that actually measured in order to account for total flow distribution.

The adrenals, thyroid, and brain were placed in 10% formalin for several days before being cut into small pieces and packed into counting vials. Other tissues were carbonized in a vented oven whose temperature was increased over 4 days from 100°C to 300°C and maintained at this level for an additional 4 days. After cooling, the carbonized tissue was ground to powder and packed into counting vials. Blood samples, wet tissue, and carbon were then counted with a Tracor well detector with a sodium iodide crystal and a 1024 channel pulse height analyzer. These procedures are described more completely elsewhere. Regional vascular resistances were calculated by dividing the pressure gradient (arterial minus right atrial mean pressures) by the regional blood flow. Peripheral plasma Ang II concentration (pAng II) was measured by radioimmunoassay according to methods previously described from this laboratory.

**Statistical Analysis**

All results are presented as mean±SEM. Statistical significance of responses to the treatments was assessed using one-way analysis of variance with repeated measures and followed, when \( p < 0.05 \), with a Student-Newman-Keuls test.

**Results**

**Systemic Hemodynamics**

Figure 1 illustrates the responses of MAP, HR, CO (determined by the microsphere method), and TPR to intravertebral and intravenous infusion of...
Angiotensin II. Intravertebral infusion of Ang II at 0.33 ng/kg/min increased MAP from 102.6 ± 1.2 to 113.2 ± 2.2 mm Hg (p < 0.001). HR increased from 88 ± 5 to 94 ± 6 beats/min (p = 0.001) and CO increased from 2,936 ± 154 to 3,604 ± 309 ml/min (p = 0.002). TPR tended to decrease although no statistically significant difference from the control level of 35.7 ± 2.1 cmH₂O/l/min occurred. Intravenous infusion of the same dose of Ang II had no effect on MAP, HR, CO, or TPR.

Intravertebral infusion of Ang II at 1.0 ng/kg/min increased MAP from 109.4 ± 1.4 to 117.6 ± 2.5 mm Hg (p < 0.001) and HR from 87 ± 4 to 96 ± 7 beats/min (p = 0.003). Intravenous infusion of the same dose of Ang II increased MAP from 109.4 ± 1.4 to 107.9 ± 2.1 mm Hg (p < 0.001) but did not change HR (Figure 1). No statistically significant changes were observed in either CO or TPR during intravertebral or intravenous infusion of Ang II. However, in six of the eight dogs, TPR was increased above control levels by both intravertebral and intravenous infusions, while the CO responses were inconclusive. Neither left nor right atrial pressures were altered by intravertebral or intravenous infusion of Ang II at either the 0.33 or 1.0 ng/kg/min dose.

The responses to intravenous infusion of Ang II at 5.0 ng/kg/min are also summarized in Figure 1. There was an increase in TPR from 33.3 ± 2.9 to 45.2 ± 2.7 mm Hg/l/min (p < 0.001), a decrease in CO from 3,150 ± 213 to 2,688 ± 123 ml/min (p < 0.001) but no change in HR. As a result of these changes, MAP increased from 101.6 ± 1.8 to 121.6 ± 2.6 mm Hg (p < 0.001). Left atrial pressure increased from 3.7 ± 0.6 to 5.6 ± 0.5 cm Hg (p < 0.001) and right atrial pressure increased from 0.4 ± 0.5 to 1.5 ± 0.6 cm Hg (p = 0.025).

Since the CO results presented above were based on microsphere data alone, an additional group of dogs instrumented with ascending aortic electromagnetic flow probes was studied under similar conditions. The results are summarized in Figure 2. Increases in MAP, similar to those observed in the microsphere studies, were produced by intravertebral and intravenous infusion of Ang II. Qualitatively, CO also responded in the same fashion. However, control CO determined electromagnetically averaged 2,264 ± 95 ml/min compared with 2,980 ± 88 ml/min determined by the microsphere method. CO increased by 264 ± 71 (p = 0.001) and 146 ± 68 ml/min (p > 0.05) during intravenous infusion of Ang II at 0.33 and 1.0 ng/kg/min, respectively; and decreased by 429 ± 46 ml/min (p < 0.001) during intravenous infusion of Ang II at 5.0 ng/kg/min.

No changes in pAng II occurred with either intravertebral or intravenous infusion of Ang II at 0.33 ng/kg/min (Figure 2). However, with intravenous infusion of Ang II at 1.0 ng/kg/min, pAng II increased from 15.1 ± 2.6 to 30.7 ± 2.3 pg/ml (p = 0.03). Intravertebral infusion of Ang II at 1.0 ng/kg/min increased pAng II from 15.1 ± 2.6 to 22.7 ± 5.0 pg/ml (p = 0.1).

Regional Blood Flow Distribution

Control values for tissue weights and blood flows are presented in Table 1. Regional brain blood flows are presented for the brain stem, midbrain, cerebellum, and cortex. The brain stem and midbrain categories include all structures from the medulla oblongata to the hypothalamus divided, respectively, along the rostral aspect of the pons. The heart was divided into left ventricular free wall (LVFW), right ventricular free wall (RVFW), septum, and atria.

Skeletal muscle was sampled in groups that included muscles of the back, trunk, pelvis and pelvic limb, thoracic limb, neck, and head. Divided in this manner, no significant differences were observed among blood flows when normalized for tissue weight for the different muscle groups. Therefore, only total flow is presented for the skeletal muscle in Table 1.

Although Table 1 presents only a total value for bone flow, this can be divided into high and low flow groups. The high flow (ml/min/100 g) group includes the femur (18.3 ± 3.1), pelvis (20.4 ± 3.5), scapula (16.2 ± 2.1), humerus (22.0 ± 3.5), ribs...
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Figure 3. Changes in regional blood flow and resistance relative to the saline control during intravertebral (solid bars) and intravenous (hatched bars) infusion of angiotensin II at 0.33 ng/kg/min. Intravertebral infusions were delivered bilaterally, so that the intravenous dose was actually 0.66 ng/kg/min.

*Significant change from saline control infusion (n=8).

(15.7 ± 1.5), and sternum (21.3 ± 3.6). Bones with low flow (ml/min/100 g) include the radius/ulna (5.2 ± 1.6), tibia/fibula (6.3 ± 2.1), mandible (3.6 ± 0.8), and the skull (8.2 ± 0.8).

Table 1 also lists the percent of CO distributed to the major organ groups in the control period. For this calculation, the actual organ blood flows were divided by the average of the values obtained for cardiac output by the microsphere and electromagnetic methods. No value is given for bone since the blood flow to the vertebral column was not measured.

Table 2 lists the absolute changes in tissue blood flow that occurred in response to Ang II infusion. Since no statistically significant changes in flow were observed in any tissue during intravenous infusion of Ang II at 0.66 or 2.0 ng/kg/min, these data are not presented. Blood flows for organs and organ systems receiving sizeable portions of CO are also presented in Figures 3–5. Splanchnic flow presented in these figures includes flows for the gastrointestinal tract, pancreas, spleen, and liver.

Figure 3 illustrates the changes in regional blood flow and resistance that occurred in response to infusion of Ang II at 0.33 ng/kg/min intravertebral and 0.66 ng/kg/min intravenous. With intravertebral infusion of Ang II, CO increased by 668 ± 198 ml/min (Figure 1). Most of this increase in flow (532 ± 60 ml/min) could be accounted for by increases in flow to the skeletal muscle, kidneys, heart and brain. Resistance in these regions decreased 10–17%, but in no case was this change statistically significant. No changes in regional blood flow or resistance were observed with intravenous infusion of Ang II at 0.66 ng/kg/min.

No statistically significant changes in regional blood flow were observed with intravertebral infusion of Ang II at 1.0 ng/kg/min or intravenous infusion of 2.0 ng/kg/min (Figure 4). Intravertebral infusion of Ang II at 1.0 ng/kg/min significantly increased brain resistance and tended to increase resistance in all regions except skeletal muscle. No significant changes in resistance were observed with intravenous infusion of Ang II at 2.0 ng/kg/min. The similarity between the responses to intravertebral and intravenous infusions of Ang II should be noted.

Intravenous infusion of Ang II at 5.0 ng/kg/min decreased CO by 462 ± 103 ml/min (Figure 1) in association with a reduction in blood flow to the
FIGURE 4. Changes in regional blood flow and resistance relative to saline control during intravertebral (solid bars) and intravenous (hatched bars) infusion of angiotensin II at 1.0 ng/kg/min. Intravertebral infusions were delivered bilaterally, so that the intravenous dose was actually 2.0 ng/kg/min. *Significant change from saline control infusion (n=8).

Discussion

The present results confirm that infusion of Ang II into the vertebral arteries of conscious dogs causes an increase in arterial pressure. The results also demonstrate that the contribution of changes in CO and TPR to the pressor action of intravertebral Ang II is markedly different depending on the dose of Ang II that is infused.

Intravertebral infusions of Ang II were intended to increase Ang II concentration only at those structures perfused by the vertebral arteries. These include the area postrema, which is the probable receptor site. With intravertebral infusion of Ang II at 0.33 ng/kg/min into each artery, MAP was increased by an increase in CO in the absence of a statistically significant change in TPR. With intravertebral infusion of Ang II at 1.0 ng/kg/min, the pressor response was greater. This increase in CO was less than that produced by 0.33 ng/kg/min and, in fact, neither the increase in CO or TPR was statistically significant. A higher level (5 ng/kg/min) of Ang II was infused intravenously so that comparison could be made to a situation where Ang II concentration was simultaneously increased in all areas of the circulation. The pressor response to this infusion resulted from an increase in TPR in association with a reduction in CO. The specificity of these responses will be examined below.

The data demonstrate that intravertebral infusion of Ang II at 0.33 ng/kg/min produced a selective increase in Ang II concentration in the circulation of the vertebral arteries since neither intravertebral nor intravenous infusion of this dose altered pAng II, and intravenous infusion of this dose of Ang II produced no changes in systemic hemodynamics. With intravenous infusion of Ang II at 2.0 ng/kg/min, pAng II was increased by 15.6 pg/ml. With intravertebral infusion at the same rate, pAng II increased by an average of 8 pg/ml. This latter increase is one half of that produced by intravenous infusion and confirms the finding of Reid et al that the brain clears 50% of infused Ang II. As discussed
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below, the increase in TPR with intravertebral infusion of the higher dose of Ang II may have resulted from a peripheral action of recirculated Ang II.

Another point that must be considered in relation to the amount of Ang II infused is the concentration actually delivered to the receptor site. Reid et al.\textsuperscript{23} made electromagnetic measurements of carotid and vertebral blood flow to calculate the local concentrations resulting from intravertebral Ang II. CO was not measured in those studies, but by using those blood flows and the average CO from the present data, total blood flow to the head would represent 15–16\% of cardiac output. However, when the present microsphere flow distributions to the vascular beds in the head are summed, the fraction of CO supplying structures in the head is estimated to be approximately 5\%. Considering this threefold difference in flow, and assuming a hematocrit of 35\% with distribution of Ang II only in the plasma, a range of possible local concentrations of Ang II can be predicted. With intravertebral Ang II at 0.33 ng/kg/min, the local concentration would be between 170 and 510 pg/ml. With intravertebral infusion at 1.0 ng/kg/min, the range would be from 520 to 1,560 pg/ml. These predictions also assume that only vertebral blood perfuses the area postrema. If there is mixed perfusion by vertebral and carotid blood the local concentrations of Ang II produced by the infusions would be less. Mixed perfusion of the medulla oblongata in the dog was reported by Baldwin and Bell.\textsuperscript{26} However, recent studies in this laboratory using microsphere injections into the vertebral and carotid arteries suggest that the vertebral arteries are almost entirely responsible for perfusion of the medulla oblongata.\textsuperscript{25}

Data from this laboratory also suggest that the local concentration of Ang II resulting from the 0.33 ng/kg/min intravertebral Ang II dose is at the extreme upper limit of levels achievable under physiological conditions. For example, pAng II levels of approximately 10–20 pg/ml are present in dogs maintained on a 70–80 meq/day sodium diet. With severe sodium restriction, pAng II levels increase to 142 pg/ml.\textsuperscript{27} With nitroprusside-induced hypotension in sodium-depleted dogs, pAng II levels increase to 160–180 pg/ml.\textsuperscript{28} In a study of two kidney, one clip renal hypertension, average pAng II varied between 66 and 147 pg/ml; however, some

\begin{figure}
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\includegraphics[width=0.8\textwidth]{figure5.png}
\caption{Changes in regional blood flow and resistance relative to saline control infusion during intravenous angiotensin II infusion at 5.0 ng/kg/min. *Significant change from saline control infusion (n=8).}
\end{figure}
individual measurements reached 250 pg/ml. Further discussion of pAng II levels in various physiological and pathological states is available in a recent review by Hall. These data demonstrate further that local Ang II levels produced by 1.0 ng/kg/min are entirely supraphysiological in nature. Furthermore, these data suggest that future studies should carefully evaluate the physiological relevance of even the 0.33 ng/kg/min intravertebral Ang II dose.

Differences in infusion rates may account, at least in part, for the controversy concerning the mechanism of the pressor response to intravertebral Ang II. Both Scroop and Lowe and Ferrario et al studied anesthetized dogs, so direct comparison with the present data is difficult. Scroop and Lowe studied the cardiovascular responses to intravertebral infusion of approximately 1 ng/kg/min and concluded that an increase in cardiac output was responsible for the pressor response. In contrast, the doses of Ang II used by Ferrario et al ranged from 1 to 50 ng/kg/min. Those authors concluded that increased TPR was responsible for the elevation in arterial pressure. These differences resemble those observed with doses of 0.33 and 1.0 ng/kg/min in the present study, and suggest that with low doses, the increase in blood pressure is due to increased CO, whereas with higher doses it is also due to increased TPR, possibly resulting from a peripheral action of recirculated Ang II.

The precise mechanisms by which intravertebral Ang II increases CO remain to be determined. Since pAng II was not changed, at least with the lower dose, the response was clearly central in origin. Heart rate was increased by intravertebral Ang II, and this could have contributed to the increase in CO. The increase in HR probably resulted from withdrawal of vagal tone to the heart as suggested by Scroop and Lowe and demonstrated directly in anesthetized dogs by Potter and Reid. Lee et al demonstrated that intravenous Ang II causes a reduction in vagal tone in conscious sheep that is normally antagonized by the arterial baroreceptors. When the Ang II-induced elevation in MAP was antagonized by simultaneous infusion of nitropreside, a dose-dependent tachycardia was observed. The present observation that HR was increased by intravertebral Ang II but was unchanged by intravenous Ang II is consistent with these findings. Presumably, the intravertebral infusions acted to decrease vagal tone, but the larger increase in MAP that occurred with intravenous Ang II apparently caused sufficient baroreceptor stimulation to override this effect on vagal tone.

Changes in HR alone should not have a significant influence on CO in the absence of changes in venous return. Indeed, examination of the current data reveals only a minor contribution to the increase in CO of the increase in HR with intravertebral infusion of 0.33 ng/kg/min Ang II. If constant stroke volume is assumed, the increase in HR can account for only 30% of the increase in CO. A neural effect of intravertebral Ang II to increase cardiac contractility might also be used to explain the increase in CO. This suggests that an increased venous return is a necessary component of the intravertebral Ang II pressor response.

With the lowest intravertebral level of Ang II, the increase in CO was distributed preferentially to the skeletal muscle, kidneys, heart, and brain. Despite significant increases in blood flow in these vascular beds, and in arterial pressure, no statistically significant decreases in regional resistances were detected (Figure 3). In vascular beds where resistance remains constant, flow should increase to the same extent as does the pressure. MAP increased by 10% and flow to the bone (9%), skin (11%), and splanchnic beds (13%) were similarly increased. Flow in the skeletal muscle (70%), kidneys (20%), heart (26%), and brain (30%) was increased to a considerably greater extent, suggesting that Ang II acts centrally to affect autonomic control of resistance in these vascular beds. These effects might be explained by selective withdrawal of sympathetic vasoconstrictor tone or activation of sympathetic cholinergic or purinergic nerves to cause vasodilation.

The pattern of regional blood flow distribution was considerably different with intravertebral infusion of Ang II at 1.0 ng/kg/min (Figure 4). Although the changes are unremarkable when considered alone, several points are evident from inspection of these data. First, the changes in regional flows that resulted from intravertebral infusion of 1.0 ng/kg/min were not different from those produced by intravenous infusion of the same dose. Second, the changes in regional flows and resistances, rather than being comparable to those produced by the lower intravertebral Ang II dose, were similar to those produced by intravenous infusion of 5.0 ng/kg/min Ang II. Finally, the resistance to blood flow in the brain was increased, probably by a direct vasoconstrictor effect. These data, together with the changes in MAP and pAng II described above, strongly suggest that the pressor response to infusion of Ang II into the vertebral circulation at doses equal to or greater than 1.0 ng/kg/min, is partly due to direct effects of recirculated Ang II on the peripheral circulation.

The blood flow responses to intravenous infusion of Ang II at 5.0 ng/kg/min are in general agreement with published reports that intravenous Ang II decreases cardiac output. However, systemic evaluations of the effect of Ang II on regional blood flow distribution in conscious animals are apparently not available. The present data confirm the known direct vasoconstrictor action of Ang II and indicate that the splanchnic, renal, and skin beds are most sensitive to this action.

In summary, the present results confirm that Ang II acts within the circulation of the vertebral arteries of conscious dogs to increase arterial pressure. With a low dose of Ang II (0.33 ng/kg/min), the pressor response results from increases in HR and
CO that are associated with increased blood flow in the vascular beds of the skeletal muscle, kidneys, heart, and brain. TPR is either unchanged or slightly decreased. With intravertebral infusion of Ang II in doses greater than 0.33 ng/kg/min, which would result in supraphysiological local concentrations of Ang II, there is a different pattern of cardiovascular responses that appear to be partly due to peripheral actions of recirculated Ang II.

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References

Key Words: vertebral arteries • angiotensin II • blood pressure • cardiac output • regional blood flow • total peripheral resistance
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