Differential Regional Hemodynamic Effects of Corticotropin in Conscious Sheep

Joerg A. Bednarik, Clive N. May

Abstract The regional hemodynamic effects of 5 days of intravenous infusion of corticotropin (ACTH) (3 µg/kg per day) were examined in conscious sheep (n=8). Mean arterial pressure increased from 81±2 to 93±3 mm Hg (P<.001) on day 2 of ACTH and remained at this level during the infusion. Cardiac output increased from 5.13±0.19 to 6.06±0.33 L/min (P<.01) because of an increase in stroke volume from 65±4 to 79±8 mL per beat (P<.01); heart rate remained unchanged. ACTH did not alter total peripheral conductance but had differential effects on regional conductances. Mesenteric conductance fell from 3.8±0.2 to a minimum of 4.9±0.3 (mL/min)/mm Hg (P<.05), and renal conductance increased from 3.5±0.3 to 4.6±0.3 (mL/min)/mm Hg (P<.001). There was a small increase in iliac conductance (P<.05) and no change in coronary conductance. Mesenteric and iliac conductances fell progressively over 24 to 48 hours, whereas renal conductance increased rapidly after 3 hours of ACTH, reaching a maximum after 6 hours. Renal blood flow was increased during ACTH infusion from 278±18 to 403±23 mL/min (P<.001); mesenteric blood flow was unchanged; there was a small increase in iliac blood flow (P<.01); and coronary blood flow increased (P<.05), paralleling the change in cardiac output. In a further five sheep, ACTH (5 µg/kg per day) increased mean arterial pressure by 17±2 mm Hg and central venous pressure by a maximum of 5.3±0.8 mm Hg. Plasma atrial natriuretic peptide concentration increased from 1.24±6.2 to 98.0±25.8 pg/mL (P<.01), but plasma endothelin concentration remained unchanged. In summary, ACTH had diverse regional hemodynamic actions, causing mesenteric vasoconstriction and renal vasodilation, with little effect on the coronary and iliac circulations. The pressor effect of ACTH resulted from the increase in cardiac output together with mesenteric vasoconstriction, which offset the renal vasodilation, resulting in no change in total peripheral conductance. (Hypertension. 1994;24:49-55.)

Key Words: • adrenocorticotropic hormone • atrial natriuretic peptide • cardiac output • central venous pressure • renal circulation • splanchnic circulation • sheep

Corticotropin (ACTH) administration increases blood pressure in both humans and experimental animals. In conscious sheep intravenous infusion of ACTH results in an increase in arterial blood pressure within 24 hours, which is sustained as long as ACTH is infused over a 5- to 10-day period. ACTH hypertension can be reproduced by infusion of a combination of adrenocortical steroids and is dependent on the presence of the adrenal glands but not on intact adrenal innervation. The hypertension is associated with an increase in plasma volume, without a significant change in extracellular fluid volume. A volume component of the hypertension is also suggested by the finding that the ACTH-induced rise in blood pressure can be modulated by alterations in sodium status. Long-term sodium loading magnifies the pressure rise produced by ACTH, and long-term dietary sodium restriction blunts the rise.

The hemodynamic profile of ACTH hypertension in conscious sheep is characterized by an elevated cardiac output (CO), with no change in total peripheral resistance. Effective renal plasma flow is markedly elevated 24 hours after the onset of ACTH infusion, as a result of a direct glucocorticoid action. For total peripheral resistance to remain constant in the presence of renal vasodilatation, vasoconstriction must be occurring in other vascular beds. In the present study the effect of ACTH infusion on regional hemodynamics was examined in conscious sheep instrumented with electromagnetic flow probes to measure CO and with transit-time flow probes to measure regional arterial blood flows. The aim of the study was to examine the regional hemodynamic effects of ACTH and to determine whether ACTH acts selectively to cause vasoconstriction in one vascular bed or whether the vasoconstriction is a more generalized phenomenon.

Methods

Merino cross ewes (35-45 kg body weight), oophorectomized and with carotid artery loops, were housed in metabolism cages in association with other sheep. They were not used for at least 4 weeks after surgery until they were accustomed to laboratory conditions and human contact. Sheep were fed a diet of oaten chaff (800 g/d containing 90 to 120 mmol/kg Na⁺ and 270 to 380 mmol/kg K⁺); water was offered ad libitum. All experimental procedures were approved by the Animal Experimentation Ethics Committee of the Howard Florey Institute under the guidelines laid down by the National Health and Medical Research Council.

Animal Instrumentation and Data Collection

Flow probes were implanted in sheep for the measurement of CO and regional flows. Brieﬂy, anesthesia was induced with sodium thiopental (15 mg/kg IV). After intubation, sheep were placed on a ventilator and maintained on 1.5% halothane in air/oxygen. An electromagnetic flow probe (20-mm diameter, In Vivo Metrics) was implanted on the ascending aorta,
and a transit-time flow probe (3 mm RS with coronary flange, Transonic Systems Inc) was implanted on the left circumflex coronary artery. After 2 weeks of recovery, transit-time flow probes were implanted on the cranial mesenteric artery (6 mm RS), left renal artery (4 mm RS), and external iliac artery (6 mm RS). In one sheep a transit-time flow probe (6 mm RS) was placed on the celiac artery; in this animal coronary flow was not measured.

The transit-time flow probes were connected to a Transonic T201CDS flowmeter via a four-channel sequential scanner (TM04, Transonic Systems), and the electromagnetic flow probes were activated by a flowmeter (Biotronex). The output voltage of the electromagnetic flowmeter was reset to zero, using an autozero circuit, during a portion of each diastole when blood flow in the ascending aorta is assumed to be zero. A month after implantation, the electromagnetic flow probes were calibrated in vivo against thermodilution over a range of CO values. Dobutamine (Dobutrex, Eli Lilly & Co) was used to increase CO from approximately 4 to 9 L/min.

Blood pressure was measured via an indwelling Tygon cannula (0.1-mm inner diameter, 1.5-mm outer diameter) inserted 15 cm into a carotid artery. The cannula was connected to a pressure transducer (TDXIII, Cobe) tied to the wool on the sheep's back, and the pressure was corrected to compensate for the height of the transducer above heart level. The transducer was calibrated daily against a mercury manometer.

Central venous pressure (CVP) was measured via a polyethylene cannula (1.18-mm inner diameter, 1.7-mm outer diameter) inserted 25 cm into a jugular vein connected to a pressure transducer (TDXIII, Cobe) and recorded on a chart recorder (RS 3400, Gould). CVP was measured between 9 and 10:30 every morning for 15 minutes, with the sheep standing quietly with their heads in a neutral position. The transducer was positioned at heart level and was calibrated against a water manometer.

Analog signals (blood pressure, CO, and regional flows) were collected using a PC 486 data-acquisition system with custom-written software. Data were collected at 100 Hz for 10 seconds at 10-minute intervals. Individual data points were pooled into 24-hour means for day-to-day comparisons. In addition, data for the first 24 hours of ACTH and saline infusions were pooled into 1-hour blocks for assessment of the onset of the hemodynamic effects of ACTH.

Experimental Protocols

Cardiovascular variables, except CVP, were monitored from 10 AM on the first day of the experiment to 9:50 AM on the last day of the experiment. Saline or ACTH(1-24) (CIBA) (5 μg/kg per day IV in saline) was infused at 1.2 mL/h from 10 AM on the first day of infusion for 5 days. For all sheep, daily measurements of water intake, urine volume, urinary Na+ excretion, and urinary K+ excretion were performed at approximately 10 AM. Daily arterial blood samples (4 mL) were taken for determination of hematocrit, plasma Na+, plasma K+, plasma osmolality, plasma total protein, and plasma glucose.

The effect of ACTH on regional hemodynamics was determined in eight conscious sheep instrumented with flow probes. Sheep were monitored for 1 preinfusion day (PRE), for 5 days with infusion of normal saline or ACTH (E1 through E5) in random order, and then for 3 postinfusion days (P1 through P3). Sheep were allowed a minimum of 10 days to recover after ACTH infusion.

In a second group of five noninstrumented sheep, the effect of ACTH on CVP and plasma levels of atrial natriuretic peptide (ANP) and endothelin-1 (ET-1) was examined. After 3 preinfusion days (PRE1 through PRE3), ACTH (5 μg/kg per day IV) was administered for 5 days (E1 through E5), followed by 3 postinfusion days (P1 through P3). Carotid arterial blood samples (12 mL) for the determination of plasma ANP and ET-1 were taken at 10 AM immediately before the onset of ACTH infusion; after 1, 3, and 5 days of ACTH infusion; and 1 and 3 days after infusion.

Plasma and Urine Analyses

Hematocrit was measured with a microhematocrit centrifuge (Biofuge A, Heraeus Sepatech). Plasma and urinary Na+ and K+ and plasma glucose were measured with a Synchro-CX-5 Clinical System (Beckman Instruments). Plasma osmolality was measured with a model 3CII osmometer (Advanced Instruments Inc).

Plasma ANP and ET-1 were assayed by radioimmunoassay after extraction from plasma (2 to 3 mL) with the use of Sep-Pak columns. The detection limit of the ANP assay was 0.8 fmol/mL of plasma, and the intra-assay and interassay coefficients of variation were 9% and 14%, respectively. For the plasma ET-1 assay the detection limit was 0.8 fmol/mL of plasma, and the intra-assay and interassay coefficients of variation were 9% and 12%, respectively.

Statistical Analyses

In the first group of eight sheep, cardiovascular parameters (pooled into 24-hour means), plasma and urinary parameters, and water intake were compared by repeated-measures ANOVA with Greenwood-Geiser correction (comparing PRE and E1 through E5 of ACTH with saline control). Hourly means of cardiovascular parameters for the first 24 hours of ACTH and saline infusions were compared by repeated-measures ANOVA. For all cardiovascular parameters in the second group of five sheep, the mean of the pretreatment days (PRE1 through PRE3) was compared with days E1 through E5 by two-way ANOVA. Differences between plasma hormone levels were assessed by comparing the preinfusion value with values on days E1 through E5 by two-way ANOVA.

Results

Daily Rhythm of Cardiovascular Parameters

During the control day the cardiovascular parameters in eight conscious sheep showed a daily rhythm that resulted mainly from feeding at 4:30 PM (Fig 1). The sheep ate their food in 30 to 60 minutes and drank approximately 1.0 to 1.5 L of water over the next 4 to 5 hours. After feeding, mean arterial pressure (MAP) increased over the next 6 hours because of an increase in CO caused by a rise in heart rate (HR). Stroke volume (SV) tended to fall, probably because of the 20% reduction in blood volume that occurs after ingestion of dry feed and the accompanying large increase in saliva flow.16 The rise in total peripheral conductance (TPC) resulted partly from a rapid rise in celiac conductance, which reached a maximum within 3 hours of feeding, and a delayed rise in mesenteric conductance, which peaked 8 hours after feeding. In the one sheep examined, celiac flow increased from 490 to 710 mL/min, and celiac conductance increased from 6.6 to 8.9 (mL/min)/(mm Hg) within 3 hours of feeding and then slowly fell until feeding the next day (data not shown). Renal and iliac conductances showed no obvious 24-hour rhythms, and changes in coronary conductance paralleled the changes in CO (Fig 2).

Onset of Cardiovascular Effects of ACTH

During the first 24 hours of ACTH infusion, MAP was significantly increased above the level in the saline control group (P < .05) (Fig 1). The increase in MAP occurred 6 hours after the onset of ACTH, and thereafter MAP remained elevated because of a rise in CO, which was consistently above control from 5 hours of
ACTH. The rise in CO was mediated mainly by an increase in SV, but the increases in CO and SV were not significant over the entire 24-hour period (Fig 1). Mesenteric conductance was significantly reduced ($P<.01$), remaining consistently below control from 14 hours (Fig 2). Renal conductance initially increased after 3 hours of ACTH infusion and thereafter remained elevated ($P<.001$). Mesenteric flow was unchanged, but renal flow, which was significantly increased overall ($P<.001$), was clearly elevated after 3 hours and continued to increase up to 14 hours of ACTH (Fig 3). ACTH infusion did not significantly change coronary and iliac flows and conductances.

Long-term Hemodynamic Effects of ACTH

The hemodynamic patterns seen over the first 24 hours continued over the remaining 4 days of ACTH. MAP increased from 81±2 mm Hg on the control day to 93±3 mm Hg on the second day of ACTH and remained at this level ($P<.001$) (Fig 4). CO was elevated from a control level of 5.13±0.19 to 6.29±0.23 L/min on day 3 and to 6.06±0.33 L/min on day 5 ($P<.001$). By day 5 of ACTH, SV had risen from 65±4 mL per beat to a maximum of 79±8 mL per beat ($P<.001$), but HR did not change throughout the ACTH infusion (Fig 4).

Although TPC was unaltered throughout the ACTH infusion, there were large, contrasting changes in the conductances in different regional beds (Fig 5). Mesenteric conductance fell from 5.8±0.2 (mL/min)/mm Hg to a minimum of 4.9±0.3 on day 2 of ACTH and to 5.2±0.5 on day 5 ($P<.05$). In the animal in which celiac...
ACTH or Saline

Fig 4. Line graphs show changes in mean arterial pressure (MAP), heart rate (HR), cardiac output (CO), stroke volume (SV), and total peripheral conductance (TPC) over 5 days of corticotropin (ACTH) infusion (5 μg/kg per day IV) or saline (1 mL/h IV) in eight conscious sheep. PRE indicates pretreatment day; E1 through E5, experimental days; and P1 through P3, posttreatment days. **P<.01, ***P<.001.

Fig 5. Line graphs show changes in coronary, mesenteric, renal, and iliac conductances ([mL/min]/mm Hg) over 5 days of corticotropin (ACTH) infusion (5 μg/kg per day IV) or saline (1 mL/h IV) in eight conscious sheep. PRE indicates pretreatment day; E1 through E5, experimental days; P1 through P3, posttreatment days. *P<.05, ***P<.001.

Conductance was measured, there was a similar fall, from 5.9 to 4.6 (mL/min)/mm Hg on day 5 of ACTH. In contrast to the vasoconstriction seen in the gastrointestinal vascular beds, renal conductance increased from 3.5±0.3 to 4.5±0.3 (mL/min)/mm Hg on day 1 and remained at this level for the remainder of the infusion. There was also a small increase in iliac conductance (P<.05) but no significant change in coronary conductance. Coronary, renal, and iliac arterial blood flows were increased during ACTH (P<.05, P<.001, and P<.01, respectively), but mesenteric flow did not change (Fig 6). Celiac flow was unchanged in the one sheep in which this was measured. Saline infusion had no effect on any of the parameters measured.

After ACTH infusion was stopped, MAP returned to control levels within 2 days, but CO and SV fell below control levels. At this time there was a reduction in TPC, which maintained MAP in the presence of the reduced CO.

Metabolic Effects of ACTH

Throughout the ACTH infusion, plasma glucose was elevated (P<.001) and plasma K⁺ was reduced (P<.001) (Table 1). Plasma osmolality was increased (P<.05), but hematocrit and plasma Na⁺ did not change. Both urine volume and water intake were increased, particularly toward the end of the ACTH infusion (P<.001 and P<.01, respectively). Urinary K⁺ excretion remained unchanged, whereas urinary Na⁺ excretion was reduced on day E1, then elevated on days E3 through E5 (P<.001). There was a postinfusion natriuresis and diuresis on the first postinfusion day.

Effect of ACTH on Central Venous Pressure and Plasma Concentrations of ANP and ET-1

In five noninstrumented sheep, ACTH increased MAP from 84±2 to 101±3 mm Hg on day 5 (P<.001), with no effect on HR. In these sheep, CVP was elevated by between 3.3±0.5 and 5.3±0.8 mm Hg throughout the 5 days of ACTH infusion (P<.001) (Table 2). The changes in MAP and HR in these five sheep were not significantly different from those in the eight sheep instrumented with flow probes.

In this group of five sheep, plasma ANP increased from a control of 4.0±2.0 pmol/L to 16.1±8.9, 31.9±8.4, and 20.1±9.1 pmol/L on days 1, 3, and 5 of ACTH, respectively (P<.001). By the third postinfusion day, ANP had returned to control levels (1.5±1.0 pmol/L). The control plasma endothelin concentration was 4.7±2.3 pmol/L, and there was no significant change during ACTH infusion. Plasma endothelin concentrations were 3.1±2.7, 2.9±2.1, 4.1±2.1, and 3.8±2.4 pmol/L on days 1, 3, and 5 of ACTH and day 3 post-ACTH, respectively.
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Regional Hemodynamic Effects of ACTH

ACTH or Saline

**Fig. 6.** Line graphs show changes in coronary, mesenteric, renal, and iliac arterial flows (mL/min) over 5 days of corticotropin (ACTH) infusion (5 μg/kg per day IV) or saline (1 mL/h IV) in eight conscious sheep. PRE indicates pretreatment day; E1 through E5, experimental days; P1 through P3, posttreatment days. *P<.05, ***P<.001.

**Discussion**

The increase in arterial blood pressure caused by ACTH infusion in conscious sheep is dependent on the secretion of adrenocortical steroids, but the mechanisms by which either ACTH or individual mineralocorticoids and glucocorticoids cause hypertension remain unclear. The present studies examined hemodynamic changes in conscious sheep during the onset and maintenance phases of ACTH-induced hypertension and after ACTH infusion was stopped. The aim was to determine the regional hemodynamic effects of ACTH, in particular to establish where in the peripheral vasculature ACTH caused vasoconstriction. In confirmation of previous studies,12,13 ACTH infusion for 5 days caused a sustained increase in MAP, accompanied by a rise in CO with no change in TPC. ACTH also produced the mineralocorticoid effects of initial urinary Na⁺ retention and hypokalemia and the glucocorticoid effects of hyperglycemia and polydipsia.

The lack of any change in TPC after 24 hours of ACTH, while renal conductance was increased, indicated that ACTH must cause vasoconstriction elsewhere. Of the vascular beds studied, ACTH caused vasoconstriction only in the gastrointestinal vasculature, as defined by the vascular beds supplied by the cranial mesenteric and celiac arteries. Mesenteric vasoconstriction became apparent approximately 10 hours after the start of the ACTH infusion, in contrast to the renal vasodilatation which began within 3 hours of ACTH. The difference in the timing of the onset of these changes accounted for the initial increase in TPC that occurred over the first 3 to 10 hours of ACTH, before TPC returned to control as mesenteric vasoconstriction developed. The sustained increase in MAP over 5 days of ACTH resulted from the rise in CO in the presence of vasoconstriction in the mesenteric and celiac vascular beds, which maintained TPC constant despite a large degree of renal vasodilatation.

The mechanism causing this selective gastrointestinal vasoconstriction, and the extent to which it can be attributed to either the mineralocorticoid or glucocorticoid actions of the steroids released by ACTH, is presently unknown. A selective increase in mesenteric sympathetic vasoconstrictor activity during ACTH, which could account for this effect, is suggested by the finding that during the established phase of ACTH hypertension, whole-body norepinephrine spillover is increased.17 This occurs in the presence of a reduced renal norepinephrine spillover (M.L. Matthai, personal communication), indicating that an increase in norepinephrine spillover from other sites, possibly the gut, may occur. ACTH could also act via indirect humoral mechanisms to cause mesenteric vasoconstriction. In the present study ACTH increased plasma ANP within 24 hours, presumably in response to increased atrial

<table>
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<th>Variable</th>
<th>PRE</th>
<th>E1</th>
<th>E2</th>
<th>E3</th>
<th>E4</th>
<th>E5</th>
<th>P1</th>
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<td>144±1</td>
<td>141±1</td>
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<td>25±1</td>
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<td>830±160</td>
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PRE indicates preinfusion day; E1 through E5, experimental days; P1 through P3, posttreatment days; UV, urine volume; U₅₇V, urinary sodium excretion; and U₅₇V, urinary potassium excretion. Corticotropin was infused at 5 μg/kg per day. Values are mean±SEM.
TABLE 2. Effects of Corticotropin on Mean Arterial Pressure, Heart Rate, and Change In Central Venous Pressure In Five Conscious Sheep

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<th>Variable</th>
<th>PRE</th>
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<th>E2</th>
<th>E3</th>
<th>E4</th>
<th>E5</th>
<th>P1</th>
<th>P2</th>
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<td>99±3</td>
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<td>3.5±1.1</td>
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<td>1.1±1.0</td>
<td>0.0±1.2</td>
<td>&lt;.001</td>
<td></td>
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</table>

PRE indicates preinfusion day; E1 through E5, experimental days; P1 through P3, posttreatment days; MAP, mean arterial pressure; HR, heart rate; bpm, beats per minute; and CVP, central venous pressure. Corticotropin was infused at 5 μg/kg per day. Values are mean±SEM.

stretch secondary to the increased plasma volume and preload. ANP causes selective mesenteric vasoconstriction in conscious dogs, suggesting that it may play a role in ACTH-induced mesenteric vasoconstriction. In addition, the elevated ANP levels probably modulate the pressor effect of ACTH, as has been shown for other forms of mineralocorticoid hypertension.

The ACTH-induced increases in renal flow and conductance have previously been demonstrated after 24 hours of ACTH using clearance techniques, but the time course of this effect was unknown. We have demonstrated that the increase in renal blood flow is rapid, beginning within 2 to 3 hours and reaching a plateau of approximately 50% above control within 10 hours. Intrarenal arterial infusions of cortisol in the ovine renal autotransplant demonstrated that the increase in renal blood flow was mediated by a glucocorticoid mechanism. In agreement, intravenous infusion of methylprednisolone or dexamethasone, glucocorticoids with minimal mineralocorticoid activity, to conscious dogs increased renal blood flow, but the mechanisms causing this renal vasodilatation are unknown.

In contrast to the opposite effects on mesenteric and renal conductances, ACTH had little effect on either the coronary or iliac vascular beds. The changes in coronary blood flow, during and after ACTH, closely paralleled the changes in CO, which is to be expected as the coronary circulation is regulated mainly by the metabolic demands of the heart. The small increases in iliac conductance and iliac flow may reflect baroreceptor-mediated withdrawal of sympathetic tone in response to the rise in blood pressure.

The ACTH-induced rises in SV and CO were probably largely caused by the increased CVP and hence preload. This was most likely secondary to the increased plasma volume and preload. ANP causes selective mesenteric vasoconstriction in conscious dogs, suggesting that it may play a role in ACTH-induced mesenteric vasoconstriction. In addition, the elevated ANP levels probably modulate the pressor effect of ACTH, as has been shown for other forms of mineralocorticoid hypertension.

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The ACTH-induced rises in SV and CO were probably largely caused by the increased CVP and hence preload. These effects were most likely secondary to the ACTH-induced expansion of plasma volume (1131-γ-globulin space) that occurs within 24 hours, although an increase in venous tone during ACTH infusion, mediated by either neural or hormonal mechanisms, may also contribute to the rise in CVP. The increase in plasma volume results from a combination of glucocorticoid-induced redistribution of extracellular fluid and mineralocorticoid-induced sodium and water retention. Further evidence that the increase in CO probably depends on both mineralocorticoid and glucocorticoid effects are the findings in humans that CO increases during the early phase of primary aldosteronism and during infusion of cortisol. Furthermore, CO is elevated in canine deoxycorticosterone (DOC) and deoxycorticosterone acetate (DOCA)-salt hypertension and during DOCA-salt hypertension in rats. Preven-

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Acknowledgments

This work was supported by an Institute Grant to the Howard Florey Institute from the National Health and Medical Research Council. ACTH was generously supplied by CIBA, Basel, Switzerland.

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Differential regional hemodynamic effects of corticotropin in conscious sheep.
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Hypertension. 1994;24:49-55
doi: 10.1161/01.HYP.24.1.49

Hypertension is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0194-911X. Online ISSN: 1524-4563

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