The Relationship between Body Fluid Volume, Sodium Ion Concentration, and Sensitivity to Pressor Effect of Angiotensin II in Dogs

Allen W. Cowley, Jr., and Thomas E. Lohmeier

SUMMARY Extraglomerular fluid volume, plasma electrolytes, and plasma angiotensin II (A II) were individually controlled to determine their influence on the acute pressor responsiveness to A II. Hemodialysis of nephrectomized dogs was used to simulate and control the changes of major variables which occur in the intact state during changes in sodium balance. A II dose-pressure response curves were determined in 11 dogs at three volume states with plasma [Na+] maintained constant and in five dogs at low, normal, and high plasma [Na+] with body fluid volume maintained constant. Parallel shifts of the log dose-response curves were obtained in the three volume states. The same rise in arterial pressure with identical doses of A II was obtained at normal, contracted, and expanded volume states, with the change of arterial pressure based on the uncompensated basal pressure level at each volume state. When the fall in pressure observed during volume depletion was returned to control levels with norepinephrine, there was no change in the A II dose-response relationship from the control state. No difference in the A II dose-pressure response relationship was obtained between states of 140, 146, and 156 mEq/liter plasma [Na+] with body fluid volume held constant. The studies indicate that short-term alterations in either sodium or water balance do not alter the "real" vascular sensitivity to A II. The "apparent" change normally observed result from preexisting endogenous levels of circulating A II present at the time the dose-response curve is determined which probably alter the availability of receptor sites to A II.

THE RENIN-ANGIOTENSIN system participates in the regulation of arterial pressure in a variety of circumstances. The time response, the short-term feedback gain, and the operational range of this hormonal pressure control system have been quantitatively well characterized in the dog and rabbit. Its compensatory role in pressure control has been demonstrated under conditions of hemorrhage, congestive heart failure, postural change in man, and sodium depletion. It is the contribution of the renin-angiotensin system to pressure control during sodium depletion that appears to be one of its most important daily functions. This occurs most rapidly through the well known vasoconstrictor actions of angiotensin II and more slowly through both direct and indirect effects on sodium and water excretion.

The present study focuses on the role of angiotensin in pressure regulation with changes in sodium intake. The evidence for such a role is based on two principal observations. First, it is well known that renin secretion is dramatically increased during conditions of both acute and chronic sodium depletion and is depressed during conditions of excess sodium intake. Second, there is a dramatic and rapid decrease of arterial pressure when inhibitors of angiotensin I-converting enzyme or competitive antagonists of angiotensin II are administered to sodium-depleted animals or upright man.

The quantitative importance of the renin-angiotensin system in pressure normalization in various states of sodium intake remains unclear and even puzzling. A contradiction has existed concerning the observation that, during salt and water depletion, on activation of the renin-angiotensin system, there is a decrease in the pressor sensitivity of the peripheral vasculature to angiotensin II and, conversely, there is an increase in pressor sensitivity during conditions of sodium excess when renin-angiotensin levels are depressed. This suggests that the compensatory actions of the renin-angiotensin pressure control system could be offset, at least in part, by opposite changes in vascular reactivity. Such alterations would influence the ability of the system to modulate changes in arterial pressure in both normal and pathological states.

For this reason, the present study was performed to quantitatively determine the relationships between extracellular fluid volume and electrolytes, angiotensin levels, and vascular sensitivity to angiotensin II. These relationships are required to evaluate the significance of alterations of angiotensin II vascular sensitivity associated with changes in sodium status on the overall role of this pressure control system. These data are also useful in examining the validity of several proposed mechanisms held to be responsible for changes in sensitivity to angiotensin II.

The experimental design employed permitted short-term simulation of those physiological events which have been observed to occur normally during both sodium deprivation and excess intake. By using nephrectomized dogs and hemodialysis procedures, endogenous renin se-
cretion was eliminated and the changes in circulating AII observed in sodium deprivation were simulated by appropriate infusion of angiotensin II. In one group of dogs studied, plasma sodium concentration was maintained constant while angiotensin II dose-pressure response relationships were determined at normal, contracted, and expanded body fluid volumes, using hemodialysis techniques. In a second group of dogs studied, body fluid volumes were maintained constant and angiotensin II dose-response curves were determined at low, normal, and high concentrations of plasma sodium.

Methods

Experiments were performed on mongrel dogs anesthetized with sodium pentobarbital (30 mg/kg). Bilateral nephrectomy was performed 24 hours prior to hemodialysis to eliminate endogenous renin secretion. Prior surgery also minimized bleeding during the 5-hour dialysis period. Catheters were placed in the femoral arteries and veins for the hemodialysis procedure, infusion of drugs, and measurement of arterial blood pressure. Ultrafiltration rate was controlled by the resistance of blood flow at the outflow end of the hemodialyzer which permitted plasma electrolytes and body fluid volumes to be controlled independently. Dextran-40 was used to fill the 80-ml priming volume of the Mini-Cobe hemodialyzer at the beginning of the experiment. The experiments were carried out with the dog placed on a balance sensitive to less than a 5.0-g change in total body weight, and these weight changes were used as an index of changes in body fluid volumes (see Fig. 1). The sodium concentration of the dialysis fluid was adjusted for each dog to the plasma concentration measured on the morning of the experiment. Dialysate potassium concentration was adjusted initially to 4 mEq/liter; magnesium and calcium to 5 mEq/liter. The dialysate fluid also contained sodium acetate, 30 g/liter, and dextrose, 0.6 g/liter.

Control AII dose-response curves were determined after a 1-hour equilibration period with the dog attached to the dialyzer. Each dose of AII was infused for 5 minutes, and the data were used only if arterial pressure returned to within 5 mm Hg of control value following the dose-response curve. In six dogs, the control dose-response curve was followed by a 1-hour period of ultrafiltration, during which time the body fluid volume was contracted by about 10 ml/kg body weight. Arterial pressure was maintained by infusion of exogenous AII, and body weight was maintained constant at the new level of ultrafiltration while the AII dose-response curve was determined. In another group of eight dogs after the control (normovolemic) dose-response curve, fluid volume was expanded by an average of 10 ml/kg body weight, and a dose-response curve was determined. AII dose-response curves for four dogs were determined before starting dialysis.

The experimental design (Fig. 1) permitted controlled simulations of the physiological events which have been observed to occur during sodium deprivation and excess sodium intake in normal animals. One infusion pump (Harvard, model 900) delivered that amount of AII required to return arterial pressure to normal during the low volume state. This background infusion of AII was maintained while a second infusion pump was used to infuse AII for the AII dose-response curve. At the normal control volume, the dose-response curves were determined by means of a fixed AII background infusion which averaged 6.1 ± 1.3 ng/kg per min. For expanded volume states, no background AII infusion was needed. To evaluate the influence of prior receptor occupancy by AII on pressor sensitivity, a second group of experiments was performed on five different dogs in which norepinephrine (Levophed bitartrate) was used in place of AII to normalize arterial pressure during alterations in fluid volume. With circulating norepinephrine levels held

![Figure 1](http://circres.ahajournals.org/)

**Figure 1** Hemodialysis and ultrafiltration techniques were used in anephric dogs to determine AII pressor sensitivity under two conditions: (1) alterations in body fluid volumes with constant plasma [Na⁺], and (2) alterations in plasma [Na⁺] with constant fluid volume. The use of two infusion pumps permitted AII dose-response curves to be superimposed on any desired circulating background level of AII or norepinephrine.
constant at the infusion rate required to normalize arterial pressure after the volume changes, the second infusion pump again was used to construct a complete A II dose-response curve. The amount of norepinephrine required to normalize pressure averaged 2.2 ± 0.6 μg/kg per min.

A third group of experiments was performed on five dogs to determine the influence of changes in extracellular sodium concentration on A II pressor sensitivity while the total body fluid volume was maintained constant by ultrafiltration. A II dose-response curves were first obtained with the sodium concentration of the dialysis fluid maintained at the normal control level of each dog determined immediately before the experiment. This was followed by dose-response curves determined first at elevated (+5 mEq/liter) and then depressed plasma sodium (-5 mEq/liter) concentrations while the total body fluid volume, represented by body weight, was maintained constant throughout the experiment. A period of approximately 80 minutes was required between each dose-response curve to obtain the desired changes in plasma sodium concentration. During the dose-response curves, an effort was made to maintain plasma potassium concentration constant by using a separate infusion pump to infuse potassium into the dialysis fluid. Plasma sodium and potassium concentrations were monitored continuously throughout the experiment by means of a flame photometer (Instrumentation Laboratory 343).

Results

A II Dose-Response Curves during Fluid Volume Changes with Fixed Electrolyte Concentrations

The A II dose-response curves of a representative dog are shown in Figure 2. In this dog, responses were obtained first at normal and then at reduced values of body fluid volume, while plasma sodium and potassium were held nearly constant by ultrafiltration. The control dose-response curve (top) was determined after a 1-hour equilibration period on the dialyzer. Again, the dose-response curve was determined in the presence of the background infusion of A II (5.0 ng/kg per min). The total amount of A II infused for the control dose-response curve is indicated by the lower scale (background A II plus superimposed infusion rates). This dose-response curve was followed by a 1-hour period of ultrafiltration which decreased body fluids by 12 ml/kg body weight and was associated with a 20 mm Hg fall of mean arterial pressure. To simulate conditions observed in an intact, sodium-depleted dog, the A II infusion rate was adjusted to that rate which returned arterial pressure to the control value for normal volume (20 ng/kg per min). Thus, as in an intact, sodium-depleted dog, a state was obtained in which there was a normal level of arterial pressure with high circulating levels of A II. In this state, a dose-response curve was again determined in the presence of the background infusion of A II (superimposed infusion rates indicated on upper scale). The total amount of A II infused is again indicated by the lower scale.

It is evident that, during the volume-contracted state when the decrease in arterial pressure was compensated for by high circulating levels of A II, there was a displacement of the dose-response curve downward and to the right. It is this shift which has been described as a decrease in the pressure sensitivity to infused A II. For example, infusion of A II, 25 ng/kg per min, in the volume replete state with a normal level of arterial pressure was associated with a pressure rise of 45 mm Hg. In the volume-depleted state, with normal arterial pressure, the same A II infusion rate was associated with an increase of only 13 mm Hg in arterial pressure. Thus, we have simulated the same phenomenon that is observed in conscious intact man and animals during sodium depletion, an apparent decrease in the pressure sensitivity to A II.

Log-Dose Angiotensin II Pressure Responses in Normal, Expanded, and Contracted Volume States

To provide better insight into the mechanism responsible for the depressed pressor sensitivity to A II seen in Figure 2, the averaged data presented in the remainder of this paper are plotted by using the log-dose of the total amount of A II infused, that is, the amount infused from both the pump infusing the fixed background A II level (pressure compensating dose) and the pump used to provide increments in the circulating levels of A II. As mentioned in Methods, in performing the experiment at normal volumes, the fixed background A II infusion rate averaged 6.1 ± 1.3 ng/kg per min, and in expanded volume states there was no background infusion. In contracted volume states the amount of A II required to return arterial pressure to normal averaged 224 ± 156 ng/kg per min.

Volume Depletion

Figure 3 summarizes the control and matched volume depletion data for six dogs that were volume contracted.
by an average of 10 ml/kg body weight. The mean arterial pressure for the control normovolemic state was normalized to the average arterial mean pressure of these six dogs, 101 ± 12.2 mm Hg. Pressure for the volume-depleted state was normalized to the average uncompensated control preinfusion pressure, 73.3 ± 6.7 mm Hg.

Figure 3 shows that a parallel downward shift in the curve was obtained with the volume-depleted state. The mild depression of slope was not statistically significant in terms of regression analysis (P > 0.2). Plasma sodium concentration was held to within an average change of 1 mEq/liter during volume depletion by hemodialysis.

Volume Expansion

Comparisons of dose-response curves in normal and volume-expanded states are summarized in Figure 4 with the total log-dose of infused AII again plotted. Pressures were normalized around the mean arterial control pressure of 89 ± 9.4 mm Hg and the control preinfusion pressure was normalized, using the average group control pressure values for each volume state. Plasma [Na+] was maintained constant by hemodialysis during volume depletion (n = six dogs).

The parallelism obtained between the control, volume-expanded, and volume-contracted states when plotting the total amount of infused AII (Figs. 3 and 4) demonstrates that pressure sensitivity, defined as change in arterial pressure for a given rate of infusion of AII, was essentially unchanged under the three conditions. When the normalized changes in arterial pressure for the total infused amount of AII are plotted for each of the three volume states, the three curves are superimposed upon each other to the extent that all three lines fall within the average standard deviation of the mean.

Log-Dose Angiotensin II Pressure Responses in Normal and Norepinephrine-Compensated Volume-Contracted States

The results shown in Figures 2-4 suggested that the observed change in sensitivity to AII was a phenomenon resulting from prior occupancy of receptor sites at increased levels of circulating AII. Therefore, an additional protocol was carried out to test this hypothesis further. Five dogs were similarly volume depleted (10 ml/kg body weight), but, following volume depletion, the arterial pressure was returned to normovolemic control levels with norepinephrine instead of AII, because norepinephrine does not compete for AII receptor sites. For comparison, AII dose-response curves were also run in a manner similar to those described for Figure 3.

Two major observations were made under these conditions. First, it is seen (Fig. 5) that the dose-response curves obtained, using AII to compensate for the fall in arterial pressure during the first dose-response curve obtained after volume expansion. The average plasma sodium concentration was held constant at 144 ± 2 mEq/liter during volume expansion, whereas the potassium concentration rose slightly from 4.9 ± 0.2 to 5.2 ± 1 mEq/liter during the volume-expanded state.

The graph clearly indicates a parallel upward shift of the dose-response curve obtained after volume expansion. The average plasma sodium concentration was held constant at 144 ± 2 mEq/liter during volume expansion, whereas the potassium concentration rose slightly from 4.9 ± 0.2 to 5.2 ± 1 mEq/liter during the volume-expanded state.
arterial pressure during volume depletion, were again moved downward as was seen in the previous group of dogs (Fig. 3) with an even more striking parallelism of the two curves. Second, when arterial pressure during volume depletion was returned to control levels (92 ± 9.1 mm Hg) by using norepinephrine rather than A II, there was no significant difference in the dose-response relationship observed between the control and the volume-depleted states (upper two curves).

Thus, irrespective of whether the fall in arterial pressure during volume changes was compensated for with A II or norepinephrine, there was little change in pressor sensitivity to A II (change in pressure per total infused A II) with the degree of volume expansion and contraction used in the present experiment. It is also clear, however, that if only the amount of A II in excess of the rate needed to normalize pressure is plotted on the dose-response curve, the impression would be that of a decreased sensitivity to A II, as was demonstrated in Figure 1. This is presumably the case in intact animals or man where, during salt and water depletion, there are high circulating levels of renin-angiotensin which contribute significantly to the normal arterial pressure that is observed in this state.

A II Pressor Sensitivity at Low, Normal, and High Plasma Sodium Concentrations with Fixed Total Body Fluid Volume

Figures 6 and 7 demonstrate that changes in plasma sodium concentrations with values ranging from 140 ± 6.1 to 156.2 ± 6.4 mEq/liter but with total body fluid volume held constant, had no influence on pressor sensitivity to A II. Following the control A II dose-response curves, plasma sodium concentrations were altered over a period of 80 minutes to first obtain the high, and then, after another 80 minutes, the low sodium state. Figure 6 is a semi-log plot of the average dose-response curve of the total amount of infused A II during the control and elevated sodium state. Total body fluid volumes as indicated by weight were controlled to within ±10 g throughout the entire experimental procedure. Arterial blood pressure was unaffected by the rise in plasma sodium concentration and averaged 90.8 ± 8.3 mm Hg in the control state and 93.7 ± 9.4 in the high sodium state (P > 0.2). Despite the efforts to maintain plasma potassium concentration constant by use of a separate infusion pump, plasma potassium levels rose by an average of 1.5 mEq/liter during sodium expansion. Similarly, Figure 7 shows that a decrease in plasma sodium concentration from 145.6 ± 3.8 to 140.1 ± 6.1 mEq/liter had no effect on the pressor sensitivity to A II. Plasma potassium again rose by an average of 1.0 mEq/liter in the sodium-depleted state. Since potassium rose both with increases and decreases in sodium relative to its control value, it is unlikely that changes in plasma potassium concentration of this magnitude had any significant effect on pressor sensitivity to A II. The same can be said for the rise in plasma potassium during the volume-expanded and volume-contracted states.

These dose-response curves clearly indicate that relatively wide fluctuations of sodium ion concentration per se have no immediate effects on the vascular pressor activity of A II.

Discussion

The changes in pressor responsiveness to A II associated with alterations in sodium intake have been difficult to interpret in intact animals. The reason for this is that there are at least three important uncontrolled variables that can significantly influence the acute arterial pressure response to A II during alterations in Na+ intake. These variables include changes in the extracellular and plasma volumes, changes in electrolyte concentrations in these fluids, and changes in plasma levels of A II. In the present study, these major variables were controlled individually to determine, quantitatively, their influence on the acute pressor responsiveness to A II. Hemodialysis was used to simulate and control the changes which occur in the intact state during the alterations in sodium status.

Changes in extracellular fluid volume, plasma sodium concentration, and the renin-angiotensin system have been studied during sodium depletion in man. In subjects maintained on a sodium intake of 10 mEq/day for 5 days,
there is a reported 5–6% decrease in extracellular fluid volume,25–28 the same as the estimated change in the present study. Plasma sodium concentration, however, has been found to be maintained within 3–4 mEq/liter of control values, even during fluctuations in sodium intake ranging from 10 to 250 mEq/day.25–28 Finally, it is well known that the activity of the renin-angiotension system increases with sodium depletion and is suppressed by sodium excess.15–17

The degree of volume depletion and expansion and the changes in electrolyte concentration achieved in the present study thus were similar to those observed in intact animals and man during alterations in sodium intake. The doses of A II administered to simulate sodium depletion are higher than would be formed endogenously and higher than those required for a comparable pressor response in conscious intact dogs.27 This can be explained by what appears to have been a very high rate of clearance of A II by hemodialysis. The effect of this clearance was demonstrated in four dogs in which a dose-response curve was obtained prior to and during hemodialysis. In these dogs, a nearly five times greater rate of A II infusion was required during dialysis to obtain the same arterial pressure rise obtained in the control period. However, ultrafiltration of A II during the time of each dose-response curve should have remained constant, since the rate of ultrafiltration was constantly adjusted to maintain body weight constant at all times and dialysate hydrostatic pressure equaled vascular hydrostatic pressure. Diffusion of A II into dialysate fluid should have been a constant factor between each dose-response curve.

The present study shows that neither acute changes in extracellular fluid volume nor extracellular sodium concentration alters A II pressor sensitivity of the vascular system. Parallel shifts in the log dose-response curve were obtained based on the absolute increments in arterial pressure observed during A II infusions. Clearly, each dose of infused A II produced nearly the same elevation of arterial pressure in the normal, contracted, and expanded volume state when the change in arterial pressure was based on the uncompensated basal pressure level for each volume. In addition, no changes in pressure sensitivity to A II were observed when extracellular fluid volume was held constant and plasma sodium concentration was altered. Thus, it appears that in states of excess sodium intake or sodium deprivation, there is not a change in the real vascular sensitivity to A II but, rather, only an “apparent” change resulting from the preexisting or endogenous levels of circulating A II present at the time the dose-response curve is determined. The only difference in the responses to A II with the various maneuvers performed in the present study was the absolute level of blood pressure at which a normal response to A II occurred.

Parallel shifts to the right of a normal A II dose-response curve have been obtained in conscious intact rats,25–26 rabbits,25 dogs,25 and man,25 but the diminished pressor sensitivity during salt depletion has been generally described as a “decrease in A II sensitivity.” Since the rise in arterial pressure for each dose of A II was less in the salt-depleted groups, it can be seen in Figure 2 why such results could be mistakenly interpreted as a decreased A II sensitivity when the data are plotted, using the change in arterial pressure from a “normal” level of arterial pressure. It is seen that when conditions like those in the intact animal are simulated, with greater amounts of A II circulating in the volume-depleted state, a greater amount of A II is required to obtain an equal rise in arterial pressure than in the normal sodium-volume state. Sch告訴kamp et al.25 and Decheneffe et al.26 have observed similar parallel shifts in A II dose response curves while studying salt-depleted anephric man.

The present results also indicate the changes in extracellular concentration of the sodium and/or potassium ions per se were not involved in causing changes in vascular sensitivity to A II, at least within the range examined. Vascular smooth muscle has been shown to be sensitive to changes in the concentrations of sodium and potassium,29 but the magnitude of change in concentration of these cations in the present study did not significantly alter the overall response of the vascular system. The shift of fluid volume from the intra- to extracellular spaces which probably occurred did not have any apparent effect on the A II pressor sensitivity.

The theory that most readily explains these results is the “receptor-occupancy” theory of drug action. This concept holds that, during the conditions of sodium depletion, the resulting higher concentrations of circulating A II would bind with and occupy a larger portion of the vascular A II receptors. Added amounts of A II at this time would then have fewer receptors to bind with, resulting in an increasingly diminished response to the same dose of administered A II. Support for this mechanism was provided by the group of dogs in which the fall in arterial pressure with volume depletion was returned to control levels by noradrenaline. During the volume deplete state, A II exhibited its full pressor effect as shown by the A II log dose-response curve which was virtually identical to that obtained in the control normovolemic state.

Considerable evidence indicates that norepinephrine is not an important factor in the response of vascular smooth muscle to angiotensin, a subject recently reviewed by Bohr.24 Absence of any synergism between A II and norepinephrine is supported by the parallelism of the three curves seen in Figure 5 which demonstrates that the rise in arterial pressure for any given increment of A II is the same both in the presence and absence of norepinephrine.

The concept of receptor-occupancy is attractive also because it is compatible with many observations on A II sensitivity under a variety of experimental and clinical conditions. For example, there are many conditions in which circulating levels of plasma renin or A II are elevated but in which a decreased pressor responsiveness to A II is commonly observed. These include malignant hypertension, cirrhosis of the liver, uncompensated congestive heart failure, pregnancy, sodium depletion, and Bartter’s syndrome. Conversely, an increased pressor responsiveness to A II is observed under conditions associated with low circulating levels of renin or A II, such as after nephrectomy or during primary aldosteronism and excess sodium intake. Kaplan et al.25 originally reported
such findings and used these predictable responses as an index of the circulating levels of AII.

Although the receptor-occupancy theory is compatible with the present results, it is by no means the only possible explanation. It is possible, for example, that there is an excess of unoccupied receptors, in spite of the administered doses of AII, and the exponential dose-response curve is a result of limited contractile properties of the smooth muscle, or limitations of the coupling mechanisms of the receptor sites to the activation of the physical shortening mechanisms, or heart failure. Limitation of the contractile machinery or cardiac failure seems unlikely, however, since the addition of other pressor agents (norepinephrine) at the maximum plateau of the AII dose-response curve resulted in even further elevation of pressure.

The present study cannot exclude the possibility that chronic long-term changes in sodium intake may have an additional influence on vascular sensitivity not observed in the present acute studies. Williams et al. have observed that with chronic sodium loading or depletion of rabbits there was an alteration in the receptor affinity for AII in isolated aortic strips. It is difficult to extrapolate the behavior of aortic strips to pressure changes in the intact animal, but it is entirely possible that, in the chronic state, additional changes in vascular sensitivity result from this mechanism. Other vascular changes may also occur with sodium depletion or excess, such as changes in the AII receptor population, vascular geometric changes with autoregulatory responses initiating alterations of vascular wall thickness, or growth or recession of blood vessels. The quantitative significance of these possible changes as they relate to the AII pressor responses in chronic sodium depletion or excess remains to be determined.

Applicability of the Results of the Present Study to Quantitative Evaluation of the Renin-Angiotensin System

It is clear that, to evaluate quantitatively the complex behavior of the renin-angiotensin system, one must know the precise relationships between sodium intake, body fluid volumes, renin secretion, and vascular responsiveness to AII. The present study provides some important links for the integration of the interrelated variables. Figure 8 is a simplified diagram of the renin-angiotensin pressure control feedback system which serves to illustrate the manner in which the present results contribute to our understanding of the significance of the apparent alterations in vascular sensitivity to AII associated with changes in sodium intake.

There are basically three elements: (1) a renal block in which release of renin is dependent on renal perfusion pressure and sodium intake; (2) showing the direct relationship between plasma renin activity and AII; and (3) block, which uses the results of the present study which quantified the relationship between angiotensin and arterial pressure as influenced by changes associated with sodium intake. Solution of the equations which

![Figure 8](http://circres.ahajournals.org/)

**Figure 8** Simplified analysis of renin-angiotensin pressure control feedback system illustrating the response of the system to a 50 mm Hg decrease in renal perfusion pressure at normal and low sodium intake.
represent these experimentally determined relationships indicates the quantitative significance of the decreased vascular responsiveness to A II during sodium depletion. For example, a decrease in renal perfusion pressure to 50 mm Hg stimulates renin secretion which, in the sodium replete state, normally raises plasma renin activity from 1.0 to 5.0 ng/ml per hour and plasma A II concentration from 10 to 50 pg/ml. This results in a rise in arterial pressure from 100 to 120 mm Hg. In contrast, in the sodium-depleted state, even before renal perfusion pressure is decreased, renin secretion is elevated and plasma renin activity is increased to 12 ng/ml per hour. Now when renal perfusion pressure is decreased to 50 mm Hg, renin activity increases to 42 ng/ml per hour and A II from 120 to 420 pg/ml per hour. Arterial pressure, which is normal in the sodium-depleted state due to high circulating levels of A II, now increases from 100 to 145 mm Hg. Thus, despite the fact that in this situation we are operating on a less responsive portion of the A II dose-response curve, the influence of the renin-angiotensin system on pressure regulation is still substantial.

This analysis can, therefore, explain the paradox that has continued to puzzled many investigators. Specifically, how can the renin-angiotensin system continue to operate to normalize arterial pressure during sodium depletion when there is a decrease in vascular sensitivity to A II? The quantitative evaluation of the basic components of this control system appears to provide an answer to this problem. That is, there is sufficient enhancement of renin release to overcome the consequences of high circulating levels of A II, even though the system is operating on a less responsive portion of the dose-response curve.

Because of the increasing application of pharmacological blockers of the renin-angiotensin system, it is relevant to point out that this type of analysis is also useful in predicting the changes in pressure that are observed when a blocker is administered at various levels of sodium intake. For example, it has been apparent that patients receiving a low sodium intake at the time the blocker is administered exhibit a significant fall in arterial pressure, whereas those on a high sodium intake do not. According to the present analysis, the observed change in pressure could be predicted on the basis of renin secretion, circulating A II levels, and the body fluid volume status of the individual.

References


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Assessment of Regional Myocardial Blood Flow and Regional Fractional Oxygen Extraction in Dogs, Using $^{15}$O-Water and $^{15}$O-Hemoglobin

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SUMMARY A new approach to the assessment of regional myocardial blood flow and fractional oxygen extraction has been developed using $^{15}$O-water ($H_2^{15}O$) and $^{15}$O-hemoglobin ($^{15}$O-Hb). Bolus doses (1 mCi) of $H_2^{15}O$ and $^{15}$O-Hb were injected 10 minutes apart into the left main coronary artery of 12 normal dogs. Sequential images of regional myocardial tracer clearance were obtained over 5 minutes with a positron camera. Myocardial blood flow calculated from the monoexponential washout of $H_2^{15}O$ after background correction was 78 ± 6 (SE) ml/100 g per min. Functional images of regional blood flow in which the image of peak activity was divided by the integrated image of $H_2^{15}O$ washout were derived by computer processing. These images demonstrated homogeneous blood flow in the normal myocardium. Fractional myocardial O$_2$ extraction was determined from an image of initial distribution of O$_2$ used (obtained by extrapolating back to time zero the series of images obtained after $^{15}$O-Hb administration), divided by initial distribution of O$_2$ delivered (obtained by back extrapolating $H_2^{15}O$ washout). These functional images showed uniform distribution of fractional O$_2$ extraction in the normal myocardium. Thus, these studies show that regional myocardial blood flow and regional oxygen extraction can be measured simultaneously by sequential imaging after serial intracoronary injections of $H_2^{15}O$ and $^{15}$O-Hb.

ALTHOUGH METHODS have been available to measure total myocardial oxygen consumption both in the experimental animal and in man, no technique has been available for the in vivo measurement of regional myocardial oxygen extraction. Since coronary artery disease affects the heart in a heterogeneous manner, the ability to assess serially regional alterations in myocardial oxygen extraction may be of considerable interest in the evaluation of myocardial metabolism in ischemic heart disease. Ter-Pogossian et al. used $^{15}$O-Hb and $H_2^{15}O$ to determine regional cerebral blood flow and regional cerebral fractional oxygen extraction. Total myocardial blood flow and total myocardial oxygen extraction have also been determined by this method. This report describes a method to assess simultaneously regional myocardial fractional oxygen extraction and regional myocardial blood flow in a canine experimental model using intracoronary administration of $^{15}$O-Hb and $H_2^{15}O$.

Methods

Isotope Production

Oxygen-15 ($T_{1/2} = 2$ minutes) was produced in a medical cyclotron located near the positron imaging laboratory. The $^{15}$O was produced by deuteron irradiation of nitrogen gas via the $^{14}$N(d,n)$^{15}$O reaction. The nitrogen gas was passed through a 0.5-liter aluminum target chamber with an aluminum foil window at a flow rate of 0.5 liter/minute while under continuous 6-MeV deuteron irradiation with a 20 to 40-$\mu$A beam current. The nitrogen gas contained 2% O$_2$ which scavenged the $^{15}$O produced as $^{15}$O$^{16}$O. A radioactive gas-handling system allowed the irradiated gas to be passed through selected paths to charcoal furnaces, to a tonometer, or to be recycled through the irradiation box. Trace amounts of ozone and oxides of nitrogen produced by the radiation were removed.

$^{15}$O-Labeled Hemoglobin

Heparinized whole blood obtained from the dog to be studied was initially oxygenated in a tonometer in an
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doi: 10.1161/01.RES.42.4.503

_Circulation Research_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7330. Online ISSN: 1524-4571

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