Role of Renin in Acute Postural Homeostasis

By Suzanne Oparil, M.D., Carlos Vassaux, M.D., Charles A. Sanders, M.D., and Edgar Haber, M.D.

SUMMARY

Plasma renin activity has been measured by radioimmunoassay at frequent intervals after passive upright tilting and correlated with pulse and blood pressure in normotensive man. In the normal response to upright posture, renin activity in both peripheral and renal veins increases consistently within a few minutes. The renin rise lags behind the increase in pulse rate and diastolic blood pressure. Renin activity falls to base-line level soon after return to the horizontal position. In the 25% of normal subjects who develop vasovagal syncope after upright tilting, the increase in renin activity is smaller in magnitude and duration than in the normal response. Renin levels fall just before syncope appears and rise sharply after return to the horizontal position. Anephric patients are able to effect adequate postural adjustments even in the absence of renin activity.

This study indicates that the renin angiotensin system participates in the acute response to postural change in normal man and that it functions abnormally in vasovagal syncope.

Additional Indexing Words:
Angiotensin
Cardiac catheterization
Posture
Sympathetic nervous system
Anephric
Vasovagal syncope
Hemodynamics

In normal man, there is a well-studied hemodynamic response which occurs within minutes of assuming the upright posture. This maintains the arterial blood pressure by increasing peripheral resistance, heart rate, and venous tone. These changes are accompanied by an increase in plasma norepinephrine and urinary catecholamines and have been attributed to increased sympathetic activity. Although renin and aldosterone levels are known to increase in the upright position, the renin-angiotensin system has generally been thought to function in relation to long-term rather than acute circulatory adjustments to the upright posture.

In this investigation, we examine the role of renin in relation to the initiation and maintenance of short-term postural homeostasis in normotensive man.

Methods

Clinical Population

Twenty healthy normotensive volunteers, 11 females and nine males, ranging in age from 19 to 38 years, were studied. None had a history of renal disease or syncope. Except for three females who were taking oral contraceptives, none was taking any medication. No attempt was made to control diet, fluid intake, or the time of day at which studies were carried out. Urinary sodium excretion was not measured in any experimental subject.

Eleven patients, five females and six males, ranging in age from 22 to 61 years, were studied in the course of diagnostic cardiac catheterization. All had hemodynamically significant mitral, aortic, or mixed mitral and aortic lesions. None had a history of hypertension or elevated diastolic...
pressure at rest. Eight of the 11 had elevated left ventricular end-diastolic pressure. Nine of 11 were on salt restricted diets, and seven of 11 had received diuretic therapy within 1 week of the study. Five anephric patients from the renal transplant unit were studied. Four of the five had significant diastolic hypertension at rest and were receiving hydralazine for blood pressure control. One was normotensive on no therapy. All were subject to hemodialysis three times weekly, and were studied at least 24 hours after their most recent dialysis. All were on a 2 g NaCl diet, and none had significant edema at the time of study.

Procedure

Each subject was allowed to rest in the supine position for 20 to 30 min, until pulse rate and blood pressure stabilized; then each was tilted to 80° on a tilt table with a foot rest. The normal volunteers were kept upright for 30 min; the catheterization patients and anephric patients, for 20 min; then all were returned to the horizontal position for an equal period. Several subjects experienced vasovagal symptoms and had to be returned to the horizontal position prematurely. Peripheral pulses and cuff blood pressures were taken at 2-min intervals throughout the study. The catheterization patients had in addition continuous electrocardiographic monitoring. A 19-gauge scalp vein needle was placed in the right arm of each volunteer for sampling of peripheral venous blood. Each catheterization patient had a central venous pressure catheter placed in his superior vena cava for sampling of peripheral blood. A no. 7 retrograde catheter placed under fluoroscopic control in his right renal vein allowed simultaneous sampling of renal venous blood. Blood was obtained from the arterial limb of the Scribner shunt in the anephric patients. All catheters were irrigated at frequent intervals with normal saline; no anticoagulant was used. Blood samples of 5 ml each were drawn during the control period and 1, 3, 5, 10, 20, and 30 min after upward and downward tilting. When a subject developed vasovagal symptoms, a blood sample was obtained before downward tilting.

Samples were anticoagulated with disodium ethylenediamine tetraacetate (EDTA) and iced immediately. Renin activity was determined by radioimmunoassay of generated angiotensin I.14 The method is highly specific and can detect levels of 25 picograms with a variation of 2.9% (1 se).

Results

There were two general patterns of response to upright tilting: (1) the normal response, in which the subject tolerated the entire upright period without untoward symptoms, and (2) vasovagal syncope. Table 1 summarizes the responses of all subjects tested. Twenty-seven of 36 (75%) showed a normal response, while nine of 36 (25%) experienced vasovagal syncope. Four of 20 volunteers (20%), four of 11 catheterization patients (36%), and one of five (20%) anephric patients were in the syncopal group.

Syncopal episodes occurred in various subjects from 30 sec to 15 min after upright tilting, the majority occurring between 10 and 15 min. Vagal symptoms, chiefly a “queasy, gassy feeling,” flushing, sweating, headache, and dizziness, preceded hemodynamic changes and loss of consciousness by 1 to 4 min. Recovery occurred within seconds of returning to the horizontal position. It was not

Table 1

<table>
<thead>
<tr>
<th>Classification of Subjects and Their Response to Tilting</th>
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<tbody>
<tr>
<td>Normal response</td>
</tr>
<tr>
<td>-----------------</td>
</tr>
<tr>
<td>Normal volunteers</td>
</tr>
<tr>
<td>Catheterization patients</td>
</tr>
<tr>
<td>Anephrics</td>
</tr>
<tr>
<td>Total</td>
</tr>
</tbody>
</table>

Figure 1

Maximum renin activity following upright tilting for all subjects studied. Each renin value is represented as percentage change from base-line level for that particular subject; figures in each column refer to mean ± se. The means were significantly different (P < 0.01) on t-test.
possible to predict which subjects would experience syncope, as their response to upright tilting was normal until the appearance of vagal symptoms. In the catheterization group, the presence of congestive heart failure as measured by right ventricular end-diastolic pressure did not protect against vasovagal syncope.

All 20 of the volunteers and 10 of the 11 catheterized patients showed measurable increases in renin activity following upward tilting. The sole exception was a catheterized patient who had a syncopal episode after 30 sec in the upright position. Figure 1 summarizes the maximum renin values for all subjects when upright expressed as percentage change from baseline level. In the normal responders, renin increased by 60 to 1,000% of baseline value, a mean of $283 \pm 52\%$ (se). In the group of vasovagal fainters, increments in renin activity were smaller. The range was $-23$ to $+178\%$, with a mean of $49 \pm 21\%$ (se). The means of the two groups were significantly different on the $t$-test, $P < 0.01$. There was no detectable renin activity in any anephric patient at any time.

The time course of renin release in the normal volunteers is represented in figure 2. Resting levels varied from 0.13 to 11.70 ng/ml/hr, with a mean of $2.87 \pm 0.80$ ng/ml/hr. The three females taking estrogens had somewhat elevated resting levels. In the normal responders, renin activity rose consistently and significantly ($P = 0.02$) from baseline level within the first 5 min after tilting, continued to rise for 20 min, then plateaued. Renin activity fell rapidly nearly to baseline levels after downward tilting.

The vasovagal fainters showed a different pattern of renin release. Resting levels were similar to those in the normal responders. The mean was $2.93 \pm 1.26$ ng/ml/hr (se), with a range of 0.50 to 5.20. The early increase in renin activity was slightly less than in the normal responders. After 10 min upright, by which time all fainters had vagal symptoms, renin levels fell slightly. This contrasts with a consistent rise in the normal responders. At 10 min upright, the renin activity of the syncopal group was significantly ($P = 0.02$) less than that of the normal responders. In the first minute after downward tilting, a significant increase ($P = 0.015$) in renin activity was seen. A rapid return to base line followed.

These general patterns also applied to the catheterized patients, as shown in table 2. The wide variations in renin levels can be explained by differences in hemodynamics and fluid and electrolyte balance. Because of this and the small numbers in each experimental group, standard errors of the means were large and have been omitted. Renin activity in renal veins paralleled that in peripheral veins but was higher by approximately 60%.

The hemodynamic responses to tilting were remarkably consistent among individuals within each group but did vary from group to group (fig. 2). Resting pulse rates were similar in both groups. Mean resting pulse rate was
Table 2

Mean Renin Activity in Cardiac Catheterization Patients in Response to Tilting

<table>
<thead>
<tr>
<th></th>
<th>Resting</th>
<th>Upright (min)</th>
<th>Supine (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Normal responders (N-7)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Renal vein</td>
<td>1.64*</td>
<td>1.99</td>
<td>2.08</td>
</tr>
<tr>
<td>Superior vena cava</td>
<td>1.02</td>
<td>1.08</td>
<td>1.38</td>
</tr>
<tr>
<td>Fainters (N-4)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Renal vein</td>
<td>3.82</td>
<td>5.24</td>
<td>4.45</td>
</tr>
<tr>
<td>Superior vena cava</td>
<td>2.08</td>
<td>4.68</td>
<td>1.05</td>
</tr>
</tbody>
</table>

*Results are expressed as nanograms of angiotensin I generated/ml of plasma/hour.

72 ± 2 (SE) beats/min (range, 52 to 88) for normal responders and 69 ± 4 (SE) beats/min (range, 60 to 78) for fainters. In both normal responders and fainters there was a uniform increase in the first minute upright. The maximum increase averaged 28 ± 3 beats/min in the normal responders and 26 ± 1 beats/min in the fainters.

The accelerated pulse rate was sustained throughout the upright period in the normal responders, and pulse rate returned to baseline levels within the first 3 min of downward tilting. In the fainters, pulse rate began to fall within 1 min after the appearance of vagal symptoms and 3 to 5 min before syncope. Pulse returned to normal only after 10 to 15 min in the supine position.

In normal responders, systolic blood pressure was stable in the face of the tilt table stimulus, whereas diastolic pressure increased promptly and significantly in response to upward tilting. Resting blood pressures were similar in both groups. Mean resting systolic pressure was 114 ± 8 mm Hg (range, 102 to 128) for the normal responders and 107 ± 3 mm Hg (range, 98 to 116) for the fainters. Mean resting diastolic pressure was 68 ± 5 mm Hg (range, 56 to 86) in the normal responders and 63 ± 4 mm Hg (range, 56 to 72) in the fainters. Mean systolic and diastolic pressures in the normal responders (fig. 2) are expressed as percentage of base-line pressures. There was no significant change in systolic pressure throughout the study. Diastolic pressure increased significantly (P < 0.01) within the first minute upright, plateaued, remained constant during the remainder of the upright period, and then fell to normal within 1 min of return to the horizontal. Thus, pulse pressure narrowed in the upright subjects.

The fainters (fig. 2) showed a slight fall in systolic pressure and an increase in diastolic pressure with a resultant marked narrowing in pulse pressure when upright. There was a symmetric decrease in systolic and diastolic pressures before syncope. Recovery of normal pressures took place in the first minute after return to the horizontal.

Hemodynamic changes in the catheterized patients were similar to those seen in the normal volunteers for both normal responders and fainters.

A comparison of hemodynamic data and renin determinations in normal responders shows that pulse rate and diastolic blood pressure increase before renin rises in the upright posture and that renin continues to rise after pulse and blood pressure have stabilized. Likewise, pulse rate and blood pressure return to normal more rapidly than does renin activity after downward tilting.

Similarly, in the vasovagal fainters, increases in pulse rate and diastolic blood pressure after upright tilting precede the increase in renin. Renin falls shortly after the appearance of vagal symptoms, concomitant with the drop in pulse rate and blood pressure. A sharp, short-lived increase in renin
activity occurs after the faint and the subsequent return to the horizontal. Blood pressure is restored to baseline level immediately after downward tilting; pulse rate returns to normal more slowly.

Figure 3 shows the response of the sole normotensive anephric patient to tilting. This response is hemodynamically similar to the pattern seen in normal responders (fig. 2) except for the increase in systolic blood pressure. Renin activity is absent. The four hypertensive hydralazine-treated anephric patients responded somewhat differently. Pulse rate rose and blood pressure fell immediately after upward tilting. Blood pressure continued to drift downward during the upright period, reaching levels far below the base line. Three of the four anephrics tolerated the procedure well; one experienced typical vasovagal syncope at 17 min.

Discussion

Postural augmentation of renin release in normal man has been documented.\(^8\)\textsuperscript{-11,15} This correlates with increases in aldosterone\(^2\)\textsuperscript{-13} and catecholamine\(^4\)\textsuperscript{-6} production and excretion as well as with changes in renal function.\(^12\),\textsuperscript{16,17} The postural increase in renin activity is independent of sodium intake\(^11\) and occurs in renovascular hypertensives,\(^9,18\) yet is dependent on a diurnal cycle.\(^15\) In most published studies relating plasma renin activity to posture, samples were taken at infrequent intervals, with little documentation of short-term changes in renin level and no extensive correlation with hemodynamic measurements.

The present study has shown that renin activity in both peripheral and renal veins of normotensive man increases consistently within a few minutes of passive upright tilting. The postural increase has been demonstrated at all times of day, with and without sodium restriction, estrogen therapy, and diuretics, in the presence of heart failure, and over a wide range of resting renin activity.

In those subjects who responded normally to the tilt table stimulus, renin began to rise after 5 min upright, peaked at 20 min, and then leveled off. Renin activity returned to normal after downward tilting. The changes in peripheral and renal vein renin activity occurred at the same time. Peripheral vein levels were consistently 60\% of renal vein levels. This suggests that renin equilibrates rapidly with the circulating blood volume and that peripheral vein levels are good indices of renin kinetics in normotensive subjects.

The postural increase in renin activity was preceded by significant increases in pulse rate and diastolic blood pressure, which occurred within 1 min of upright tilting. Systolic blood pressures remained unchanged. This is in agreement with the findings of Brigden and associates,\(^1\) Hellebrandt and Franseem,\(^19\) and Tuckman and Shillingford\(^20\) on unselected normal subjects of widely varying ages.

Anephric patients in this study were able to maintain postural homeostasis despite the absence of renin activity. This and the temporal precedence of hemodynamic changes over renin release suggest that some mechanism other than the renin-angiotensin system has the primary role in initiating acute postural adjustments in normal man. A large body of evidence favors the sympathetic nervous system for this role.\(^4\)\textsuperscript{-7}
The association of elevated diastolic blood pressure with increased renin in the upright subjects and of decreased diastolic pressure with falling renin after return to the horizontal seems paradoxical, since alterations in arterial pressure have been shown to produce inverse changes in renin release.\textsuperscript{21} Altered intrarenal hemodynamics may account for this apparent paradox. In the upright position, renal blood flow and glomerular filtration rate fall\textsuperscript{16, 17} despite maintenance of central arterial pressure; this observation suggests that intrarenal vasoconstriction takes place as part of a widespread systemic vasoconstriction. In this way, decreased blood flow to the glomerulus may contribute to the postural augmentation of renin release.

Twenty-five per cent of our subjects experienced vasovagal syncope on the tilt table at varying intervals after upward tilting. Vagal symptoms always preceded syncope. This has been seen in 20\% of 111 normals subjected to tilt table stress.\textsuperscript{2} In our study, fainters showed hemodynamic adjustments to upright posture identical to those of the nonfainters until vagal symptoms appeared. At that time pulse rate began to decrease and pulse pressure narrowed. Renin levels fell slightly with the appearance of vagal symptoms and continued to fall in the presence of declining blood pressure and bradycardia as long as the subject remained upright. This contrasts with the increase in renin levels which normally occurs in the early minutes of upright tilting. The mechanism of failure of renin release in this situation is obscure. It is clear, however, that there was no absolute impairment in the ability to secrete renin in response to other stimuli, since renin rose markedly as soon as the subject was returned to the horizontal. Abnormalities in renal hemodynamic regulation which are reversible upon downward tilting may prevent renin release during vasovagal hypotension. DeWardener and McSwiney\textsuperscript{22} have demonstrated decreased renovascular resistance in response to posturally induced vasovagal syncope. In this way, blood flow to the glomerulus could be preserved despite falling blood pressure. This would account for the inhibition of renin release observed. DeWardener and McSwiney\textsuperscript{25} also showed that renovascular resistance increased promptly upon return to the horizontal position, accounting for increased renin release observed in our studies.

Expanding intravascular volume does protect against vasovagal syncope\textsuperscript{28} by increasing venous return without affecting peripheral resistance. In patients with congestive heart failure,\textsuperscript{24, 25} venous return and right heart pressures are well preserved following upright tilting. This suggests that such patients should be protected against vasovagal syncope. This was not the case with our experimental group. However, additional factors such as low salt intake, diuretic therapy, valvular obstruction, and low output may have predisposed our patients to postural syncope.

From these experiments it is evident that renin levels change in man within minutes of postural alterations. Renin cannot be evoked as the sole cause of hemodynamic adjustments associated with postural changes, but subjects who experience vasovagal syncope clearly have a different renin response from those who do not.

**Acknowledgment**

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