Role of the Renin-Angiotensin System in Blood Pressure Regulation

The Cardiovascular Effects of Converting Enzyme Inhibition in Normotensive Subjects

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SUMMARY The role of the renin-angiotensin system in the regulation of blood pressure in normal human subjects was investigated by administering to them the converting enzyme inhibitor (SQ 20881) during sodium-replete and sodium-depleted states. In the sodium-replete state (150 mEq sodium intake for 5 days) in eight normal subjects, converting enzyme inhibitor decreased the average mean arterial pressure from 75 ± 4 to 65 ± 5 mm Hg (P < 0.005) because of a decrease in peripheral resistance from 17 ± 1 to 14 ± 1 U (P < 0.025). Cardiac output did not change because of a simultaneous decrease in venous return. Sodium depletion (10 mEq sodium intake for 5 days) in six subjects resulted in an insignificant decrease in blood pressure (from 75 ± 4 to 69 ± 2 mm Hg), whereas cardiac output decreased from 5.15 ± 0.29 to 3.91 ± 0.22 liters/min (P < 0.05). Plasma renin activity increased with sodium depletion from 2.13 ± 0.38 to 7.3 ± 1.3 ng/ml per hour (P < 0.005). Converting enzyme inhibitor administration in the sodium-depleted state (n = 8) decreased mean arterial pressure from 69 ± 2 to 53 ± 5 mm Hg (P < 0.005) because of a decrease in peripheral resistance from 18 ± 1 to 12 ± 1 U (P < 0.005), whereas cardiac output increased from 3.91 ± 0.33 to 4.40 ± 0.30 liters/min (P < 0.005). The maximum decrease in diastolic blood pressure caused by the inhibitor correlated to the control plasma renin activity (r = 0.76, P < 0.01, n = 14 measurements). These results indicate that the renin-angiotensin system participates in the regulation of blood pressure and cardiac function in normal subjects, even in the sodium-replete state. This role of the renin-angiotensin system in cardiovascular homeostasis in normal subjects becomes more crucial during sodium depletion when plasma renin (angiotensin II) is markedly increased.

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RECENT studies (Laragh, 1978) have provided evidence supporting a possible role for the renin-angiotensin system in the pathogenesis and maintenance of elevated arterial pressure in essential and renovascular hypertension in human subjects. This pathogenetic role of angiotensin II has been investigated more precisely because of the availability, initially, of the angiotensin II competitive antagonist, saralasin (P 113), and, more recently, of the inhibitors of the angiotensin-converting enzyme. These agents, unlike saralasin, have no intrinsic agonistic activity, since they act by blocking the conversion of angiotensin I to angiotensin II, thereby eliminating the cardiovascular and endocrine effects of circulating angiotensin II. However, the participation of the renin-angiotensin system in the regulation of arterial pressure in normal human subjects has not been characterized fully because so far no complete hemodynamic measurements have been performed in normal subjects during converting enzyme inhibition. Haber and associates (Sancho et al., 1976; Haber, 1976), by administering the converting enzyme inhibitor in sodium-repleted and sodium-deprived normal subjects, concluded that angiotensin II is essential for blood pressure maintenance in normal subjects, but only in the sodium-depleted state.

The purpose of the present study was to investigate further the role of the renin-angiotensin system in sodium-repleted and sodium-depleted normal human subjects given the converting enzyme inhibitor (SQ 20881), Teprotide) in its usual antihypertensive dose (1 mg/kg of body weight). In this study, not only were effects on blood pressure and heart rate followed, but concurrent effects on cardiac output, peripheral resistance, left ventricular function, and venous tone, as well as on renin secretion and catecholamine release, also were studied.

Our results indicate that angiotensin II inhibition results in an important decrease in blood pressure (from 5 to 26 mm Hg, or by 10–42% of control) in sodium-replete normotensive subjects, and this effect is due to the concurrent decrease in peripheral resistance. However, the hypotensive effects of the
Subjects

Eight paid, fully informed, and consenting normal volunteers were investigated. Seven were male and one was female. Their ages ranged from 26 to 58 years. All subjects were screened during a preliminary outpatient visit when they were found to be normal by history and a brief clinical examination. A consent form (approved by the Human Rights Research Committee), describing in detail the various parts of the protocol (metabolic diet, invasive hemodynamic studies, administration of a new investigational drug), was presented, and all subjects signed it according to their own free will. A provision in the protocol stated that subjects would be allowed to withdraw from these studies at any time during the protocol period. Those subjects initially found to be normal, but after admission to the hospital discovered to have any abnormalities in their routine laboratory tests, were excluded from the study.

Methods

All subjects (n = 8) were admitted to the Clinical Research Center and were placed on an isocaloric diet containing 10 mEq of sodium and 60 mEq of potassium per 24 hours. During the normal sodium-intake period, 140 mEq of sodium were added to the diet. The first administration of the SQ 20881 and the hemodynamic study (see below) were performed on the 5th day of the diet when metabolic balance had been achieved. The added sodium then was removed from the diet, and the second administration of the SQ 20881 and hemodynamic study were repeated on the 5th day of the 10-mEq/24 hour sodium diet. Blood pressure and body weight were recorded daily during both diet periods. Urine was collected daily for sodium and potassium determination (by flame photometry). Urinary aldosterone was measured by radioimmunoassay (Sealey et al., 1972) on the day of the hemodynamic study on both the 150- and 10-mEq sodium diets. Plasma renin activity was measured by radioimmunoassay (Sealey and Laragh, 1975).

Hemodynamic Measurements

During the hemodynamic studies, blood pressure was recorded continuously intraarterially from the brachial artery through a catheter (Seldicath, Abbott Laboratories) and a Statham transducer on the E for M recorder. Central venous pressure was recorded through a venous catheter (Abbocath, Abbott Laboratories) and a Statham transducer on the E for M recorder. Both catheters were introduced percutaneously under local anesthesia. Heart rate was counted from the continuously recorded electrocardiogram (lead II) on the E for M recorder.

Cardiac output (in duplicate) was measured by dye dilution. A dose of 5 mg of cardiogreen (Hynson, Westcott and Dunning Inc.) was injected through a connecting tube, which was attached to the venous catheter. Blood was drawn with a Harvard pump (25 ml/min) through a tubing system and cuvette densitometer (Lexington Instruments Corporation), which was connected to the arterial catheter. The cardiac output curves were inscribed on paper on the E for M recorder. The arterial blood was reinfused after the inscriptions of each cardiac output curve. Cardiac output was calculated according to the method of Stuart and Hamilton (Yang et al., 1978). All derived variables were calculated from the cardiac output, heart rate, and blood pressure values, according to standard formulas (Yang et al., 1978). In our laboratory, cardiac output measurement by dye dilution has a variability of 4-7% \( r = 0.96, n = 20 \) measurements.

In addition to cardiac output, the mean rate of left ventricular ejection (MRLVE) was used as an index of left ventricular function. The MRLVE was derived by dividing stroke volume by ejection time during systole. Ejection time was calculated from the beginning of the upstroke of the blood pressure pulse to the dicrotic notch. The averaged value of five consecutive pressure curves was used for the calculation of MRLVE.

Study Protocol

The hemodynamic studies were performed with the subject in the seated position during both diets, according to the following protocol: after the arterial and venous catheters had been introduced and the initial recordings of pressures and cardiac output in the supine position obtained, the subject was seated in a comfortable chair. When blood pressure and heart rate had stabilized, usually within half an hour after changing to the seated position, and after readjustment of both transducers to the heart level, central venous pressure (when possible), arterial pressure, (phasic and electronic mean), and cardiac output were recorded. Blood was drawn, processed, and stored appropriately for the measurement of plasma renin activity and plasma catecholamines. Plasma catecholamines were measured by the radioenzymatic method by Upjohn Laboratories (Upjohn Laboratory Procedures, Inc.). The coefficient of variation of this method is 3-7%. After we obtained the control measurements, the converting enzyme inhibitor (SQ 20881 or Teprotide, Squibb Institute for Medical Research) was injected intravenously (1 mg/kg of body weight) over a 2-minute
period. The electrocardiogram (heart rate) and venous and arterial pressures were monitored throughout the period of each study. Cardiac output measurements and blood samples for renin and catecholamines were taken again 15 and 30 minutes after the administration of the inhibitor. At the end of each study, in the seated position, the subjects were asked to stand for 5 minutes, and after the readjustment of the transducers, all hemodynamic measurements were repeated in the standing position. This phase of the study was performed in only four subjects on both sodium diets, and no biochemical measurements are available.

All results are expressed as mean ± SEM. The significance of the results was assessed by using the paired or unpaired Student's t-test as indicated, and correlation coefficients were calculated by the Spearman method. Values of $P$ less than 0.05 were accepted as significant.

Results

Effects of the Converting Enzyme Inhibitor during the 150-mEq Sodium Intake

In all subjects on the day of the hemodynamic study, the 24-hour urine excretion was 136 ± 6 mEq. The control (before the administration of the inhibitor) plasma renin activity in the seated position was 2.01 ± 0.35 ng/ml per hour. The effects of the inhibitor on mean arterial pressure in each normal subject 15 and 30 minutes after the administration of the inhibitor are shown in Table 1. It can be seen that, although the average decrease in mean arterial pressure was significant at both the 15- and 30-minute periods, a substantial decrease (i.e., by more than 5 mm Hg or by 10% of control) in mean arterial pressure occurred in five of the eight subjects, whereas, in the remaining three (subjects 1, 4, 7), no decrease in blood pressure was observed. In the five subjects who responded to the inhibitor, the control plasma renin activity was 2.5 ± 0.04 ng/ml per hour (Fig. 1), whereas, in the three nonresponders, the control plasma renin activity was 1.2 ± 0.3 ng/ml per hour ($P < 0.05$). The 24-hour sodium in the urine was 135 ± 10 and 120 ± 12 mEq, respectively ($P$:NS).

The hemodynamic effects of the inhibitor are shown in Figure 2. In all subjects ($n = 8$) 15 minutes after the administration of the inhibitor, mean arterial pressure was decreased from 75 ± 4 to 65 ± 5 mm Hg (or by 13 ± 4%, $P < 0.005$), and the fall in pressure was caused by a decrease in total peripheral resistance, from 17 ± 1 to 14 ± 1 U (or by 16 ± 6%, $P < 0.025$); cardiac output did not change. Heart rate was increased slightly (Fig. 2). Central venous pressure (measurement available in six sub-

![Figure 1 Control plasma renin activity (PRA) and blood pressure response to SQ 20881 in normal subjects during the 150- and 10-mEq sodium intake. During the 150-mEq sodium intake, the responders (R) to SQ 20881 had significantly higher control PRA in comparison with the nonresponders (NR). The control PRA was significantly higher during the 10-mEq sodium intake.](http://circres.ahajournals.org/lookup/fig/1)

### Table 1

<table>
<thead>
<tr>
<th>Subject no.</th>
<th>Control (ng/ml/h)</th>
<th>15 min post CEI</th>
<th>30 min post CEI</th>
<th>Control (ng/ml/h)</th>
<th>15 min post CEI</th>
<th>30 min post CEI</th>
</tr>
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<td>39*</td>
<td>36*</td>
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<td>2</td>
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<td>83</td>
<td>86</td>
<td>ND</td>
<td>ND</td>
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</tr>
<tr>
<td>3</td>
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<td>83</td>
<td>78</td>
<td>92</td>
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<td>48*</td>
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<td>62</td>
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<td>49*</td>
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<td>Mean ± SEM</td>
<td>75 ± 3</td>
<td>65 ± 3</td>
<td>65 ± 3</td>
<td>69 ± 2</td>
<td>56 ± 3</td>
<td>53 ± 5</td>
</tr>
</tbody>
</table>

$P < 0.05$ $P < 0.01$ $P < 0.0005$ $P < 0.005$

ND = not done; CEI = converting enzyme inhibitor; $P$ = comparison with control.

* Subject fainted.
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**Figure 2.** Hemodynamic effects of the converting enzyme inhibitor during the 150- and 10-mEq sodium intake. MAP = mean arterial pressure; TPR = total peripheral resistance; CO = cardiac output; HR = heart rate. * = significantly different from control.

Plasma renin activity was increased by the inhibitor (Fig. 3) from 2.01 ± 0.35 to 4.16 ± 1.14 ng/ml per hour (or by 100 ± 37%, P < 0.025). The decrease in blood pressure and peripheral resistance was still maintained 30 minutes after the administration of the inhibitor (Fig. 2), whereas the slight increase in heart rate (by 4 ± 1%) was now just significantly greater than the control value (P < 0.05). The central venous pressure at this point also remained below the control value. The mean rate of left ventricular ejection was not significantly affected by the inhibitor, the control values being 279 ± 42 ml/sec and 261 ± 40 ml/sec 15 and 30 minutes after SQ 20881, respectively. Plasma renin activity (average value in all subjects) increased to 5.23 ± 1.27 ng/ml per hour (or by 146 ± 26%, P < 0.01) 30 minutes after SQ 20881 (Fig. 3).

Plasma catecholamines did not change following the administration of SQ 20881. The control epinephrine in the seated position was 74 ± 15 pg/ml, 87 ± 16 pg/ml 15 minutes after SQ 20881 (0.10 > P > 0.05) and 90 ± 24 pg/ml 30 minutes post SQ 20881. Plasma norepinephrine levels were 301 ± 35 pg/ml, 368 ± 65 pg/ml, and 332 ± 58 pg/ml, respectively.

The hemodynamic changes during 5 minutes of standing (about 40 minutes after SQ 20881 administration) are shown in Figure 4. Mean arterial pressure increased slightly but significantly (by 14 ± 4%, P < 0.01), mainly because of an increase in diastolic blood pressure. The increase in mean arterial pressure was caused by the concurrent increase in peripheral resistance (by 45 ± 5%, P < 0.01), whereas cardiac output fell during standing by 31 ± 1% (P < 0.025), despite the concurrent increase in heart rate (by 18 ± 6%, P < 0.05).

**Humoral and Hemodynamic Effects of Sodium Depletion**

Although all eight subjects completed the hemodynamic studies during the 150-mEq sodium intake period, in two subjects, hemodynamic studies could not be repeated (inability to introduce venous catheter percutaneously) during the 10-mEq sodium intake period. Thus, the humoral and hemodynamic effects of sodium depletion in six subjects who undertook both hemodynamic studies during the 150- and 10-mEq sodium intake are shown in Table 2.

**Effects of Converting Enzyme Inhibitor during Sodium Depletion (n = 6)**

The effects of the inhibitor on mean arterial pressure in each subject also are shown in Table 1. During the sodium-depleted state, all subjects showed a marked decrease in blood pressure, including those (subjects 4, 7) who did not exhibit a hypotensive response during the sodium-replete state. The control plasma renin activity in each individual subject is shown in Figure 1.

The hemodynamic effects of the inhibitor are shown in Figure 2. Fifteen minutes after its administration, mean arterial pressure was decreased from 69 ± 2 to 56 ± 3 mm Hg (or by 19 ± 3%, P < 0.0005), and this fall in pressure was due to a decrease in peripheral resistance, from 18 ± 1 to 14 ± 1.5 U (or by 23 ± 3%, P < 0.005). Cardiac output and heart rate were not significantly increased at this time. Central venous pressure (readings available in four of the six subjects) was decreased by 2 mm Hg in one subject and increased from 3 to 11 mm Hg in the remaining three subjects. The mean rate of left ventricular ejection 15 minutes post SQ 20881 increased from 197 ± 21 to 207 ± 25 ml/sec (P:NS) and to 221 ± 16 ml/sec 30 minutes post SQ 20881 (or by 24 ± 8%, P < 0.025). The hemodynamic
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75-
MAP (mmHg)
65-
55-
Standing
Sitting
HR (beats/min)
85-
75-
65- l-r
MAP (mmHg)
85-
75-
65 l-r
TPR (units)
15-
10
Standing
Sitting
50-
Cordioc
Output 40-
(L/mm)
30
50-

FIGURE 4  Hemodynamic effects of standing during angiotensin II blockade with the converting enzyme inhibitor (n = 4) in the sodium-replete and sodium-depleted state. * = significantly different from sitting.

effects of the inhibitor, with the exception of heart rate, were more pronounced at the 30-minute period (Fig. 2).

Plasma catecholamines were not affected by the inhibitor. Thus, the control plasma epinephrine was 54 ± 10 pg/ml; 15 minutes after the administration of SQ 20881, plasma epinephrine was 73 ± 9 pg/ml; 30 minutes after SQ 20881, plasma epinephrine was 91 ± 14 pg/ml. The level of plasma norepinephrine was 367 ± 109, 395 ± 97, and 358 ± 83 pg/ml, respectively.

The hemodynamic changes produced by assuming the standing position on the 10-mEq sodium diet and 40 minutes after the administration of the SQ 20881 are shown in Figure 4. Mean arterial pressure was increased slightly because of an increase in diastolic blood pressure. Pressure was maintained by an increase in peripheral resistance (P < 0.05), whereas cardiac output fell by 30 ± 4% (P < 0.005). The increase in heart rate was variable, averaging 30 ± 7% (0.10 > P > 0.05).

Comparison between Hemodynamic Effects of the Inhibitor on 150- and 10-mEq Sodium Intakes (n = 6)

In the six subjects who went through both studies, the hemodynamic effects and effects on plasma renin activity of the inhibitor were significantly greater during the 10-mEq sodium intake. Thus, during the low sodium intake, and at the 30-minute period after the administration of the inhibitor, the decrease in mean arterial pressure was 24 ± 5% of control, the decrease in peripheral resistance was 34 ± 5%, and the increase in cardiac output was 14 ± 3%. The increase in plasma renin activity was 296 ± 64%. All these changes induced by the inhibitor are significantly greater in comparison with the respective changes during the 150-mEq sodium intake. During standing (n = 4), the average decrease in systolic blood pressure during the 150-mEq sodium diet was 4 mm Hg, whereas the average increase in diastolic blood pressure was 16 mm Hg. During the 10-mEq diet, standing resulted in a greater decrease in systolic blood pressure (average −16 mm Hg), whereas the increase in diastolic blood pressure was attenuated (+9 mm Hg).

Relationship of the Converting Enzyme Inhibitor-Induced Hemodynamic Changes to Plasma Renin Activity

In all subjects, a significant correlation (Fig. 5) existed between control plasma renin activity and the maximum decrease in diastolic blood pressure (r = 0.76, P < 0.01, n = 14 measurements). A stronger correlation existed between the control plasma renin activity and the maximum decrease caused by the inhibitor in the diastolic blood pres-

### Table 2  Hemodynamic and Humoral Effects of Sodium Depletion in Normal Subjects (n = 6)

<table>
<thead>
<tr>
<th>Sodium intake (mEq/24 hrs)</th>
<th>150 mEq</th>
<th>10 mEq</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate (beats/min)</td>
<td>65 ± 3</td>
<td>69 ± 5</td>
<td>NS</td>
</tr>
<tr>
<td>Mean arterial pressure (mm Hg)</td>
<td>75 ± 4</td>
<td>69 ± 2</td>
<td>NS</td>
</tr>
<tr>
<td>Cardiac output (liters/min)</td>
<td>5.15 ± 0.29</td>
<td>3.91 ± 0.33</td>
<td>&lt; 0.025</td>
</tr>
<tr>
<td>Peripheral resistance (U)</td>
<td>14 ± 1</td>
<td>18 ± 1</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>Mean rate of left ventrical ejection (ml/sec)</td>
<td>279 ± 42</td>
<td>197 ± 21</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>Plasma epinephrine (pg/ml)</td>
<td>73 ± 18</td>
<td>64 ± 10</td>
<td>NS</td>
</tr>
<tr>
<td>Plasma norepinephrine (pg/ml)</td>
<td>279 ± 23</td>
<td>366 ± 109</td>
<td>NS</td>
</tr>
<tr>
<td>Plasma renin activity (ng/ml per hr)</td>
<td>2.13 ± 0.38</td>
<td>7.36 ± 1.3</td>
<td>&lt; 0.005</td>
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<tr>
<td>Urine sodium (mEq/24 hr)</td>
<td>136 ± 6</td>
<td>13 ± 4</td>
<td>&lt; 0.0005</td>
</tr>
<tr>
<td>Urine potassium (mEq/24 hr)</td>
<td>66 ± 6</td>
<td>67 ± 8</td>
<td>NS</td>
</tr>
<tr>
<td>Urine aldosterone (µg/24 hr)</td>
<td>10 ± 2</td>
<td>36 ± 7</td>
<td>&lt; 0.005</td>
</tr>
<tr>
<td>Body weight (kg)</td>
<td>74.15 ± 3.44</td>
<td>72.87 ± 3.51</td>
<td>&lt; 0.005</td>
</tr>
</tbody>
</table>

NS = not significant.
Figure 5 Relationship between control PRA and maximal decrease in diastolic blood pressure (DBP) during both the 150- and 10-mEq sodium intake.

Discussion

Role of the Renin-Angiotensin System in Blood Pressure Regulation in Normal Subjects

The results of the present study clearly show (Table 1) that converting enzyme inhibition decreases arterial pressure in normal subjects (63% of the subjects studied), even in the sodium-replete state. During the sodium-replete state, the responders to the converting enzyme inhibitor had significantly higher control plasma renin activity in comparison with the nonresponders (Fig. 1). The decrease in diastolic blood pressure caused by the inhibitor was related to the control plasma renin activity, although not significantly ($r = 0.53$), possibly because of the small number of subjects studied ($n = 8$). In one subject, the marked decrease in blood pressure without concurrent increase in flow was associated with fainting. These observations taken all together support the view that angiotensin II participates in the regulation of arterial pressure in normal subjects, often even in the sodium-replete state and while exhibiting "normal" renin values. However, some normal subjects whose renin levels are on the lower side of the normal range, such as the nonresponders of the present study, probably maintain blood pressure mainly by sodium-volume factors, since these subjects responded to SQ 20881 after sodium depletion. Thus it appears that in normotensive subjects, just as in subjects with various types of hypertension (Case et al., 1977), plasma renin activity levels in excess of about 2 ng/ml per hour begin to participate increasingly in the regulation of arterial pressure.

Our findings are similar to those of Haber and associates (Sancho et al., 1976; Haber, 1976), who reported that converting enzyme inhibition decreased blood pressure but transiently and by a smaller degree in normal subjects during a 110-mEq sodium intake. In our study, however, a more sustained effect on blood pressure was observed. Differences in procedure may account for this discrepancy. First, Haber and associates (Sancho et al., 1976; Haber, 1976) may have had less range of variation in control renin levels than we encountered. Thus, had we studied only normal subjects with the lower renin values (nonresponders of the present investigation), we may have reached similar conclusions. Second, our studies were performed with the subjects in the seated position, which is associated with a slight reduction in cardiac output, an increase in peripheral resistance, and activation of the renin angiotensin system (Niarchos et al., unpublished observations), probably because of the increase in renal sympathetic nerve activity associated with sitting. Third, we administered a larger dose of the inhibitor (1 mg/kg/body weight); Haber and associates administered 0.25 mg/kg/body weight. It is known that the hypotensive and other effects of the converting enzyme inhibitor are dose dependent (Bianchi et al., 1973). Our findings are supported further by studies in normotensive, normovolemic animals in which antibody to converting enzyme decreased blood pressure by a nonimmune mechanism (Soffer and Sonneblick, 1978).

The hypotensive effects of converting enzyme inhibitor were more pronounced in the sodium-depleted state (Table 1, Fig. 2). Even the nonresponders in the sodium-replete state exhibited a marked hypotensive response to SQ 20881, and during these studies, three subjects fainted. In the sodium-depleted state, the decrease in diastolic blood pressure caused by the inhibitor was strongly correlated with the control plasma renin activity ($r = 0.81$). As a group, the six subjects during the low
sodium intake had a significantly higher renin than the nonresponders and responders during the sodium-replete state (Fig. 1). The above findings taken together strongly support the view that, in normal human subjects, as in the normal dog (Liang et al., 1978), and in hypertensive human subjects (Gavras et al., 1974) and during sodium and volume depletion in both animal and man (Haber, 1976; Miller et al., 1975; Coleman et al., 1975), activation of the renin-angiotensin system is the most important compensatory mechanism in blood pressure maintenance during sodium and volume depletion. Furthermore, the observations of the present study that normal subjects are nonresponsive to the converting enzyme inhibitor in the sodium-replete state, but become responsive to the inhibitor during sodium depletion, provide evidence that the bipolar concept of volume-vasoconstriction can be applied to explain blood pressure regulation not only in hypertensive (Laragh, 1973) but also in normotensive human subjects.

**Hemodynamic Effects of Converting Enzyme Inhibitor in Normal Subjects**

The decrease in blood pressure after the administration of the inhibitor was due to a decrease in peripheral resistance (peripheral vasodilation) during both the sodium-replete and sodium-depleted states (Fig. 2). Similar action has been documented in the normal dog (Liang et al., 1978) and in hypertensive subjects (Niarchos et al., 1978; 1979). The hemodynamic effects of the inhibitor were enhanced during the sodium-depleted state, when peripheral resistance had increased. The vasoconstrictor effects of angiotensin II on cardiac output and increased survival during the administration of the converting enzyme inhibitor during the sodium-depleted state may be explained by vasoconstriction due to sympathetic nervous stimulation resulting from the marked decrease in blood pressure, since plasma epinephrine increased by 42%; although this change was not significant because of the small number of subjects, it probably had a vasoconstrictor effect (Shepherd and Vanhoutte, 1975).

The increase in stroke volume (and hence cardiac output) caused by the converting enzyme inhibitor during the sodium-depleted state in normal subjects with elevated plasma renin levels is consistent with our previous findings in hypertensive subjects with elevated plasma renin activity (Niarchos et al., 1978, 1979). The present study was not designed to assess the effects of SQ 20881 on myocardial contractility. However, it is known that, although angiotensin II has a positive inotropic effect on the isolated papillary muscle (Koch-Weser, 1964; Dempsey et al., 1971), it nevertheless has a negative inotropic effect in the intact heart (Ahmed et al., 1975). A myocardial depressant factor has been identified in some shock states and was significantly diminished by the SQ 14225 converting enzyme inhibitor with hemodynamic improvement (Trachte and Lefer, 1978). Moreover beneficial hemodynamic effects and increased survival during the administration of SQ 20881 converting enzyme inhibitor have been observed in marked hypovolemia caused by extensive hemorrhage (Morton et al., 1977). Coronary blood flow, not measured in the present study, has been found to increase during angiotensin inhibition with SQ 20881 in the normal sodium-depleted dog (Liang et al., 1978; Gavras et al., 1978), and such a mechanism may have contributed to the improvement in cardiac function in the normal subjects of our study.

One of the main determinants of the increase in stroke volume after angiotensin inhibition during the sodium-depleted state in the present study probably was the reduction by the inhibitor in afterload (peripheral resistance) with the consequence of better ventricular emptying. Similar changes in peripheral resistance have been observed in the sodium-depleted normal dog (Liang et al., 1978).
In our study during the sodium-depleted state, the changes in peripheral resistance induced by the inhibitor were related to the control plasma renin activity (r = 0.77) as has been observed in hypertensive patients (Niarchos et al., 1978; 1979) and in patients with heart failure associated with increased plasma renin activity (Curtis et al., 1978).

During the sodium-replete state, however, the decrease in afterload caused by the inhibitor, although smaller in magnitude, did not result in an increase in cardiac output, because the concurrent decrease in central venous pressure due to the dilation of the capacitance vessels and consequent decrease in the filling pressure of the heart counteracted the effects of afterload reduction on cardiac output. On the contrary, during the sodium-depleted state when the filling pressure was maintained during angiotensin inhibition (as can be inferred by the fact that venous pressure increased), stroke volume and cardiac output were increased. Thus, it appears that the increase in cardiac function caused by the converting enzyme inhibitor in the sodium-depleted state has a dual hemodynamic basis: a decrease in afterload and preservation of, or an actual increase in, venous return.

The increase in the mean rate of left ventricular ejection during angiotensin inhibition further supports the view that cardiac performance increased. Although this index of ventricular function is an insensitive one, it nevertheless represents the combined effects of the inhibitor on venous return, myocardial contractility, and afterload (Yang et al., 1978).

Role of Bradykinin

The converting enzyme inhibitor also blocks the degradation of bradykinin and, thereby, may potentiate, at least under some circumstances (Williams and Hollenberg, 1977), the vasodilatory (arteriolar and venous) effects of bradykinin (Ferreira et al., 1970). Although bradykinin plasma levels were not measured in the present study, evidence from previous studies in which bradykinin levels were not found to be increased (Sancho et al., 1976; Miller et al., 1975; Vinci et al., 1977) support the view that the hypotensive and other hemodynamic effects observed during converting enzyme inhibition are due mainly to the inhibition of the effects of angiotensin, rather than to the potentiation of bradykinin. Furthermore, angiotensin II antagonism with saralasin, an angiotensin analogue which in the dose used does not have an effect on bradykinin degradation, does decrease blood pressure in the sodium-depleted normal subject (Fagard et al., 1978).

It may be argued that sodium depletion or other physiological maneuvers activate in parallel the renin-angiotensin system and the kinin system (Margolius et al., 1974; Wong et al., 1975). If that were universally the case, then in our subjects an important rise in bradykinin during sodium depletion should have prevented the increase in peripheral resistance by producing vasodilation, but the opposite, that is vasoconstriction, was observed (Table 2). Moreover, acute bradykinin administration increases cardiac output mainly by a marked increase in heart rate, whereas its effects on stroke volume are rather small and inconsistent (Haddy et al., 1970). This hemodynamic response is the reverse of the one observed in the present and previous studies (Niarchos et al., 1978, 1979) in which cardiac output was increased because of an increase in stroke volume. The preliminary evidence (Vinci et al., 1977) supporting a possible role for prostaglandin E (vasodilatory) accumulation in the fall of blood pressure after converting enzyme inhibitor administration needs further confirmation.

Baroreflex Function during Angiotensin Inhibition

In the present study, as well as in previous studies in normal human subjects (Haber, 1976), normal dogs (Liang et al., 1978), and in hypertensive human subjects (Niarchos et al., 1978, 1979), the expected compensatory increase in heart rate during the fall in blood pressure after SQ 20881 administration was either minimal or virtually absent. Although the mechanism for this phenomenon needs further investigation, inhibition of angiotensin II may eliminate (Curtis et al., 1978) the hormone's potentiating effects on catecholamine release, but this does not appear to be the case in the present study, since plasma catecholamines were not decreased significantly by the inhibitor. Furthermore, it is possible that the gradual decrease in blood pressure somehow modulates baroreceptor responsiveness, or angiotensin inhibition may enhance parasympathetic activity (Bravo and Tarazi, 1978).

Although the baroreflex during angiotensin inhibition appears to be inoperative in the supine (Niarchos et al., 1978; Cody et al., 1978) and seated position (Niarchos et al., 1978), our results provide evidence that baroreflex function is normal during converting enzyme inhibition, as can be judged from the tachycardia and vasoconstriction (Fig. 4) which occur during a short period of standing. Similar findings during short periods of head-up tilt have been reported (Cody et al., 1978) in hypertensive patients during chronic angiotensin inhibition with the oral converting enzyme inhibitor SQ 14225. However, in other studies in normal subjects (Haber, 1976; Sancho et al., 1976), when prolonged (30 minutes) head-up tilt was used during angiotensin inhibition combined with volume depletion, marked decreases in blood pressure and fainting occurred. The findings from these later studies are suggestive that a marked reduction in cardiac output caused by the prolonged passive head-up tilt probably contributed to the hypotension induced by angiotensin inhibition.

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