Haemodynamics of orally-active converting enzyme inhibitor (SQ 14225) in hypertensive patients

R. J. CODY, JR, R. C. TARAZI, E. L. BRAVO AND F. M. FOUAD

Research Division, The Cleveland Clinic Foundation, Cleveland, Ohio, U.S.A.

(Received 21 February 1978; accepted 14 June 1978)

Summary

1. The haemodynamic effects of oral converting enzyme inhibitor (SQ 14225) were assessed in eight patients with severe essential or renovascular hypertension.

2. Mean arterial pressure fell (149 ± 5 to 127 ± 8 mmHg, P < 0.02), because of a fall in total peripheral resistance (6.9 ± 0.53 to 5.7 ± 0.40 kPa l⁻¹ s m⁻²) without a significant change in cardiac index. Two of the eight patients were non-responders without pressure reduction or a haemodynamic change. Sodium restriction (10 mmol/day) while the same dose of SQ 14225 was continued further lowered arterial pressure (137 ± 8 to 111 ± 12 mmHg, P < 0.05) through further resistance reduction (6.5 ± 0.53 to 5.2 ± 0.40 kPa l⁻¹ s m⁻², P < 0.05).

3. Haemodynamic responses to head-up tilt (increased heart rate and resistance, decreased cardiac index) were unaffected by SQ 14225 regardless of sodium intake.

4. The pattern of reduction in peripheral resistance, with unchanged cardiac index, was similar to that produced by vasodilators acting at both arteriolar and venular levels.

Key words: baroreceptor response, converting enzyme inhibitor, renin–angiotensin haemodynamics, SQ 14225.

Introduction

Despite intensive investigations, the exact role of the renin–angiotensin system in different types of hypertension has not been precisely established. The key step in the renin cascade is the formation of angiotensin II, whose potent pressor effect is well recognized (Bunag, 1974; Johnson & Davis, 1973), including its possible role in initiating renovascular hypertension (Miller, Samuels, Haber & Barger, 1975). In light of this, several compounds have been employed that either specifically antagonize angiotensin II (Khosla, Hall, Smeby & Bumpus, 1974; Hollenberg, Williams, Barger, Ishikawa & Adams, 1976; Bravo, Khosla & Bumpus, 1975; Oparil & Haber, 1974) or inhibit the enzyme (a dipeptidyl carboxypeptidase) responsible for its formation from angiotensin I (Collier, Robinson & Vane, 1973; Williams & Hollenberg, 1977; Gavras, Brunner, Laragh, Sealey, Gavras & Vukovich, 1974; Sancho, Re, Burton, Barger & Haber, 1976; Keim, Kirpan, Peterson, Murphy, Hassert & Poutsiake, 1972).

Despite the development of many angiotensin antagonists and an intravenous converting enzyme inhibitor (SQ 20881), little has been reported regarding the systemic or pulmonary haemodynamic effect of interfering with the potent angiotensin pressor mechanism. Yet evaluation of altered angiotensin mechanisms is important for developing this approach to antihypertensive therapy, and establishing safe guidelines for potential clinical application.

We have evaluated the haemodynamic response
of patients with renovascular and essential hypertension to orally-active converting enzyme inhibitor (SQ 14225) (Ondetti, Rubin & Cushman, 1977) under different conditions of sodium intake. Our initial experience with the newly developed SQ 14225 suggests that the haemodynamic effects of enzyme inhibition are quite different from those of angiotensin analogues (Bravo & Tarazi, 1978; Wallace, Keim, Case, Lopez & Laragh, 1976).

Methods

Patients

Eight patients (five men, three women) aged 37–65 years, with either severe essential or renovascular hypertension, were studied. Clinical findings are summarized in Table 1. After approval by the Research Projects and Institutional Review Committee of the Cleveland Clinic Foundation, the investigational nature of SQ 14225 and details of the haemodynamic study were discussed with the patients and all freely consented to participate.

Patients were removed from previous drug regimens, except for one (L.A.) who was maintained on frusemide (80 mg/day) and spironolactone (150 mg/day) through all phases of the study, because of previous congestive heart failure. All patients were maintained on a 100 mmol of sodium/day, isocaloric, diet throughout the study. They were studied after being maintained for at least 3 days on the maximal allowed dose of SQ 14225 (250 mg every 6 h in four patients) or on a dose that normalized blood pressure (mean 80 ± 40 mg every 6 h in four patients). Patients underwent haemodynamic evaluation during the following phases: control (8/8 patients), maintenance SQ 14225 therapy (normotensive response or maximum of 1000 mg/day) (8/8 patients), and after withdrawal of SQ 14225 (5/8 patients), over 2–3 weeks. Of the eight patients studied, two whose mean arterial pressure fell less than 10 mmHg at the time of their second study (maintenance SQ 14225) were considered clinical non-responders; the remaining six were considered responders.

From the group of eight patients, three responders to SQ 14225 (but not to normotensive values) as well as one of two non-responders were placed on a 10 mmol of sodium/day diet in addition to SQ 14225 and restudied after 3–5 days of combined therapy. All patients were studied without premedication, in the morning after an overnight fast and after at least 30 min of supine rest.

Table 1. Initial data for patients

Values obtained from patients during the equilibration period before haemodynamic study. Patient no. 5 (L.A.) was on diuretic therapy at this time; all others were withdrawn from previous medication. PRA = plasma renin activity (pmol h⁻¹ ml⁻¹) (at time of admission); LVH = left ventricular hypertrophy; CRI = chronic renal insufficiency; CVA = cerebrovascular accident (old); CHF = congestive heart failure (by history). Response to SQ 14225 (+) is defined as at least 10 mmHg mean arterial pressure decrement with 3–7 days of SQ 14225 therapy while on a 100 mmol of sodium/day diet.

<table>
<thead>
<tr>
<th>Patient no.</th>
<th>Age (years)</th>
<th>Aetiology*</th>
<th>Blood pressure† (mmHg)</th>
<th>Fundi grade‡</th>
<th>Target organ changes</th>
<th>Serum creatinine (mmol/l)‡‡</th>
<th>Plasma volume (ml/cm)</th>
<th>PRA</th>
<th>Response to SQ 14225</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (J.B.)</td>
<td>49/M</td>
<td>Essential</td>
<td>189/119</td>
<td>2</td>
<td>LVH</td>
<td>0·11</td>
<td>19·4</td>
<td>0·3</td>
<td>–</td>
</tr>
<tr>
<td>2 (J.D.)</td>
<td>65/F</td>
<td>Essential</td>
<td>188/117</td>
<td>2</td>
<td>—</td>
<td>0·06</td>
<td>17·8</td>
<td>2·3</td>
<td>+</td>
</tr>
<tr>
<td>3 (C.C.)</td>
<td>50/M</td>
<td>Essential</td>
<td>224/142</td>
<td>3</td>
<td>CRI</td>
<td>0·26</td>
<td>14·5</td>
<td>3·8</td>
<td>+</td>
</tr>
<tr>
<td>4 (J.S.)</td>
<td>51/M</td>
<td>Renovascular</td>
<td>161/110</td>
<td>1</td>
<td>—</td>
<td>0·10</td>
<td>14·8</td>
<td>1·6</td>
<td>+</td>
</tr>
<tr>
<td>5 (L.A.)</td>
<td>63/F</td>
<td>Renovascular</td>
<td>192/111</td>
<td>2</td>
<td>LVH → CHF, CVA</td>
<td>0·10</td>
<td>17·3</td>
<td>18·5</td>
<td>+</td>
</tr>
<tr>
<td>6 (W.D.)</td>
<td>49/M</td>
<td>Essential</td>
<td>212/135</td>
<td>2</td>
<td>CRI</td>
<td>0·21</td>
<td>20·6</td>
<td>1·0</td>
<td>+</td>
</tr>
<tr>
<td>7 (M.S.)</td>
<td>37/F</td>
<td>Renovascular</td>
<td>206/117</td>
<td>2</td>
<td>LVH</td>
<td>0·49</td>
<td>16·7</td>
<td>11·9</td>
<td>–</td>
</tr>
<tr>
<td>8 (T.J.)</td>
<td>54/M</td>
<td>Renovascular</td>
<td>177/114</td>
<td>2</td>
<td>CRI, CVA, LVH</td>
<td>0·13</td>
<td>15·2</td>
<td>1·8</td>
<td>+</td>
</tr>
</tbody>
</table>

* Aetiology after complete evaluation; renovascular documented by arteriography and lateralization study.
† Average cuff blood pressures during the pre-study period, 4 times/day, supine and standing.
‡ Keith, Wagener and Barker classification.
‡‡ Normal creatinine: 0·07–0·13 mmol/l.
Plasma volume was determined by radioiodinated (125I) serum albumin with a 10-min equilibration period; total blood volume was calculated from the plasma volume and simultaneously determined corrected packed cell volume (Tarazi, Frohlich & Dustan, 1968). Results were expressed in ml/cm height; normal values (±1 sd) in our laboratory for plasma volume average 15.3 ± 1.68 ml/cm (women) and 18.4 ± 1.95 ml/cm (men). Blood samples obtained simultaneously were assayed for plasma renin activity estimated by radioimmunoassay of generated angiotensin (Bravo, Tarazi & Dustan, 1974). Values in normal supine subjects average 0.7 ± 0.2 (sd) pmol h⁻¹ ml⁻¹ for a 24 h urinary sodium excretion of 100–150 mmol.

Haemodynamic study

Cardiac output was determined by thermal dilution with an Instrumentation Laboratories 7 Fr. thermal dilution catheter (model no. 44166-110CM). This was introduced under local anaesthesia by a modified Seldinger technique via either the basilic or cephalic vein. With fluoroscopic guidance, the catheter tip was placed in a major segment of the pulmonary arterial bed, with pulmonary wedge pressure obtained intermittently. Cardiac output was determined from three to five sequential thermodilution curves: 10 ml of 5% glucose solution was used at 0°C. Manual injection over less than 3 s was employed; results represent an average of all determinations, only incomplete or delayed injections being discarded. Instrumentation Laboratories Cardiac Output Computer 601 provided cardiac output, with simultaneous digital display and paper recording. Correlation of this method (y) with simultaneous measurements by indocyanine dye dilution (x) during two separate series gave \( y = 1.09x - 0.234, r = 0.87 \) and \( y = 1.05x - 0.143, r = 0.92 \) (\( P < 0.001 \) for both). Lead II of the ECG and pulmonary artery pressure were recorded continuously on a multichannel recorder; multiple brachial blood pressure determinations were obtained during each haemodynamic study with cuff sphygmomanometer; Korotkoff phase V was used as diastolic blood pressure. This, combined with thermal dilution cardiac outputs, allowed multiple studies over a short period of time with minimal invasion. All haemodynamic values were obtained simultaneously. Measured values included heart rate \( (f_h) \), cardiac output \( (Q, l/min) \), systemic blood pressure \( (\text{mmHg}) \), pulmonary artery pressure \( (\text{mmHg}) \) and pulmonary wedge pressure \( (\text{mmHg}) \).

The following indices were derived (Tarazi, Frohlich & Dustan, 1973): stroke index \( (\text{ml/beat per m}^3) \), cardiac index \( (\text{l/min per m}^2) \), mean arterial pressure \( (\text{mmHg}) \), total peripheral resistance \( (\text{kPa l}^{-1} \text{s m}^2) \), mean pulmonary artery pressure \( (\text{mmHg}) \) and pulmonary vascular resistance \( (\text{kPa l}^{-1} \text{s m}^2) \).

After study lying supine, six patients underwent graded head-up tilt with the thermal dilution catheter in place, the tilt stopping for 2 min at 30° and then 60°, and for 5 min at 75°. Haemodynamic variables were measured at each tilt position. The patients were then returned to the supine position and the venous catheter was removed.

Comparisons were made by paired t-test, each subject serving as his own control. Values are given as mean ±1 SEM.

Results

All eight patients had documented severe hypertension (Table 1), and all but one patient (patient no. 5) had discontinued all treatment; four had essential and four had renovascular hypertension. Despite this clinical spectrum, the haemodynamic pattern of the depressor response to SQ 14225 was similar in all patients (see below).

Haemodynamic response to SQ 14225. Supine haemodynamic response to SQ 14225 while on 100 mmol of sodium/day diet (Table 2) shows that in the eight patients mean blood pressure fell from a control value of 149 ± 5 to 127 ± 8 mmHg \( (P < 0.02) \); this was associated with a significant rise in total peripheral resistance from 6.9 ± 0.53 to 5.7 ± 0.40 kPa l⁻¹ s m⁻² \( (P < 0.05) \). There was no significant change of cardiac index \( (2.98 ± 0.26 \text{ to } 3.03 ± 0.21 \text{ l min}^{-1} \text{ m}^{-2}) \), nor in \( f_{c,}\) (82 ± 8 to 80 ± 4 beats/min) despite the decrease in mean arterial pressure and total peripheral resistance. However, in the six of eight patients whose blood pressure was markedly reduced by treatment \( (147 \text{ to } 118 \text{ mmHg, } P < 0.002) \), cardiac index increased by 4% \( (2.78 \text{ to } 2.90, P < 0.05) \) whereas \( f_{c} \) was unchanged \( (80 \text{ to } 79, P < 0.1) \). Pulmonary haemodynamics also showed no statistically significant change. Plasma volume increased with therapy, from 16.9 ± 0.7 to 17.8 ± 0.5 ml/cm \( (P < 0.05) \). Plasma renin activity increased during SQ 14225 therapy, from 6.3 ± 3.2 to 19.2 ± 5.2 pmol h⁻¹ ml⁻¹ \( (P < 0.005) \). This reflects inhibition of the angiotensin II negative feedback loop on renin release (Sancho et
TABLE 2. Haemodynamic changes after SQ 14225 therapy in eight supine patients

Summary of the haemodynamic findings (mean values ± se) associated with SQ 14225 therapy in patients on 100 mmol of sodium/day diet. The reduction of mean arterial pressure was primarily associated with a decrease of peripheral resistance and plasma volume expansion. Plasma renin activity in Tables 2 and 3 was measured at the time of the haemodynamic study. MAP = mean arterial pressure; TPR = total peripheral resistance; CI = cardiac index; $f_c$ = heart rate; PWP = pulmonary wedge pressure; MPAP = mean pulmonary artery pressure; PVR = pulmonary vascular resistance; PV = plasma volume; PRA = plasma renin activity. N.S., Not significant.

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>SQ 14225* therapy</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>MAP (mmHg)</td>
<td>149 ± 5</td>
<td>127 ± 8</td>
<td>&lt;0.02</td>
</tr>
<tr>
<td>TPR (kPa l⁻¹ s m⁻²)</td>
<td>6.9 ± 0.53</td>
<td>5.7 ± 0.40</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>CI (l min⁻¹ m⁻²)</td>
<td>2.98 ± 0.26</td>
<td>3.03 ± 0.21</td>
<td>N.S.</td>
</tr>
<tr>
<td>$f_c$ (beats/min)</td>
<td>82 ± 8</td>
<td>80 ± 4</td>
<td>N.S.</td>
</tr>
<tr>
<td>PWP (mmHg)</td>
<td>6 ± 1</td>
<td>6 ± 1</td>
<td>N.S.</td>
</tr>
<tr>
<td>MPAP (mmHg)</td>
<td>13 ± 1</td>
<td>12 ± 2</td>
<td>N.S.</td>
</tr>
<tr>
<td>PVR (kPa l⁻¹)</td>
<td>0.35 ± 0.03</td>
<td>0.31 ± 0.04</td>
<td>N.S.</td>
</tr>
<tr>
<td>PV (ml/cm)</td>
<td>16.9 ± 0.7</td>
<td>17.8 ± 0.5</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>PRA (pmol h⁻¹ ml⁻¹)</td>
<td>6.3 ± 3.2</td>
<td>19.2 ± 5.2</td>
<td>&lt;0.005</td>
</tr>
</tbody>
</table>

* Dose providing attainment of normotensive pressures, or a maximal oral dose of 250 mg four times a day (3–7 days of maintenance dosage).
† Values obtained in only seven of the eight treated (SQ 14225) patients; all other values were obtained in all eight patients.
‡ Measured at time of haemodynamic study.

al., 1976), and served as a measure of interrupted angiotensin II formation (Ferguson, Turini, Brunner & Gavras, 1977).

Addition of low sodium diet. At the time of repeat study, the four patients receiving a 10 mmol of sodium/day diet had an average 24 h urinary sodium excretion of 12 ± 4 mmol, a weight loss of 0.7 ± 0.3 kg and an increase of plasma renin activity from 14.2 ± 6.5 to 24.2 ± 11.5 pmol h⁻¹ ml⁻¹. Blood pressures were stable at the onset of diet alteration, the patients having been on SQ 14225 for 5–7 days. With the addition of the 10 mmol of sodium/day diet, a further reduction in blood pressure occurred from 137 ± 8 to 111 ± 12 mmHg (P < 0.05) after 3–5 days on combined therapy (Table 3). This augmented response was due to further decrease of total peripheral resistance from 6.5 ± 0.5 to 5.2 ± 0.40 kPa l⁻¹ s m⁻² (P < 0.05). Despite the small number of patients, the changes were statistically significant.

However, there was no significant change in cardiac index, from 2.82 ± 0.05 to 2.79 ± 0.12 l min⁻¹ m⁻², despite sodium depletion. Neither the change in $f_c$ (75 ± 6 to 82 ± 5 beats/min) nor the reduction in plasma volume (17.4 ± 1.0 to 17.3 ± 1.2 ml/cm) were significant, possibly owing to the small number of patients.

Drug withdrawal. Five patients were studied again after withdrawal of SQ 14225 therapy, having achieved maximum pressure reduction with either SQ 14225 alone or in combination with a 10 mmol of sodium/day diet. The study was performed when hospital blood pressures showed a definite upward trend and, for ethical reasons, was not delayed until achievement of pretreatment control pressures. In all five patients withdrawal of SQ 14225 was associated with a gradual increase of blood pressure over 2–3 days regardless of sodium intake and occurred through a gradual increase of total peripheral resistance.

Haemodynamic response to head-up tilt (Table 4). Haemodynamic responses to head-up tilt were studied in six patients during the control period and after treatment with SQ 14225; changes with tilt (calculated as percentage change from supine values) were not significantly different in the two periods. The increase in $f_c$ and total peripheral resistance with tilt suggested that treatment did not alter reflex responses to decreased venous return. Head-up tilt was repeated in two patients who became normotensive with SQ 14225 and 10 mmol of sodium/day diet; both demonstrated adequate
Mean values ± SE are shown. For both control and SQ 14225 therapy, all changes during maximal tilt were statistically significant (P < 0.005) compared with supine values, except mean arterial pressure (MAP), which did not change with tilt. Comparison of tilt response between SQ 14225 therapy and the control period, expressed as percentage change (Δ%), reveals no appreciable difference.

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>SQ 14225 therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>MAP (mmHg)</td>
<td>146 ± 8</td>
<td>116 ± 8</td>
</tr>
<tr>
<td>CI (l min⁻¹ m²)</td>
<td>2.60 ± 0.18</td>
<td>2.87 ± 0.16</td>
</tr>
<tr>
<td>TPR (kPa l⁻¹ s m²)</td>
<td>7-70 ± 0.8</td>
<td>5-50 ± 0.4</td>
</tr>
<tr>
<td>f_c (beats/min)</td>
<td>78 ± 9</td>
<td>80 ± 5</td>
</tr>
</tbody>
</table>

Discussion

The reduction of arterial pressure achieved by SQ 14225 in patients with essential or renovascular hypertension occurred through decreased total peripheral resistance. This was associated with minimal change in cardiac index, heart rate or pulmonary haemodynamics for all patients. Plasma volume increased significantly. Addition of a 10 mmol of sodium/day diet to the SQ 14225 therapy reduced arterial pressure further; again the fall in blood pressure was mediated through decreased total peripheral resistance. In all patients tested, haemodynamic responses to tilt were unaffected by SQ14225 regardless of sodium intake. This response pattern is in striking contrast to the effects of two other agents that interfere with the renin–angiotensin system. Propranolol, which inhibits renin release (Bühler, Laragh, Baer, Vaughan & Brunner, 1972), leads initially to reduction of cardiac output with full compensatory rise of peripheral resistance (Frohlich, Tarazi, Dustan & Page, 1968); with maintained therapy subsequent lowering of arterial pressure is related to readaptation of peripheral resistance, although output remains depressed (Tarazi & Dustan, 1972). Angiotensin II analogues are associated with a reduction in cardiac output and variable change of total peripheral resistance, irrespective of arterial pressure response (Wallace et al., 1976; DeCarvalho, Dunn, Kem, Chrysant & Frohlich, 1978). Thus interference with the renin–angiotensin system can give rise to different haemodynamic patterns, dependent in part on the agent used.

The association of diminished peripheral resistance and arterial pressure with unaltered cardiac output may occur in several situations. The first is cardiac decompensation; this is unlikely in the present study as pulmonary wedge pressure was maintained at normal values. Secondly, decreased intravascular volume could conceivably dampen cardiac output augmentation; yet we actually observed a significant increase of plasma volume compared with pretreatment values. Thirdly, and most likely, absence of the expected rise in cardiac output despite volume expansion could be due to the combined effect of venous and arteriolar dilatation. The haemodynamic pattern produced by SQ 14225 administration appeared similar to that produced by those vasodilators where both arteriolar dilatation (decreased resistance) and venular dilatation (unchanged or diminished cardiac output) occur. Such a response is observed with nitroprusside (Tarazi et al., 1976; Schlant, Tsagaris & Robertson, 1962) and prazosin (Lund-Johansen, 1975), in contrast to the response to hydralazine, where dilatation restricted to the arteriolar level is associated with reflex tachycardia and increased cardiac output (Tarazi et al., 1976). That SQ 14225 may result in venodilatation is suggested by Collier & Robinson (1974), who have shown that blockade of angiotensin II formation by intravenous converting enzyme inhibitor (SQ 20881) results in dilatation of hand veins.
Vasodilators that affect veins as well as arterioles have been reported to produce less reflex tachycardia than those affecting arterioles predominantly (Franciosa, Pierpont & Cohn, 1977; Tarazi et al., 1976). Although a possible factor in the absence of heart rate change at rest during therapy, this does not fully explain the stable heart rate despite blood pressure reduction; further, baroreceptor reflexes remained operative in all, as demonstrated by haemodynamic response to tilt (Table 4).

The mechanism of vasodilatation is uncertain, especially as the drug has no direct vasodilator effect (Murthy, Waldron, Goldberg & Vollmer, 1977) and, in preliminary reports, is said not to cross the blood—brain barrier (Vollmer & Boccagno, 1977). Interference with the potent direct pressor action of angiotensin II by blockade of its formation might be an important component of SQ 14225 action. However, while this mode conceivably applies to patients with high plasma renin activity, it is difficult to accept for situations with low or low-normal plasma renin activity in which the drug was shown to be effective (Table 1). The possible hypotensive effect of increased bradykinin concentrations through inhibition of kininase-mediated degradation has been raised by studies with intravenous converting enzyme inhibition (Williams & Hollenberg, 1977). Yet inferential data are against a significant role for bradykinin (deFreitas, Faraco & deAzevedo, 1964; Streeten, Kerr, Kerr, Prior & Dalakos, 1972). This question can be answered only with sequential determination of bradykinin concentrations during chronic SQ 14225 therapy.

**Haemodynamic response to SQ 14225 and low sodium diet**

In the present study, combination of SQ 14225 and 10 mmol of sodium/day diet for 3–5 days enhanced the depressor effect of drug alone. Studies have demonstrated the importance of angiotensin II in maintaining vascular tone during sodium depletion (Gavras et al., 1973). Sancho et al. (1976) have shown that an augmented pressure reduction during converting enzyme inhibition occurred either with low sodium diet or diuretic therapy; similar results were obtained in our patients with the orally-active form of converting enzyme inhibitor and 10 mmol of sodium/day diet. However, our data revealed an unexpected haemodynamic pattern: the fall in arterial pressure occurred through a further reduction of peripheral resistance with no appreciable changes in cardiac index or plasma volume for the group. Further, head-up tilt on combined therapy did not elicit orthostatic hypotension.

In summary, our results suggest that the haemodynamic effects of SQ 14225, whatever the complexity of humoral interactions it may evoke, are similar to those of direct vasodilators with combined venular and arteriolar action. This pattern may provide a guideline for therapeutic application and expected response. The lack of tachycardia, the effect on peripheral resistance and the assumed venular action suggest that it may be used with advantage even in hypertensive patients with heart disease.

**Acknowledgments**

The oral converting enzyme inhibitor (SQ14225) was kindly supplied by E. R. Squibb and Sons Inc. and the authors are grateful to Dr D. McKinstry for her help and courtesy. We are indebted to M. K. Kruchan, M. G. Fitzgerald and S. Vaughn for their skilled assistance during the haemodynamic studies and to E. Libby for her secretarial assistance. This study was supported in part by grant HL-6835 from the National Heart, Lung and Blood Institute, National Institutes of Health, Bethesda, Maryland, U.S.A.

**References**


