Renin, blood volume and response to saralasin in patients on chronic haemodialysis: evidence against volume- and renin-‘dependent’ hypertension

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Summary

1. No significant relationship was found between blood pressure and blood volume, sulphate space or plasma angiotensin II concentration in 59 non-nephrectomized haemodialysis patients, of whom 42 were hypertensive. Supine mean blood pressure was only weakly correlated with plasma renin activity and the correlation was not improved when blood pressure was related to expressions combining renin and volume.

2. Changes in supine mean blood pressure during saralasin infusion were related to pre-infusion plasma renin activity (P<0·001) or plasma angiotensin II (P<0·02) but also to blood volume (P<0·001) or sulphate space (P<0·001). A fall of more than 10% in mean blood pressure during saralasin infusion was observed in only 12 patients (one normotensive), in five of whom there was evidence of volume depletion.

3. Thirteen patients (nine hypertensive) were studied at two levels of dietary sodium: 100 mmol/day and <20 mmol/day. Supine mean blood pressure in hypertensive patients was lower during the period of higher salt intake despite increased volumes.

4. Hypertension in haemodialysis patients cannot be adequately explained by abnormalities either in volume homeostasis and/or in the renin–angiotensin system.

Key words: angiotensin II, blood volume, haemodialysis patients, hypertension, renin activity, saralasin, sulphate space.
Abbreviation: PRA, plasma renin activity.

Introduction

Hypertension in patients established on chronic haemodialysis treatment is normally controlled by dialysis ultrafiltration and by dietary sodium and water restriction (Brown, Dusterdieck, Fraser, Lever, Robertson, Tree & Weir, 1971). The success of these measures has led to the supposition that the usual cause of hypertension in such patients is sodium and water retention (Blumberg, Nelp, Hegstrom & Scribner, 1967; Brown et al., 1971), with plasma renin and angiotensin II perhaps inappropriately high for the degree of volume expansion (Rosen & Robinson, 1973; Weidmann, Beretta-Piccoli, Steffen, Blumberg & Reubi, 1976). Rarely, when sodium and water depletion do not control arterial pressure, plasma renin may reach very high values with hypertension then described as ‘renin-dependent’ (Toussaint, Verniory, Cremer, Vereerstraeten, Kinnart & van Geertruyden, 1968; Vertes, Cangiano, Berman & Gould, 1969). However, the demonstration that blood pressure can be lowered by sodium and water depletion does not prove that sodium and water retention is the primary cause of the elevated pressure. Nor is it clear to what extent the high renin values observed in some hypertensive dialysis patients may be an appropriate response to
chronic sodium and volume depletion. Moreover, high renin values are not confined to those dialysis patients whose blood pressure is raised and have been observed in normotensive patients without evidence of sodium or volume depletion (Weidmann et al., 1976).

A method of investigating the activity of the renin–angiotensin system, other than that of plasma assays with their inherent difficulties and lack of standardization, is the use of specific inhibitors. The fall in blood pressure in response to plasma assays with their inherent difficulties and lack of standardization, is the use of specific inhibitors. The fall in blood pressure in response to saralasin (Sar',Ala'–angiotensin II) has been used to assess the contribution of angiotensin II to various forms of hypertension (Streeten, Anderson & Dalakos, 1976), including the hypertension of chronic renal failure (Lifschitz, Gibney & Kirschenbaum, 1975). A significant fall in blood pressure during saralasin infusion has been taken as a criterion for bilateral nephrectomy in hypertensive haemodialysis patients (Lifschitz et al., 1975), and a failure to respond has been suggested as an indication of volume-dependent hypertension in such patients (Mimran, Deschodt, Polito, Barjon, Mion & Shaldon, 1976).

The relationship between blood pressure, its response to saralasin, and measurement of plasma renin activity, plasma angiotensin II concentration, blood and extracellular fluid volumes are explored in this study of 59 patients with retained diseased kidneys and six anephric patients on regular haemodialysis. The wide variations in body fluid volumes likely to occur in patients without significant renal function make this group an ideal one to examine the ways in which sodium and volume factors affect the response to inhibition of angiotensin II.

Patients and methods
Sixty-five patients (40 male, 25 female), aged 17–55 years (mean 40 years), were studied on the day after a regular haemodialysis treatment. All patients gave informed consent, had been established on haemodialysis for a minimum of 3 months (3–110 months) and were studied whilst on their normal diet and dialysis schedule (Kiiil multi-point, 4–6 h, 3 times per week). The primary diagnoses were as follows: hypertensive nephrosclerosis, 13 patients (one anephric); chronic glomerulonephritis, 30 patients; chronic pyelonephritis due to reflux, congenital abnormalities of the urinary tract or associated with calculi, 14 patients (four anephric); polycystic disease, five patients; analgesic nephropathy, two patients (one anephric); cortical necrosis, one patient. Forty-two patients were hypertensive, 17 normotensive and six were anephric. Twenty-six patients had previously received anti-hypertensive drugs, which were withdrawn at least 7 days before study.

Blood pressure (Arteriosonde) and pulse rate (Harvard 362 crystal transducer) were recorded at 2 min intervals in each study. After 10 min of observations with the patient standing, plasma sodium and potassium concentrations, plasma volume (125I-labelled albumin), peripheral packed cell volume (Coulter model S automatic cell counter) and sulphate space ([35S]sulphate; McGrath, Tiller, Horvath & Johnson, 1976) were measured during a 60 min period of resting supine (control period). Glucose solution (5%) was infused at 1 ml/min into a forearm vein (with a Sage 355 syringe pump) for the last 20 min of the control period, followed by an infusion of saralasin (in 5% glucose solution at the same rate) at 1·0 nmol min⁻¹ kg⁻¹ and then 5·2 nmol min⁻¹ kg⁻¹, each for 20 min. Finally, the patient stood for a 10 min period, during which time the saralasin infusion (5·2 nmol min⁻¹ kg⁻¹) was continued. Blood samples for measurement of plasma renin activity (PRA) (Sealey & Laragh, 1975) and angiotensin II (Ruiz-Maza, Tiller & Walker, 1974) were taken at the end of the supine control period and PRA was measured again at the end of the saralasin infusion in the supine position.

A more detailed study was performed in 13 patients (all with kidneys) after 5 days on each of two diets: high sodium (100 mmol/day) and low sodium (<20 mmol/day). On the low sodium diet, volume replacement during dialysis was made with 5% glucose in water instead of sodium chloride solution (150 mmol/l). The sodium concentration of the dialysis fluid was constant for each patient. In these patients the effects of tilt alone (40° head-up for 20 min) were assessed after 60 min supine followed by a post-tilt 30 min supine recovery period and then by saralasin infusion over three consecutive 20 min periods (1·0 nmol min⁻¹ kg⁻¹, supine, 10·5 nmol min⁻¹ kg⁻¹ supine and 10·5 nmol min⁻¹ kg⁻¹ with tilt). PRA was measured at the end of each phase.

Supine systolic, diastolic and mean (diastolic +1/3 pulse pressure) blood pressure and pulse rate readings were averaged over the last 20 min of control observations and for the 20 min of the higher dose saralasin infusion (5·2 or 10·5 nmol min⁻¹ kg⁻¹). Average blood pressures and pulse rates for standing and tilt studies were also compared with average control observations. An initial transient pressor response was frequently
observed at the beginning of saralasin infusion (McGrath, Ledingham & Benedict, 1977).

Blood volume was calculated from plasma volume and peripheral packed cell volume, with a correction factor of 0.915 for total body packed cell volume (PCV). This was the mean value for the ratio total body PCV/peripheral PCV obtained in a preliminary study of 23 dialysis patients in whom simultaneous measurements were made of plasma volume (125I-labelled albumin), erythrocyte mass (131Cr-labelled erythrocytes) and peripheral venous packed cell volume (B. P. McGrath, unpublished observations). Blood volume measurements were related to height and expressed as % of normal to allow for sex differences (Tarazi, Dustan, Fröhlich, Gifford & Hoffman, 1970). Sulphate space was expressed as 1/m² of body surface area and as 1/cm⁻³ height.

Statistical methods employed were the paired t-test and linear and multiple regression analysis (Snedecor & Cochrane, 1969).

Results

Relationships between blood pressure, blood volume and PRA

No significant relationship was found between blood pressure (supine or standing) and blood volume or sulphate space (Table 1). A weak correlation was observed between supine mean blood pressure and PRA (r = 0.22, P<0.05). However, this relationship was not significantly strengthened by substituting for PRA any of the renin x volume computations shown in Table 2.

A significant inverse correlation was found between blood volume and PRA (r = −0.43, P<0.001) and also between sulphate space and PRA (r = −0.42, P<0.001). No difference was discernible in these renin–volume plots between hypertensive (supine mean blood pressure >110 mmHg, n = 42) and normotensive (supine mean blood pressure ≤110 mmHg, n = 17) patients (Fig. 1).

Blood pressure response to saralasin

All six anephric patients and 25 of the 59 non-nephrectomized patients showed a modest and sustained increase in mean blood pressure during saralasin infusion. The change in mean blood pressure during saralasin infusion was significantly and inversely related to pre-infusion PRA and angiotensin II values (Fig. 2) and directly related to blood volume (r = 0.50, P<0.001; Fig. 3) and sulphate space measurements (r = 0.47, P<0.001) in the non-nephrectomized group. The change in

| Table 1. Relationship between mean blood pressure and measured variables |
| Supine MBP = mean blood pressure (diastolic + ½ pulse pressure) calculated for the last 20 min of the 60 min control period (10 readings). PRA, Plasma renin activity; AI1, angiotensin II; NS, not significant (P > 0.1). |
| Simple regression analysis | n | Correlation coefficient | P |
| Supine MBP vs blood volume (as % of normal) | 59 | −0.19 | NS |
| vs blood volume (1/cm⁻³ height) | 59 | −0.09 | NS |
| vs sulphate space (1/m⁻² body surface area) | 59 | −0.06 | NS |
| vs sulphate space (1/cm⁻³ height) | 59 | 0.07 | NS |
| vs log PRA | 59 | 0.22 | <0.05 |
| vs log plasma AI1 | 49 | 0.19 | NS |
| vs supine pulse rate | 59 | 0.30 | <0.02 |

| Table 2. Relationship between mean blood pressure and products of measured variables |
| Plasma renin activity (PRA) is expressed as pmol of angiotensin I min⁻¹ l⁻¹ to avoid negative logarithms. Supine MBP, mean blood pressure (diastolic + ½ pulse pressure) calculated for the last 20 min of the 60 min control period (10 readings). NS, Not significant (P > 0.1) |
| n | Correlation coefficient | P |
| Supine MBP vs [blood volume (%) × log PRA] | 59 | 0.12 | NS |
| vs [blood volume (1/cm⁻³ height) × log PRA] | 59 | 0.11 | NS |
| vs [sulphate space (1/m⁻² body surface area) × log PRA] | 59 | 0.18 | <0.01 |
| vs [sulphate space (1/cm⁻³ height) × log PRA] | 59 | 0.26 | <0.05 |
PRA induced by saralasin was significantly and inversely correlated with the blood pressure response ($r = -0.60, P<0.001$).

In only 12 patients (one normotensive) was the fall in mean blood pressure during saralasin infusion greater than 10% of the control value. As shown in Fig. 1, these patients had not only the highest PRA values but also the lowest blood volume measurements. Multiple regression analysis suggested that blood volume was exerting an influence on the blood pressure response to saralasin which was independent of this relationship between renin and volume ($F = 5.5, P<0.05$).

The changes in mean blood pressure induced by saralasin infusion were not significantly different between the upright and the supine positions ($-6.9 \pm \text{SEM } 1.8 \text{ mmHg} \text{ vs } -4.2 \pm \text{SEM } 1.6 \text{ mmHg}; P > 0.10$).

**Effects of dietary sodium manipulation**

Changes in dietary sodium in 13 patients (nine hypertensive, four normotensive) resulted in significant changes in body weight, plasma sodium, plasma volume, packed cell volume and sulphate space (Table 3). When the data from the two dietary periods were compared, mean PRA was higher after the low sodium diet but the difference was not significant ($P > 0.1$).

In the nine hypertensive patients in whom salt restriction was associated with significant falls in volume and weight, supine mean blood pressure was significantly higher on the low sodium diet ($132 \pm 4 \text{ vs } 126 \pm 3 \text{ mmHg}; P < 0.02$). In these hypertensive patients saralasin lowered mean blood pressure in the supine ($P < 0.001$) and tilt ($P < 0.02$) positions on the low sodium diet, but only in the tilt position on the high sodium diet ($P < 0.02$). The four normotensive patients had a slight fall in tilt mean blood pressure during saralasin infusion on the low sodium diet (Table 4).

![Fig. 1. Relationship between log PRA (pre-infusion) and blood volume (related to height and expressed as % of normal) in 59 non-nephrectomized haemodialysis patients. O, supine 'control' mean blood pressure (MBP) < 110 mmHg; •, supine control MBP > 110 mmHg. *Patients who showed >10% fall in MBP during saralasin infusion. $r = -0.43, P<0.001$.](image)

![Fig. 2. Relationship between the change in supine mean blood pressure (MBP) during saralasin infusion at 5 μg min$^{-1}$ kg$^{-1}$ (5.2 nmol min$^{-1}$ kg$^{-1}$) and PRA (left) or plasma angiotensin II concentration (right) in patients on chronic haemodialysis. Supine MBP was averaged for 10 readings at intervals of 2 min during control (final 20 min of control) and saralasin infusion periods and the change in MBP expressed as a % of the 'control' MBP. PRA and angiotensin II concentrations are pre-infusion measurements. ■, Anephric patients; ○, non-nephrectomized patients, supine 'control' MBP < 110 mmHg; ●, non-nephrectomized patients, supine 'control' MBP > 110 mmHg. For the non-nephrectomized group, $r = -0.72, P<0.001$ for PRA and $r = -0.34, P<0.02$ for angiotensin II.](image)
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Relationship of PRA to plasma sodium and potassium concentrations

Plasma renin activity was found to be inversely related to both plasma sodium \( (r = -0.28, n = 72, P < 0.01) \) and plasma potassium concentrations \( (r = -0.39, n = 72, P < 0.01) \) in the dialysis patients with kidneys. The plasma sodium and potassium concentrations were not significantly related to one another.

Discussion

The lack of any significant relationship between blood pressure and blood volume or extracellular fluid volume (sulphate space) measurements in non-nephrectomized haemodialysis patients is in agreement with the findings of Dathan, Johnson & Goodwin (1973) and Weidmann et al. (1976).

Table 3. Effects of change in sodium balance: dialysis patients \( (n = 13) \)

Results are mean values ± SEM; PRA, plasma renin activity; AI, angiotensin I.

<table>
<thead>
<tr>
<th>Diet (mmol of Na/day)</th>
<th>Weight (kg)</th>
<th>Plasma Na (mmol/l)</th>
<th>Peripheral packed cell volume (%)</th>
<th>Plasma volume (l)</th>
<th>Sulphate space (l)</th>
<th>PRA (pmol of AI h⁻¹ ml⁻¹)</th>
</tr>
</thead>
<tbody>
<tr>
<td>20</td>
<td>60.5 ± 2.5</td>
<td>132 ± 1</td>
<td>23.4 ± 1.4</td>
<td>3.80 ± 0.20</td>
<td>11.44 ± 0.63</td>
<td>9.4 ± 1.9</td>
</tr>
<tr>
<td>100</td>
<td>61.4 ± 2.5</td>
<td>136 ± 1</td>
<td>21.8 ± 1.3</td>
<td>4.09 ± 0.25</td>
<td>12.53 ± 0.55</td>
<td>7.8 ± 1.7</td>
</tr>
<tr>
<td>( P )</td>
<td>&lt;0-025</td>
<td>&lt;0-005</td>
<td>&lt;0-005</td>
<td>&lt;0-01</td>
<td>&lt;0-005</td>
<td>&gt;0-1</td>
</tr>
</tbody>
</table>

Table 4. Effects of change in sodium balance on response to saralasin: dialysis patients

MBP, Mean blood pressure; PRA, plasma renin activity.

Significance: \***P < 0.001; **P < 0.01; *P < 0.05.

<table>
<thead>
<tr>
<th>Sodium intake</th>
<th>Control</th>
<th>Saralasin</th>
<th>Control</th>
<th>Saralasin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertensive patients ( (n = 9) )</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MBP (mmHg)</td>
<td>Low</td>
<td>132 ± 4</td>
<td>117 ± 5***</td>
<td>132 ± 4</td>
</tr>
<tr>
<td></td>
<td>High</td>
<td>126 ± 3*</td>
<td>119 ± 5</td>
<td>132 ± 3</td>
</tr>
<tr>
<td>Pulse rate (beats/min)</td>
<td>Low</td>
<td>79 ± 3</td>
<td>80 ± 4</td>
<td>83 ± 3</td>
</tr>
<tr>
<td></td>
<td>High</td>
<td>81 ± 4</td>
<td>81 ± 3</td>
<td>84 ± 4</td>
</tr>
<tr>
<td>PRA (pmol of AI h⁻¹ ml⁻¹)</td>
<td>Low</td>
<td>11.9 ± 2.3</td>
<td>14.2 ± 3.3*</td>
<td>14.1 ± 3.4</td>
</tr>
<tr>
<td></td>
<td>High</td>
<td>8.3 ± 1.6</td>
<td>11.2 ± 3.6</td>
<td>10.1 ± 2.1</td>
</tr>
<tr>
<td>Normotensive patients ( (n = 4) )</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MBP (mmHg)</td>
<td>Low</td>
<td>93 ± 3</td>
<td>93 ± 2</td>
<td>97 ± 4</td>
</tr>
<tr>
<td></td>
<td>High</td>
<td>97 ± 4</td>
<td>99 ± 5</td>
<td>98 ± 4</td>
</tr>
<tr>
<td>Pulse rate (beats/min)</td>
<td>Low</td>
<td>73 ± 3</td>
<td>76 ± 5</td>
<td>79 ± 5</td>
</tr>
<tr>
<td></td>
<td>High</td>
<td>74 ± 4</td>
<td>75 ± 5</td>
<td>79 ± 4</td>
</tr>
<tr>
<td>PRA (pmol of AI h⁻¹ ml⁻¹)</td>
<td>Low</td>
<td>3.7 ± 1.6</td>
<td>3.5 ± 1.6</td>
<td>3.7 ± 1.6</td>
</tr>
<tr>
<td></td>
<td>High</td>
<td>2.6 ± 0.8</td>
<td>2.8 ± 1.2</td>
<td>3.8 ± 1.0</td>
</tr>
</tbody>
</table>

\† Two patients fainted and PRA samples were not taken.
Moreover in the nine hypertensive patients studied at two levels of dietary sodium intake, supine mean blood pressure was lower on the high salt intake, despite the higher volumes induced by that diet (Tables 3 and 4). These results are surprising in view of the widespread belief that hypertension in the majority of patients requiring regular haemodialysis is 'volume dependent' (Blumberg et al., 1967; Vertes et al., 1969; Brown et al., 1971).

Although Brown, Curtis, Lever, Robertson, de Wardener & Wing (1969) and Wilkinson, Scott, Uldall, Kerr & Swinney (1970) found a correlation between plasma renin concentration and blood pressure in dialysed patients, others have not confirmed this (Zech, Sassard, Moskovtchenko, Pozet & Traeger, 1968; Craswell, Hird, Judd, Baillod, Varghese & Moorhead, 1972). In these early studies the effects of the wide variations in body fluid volumes characteristic of dialysed patients were not examined. Various methods of taking account of the effects of volume changes on renin activity have since been employed. Rosen & Robinson (1973) have suggested estimating 'effective' renin by calculating the product of exchangeable sodium and the logarithm of plasma renin concentration and noted a significant relationship between 'effective' renin and blood pressure in a group of patients on haemodialysis. In a similar manner Weidmann et al. (1976) calculated 'sodium–renin' and 'volume–renin' products and found significant relationships between supine mean blood pressure and both products. In contrast, we have found only a weak correlation between supine mean blood pressure and the product of sulphate space (l/cm−3 height) and log PRA, and no relationship between blood pressure and the product of blood volume and log PRA (Table 2). Although we have not measured exchangeable sodium in this study, there is a close relationship between exchangeable sodium and sulphate space in haemodialysis patients (McGrath et al., 1976) and therefore we have no reason to suspect that any 'sodium–renin' product would have greater discriminatory value than the 'sulphate space–renin' product.

As shown in Fig. 1, and from previous studies (Warren & Ferris, 1970; Weidmann et al., 1976), it is clear that many dialysis patients have PRA values which are not appropriately suppressed despite evidence of volume expansion. However, the significance of this observation in relation to the cause of the raised blood pressure is uncertain since inappropriately high renin values were observed in normotensive as well as hypertensive patients.

Factors other than volume changes may also influence renin values in patients with chronic renal failure. The inverse relationship between PRA and plasma sodium concentration observed in the non-nephrectomized haemodialysis patients in this study has been observed previously in a variety of hypertensive states with and without renal failure (Brown, Davies, Lever & Robertson, 1965; Toussaint et al., 1969). Potassium balance also influence plasma renin values in normal subjects and hypertensive patients without renal failure (Brown, Baer, Sealey, Ledingham & Laragh, 1970). The inverse relationship between PRA and plasma potassium concentration observed in this study suggests that changes in potassium balance may also affect renin values in dialysed patients.

Saralasin infusion was used in this study to explore the possibility that 'angiotensin-dependent' hypertension may not be revealed by determination of venous plasma renin and angiotensin II values. The close relationship between the blood pressure response to saralasin infusion and pre-infusion values of plasma renin or angiotensin II seen in haemodialysis patients (Fig. 2) has been observed in other forms of hypertension (Case, Wallace, Keim, Sealey & Laragh, 1976; Geyskes, Vos, Boer & Dorhout Mees, 1976) and confirms that in patients with high values for circulating renin and angiotensin II, the renin–angiotensin system is playing some part in maintaining the elevated blood pressure. However, it does not support the existence of occult 'angiotensin-dependent' hypertension in patients in whom renin and angiotensin II values are not raised. Moreover, a marked fall in blood pressure in response to saralasin does not differentiate between a primary over-production of renin or an appropriate response to volume depletion. Conversely an insignificant response, or a rise in pressure, may be observed in the presence of volume expansion (Streeten et al., 1976; Case et al., 1976; Geyskes et al., 1976; Donker & Leenen, 1974). The possibility that longer maintained infusions of saralasin might have decreased arterial pressure when shorter ones did not was not explored. Multiple regression analysis of our results in 59 non-nephrectomized patients suggested a possible influence of volume on the blood pressure response to saralasin which appeared to be independent of the effects of volume changes on the renin–angiotensin system.

There are other limitations to saralasin. It possesses significant agonist activity (Case et al., 1976), which is more pronounced in the sodium- and volume-repleted state (Streeten et al., 1976;
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Case et al., 1976; Donker & Leenen, 1974) and when plasma renin values are low (Case et al., 1976). Furthermore, a rise in plasma noradrenaline concentration has been observed during saralasin infusion (McGrath et al., 1977; Röckel, Heidland, Appel & Palm, 1977), which suggests that the antagonist may have some angiotensin II-like actions on the central or peripheral autonomic nervous system or on the adrenal medulla as well as vascular receptors.

Posture may also influence the response to saralasin, as shown by the fall in tilt mean blood pressure induced by the antagonist in nine sodium-replete hypertensive dialysis patients in whom no such fall was observed when supine (Table 4).

These observations suggest that the blood pressure response to saralasin may be a useful and rapid estimate of the amount of circulating angiotensin II, but does not help to clarify the possible importance of the renin–angiotensin system in the pathogenesis of hypertension in patients undergoing regular haemodialysis. Although a significant fall in blood pressure occurred in patients with very high PRA and angiotensin II values (Fig. 2), such a response was observed in normotensive as well as hypertensive patients and was most pronounced in those patients with evidence of volume depletion (Fig. 1 and Fig. 3).

The analysis of blood pressure, PRA, plasma angiotensin II and volume measurements presented in this study does not exclude contributions from both the renin–angiotensin system and sodium retention to the hypertension of end-stage renal disease. Even so, others have also failed to find a satisfactory explanation of hypertension in dialysed patients from inappropriate activity of the renin–angiotensin system and/or sodium retention with volume expansion (Cannella, Castellani, Mioni, Usberti, Guerra, Albertini & Maiorca, 1977). There is increasing evidence of disturbed autonomic function in some of these patients (Lilley, Golden & Stone, 1976; Atuk, Westervelt & Peach, 1975), a disorder which may contribute to hypertension more than has hitherto been recognized (McGrath, Tiller, Bune, Chalmers, Konner & Uther, 1977).

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References


