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Baroreflex sensitivity in renal failure

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Summary

1. Baroreflex sensitivity was evaluated in 22 non-dialysed patients with chronic renal failure secondary to chronic glomerulonephritis. Baroreflex sensitivity was judged by the slope of the linear regression of the pulse interval on the rise in systolic blood pressure with injection of phenylephrine or reduction by amyl nitrite inhalation.

2. Baroreflex sensitivity was reduced in these patients as compared with normal controls. Reduction of baroreflex sensitivity was significantly greater in nine hypertensive than 13 normotensive patients with chronic renal failure.

3. A significant positive correlation was found between baroreflex sensitivity and motor nerve conduction velocity measured on ulnar nerve in 13 patients examined.

4. Saline was given with high dietary salt intake to seven normotensive patients with chronic renal failure for 2 or 5 days in order to determine whether the severe depression of baroreflex sensitivity can be an initiating factor for hypertension. Blood pressure was raised to hypertensive levels within 5 days in two patients in whom baroreflex sensitivity was nearly as low as that of hypertensive patients, but not in five cases whose baroreflex sensitivity was normal or only mildly depressed. Plasma volume increased to the same degree in both groups. Baroreflex sensitivity did not change in the former two cases despite blood pressure elevation.

5. It is concluded that reduced baroreflex sensitivity in chronic renal failure correlated with the presence of hypertension, as well as uraemic neuropathy, and may be one of the pathogenetic mechanisms of hypertension in end-stage chronic glomerulonephritis.

Key words: baroreflex sensitivity, chronic renal failure, hypertension, motor nerve conduction velocity, uraemic neuropathy.

Introduction

Although hypertension is one of the major complications in chronic renal failure, the mechanism of hypertension has not yet been fully elucidated. The roles of salt-water retention and the renin-angiotensin system have been intensively studied, but relatively little is known about the role of the autonomic nervous system.

A quantitative method of testing the sensitivity of the baroreceptor reflex has been developed by Smyth, Sleight & Pickering (1969), which expresses it as the reflex slowing of pulse interval produced by a unit rise of arterial pressure after an intravenous injection of a pressor drug such as phenylephrine. There have been a few reports (Pickering, Gribbin & Oliver, 1972; Lazarus, Hampers, Lowrie & Merrill, 1973; Lilley, Golden & Stone, 1976) that baroreflex sensitivity measured by this method is depressed and related to hypertension in patients on long-term haemodialysis. However, it is not known what caused baroreceptor dysfunction or whether depressed baroreceptor reflex sensitivity is involved in hypertension.
In the present experiments we measured baroreflex sensitivity in patients with chronic renal failure, not undergoing haemodialysis (which could influence baroreceptor reflex function), and evaluated some clinical factors associated with chronic renal failure which would influence baroreflex activity. We also investigated the role of baroreceptor reflex activity in hypertension by observing the susceptibility to volume-dependent hypertension by means of saline infusion.

Materials and methods

Twenty-two non-dialysed patients with chronic renal failure, who were admitted to our department between 1974 and 1977, were included in this study. Chronic renal failure was defined as serum creatinine concentration constantly being 265-5 \mu mol/l (3.0 mg/100 ml) or more. Twenty-one patients had chronic glomerulonephritis and one had Alport’s syndrome. Eight were women and 14 were men. Ages ranged from 20 to 68 years. Known duration of the renal failure was from 3 months to 6 years. All medications were discontinued at least 2 weeks before the study and all participants were placed on 100 mmol of sodium/day.

Blood pressure measurements were obtained with standard cuff and sphygmomanometer in the supine position at 08.00 hours for 3 consecutive days immediately before the study, and mean blood pressure was calculated as the sum of the diastolic pressure and one-third of the pulse pressure. Hypertension was defined as a mean blood pressure of 110 mmHg or more, normotension as a mean blood pressure below 110 mmHg for 3 consecutive days.

All patients were clinically stable and had no history or evidence by physical examination, chest X-ray or electrocardiogram of heart disease, congestive heart failure, uraemic cardiomyopathy or atherosclerotic changes of the aortic arch. The study was explained to the patients and informed consent was obtained from all participants.

After recumbency for 3 h the brachial artery pressure was recorded via an intra-arterial cannula (19 gauge) connected to a Statham transducer, arterial pressure and electrocardiogram being recorded simultaneously on a multichannel oscillographic recorder at a paper speed of 25 mm/s. When blood pressure and pulse rate had stabilized, 50–150 \mu g of phenylephrine was given by bolus injection and an increase in systolic blood pressure of 30–50 mmHg was obtained. After return of blood pressure and pulse rate to baseline values, single inhalation of an amyl nitrite ampoule was carried out, which caused a fall in systolic blood pressure of 30–50 mmHg. Baroreflex sensitivity was calculated by plotting the R–R interval of each beat against the systolic pressure of the preceding beat, the technique of Smyth et al. (1969) being used. Plotting was started at the end of injection or inhalation and continued to the highest or lowest systolic pressure. These points were then analysed for linear correlation. The baroreflex sensitivity was expressed as the slope of the regression line. The slope was used for further comparison if the r value (correlation coefficient) was more than 0.70.

Serum creatinine concentrations were measured with an autoanalyser.

Motor nerve conduction velocity was measured on the ulnar nerve (Kitaoka, 1976). Its normal range is more than 49 m/s.

Intravenous infusions of 1.5 litres of sodium chloride solution (154 mmol/l: saline) were given to six normotensive patients, from 09.00 to 21.00 hours daily for 5 days and to one normotensive patient for 2 days. Concurrently, the sodium content in the diet was increased to 280 mmol/day. Changes of blood pressure, pulse rate, plasma volume and body weight were followed every day. Baroreflex sensitivity was measured on days 1 and 5 in six patients to whom saline was given for 5 days, and on days 1 and 3 in one patient to whom saline was given for 2 days. All these parameters were checked at 08.00 hours to avoid the direct influence of saline infusion (Cowley & Guyton, 1975; Young, 1975). Blood pressure, pulse rate, plasma volume and baroreflex sensitivity were checked when the patients had been recumbent for 3 h and were considered to be stable. Plasma volume was measured at 08.00 hours on day 1 by dye-dilution technique, with Evans Blue, and its daily changes (increment of plasma volume) were estimated from the packed cell volume (PCV) of venous blood collected at 08.00 hours daily.

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\text{Increment of plasma volume} = \frac{100 - 0.91 \text{ PCV}\_1}{100 - 0.91 \text{ PCV}\_0} \times \frac{\text{plasma volume of day 1}}{\text{plasma volume of day 1}} - \text{plasma volume of day 1}
\]

where PCV\_0 indicates venous packed cell volume of day 1, PCV\_1 denotes venous packed cell volume of day 1, and 0.91 represents the ratio of overall cell percentage to venous cell percentage (Chaplin, Mollison & Vetter, 1953).
A possible mechanism of hypertension

There were no complications from arterial cannulation. Patients were carefully observed throughout the study and no signs or symptoms of cardiac failure were noted in any of the patients.

Statistical significance was determined by the Student’s t-test. All values described in the text, Figures and Table are means ± SD.

Results

Baroreflex sensitivity in patients with chronic renal failure

At the time of this study, 13 patients had a mean blood pressure below 110 mmHg and were considered normotensive. Nine patients had a mean blood pressure of 110 mmHg or more and were considered hypertensive (Table 1).

Baroreflex sensitivities of the normotensive and hypertensive groups are shown in Fig. 1. Sensitivities measured with phenylephrine injection were $9.02 ± 3.81$ and $5.10 ± 2.27$ ms/mmHg respectively. Baroreflex sensitivity of the normotensive group was significantly greater than that of the hypertensive group ($P < 0.05$). Both were apparently lower than that of normal controls ($16.00 ± SE 2.00$ ms/mmHg) as reported by Takeshita, Tanaka, Kuroiwa & Nakamura (1975).

Baroreflex sensitivities of both groups measured by amyl nitrite inhalation were $5.68 ± 1.38$

| Table 1. Patients’ profiles |

No differences in age, serum creatinine concentration, and packed cell volumes are noted between normotensive and hypertensive groups. Mean values ± SD are shown. N.S., Not significant.

<table>
<thead>
<tr>
<th>Group</th>
<th>Blood pressure (mmHg)</th>
<th>Age (years)</th>
<th>Serum creatinine (μmol/litre)</th>
<th>Packed cell volume (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Systolic</td>
<td>Diastolic</td>
<td>Mean blood pressure (mmHg)</td>
<td></td>
</tr>
<tr>
<td>Normotensive</td>
<td>13</td>
<td>130 ± 14</td>
<td>76 ± 8</td>
<td>97 ± 10</td>
</tr>
<tr>
<td>Hypertensive</td>
<td>9</td>
<td>178 ± 28</td>
<td>108 ± 16</td>
<td>132 ± 15</td>
</tr>
</tbody>
</table>

![Fig. 1. Baroreflex sensitivity in chronic renal failure measured with injection of phenylephrine (a) and amyl nitrite inhalation (b) in normotensive patients (○) and hypertensive patients (●). The shaded areas indicate normal ranges. Mean (long bar) and SD (short bars) are indicated.](image-url)
ms/mmHg and 3.27 ± 1.46 ms/mmHg respectively. Similarly, the former was significantly greater than the latter ($P < 0.05$), and both were lower than that of the controls (9.10 ± SE 1.30 ms/mmHg) as reported by Lazarus et al. (1973).

**Baroreflex sensitivity and serum creatinine concentration, duration of chronic renal failure, age and anaemia**

There were no statistically significant correlations between baroreflex sensitivity, measured either by injection of phenylephrine or amyl nitrite inhalation, and serum creatinine concentration, duration of chronic renal failure, patient's age or packed cell volume.

**Baroreflex sensitivity and motor nerve conduction velocity**

Motor nerve conduction velocity was delayed in two normotensive patients and four hypertensive patients of 13 patients measured, and there was a significant correlation between motor nerve conduction velocity and baroreflex sensitivity, measured either with injection of phenylephrine ($r = 0.78; P < 0.05$) or amyl nitrite inhalation ($r = 0.64; P < 0.05$) (Fig. 2).

**Effect of saline infusion on blood pressure**

Saline was given to seven normotensive patients with increased dietary sodium intake in order to determine whether baroreceptor dysfunction could be an initiating factor in volume-dependent hypertension in chronic renal failure (Fig. 3). In one normotensive patient, in whom baroreflex sensitivity measured with injection of phenylephrine was severely impaired (3.70 ms/mmHg), blood pressure was raised from 128/84 mmHg (mean blood pressure: 98.7 mmHg) on day 1 to 146/100 mmHg (mean blood pressure: 115.3 mmHg) on day 3, and plasma volume increased from 55.0 to 67.1 ml/kg body weight and body weight increased by 0-60 kg in 2 days. Similarly in another patient whose baroreflex sensitivity measured with injection of phenylephrine was markedly low (5.10 ms/mmHg), blood pressure rose from 130/78 mmHg (mean blood pressure: 95.3 mmHg) on day 1 to 172/96 mmHg (mean blood pressure: 121.3 mmHg) on day 5 and stayed at a hypertensive level on day 6, and plasma volume increased from 60.2 to 73.3 ml/kg body weight on day 5 and body weight increased by 1.90 kg in 5 days. In contrast, in five patients who did not become hypertensive, baroreflex sensitivity measured with injection of phenylephrine was normal or only mildly depressed (14.96, 9.50, 9.20, 11.52 ms/mmHg respectively). Plasma volumes on day 1 were 64.6, 60.1, 52.3, 62.5 and 60.9 ml/kg body weight respectively and seemed no less than those of the former two patients. In these five cases, blood pressure was not raised, although plasma volume and body weight increased in 5 days by 9.8 to 15.2 ml/kg and 0.50 to 1.90 kg respectively, i.e. to the same degree as in those who became hypertensive. Baroreflex sensitivities measured with amyl nitrite inhalation were 2.2 and 2.5 ms/mmHg in the former two patients, and 9.5, 7.6, 7.2, 6.8 and 6.4 ms/mmHg in the latter five patients. No further depression of baroreflex sensitivity measured either with injection of phenylephrine or amyl nitrite inhalation was noted in the former two patients despite the development of hypertension during the period of observation.

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**FIG. 2.** Correlation between motor nerve conduction velocity and baroreflex sensitivity measured with phenylephrine injection (a) and amyl nitrite inhalation (b). Broken lines represent the lower limit of the normal range of motor nerve conduction velocity. Continuous lines were fitted by linear regression, with equations as shown. Motor nerve conduction velocity was delayed in two normotensive (○) and four hypertensive (●) patients of 13 patients measured.
Bradycardia was not observed throughout this procedure in any of the patients.

Discussion

The results of this study indicate that baroreflex sensitivity, obtained by relating reflex changes of R–R interval of the electrocardiogram to drug-induced blood pressure elevation or reduction (Smyth et al., 1969) is reduced in patients with chronic renal failure, who are not undergoing haemodialysis (Fig. 1). Similar results have been obtained by other investigators from the study of the patients on long-term haemodialysis (Pickering et al., 1972; Lazarus et al., 1973; Lilley et al., 1976). The genesis of baroreceptor dysfunction, however, was not fully explained in their studies.

We found no correlation between baroreflex sensitivity and anaemia (Lazarus et al., 1973), age (Gribbin, Pickering, Sleight & Peto, 1971) or the severity or duration of the renal failure. No patients had a history or other evidence of heart disease, and thus it is unlikely that heart disease had induced important changes in baroreceptor function (Eckberg, Drabinsky & Braunwald, 1971).

On the other hand, it was shown that baroreflex sensitivity diminishes with decrease of motor nerve conduction velocity (Fig. 2). There are several lines of evidence (Hennessy & Siemen, 1968; Goldberger, Thompson, Guha, Kramer & Parrish, 1971; Kersh, Kronfield, Unger, Popper, Cantor & Cohn, 1974) that in chronic renal failure autonomic neuropathy coexists with somatic neuropathy, and uraemic neuropathy (including autonomic neuropathy) might account for the reduction of baroreflex sensitivity in those patients in whom motor nerve conduction velocity is delayed.
Another finding in our study is that baroreflex sensitivity is more severely impaired in hypertensive than in normotensive patients (Fig. 1), indicating that depressed baroreflex sensitivity is also related to hypertension. Similar results have been reported by some other investigators (Pickering et al., 1972; Lazarus et al., 1973). The nature of this relationship between hypertension and depressed baroreflex sensitivity has, however, been unclear.

It has been reported that persistent hypertension developed after baroreceptor denervation in animals (Ferrario, McCubbin & Page, 1969; Burstyn, Horrobin & Lloyd, 1972; McRitchie, Vatner, Heyndrickx & Braunwald, 1976) or man (Holton & Wood, 1965; Ripley, Hollisfield & Nies, 1977). On the other hand, resetting and diminished reflex sensitivity of baroreceptor reflex are reported to follow the elevation in arterial pressure in experimental renal hypertension (Aars, 1968; Krieger, 1970; Sleight, Robinson, Brooks & Rees, 1977).

Pickering et al. (1972) reported that in patients whose hypertension was thought to have preceded renal failure, reflex sensitivity was no lower than in those whose hypertension was secondary to renal disease. This would favour the view that severely depressed baroreflex sensitivity in hypertensive patients with chronic renal failure is the result of hypertension, though baroreceptor reflex function might possibly be affected also by factors other than blood pressure, which had been modified or altered by long-term haemodialysis. Lazarus et al. (1973) have reported that in nephrectomized patients on dialysis, baroreflex sensitivity in hypertensive patients approached that of normotensive patients. They could not incriminate the depressed baroreflex sensitivity as a cause of hypertension in patients with chronic renal failure. Thus although baroreceptor dysfunction does not by itself appear to cause persistent hypertension in chronic renal failure, denervation of baroreceptors has been found by some workers (Kezdi, 1960; Lawrence & Dickinson, 1964) to augment renal hypertension or at least to accelerate the rise of pressure (Liard, Cowley, McCaa, McCaa & Guyton, 1974; Cowley & Guyton, 1975).

In our study, isotonic saline was given with high salt intake to seven normotensive nondialysed patients for 2 or 5 days in order to determine whether the severe reduction of baroreflex sensitivity could be an initiating factor of volume-dependent hypertension in chronic renal failure. Blood pressure was raised to hypertensive levels within 5 days only in two patients, in whom baroreflex sensitivity was nearly as low as that of hypertensive patients, but not in five cases whose baroreflex sensitivity was normal or mildly depressed. Plasma volume and body weight increased to the same degree in both groups. However, bradycardia was not noted and baroreflex sensitivity did not show apparent alteration in the former two cases despite blood pressure elevation (Fig. 3). Absence of bradycardia reflects a resetting of the baroreflex system to the higher pressure (Aars, 1968; Krieger, 1970; Cowley & Guyton, 1975). The observation period might be too short for the reflex sensitivity of the baroreceptors to change (Aars, 1968; Sleight et al., 1977). Our data suggest that the normotensive patients with chronic renal failure, who have lower baroreflex sensitivity, do not buffer blood pressure elevation induced by salt–water load more effectively than those having higher baroreflex sensitivity, and a reset baroreceptor plays some role in the hypertension of these patients. In chronic renal failure, where the feedback mechanism of body fluid–pressure control is impaired (Guyton, Coleman, Cowley, Scheel, Manning & Norman, 1972), baroreceptor dysfunction may well be a relatively important factor for blood pressure elevation after salt–water retention. Such repeated short-term pressor episodes resulting from transient increase in salt and water intake or from transient change in renal function may cause irreversible medial hypertrophy in the resistance vessels, increase in peripheral resistance and ultimately lead to persistent hypertension (Folkow, 1971). Furthermore, increases in blood pressure may be less efficiently buffered in hypertensive subjects, whose baroreflex sensitivity is severely depressed, and therefore hypertension might be accelerated.

Acknowledgments

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