Impaired renal functional reserve and albuminuria in essential hypertension

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Abstract

The stimulatory effects of an infusion of amino acids on glomerular filtration rate has previously been used to measure renal functional reserve and detect glomerular hyperfiltration. Thirty four patients with mild to moderate essential hypertension and seemingly normal renal function and 22 healthy controls were given infusions of amino acids to investigate whether renal functional reserve is reduced in essential hypertension and to detect patients at risk of renal damage. Although basal creatinine clearance increased after the infusion of amino acids in the controls (mean 27.9 ml/min; 95% confidence interval 18.2 to 37.6), the overall change was lower in the patients (mean 13.4 ml/min; 8.3 to 18.5), 11 of the 34 showing no increase at all. In these 11 non-responders the mean systolic blood pressure was higher than that in the 23 others (178.5 mm Hg *v* 157 mm Hg, respectively). Mean urinary albumin excretion was abnormal in the patients (93.3 mg/24 h; 44.2 to 142.4); eight of the 11 non-responders had an albumin excretion above the normal range (>20 mg/24 h). In the 11 patients without renal functional reserve a positive correlation was found between basal creatinine clearance and albumin excretion ($r=0.695$).

As consumed renal reserve and albuminuria are markers of glomerular hyperfiltration studying renal function before and after infusion of amino acids can detect hypertensive patients at risk of progressive renal damage.

Introduction

Although most patients with early essential hypertension would be considered to have normal renal function according to commonly used clinical criteria, renal impairment has been detected during the course of the untreated disease in as many as 42% of patients.¹ The factors responsible for the decrease in glomerular filtration rate are still unknown, though hypertension itself seems to play an important part as shown by the decline in renal function with age.^{2,3} As haemodynamic studies in essential hypertension have shown that renal blood flow is quickly reduced⁴ and normal glomerular filtration rate maintained by efferent arteriolar constriction⁵ it has been proposed that the subsequent intraglomerular hypertension can cause progressive glomerular damage by the mechanism of hyperfiltration.^{6,7}

Infusion of amino acids in healthy subjects produces a significant increase in glomerular filtration rate, which is considered to be a measure of renal functional reserve; in previous studies such infusion has been used as a test to detect states of glomerular hyperfiltration with consumed renal reserve.⁸⁻¹⁰ We measured the effects of a short term infusion of amino acids on renal function in a

group of patients with essential hypertension and seemingly normal renal function to see whether renal functional reserve is reduced in essential hypertension and to detect patients at risk of progressive renal damage.

Subjects and methods

We studied 34 patients (26 men, eight women) with untreated mild to moderate essential hypertension and no signs of renal damage. All patients attended the same blood pressure clinic and were sequentially enrolled in the study. The control group consisted of 22 healthy volunteers from the hospital staff, who were matched for body size and sex (15 men, seven women). Although the average age of the controls was 7.6 years younger, we considered the difference to be unimportant as previous studies have shown that age does not affect the renal response to infusion of amino acids.^{9,10} Table I shows relevant clinical and laboratory data.

TABLE I—Characteristics of subjects studied. Values are means (SD)

	Controls (n=22)	Patients (n=34)
No of men	15	26
No of women	7	8
Age (years)	38 (17.8)	45.6 (12.1)
Blood pressure (mm Hg):		
Systolic	122 (18.8)	164.7 (20.9)
Diastolic	83 (9.7)	104.5 (10.1)
Body surface area (m ²)	1.79 (0.15)	1.82 (0.16)

Blood pressure was measured on at least two occasions by auscultation with a standard arm cuff and mercury manometer, phase V being taken as diastolic pressure, while the subjects were supine after resting for 20 minutes. Amino acids were infused in the morning after the subjects had fasted for 12 hours. All subjects had been eating an omnivorous diet without sodium restriction and had taken no drugs for the two weeks before the study. During the hour preceding the test subjects drank water (20 ml/kg body weight) to obtain an output of urine of about 10 ml/min; this flow was maintained throughout the test, which consisted of three periods of 120 minutes each. Urine samples were collected in each period and batched for measurement of creatinine clearance and sodium and albumin excretion. Blood was taken at 120, 240, and 360 minutes and a mean was taken of the values for the samples from the beginning and end of each period. The baseline values of the variables studied were derived from the results of the first period. At the end of this period the infusion was started. The solution infused was 8.5% amino acids (Freamine III, Baxter, Trieste, Italy) and contained L-isoleucine, L-lysine, L-leucine, L-methionine, L-phenylalanine, L-threonine, L-tryptophan, L-valine, L-alanine, L-arginine, L-histidine, L-proline, and L-serine as well as sodium (10 mmol/l), chloride (12 mmol/l), potassium (30 mmol/l), and magnesium (4 mmol/l). The osmolality of the solution was 860 mmol/kg.

The rate of infusion was maintained at 1.5 ml/minute for 240 minutes. Pilot studies performed under the same experimental conditions had given a mean coefficient of variance (for tests performed on the same morning in the same subjects) of 3.3% for creatinine clearance and 4.9% for serum β_2 microglobulin concentration. During the test subjects were supine, and blood pressure and heart rate were recorded regularly.

Creatinine clearance was determined in plasma and urine by the Jaffé rate method; creatinine clearance was calculated for each period of the test and was corrected for 1.73 m² surface area. β_2 Microglobulin concentration was measured with a radioimmunological method (Phadebas, Pharmacia Diagnostics, Uppsala, Sweden).¹¹ Sodium concentration in serum and urine was determined by using an ion selective electrode (System E2A, Beckman). Albuminuria was determined by a sensitive immunofluorimetric assay.¹² Plasma osmolality was measured by depression of the freezing point.

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Statistical analysis—Results are expressed as means and 95% confidence intervals.¹³ Means were compared by paired and unpaired Student's *t* tests; the correlation coefficient of the data was calculated as described elsewhere.¹⁴ Non-uniformity of variances were corrected with log transformation.

Results

Infusion of amino acids produced several modifications of renal function in the subjects studied (table II). Although basal values of serum creatinine concentration and creatinine clearance were comparable in patients and controls, the rise in creatinine clearance induced by the infusion was lower in the patients (13.4 ml/min (95% confidence interval 8.3 to 18.5) *v* 27.9 ml/min

FIG 1—Increase in creatinine clearance induced by infusion of amino acids in controls and hypertensive patients.

FIG 2—Correlation between unstimulated basal creatinine clearance and albumin excretion in 11 hypertensive patients without renal functional reserve ($p < 0.05$, $r = 0.696$, $y = 1.94x - 65.8$).

(18.2 to 37.6), respectively); the difference between the two groups (14.5 ml/min; 4.3 to 24.7) was significant ($t = 3.03$, $p < 0.01$). Eleven of the 34 patients showed no response to the infusion (fig 1). Mean basal creatinine clearance in these non-responders was not significantly different from that in the 23 responders (100 ml/min (73.2 to 126.8) *v* 92.3 ml/min (79 to 105.6), respectively). Statistical comparison showed that systolic blood pressure was higher in the non-responders than responders (178.5 mm Hg (163.9 to 193.1) *v* 157 mm Hg (149.7 to 164.3), respectively) ($t = 3.0$, $p < 0.01$).

Serum β_2 microglobulin concentration in the control group decreased significantly by a mean of 0.34 mg/l (0.06 to 0.62) after infusion of amino acids. Although this reduction was smaller in the patients, the difference (-0.12 mg/l; -0.08 to -0.32) was not significant. The 11 patients who did not show an increase in creatinine clearance showed no decrease in β_2 microglobulin concentrations.

TABLE II—Effects of infusion of amino acids in controls and hypertensive patients. Values are means (95% confidence intervals)

	Controls		Patients		Difference between means (after infusion minus basal values) of controls and patients
	Basal values	After infusion	Basal values	After infusion	
Serum creatinine (μ mol/l)	91.8 (84.6 to 99)	78.7 (69.6 to 87.8)*	84.5 (79.3 to 89.7)	78.6 (73.9 to 83.3)	7.2 (6.7 to 7.7)
Creatinine clearance (ml/min)	90.8 (79.2 to 102.4)	118.7 (104.4 to 132)*	94.5 (82 to 107)	107.9 (95.2 to 120.6)	14.5 (4.3 to 24.7)
Serum β_2 microglobulin (mg/l)	1.53 (1.31 to 1.75)	1.19 (1.03 to 1.35)*	1.77 (1.53 to 2.01)	1.55 (1.36 to 1.74)	0.12 (-0.08 to 0.32)
Sodium excretion (mmol/24 h)	230.4 (139.2 to 321.6)	544.8 (451.2 to 638.4)*	259.2 (204 to 314.4)	463.2 (345.6 to 580.8)*	110.4 (-67.2 to 288)
Fractional excretion of sodium (%)	1.11 (0.72 to 1.5)	1.6 (1.3 to 1.9)*	1.3 (0.94 to 1.66)	2.23 (1.63 to 2.83)*	0.44 (-0.3 to 1.18)
Diastolic pressure (mm Hg)	96.6 (90.8 to 102.4)	98.1 (93 to 103.2)	124.5 (119.9 to 129.1)	123 (117.1 to 128.9)	3 (-1.9 to 7.9)

* $p < 0.05$ When compared with basal values.

Urinary sodium excretion and the fractional excretion of sodium increased significantly after infusion in both groups. In the controls sodium excretion increased by 314.4 mmol/24 h (171.2 to 457.6) ($t=4.6$, $p<0.01$) and in the hypertensive patients by 204 mmol/24 h (89 to 319) ($t=3.39$, $p<0.02$). Basal values and those after infusion showed no significant differences between the two groups (table II). The patients who did not show an increase in creatinine clearance after infusion also showed no increase in sodium excretion. The fractional excretion of sodium increased by 0.49% (0.08 to 0.9) ($t=2.57$, $p<0.05$) in controls and by 0.93% (0.30 to 1.56) ($t=3.05$, $p<0.02$) in patients.

Urinary albumin excretion was 93.3 mg/24 h (44.2 to 142.4) in the hypertensive patients and 5.9 mg/24 h (2.01 to 9.79) in the controls. Patients who showed no increase in creatinine clearance after infusion of amino acids had a higher basal albumin excretion than those with a normal response (131 mg/24 h (70.5 to 191.5) v 79.2 mg/24 h (17.8 to 140.6), respectively), but the difference was not significant; moreover, eight of the 11 unresponsive patients had an abnormal basal albumin excretion (>20 mg/24 h). When albumin excretion was compared with creatinine clearance in the group of patients unresponsive to the infusion a significant positive correlation was found (fig 2).

No significant changes in plasma osmolality were found after infusion in controls and patients, and blood pressure and heart rate did not change during and after the infusion in either patients or controls.

Discussion

There are two main findings from this study. The first is that patients with essential hypertension and seemingly normal renal function did not show as great an increase in glomerular filtration rate as controls in response to an infusion of amino acids. The overall response was lower, being absent in 11 out of 34 patients. This suggests that the so called "renal functional reserve" is being used up.¹⁵ In our patients this renal abnormality was associated with high systolic blood pressure. This agrees with the findings of Christensen and Morgensen that in incipient diabetic nephropathy, a typical hyperfiltration state, glomerular filtration rate is negatively correlated with diastolic blood pressure.¹⁶

Our second finding concerns the rate of albumin excretion and its relation to exhausted renal reserve. In our patients albumin excretion was higher than that in the healthy controls as previously observed by Parving *et al*¹⁷; we also found that 73% of patients without renal reserve showed abnormal albumin excretion (>20 mg/24 h). Furthermore, in these unresponsive patients we established a positive correlation between basal glomerular filtration rate and albumin excretion. This finding can be regarded as a derangement in renal haemodynamics that is characteristic of essential hypertension, in which glomerular filtration rate is maintained when renal blood flow is reduced by an increase in efferent arteriolar resistance. The subsequent proportional increase in glomerular capillary hydraulic pressure, which is inversely correlated with renal blood flow, is responsible for the injury induced by hyperfiltration, the sign of such injury being albuminuria.^{18 19}

Whether our findings apply to a phase of the disease or a particular group of patients cannot be stated. The condition seems to be transitory as long term glomerular hypertension capable of inducing albuminuria and using up renal reserve inevitably leads to a much reduced glomerular filtration rate and anatomical damage⁷ unless treatment aimed specifically at reducing intraglomerular hypertension is given.^{20 21} Although the normal basal glomerular filtration rate seems a favourable indication in our patients, we cannot definitely comment on whether it will always be constant.

In conclusion, our cross sectional study showed a group of patients with mild to moderate essential hypertension who were at risk of progressive renal damage. A longitudinal study to elucidate thoroughly this renal abnormality of essential hypertension needs to be performed.

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ONE HUNDRED YEARS AGO

MR. A. S. MURRAY, Keeper of Greek and Roman Antiquities, British Museum, delivered an interesting lecture at the Parkes Museum on Thursday, March 22nd, on the "Physical Training of the Greeks and Romans." He observed that it had been said in ancient times that the two things which the Greeks desired most were to be healthy and to be beautiful. Beauty in their eyes was attainable largely by a careful system of physical training. We see, he observes, their idea of physical beauty nowhere better than on the sculptured frieze of the Parthenon at Athens, now in the British Museum, for the greater part of it is a simple glorification of the beauty of youth as developed by physical training on horseback and in chariot racing. There was no more marked difference between the Greeks and the semi-barbarous races that surrounded them than in this matter of physical training. In one of his dialogues Lucian introduces the Scythian Prince, Anacharisis, who visited Athens in the sixth century B.C., and in the course

of his visit went to the Palaistra. He was much surprised at the various exercises of the youth, thinking them ridiculous. He asked Solon, the legislator, how he could defend such folly. Solon explained that the exercises of the youth might seem absurd to an onlooker, but that they were meant to train up a race of men who, largely by this training, should become valuable citizens, capable of taking their part in war through the skill of body they had thus acquired, and capable of taking a share in the administration of public affairs through the clearness of head and ready judgment which the habitual training of the Palaistra fostered in them. The lecturer then proceeded to describe the ordinary exercises of boys previous to their reaching the age of joining the Palaistra; and, secondly, the series of athletic contests which they practised in the Palaistra, giving instances of the skill attained in the various contests of leaping, running, wrestling, boxing, throwing the disc and the spear. Lastly, he noticed the physical training of girls, to whom running was the only form of public contest allowed, and that only in a very restricted degree. He concluded with a brief sketch of a limited range of physical exercises, as practised by the Romans. (*British Medical Journal* 1888;i:708.)