Cardiovascular responses to upright tilting in hypertensive patients, with and without renal impairment and before and following nisoldipine treatment

M. M. A. E. WAHBHA, J. WILSON¹ & R. HAINSWORTH

Departments of Cardiovascular Studies and ¹Medicine (Leeds General Infirmary), University of Leeds, Leeds LS2 9JT

1 Cardiovascular responses to upright tilting were determined before and after treatment with the calcium antagonist, nisoldipine, in patients with essential hypertension and in patients of similar ages and similar degrees of hypertension complicated by renal impairment.

2 Cardiac output was determined by a single breath respiratory method and heart rate and blood pressure by an automatic sphygmomanometer.

3 During placebo treatment, the supine values of heart rate and blood pressure were similar in the two groups, but the renal patients had significantly higher cardiac outputs. Following nisoldipine treatment blood pressure was lower in both groups due to decreased vascular resistance; cardiac output was unchanged.

4 Upright tilting lowered cardiac output in both groups, but the fall in the patients with renal disease was greater. There were similar increases in heart rate, diastolic blood pressure and vascular resistance in both groups. After nisoldipine, in the renal patients the fall in cardiac output was again greater and there was also a fall in systolic blood pressure.

5 These results indicate that patients with hypertension complicated by renal impairment may have reduced orthostatic tolerance particularly after treatment with nisoldipine.

Keywords hypertension renal failure cardiovascular reflex nisoldipine

Introduction

Patients with hypertension tend to have a lower baroreceptor reflex sensitivity than comparable normotensive subjects (Bevegard *et al.*, 1980; Bristow *et al.*, 1969; Pickering *et al.*, 1972) and this may lead to an impaired orthostatic tolerance (Cuhe *et al.*, 1974; Esler & Nestel, 1973; Frolich *et al.*, 1967; Lazarus *et al.*, 1973). When hypertension is complicated by renal impairment, orthostatic tolerance may be even further reduced (Lilley *et al.*, 1976). However, it is not clear as to whether the diminished responses that have been reported in hypertensive patients with renal disease are largely the result of renal dialysis as this has been shown to impair ortho-

static tolerance (Kim *et al.*, 1979; Maher *et al.*, 1965; Naik *et al.*, 1981). Furthermore, in the previous studies on patients with hypertension and renal impairment, responses to standing and upright tilting have been compared only with those in normotensive healthy subjects or uraemic patients rather than with comparable hypertensives who did not have renal involvement.

Passive upright tilting is an effective way of producing a reproducible orthostatic stress and recent work from our laboratory has determined the responses in healthy normotensive subjects of various ages (Hainsworth & Al-Shamma,

Correspondence: Dr R. Hainsworth, Department of Cardiovascular Studies, University of Leeds, Leeds LS2 9JT

1988). One aim of the present study was to determine the responses to passive upright tilting in moderately hypertensive patients and to determine whether there were any differences in the responses to tilting in patients in whom hypertension was complicated by renal impairment in comparison with subjects of similar ages and similar degrees of hypertension but without renal disease.

Patients with either essential hypertension or hypertension with renal impairment are commonly treated with calcium channel blockers and, because of their effect on blood vessels, it is possible that such treatment may affect orthostatic responses. We therefore, determined the responses to tilt following treatment of hypertension with nisoldipine, a new calcium channel blocker, which has been shown to have potent vasodilator properties (Graefe *et al.*, 1987; Pasanisi *et al.*, 1985; Warltier *et al.*, 1981).

Methods

Studies were carried out on eight patients (two females) with mild to moderate hypertension complicated by renal impairment and eight patients (one female) selected to be of similar ages and to have similar degrees of hypertension but with normal renal function. Four of the renal patients had polycystic disease, three had glomerulonephritis and one had Alport's Syndrome. None had been subjected to renal dialysis.

Prior to the start of the study, five of the patients with renal disease had been treated with β -adrenoceptor antagonists and one on each of the following: β -adrenoceptor blocker plus diuretic, methyl dopa, and nifedipine. Five of the uncomplicated patients had been treated with β -adrenoceptor blockers and three with β -adrenoceptor blockers plus a diuretic. None of the patients had been given any other drug treatment.

The study was approved by Leeds Western Health Authority Research Ethics Committee and all patients gave informed written consent.

At the start of the study, all patients stopped active treatment and were given placebo tablets for 4 weeks. At that time they attended the laboratory and glomerular filtration rate (EDTA clearance, Wilson *et al.*, 1989), plasma creatinine, and packed cell volume were determined. A tilt test was then performed. Following this study, patients received nisoldipine 10 mg tablets and were instructed to take one twice daily for 6 weeks. They then returned to the laboratory and the tilt test was repeated.

The tilt tests were carried out as previously described (Hainsworth & Al-Shamma, 1988). The patient rested supine on a tilt table for at least 15 min. Then at 5 min intervals four estimates were made of heart rate and blood pressure (automatic sphygmomanometer; Infrasonde, Puritan Bennett Corp.) and cardiac output (Al-Shamma *et al.*, 1987). The patient was then tilted 60° head up and, after 10 min, four further sets of estimates were made over a period of 10 min. In normotensive subjects the automatic sphygmomanometer had been shown to provide estimates of systolic and diastolic blood pressures which had repeatabilities of ± 4.3 and 4.5 mm Hg (two standard deviations of repeated estimates) and mean values which did not differ from those obtained by a random zero sphygmomanometer (Hainsworth & Al-Shamma, 1988). The technique for estimating cardiac output had a repeatability of ± 0.6 l min⁻¹ (two s.ds) and the mean values did not differ from those obtained by the direct Fick method (Al-Shamma *et al.*, 1987).

Cardiac index was calculated as cardiac output divided by calculated body surface area and vascular resistance index as mean blood pressure (diastolic + 1/3 pulse pressure) divided by cardiac index.

All studies were carried out in the same laboratory (temperature 22–24° C) at about 15.00 h and by the same investigators. Patients were requested not to smoke on the day of the study and to take only a light lunch. The morning dose of placebo or nisoldipine was omitted on the day of the study to avoid an acute dose effect (Pasanisi *et al.*, 1985). Statistical analyses were made by analysis of variance.

Results

Supine data and responses to tilting following placebo administration

The data obtained at the end of the placebo period from individual patients, with and without renal impairment, are listed in Table 1. The values of patients' ages, weights, duration of diagnosed hypertension and blood pressures in the two groups were similar. However, the values of EDTA clearance, plasma creatinine, and packed cell volume were all significantly different between the two groups.

In the patients with renal impairment, cardiac index was significantly greater and, because mean blood pressure was not different between the groups, the calculated vascular resistance was significantly smaller.

Table 1 Data from patients with essential hypertension and hypertension complicated by renal impairment. Patients in both groups are arranged in order of age

Patient	Age (years)	Weight (kg)	Duration (years)	Syst/diast BP (mm Hg)	Creatinine ($\mu\text{mol l}^{-1}$)	EDTA clearance	PCV
<i>Essential hypertensives</i>							
1	33	86	0.5	142/102	96	99	0.49
2	41	65	8	140/95	62	128	0.42
3	47	72	3	171/104	84	97	0.41
4	47	76	6	152/100	98	91	0.43
5	48	87	0.5	165/98	109	84	0.41
6	49	85	1	146/96	87	85	0.44
7	58	66	14	141/97	81	80	0.40
8	61	81	6	145/97	96	120	0.44
Mean	48	77	4.8	150/99	89	98	0.43
s.e. mean	3.2	3.2	1.7	4.2/1.1	5.1	6	0.01
<i>Patients with renal disease</i>							
9	35	66	3	161/102	326	19	0.30
10	39	68	4	147/94	143	61	0.37
11	42	79	2	155/96	138	47	0.39
12	43	75	4	149/98	137	39	0.40
13	45	72	4	139/95	110	44	0.39
14	48	72	8	152/91	165	29	0.37
15	58	83	6	154/104	575	9	0.41
16	62	96	6	147/93	125	42	0.35
Mean	47	76	4.6	150/97	215*	36**	0.37*
s.e. mean	3.2	3.5	0.7	2.3/1.6	57	6	0.01

* and ** indicate that values are significantly different ($P < 0.05$ and 0.005) from corresponding values in essential hypertensives. Creatinine is serum creatinine level. Units of EDTA clearance (glomerular filtration rate) are in $\text{ml min}^{-1} (1.73 \text{ m})^{-2}$

The responses to passive upright tilting in the two groups of patients are compared in Figure 1. There was no significant change in systolic pressure in either group, but there were significant decreases in cardiac index and significant increases in diastolic blood pressure, peripheral vascular resistance and heart rate. In the patients with renal impairment, the decrease in cardiac index, expressed both as an absolute value and as a percentage change, was significantly

($P < 0.05$) greater than that in the patients with essential hypertension.

Supine data and responses to tilting following nisoldipine treatment

Following nisoldipine, in the supine position, there were highly significant decreases in systolic and diastolic blood pressures and vascular resistance in both groups (Table 2). Cardiac index was

Table 2 Supine data obtained following placebo and nisoldipine treatment. Values of means $\pm$ s.e. mean of eight patients in each group

	Placebo		Nisoldipine	
	Essential	Renal	Essential	Renal
Systolic BP (mm Hg)	150 $\pm$ 4.2	150 $\pm$ 2.3	137 $\pm$ 2.9††	141 $\pm$ 2.5††
Diastolic BP (mm Hg)	99 $\pm$ 1.1	97 $\pm$ 1.6	84 $\pm$ 2.0††	86 $\pm$ 3.0††
Heart rate (beats min^{-1})	64 $\pm$ 2.9	64 $\pm$ 2.4	65 $\pm$ 3.4	60 $\pm$ 3.9†
CI ($\text{l min}^{-1} \text{m}^{-2}$)	2.3 $\pm$ 0.13	2.7 $\pm$ 0.16*	2.4 $\pm$ 0.10	2.7 $\pm$ 0.14*
VRI ($\text{mm Hg l}^{-1} \text{min m}^2$)	51 $\pm$ 2.7	43 $\pm$ 2.5*	42 $\pm$ 3.5††	39 $\pm$ 2.2††

* indicates values are significantly different from corresponding values in patients with essential hypertension ($P < 0.05$); † and †† indicates values are significantly different from corresponding values during placebo treatment ($P < 0.05$ and 0.005). Abbreviations: CI, cardiac index; VRI, total peripheral vascular resistance index.

Figure 1 Responses to passive upright tilting by 60° following placebo treatment. Solid bars: responses in patients with essential hypertension; hatched bars: responses from patients with renal impairment. Responses of systolic and diastolic blood pressures (SBP, DBP), cardiac index (CI), heart rate (HR) and vascular resistance index (VRI). * indicates responses in the two groups are significantly different ($P < 0.05$).

not significantly changed and it remained significantly higher in the patients with renal disease. Heart rate following nisoldipine was significantly lower in the patients with renal disease.

Upright tilting following nisoldipine resulted in qualitatively similar responses to those obtained following placebo (Figure 2). However, in the patients with renal disease the decreases in systolic blood pressure and cardiac index (both absolute values and percentage changes) were significantly greater than the changes in the same patients before nisoldipine and greater than the changes in the patients with essential hypertension before or after nisoldipine.

Discussion

One of the objectives of this study was to compare the orthostatic responses in patients who had similar degrees of hypertension but with or

without renal impairment. For such a comparison to be valid it was necessary to ensure that there were no important differences in other variables which might influence orthostatic tolerance. The patients with renal disease were matched as closely as possible for age from a larger available group of patients with essential hypertension. As shown in Table 1, the matching not only for age, but also for weight, duration of diagnosed hypertension and blood pressures, was very close.

The methods used in this study were all 'non-invasive' and have been evaluated in our laboratory (Al-Shamma *et al.*, 1987; Hainsworth & Al-Shamma, 1988). The avoidance of intravascular catheterization prevents changes in the responses to tilting and the high incidence of syncope which are known to occur following the introduction of catheters (e.g. Stevens, 1966).

The initial studies were carried out in both groups of patients after 4 weeks without active

Figure 2 Responses to tilting following nisoldipine treatment. Abbreviations as in Figure 1. * and ** indicates responses in the two groups are significantly different ($P < 0.05$ and 0.01).

therapy. It was considered that by this time any effect of previous therapy should have ceased. Comparison of the supine haemodynamic data following the period of placebo treatment in the two groups of hypertensive subjects revealed that the only difference was that in the patients with renal impairment there was a higher cardiac index and, therefore, since blood pressures were similar, vascular resistance was lower. The greater cardiac index in the renal patients is probably at least partly related to their lower packed cell volumes. There is evidence from human and animal experiments that cardiac output is increased following haemodilution (Guyton *et al.*, 1973). The lower packed cell volume also explains the apparently lower vascular resistance in the renal patients. Resistance was calculated simply by dividing pressure by flow. However, this simplified calculation disregards the contribution of blood viscosity to the pressure/flow ratio. From Poiseuille's equation, at any given state of constriction of resistance vessels, this ratio is directly related to viscosity.

Orthostatic responses were studied using the technique of passive upright tilting. This is an effective method for decreasing venous return due to blood accumulating in the veins in the lower parts of the body. It provides a more reproducible stress than standing since the subjects are usually more relaxed due to their being supported by the tilt table. In the present study, following placebo treatment the responses were very similar to those described previously in healthy subjects (Hainsworth & Al-Shamma, 1988): a decrease in cardiac index, increases in heart rate, diastolic blood pressure and vascular resistance, and no consistent change in systolic blood pressure. The only difference in the responses to tilting that we observed following placebo treatment in the two groups of patients was that the patients with renal disease had a significantly larger fall in cardiac index. This difference was significant both in absolute terms and as percentage changes. This resulted in the absolute values of cardiac index in the upright position being almost identical in the two groups.

Following nisoldipine treatment, the baseline

values of blood pressures in the two groups were lower than before but they remained not significantly different from each other. Values of cardiac index were not changed and this indicated that there had been a decrease in total systemic vascular resistance. After nisoldipine, as found before nisoldipine, tilting resulted in a larger decrease in cardiac index in the patients with renal disease than in those with essential hypertension. There was also a significantly greater fall in systolic blood pressure.

Previous reports of the responses to tilting in hypertensive patients with renal impairment have provided conflicting results with some claiming a reduced orthostatic tolerance (Lazarus *et al.*, 1973; Lilley *et al.*, 1976; Naik *et al.*, 1981). However, in the previous studies, the patients had been treated by renal dialysis and this may affect plasma volume (Kim *et al.*, 1970; Lilley *et al.*, 1976; Maher & Schreiner, 1965). Furthermore, in patients with disease severe enough to require dialysis there is the possibility of

autonomic dysfunction (Lazarus *et al.*, 1973; Lilley *et al.*, 1976). Ours is the first study to compare responses in patients with similar degrees of hypertension, with and without moderate renal impairment. It is also the first study to determine responses of cardiac output and vascular resistance without intravascular catheterization.

Our main findings are that patients with hypertension complicated by renal impairment have higher supine values of cardiac index and larger decreases in response to upright tilting in comparison with patients with essential hypertension. Responses of blood pressure, vascular resistance and heart rate were similar in the two groups. Following treatment of both groups with a calcium channel blocker, there was still a larger fall in cardiac index in the patients with renal disease but there was then also a decrease in systolic blood pressure. This could conceivably lead to the possibility of a reduced orthostatic tolerance in some patients.

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