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The effect of captopril on the superior mesenteric artery and portal venous blood flow in normal man

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1 Measurements of superior mesenteric artery and portal venous blood flow were made non-invasively along with systemic and other regional (cardiac index, forearm and cutaneous blood flow) vascular responses to acute ingestion of the ACE inhibitor captopril (50 mg) or placebo (50 mg vitamin C), in 12 healthy subjects while supine and during head-up tilt.

2 After captopril, superior mesenteric artery and portal blood flow rose markedly with a reduction in superior mesenteric artery vascular resistance. Supine blood pressure was unchanged but cardiac index and forearm blood flow rose; during head-up tilt, blood pressure fell in some subjects.

3 There was a rise in levels of plasma renin activity and a fall in levels of plasma angiotensin II after captopril. After placebo, there were no significant changes in splanchnic blood flow, systemic or other regional responses and in biochemical measurements, while supine.

4 Our studies indicate that captopril is a potent dilator of the splanchnic vascular bed and suggest that this action may contribute to its therapeutic effects. The studies indicate a role for angiotensin II in the control of this large vascular bed although other agents (bradykinin, prostacyclin) may contribute.

Keywords captopril superior mesenteric artery blood flow portal blood flow splanchnic angiotensin II

Introduction

Captopril is an angiotensin converting enzyme (ACE) inhibitor which causes arteriolar vasodilatation, and lowers blood pressure (BP) and systemic vascular resistance in normal subjects and patients with hypertension and heart failure (Cody & Laragh, 1982; Faxon *et al.*, 1984; Ventura *et al.*, 1985; Williams, 1988). In normal man, captopril causes renal and skeletal muscular vasodilatation but its effect on the large splanchnic vascular bed, which plays an important part in BP regulation in man, is unclear (Banas, 1992; Crossley *et al.*, 1984; Tesar *et al.*, 1988). As previously there have been no studies using non-invasive assessment measurements of superior mesenteric artery and portal blood flow after captopril in normal man we report on these responses to a single dose of oral captopril in 12 healthy subjects. Systemic, other regional (cardiac index, forearm and cutaneous blood flow), and neurohormonal responses to captopril were also studied. Measurements were also made during head-up tilt so as to assess the effect of captopril on the vascular responses influenced by the sympathetic nervous system.

Methods

Twelve healthy subjects (mean age 31 years, range 20–64 years, male = 4, female = 8) were studied on two separate occasions, at least 1 week apart. All were on an unrestricted salt diet and fasted overnight before each study day to exclude the established effect of food on superior mesenteric artery blood flow (SMABF) (Moneta *et al.*, 1988). None was on medication and all were studied in a temperature controlled room (24° C) at 09.30 h after supine rest for 30 min to allow familiarisation with equipment. An indwelling venous cannula (Abbocath, 18G) was inserted into a forearm vein under local anaesthesia (2% lignocaine) for blood collection.

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The intravenous cannula was kept patent with heparinized saline solution. The study was approved by the Ethics Committee of St Mary's Hospital.

Measurements

1. Blood pressure and heart rate (BP, HR): by automatic sphygmomanometry (Sentron, Bard Biomedical, USA) before and every 5 min following captopril or placebo ingestion.
2. Stroke distance (SD, a measure of stroke volume): by a continuous wave Doppler ultrasound method (Exerdop, Quinton Instruments Co., a division of A. H. Robbins Inc, Seattle, Washington) before and every 30 min following captopril or placebo ingestion.
3. Forearm blood flow (FBF): by venous occlusion strain gauge plethysmography before and every 30 min following captopril or palcebo ingestion.
4. Digital (thumb) skin blood flow (DSBF): by a laser Doppler flowmeter (Periflux PF2b, Perimed Ltd Sweden) before and measured continuously throughout the study period.
5. Superior mesenteric artery and portal blood flow (SMABF, PBF) and Pulsatility Index (PI): by a real-time pulsed Doppler ultrasound method (Acuson 128 Computed Sonography System, Acuson Corporation, California; 3.5 MHz. Sector Transducer) before and every 30 min following captopril or placebo ingestion.

All measurements were non-invasive and have been previously described in detail (Chaudhuri *et al.*, 1991; Huntsman *et al.*, 1983; Moneta *et al.*, 1988; Qamar *et al.*, 1986a; Whitney, 1953) except for PI, PBF and DSBF.
Mean arterial blood pressure (MABP) was calculated from the formula, systolic BP + twice diastolic pressure divided by three.
CI (relative cardiac output) was calculated from multiplying the stroke distance by heart rate and mean of 20 complete and consecutive cycles were taken.
DSBF was measured continuously by a laser Doppler flowmeter which produces frequency shift of the laser light produced by the instrument. The frequency shift was detected by photodetectors and produced a voltage signal directly proportional to quantity of blood flow in the microvasculature of the superficial skin. The signal was recorded on a chart recorder (BBC SE120, UK) and expressed in arbitary units.
Pulsatility index (PI) of the SMA blood velocity waveforms was measured to assist observations. PI was defined as a peak to peak amplitude of a waveform divided by the mean amplitude over the cardiac cycle (Gosling & King, 1974). It is a measure of downstream resistance in the SMA and is independent of the angle of insonation and measurement of diameter of SMA, the two parameters which may cause errors in measurement of SMABF. It has been used previously in relation to SMA during feeding, and on other vascular beds in man (Gangar *et al.*, 1991; Qamar *et al.*, 1986b; Vyas *et al.*, 1989).
PBF was measured using the same machine and a similar Doppler principle after visualisation of the portal vein on its long axis using an intercostal approach (Brown *et al.*, 1989). The sample volume cursor was positioned at the centre of the lumen of the vein midway between the confluence of the splenic and superior mesenteric veins and the division of the portal vein into left and right hepatic branches. PBF was calculated similar to SMABF.
Forearm vascular resistance (FVR), digital skin vascular resistance (DSVR) and the SMA vascular resistance (SMAVR) were calculated from the ratio of the MAP and respective blood flow values, assuming zero venous pressure.

Blood collection and analsyis

Blood was collected for measurements of plasma noradrenaline, adrenaline, renin activity (PRA), angiotensin II (AII), insulin, electrolytes (sodium and potassium) and glucose. Blood samples (20 ml on each occasion) after captopril or placebo were collected in tubes stored in ice until centrifugation at 4° C for separation of plasma.

Plasma noradrenaline and adrenaline were measured by high performance liquid chromatography with an electochemical detector (Smeddes *et al.*, 1982), *PRA* was measured by radioimmunoassay of angiotensin I (Boyd *et al.*, 1969), *AII* by solid phase radioimmunoassay (Eurodiagnostics Angiotensin II kit), *glucose* by a glucose oxidase method using a Chemlab continuous flow analyzer (Trinder, 1969) and *insulin* by radioimmunoassay (RSL ^{125}I Insulin kit, ICN Biomedicals, Inc.). The intra assay and interassay coefficients of variation were 6.6% and 9% (noradrenaline), 11% and 8% (adrenaline), 4% and 7% (PRA), 5% and 8% (AII), 3.2% and 4.8% (glucose) and 2.7% and 5.4% (insulin) respectively.

Protocol

After baseline measurements and blood collection, subjects were given either oral captopril (50 mg, Capoten, Squibb) or placebo (50 mg, vitamin C, Boots) randomly on separate days, while supine with 50 ml water, at least 1 week apart. Measurements (except BP and HR) and blood collection (except AII and electrolytes) were made at 30 min intervals for 120 min. Blood samples for plasma AII and electrolyte measurements were taken at 60 min intervals. Subjects were then tilted head-up at 45° for 10 min and measurements and blood collection were repeated during tilt. Head-up tilt was reversed earlier in subjects who felt dizzy and lightheaded.

Statistical analysis

Data are presented as means ± s.e. mean. Analysis of variance (Minitab data analysis software, Minitab Inc, 1989) and area under the curve using the method of summary measures were used for data analysis (Matthews *et al.*, 1990). Multiple *t*-tests with Bonferroni correction were performed on means at 0, 30, 60, 90, 120 min and during head-up tilt to characterize further significant differences. Changes in haemodynamic and biochemical measurements in the captopril and placebo phase were compared by area under the curve using the method of summary measures. $P < 0.05$ was considered significant.

Variability of the various measurements were obtained, based on basal readings on the two study days, by dividing the standard deviation by the mean. Variability is then expressed as the mean coefficients of variability.

The *coefficients of variation* were 7.4% for CI, 7.2% for FBF, 11.4% for DSBF, 7.3% for SMABF and 12.2% for PBF.

Results

Haemodynamic measurements

Systolic, diastolic and MABP After captopril, there were no significant changes in systolic BP though there was a small but insignificant fall in diastolic and MABP (Figure 1). During head-up tilt, systolic and diastolic BP tended to fall, though not significantly (115 ± 3 to 105 ± 6 systolic and 65 ± 2 to 60 ± 2 mm Hg diastolic at 120 min). MABP also was lower during head-up tilt (82 ± 2 to 75 ± 3, P = NS, Figure 1). There was a fall in MABP in three out of the four subjects who felt faint when tilted after captopril. In two of these subjects MABP was lower while supine at 120 min, after captopril.

After placebo, there were no changes in systolic, diastolic and MABP while supine and during head-up tilt (Figure 1).

Diameter of the SMA Resting mean diameter of the SMA was 7.41 ± 0.09 mm during captopril and 7.32 ± 0.07 mm during placebo. After captopril, diameter of the SMA increased ($P < 0.05$, Figure 2) but was unchanged after placebo. During head-up tilt, diameter of the SMA fell after captopril and placebo.

SMABF and SMAVR Resting SMABF was 430 ± 22 ml min^{-1} on the captopril phase and 432 ± 21 ml min^{-1} on the placebo phase. After captopril, SMABF rose to 715 ± 60 ml min^{-1} at 120 min ($P < 0.001$, Figure 3). SMABF fell during head-up tilt as has been shown to occur in previous studies, in normal man (Chaudhuri *et al.*, 1991). After captopril, there was a corresponding fall in calculated SMAVR, from 0.19 ± 0.01 units to 0.12 ± 0.01 units at 120 min ($P < 0.001$, Figure 3). During head-

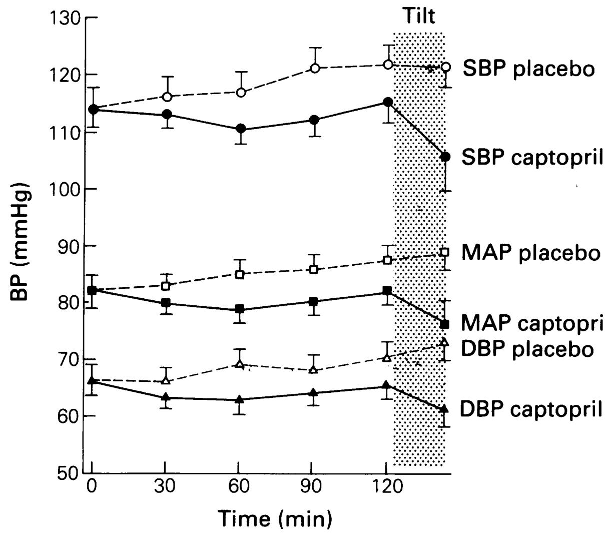

Figure 1 Changes in systolic blood pressure (SBP), diastolic blood pressure (DBP) and mean arterial blood pressure (MAP) at 0, 30, 60, 90, 120 min and during head-up tilt (shaded area) after captopril (continuous line) and placebo (dotted line).

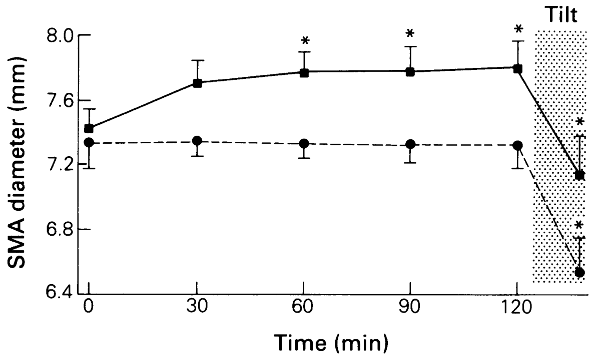

Figure 2 Changes in the diameter of the superior mesenteric artery (SMA) at 0, 30, 60, 90, 120 min and during head-up tilt (shaded area) after captopril (continuous line, ■) and placebo (dotted line, ●). *$P < 0.05$.

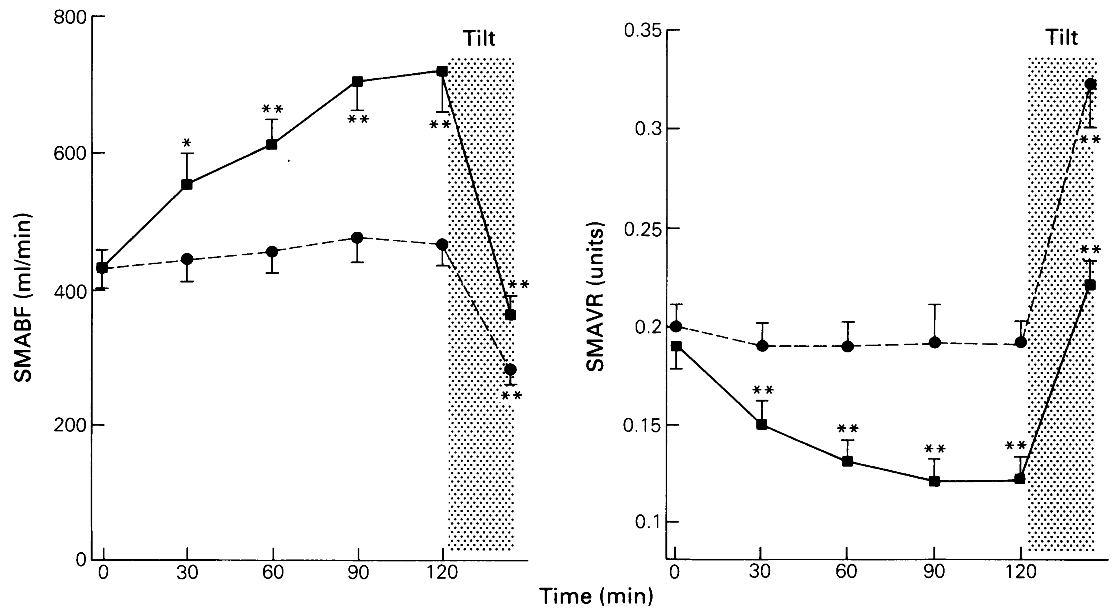

Figure 3 Changes in superior mesenteric artery blood flow (SMABF) and superior mesenteric artery vascular resistance (SMAVR) at 0, 30, 60, 90, 120 min and during head-up tilt (shaded area) after captopril (continuous line, ■) and placebo (dotted line, ●). *$P < 0.03$, **$P < 0.005$.

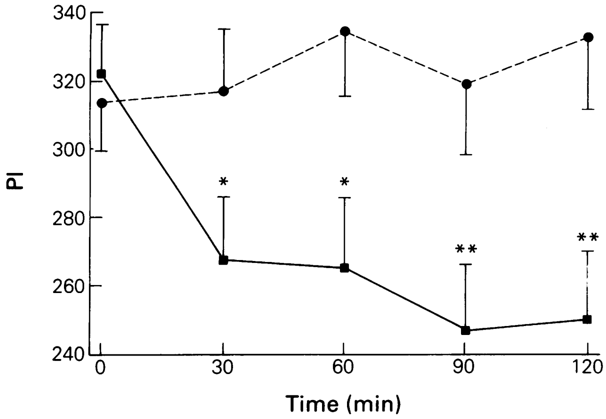

Figure 4 Changes in the pulsatility index (PI) of superior mesenteric artery velocity waveform at 0, 30, 60, 90, and 120 min after captopril (continuous line, ■) and placebo (dotted line, ●). $*P < 0.05$, $**P < 0.01$.

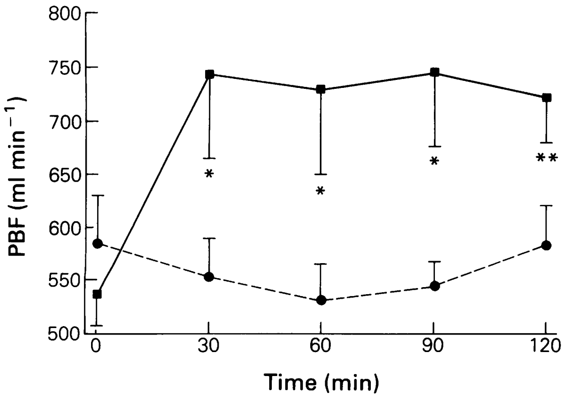

Figure 5 Changes in the portal blood flow (PBF) at 0, 30, 60, 90, and 120 min after captopril (continuous line, ■) and placebo (dotted line, ●). $*P < 0.05$, $**P < 0.005$.

up tilt, SMAVR rose (0.12 ± 0.01 to 0.22 ± 0.01, $P < 0.001$). After placebo, SMABF and SMAVR were unchanged except during head-up tilt, when SMABF fell with a corresponding rise in SMAVR (Figure 3).

PI Resting PI was 322 ± 13 during captopril and 314 ± 13 during the placebo phase. After captopril, PI of the SMA velocity waveform fell ($P < 0.05$, Figure 4) due to increased diastolic flow in the SMA, confirming vasodilatation. After placebo, PI of the SMA velocity waveform was unchanged (Figure 4). During head-up tilt, PI remained unchanged after captopril and placebo.

PBF Resting PBF was 536 ± 26 ml min^{-1} during captopril, and 586 ± 42 ml min^{-1} during the placebo phase. After captopril, PBF rose from 536 ± 26 to 719 ± 40 ml min^{-1} at 120 min ($P < 0.05$, Figure 5). After placebo, changes in PBF were not significant (Figure 5). Measurement of PBF was not made during head-up tilt owing to difficulty in visualisation of the portal vein.

HR After captopril and placebo, HR was unchanged except during head-up tilt when it rose after captopril and placebo (Figure 6). Heart rate did not rise during head-up tilt in three out of four subjects who felt faint while tilted after captopril.

CI Resting CI was 747 ± 67 units during captopril and 885 ± 82 during placebo. CI rose after captopril and fell during tilt (Figure 6). After placebo, changes in CI were not significant.

FBF and FVR FBF rose after captopril with a corresponding fall in FVR but was unchanged after placebo (Table 1).

DSBF and DSVR Changes in DSBF and DSVR were not significant although there was a trend towards a higher DSBF after captopril (Table 1).

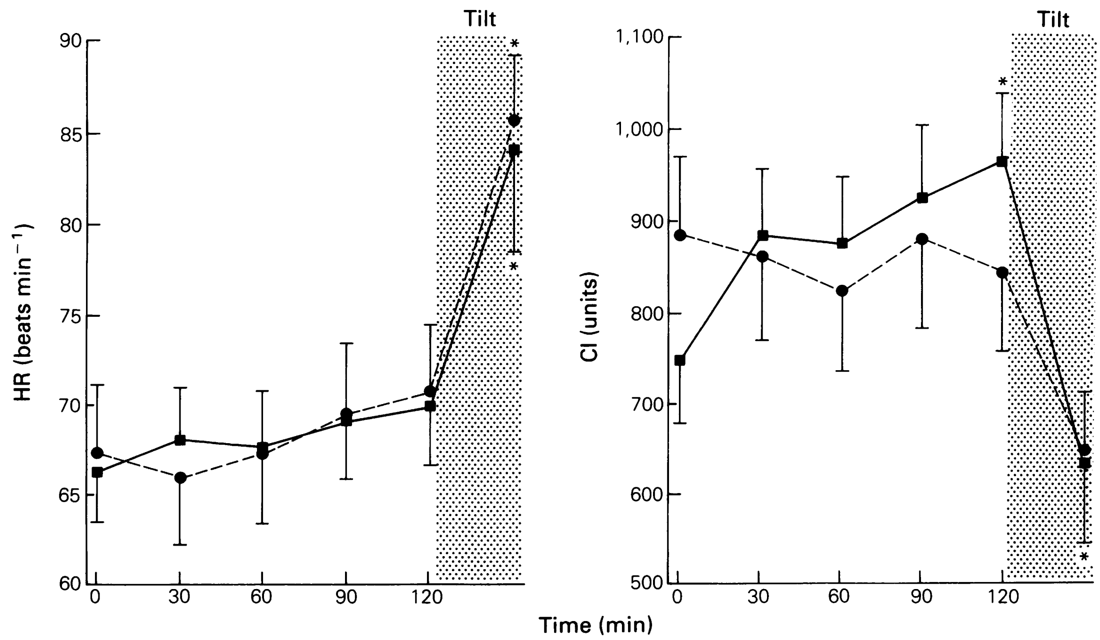

Figure 6 Changes in heart rate (HR) and cardiac index (CI) at 0, 30, 60, 90, 120 min and during head-up tilt (shaded area) after captopril (continuous line, ■) and placebo (dotted line, ●). $*P < 0.05$.

Table 1 Changes in forearm blood flow (FBF), forearm vascular resistance (FVR), digital skin blood flow (DSBF) and digital skin vascular resistance (DSVR) before (0), at 30, 60, 90, 120 min and during head-up tilt (T) after captopril (C) or placebo (P) ingestion in 12 healthy subjects

		Time (min) 0	30	60	90	120	T
FBF	c	2.9 ± 0.1	3.1 ± 0.2	3.3 ± 0.2	3.4 ± 0.2	3.8 ± 0.2*	2.1 ± 0.3*
(ml 100 ml^{-1} min^{-1})	p	3 ± 0.1	3 ± 0.2	3 ± 0.1	3 ± 0.1	3 ± 0.1	1.8 ± 0.3*
FVR	c	28.6 ± 2	26.5 ± 2	24.8 ± 2	24.4 ± 2	22.3 ± 1*	42.4*
(units)	p	27.9 ± 1	28.6 ± 1	29.2 ± 1	29 ± 1	29 ± 1	62 ± 12*
DSBF	c	17 ± 2	19 ± 2	22 ± 2	20 ± 2	21 ± 3	13 ± 2*
(%)	p	18 ± 2	18 ± 2	17 ± 2	18 ± 2	18 ± 2	13 ± 1*
DSVR	c	5.7 ± 0.6	5.1 ± 0.6	4.7 ± 0.6	5 ± 0.7	5.3 ± 0.8	7 ± 1*
(units)	p	4.8 ± 0.4	4.8 ± 0.5	5.4 ± 0.6	5.3 ± 0.6	5.4 ± 0.7	8 ± 1

* = $P < 0.05$.

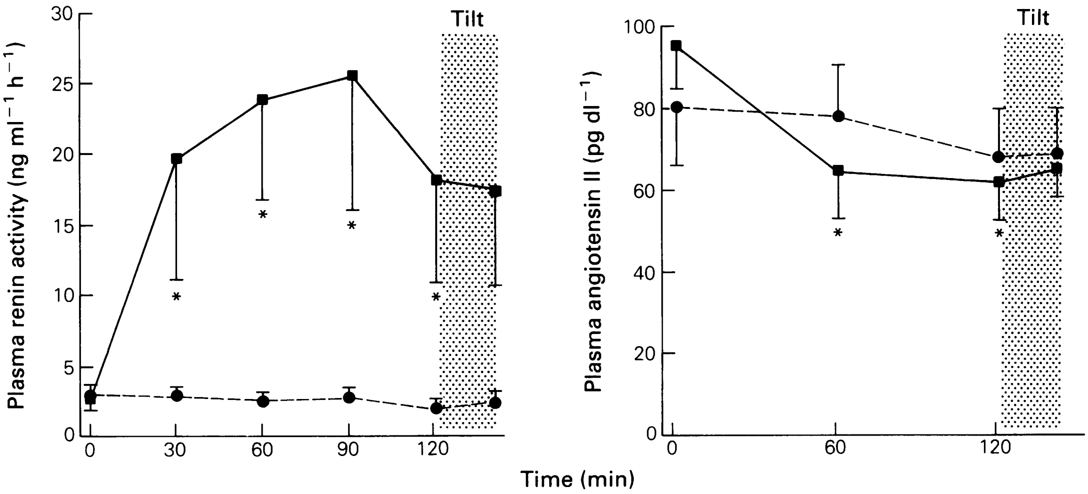

Figure 7 Changes in plasma renin activity at 0, 30, 60, 90, 120 min, and plasma angiotensin II (at 0, 60, 120 min) and during head-up tilt (shaded area) after captopril (continuous line, ■) and placebo (dotted line, ●). $^*P < 0.05$.

Biochemical measurements

PRA Basal values of PRA were 2.6 ± 0.3 ng ml^{-1} h^{-1} during captopril and 3 ± 0.5 ng ml^{-1} h^{-1} during placebo. After captopril, PRA rose ($P < 0.05$, Figure 7) but was unchanged after placebo.

AII Basal AII levels were 95 ± 11 pg 100 ml^{-1} during captopril and 80 ± 15 pg 100 ml^{-1} during placebo. AII fell after captopril ($P < 0.05$, Figure 7) but not after placebo.

Noradrenaline (NA) and adrenaline Plasma NA concentrations were unchanged after captopril and placebo, while subjects were supine (Table 2). During head-up tilt, plasma NA tended to rise after captopril though this was not significant ($P = 0.01$). However, in three out of four subjects who felt faint while tilted after captopril, plasma NA did not rise appreciably. After placebo, during head-up tilt, NA rose (Table 2).

Insulin, glucose and serum electrolytes Changes in plasma insulin, glucose and electrolyte levels were not significant after captopril or placebo (Table 2).

Symptoms

All subjects were asymptomatic while supine, after captopril or placebo. During head-up tilt, four subjects felt faint after captopril. These symptoms were rapidly reversed on return to the horizontal position.

Discussion

In this study, we have demonstrated a marked increase in SMABF and PBF in normal subjects after ACE inhibition by captopril which caused a significant rise in PRA levels and a fall in plasma AII concentrations. There were no other significant biochemical changes after captopril, particularly in plasma catecholamine levels. After captopril, there was also a rise in FBF and cardiac output with a trend towards a lower BP, particularly during head-up tilt. The results of non-invasive measurement of SMABF and PBF after captopril in our study differ from previous reports using invasive and indirect measurements. After captopril, in heart failure, hypertensive or cirrhotic patients there is either no

Table 2 Plasma electrolyte and hormonal responses before (0), at 30, 60, 90, 120 min and during head-up tilt (T) after captopril (C) or placebo (P) ingestion in 12 healthy subjects

		Time (min)					
		0	*30*	*60*	*90*	*120*	*T*
Sodium	C	140.9 ± 0.8	—	141.1 ± 0.7	—	140.0 ± 0.3	—
(mmol l^{-1})	P	139.4 ± 0.9	—	139.8 ± 0.7	—	140.8 ± 0.6	—
Potassium	C	4.0 ± 0.08	—	4.1 ± 0.1	—	4.0 ± 0.1	—
(mmol l^{-1})	P	4.0 ± 0.06	—	3.9 ± 0.07	—	3.8 ± 0.05	—
Noradrenaline	C	416 ± 97	385 ± 93	511 ± 129	455 ± 104	483 ± 116	755 ± 150
(pg ml^{-1})	P	270 ± 36	294 ± 48	310 ± 34	298 ± 25	323 ± 32	549 ± 66*
Adrenaline	C	69 ± 36	84 ± 53	66 ± 25	83 ± 43	77 ± 30	79 ± 34
(pg ml^{-1})	P	78 ± 31	91 ± 41	136 ± 82	102 ± 33	121 ± 58	173 ± 115
Glucose	C	4.6 ± 0.1	4.8 ± 0.1	4.9 ± 0.1	5.0 ± 0.1	5.0 ± 0.1	—
(mmol l^{-1})	P	4.7 ± 0.1	4.7 ± 0.2	4.8 ± 0.1	4.9 ± 0.1	4.8 ± 0.1	—
Insulin	C	5.3 ± 0.5	4.9 ± 0.5	5.2 ± 0.4	4.9 ± 0.6	5.7 ± 0.8	—
(mu l^{-1})	P	6.4 ± 1.3	5.9 ± 0.8	5.0 ± 0.6	5.3 ± 0.9	6.0 ± 0.6	—

* = $P < 0.05$.

change or a decrease in hepatic blood flow measured by the indocyanine green clearance method, although some observed a reduction in splanchnic vascular resistance and hepatic venous wedge pressure (Crossley *et al.*, 1984; Eriksson *et al.*, 1984; Faxon *et al.*, 1984; Ventura *et al.*, 1985). The indocyanine green clearance method which indirectly measures hepatic blood flow, however, is dependent on hepatic metabolism and clearance. The latter can be reduced by 20% in cirrhosis and congestive cardiac failure, thus resulting in errors (Caesar *et al.*, 1961); this may explain the variable results in such studies.

The non-invasive Doppler ultrasound method we used to measure SMABF and PBF, is now well established and provides real-time measurement of blood flow to the duodenum (except the first part), the small and large intestine up to the right half of the transverse colon as the SMA, a major contributor to the splanchnic vascular bed. The method is reproducible, has been validated and correlates well with results of invasive studies (Clark *et al.*, 1980; Chaudhuri *et al.*, 1991). We additionally measured the PI of the SMA blood velocity waveforms. This Doppler index correlates inversely with changes in SMABF, is independent of the angle of insonation and measurement of the diameter of SMA and is a reliable indicator of changes in downstream resistance in the SMA. The fall in PI after captopril was probably due to vasodilatation causing an increase in diastolic flow in the SMA, as has been observed also after food ingestion (Qamar *et al.*, 1986b). Why PI was unchanged during head-up tile is unclear. It may be that PI values were underestimated during tilt due to a fall in cardiac output, which influences the shape of blood velocity waveforms and thus PI.

Measurements of gastro-intestinal venous outflow were made in the portal vein. There was a rise in PBF after captopril, further indicating vasodilatation in the splanchnic vascular bed. This is similar to the 32% rise in portal blood flow observed in a study using a Dopplerian flowmeter, after a single 25 mg dose of captopril, in normal subjects (Tesar *et al.*, 1988).

Splanchnic vasodilatation after captopril may result from inhibition of ACE as indicated by the rise in PRA and a fall in AII. Captopril however has other actions such as inhibition of AII formation in cardiac and vascular tissues and selective superior mesenteric vasodilatation either by scavenging superoxide radicals or by interacting with the dynamics of the L-arginine-nitric oxide system (Gardiner *et al.*, 1990; Muller *et al.*, 1990; Swales & Heagerty, 1987; Westlin & Mullanc, 1988). Captopril is also known to augment the release of the vasodilator bradykinin, which may release prostacyclin or endothelium-derived relaxing factor (EDRF), which are potent vasodilators (Gardiner *et al.*, 1992; Vanhoutte *et al.*, 1989). Thus, studies using specific AII antagonists will be needed to further define the role of angiotensin II on the splanchnic vascular bed in man.

Captopril has sympatho-inhibitory actions both *in vivo* and *in vitro* (Clough *et al.*, 1982; De Jonge *et al.*, 1981; Vanhoutte *et al.*, 1989). It may be argued, that in our study, the splanchnic vasodilatation after captopril was due to such effects, especially as the sympathetic nervous system is known to influence this vascular bed. However, there were no changes in plasma catecholamine levels after captopril. Furthermore, during head-up tilt the SMA constricted and the plasma NA rose in the majority of subjects indicating preserved sympathoneural responses in this vascular bed. It is therefore unlikely that sympatho-inhibition played a part in the splanchnic vasodilatation.

In our study, forearm blood flow and cardiac output rose after captopril as has been previously reported (Banas *et al.*, 1992; Ventura *et al.*, 1985). There was a small but insignificant rise in cutaneous blood flow. Systemic BP was maintained in the majority, despite vasodilatation in skeletal muscle, splanchnic, cutaneous and, we assume, the renal vascular beds. This maintenance of BP may have been due to a compensatory rise in cardiac output, though this was probably inadequate in some subjects, in whom BP tended to be lower after captopril particularly during head-up tilt, during which there could have been a further translocation of blood into dependent veins. The marked fall in BP in three out of the four subjects who felt faint when tilted after captopril, could thus be due to a combination of vasodilatation in splanchnic and other regions, and through activation of the Bezold-Jarisch reflex (Mark, 1983). This reflex results in hypotension and bradycardia and has been proposed as a mechanism for the fall in BP in heart failure patients after the first dose of captopril (MacFayden *et al.*, 1991).

We would like to speculate on the clinical implications of these findings. In essential hypertension there is a selective increase in superior mesenteric artery vascular resistance (Thomaides *et al.*, 1991); reversal of these changes by captopril may be a major haemodynamic mechanism to lower BP although this has not yet been studied. Furthermore, after captopril, there is no interference with the sympatho-neural control of this large vascular bed, where lack of control may contribute to postural hypotension, as demonstrated in patients with sympathetic failure (Ray-Chaudhuri *et al.*, 1992). This may explain the lack of postural hypotension by captopril and other ACE-inhibitors, when given chronically.

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