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ABNORMALITY OF SUPERIOR MESENTERIC ARTERY BLOOD FLOW RESPONSES IN HUMAN SYMPATHETIC FAILURE

BY K. RAY CHAUDHURI, T. THOMAIDES AND C. J. MATHIAS

From the Cardiovascular Medicine Unit, Department of Medicine, St Mary's Hospital Medical School/Imperial College of Science, Technology and Medicine, and the Autonomic Unit, University Department of Clinical Neurology, Institute of Neurology, and National Hospital for Neurology and Neurosurgery, Queen Square, London

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SUMMARY

1. Systemic and regional haemodynamic responses, including superior mesenteric artery blood flow, were measured during stimuli which increase sympatho-neural activity in age-matched normal subjects (controls) and in two groups of patients with sympathetic failure (pure autonomic failure and multiple system atrophy). The stimuli included the pressor tests (mental arithmetic, cutaneous cold and isometric exercise) and head-up tilt.

2. In the controls, the blood pressure did not rise in some during mental arithmetic, but rose in all subjects during cutaneous cold and isometric exercise and was maintained during head-up tilt. In sympathetic failure patients, blood pressure was unchanged during each pressor test and fell during head-up tilt.

3. In the controls, superior mesenteric artery blood flow did not fall significantly during mental arithmetic but fell (with a corresponding rise in calculated superior mesenteric artery vascular resistance), during cutaneous cold, isometric exercise and head-up tilt. In sympathetic failure patients, there were no changes in superior mesenteric artery blood flow and vascular resistance during the pressor tests and head-up tilt.

4. There were no changes in cardiac index or forearm blood flow during each pressor test in both controls and patients. Cardiac index fell and forearm vascular resistance rose during head-up tilt in the controls only.

5. In conclusion, active constriction of the superior mesenteric artery occurs in normal subjects during sympatho-neural activation induced by stimuli such as cutaneous cold, isometric exercise and head-up tilt. This does not occur in patients with sympathetic failure and probably contributes to postural hypotension, emphasizing the role of the splanchnic vascular bed in overall blood pressure control. This study confirms the necessity of integrity of sympathetic pathways in the neural control of the splanchnic vascular bed.

INTRODUCTION

The splanchnic vascular bed contains up to 30% of total blood volume and receives up to 25% of the resting cardiac output (Rowell, 1975). This vascular bed

plays an important part in blood pressure regulation and invasive studies in animals and man indicate that vasoconstriction occurs when sympathoneural stimulation is induced by upright or supine exercise (Wade, Combes, Childs, Wheeler, Cournard & Bradley, 1956; Rowell, Blackmon, Martin, Mazzarella & Bruce, 1965), lower body negative pressure (Rowell, Wyss & Brengelmann, 1973), thermoregulatory stress (Glaser, Berridge & Prior, 1950; Rowell, 1975), haemorrhage (Chien, 1967) and short-lived pressor stimuli (Chaudhuri, Thomaides, Hernandez, Alam & Mathias, 1991*a*). Rowell (1975) demonstrated that the fall in splanchnic conductance induced by lower body negative pressure (LBNP) accounted for about one-third of the decrease in total vascular conductance and Price, Deutsch, Marshall, Stephen, Behar & Neufield (1966) showed a 40% reduction of splanchnic blood volume on removal of 15–20% of total blood volume in conscious patients. Changes in superior mesenteric artery (SMA) blood flow can be measured non-invasively using a Doppler ultrasound method initially described by Nimura, Miyatake, Kinoshita, Okamoto, Kawamura, Beppu & Sakakibera in 1983 and utilized by other workers (Qamar, Read, Skidmore, Evans & Wells, 1986*a*; Nakamura, Moriyasu, Ban, Nishida, Tamada, Kawasaki, Sakai & Uchino, 1989; Kooner, Armstrong, Peart, Bannister & Mathias, 1990). Using this technique in young normal subjects we have demonstrated that sympathoneural stimuli which raise or maintain blood pressure actively constrict the superior mesenteric artery (Chaudhuri, Thomaides, Hernandez & Mathias, 1991*b*). With some of these stimuli, such as head-up tilt, it was not clear if humoral changes may have contributed to the observed fall in SMA blood flow and rise in superior mesenteric artery vascular resistance. We now describe studies aimed at evaluating the role of neural factors in such responses, by observations in two groups of patients with autonomic failure, who on the basis of a range of physiological and biochemical tests have widespread sympathetic denervation. Comparisons have been made in age-matched healthy subjects (controls).

METHODS

Subjects

Thirteen subjects with chronic primary autonomic failure (AF, mean age, 56 years; range, 46–72 years) and ten age-matched controls (mean age, 52 years; range, 36–68 years) were studied. All AF patients had severe postural hypotension (systolic fall of blood pressure > 30 mmHg) due to sympathetic failure and the majority had cardiac parasympathetic involvement. The diagnosis was confirmed by a series of autonomic function tests as described by Mathias & Bannister, 1992 (Table 1). Of the thirteen patients with AF, eight had pure autonomic failure (PAF, autonomic failure with no other neurological deficits) and five had multiple system atrophy (MSA, autonomic failure with pyramidal, extrapyramidal and/or cerebellar manifestations) (Mathias, 1991). Despite a similar degree of sympathetic failure, there were differences in plasma noradrenaline levels suggesting that, in the two groups, the functional site of lesion was different. On the basis of a range of other studies this is thought to be mainly central in MSA but more peripheral in PAF (Polinsky, 1988). Results in these two groups will therefore be considered separately. Ten healthy controls were studied in an identical manner. The study was approved by the ethics committee of St Mary's Hospital.

None of the controls were on drugs. In the patients medication consisted of fludrocortisone which was withdrawn 2 days prior to the study. They were studied after an overnight fast to exclude the established effect of food on superior mesenteric artery (SMA) blood flow and ensure optimum ultrasound visualization of the SMA (Qamar, Read, Skidmore, Evans & Wells, 1986*b*; Moneta, Taylor, Helton, Mulholland & Strandness, 1988). The study began at 09.30 h in a temperature-controlled room (24 °C). After an initial supine rest for 30 min to allow for familiarization with

equipment and stabilization, measurements were made of SMA blood flow (Acuson 128 Computed Sonography System, Acuson Corporation, CA, USA; 3·5 MHz Sector Tranducer), blood pressure (BP) and heart rate (HR) (Automated Sphygmomanometer, Sentron, Bard Biomedical, USA), forearm blood flow (mercury-in-silastic strain gauge plethysmography, the forearm being kept horizontal and at the level of the heart during each measurement), and cardiac index (continuous

TABLE 1. Results of a series of autonomic function tests and plasma noradrenaline (NA) levels in eight patients with pure autonomic failure (PAF) and five patients with multiple system atrophy (MSA)

Patients	Tilt BP/HR	Valsalva BP/HR	Pressor tests BP	Sinus arrythmia HR	Hyperventilation BP/HR	Plasma NA (pg ml^{-1}) Supine	Plasma NA (pg ml^{-1}) Tilt
PAF							
1	A	A	A	A	A	77	78
2	A	A	A	A	A	77	67
3	A	A	A	A	—	115	125
4	A	A	A	A	—	74	70
5	A	A	A	A	—	72	59
6	A	A	A	A	A	89	117
7	A	A	A	N	—	32	UD
8	A	A	A	A	—	113	160
MSA							
1	A	A	A	A	—	290	411
2	A	A	A	A	—	293	269
3	A	A	A	A	A	131	199
4	A	A	A	N	A	219	388
5	A	A	A	A	—	483	423

Valsalva, Valsalva manoeuvre; BP, blood pressure; HR, heart rate; A, abnormal; N, normal; UD, undetectable (< 5 pg ml^{-1}). Normal supine levels of plasma NA = 300 ± 40 pg ml^{-1} and during head-up tilt = 490 ± 65 pg ml^{-1}.

wave Doppler ultrasound, Exerdop, Quinton Instruments, USA). Subjects then non-randomly underwent a series of pressor tests which included mental arithmetic (serial 17 subtraction from 700 for 120 s), cutaneous cold (free hand immersed in ice slush at 4 °C for 120 s), isometric exercise (gripping a rolled blood pressure cuff for 120 s at one-third maximal pressure using the dominant hand). They were then subjected to 45 deg head-up tilt for 10 min with measurements at 2 and 10 min. A 10 min period of equilibration was allowed between each stimulus and measurements were made before (10 min) and during (at 120 s) each stimulus.

Calculations

SMA blood flow was measured by using a real time pulsed Doppler ultrasound method which has been previously described (Qamar *et al.* 1986*a*, Chaudhuri *et al.* 1991*a*). Briefly, in this technique, the 3·5 MHz transducer is placed in the epigastric area of the supine subject to obtain a picture of the SMA on its long axis near its origin from the aorta. By placing the cursor within the lumen of the artery a characteristic SMA signal is obtained which can be clearly distinguished from the neighbouring vessels, namely the aorta and coeliac artery. The real time amplitude weighted frequencies displayed on the Doppler screen are then converted by the computer software assuming laminar flow to time-average velocity (TAV) by using the Doppler formula:

$$F_d = \frac{2F_o v \cos\theta}{c}$$

where F_d is Doppler frequency shift, F_o is incident frequency, v is flow velocity, c is speed of sound in tissue and θ is the angle of insonation (angle between the Doppler beam and longitudinal axis of the blood flow, usually kept within 40 deg).

The diameter of SMA at the point of spectral sampling can be measured in real time using a high resolution enlarging system incorporated in the machine. The blood flow (in ml min^{-1}) can then be calculated from the formula:

$$BF = \pi r^2 \times TAV \times 60,$$

where BF is blood flow, r is the radius of SMA at the point of sampling and TAV is the time-averaged velocity. To reduce error in calculation a mean of at least three TAV values obtained from three Doppler displays (each containing at least three cardiac cycles) and corresponding measurements of three separate diameters were taken for each observation.

Cardiac index was calculated by multiplying stroke distance (a measure of stroke volume) with heart rate and was used as a measure of relative cardiac output. Stroke distance was derived from the integral of peak velocity profile of ascending aortic blood flow by Doppler ultrasound technique. A mean value of twenty consecutive and complete cardiac cycles were taken for each observation. This method has been validated as a measure of cardiac output by other workers (Huntsman, Stewart, Barnes, Franklin, Colocousis & Hessel, 1983; Mehta, Iyawe, Cummin, Bayley, Saunders & Bennet, 1985).

Forearm blood was measured by venous occlusion plethysmography with double-stranded mercury-in-silastic strain gauge as described by Whitney (1953). The hand circulation was occluded by inflating the wrist cuff above the arterial pressure and the cuff around the upper arm was inflated above 40 mmHg for venous occlusion. With the arm resting horizontally and at the level of the heart, changes in the circumference of the forearm were measured using the double-stranded gauge (model 2582, Ormed Ltd, Welwyn Garden City) and the signals from the gauge were transferred to the coupling unit (model 2583, Lectromed, St Peter, Jersey) for temperature compensation and to the preamplifier (type MX2P, Lectromed). Six plethysmographic slopes were then recorded on a two-channel chart recorder (type MX216, Lectromed) before and during each stimuli. The slopes were then converted to flows (in ml $(100\ ml)^{-1}\ min^{-1}$) using a previously described formula (Greenfield, Whitney & Mowbray, 1963).

Mean arterial pressure (MAP) was calculated from the formula systolic BP + twice diastolic BP divided by three. Vascular resistance was calculated by dividing MAP by blood flow.

Statistics

Statistical analyses were carried out using a standard version Minitab data analysis software (Minitab, Inc, 1989). Blood flow (SMA and forearm), BP, HR and cardiac index values before and during each stimulus were compared by paired t tests and $P < 0{\cdot}05$ was considered significant. Changes in BP, SMA blood flow and SMA vascular resistance between controls and patients and mean baseline SMA blood flow values preceding each test, were compared by analysis of variance (ANOVA). Within subject coefficients of variation of SMA blood flow measurement were obtained by dividing the standard deviation by the mean and was then expressed as the mean of coefficients of variation. Data are presented as means ± S.E.M.

RESULTS

Mean arterial blood pressure

In the controls, during mental arithmetic, BP rose in six subjects and was unchanged in four, with no significant change in mean BP during mental arithmetic ($94{\cdot}6 \pm 4{\cdot}4$ to $101{\cdot}1 \pm 4{\cdot}3$ mmHg, $P = 0{\cdot}11$) (Fig. 1). BP (in mmHg) rose during cutaneous cold (91 ± 3 to 102 ± 3) and isometric exercise (89 ± 4 to 109 ± 8) ($P < 0{\cdot}05$ in each case). BP was maintained during tilt at 2 min (89 ± 2 to 93 ± 3) and 10 min (89 ± 2 to 93 ± 3). In the PAF patients, BP was unchanged during mental arithmetic ($112{\cdot}1 \pm 6{\cdot}2$ to $117{\cdot}1 \pm 6{\cdot}1$), cutaneous cold ($113{\cdot}8 \pm 6{\cdot}3$ to $120{\cdot}7 \pm 4{\cdot}8$) and isometric exercise ($112{\cdot}2 \pm 5{\cdot}7$ to $114{\cdot}7 \pm 4{\cdot}3$) (n.s. in each case). However, BP fell markedly during tilt at 2 min ($111{\cdot}2 \pm 5{\cdot}3$ to $68{\cdot}6 \pm 7{\cdot}4$) and 10 min ($111{\cdot}2 \pm 5{\cdot}3$ to $63{\cdot}8 \pm 4{\cdot}5$) ($P < 0{\cdot}01$ in each case) (Fig. 1).

In the MSA patients, BP was also unchanged during mental arithmetic

(107·8±7·9 to 104·8±7·1), cutaneous cold (104·0±7·1 to 113·7±8·9) and isometric exercise (109·4±9·5 to 110·8±8·4) (n.s. in each case). BP fell during tilt at 2 min (110·0±9·9 to 77·7±3·1) and 10 min (110·0±9·9 to 79·1±3·8) ($P < 0·01$ in each case).

When compared by ANOVA, in controls, the rise in BP during cutaneous cold (14±1%) and isometric exercise (21±3%) but not during mental arithmetic

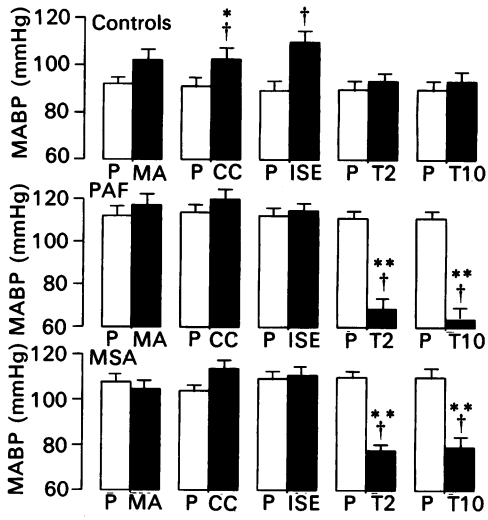

Fig. 1. Changes in mean arterial blood pressure (MABP) before (P) and during mental arithmetic (MA), cutaneous cold (CC), isometric exercise (ISE) and tilt at 2 min (T2) and 10 min (T10) in controls, pure autonomic failure (PAF) and multiple system atrophy (MSA) patients. † = $P < 0·05$ *vs.* Pre; * = $P < 0·01$ *vs.* PAF and MSA; ** = $P < 0·001$ *vs.* controls.

(6·9±1·6%), was significantly higher ($P < 0·01$ in each case) compared to PAF or MSA. The fall in BP during head-up tilt in PAF (38·5±5·5%) and MSA (27·3±5·8%) was, however, markedly higher compared to controls (each $P < 0·001$, Fig. 1).

Superior mesenteric artery blood flow

In the controls, mean resting SMA blood flow (in ml min^{-1}) was 439±61 (range 280–769). There was a non-significant reduction in SMA blood flow during mental arithmetic (439±61 to 318±54, n.s., paired *t* test) though when compared by ANOVA, the percentage change in SMA blood flow was significantly higher than in the patients. However, the SMA blood flow fell during cutaneous cold (462±50 to 289±40), isometric exercise (511±49 to 295±36) and tilt at 2 min (483±57 to 271±40) and 10 min (483±57 to 266±41) ($P < 0·05$ in each case) (Fig. 2).

In the patients with PAF, the mean resting SMA blood flow was not significantly higher (546±42, range 330–725) than controls or MSA. There were no significant changes in SMA blood flow during mental arithmetic (546±42 to 444±36), cutaneous cold (592±41 to 529±56) and isometric exercise (606±43 to 492±52). During tilt there were no significant changes in SMA blood flow either at 2 min (585±47 to 491±57) or 10 min (585±47 to 476±57) (n.s. in each case) though there was a marked fall in BP (Fig. 2).

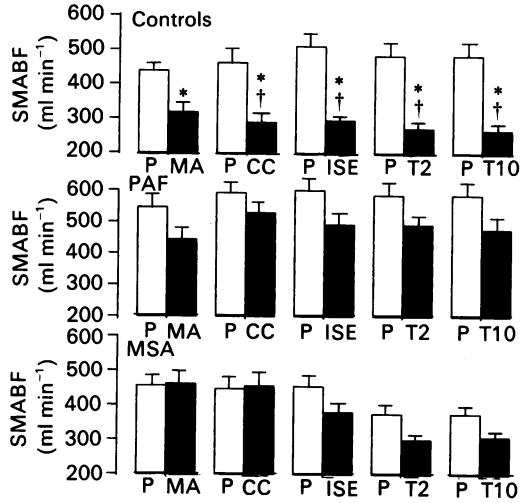

Fig. 2. Changes in superior mesenteric artery blood flow (SMABF) before (P) and during mental arithmetic (MA), cutaneous cold (CC), isometric exercise (ISE) and tilt at 2 min (T2) and 10 min (T10) in controls, pure autonomic failure (PAF) and multiple system atrophy (MSA) patients. † = $P < 0{\cdot}05$ *vs.* *Pre*; * = $P < 0{\cdot}01$ *vs.* PAF and MSA.

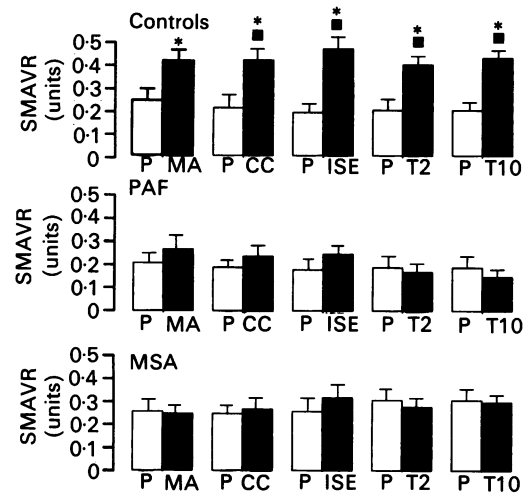

Fig. 3. Changes in superior mesenteric artery vascular resistance (SMAVR) before (P) and during mental arithmetic (MA), cutaneous cold (CC), isometric exercise (ISE) and tilt at 2 min (T2) and 10 min (T10) in controls, pure autonomic failure (PAF) and multiple system atrophy (MSA) patients. † = $P < 0{\cdot}05$ *vs.* Pre; * = $P < 0{\cdot}01$ *vs.* PAF and MSA.

In the MSA patients, resting SMA blood flow was 456 ± 73 (range 260–696). There were no significant changes in SMA blood flow during mental arithmetic (456 ± 73 to 461 ± 59), cutaneous cold (447 ± 68 to 455 ± 82), isometric exercise (454 ± 64 to 380 ± 53), tilt at 2 min (375 ± 59 to 300 ± 45) and 10 min (375 ± 59 to 308 ± 58) (n.s. in each case) (Fig. 2).

In the controls, rise in the calculated SMA vascular resistance (in units) was non-significant during MA (0·23 ± 0·03 to 0·39 ± 0·09, n.s., paired *t* test). The SMA vascular resistance rose during cutaneous cold (0·21 ± 0·02 to 0·42 ± 0·07), isometric exercise (0·19 ± 0·03 to 0·47 ± 0·12) and tilt at 2 min (0·2 ± 0·02 to 0·4 ± 0·06) and 10 min

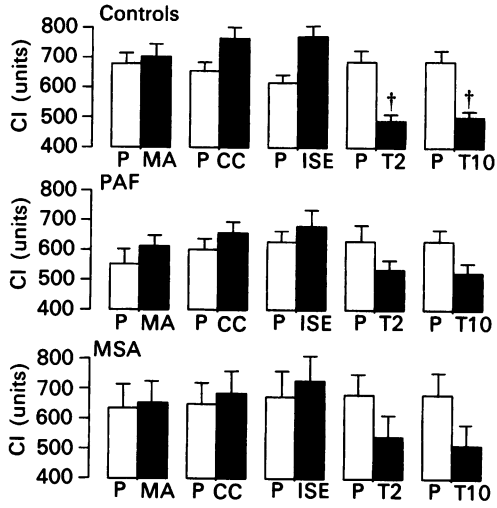

Fig. 4. Changes in cardiac index (CI) before (P) and during mental arithmetic (MA), cutaneous cold (CC), isometric exercise (ISE) and tilt at 2 min (T2) and 10 min (T10) in controls, pure autonomic failure (PAF) and multiple system atrophy (MSA) patients. † = $P < 0·05$ *vs.* Pre.

(0·2 ± 0·02 to 0·43 ± 0·07) ($P < 0·05$ in each case), indicating active constriction of the SMA during these stimuli (Fig. 3). In the PAF and MSA patients, there were no changes in calculated SMA vascular resistance during mental arithmetic, cutaneous cold, isometric exercise or tilt (Fig. 3).

Analysis of mean baseline SMA blood flow values preceding each stimulus in controls, PAF and MSA patients using ANOVA showed no significant difference, though in MSA patients pre-tilt SMA blood flow values tended to be lower. Changes in SMA blood flow and vascular resistance during each stimulus in controls were significantly ($P < 0·01$, ANOVA) higher when compared to the patients. (Figs 2 and 3).

Within-subject mean coefficients of variation of resting SMA blood flow values were 8·3% in the controls and 11·3% in AF patients.

Cardiac index

In the controls, there were no significant changes in the cardiac index during the pressor tests though the cardiac index was higher during isometric exercise (617 ± 48 to 771 ± 60, n.s.). The cardiac index fell during tilt at 2 min (687 ± 43 to 489 ± 68) and 10 min (687 ± 43 to 502 ± 65) ($P < 0·05$ in each case) (Fig. 4).

In the PAF and MSA patients, the cardiac index remained unchanged during the pressor tests and head-up tilt, though values tended to be lower during tilt (Fig. 4).

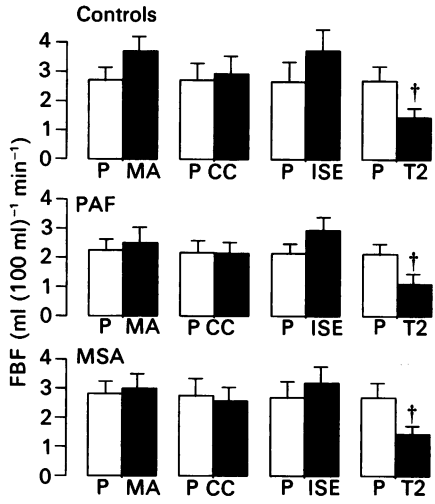

Fig. 5. Changes in forearm blood flow (FBP) before (P) and during mental arithmetic (MA), cutaneous cold (CC), isometric exercise (ISE) and tilt at 2 min (T2) in controls, pure autonomic failure (PAF) and multiple system atrophy (MSA) patients. † = $P < 0{\cdot}05$ *vs.* Pre.

TABLE 2. Changes in heart rate (beats min^{-1}) during mental arithmetic (MA), cutaneous cold (CC), isometric exercise (ISE) and tilt at 2 min (T2) and 10 min (T10) in controls, pure autonomic failure (PAF) and multiple system atrophy (MSA) patients

	Controls		PAF		MSA	
	Before	During	Before	During	Before	During
MA	73±2	77±3	72±2	73±2	75±5	76±4
CC	71±2	77±3	70±2	72±2	75±5	78±6
ISE	71±2	77±3	72±2	74±2	73±5	78±4
T2	69±2	79±4	70±2	74±2	74±5	80±3
T10	69±2	79±4	70±2	74±2	74±5	81±5

Heart rate

Changes in heart rate were not significant in the controls, the PAF or MSA patients during the various stimuli. Heart rate tended to rise in controls during head-up tilt but this failed to reach statistical significance (Table 2).

Forearm blood flow

In the controls, changes in forearm blood flow (in ml (100 ml)$^{-1}$ min^{-1}) were not significant during the pressor tests though there was a trend towards a higher blood flow and lower vascular resistance during mental arithmetic and isometric exercise (Figs 5 and 6). In the controls, the forearm blood flow fell during tilt in controls at 2 min (2·7±0·3 to 1·4±0·2, $P < 0{\cdot}05$) (Fig. 5) with a corresponding rise in forearm vascular resistance (41·8±8 to 83·3±17 units, $P < 0{\cdot}05$) (Fig. 6) indicating an active forearm vasoconstrictor response. In the PAF and MSA patients, changes in blood flow and vascular resistance during the pressor tests were not significant. Forearm

blood flow fell during tilt (2·13 ± 0·24 to 1·11 ± 0·1 in PAF and 2·7 ± 0·3 to 1·3 ± 0·19 in MSA, $P < 0·05$ in each case) (Fig. 5) but without a corresponding significant rise in the calculated forearm vascular resistance (55·1 ± 4·5 to 64·0 ± 7·6 units in PAF and 42·0 ± 4·9 to 58·0 ± 9 units in MSA, in each case n.s. (Fig. 6).

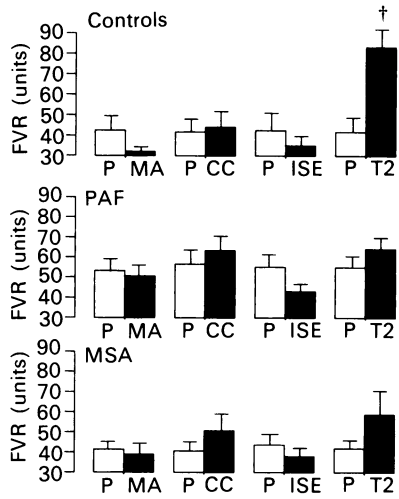

Fig. 6. Changes in forearm vascular resistance (FVR) before (P) and during mental arithmetic (MA), cutaneous cold (CC), isometric exercise (ISE) and tilt at 2 min (T2) in controls, pure autonomic failure (PAF) and multiple system atrophy (MSA) patients. † = $P < 0·05$ *vs.* Pre.

DISCUSSION

Consideration will be given to the technique used to measure superior mesenteric artery blood flow in our study, before discussing the physiological implications. Previous studies of splanchnic blood flow in man have utilized either invasive or indirect methods (Bradley, Ingelfinger, Bradley & Curry, 1945; Rowell, 1974) which differed from the non-invasive method we have used. The latter allowed rapid (though not instantaneous) and multiple measurements of blood flow in the superior mesenteric artery. This technique correlates well with an *in vitro* pulsatile system used in our laboratory (Kooner, Peart & Mathias, 1989) and we have confirmed its reproducibility, both in normal subjects (Chaudhuri *et al.* 1991*a*), and in this study in patients with autonomic failure. The basal SMA blood flow recordings obtained in this study were comparable to those of other workers using a similar or invasive technique. The method we used has also been utilized to measure SMA blood flow in disease states such as diabetes mellitus (Best, Pitzele, Green, Halperin, Mason & Giron, 1991), intestinal ischaemia (Nicholls, Kohler, Martin & Strandness, 1986) and cirrhosis of the liver (Sato, Ohnishi, Sugita & Okuda, 1987).

The superior mesenteric artery is one of three vessels contributing to the splanchnic arterial supply. It is, however, a major vessel supplying the duodenum (except the superior part), the entire small intestine and the ascending colon (except the distal part). It is richly innervated by sympathetic vasoconstrictor nerves and

also has an anatomical advantage for ultrasonic visualization, as it is anteriorly placed and allows a lower angle of insonation when the sample volume is placed within the proximal portion of the SMA. Measurement of SMA blood flow therefore provides a reasonable indication of haemodynamic change in this large vascular bed.

In our normal subjects, stimuli known to cause sympatho-neural activation, such as cutaneous cold, isometric exercise and head-up tilt, actively constricted the superior mesenteric artery. This occurred to a lesser extent during mental arithmetic in controls, when there was an impaired elevation of blood pressure during this particular stimulus, unlike during cutaneous cold and isometric exercise. This may have been due to reduced responses in some of our older controls and is consistent with previous data indicating a selective impairment of the pressor response to mental arithmetic in older but not young healthy subjects: the reasons for this difference remain unclear (Chaudhuri, Thomaides & Mathias, 1992). However, changes in mesenteric responses were still significantly greater in controls during mental arithmetic in comparison to the patients. Constriction of the superior mesenteric artery occurred during the other pressor stimuli (cutaneous cold and isometric exercise) which also induced pressor effects rapidly; the constriction therefore was likely to have been mediated neurally. We could not, however, definitely exclude humoral factors contributing to the constriction of the superior mesenteric artery, especially during head-up tilt in the controls. This is because sympathetic stimulation during head-up tilt releases various hormones and neuropeptides with vasoactive effects, the best examples being the associated elevation of angiotensin and vasopressin, both of which are potent constrictors of the splanchnic vascular bed (Granger, Richardson, Kveitys & Mortillaro, 1980).

In both groups of AF patients (PAF and MSA), there were no changes in blood pressure or SMA blood flow during the pressor tests. Furthermore, during head-up tilt, blood pressure fell markedly although there were no significant changes in SMA blood flow or vascular resistance. The abnormal splanchnic haemodynamic responses in these patients were most probably due to lack of vasoconstrictor nerve activity, though other possibilities may exist. In our older patients, failure of constriction of the SMA may have been due to more rigid vessels, as may occur with ageing. This is unlikely, however, as there was adequate constriction in age-matched controls and furthermore, previous studies in such patients have excluded stiff 'fixed' vessels, as they are capable of the reverse, dilatation, after food ingestion (Kooner *et al.* 1990). Abnormal humoral responses (renin–angiotensin and vasopressin) to sympathetic stimulation during head-up tilt remain as other possibilities. Renin levels may rise in some patients with AF during head-up tilt (Mathias, Matthews & Spalding, 1977) but not in other patients (Bannister, Sever & Gross, 1977). Vasopressin levels also rise during head-up tilt in PAF patients (Zerbe, Henry & Robertson, 1983) but this does not occur in MSA patients (Puritz, Lightman, Wilcox, Forsling & Bannister, 1983). Constriction of the superior mesenteric artery during head-up tilt did not occur in either PAF or MSA, making it unlikely that lack of vasopressin alone played a singular role in the abnormal splanchnic responses. The haemodynamic abnormalities, especially in relation to superior mesenteric artery constriction in these patients, therefore, were probably the result of sympatho-neural failure.

The results of this study suggest that during the stimuli we used, responses in the

splanchnic region may play a greater role in overall blood pressure regulation than those in other regional vascular beds, such as in skeletal muscle. However, we only measured forearm blood flow and certain aspects of cardiac function, and do not know what happened in other major vascular beds such as the renal and cerebral, although it was unlikely that they could account for the overall blood pressure responses during the stimuli used in normal man. The renal vascular bed has a strong autoregulatory mechanism as demonstrated in conscious animals during low cardiac output states and hypotension (Vatner & Braunwald, 1975). Cerebral autoregulation similarly normally ensures a preservation of oxygenation despite changing perfusion pressure during controlled haemorrhage (Owman, 1986). Although our study was not directed towards determining the role of individual vascular beds in blood pressure control, it suggests that during postural change, for instance, the level of constriction of the superior mesenteric artery is a major contributor to maintenance or fall of blood pressure. This may have therapeutic implications, as drugs which have selective constrictor effects on this vascular bed may have a greater therapeutic value in preventing postural hypotension in autonomic failure patients. The major neural defect in splanchnic control observed in our patients may explain why postural change after food ingestion considerably enhances symptoms of postural hypotension in some patients with autonomic failure (Mathias, Holly, Armstrong, Shareef & Bannister, 1991).

We conclude that in normal man sympatho-neural activation by pressor stimuli which raise blood pressure, or head-up tilt which maintains blood pressure, causes active constriction of the superior mesenteric artery. This does not occur in patients with human sympathetic failure who are not capable of reflex sympathetic vasoconstriction. The lack of constriction of the superior mesenteric artery probably contributes to the severe postural hypotension seen in these patients. This study indicates the importance of the integrity of sympathetic pathways in the neural control of the splanchnic vascular bed and its role in overall blood pressure regulation, especially during postural change.

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