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ORIGINAL ARTICLE

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Arterial diameter during central volume depletion in humans

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Abstract The luminal diameter of the radial artery was followed by high frequency ultrasound during 50° head-up tilt-induced central volume depletion in ten healthy subjects of whom six were tilted twice and pretreated with the serotonin receptor antagonist methysergide or placebo following a double-blind randomized design. Eight subjects without active treatment experienced presyncopal symptoms after 16–45 (mean 32 min). Central volume depletion was indicated by an increase in mean thoracic electrical impedance [from 31.5 (SEM 1.6) to 33.4 (SEM 1.7) Ω; $P < 0.05$]. Cardiac output decreased [from 4.1 (SEM 0.3) to 2.2 (SEM 0.3) $l \cdot min^{-1}$] and heart rate [HR, from 64 (SEM 3) to 100 (SEM 7) beats $\cdot min^{-1}$], mean arterial pressure {MAP, from 77 (SEM 4) to 89 (SEM 2) mmHg [10.3 (SEM 0.53 to 11.9 (SEM 0.27) kPa]} and total peripheral resistance {TPR, from 19 (SEM 2) to 34 (SEM 4) mmHg $\cdot$ min $\cdot 1^{-1}$ [2.5 (SEM 0.27) to 4.5 (SEM 0.53) kPa $\cdot$ min $\cdot 1^{-1}$]} increased; but with the appearance of presyncopal symptoms, HR, MAP and TPR were reduced to 65 (SEM 8) beats $\cdot min^{-1}$, 46 (SEM 4) mmHg [6.1 (SEM 0.53) kPa] and 18 (SEM 3) mmHg $\cdot$ min $\cdot 1^{-1}$ [2.4 (SEM 0.4) kPa $\cdot min^{-1} \cdot 1^{-1}$], respectively ($P < 0.05$). Vascular resistance was reflected in the arterial diameter which decreased from 2.42 (SEM 0.17) to 2.27 (SEM 0.14) mm during head-up tilt and increased to 2.71 (SEM 0.14) mm with the appearance of presyncopal symptoms ($P < 0.05$). Methysergide reduced the resting radial ($15 \pm 2\%$) and temporal artery diameters ($10 \pm 3\%$) ($P < 0.05$); however, it affected neither tilt-tolerance nor the central cardiovascular response to tilt. The results suggested a serotonergic influence on arterial tone at rest, and demonstrated that vessels as large as the radial artery participated in vascular control during central volume depletion independent of such a serotonergic influence.

Key words Methysergide · Serotonin · Total peripheral resistance · Vasoconstriction · Vasodilatation

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Introduction

Central volume depletion has been shown to be associated with moderate tachycardia and increased peripheral resistance mediated by activation of central volume receptors together with arterial baroreceptors when mean arterial pressure (MAP) is affected (Abboud et al. 1979). However, it has been reported that if the central blood volume is lowered by approximately 30%, presyncopal symptoms appear with a markedly reduced MAP (Jacobsen and Secher 1994). As has been shown the reduction in MAP is a consequence of lower total peripheral resistance (TPR) as derived from the ratio of MAP to cardiac output (CO) as well as to lower leg (Matzen et al. 1991b) and arm blood flows (Barcroft et al. 1944). It has been found that the reduced peripheral resistance during shock depends on an intact sympathetic innervation (Barcroft and Edholm 1945) and that it may be influenced by serotonergic mechanisms as has been demonstrated in the cat (Morgan et al. 1988). In contrast to the arteries, the veins have been hypothesized to maintain constriction (Epstein et al. 1968) as some patients are cyanotic. Despite this, this type of vasovagal syncope has been associated with a normal arterial oxygen tension and in turn with a normal oxygen saturation (Matzen and Secher 1993).

The TPR is considered to be dominated by the arterioles, but the whole arterial tree may be affected by

modulation of vascular tone. It is possible to investigate this hypothesis, as it has been shown that the diameter of superficial arteries can be monitored by high frequency ultrasound (Nielsen et al. 1990; Iversen et al. 1990; Olesen et al. 1995). We hypothesized that vessels as large as the radial artery can respond to changes in the central blood volume, and that such modulation of arterial tone is influenced by a serotonergic mechanism. In subjects allocated to placebo or the serotonin receptor antagonist methysergide, hypovolaemic shock was induced by head-up tilt and the radial artery luminal diameter was followed. In addition, in one subject, the cephalic vein luminal diameter was determined.

Methods

Subjects

After informed consent eight men and two women (mean age 27 (range 20–36) years, mean body mass 70 (range 65–94) kg and mean body height 1.85 (range 1.68–1.88) with normal orthostatic tolerance participated in the study as accepted by the Ethics Committee of Copenhagen and the Danish National Board of Health and Welfare. Six subjects each performed two head-up tilt experiments as administration of methysergide of a placebo was randomized in a double-blind design. Separated by at least 6 days, 2, 2 and 3 mg of methysergide (Deseril, Sandoz, Copenhagen, Denmark) or placebo was administered 24, 12 and 1 h respectively before the study.

Protocol

The subjects arrived in the laboratory at 8.30 a.m. following an overnight fast. A catheter [1.0-mm i.d. (20-gauge)] was inserted in the brachial artery of the nondominant arm for measurement of blood pressures, and another catheter [1.7-mm i.d. (16-gauge)] was placed in the superior caval vein through the left basilic vein for measurement of central venous pressure (CVP). The subjects rested supine for the following hour. For support, the tilt-table was provided with a bicycle saddle but no footboard. Passive head-up tilt to 50° was performed in increments during a 10 min period interrupted at each 10° to allow time for measurements. The 50° tilt position was maintained for 1 h, or until presyncopal signs or symptoms appeared (relative bradycardia, hypotension, dizziness and a feeling of heat). When such symptoms or signs became manifest, the subjects were immediately returned to the supine position and the variables were followed for an additional 30 min of recovery.

Arterial pressures and CVP were monitored by transducers (Bentley, Uden, Holland) positioned at the level of the right atrium in the midaxillary line. The heart rate (HR) was derived from a two-lead electrocardiogram and integrated together with pressures over 6 s (8041, Simonsen and Weel, Copenhagen, Denmark). Central blood volume-depletion was followed by thoracic electrical impedance (TI; Matzen et al. 1991a; Pawelczyk et al. 1994; Hanel et al. 1994). Two electrodes were placed on the right sternocleid muscle and two other electrodes on the lower left ribs in the midaxillary line. The outer two electrodes served for current, and they were each spaced 5 cm from their corresponding inner electrode. The monitor calculated stroke volume (SV) from TI and changes accompanying cardiac activity (Simonsen and Weel). The CO was derived from SV and HR, and the TPR was the quotient of MAP and CO. These estimations of SV and CO reflected the expected changes during head-up tilt (Matzen et al. 1991).

The luminal diameter of the radial artery was measured at the distal volar crest of the right wrist by a high resolution ultrasound unit with A-, B- and M-mode facilities (Dermascan CR, Cortex Technology, Hadsund, Denmark). The position was secured by a constant distance from the radial styloid process. High frequency ultrasound (20 MHz; band width 15 MHz) was directed perpendicular to the plane of the skin, and the artery was located in B-mode. The artery was identified as its walls pulsated and it appeared as an ovoid structure because the lateral resolution was expanded 3.2 times relative to the axial direction. The diameter of the artery was determined in the corresponding A-mode as the high amplitudes reflecting the interface between blood and the vessel wall. The two-point discrimination was 0.05 mm (Iversen et al. 1990). A free space was maintained with ultrasound gel (Blue Scan, Nikomed, Denmark) between the probe and the skin to avoid compression. The M-mode signal was obtained 12 times $\cdot s^{-1}$ for approximately 2 s at the sound velocity of blood (1605 m $\cdot s^{-1}$ at 37 °C; Nielsen et al. 1990). The mean of four randomly selected values is reported. In addition to measurements of the diameter of the radial artery, the right frontal-branch diameter of the superficial temporal artery was assessed during supine rest. The position of measurement was secured by a constant angle and distance to the orbito-meatal line. Also, the luminal diameter of the cephalic vein of the forearm was followed in one subject during the tilt.

Statistics

Data were evaluated for effects of time and pretreatment with multivariate analysis of variance, and, given an effect, changes significantly different from baseline were subsequently located. As the subjects experienced presyncopal symptoms at different times, data are related to the mean head-up tilt time and data from the period of sustained 50° head-up tilt are given corresponding to half the tilt-time for each subject. A P-value less than 0.05 was considered significant.

Results

Methysergide was not associated with any adverse symptoms or changes in central cardiovascular data either during supine rest or during tilt. Tilt-tolerance was similar during administration of placebo [mean 32 (range 16–45) min] and methysergide [mean 23 (range 6–56) min]. At rest methysergide reduced the radial artery diameter by 15 ± 2 % [2.06 (SEM 0.18) vs 2.42 (SEM 0.17) mm during placebo] and the temporal artery diameter by 10 ± 3 % [1.08 (SEM 0.05) vs 1.19 (SEM 0.06) mm]. However, the magnitude of the tilt-induced radial artery diameter response was not affected by methysergide. Two placebo-treated subjects did not experience presyncopal symptoms within the 60 min of head-up tilt and their data are presented separately.

All variables stabilized during the hour of supine rest (Fig. 1). Tilt-up to 50° increased TI [31.5 (SEM 1.6) to 32.7 (SEM 1.5) Ω; $P < 0.01$], HR [64 (SEM 3) to 86 (SEM 4) beats $\cdot min^{-1}$; $P < 0.001$], diastolic pressure {DAP, 62 (SEM 3) to 68 (SEM 1) mmHg [8.3 (SEM 0.4) to 9.1 (SEM 0.13) kPa]}, MAP {77 (SEM 4) to 89 (SEM 2) mmHg [10.3 (SEM 0.53) to 11.9 (SEM 0.27) kPa]} and TPR {19 (SEM 2) to 34 (SEM 4) mmHg $\cdot$ min $\cdot 1^{-1}$

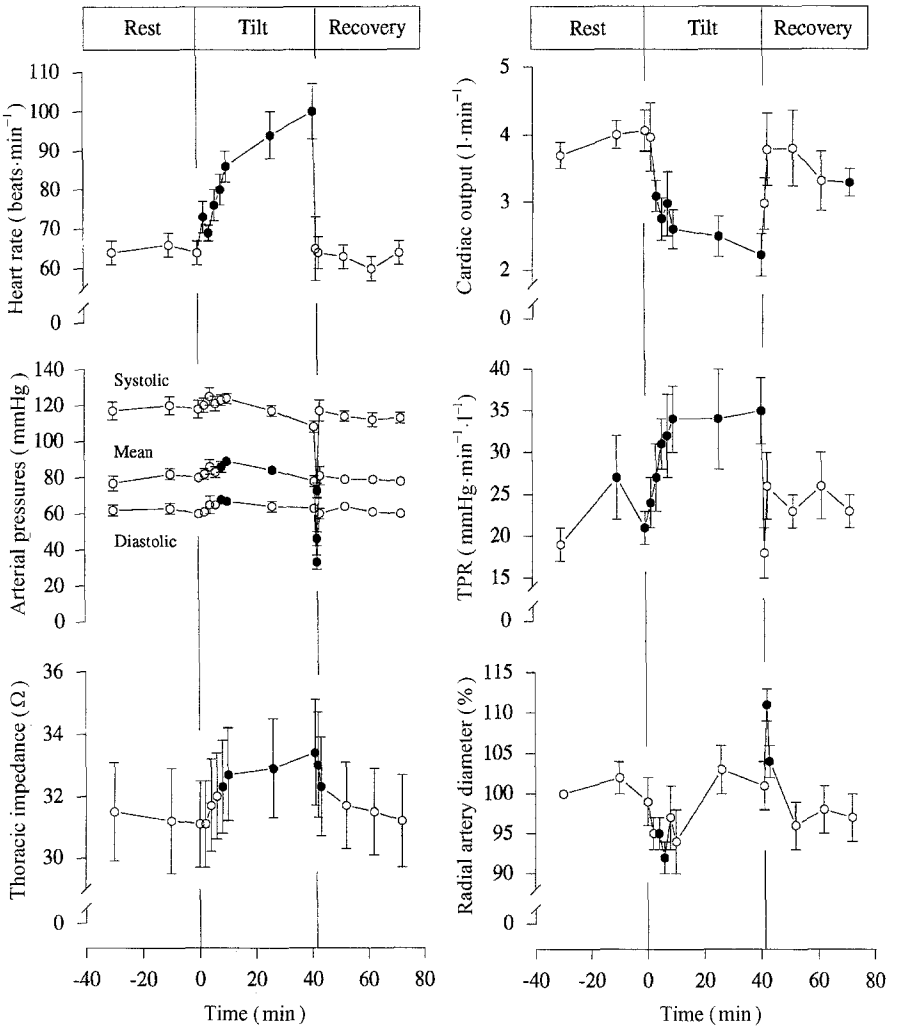

Fig. 1 Mean and SEM values for eight nonmedicated subjects for heart rate, arterial pressures, thoracic electrical impedance, cardiac output, total peripheral resistance (*TPR*) and radial artery diameter at rest, during 50° head-up tilt and recovery. Data are related to the mean head-up tilt time. *Filled symbols* indicated significant difference from rest ($P < 0.05$)

[2.5 (SEM 0.27) to 4.5 (SEM 0.53) KPa·min·1^{-1}], $P < 0.01$}, while systolic pressure {SAP, 117 (SEM 5) to 124 (SEM 3) mmHg [15.6 (SEM 0.67) to 16.5 (SEM 0.4) kPa]} did not change significantly, and CO [4.1 (SEM 0.3) to 2.6 (SEM 0.3) $l \cdot min^{-1}$] and CVP decreased {3 (SEM 1) to 1 (SEM 1) mmHg [0.4 (SEM 0.13) to 0.13 (SEM 0.13) kPa]}. With tilt-up the radial diameter decreased from 2.42 (SEM 0.17) to 2.30 (SEM 0.14) mm at 20° and was similar [2.27 (SEM 0.14) mm] at a tilt angle of 50° (Figs. 1).

Half way through the sustained head-up tilt period, the radial artery diameter returned to the resting level [2.44 (SEM 0.17) mm] (Figs. 1). The TI [to 32.9 (SEM 1.6) Ω] and HR [to 94 (SEM 6) beats·min^{-1}] increased further, while SAP and MAP decreased {117 (SEM 3) and 84 (SEM 2) mmHg [15.6 (SEM 0.4) and 11.2 (SEM 0.27) kPa], respectively}, and TPR and CVP remained unchanged. The CO decreased further [to 2.2 (SEM 0.3) $l \cdot min^{-1}$]. Immediately before the presyncopal symptoms developed [mean 1.2 (range 0.5–2.0) min] SAP, MAP and DAP decreased to 108 (SEM 3), 78 (SEM 3) and 63 (SEM 2) mmHg [14.7 (SEM 0.4), 10.4 (SEM 0.4) and 8.4 (SEM 0.27) kPa], respectively, and the increases in TI and HR continued, reaching 33.4 (SEM 0.17) Ω and 100 (SEM 7) beats·min^{-1}, while the radial artery diameter remained at 2.45 (SEM 0.14) mm.

With the development of presyncopal symptoms the radial artery diameter increased to 2.71 (SEM 0.14) mm (Figs. 1) and HR [to 65 (SEM 8) beats·min^{-1}], SAP {to 73 (SEM 4) mmHg [9.7 (SEM 0.53) kPa]; $P < 0.001$}, MAP {to 46 (SEM 4) mmHg [6.0 (SEM 0.53) kPa]; $P < 0.001$}, DAP {to 33 (SEM 4) mmHg [4.4 (SEM 0.53) KPa] $P < 0.001$} and TPR {to 18 (SEM 3) mmHg·min·l^{-1} 2.4 (SEM 0.4) kPa·min·1^{-1}]} decreased. The CO recovered to 3.0 (SEM 0.4) $l \cdot min^{-1}$ and the CVP was unchanged. After return to the supine position [mean 1.7 (range 1.0–4.0) min] variables returned to the values at rest, except for the radial artery diameter and TI which remained elevated for approximately 10 min. The cephalic vein and radial artery diameter responses as determined in one subject showed dilatation of the vein and constriction of the artery during normotensive tilt, but constriction of the vein and dilatation of the artery when hypotension and presyncopal symptoms appeared.

Of the two subjects who did not experience presyncopal symptoms, in one subject the radial artery diameter was stable for the first 50 min of head-up tilt and then constricted. The other subject became pale, sweaty and nauseated at the moment (60 min) when the position was changed from 50° head-up tilt to supine. In this subject, the radial artery diameter, arterial pressures and HR showed marked fluctuations. Immediately after return to the supine position, pulsatile changes in the arterial diameter were observed consistent with vasospasm at a frequency of $14 \cdot min^{-1}$, in addition to the normal HR-related pulsations.

Discussion

This study made two important findings:

1. The changes in radial artery diameter reflected the progressive changes in central hypovolaemia largely in parallel with changes in total peripheral vascular resistance. During control head-up tilt, the radial artery diameter decreased by approximately 6 % and TPR increased: it increased to approximately 12 % above the rest value when hypotension ensued and TPR reached its lowest level.
2. Serotonine receptor-blockade with methysergide decreased resting artery diameter, but was of no consequence for the responses to head-up tilt.

Central volume depletion induced by head-up tilt was reflected in TI but not in CVP as shown by Matzen et al. (1991a) and Pawelczyk et al. (1994), and the initial reduction in CVP could be explained by a tilt-induced change in the position of the heart relative to the transducer. As Jacobsen and Secher (1994), have shown the MAP and HR responses to the central volume depletion induced by head-up tilt were biphasic. Head-up tilt elicited an increase in MAP and HR (see Sander-Jensen et al. 1986a; Matzen et al. 1991), and subsequently a moderate reduction in MAP with a further increase in HR immediately before the phase of bradycardia and hypotension. Our experience from 49 non-medicated men [mean 26 (range 2–60) min] and 8 women [mean 29 (range 8–56) min] has indicated no sex-related difference in the tolerated tilt-time.

The HR and MAP increments induced by head-up tilt have been shown to correspond to increased sympathetic nerve activity as indicated by increases in plasma noradrenaline concentration but not always by that of plasma adrenaline (Sander-Jensen et al. 1986a,b; Matzen et al. 1991). Also, (muscle-) sympathetic nerve activity has been found to increase during normotensive head-up tilt (Burke et al. 1977), lower body negative pressure and haemorrhage (Sanders and Ferguson 1989; Rea et al. 1991). It has been reported that the hypotension-bradycardia (vaso-vagal syncope) may be elicited by activation of unmyelinated vagal afferents from left ventricular mechanoreceptors by a combination of a reduced left ventricular volume and an increased inotropic state (Thorén 1979; Schadt and Ludbrook 1991). The reduction of HR has been shown to be a vagal reaction (Sander-Jensen et al. 1986a,b) and the concomitant decrease in TPR and MAP has been found to be due to withdrawal of sympathetic outflow as reflected by changes in plasma noradrenaline concentration (Sander-Jensen et al. 1986a; Matzen et al. 1991) and muscle sympathetic nerve activity (Burke et al. 1977; Sanders and Ferguson 1989). In consequence to the reduced peripheral resistance the CO has been found to recover to the rest value (Madsen et al. 1993).

Radial artery diameter has been found to reflect changes in sympathetic nerve outflow, and sympathoexcitation by placing a hand in ice-cold water sufficiently long to decrease the radial artery diameter on the contralateral side (Anderson and Mark 1989). Also, during migraine headaches both the radial and temporal artery diameters have been reported to be reduced on the pain free side (Iversen et al. 1990). However, other mechanisms may also affect arterial diameter. As has been demonstrated for one subject, the veins distend during tilt-up and a local veno-arterial axon reflex could affect the radial artery (Henriksen 1977), but the head-up tilt caused venous distension and arterial constriction only for as long as MAP remained in the normal range. The initial increase in MAP could have provoked a myogenic response resulting in a reduced arterial diameter. However, myogenic autoregulation of arteries has been shown to be inconsequential (Folkow 1964) and cannot alone account for reductions in radial artery diameter below the control level. The increase of artery diameter could be flow-mediated as has been reported by Anderson and Mark (1989). However, the enlarged radial artery diameter during sustained tilt was not flow mediated, as CO (Matzen et al. 1991) and arm blood flow have been shown to be low (Barcroft et al. 1945). It could also be speculated that the arterial diameter was distended by the intravascular blood pressure. However, the radial artery diameter became small when MAP increased during early tilt, and increased as MAP became low with the appearance of precyncopal symptoms. It is noteworthy that, a small increase in arterial diameter took place during the tilt with no change in TPR, and also the moderate decrease in MAP just before the development of presyncopal symptoms was not reflected in the radial artery diameter.

The cephalic vein showed dilatation during tilt-up, but constriction at the onset of hypotension. The dilatation corresponded to venous stasis when the hand was lowered relative to the heart, while the constriction at the onset of hypotension was in contrast to the observed arterial dilatation. Venous constriction at the appearance of the presyncopal symptoms would help to explain the normal CVP despite the reduced venous return.

Both the radial and temporal artery diameters decreased after the administration of methysergide to

about the same magnitude as has been shown after 0.5-mg intravenous ergotamine (Nielsen et al. 1990). However, this did not influence the magnitude of the responses of radial artery diameter induced by head-up tilt, although methysergide-induced renal artery sympatho-inhibition has been reported during haemorrhage in the rat (Morgan et al. 1988). A difference between oral and intravenous administration may be important. During rest, the constricting effect of methysergide is not easily explained by virtue of its 5-HT_2 antagonist properties. After oral administration, methysergide has been shown to be converted to methylergometrine (Bredberg et al. 1986) and at the time of measurement (about 1 h after the last methysergide intake) methylergometrine would be expected to dominate with 5-HT_2 agonist properties (Tfelt-Hansen et al. 1987). Also, both substances, have been reported to act as agonists on $5HT_1$-like receptors which are distributed mainly in the carotid bed (Saxena 1974).

In conclusion, methysergide reduced the resting radial and temporal artery diameters but it did not affect the radial artery diameter response to head-up tilt. Thus, with or without methysergide, the radial artery response to central volume depletion followed closely reported changes in (muscle)-sympathetic outflow during central hypovolaemia.

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