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## Neurohumoral antecedents of vasodepressor reactions

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Received 18 October 1994 and in revised form 13 February 1995; accepted 21 February 1995

**Abstract.** Vasodepressor (vasovagal) syncope, the most common cause of acute loss of consciousness, can occur in otherwise vigorously healthy people during exposure to stimuli decreasing cardiac filling. Antecedent physiological or neuroendocrine conditions for this dramatic syndrome are poorly understood. This study compared neurocirculatory responses to non-hypotensive lower body negative pressure (LBNP) in subjects who subsequently developed vasodepressor reactions during hypotensive LBNP with responses in subjects who did not. In 26 healthy subjects, LBNP at  $-15$  and  $-40$  mmHg was applied to inhibit cardiopulmonary and arterial baroreceptors. All the subjects tolerated 30 min of LBNP at  $-15$  mmHg, but during subsequent LBNP at  $-40$  mmHg 11 subjects had vasodepressor reactions, with sudden hypotension, nausea, and dizziness. In these subjects, arterial plasma adrenaline responses to LBNP both at  $-15$  and at  $-40$  mmHg exceeded those in subjects who did not experience these reactions. In 16 of the 26 subjects, forearm noradrenaline spillover was measured; in the eight subjects with a vasodepressor reaction, mean forearm noradrenaline spillover failed to increase during LBNP at  $-15$  mmHg ( $\Delta = -0.06 \pm (\text{SEM}) 0.04$  pmol  $\text{min}^{-1} 100 \text{ mL}^{-1}$ ), whereas in the eight subjects without a vasodepressor reaction, mean forearm noradrenaline spillover increased significantly ( $\Delta = 0.31 \pm 0.13$  pmol  $\text{min}^{-1} 100 \text{ mL}^{-1}$ ). Plasma levels of  $\beta$ -endorphin during LBNP at  $-15$  mmHg increased in some subjects who subsequently had a vasodepressor reaction during LBNP at  $-40$  mmHg. The findings suggest that a neuroendocrine pattern including adrenomedullary stimulation, skeletal sympathoinhibition, and release of endogenous opioids can precede vasodepressor syncope.

**Keywords.** Adrenaline, catecholamines, fainting, kinetics, noradrenaline.

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### Introduction

Vasodepressor syncope, or fainting, is the most frequent cause of sudden loss of consciousness [1] and can occur in otherwise healthy people during exposure to emotional stress, heat, prolonged upright posture, or pain. The haemodynamic hallmark of vasodepressor reactions is systemic vasodilation [2], especially in skeletal muscle [3,4], with or without vagally mediated bradycardia. Microneurographic studies have shown that precipitously decreased skeletal sympathetic nervous outflow accompanies the vasodilation [5]. Plasma noradrenaline (NA) levels, measured immediately after or at the time of fainting, are decreased or inappropriately normal [6,7] and release of NA into the venous drainage in the heart [8] and kidneys [9] decreases virtually to zero. In contrast, plasma adrenaline (A) levels often are increased [6]. Vagal bradycardia does not cause vasodepressor reactions, because parasympatholytic drugs may not reverse or prevent the hypotension [10].

Mechanisms responsible for the abrupt decreases in sympathetic outflows have been unclear. One possibility is sudden central resetting of baroreflexes, so that hypotension fails to release sympathoneural outflows from baroreceptor restraint. Since endogenous opioids augment the extent of sympathoinhibition during a hypotensive stimulus (e.g. haemorrhage [11], sudden release of endogenous opioids in the brain could contribute to baroreflex resetting and thereby produce sympathoinhibition despite hypotension. Vasopressin also augments baroreflex restraint of sympathoneural outflows [12], and extremely high circulating vasopressin levels often accompany vasodepressor syncope [13]. Alternatively, stimulation of ventricular stretch receptors that increase activity of non-myelinated, inhibitory afferent C-fibres [14,15], or collapse-firing of low pressure baroreceptors in the right atrium and great veins [16], evoke vasodepressor reactions. The common feature of the central and peripheral hypothesized mechanisms is sympathoinhibition despite hypotension.

The suddenness and unexpectedness of vasodepressor reactions have hampered efforts to identify

antecedent haemodynamic and neurohumoral events. Prolonged head-up tilt, with or without intravenous isoproterenol infusion [17], or relatively large amounts of lower body negative pressure (LBNP) [18] can provoke these episodes. In the current study, we examined circulatory, catecholaminergic, and  $\beta$ -endorphin responses to a small decrease in cardiac filling during mild LBNP ( $-15$  mmHg) and to systemic hypotension during subsequent more intense LBNP ( $-40$  mmHg) in healthy people. LBNP at less than  $-20$  mmHg reduces central venous pressure without altering arterial blood pressure or pulse pressure, suggesting relatively selective inhibition of cardiac baroreceptors [19], whereas higher intensity LBNP decreases blood pressure and pulse pressure, inhibiting cardiac and arterial baroreceptors. We compared responses in groups of subjects who did, vs. those who did not, develop a vasodepressor reaction during high-intensity LBNP, in order to identify possible neurochemical antecedents of vasodepressor syncope.

To assess neurohumoral responses during inhibition of cardiopulmonary and arterial baroreceptors, plasma catecholamine concentrations were measured. Plasma NA levels, however, have some limitations as a measure of sympathetic activity since they are the net result of the rate by which NA spills over into the circulation (after neuronal release and neuronal uptake) and the rate by which NA is removed from the plasma. Therefore we used the radiotracer dilution technique [20] that enables calculation of the total body spillover of NA into the circulation. This is a better, although not ideal, measure of total body neuronal NA release and thus over-all sympathetic activity. Since in many conditions sympathetic outflow is not uniformly distributed to different organs, calculation of the regional spillover of NA in an organ is preferred as a measure of regional sympathetic activity. Forearm spillover and removal of NA can be calculated by measuring forearm blood flow, venous and arterial plasma NA levels and the extraction of the tracer tritiated NA. Measurement of NA spillover and removal in the forearm enables to identify whether increments in venous forearm plasma NA levels are due to an increased neuronal release to or to a decreased removal of NA from the forearm circulation.

## Patients and methods

### Subjects

Twenty-six healthy male subjects participated in the study after giving their written informed consent. The study protocol was approved by the Hospital Ethics Committee. Before entry into the study, all participants had a normal physical examination. None suffered from cardiovascular or other major diseases, and they took no medication. None of the participants had a history of syncopal attacks.

### Study protocol

All subjects abstained from nicotine, alcohol and caffeinated foods and beverages for at least 24 h before the study. The subjects were allowed to eat a light breakfast 2 h before the study. All experiments were carried out in the morning in a temperature-controlled observation room.

During the study, the subjects remained supine, with the lower body sealed at the iliac crests in an airtight Plexiglas<sup>TM</sup> box. The applied LBNP pressure was recorded by a manometer connected to the inside of the box.

After local anaesthesia using lignocaine, a cannula was inserted percutaneously into a brachial artery, for monitoring arterial blood pressure and heart rate (Hewlett Packard GmbH, Boblingen, Germany) and for drawing arterial blood samples. In the same arm, a cannula was inserted for collecting venous blood.

In 16 of the 26 subjects, another venous cannula was inserted in the contralateral arm, for infusion of [<sup>3</sup>H]-noradrenaline ([<sup>3</sup>H]-NA).

Forearm blood flow (FBF) was measured using venous occlusion strain-gauge plethysmography [21]. The forearm contralateral to that used for [<sup>3</sup>H]-NA infusion was positioned 10 cm above the mid-thoracic level. Measurements of FBF and blood samples were obtained after exclusion of the hand circulation by inflating a wrist cuff to 100 mmHg above systolic blood pressure for at least 1 min [22].

After instrumentation, the subjects rested for at least 30 min. During the last 3 min, baseline recordings of blood pressure, heart rate, and FBF (nine flow curves) were obtained. Blood pressure was recorded simultaneously with each FBF measurement. Thereafter, arterial and venous blood samples were drawn simultaneously for determinations of plasma catecholamines.

LBNP at  $-15$  mmHg was then applied for 30 min. Blood pressure, heart rate, FBF recordings and blood samples were taken in sequence beginning after 7, 17 and 27 min of LBNP, so that the blood samples were drawn at 10, 20 and 30 min of LBNP. A 30 min rest period ensued, followed by another 30 min of LBNP  $-40$  mmHg. Blood pressure, pulse rate, FBF, and blood samples were obtained at the same time points as for LBNP  $-15$  mmHg.

### [<sup>3</sup>H]-NA infusion

[<sup>3</sup>H]-NA (levo-[ring-2,5,6-<sup>3</sup>H]-NA) was infused to assess plasma noradrenaline kinetics. Tritiated NA was obtained from Du Pont New England Nuclear ('s-Hertogenbosch, the Netherlands). The radionuclide was sterilized using a  $0.22$   $\mu$ m filter and diluted in 0.9% NaCl containing acetic ( $0.2$  mol L<sup>-1</sup>) and ascorbic ( $1$  mg mL<sup>-1</sup>) acid. Aliquots of  $50$   $\mu$ Ci [<sup>3</sup>H]-NA were stored at  $-80^{\circ}$ C until used. Sterilization, dilution and aliquoting were carried out under nitrogen. Just before use, an aliquot was diluted in 0.9% NaCl. The radiotracer was administered intravenously

as a bolus of  $15 \mu\text{Ci m}^{-2}$  followed by a constant infusion of  $0.35 \mu\text{Ci min}^{-1} \text{m}^{-2}$  for 120 min. The first LBNP application began at 30 min of infusion of  $[^3\text{H}]\text{-NA}$ . The weight of the syringe containing the radio-tracer was measured just before and just after the infusion, in order to check the infusion rate. Samples of the infusate were taken at the end of the infusion.

### Analytical methods

Blood samples were collected in chilled tubes containing glutathione ( $0.2 \text{ mol L}^{-1}$ ) and EGTA ( $0.25 \text{ mol L}^{-1}$ ). The tubes were centrifuged at  $4^\circ\text{C}$  and the plasma separated and stored at  $-20^\circ\text{C}$ . Assays of all samples and infusates occurred within 2 months of each study.

Plasma samples were assayed for concentrations of adrenaline (A), total NA, and  $[^3\text{H}]\text{-NA}$ , using high-performance liquid chromatography (HPLC) with fluorimetric detection after precolumn derivatization with the fluorescent agent 1,2-diphenylethylenediamine [23]. A fraction collector connected to an automatic sample injector (WISP 710B, Waters-Millipore, Milford, MA, USA), was used for collecting  $[^3\text{H}]\text{-NA}$  into scintillation vials, according to the retention time of NA standard.

Arterial plasma immunoreactive  $\beta$ -endorphin levels were measured by a radioimmunoassay [24] in the 16 subjects in whom plasma noradrenaline kinetics were studied.

### Data analysis

Forearm vascular resistance (FVR) was calculated by dividing mean arterial blood pressure by FBF and was expressed in resistance units (RU). The clearance of NA from arterial plasma, CL, was calculated from the infusion rate of  $[^3\text{H}]\text{-NA}$  and the steady-state arterial plasma concentration of  $[^3\text{H}]\text{-NA}$ ,  $[^3\text{H}]\text{-NA}_a$ :

$$\text{CL (L min}^{-1}\text{)} = \frac{\text{Infusion rate (dpm min}^{-1}\text{)}}{[^3\text{H}]\text{-NA}_a \text{ (dpm L}^{-1}\text{)}} \quad (1)$$

'Total body' NA spillover, TB Spill, the estimated rate of appearance of endogenous NA in arterial plasma, was calculated from the arterial plasma NA concentration ( $\text{NA}_a$ ) and the arterial steady-state clearance of NA, according to the equation:

$$\text{TB spill (nmol min}^{-1}\text{)} = \text{NA}_a \text{ (nmol L}^{-1}\text{)} \times \text{CL (L min}^{-1}\text{)} \quad (2)$$

Analogously, NA spillover in the forearm, FA Spill, was estimated from:

$$\text{FA spill (pmol min}^{-1} \text{100 mL}^{-1}\text{)} = \{\text{FPF} \times \text{NA}_a \times f_{\text{NA}}\} + \{\text{FPF} \times (\text{NA}_v - \text{NA}_a)\} \quad (3)$$

where  $f_{\text{NA}} = ([^3\text{H}]\text{-NA}_a - [^3\text{H}]\text{-NA}_v) / [^3\text{H}]\text{-NA}_a$ , the fractional extraction of the tracer in the forearm; FPF is the forearm plasma flow, in units of  $\text{mL min}^{-1} \text{100 mL}^{-1}$ , calculated from the forearm blood flow

and haematocrit; and  $[^3\text{H}]\text{-NA}_v$  is the venous plasma concentration of  $[^3\text{H}]\text{-NA}$ .

The removal of NA in the forearm, FA Rem, was calculated from:

$$\text{FA Rem (pmol min}^{-1} \text{100 mL}^{-1}\text{)} = \text{FPF} \times \text{NA}_a \times f_{\text{NA}} \quad (4)$$

Subjects were classified *post hoc* into two groups. Subjects in group A underwent both 30 min periods of LBNP without experiencing dizziness, nausea, weakness or hypotension. Subjects in group B underwent LBNP at  $-15 \text{ mmHg}$  without symptoms but developed a vasodepressor reaction during LBNP at  $-40 \text{ mmHg}$ . The criteria for a vasodepressor reaction were hypotension (systolic blood pressure  $< 100 \text{ mmHg}$  or a rapid decrease of  $> 20 \text{ mmHg}$ ) and symptoms (nausea, dizziness, or weakness).

Results are expressed as means  $\pm$  SEM. For each LBNP period, values for all dependent variables were averaged across the three time points during LBNP. To assess the effects of LBNP, the Wilcoxon signed rank test was used to compare the baseline with the average value of a variable during LBNP. Responses at each time point were expressed as the absolute change at a time point from the baseline value, and two-way analyses of variance (ANOVA's) for repeated measures were used to compare the changes as a function of time in the two groups. A *P* value less than 0.05 defined statistical significance.

### Results

Of the 26 subjects, 15 (group A) underwent 30 min of LBNP at  $-15 \text{ mmHg}$  as well as at  $-40 \text{ mmHg}$  without any signs of a vasodepressor reaction. The remaining 11 subjects (group B) developed a vasodepressor reaction during LBNP at  $-40 \text{ mmHg}$ . There were no differences in age, resting blood pressure, or heart rate between the two groups (Table 1).

All but one subject in group B had both hypotension and bradycardia during LBNP at  $-40 \text{ mmHg}$ , bradycardia being defined as a pulse rate less than 50 bpm or a rapid decrease of more than 10 bpm. In

**Table 1.** Clinical characteristics of group A (without syncope) and group B (with syncope)

Parameter	Group A	Group B
Number ( <i>n</i> )	15	11
Age (years)	$30 \pm 5$	$29 \pm 6$
Height (cm)	$184 \pm 8$	$184 \pm 9$
Weight (kg)	$82.0 \pm 10.6$	$81.7 \pm 10.3$
Quetelet index ( $\text{kg m}^{-2}$ )	$24.4 \pm 3.2$	$24.2 \pm 3.6$
SBP (mmHg)	$120 \pm 9$	$125 \pm 10$
DBP (mmHg)	$72 \pm 8$	$73 \pm 9$
HR (bpm)	$70 \pm 10$	$67 \pm 7$

Mean  $\pm$  SD are given. The data in this table show blood pressure and heart rate values obtained at the screening visit prior to entry in the study. SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate.

**Table 2.** Haemodynamic data during LBNP at  $-15$  mmHg in group A (without syncope,  $n = 15$ ) and group B (with syncope,  $n = 11$ )

		Group A	Group B
FBF ( $\text{mL min}^{-1} 100 \text{ mL}^{-1}$ )	Baseline	$1.61 \pm 0.19$	$1.46 \pm 0.19$
	LBNP-15	$1.16 \pm 0.15^{**}$	$1.06 \pm 0.15^{**}$
FVR (resistance units)	Baseline	$64 \pm 8$	$71 \pm 10$
	LBNP-15	$90 \pm 10^{**}$	$99 \pm 13^{**}$
SBP (mmHg)	Baseline	$126 \pm 4$	$128 \pm 4$
	LBNP-15	$127 \pm 3$	$130 \pm 4$
DBP (mmHg)	Baseline	$73 \pm 3$	$67 \pm 2$
	LBNP-15	$75 \pm 3$	$69 \pm 3$
Pulse pressure (mmHg)	Baseline	$61 \pm 2$	$64 \pm 2$
	LBNP-15	$59 \pm 2$	$61 \pm 2$
Heart rate (bpm)	Baseline	$55 \pm 3$	$59 \pm 2$
	LBNP-15	$54 \pm 3$	$60 \pm 2$

Mean  $\pm$  SEM are given. SBP, systolic blood pressure; DBP, diastolic blood pressure; FBF, forearm blood flow; FVR; forearm vascular resistance.  $** P < 0.01$  with respect to baseline.

group B subjects, LBNP at  $-40$  mmHg was terminated immediately when the first signs of a vasodepressor reaction emerged. All group B subjects complained of nausea, and some became pale; one lost consciousness. The vasodepressor response occurred in the first 10 min of LBNP at  $-40$  mmHg in two subjects, between 10 and 20 min in seven subjects, and in the last 10 min in two subjects. Consequently, the data summarized below for LBNP at  $-40$  mmHg are incomplete for group B.

#### LBNP at $-15$ mmHg

During LBNP at  $-15$  mmHg, FBF decreased and FVR increased significantly in both groups (Table 2), and the groups did not differ in values for these variables. Blood pressure, pulse pressure, and heart rate did not change during LBNP at  $-15$  mmHg in either group.

Baseline levels of venous plasma NA were similar in the two groups ( $0.92 \pm 0.10 \text{ nmol L}^{-1}$  in group A and  $1.00 \pm 0.09 \text{ nmol L}^{-1}$  in group B). During LBNP, venous plasma NA levels increased significantly in both groups to  $1.38 \pm 0.13 \text{ nmol L}^{-1}$  in group A and  $1.26 \pm 0.11 \text{ nmol L}^{-1}$  in group B at 30 min of LBNP. There was a tendency for smaller venous plasma NA responses in the group with subsequent syncope but the increments in venous NA levels were not significantly different between the two groups (Fig. 1).

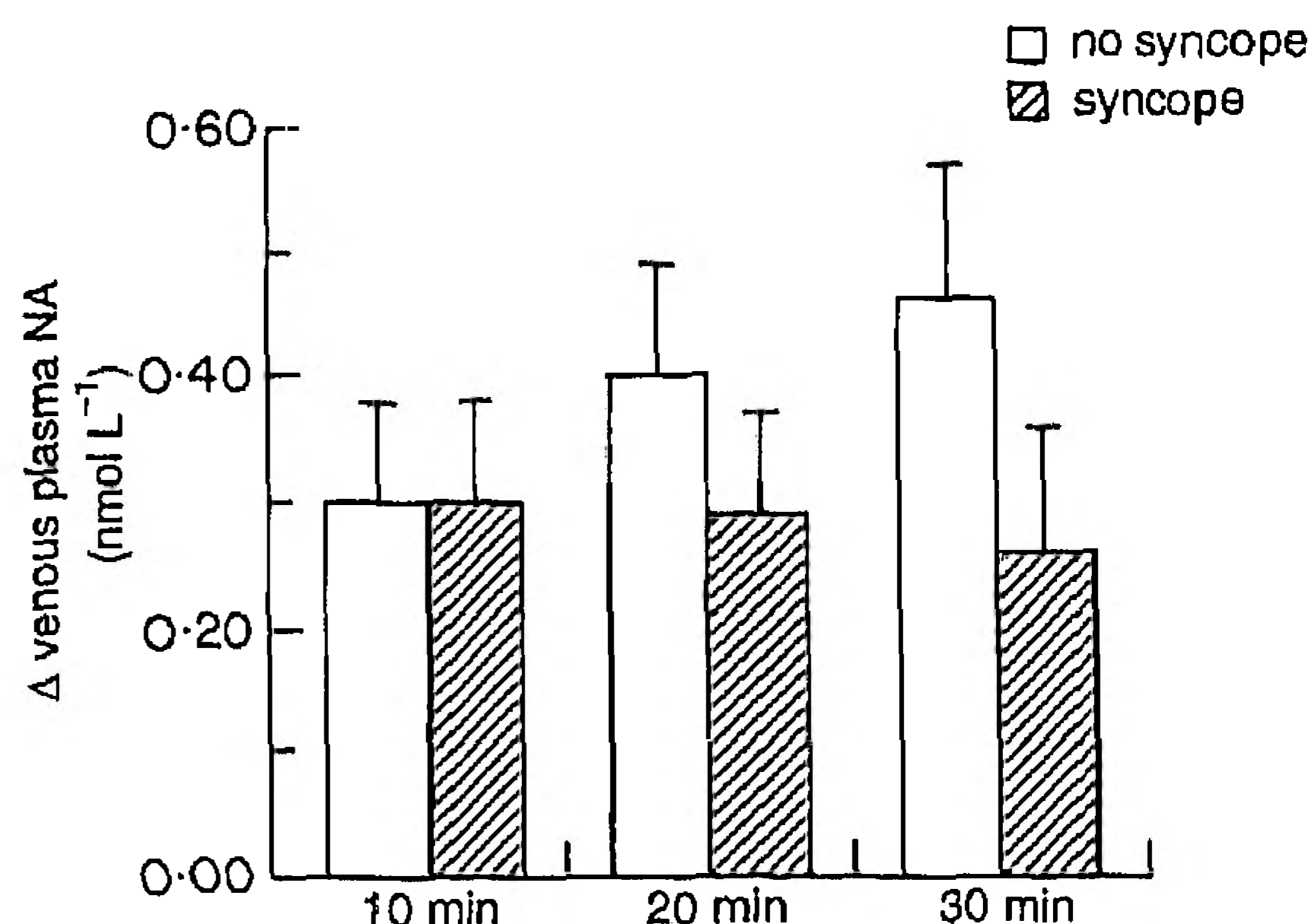
Baseline arterial plasma NA levels also did not differ between the groups. Arterial NA levels increased from  $0.94 \pm 0.08$  to a maximal value of  $1.10 \pm 0.08 \text{ nmol L}^{-1}$  in group A and from  $0.92 \pm 0.11 \text{ nmol L}^{-1}$  to  $1.03 \pm 0.09 \text{ nmol L}^{-1}$  in group B.

Baseline arterial A levels were similar in the two groups ( $0.16 \pm 0.03 \text{ nmol L}^{-1}$  in group A and  $0.17 \pm 0.03 \text{ nmol L}^{-1}$  in group B). In both groups, arterial A levels increased significantly during LBNP

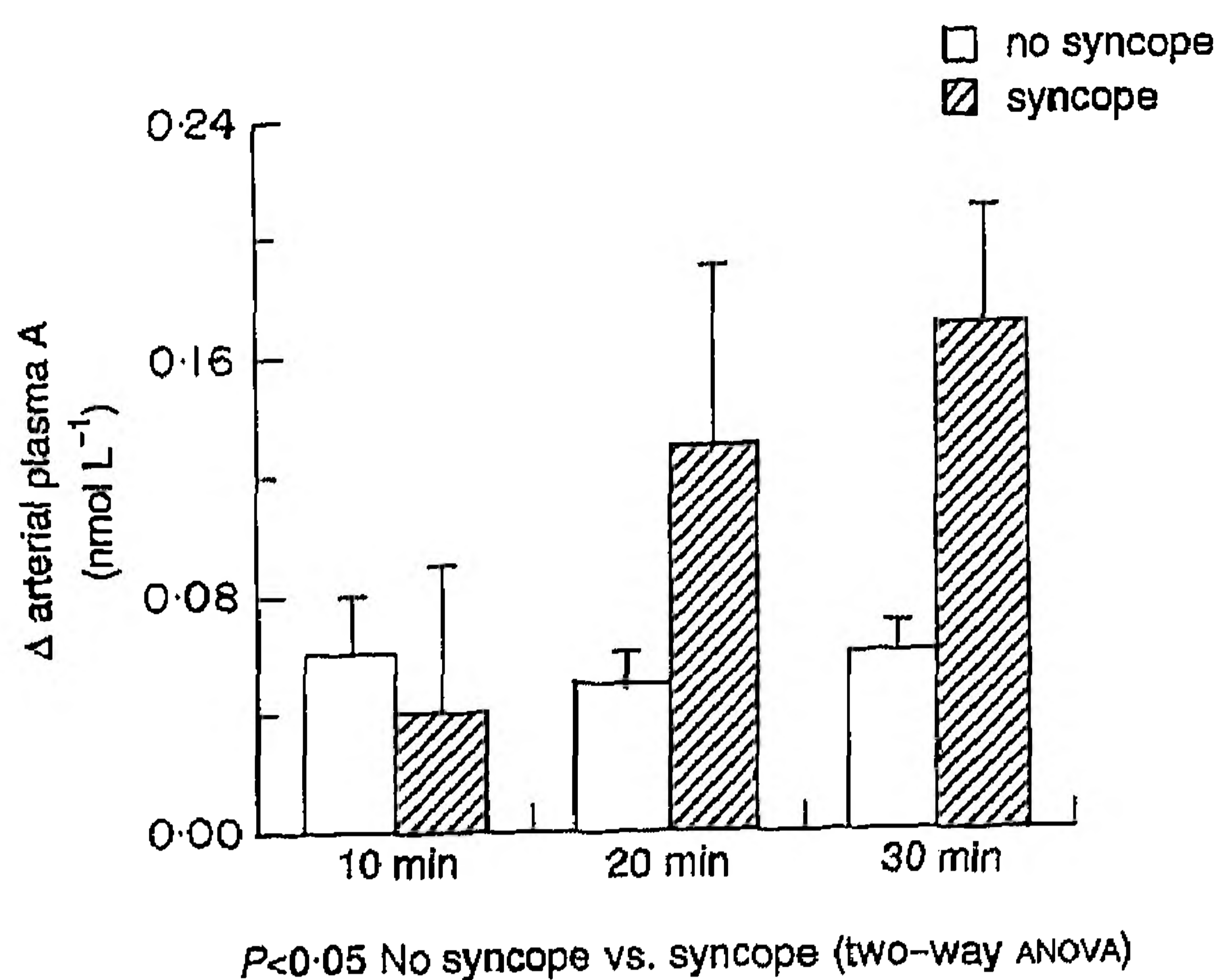
at  $-15$  mmHg; however, in group A, arterial A levels plateaued at about  $0.22 \text{ nmol L}^{-1}$  after 10 min, whereas in group B, arterial A levels progressively rose to a peak value of  $0.34 \pm 0.05 \text{ nmol L}^{-1}$ . Thus, the absolute increments in arterial A levels were larger in the group with than in the group without subsequent syncope (Fig. 2). Venous plasma A responses did not differ between the two groups.

In the 16 subjects who received a [ $^3\text{H}$ ]-NA infusion, mean FA Spill at baseline was not significantly different between group A ( $n = 8$ ) and group B ( $n = 8$ ) subjects ( $0.63 \pm 0.16$  vs.  $0.76 \pm 0.16 \text{ pmol min}^{-1} 100 \text{ mL}^{-1}$ , Table 3). During LBNP at  $-15$  mmHg, the average response of FA Spill across all time points was larger in the group A subjects ( $0.31 \pm 0.13 \text{ pmol min}^{-1} 100 \text{ mL}^{-1}$ ) than in the group B subjects ( $-0.06 \pm 0.04 \text{ pmol min}^{-1} 100 \text{ mL}^{-1}$ ,  $P < 0.05$ , Fig. 3).

Values for TB Spill did not change significantly in either group during LBNP at  $-15$  mmHg (Table 3).



**Figure 1.** Increments in venous plasma noradrenaline (NA, means  $\pm$  SEM) after 10, 20 and 30 min of lower body negative pressure for group A ( $n = 15$ , no syncope) and group B ( $n = 11$ , syncope).



**Figure 2.** Increments in arterial plasma adrenaline (A, means  $\pm$  SEM) after 10, 20 and 30 min of lower body negative pressure for group A ( $n = 15$ , no syncope) and group B ( $n = 11$ , syncope).

Values for CL decreased by about 30% in group A and did not change in group B. In neither group did values for FA Rem change during LBNP at  $-15$  mmHg.

Baseline plasma  $\beta$ -endorphin levels did not differ between the groups and did not change significantly during LBNP at  $-15$  mmHg in group A ( $27 \pm 3$  pg mL<sup>-1</sup> at baseline to  $30 \pm 4$  pg mL<sup>-1</sup> during LBNP). In group B, plasma  $\beta$ -endorphin increased in three of the eight subjects; the average increase, from  $38 \pm 11$  pg mL<sup>-1</sup> at baseline to  $62 \pm 28$  pg mL<sup>-1</sup> during LBNP at  $-15$  mmHg, was not significant.

#### LBNP at $-40$ mmHg

In both group A and group B, FBF decreased and FVR increased during LBNP at  $-40$  mmHg, analogous to the changes during LBNP at  $-15$  mmHg (Table 4); however, the changes in values for both

variables were larger during LBNP at  $-40$  mmHg than during LBNP at  $-15$  mmHg. Systolic blood pressure and pulse pressure decreased and heart rate increased, both in the group A subjects and in the nine group B subjects.

Baseline levels of venous plasma NA were similar in the two groups ( $1.08 \pm 0.13$  nmol L<sup>-1</sup> in group A and  $1.10 \pm 0.12$  nmol L<sup>-1</sup> in group B). During LBNP, venous plasma NA levels increased significantly in both groups to  $2.12 \pm 0.22$  nmol L<sup>-1</sup> in group A and  $2.11 \pm 0.22$  nmol L<sup>-1</sup> in group B.

In the group A subjects, arterial plasma NA increased from  $1.01 \pm 0.10$  to  $1.76 \pm 0.09$  nmol L<sup>-1</sup> ( $P < 0.01$ ). In the nine group B subjects, the arterial plasma NA response (from  $0.93 \pm 0.10$  to  $1.50 \pm 0.14$  nmol L<sup>-1</sup>,  $P < 0.01$ ) after 10 min of LBNP at  $-40$  mmHg did not differ significantly from that in the group A subjects.

Arterial plasma A levels increased in the group A subjects from  $0.21 \pm 0.02$  nmol L<sup>-1</sup> to  $0.39 \pm 0.04$  nmol L<sup>-1</sup> ( $P < 0.01$ ) during LBNP at  $-40$  mmHg and increased markedly in the nine group B subjects from  $0.30 \pm 0.04$  nmol L<sup>-1</sup> to  $1.24 \pm 0.44$  nmol L<sup>-1</sup> ( $P < 0.01$ ) after 10 min of LBNP.

In group A total body NA spillover increased significantly by about 30% during LBNP at  $-40$  mmHg, and NA clearance decreased significantly by about 40% (Table 5); in group B, total body NA spillover increased in five subjects, but this response was not significant (Table 5). Forearm NA spillover increased in the group A subjects, from  $0.73 \pm 0.19$  to  $1.32 \pm 0.36$  pmol min<sup>-1</sup> 100 mL<sup>-1</sup>,  $P < 0.05$ , whereas in group B there was no significant change (Table 5).

Plasma  $\beta$ -endorphin levels did not change during LBNP at  $-40$  mmHg in group A ( $34 \pm 6$  pg mL<sup>-1</sup> at baseline,  $38 \pm 5$  pg mL<sup>-1</sup> during LBNP), whereas in group B plasma  $\beta$ -endorphin increased in six of the eight subjects; the average increase, from

**Table 3.** Noradrenaline kinetics values during LBNP at  $-15$  mmHg in group A (without syncope,  $n = 8$ ) and group B (with syncope,  $n = 8$ )

		Group A	Group B
Arterial plasma NA (nmol L <sup>-1</sup> )	Baseline	$0.90 \pm 0.06$	$0.88 \pm 0.15$
	LBNP-15	$1.10 \pm 0.12^*$	$0.95 \pm 0.10$
Forearm NA spillover (pmol min <sup>-1</sup> 100 mL <sup>-1</sup> )	Baseline	$0.63 \pm 0.16$	$0.76 \pm 0.16$
	LBNP-15	$0.94 \pm 0.23^*$	$0.70 \pm 0.13$
Total body NA spillover (nmol min <sup>-1</sup> m <sup>-2</sup> )	Baseline	$1.39 \pm 0.19$	$0.99 \pm 0.16$
	LBNP-15	$1.37 \pm 0.15$	$1.26 \pm 0.16$
Total body NA clearance (L min <sup>-1</sup> m <sup>-2</sup> )	Baseline	$1.56 \pm 0.18$	$1.30 \pm 0.14$
	LBNP-15	$1.26 \pm 0.08^*$	$1.32 \pm 0.07$

Means  $\pm$  SEM are given. NA, noradrenaline. \*  $P < 0.05$  with respect to baseline.

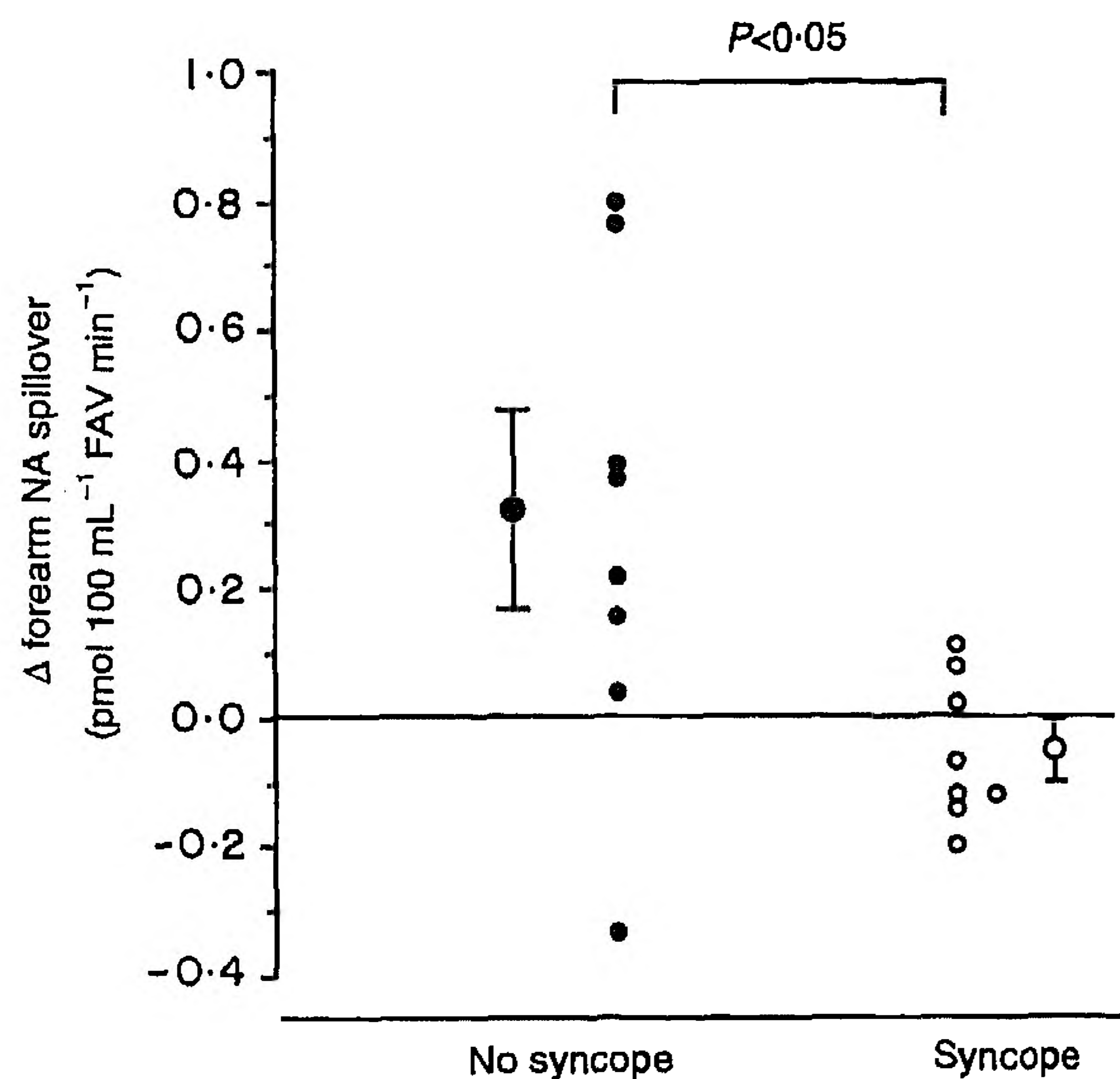


Figure 3. Individual responses of forearm noradrenaline (NA) spillover in eight subjects without and eight subjects with syncope. FA V = forearm volume.

$59 \pm 12 \text{ pg mL}^{-1}$  at baseline to  $82 \pm 22 \text{ pg mL}^{-1}$  during LBNP at  $-40 \text{ mmHg}$ , was not significant.

## Discussion

Few occurrences in clinical medicine match vaso-depressor reactions for abruptness, unexpectedness and drama. The neurocirculatory basis for vaso-depressor reactions was long presumed to be diffusely increased vagal 'tone', since people experiencing them often have nausea, sweating and bradycardia;

however, cholinergic blockade may not prevent or reverse the hypotension. More recently, microneurographic [5] and neurochemical [6,7] evidence has convincingly demonstrated virtually complete shut-down of sympathoneural cardiovascular outflows, with generally preserved or augmented adrenomedullary secretion [25]. This combination could contribute to the skeletal vasodilation that virtually always accompanies vasodepressor reactions.

Lower body negative pressure at  $-15 \text{ mmHg}$  inhibits cardiac 'low pressure' baroreceptors. During LBNP at  $-15 \text{ mmHg}$ , skeletal muscle sympathoneural outflow normally increases reflexively [7,26,27]. Exposure to LBNP at  $-40 \text{ mmHg}$  inhibits cardiac and arterial baroreceptors, increasing sympathoneural outflow in several vascular beds and concurrently increasing adrenomedullary secretion. Diffuse reflexive sympathoadrenal stimulation in this setting probably supports systemic blood pressure and cerebral perfusion.

In the present study, sudden vasodepressor reactions occurred in 11 of 26 healthy subjects during prolonged exposure to LBNP at  $-40 \text{ mmHg}$ . The study design enabled review of catecholaminergic function *before* the actual vasodepressor reactions, that is during LBNP at  $-15 \text{ mmHg}$ . The findings indicate that a combination of attenuated noradrenergic and exaggerated adrenomedullary and possibly endogenous opioid responses to mildly decreased cardiac filling (LBNP at  $-15 \text{ mmHg}$ ) characterized subjects who subsequently developed vasodepressor reactions during exposure to more severely decreased cardiac filling (group B). These subjects failed to increase forearm NA spillover during exposure to LBNP at  $-15 \text{ mmHg}$  and had enhanced increases in arterial A levels.

Table 4. Haemodynamic data during LBNP at  $-40 \text{ mmHg}$  in group A (without syncope,  $n = 15$ ) and group B (with syncope,  $n = 9^*$ )

		Group A	Group B
FBF ( $\text{mL min}^{-1} 100 \text{ mL}^{-1}$ )	Baseline	$1.49 \pm 0.17$	$1.16 \pm 0.16$
	LBNP-40	$0.88 \pm 0.14^\ddagger$	$0.65 \pm 0.10^\ddagger$
FVR (resistance units)	Baseline	$71 \pm 8$	$94 \pm 11$
	LBNP-40	$135 \pm 18^\ddagger$	$165 \pm 21^\ddagger$
SBP (mmHg)	Baseline	$129 \pm 2$	$140 \pm 5$
	LBNP-40	$125 \pm 3^\ddagger$	$131 \pm 5^\ddagger$
DBP (mmHg)	Baseline	$73 \pm 3$	$75 \pm 3$
	LBNP-40	$75 \pm 3$	$75 \pm 3$
Pulse pressure (mmHg)	Baseline	$57 \pm 3$	$65 \pm 3$
	LBNP-40	$50 \pm 4^\ddagger$	$56 \pm 3^\ddagger$
Heart rate (bpm)	Baseline	$54 \pm 2$	$57 \pm 2$
	LBNP-40	$62 \pm 3^\ddagger$	$68 \pm 4^\ddagger$

Means  $\pm$  SEM are given. SBP, systolic blood pressure; DBP, diastolic blood pressure; FBF, forearm blood flow; FVR, forearm vascular resistance. \* Represents the data of nine subjects of group B ( $n = 11$ ) who tolerated the first 10 min of LBNP at  $-40 \text{ mmHg}$  but who later developed a vasodepressor reaction. Two subjects had a vasodepressor reaction in the first 10 min of LBNP at  $-40 \text{ mmHg}$ .  $^\ddagger P < 0.01$ ,  $^\ddagger P < 0.001$  with respect to baseline.

**Table 5.** Noradrenaline kinetics values during LBNP at -40 mmHg in group A (without syncope,  $n = 8$ ) and group B (with syncope,  $n = 6^*$ )

		Group A	Group B
Arterial plasma NA (nmol L <sup>-1</sup> )	Baseline	1.01 ± 0.12	0.82 ± 0.11
	LBNP-40	1.88 ± 0.08‡	1.50 ± 0.21†
Forearm NA spillover (pmol min <sup>-1</sup> 100 mL <sup>-1</sup> )	Baseline	0.73 ± 0.19	0.60 ± 0.17
	LBNP-40	1.32 ± 0.36†	0.73 ± 0.15
Total body NA spillover (nmol min <sup>-1</sup> m <sup>-2</sup> )	Baseline	1.47 ± 0.20	1.05 ± 0.18
	LBNP-40	1.91 ± 0.15‡	1.87 ± 0.24
Total body NA clearance (L min <sup>-1</sup> m <sup>-2</sup> )	Baseline	1.51 ± 0.17	1.25 ± 0.10
	LBNP-40	1.02 ± 0.07‡	1.31 ± 0.20

Means ± SEM are given. NA, noradrenaline. \* Represents the data for six subjects of group B ( $n = 8$ ) who tolerated the first 10 min of LBNP at -40 mmHg but who developed a vasodepressor reaction later. Two subjects had a vasodepressor reaction in the first 10 min of LBNP at -40 mmHg. † $P < 0.05$  and ‡ $P < 0.01$  with respect to baseline.

Forearm vasoconstriction occurred in the group B subjects during LBNP at -15 mmHg, despite the absence of increased forearm NA spillover. The basis for the forearm vasoconstriction without concurrently increased regional NA spillover cannot be determined from the present data. Several explanations are possible, including augmented extraneuronal removal of NA escaping the neuroeffector junctions, release of vasoconstrictor peptides such as NPY or ATP, blockade of formation of endothelium-derived relaxing factors, or concurrent inhibition of sympathetic cholinergic vasodilation.

It is a possibility that this pattern of sympathoinhibition and adrenomedullary stimulation reflects a central neural process and arises from sudden resetting of baroreflexes. Analogous resetting occurs during haemorrhage [28] and hypoglycaemia [29] in laboratory animals and produces a neurocirculatory positive feedback loop that leads rapidly to hypotension and circulatory shock. Moreover, electrical stimulation of specific hypothalamic regions can concurrently increase vagal and decrease sympathoneural outflows, evoking hypotension [30]. Disruption of vagal afferents or blockade of receptors for vasopressin or endogenous opioids can reverse the sympathoinhibition attending haemorrhage or hypoglycaemia, and it is therefore possible that central processes involving these compounds may also operate in some vasodepressor reactions.

Vasovagal syncope frequently occurs in emotionally distressing circumstances. Individuals who developed a vasodepressor reaction had enhanced plasma A responses. Exaggerated endogenous A responses may also be part of a centrally generated pattern that triggers or reinforces a neurocirculatory positive feedback loop. Consistent with this view, a recent study in a small group of subjects also reported increases in plasma A levels before the onset of

fainting and suggested that increased plasma A contributed to the vasodilation [31]. This helps to explain why  $\beta$ -adrenoceptor blockade can be useful in treating patients with recurrent vasodepressor syncope [32,33]. Exogenous administration of A alone does not cause syncope in healthy people.

Several investigators have proposed that in volume-depleted subjects, cardiac contraction around a near-empty ventricle at end-systole can paradoxically stimulate inhibitory ventricular myocardial receptors, evoking a depressor reflex [14]. This mechanism, although widely accepted, has never actually been demonstrated as a cause of vasovagal syncope. On the contrary, infusion of a vasodilator has been reported to evoke vasodepressor syncope in a heart transplant recipient who lacked cardiac innervation [34], and heart transplant recipients do not differ from healthy control subjects in their susceptibility to LBNP-induced vasodepression [35]. In cats and rats, but not in dogs, interference with cardiac vagal C-fibre afferents prevents haemorrhage-induced vasodepression [15]. These findings suggest that the occurrence of vasodepressor syncope in humans may not require altered neuronal afferent input from ventricular baroreceptors and that the relative contributions of peripheral and central mechanisms vary among species.

The central aetiology hypothesis has direct therapeutic implications, since  $\beta$ -adrenoceptor blockade, administration of an  $\alpha$ -adrenoceptor agonist or sympathomimetic amine, blockade of endogenous opiate effects, or blockade of vasopressin receptors would be expected to abort or prevent vasodepressor syncope. The beneficial effects of  $\beta$ -blockade were noted above [32, 33]. Treatment with dextroamphetamine [36], pseudoephedrine or phenylephrine [37] appears to prevent syncope in patients with positive tilt testing. Pre-treatment with naloxone, however, does not



prevent vasodepressor responses during repeat exposure to LBNP in healthy subjects with previous LBNP-induced syncope [38]. We did not find reports about effects of vasopressin antagonists.

In summary, healthy subjects who developed vasodepressor reactions during high-intensity LBNP had antecedent exaggerated adrenomedullary and attenuated sympathoneural responses during mild LBNP; some subjects who developed a vasodepressor reaction during high-intensity LBNP had  $\beta$ -endorphin responses during mild LBNP. The findings are consistent with the view that sudden, central resetting of baroreflex function can evoke a pattern of sympathoneural inhibition combined with adrenomedullary and vagal activation, producing neurocirculatory positive feedback loops that lead precipitously to hypotension and syncope.

### Acknowledgment

This work was supported by a grant from the Dutch Heart Association [No 89212].

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