



## UvA-DARE (Digital Academic Repository)

### Central and cerebrovascular effects of leg crossing in humans with sympathetic failure

Harms, M.P.; Wieling, W.; Colier, W.N.; Lenders, J.W.; Secher, N.H.; van Lieshout, J.J.

**DOI**

[10.1042/CS20090038](https://doi.org/10.1042/CS20090038)

**Publication date**

2010

**Document Version**

Final published version

**Published in**

Clinical science

[Link to publication](#)

**Citation for published version (APA):**

Harms, M. P., Wieling, W., Colier, W. N., Lenders, J. W., Secher, N. H., & van Lieshout, J. J. (2010). Central and cerebrovascular effects of leg crossing in humans with sympathetic failure. *Clinical science*, 118(9-10), 573-581. <https://doi.org/10.1042/CS20090038>

**General rights**

It is not permitted to download or to forward/distribute the text or part of it without the consent of the author(s) and/or copyright holder(s), other than for strictly personal, individual use, unless the work is under an open content license (like Creative Commons).

**Disclaimer/Complaints regulations**

If you believe that digital publication of certain material infringes any of your rights or (privacy) interests, please let the Library know, stating your reasons. In case of a legitimate complaint, the Library will make the material inaccessible and/or remove it from the website. Please Ask the Library: <https://uba.uva.nl/en/contact>, or a letter to: Library of the University of Amsterdam, Secretariat, Singel 425, 1012 WP Amsterdam, The Netherlands. You will be contacted as soon as possible.

*UvA-DARE is a service provided by the library of the University of Amsterdam (<https://dare.uva.nl>)*

# Central and cerebrovascular effects of leg crossing in humans with sympathetic failure

Mark P.M. HARMS\*, Wouter WIELING\*, Willy N.J.M. COLIER†, Jacques W.M. LENDERS‡, Niels H. SECHER§ and Johannes J. VAN LIESHOUT\*||¶

\*Department of Internal Medicine, AMC Center for Heart Failure Research, Academic Medical Center, Amsterdam, The Netherlands, †Department of Geriatric Medicine, Division of General Internal Medicine, Radboud University Nijmegen Medical Center, Nijmegen, The Netherlands, ‡Department of Internal Medicine, Division of General Internal Medicine, Radboud University Nijmegen Medical Center, Nijmegen, The Netherlands, §Department of Anaesthesia, The Copenhagen Muscle Research Center, Rigshospitalet, Copenhagen, Denmark, ||Special Medical Care, AMC Center for Heart Failure Research, Academic Medical Center, Amsterdam, The Netherlands, and ¶Laboratory for Clinical Cardiovascular Physiology, AMC Center for Heart Failure Research, Academic Medical Center, Amsterdam, The Netherlands

## A B S T R A C T

Leg crossing increases arterial pressure and combats symptomatic orthostatic hypotension in patients with sympathetic failure. This study compared the central and cerebrovascular effects of leg crossing in patients with sympathetic failure and healthy controls. We addressed the relationship between MCA  $V_{\text{mean}}$  (middle cerebral artery blood velocity; using transcranial Doppler ultrasound), frontal lobe oxygenation [ $\text{O}_2\text{Hb}$  (oxyhaemoglobin)] and MAP (mean arterial pressure), CO (cardiac output) and TPR (total peripheral resistance) in six patients (aged 37–67 years; three women) and age- and gender-matched controls during leg crossing. In the patients, leg crossing increased MAP from 58 (42–79) to 72 (52–89) compared with 84 (70–95) to 90 (74–94) mmHg in the controls. MCA  $V_{\text{mean}}$  increased from 55 (38–77) to 63 (45–80) and from 56 (46–77) to 64 (46–80) cm/s respectively ( $P < 0.05$ ), with a larger rise in  $\text{O}_2\text{Hb}$  [1.12 (0.52–3.27)] in the patients compared with the controls [0.83 (–0.11 to 2.04)  $\mu\text{mol/l}$ ]. In the control subjects, CO increased 11% ( $P < 0.05$ ) with no change in TPR. By contrast, in the patients, CO increased 9% ( $P < 0.05$ ), but also TPR increased by 13% ( $P < 0.05$ ). In conclusion, leg crossing improves cerebral perfusion and oxygenation both in patients with sympathetic failure and in healthy subjects. However, in healthy subjects, cerebral perfusion and oxygenation were improved by a rise in CO without significant changes in TPR or MAP, whereas in patients with sympathetic failure, cerebral perfusion and oxygenation were improved through a rise in MAP due to increments in both CO and TPR.

## INTRODUCTION

In humans, the upright position challenges the cardiovascular system by gravitational displacement of blood to lower parts of the body with a decline in venous return

and CO (cardiac output), and a reduction in cerebral perfusion pressure [1]. Adjustment to the postural decrease in central blood volume involves increased systemic vascular resistance through autonomic reflex activity, but patients with sympathetic dysfunction lack

**Key words:** autonomic disease, blood flow velocity, cardiac output, leg crossing, near-IR spectroscopy (NIRS), sympathetic nervous system.

**Abbreviations:** BP, blood pressure; CA, cerebral autoregulation; CBF, cerebral blood flow; CO, cardiac output; HHb, deoxyhaemoglobin; HR, heart rate; MAP, mean arterial pressure;  $\text{MAP}_{\text{heart}}$ , MAP at the heart level; MCA, middle cerebral artery;  $\text{MAP}_{\text{mca}}$ , MAP at the brain level; MCA  $V_{\text{mean}}$ , MCA flow velocity; NIRS, near-infrared spectroscopy;  $\text{O}_2\text{Hb}$ , oxyhaemoglobin;  $P_{\text{ETCO}_2}$ , end-tidal  $\text{CO}_2$ ; SV, stroke volume; TI, thoracic electrical impedance; TPR, total peripheral resistance.

**Correspondence:** Dr Johannes J. van Lieshout (email j.j.vanlieshout@amc.uva.nl).

**Table 1** Patient characteristics

PAF, pure autonomic failure; MSA, multiple system atrophy; BPsup, supine BP; BPstd, standing BP; HUT, sleeping 12° head-up-tilt; NaCl, dietary salt supplementation; Flu, fludrocortisone.

Patient	Gender	Disease	Treatment	BPsup (mmHg)	BPstd (mmHg)	Age (years)	Weight (kg)	Height (cm)
S1	Male	PAF	None	156/68	97/51	65	78	172
S2	Male	PAF	HUT	175/101	76/47	51	83	176
S3	Female	PAF	None	175/99	85/48	40	65	176
S4	Female	PAF	NaCl/Flu	112/71	73/49	37	56	164
S5	Male	PAF	Flu	159/81	60/42	65	80	175
S6	Female	PAF	NaCl/Flu	163/98	75/55	61	65	160
S7	Male	MSA	Flu/HUT	135/84	76/45	54	96	196
S8	Male	PAF	NaCl/Flu/HUT	192/102	68/47	67	98	189

this ability to increase vasomotor tone resulting in a decrease in MAP (mean arterial pressure) [2,3]. In these patients, the transcranial Doppler-determined MCA  $V_{\text{mean}}$  [MCA (middle cerebral artery) flow velocity] and the frontal lobe oxygenation [ $\text{O}_2\text{Hb}$  (oxyhaemoglobin)] determined by NIRS (near-IR spectroscopy) decrease markedly, and they develop symptoms of cerebral hypoperfusion when standing [4].

Both patients with sympathetic dysfunction [5] and recurrent vasovagal syncope [6] can combat symptomatic orthostatic hypotension by crossing one leg against the other (leg crossing). Leg crossing in the upright position in healthy subjects increases central venous pressure and CO with a reduction in low-frequency arterial pressure variability, signifying reduced sympathetic activity and suggesting that the central blood volume is restored [7]. Although leg crossing has no effect on MAP in healthy subjects, both MCA  $V_{\text{mean}}$  and  $\text{O}_2\text{Hb}$  increase signifying enhanced cerebral perfusion [7]. However, the effects of leg crossing on cerebral perfusion have not been evaluated in patients with orthostatic hypotension due to sympathetic failure. We therefore tested the hypothesis that in patients with autonomic failure, leg crossing enhances cerebral perfusion, by evaluating the cerebrovascular and central cardiovascular adaptation to orthostatic stress in patients with orthostatic hypotension due to sympathetic failure, and in age- and gender-matched control subjects.

## MATERIALS AND METHODS

### Patients

Eight patients (range, 37–67 years; three females) with severe orthostatic hypotension related to sympathetic failure classified as PAF (pure autonomic failure;  $n=7$ ) and MSA (multiple system atrophy;  $n=1$ ), but with no symptoms or signs of heart disease participated in the present study (Table 1). Oral and written informed consent was obtained, and the study was approved by the Ethics Committee of the Academic Medical Center. Age- and gender-matched healthy subjects with intact

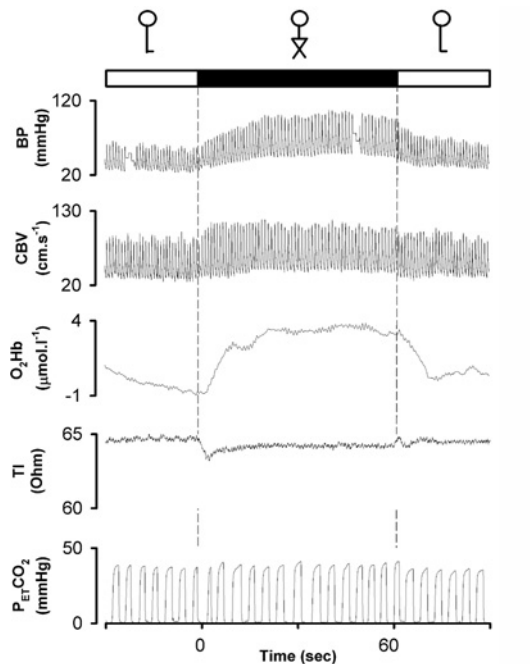
autonomic circulatory control and normal orthostatic tolerance served as controls.

### Protocol

At 08:00 h, after an overnight fast, all subjects reported to the laboratory that was maintained at 22°C. The subjects were supine when instrumented at least 2 h after a light breakfast without caffeine-containing beverages. After instrumentation, a test run was performed to familiarize the subjects with the protocol. After 10 min of supine rest, the subjects stood up, and after 2 min upright, they crossed their legs and maintained that position for 1 min, then they uncrossed the legs and maintained upright for another minute (Figure 1). The duration of orthostatic stress was set so as to enable the patients to fulfil the protocol without symptoms of cerebral hypoperfusion, and the protocol was repeated twice.

### Measurements

Arterial pressure was measured with a Finapres™ model 5 (Netherlands Organization for Applied Scientific Research, Biomedical Instrumentation) from the middle finger of the non-dominant arm fixed in the anterior axillary line at heart level. Finger arterial pressure tracks beat-to-beat changes in arterial pressure during hypotension. Cerebral oxygenation was monitored using NIRS based on the transparency of tissue to light in the near-infrared region with the  $\text{O}_2$  status dependent changes on absorption caused by chromophores dominated by  $\text{O}_2\text{Hb}$  and HHb (deoxyhaemoglobin) [8–10]. To estimate the concentration changes in  $\text{O}_2\text{Hb}$  and HHb, a differential path length factor of 6.0 was applied to account for the scattering of light in the tissue. A continuous wave NIRS instrument with three wavelengths (901, 848 and 770 nm) and 10-Hz sampling time was used (Oxymon; Artinis Medical Systems). The NIRS optodes were attached high on the forehead avoiding the temporalis muscle but sufficiently lateral to avoid the superior sagittal sinus with the transmitting and receiving optodes placed 5.5 cm apart [10]. Changes in  $\text{O}_2\text{Hb}$  and HHb ( $\mu\text{mol/l}$ )



**Figure 1** Leg crossing in a patient with pure autonomic failure

Solid box, leg crossing; open boxes, standing legs uncrossed. Leg crossing induced an instantaneous increase in arterial pressure (BP), and CBV and oxygenation ( $O_2Hb$ ) with a reduction in TI, indicating an acute increase in thoracic blood volume.

were reported with steady-state standing values set at  $0 \mu\text{mol/l}$ .

The MCA  $V_{\text{mean}}$  was measured in the proximal segment and insonated (DWL Multidop X4) through the posterior temporal ultrasound window. Once the optimal signal-to-noise ratio was obtained, the probe was secured with a head band. Both at rest and during exercise, determination of the MCA  $V_{\text{mean}}$  has a coefficient of variation of  $\sim 5\%$  [11]. The MCA  $V_{\text{mean}}$  was obtained from the maximal TCD (transcranial Doppler ultrasound) frequency shifts over one beat divided by the corresponding beat interval and changes in MCA  $V_{\text{mean}}$  were taken to represent those in CBF (cerebral blood flow).

$P_{\text{ETCO}_2}$  (end-tidal  $\text{CO}_2$ ) was measured using an IR analyser (Hewlett Packard 78345A) as a reflection of partial arterial  $\text{CO}_2$  pressure [12]. TI (thoracic electrical impedance) [13] (Kardio-Dynagraph) was used as an index of changes in central blood volume, whereas SV (stroke volume) was obtained from the BP (blood pressure) waveform using the Model flow method incorporating age, gender, height and weight (BeatScope 1.0 software) [14]. Model flow tracks fast changes in SV during postural stress as well as static exercise of relevance for leg crossing [15].

## Data acquisition and analysis

The signals of arterial pressure, the spectral envelope of MCA velocity, TI,  $P_{\text{ETCO}_2}$  and a marker signal were A/D converted at 100 Hz with NIRS data sampled at 10 Hz. Signals were routed through an interface providing electrical isolation with offset and sensitivity adjustments when appropriate. Variables were also recorded on a thermo-writer (Grampac WR7700<sup>TM</sup>; Western Grampac) for online inspection. The MCA  $V_{\text{mean}}$  was expressed as the integral of the maximal frequency shifts over one beat divided by the corresponding beat interval. MAP was the integral of pressure over one beat divided by the beat interval and expressed both at heart and brain level ( $\text{MAP}_{\text{heart}}$  and  $\text{MAP}_{\text{mca}}$ ). HR (heart rate) was the inverse of the interbeat pressure interval in beats/min, CO was  $\text{SV} \times \text{HR}$ , and TPR (total peripheral resistance) was the ratio of MAP to CO.

Beat-to-beat data were transformed to equidistantly re-sampled data at 2 Hz by polynomial interpolation, and averages for both groups are shown in Figure 2. BP, HR, MCA  $V_{\text{mean}}$ ,  $P_{\text{ETCO}_2}$  and TI were expressed in absolute values, whereas resting supine values for SV, CO and TPR were set at 100% (control), and changes were expressed as percentages. Within each subject, the average of all supine values measured over a period of 30 s prior to standing up was used as the baseline value and compared with the average value of 55 to 65 s of standing. Similarly, the average of all values measured over a period of 30 s of quiet standing before leg crossing was used as the baseline value and compared with the average of the last 10 s of leg crossing. The average of the 30 s of quiet standing before leg crossing was then used as the baseline for evaluating the effect of leg crossing, the data of the three runs being averaged. The effect of leg crossing on cerebral and systemic circulatory variables were evaluated by the Wilcoxon signed rank test, whereas differences between patients and controls were analysed by the Mann-Whitney rank sum test. Correlation between variables were evaluated by non-linear regression analysis. A  $P$  value  $< 0.05$  was considered to indicate a statistically significant difference.

## RESULTS

In one patient (S2), the quality of the Doppler velocity spectrum in the upright posture was insufficient, and in the standing position, one patient (S5) developed serious orthostatic complaints and could, therefore, not complete three runs, and these data were excluded from the analysis. As a result, responses from six patients and their matched controls are reported of whom two patients (S7 and S8) had minor orthostatic complaints during standing which, however, disappeared with leg crossing.

## Posture

In the supine position, MAP and MCA  $V_{\text{mean}}$  were high in the patients (Table 2). Standing induced a large fall

**Table 2 Postural cardiovascular and cerebral blood velocity responses**

Values are medians (range). \* $P < 0.05$  compared with supine; † $P < 0.05$  compared with controls.

Measurement	Supine	Standing
<b>MAP<sub>heart</sub> (mmHg)</b>		
Controls	84 (65–94)	84 (70–95)
Patients	106 (85–134)†	57 (42–79)*†
<b>MAP<sub>mca</sub> (mmHg)</b>		
Controls	84 (65–94)	62 (56–73)*
Patients	106 (85–134)†	36 (19–58)*†
<b>MCA <math>V_{\text{mean}}</math> (cm/s)</b>		
Controls	58 (47–83)	56 (46–77)
Patients	77 (64–123)†	55 (38–77)*
<b><math>P_{\text{ETCO}_2}</math> (mmHg)</b>		
Controls	38 (30–40)	35 (31–38)
Patients	37 (26–46)	36 (28–39)
<b>HR (beats/min)</b>		
Controls	58 (46–68)	74 (72–86)*
Patients	66 (49–78)	75 (64–97)*†
<b>SV (%)</b>		
Controls	100	68 (54–85)*
Patients	100	54 (45–59)*†
<b>CO (%)</b>		
Controls	100	93 (75–109)
Patients	100	66 (58–79)*†
<b>TPR (%)</b>		
Controls	100	113 (93–126)
Patients	100	84 (58–115)†
<b>TI (Ohm)</b>		
Controls	57 (47–80)	60 (54–80)
Patients	56 (47–66)	60 (55–64)

in MAP in the patients [−46 (−11 to 78) mmHg] but not in the controls [−4 (−8 to 8) mmHg] ( $P < 0.05$ ); accompanied by a larger fall in SV [46 (41–55)%] compared with 32 (15–46)%;  $P < 0.05$ ] and CO [34 (21–42)% compared with 7 (−9 to 25)%;  $P < 0.05$ ] without the trend of an increase in TPR seen in the controls, such that TPR was significantly different in patients and controls during standing. Resting HR did not differ between the two groups of subjects when supine; during standing, HR increased to a comparable level in the two groups, whereas MCA  $V_{\text{mean}}$  decreased only in the patients [from 77 (64–123) to 55 (38–77) cm/s], resulting in a comparable MCA  $V_{\text{mean}}$  for patients and controls. Upon standing, the decrease in O<sub>2</sub>Hb was also larger in the patients [−13.1 (−16.9 to −4.0) compared with −4.9 (−14.6 to −2.8)  $\mu\text{mol/l}$ ;  $P < 0.05$ ], whereas the HHb increased in both groups of subjects, the larger increase being in the patients [7.5 (3.7–10.9) compared with 2.2 (1.7–9.1)  $\mu\text{mol/l}$ ;  $P < 0.05$ ] (Table 3). The  $P_{\text{ETCO}_2}$  was comparable for patients and control subjects and independent of body position and resting

TI, and the trend for TI to increase on standing were also similar in the patients and control subjects (Table 2).

### Cardiovascular effects of leg crossing

At the onset of leg crossing, in each group, CO and MAP increased (Figure 2), whereas TPR decreased. When analysed in the final 10 s of leg crossing, in the controls, there was an increase in SV (16%) and CO (10%), a trend for a lower HR, but no significant change in TPR or MAP (Table 3 and Figure 2). Pulse pressure increased from 48 (38–55) to 55 (50–58) mmHg ( $P < 0.05$ ). By contrast, in patients, leg crossing induced an increase in MAP and in pulse pressure [from 33 (23–48) to 40 (28–55) mmHg;  $P < 0.05$ ]. The underlying haemodynamic change was an increase in SV (8%), CO (6%) and TPR (11%). HR did not change (Table 3 and Figure 2).

Representative examples of the reproducibility of the responses to leg crossing manoeuvre in patients are provided in Figures 3 and 4.

In both patients and healthy subjects, a marked transient decrease in TI (increase in central blood volume) in response to leg crossing was observed in 13 out of 18 of each group (sign test  $P < 0.05$ ). After the initial fall, TI increased again, and there was no significant change over 1 min of leg crossing.

### Cerebrovascular effects of leg crossing

In both patients and controls, leg crossing induced a similar increase in MCA  $V_{\text{mean}}$  with a concomitant rise in O<sub>2</sub>Hb in the patients and a trend towards lower values for HHb (Figures 2–5 and Table 3). The  $P_{\text{ETCO}_2}$  was comparable for patients and controls and did not change during leg crossing. Within 1 min after leg crossing, all values returned to baseline. The relationship between MCA  $V_{\text{mean}}$  and MAP and CO during free standing, leg crossing and again free standing with three data points plotted for each subject is shown in Figure 5. In the patients, the regression coefficient for MAP and MCA  $V_{\text{mean}}$  was 0.61 ( $P < 0.02$ ), and for CO and MCA  $V_{\text{mean}}$ , it was 0.52 ( $P < 0.05$ ). In the control subjects, this value for MAP and MCA  $V_{\text{mean}}$  was 0.34 (not significant), whereas this was 0.71 for CO and MCA  $V_{\text{mean}}$  ( $P < 0.05$ ).

## DISCUSSION

In the present study, leg crossing consistently improved cerebral perfusion and oxygenation in patients with orthostatic hypotension related to sympathetic failure as in controls. However, the mechanisms of enhanced cerebral perfusion and oxygenation induced by leg crossing appeared different for healthy subjects in whom leg crossing increased CO without significantly affecting TPR or MAP. In the patients, MAP was increased, and this was supported by an increase in TPR as well as in CO. The immediate drop in TI at the onset of leg

**Table 3 Cardiovascular and cerebral responses to leg crossing in standing position**Values are medians (range). \* $P < 0.05$  in comparison to standing before leg cross, † $P < 0.05$  compared with controls.

Measurement	Standing	Leg cross	Standing
<b>MAP<sub>heart</sub> (mmHg)</b>			
Controls	84 (70–95)	90 (74–94)	86 (70–94)
Patients	58 (42–79)†	72 (52–89)*	60 (41–82)†
<b>MAP<sub>mca</sub> (mmHg)</b>			
Controls	62 (56–73)	71 (59–72)	64 (55–72)
Patients	36 (19–58)†	50 (28–73)*	39 (17–62)†
<b>MCA <math>V_{\text{mean}}</math> (cm/s)</b>			
Controls	56 (46–77)	64 (46–80)*	57 (47–72)
Patients	55 (38–77)	63 (45–80)*	57 (38–78)
<b><math>\Delta O_2\text{Hb}</math> (<math>\mu\text{mol/l}</math>)</b>			
Controls	0	0.83 (–0.11 to 2.04)	0.69 (–0.11 to 0.93)
Patients	0	1.12 (0.52–3.27)*	0.46 (–0.12 to 0.89)
<b><math>\Delta\text{HHb}</math> (<math>\mu\text{mol/l}</math>)</b>			
Controls	0	–0.33 (–0.92 to 0.01)	–0.05 (–0.80 to 0.45)
Patients	0	–0.53 (–2.33 to 0.16)	0.07 (–0.23 to 0.66)
<b><math>P_{\text{ETCO}_2}</math> (mmHg)</b>			
Controls	35 (31–38)	35 (34–42)	35 (33–40)
Patients	36 (28–39)	36 (29–40)	35 (29–39)
<b>HR (beats/min)</b>			
Controls	74 (72–86)	71 (58–79)†	73 (65–83)
Patients	75 (64–97)	75 (59–92)	74 (63–95)
<b>SV (%)</b>			
Controls	68 (54–85)	84 (73–102)*	69 (61–92)
Patients	54 (45–59)†	62 (56–69)*†	53 (43–61)†
<b>CO (%)</b>			
Controls	93 (75–109)	103 (91–119)*	88 (82–114)
Patients	66 (58–79)†	72 (66–95)*†	67 (51–83)†
<b>TPR (%)</b>			
Controls	113 (93–126)	105 (82–117)	112 (81–124)
Patients	84 (58–115)†	95 (68–118)*	89 (65–113)
<b>TI (Ohm)</b>			
Controls	60 (54–80)	60 (54–78)	61 (54–80)
Patients	60 (55–64)	60 (55–64)	60 (55–64)

crossing in both patients and healthy subjects suggests translocation of blood to the chest with less pooling due to sustained muscle tensing. However, given the defective vasomotor control in the patients, the increase in TPR induced by leg crossing is likely to be related to compression of venous and arterial vascular beds.

In healthy subjects, the postural fall in venous return as a consequence of pooling of blood reduces SV and CO [4]. However, an increase in vasomotor tone in response to cardiopulmonary and arterial baroreflex-mediated sympathoexcitation, local myogenic responses and venoarteriolar axon reflex activity, elevates mean and diastolic arterial pressure [3,16]. By contrast, patients with sympathetic failure cannot modulate vascular tone and thus develop orthostatic hypotension [2,3] because of an excessive fall in SV and CO, attributable to both increased

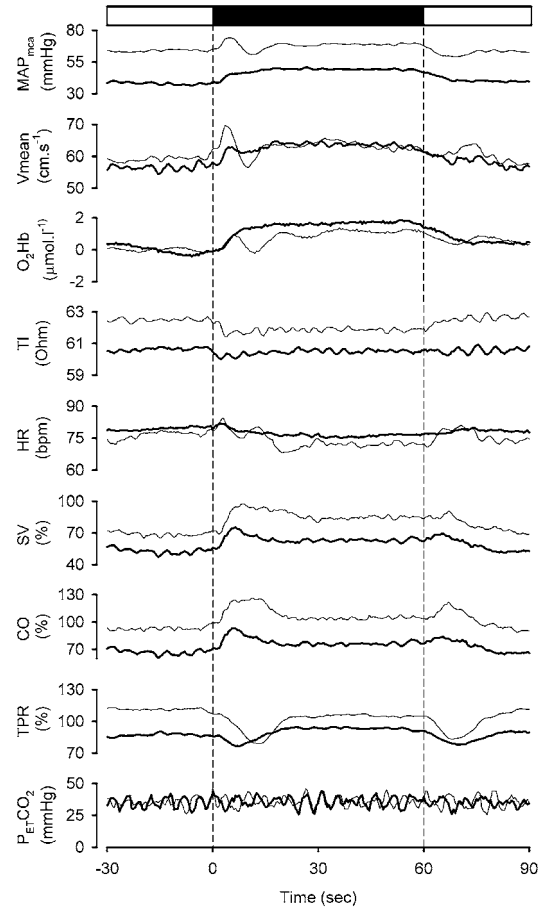
pooling of venous blood and impaired inotropic and chronotropic cardiac responses [2]. The tendency for TI to be higher upon standing is consistent with a reduction in central blood volume in both groups (Table 2). In addition to the marked reduction in MAP and CO, a decrease in  $P_{\text{ETCO}_2}$  as an index of the arterial value might have contributed to the observed reduction in MCA  $V_{\text{mean}}$  that occurred in the patients on standing. However, the contribution of  $P_{\text{ETCO}_2}$  to the postural reduction in MCA  $V_{\text{mean}}$  is transient [17], and in the present study, any such influence must have been small, if any. In addition, leg crossing did not change  $P_{\text{ETCO}_2}$  rendering a contribution of partial arterial  $\text{CO}_2$  pressure to the increase in cerebral perfusion during leg crossing unlikely. In healthy subjects, autonomic neural control of the cerebral circulation is tonically active [18–20], but in patients with

autonomic failure, a reduced spillover of noradrenaline from the brain renders such an influence unlikely [21].

Under normal circumstances, CBF is maintained across a range of MAP of  $\sim 60$  to 150 mmHg by CA (cerebral autoregulation). Furthermore, a reduction in MAP below the lower limit of CA challenges CBF and a reduction in central blood volume, and therefore in CO, adversely influences the lower limit of CA [20,22–24]. The significant relationship between MAP and MCA  $V_{\text{mean}}$  in the upright position in the patients (Figure 5) suggests that leg crossing in the patients raised MAP from below to within the accepted autoregulatory range [25]. Patients with autonomic failure are remarkably tolerant of postural hypotension [26] suggesting they have well-maintained cerebral autoregulatory capacity. On the other hand, a parallel postural reduction in MAP and MCA  $V_{\text{mean}}$  does occur in these patients suggesting a reduced autoregulatory capacity [27]. Thus whether CA is maintained in autonomic dysfunction remains debatable.

In the present study, MCA  $V_{\text{mean}}$  was used as a measure of cerebral perfusion, assuming that in patients with sympathetic failure changes in MCA  $V_{\text{mean}}$  are representative of those in CBF. However, critical for the interpretation of the data is the extent to which MCA  $V_{\text{mean}}$  reflects volume flow in cerebral circulation. Changes in resistance to flow occur mainly in the cerebral arteriolar bed; the major cerebral conductance arteries are non-compliant and act as a conduit for the pulsatile arterial flow. This is important because MCA  $V_{\text{mean}}$  calculated from the frequency distribution of the Doppler shifts is related to CBF only if the insonated vessel diameter remains constant. This has been shown to be the case for the MCA over a  $\sim 30$ -mmHg range of BP such that changes with MCA  $V_{\text{mean}}$  do reflect changes in CBF [28]. Indeed, direct observations made during craniotomy have revealed that lowering BP by sodium nitroprusside does not affect MCA diameter [29]. Moreover, orthostatic stress, as simulated by lower body negative pressure, does not alter the MCA diameter as assessed with MR imaging [30]. Nevertheless, the low BP levels developed in the patients with sympathetic failure do not rule out the possibility that a considerable fall in BP might have reduced the diameter of the MCA, such that the measurement of MCA  $V_{\text{mean}}$  led to underestimation of the postural reduction in CBF [31].

An attempt was therefore made to overcome this possibility by combining the use of the transcranial Doppler technique with the use of NIRS, which is based on different physical principles, as an alternative means of assessing changes in CBF. The NIRS signal for the frontal lobe, which depends on oxygenation at the level of the capillaries, has been shown to reflect the brain capillary  $O_2$  saturation over a 2-fold variation in CBF [32]. Furthermore, with postural stress, cerebrovascular oxygenation as determined by NIRS has been shown to be directly related to cerebral perfusion as determined by the transcranial Doppler technique [9,33]. Thus, when MCA  $V_{\text{mean}}$

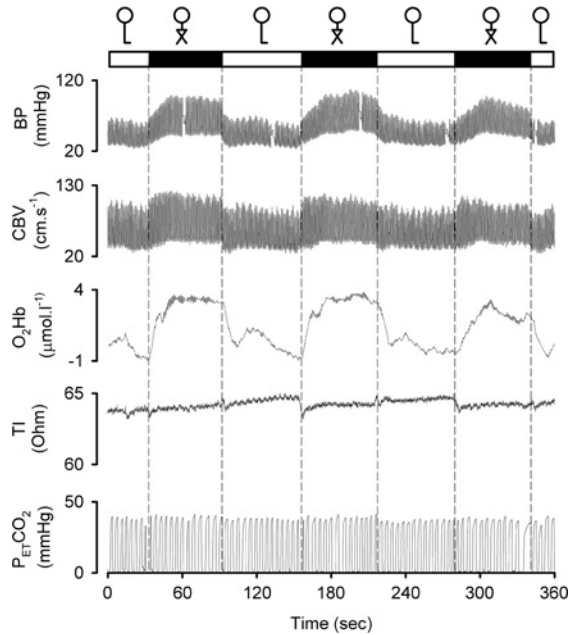


**Figure 2 Cardiovascular and cerebral perfusion and oxygenation responses to leg crossing**

Solid box, leg crossing; open box, standing. Bold lines, patients; thin lines, controls (averaged responses).

and  $O_2Hb$  increase in parallel, we believe it is reasonable to conclude that CBF changed in the same direction, as has been confirmed by clinical evaluation [9,32,34–36].

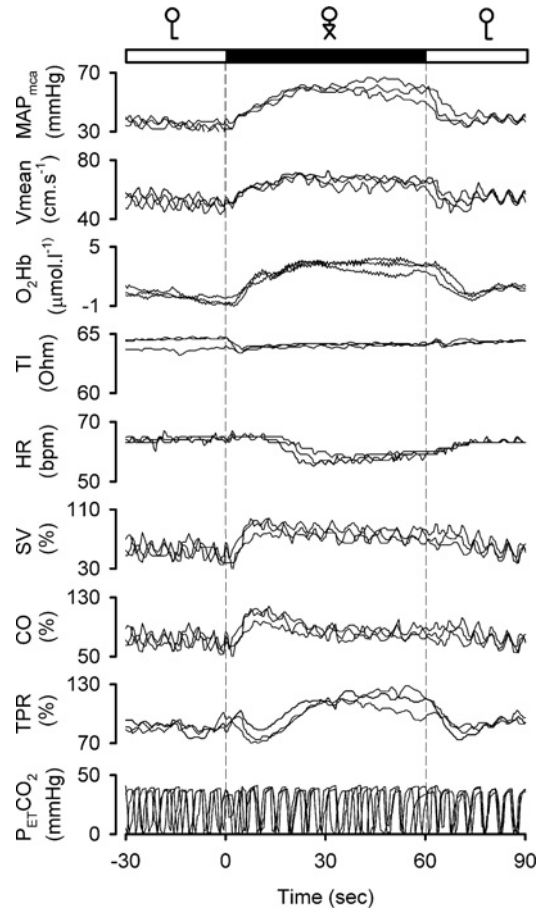
It must be acknowledged that there are potential complications when interpreting changes in cerebral perfusion in the upright position. Although the brain is elevated above the heart, the contention that the cerebral perfusion pressure falls accordingly [37–39] is not generally accepted [40]. For the brain, not only the inflow pressure but also the venous and cerebral spinal fluid pressures decline in proportion to the vertical distance above the heart [1,41–44], and veins above the heart collapse because the surrounding tissue pressure is greater than the pressure inside the veins, so creating a Starling resistor [45]. Within the brain, a potential siphon exists at the level of the sinus sagittalis which, in contrast to the jugular veins, does not collapse upon standing up [46]. However, because of the collapsible veins, gravitational pressure gradients are not matched on the arterial and venous sides of the circulation at all levels above the heart



**Figure 3** Effects of repeated leg crossing on brain perfusion and oxygenation in a patient with pure autonomic failure. Original tracings in a patient with pure autonomic failure. Solid box, leg crossing; open box, standing.

as would be necessary for a siphon to operate [37,47]. Indeed, the effects of posture on spinal fluid pressure [48] and internal jugular vein cross-sectional area [48,49] have been evaluated in healthy subjects, and it has been shown that when humans are upright, the prevailing pressure for both the venous outflow and for the spinal fluid approaches zero at the base of the brain, so negating the idea that a siphon supports CBF. Thus, it seems that in upright humans, the magnitude of cerebrovascular resistance breaks the continuity requirement for a siphon, implying that the heart has to work against gravity to perfuse the brain. As far as the present study is concerned, we have no reason to suppose that these principles apply differently to patients with sympathetic failure.

In the present study on healthy subjects, both the MCA  $V_{\text{mean}}$  and  $\text{O}_2\text{Hb}$  increased in response to leg crossing without significant changes in MAP confirming earlier findings [7] and suggesting an increase in cerebral perfusion. There was a direct relationship between CO and MCA  $V_{\text{mean}}$  that cannot be explained by changes in MAP (Figure 5) [50,51]. In the patients, the increase in cerebral perfusion as indicated by the increase in MCA  $V_{\text{mean}}$  was comparable, but in contrast, MCA  $V_{\text{mean}}$  was related to both CO and MAP. In healthy subjects, the arterial baroreflex instantaneously maintains MAP by buffering changes in preload. However, patients with sympathetic failure lack this buffering capacity, and MAP is largely dependent on cardiac preload and CO. Thus, on this basis alone, it is not clear whether cerebral



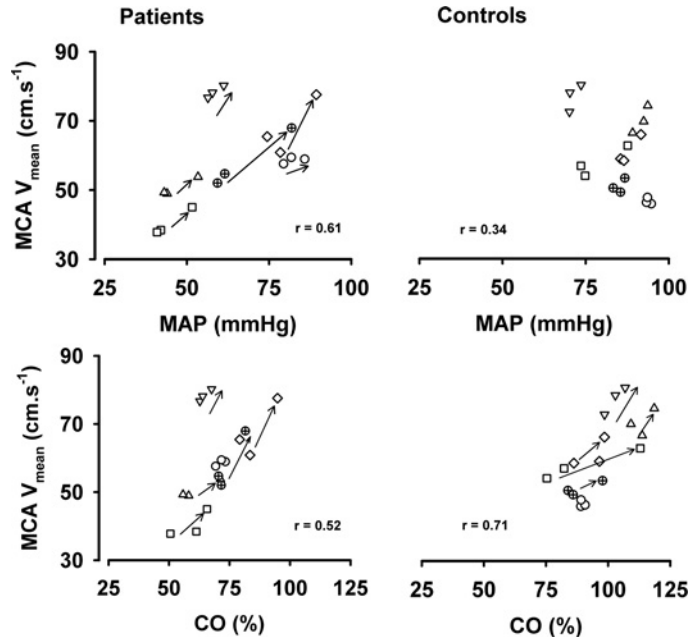
**Figure 4** Reproducibility of systemic and cerebral responses to leg crossing in a patient with pure autonomic failure

Recordings obtained in three separate experimental runs are superimposed.

perfusion is determined by MAP as well as by CO (Figure 5). However, if we consider our results in more detail, it is clear that leg crossing increased MAP in each individual patient, and there was an associated increase in MCA  $V_{\text{mean}}$ . Indeed, it seems that leg crossing increased MAP in the patients from below to within in the accepted cerebral autoregulatory range. In other words, the direct relationship between MCA  $V_{\text{mean}}$  and MAP may be accounted for because standing allowed MAP to fall below the autoregulatory range. When MAP is within the autoregulatory range, there is no reason to suppose that the factors that regulate cerebral perfusion are different in healthy subjects and patients with sympathetic failure.

In conclusion, leg crossing consistently improves cerebral perfusion in patients with sympathetic failure as reflected by a rise of cerebral blood velocity and in cerebral oxygenation, and this is associated with a relief of symptoms. In healthy subjects, CO increases during leg crossing without significant changes in MAP, whereas in the patients, there is an increase in MAP that





**Figure 5** Relationship between MAP, CO and MCA  $V_{\text{mean}}$  during leg crossing

Standing–leg crossing–standing as three data points plotted for each subject.

is supported by an increase in TPR. There is no definite explanation for this increase in TPR in the patients with sympathetic failure, but we hypothesize that the positive mechanical effect of leg crossing on TPR overcomes the vasodilator effect caused by the absence of sympathetic vascular control. Patients with orthostatic intolerance should, therefore, be advised, in addition to increasing their salt intake and to sleep head-up tilted, also to apply leg crossing when they stand up as a simple means of maintaining cerebral perfusion and avoiding postural syncope.

## FUNDING

This study was supported by the Netherlands Heart Foundation (grant number 94.132).

## REFERENCES

- Rosner, M. J. and Coley, I. B. (1986) Cerebral perfusion pressure, intracranial pressure, and head elevation. *J. Neurosurg.* **65**, 636–641
- Bevegård, B. S., Jonsson, B. and Karlöf, I. (1962) Circulatory response to recumbent exercise and head-up tilting in patients with disturbed sympathetic cardiovascular control (postural hypotension): observations on the effect of norepinephrine infusion and antigravity suit inflation in the head-up tilted position. *Acta Med. Scand.* **172**, 623–636
- Smit, A. A. J., Halliwill, J. R., Low, P. A. and Wieling, W. (1999) Pathophysiological basis of orthostatic hypotension in autonomic failure. *J. Physiol.* **519**, 1–10
- Harms, M. P. M., Colier, W. N. J. M., Wieling, W., Lenders, J. W., Secher, N. H. and Van Lieshout, J. J. (2000) Orthostatic tolerance, cerebral oxygenation, and blood velocity in humans with sympathetic failure. *Stroke* **31**, 1608–1614
- Van Lieshout, J. J., Ten Harkel, A. D. J. and Wieling, W. (1992) Physical manoeuvres for combating orthostatic dizziness in autonomic failure. *Lancet* **339**, 897–898
- Krediet, C. T., Van Lieshout, J. J., Bogert, L. W., Immink, R. V., Kim, Y. S. and Wieling, W. (2006) Leg crossing improves orthostatic tolerance in healthy subjects: a placebo-controlled crossover study. *Am J. Physiol. Heart Circ. Physiol.* **291**, H1768–H1772
- Van Lieshout, J. J., Pott, F., Madsen, P. L., Van Goudoever, J. and Secher, N. H. (2001) Muscle tensing during standing: effects on cerebral tissue oxygenation and cerebral artery blood velocity. *Stroke* **32**, 1546–1551
- Colier, W. N. J. M., Binkhorst, R. A., Hopman, M. T. and Oeseburg, B. (1997) Cerebral and circulatory haemodynamics before vasovagal syncope induced by orthostatic stress. *Clin. Physiol.* **17**, 83–94
- Madsen, P. L. and Secher, N. H. (1999) Near-infrared oximetry of the brain. *Prog. Neurobiol.* **58**, 541–560
- Al-Rawi, P. G., Smielewski, P. and Kirkpatrick, P. J. (2001) Evaluation of a near-infrared spectrometer (NIRO 300) for the detection of intracranial oxygenation changes in the adult head. *Stroke* **32**, 2492–2500
- Pott, F., Jensen, K., Hansen, H., Christensen, N. J., Lassen, N. A. and Secher, N. H. (1996) Middle cerebral artery blood velocity and plasma catecholamines during exercise. *Acta Physiol. Scand.* **158**, 349–356
- Immink, R. V., Secher, N. H., Roos, C. M., Pott, F., Madsen, P. L. and Van Lieshout, J. J. (2006) The postural reduction in middle cerebral artery blood velocity is not explained by PaCO<sub>2</sub>. *Eur. J. Appl. Physiol.* **96**, 609–614
- Jonsson, F., Madsen, P., Jørgensen, L. G., Lunding, M. and Secher, N. H. (1995) Thoracic electrical impedance and fluid balance during aortic surgery. *Acta Anaesthesiol. Scand.* **39**, 513–517
- Harms, M. P. M., Wesseling, K. H., Pott, F., Jenstrup, M., Van Goudoever, J., Secher, N. H. and Van Lieshout, J. J. (1999) Continuous stroke volume monitoring by modelling flow from non-invasive measurement of arterial pressure in humans under orthostatic stress. *Clin. Sci.* **97**, 291–301

- 15 Van Dijk, N., de Bruin, I. G., Gisolf, J., de Bruin-Bon, H. A., Linzer, M., van Lieshout, J. J. and Wieling, W. (2005) Hemodynamic effects of legcrossing and skeletal muscle tensing during free standing in patients with vasovagal syncope. *J. Appl. Physiol.* **98**, 584–590
- 16 Wieling, W. and Van Lieshout, J. J. (2008) Maintenance of postural normotension in humans. In *Clinical Autonomic Disorders* (Low, P. A. and Benarroch, E. F. eds), pp. 69–78, Lippincott, Williams & Wilkins
- 17 Immink, R. V., Truijien, J., Secher, N. H. and Van Lieshout, J. J. (2009) Transient influence of end-tidal carbon dioxide tension on the postural restraint in cerebral perfusion. *J. Appl. Physiol.* **107**, 816–823
- 18 Zhang, R., Zuckerman, J. H., Iwasaki, K., Wilson, T. E., Crandall, C. G. and Levine, B. D. (2002) Autonomic neural control of dynamic cerebral autoregulation in humans. *Circulation* **106**, 1814–1820
- 19 Ogoh, S., Brothers, R. M., Eubank, W. L. and Raven, P. B. (2008) Autonomic neural control of the cerebral vasculature: acute hypotension. *Stroke* **39**, 1979–1987
- 20 Van Lieshout, J. J. and Secher, N. H. (2008) Sympathetic activity does/does not influence cerebral blood flow. *J. Appl. Physiol.* **105**, 1364–1366
- 21 Mitchell, D. A., Lambert, G., Secher, N. H., Raven, P. B., van Lieshout, J. J. and Esler, M. D. (2009) Jugular venous overflow of noradrenaline from the brain: a neurochemical indicator of cerebrovascular sympathetic nerve activity in humans. *J. Physiol.* **587**, 2589–2597
- 22 Waldemar, G., Vorstrup, S., Andersen, A. R., Pedersen, H. and Paulson, O. B. (1989) Angiotensin-converting enzyme inhibition and regional cerebral blood flow in acute stroke. *J. Cardiovasc. Pharmacol.* **14**, 722–729
- 23 Jørgensen, L. G., Perko, M., Perko, G. and Secher, N. H. (1993) Middle cerebral artery velocity during head-up tilt induced hypovolaemic shock in humans. *Clin. Physiol.* **13**, 323–336
- 24 Truijien, J., Bundgaard-Nielsen, M. and van Lieshout, J. J. (2009) A definition of normovolaemia and consequences for cardiovascular control during orthostatic and environmental stress. *Eur. J. Appl. Physiol.*, doi: 10.1007/s00421-009-1346-5
- 25 Panerai, R. B. (2008) Cerebral autoregulation: from models to clinical applications. *Cardiovasc. Eng.* **8**, 42–59
- 26 Thomas, D. J. and Bannister, R. (1980) Preservation of autoregulation of cerebral blood flow in autonomic failure. *J. Neurol. Sci.* **44**, 205–212
- 27 Lagi, A., Bacalli, S., Cencetti, S., Paggetti, C. and Colzi, L. (1994) Cerebral autoregulation in orthostatic hypotension. A transcranial Doppler study. *Stroke* **25**, 1771–1775
- 28 Giller, C. A., Bowman, G., Dyer, H., Mootz, L. and Krippner, W. (1993) Cerebral arterial diameters during changes in blood pressure and carbon dioxide during craniotomy. *Neurosurgery* **32**, 737–741
- 29 Qureshi, A. I., Wilson, D. A., Hanley, D. F. and Traystman, R. J. (1999) Pharmacologic reduction of mean arterial pressure does not adversely affect regional cerebral blood flow and intracranial pressure in experimental intracerebral hemorrhage. *Crit. Care Med.* **27**, 965–971
- 30 Serrador, J. M., Picot, P. A., Rutt, B. K., Shoemaker, J. K. and Bondar, R. L. (2000) MRI measures of middle cerebral artery diameter in conscious humans during simulated orthostasis. *Stroke* **31**, 1672–1678
- 31 Thoresen, M., Haaland, K. and Steen, A. (1994) Cerebral Doppler and misinterpretation of flow changes. *Arch. Dis. Child.* **71**, F103–F106
- 32 Rasmussen, P., Dawson, E. A., Nybo, L., Van Lieshout, J. J., Secher, N. H. and Gjedde, A. (2007) Capillary-oxygenation-level-dependent near-infrared spectrometry in frontal lobe of humans. *J. Cereb. Blood Flow Metab.* **27**, 1082–1093
- 33 Madsen, P. L., Pott, F., Olsen, S. B., Nielsen, H. B., Burcev, I. and Secher, N. H. (1998) Near-infrared spectrophotometry determined brain oxygenation during fainting. *Acta Physiol. Scand.* **162**, 501–507
- 34 Van Lieshout, J. J., Wieling, W., Karemaker, J. M. and Secher, N. H. (2003) Syncope, cerebral perfusion, and oxygenation. *J. Appl. Physiol.* **94**, 833–848
- 35 Pott, F., Van Lieshout, J. J., Ide, K., Madsen, P. and Secher, N. H. (2003) Middle cerebral artery blood velocity during intense static exercise is dominated by a Valsalva maneuver. *J. Appl. Physiol.* **94**, 1335–1344
- 36 Kim, Y. S., Bogert, L. W., Immink, R. V., Harms, M. P., Colier, W. N. and Van Lieshout, J. J. (2009) Effects of aging on the cerebrovascular orthostatic response. *Neurobiol. Aging*, doi:10.1016/j.neurobiolaging.2009.02.019
- 37 Hill, L. and Barnard, H. (1897) The influence of the force of gravity on the circulation. Part II. *J. Physiol.* **22**, 323–352
- 38 Rosner, M. J. and Coley, I. B. (1986) Cerebral perfusion pressure, intracranial pressure, and head elevation. *J. Neurosurg.* **65**, 636–641
- 39 Gisolf, J., Gisolf, A., Van Lieshout, J. J. and Karemaker, J. M. (2005) The siphon controversy: an integration of concepts and the brain as baffle. *Am. J. Physiol. Regul. Integr. Comp. Physiol.* **289**, R627–R629
- 40 Hicks, J. W. and Munis, J. R. (2005) The siphon controversy counterpoint: the brain need not be 'baffling'. *Am. J. Physiol. Regul. Integr. Comp. Physiol.* **289**, R629–R632
- 41 Ng, I., Lim, J. and Wong, H. B. (2004) Effects of head posture on cerebral hemodynamics: its influences on intracranial pressure, cerebral perfusion pressure, and cerebral oxygenation. *Neurosurgery* **54**, 593–597
- 42 Asgeirsson, B. and Grände, P. O. (1996) Local vascular responses to elevation of an organ above the heart. *Acta Physiol. Scand.* **156**, 9–18
- 43 Kongstad, L. and Grände, P. O. (1999) The role of arterial and venous pressure for volume regulation of an organ enclosed in a rigid compartment with application to the injured brain. *Acta Anaesthesiol. Scand.* **43**, 501–508
- 44 Dawson, S. L., Panerai, R. B. and Potter, J. F. (1999) Critical closing pressure explains cerebral hemodynamics during the Valsalva maneuver. *J. Appl. Physiol.* **86**, 675–680
- 45 Lopez-Muniz, R., Stephens, N. L., Bromberger-Barnea, B., Permutt, S. and Riley, R. L. (1968) Critical closure of pulmonary vessels analyzed in terms of Starling resistor model. *J. Appl. Physiol.* **24**, 625–635
- 46 Mosso, M., Schmid-Priscoveanu, A., Straumann, D. and Baumgartner, R. W. (2008) Absence of gravity-dependent modulation of straight sinus flow velocity in healthy humans. *Ultrasound Med. Biol.* **34**, 726–729
- 47 Seymour, R. S. and Johansen, K. (1987) Blood flow uphill and downhill: does a siphon facilitate circulation above the heart? *Comp. Biochem. Physiol. A* **88**, 167–170
- 48 Dawson, E. A., Secher, N. H., Dalsgaard, M. K., Ogoh, S., Yoshiga, C. C., González-Alonso, J., Steensberg, A. and Raven, P. B. (2004) Standing up to the challenge of standing: a siphon does not support cerebral blood flow in humans. *Am. J. Physiol. Regul. Integr. Comp. Physiol.* **287**, R911–R914
- 49 Gisolf, J., Van Lieshout, J. J., Van Heusden, K., Pott, F., Stok, W. J. and Karemaker, J. M. (2004) Human cerebral venous outflow pathway depends on posture and central venous pressure. *J. Physiol.* **560**, 317–327
- 50 Ogoh, S., Brothers, R. M., Barnes, Q., Eubank, W. L., Hawkins, M. N., Purkayastha, S., O-Yurvati, A. and Raven, P. B. (2005) The effect of changes in cardiac output on middle cerebral artery mean blood velocity at rest and during exercise. *J. Physiol.* **569**, 697–704
- 51 Secher, N. H., Seifert, T. and Van Lieshout, J. J. (2008) Cerebral blood flow and metabolism during exercise, implications for fatigue. *J. Appl. Physiol.* **104**, 306–314

Received 19 January 2009/8 October 2009; accepted 16 October 2009  
 Published as Immediate Publication 16 October 2009, doi:10.1042/CS20090038