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## Central and Cerebrovascular Effects of Leg Crossing in Humans with Sympathetic Failure

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**ABSTRACT**

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 middle cerebral artery blood velocity (MCA  $V_{\text{mean}}$ , TCD), frontal lobe oxygenation (oxyhemoglobin ( $\text{O}_2\text{Hb}$ ) and mean arterial pressure (MAP), cardiac output (CO) and total peripheral resistance (TPR) in 6 patients (aged 37 to 67 years; 3 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) vs. 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)  $\text{cm}\cdot\text{s}^{-1}$ , respectively ( $p<0.05$ ) with a larger rise in  $\text{O}_2\text{Hb}$  (1.12 (0.52-3.27)) in the patients vs. the controls (0.83 (-0.11-2.04)  $\mu\text{mol}\cdot\text{l}^{-1}$ ). 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 improve by a rise in CO without significant changes in TPR or MAP, whereas in patients with sympathetic failure cerebral perfusion and oxygenation improve 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 cardiac output (CO), 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 this ability to increase vasomotor tone resulting in a decrease in mean arterial pressure (MAP) [2;3]. In these patients the transcranial Doppler-determined middle cerebral artery flow velocity (MCA  $V_{\text{mean}}$ ) and the frontal lobe oxygenation ( $\text{O}_2\text{Hb}$ ) determined by near-infrared 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 cerebro- and central cardiovascular adaptation to orthostatic stress in patients with orthostatic hypotension due to sympathetic failure, and in age and gender matched control subjects.

## METHODS

Eight patients (range 37-67 yr, 3 females) with severe orthostatic hypotension related to sympathetic failure classified as pure autonomic failure (PAF; n=7) and multiple system atrophy

(MSA; n=1) but with no symptoms or signs of heart disease participated in the study (Table 1). Oral and written informed consent was obtained and the study was approved by 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 8:00 AM 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 hours after a light breakfast without caffeine containing beverages. After instrumentation a test run was performed to familiarize the subjects to the protocol. After 10 minutes of supine rest, the subjects stood up and after 2 minutes upright they crossed their legs and maintained that position for 1 min, then they uncrossed the legs and maintained upright for another minute (Fig. 1). The duration of orthostatic stress was set so as to enable the patients to fulfill 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, TNO-BMI, Amsterdam) 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 near infrared spectroscopy (NIRS) based on the transparency of tissue to light in the near-infrared region with the O<sub>2</sub> status dependent changes on absorption caused by chromophores dominated by oxy- and deoxy-haemoglobin (O<sub>2</sub>Hb and HHb) [8-10]. To estimate the concentration changes in O<sub>2</sub>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, Zetten, The Netherlands). 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  $O_2Hb$  and  $HHb$  ( $\mu\text{mol.l}^{-1}$ ) were reported with steady state standing values set at  $0 \mu\text{mol.l}^{-1}$ .

The MCA  $V_{\text{mean}}$  was measured in the proximal segment and insonated (DWL Multidop X4, Sipplingen, Germany) 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  $V_{\text{mean}}$  was obtained from the maximal TCD frequency shifts over one beat divided by the corresponding beat interval and changes in MCA  $V_{\text{mean}}$  were taken to represent those in cerebral blood flow (CBF).

End-tidal  $\text{CO}_2$  ( $P_{\text{ETCO}_2}$ ) was measured by an infrared analyzer (Hewlett Packard 78345A, Roeblingen, Germany) as a reflection of partial arterial  $\text{CO}_2$  pressure [12]. Thoracic electrical impedance (TI) [13] (Kardio-Dynagraph, Diefenbach GmbH, Frankfurt/Main, Germany) was used as an index of changes in central blood volume whereas stroke volume (SV) was obtained from the blood pressure waveform using the Model flow method incorporating age, gender, height, and weight (BeatScope 1.0 software, FMS, Amsterdam, The Netherlands) [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 (Graphtec WR7700 <sup>TM</sup>, Western Graphtec Inc., Irvine, CA) for on-line 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 ( $MAP_{mca}$ ). Heart rate (HR) was the inverse of the inter-beat pressure interval in  $\text{beats}\cdot\text{min}^{-1}$  (bpm), CO was SV times HR, and total peripheral resistance (TPR) 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 Fig 4. Blood pressure, HR,  $V_{\text{mean}}$ ,  $P_{\text{ETCO}_2}$ , 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 seconds prior to standing up was used as the baseline value and compared with the average value of 55 to 65 seconds of standing. Similarly, the average of all values measured over a period of 30 seconds of quiet standing before leg crossing was used as the baseline value and compared with the average of the last 10 seconds of leg crossing. The average of the 30 seconds 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 analyzed by the Mann-Whitney rank sum test. Correlation between variables were evaluated by nonlinear 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 6 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 in MAP in the patients (-46 (11-78)) but not in the controls (-4 (-8-8)) mmHg ( $P < 0.05$ ); accompanied by a larger fall in SV (46 (41-55) vs. 32 (15-46) %;  $P < 0.05$ ) and CO (34 (21-42) vs. 7 (-9-25) %;  $P < 0.05$ ) 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 and 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)  $\text{cm}\cdot\text{s}^{-1}$ ) resulting in a comparable MCA  $V_{\text{mean}}$  for patients and controls. Upon standing, the decrease in  $\text{O}_2\text{Hb}$  was also larger in the patients (-13.1 (-16.9 - -4.0) vs. -4.9 (-14.6 - -2.8)  $\mu\text{mol}\cdot\text{l}^{-1}$ ;  $P < 0.05$ ), whereas the HHb increased in both groups of subjects, the larger increase being in the patients (7.5 (3.7-10.9) vs. 2.2 (1.7-9.1)  $\mu\text{mol}\cdot\text{l}^{-1}$ ;  $P < 0.05$ ). The  $\text{P}_{\text{ET}}\text{CO}_2$  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 (Fig 4) whereas TPR decreased. When analysed in the final 10 sec 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, Fig 4). 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 hemodynamic change was an increase in SV (8%), CO (6%) and TPR (11%). HR did not change (Table 3, Fig 4).

Representative examples of the reproducibility of the responses to leg crossing manoeuvre in patients are provided in figures 2 and 3.

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 of 18 of each group (sign test  $p < 0.05$ ). After the initial drop, TI increased again and there was no significant change over one minute 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  $O_2\text{Hb}$  in the patients and a trend towards lower values for HHb (Figures 2-5 and Table 3). The  $P_{\text{ET}}\text{CO}_2$  was comparable for patients and controls and did not change during leg crossing. Within one minute 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 (NS), 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 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 veno-arteriolar axon reflex activity, elevates mean and diastolic arterial pressure [3;16]. By contrast, patients with sympathetic failure, however, 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  $P_{ETCO_2}$  as an index of the arterial value might have contributed to the observed reduction in MCA  $V_{mean}$  that occurred in the patients on standing. However, the contribution of  $P_{ETCO_2}$  to the postural reduction in MCA  $V_{mean}$  is transient [17] and in the present study, any such influence must have been small, if any. Also, leg crossing did not change  $P_{ETCO_2}$  rendering a contribution of partial arterial  $CO_2$  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 ~ 60 to 150 mmHg by cerebral autoregulation (CA). Further, 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 [22-24]. The significant relationship between MAP and MCA  $V_{\text{mean}}$  in the upright position in the patients (Fig 5) suggests that leg crossing in the patient 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 mainly; the major cerebral conductance arteries are non-compliant and acting 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 ~30 mmHg range of blood pressure such that with MCA  $V_{\text{mean}}$  do reflect changes in CBF [28]. Indeed, direct observations made during craniotomy have revealed that lowering blood pressure 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 blood pressure levels developed in the patients with sympathetic failure do not rule out the possibility that a considerable fall in blood pressure 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 two-fold variation in CBF [32]. Further, 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  $V_{\text{mean}}$  and  $O_2\text{Hb}$  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;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 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 [41-44] and veins above 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 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 jugular cross-sectional area [49;50] 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 in healthy subjects, both the MCA  $V_{\text{mean}}$  and  $O_2\text{Hb}$  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 (Fig 5) [51;52]. 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 instantaneously. 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 perfusion is determined by MAP as well as by CO (Fig 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 reflected in a rise of cerebral blood velocity and in cerebral oxygenation and this is associated with a relieve 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 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 effected 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 use sleeping head-up tilted, also to apply leg crossing when

they stand up as a simple means of maintaining cerebral perfusion and avoiding postural syncope.

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**Table 1. Patient characteristics**

Pure autonomic failure (PAF), multiple system atrophy (MSA), supine blood pressure (BP<sub>sup</sub>), standing blood pressure (BP<sub>std</sub>), sleeping 12° head-up-tilt (HUT), dietary salt supplementation (NaCl), and Fludrocortisone (Flu)

Patients	Gender	Disease	Treatment	BP <sub>sup</sub> (mmHg)	BP <sub>std</sub> (mmHg)	Age (yr)	Weight (kg)	Height (cm)
S1	m	PAF	none	156/68	97/51	65	78	172
S2	m	PAF	HUT	175/101	76/47	51	83	176
S3	f	PAF	none	175/99	85/48	40	65	176
S4	f	PAF	NaCl/Flu	112/71	73/49	37	56	164
S5	m	PAF	Flu	159/81	60/42	65	80	175
S6	f	PAF	NaCl/Flu	163/98	75/55	61	65	160
S7	m	MSA	Flu/HUT	135/84	76/45	54	96	196
S8	m	PAF	NaCl/Flu/HUT	192/102	68/47	67	98	189

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

Mean arterial pressure (MAP), middle cerebral artery mean blood velocity (MCA  $V_{\text{mean}}$ ), end-tidal  $\text{CO}_2$  ( $P_{\text{ETCO}_2}$ ), heart rate (HR), stroke volume (SV), cardiac output (CO), total peripheral resistance (TPR) and thoracic electrical impedance (TI). Data are median and range. \*  $P < 0.05$  vs. supine, †  $P < 0.05$  patients vs. controls.

	Supine	Standing
MAP <sub>heart</sub> (mmHg)		
Controls	84 (65-94)	84 (70-95)
Patients	106 (85-134) <sup>†</sup>	57 (42-79) <sup>*†</sup>
MAP <sub>mca</sub> (mmHg)		
Controls	84 (65-94)	62 (56-73) <sup>*</sup>
Patients	106 (85-134) <sup>†</sup>	36 (19-58) <sup>*†</sup>
MCA $V_{\text{mean}}$ (cm.s <sup>-1</sup> )		
Controls	58 (47-83)	56 (46-77)
Patients	77 (64-123) <sup>†</sup>	55 (38-77) <sup>*</sup>
$P_{\text{ETCO}_2}$ (mmHg)		
Controls	38 (30-40)	35 (31-38)
Patients	37 (26-46)	36 (28-39)
HR (beats.min <sup>-1</sup> )		
Controls	58 (46-68)	74 (72-86) <sup>*</sup>
Patients	66 (49-78)	75 (64-97) <sup>*†</sup>
SV (%)		
Controls	100	68 (54-85) <sup>*</sup>
Patients	100	54 (45-59) <sup>*†</sup>
CO (%)		
Controls	100	93 (75-109)
Patients	100	66 (58-79) <sup>*†</sup>
TPR (%)		
Controls	100	113 (93-126)
Patients	100	84 (58-115) <sup>†</sup>
TI (Ohm)		
Controls	57 (47-80)	60 (54-80)
Patients	56 (47-66)	60 (55-64)

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**Table 3. Cardiovascular and cerebral responses to leg crossing in standing position**

Mean arterial pressure at heart ( $MAP_{\text{heart}}$ ) and brain level ( $MAP_{\text{mca}}$ ), middle cerebral artery mean blood velocity ( $MCA V_{\text{mean}}$ ), oxy- and deoxyhemoglobin ( $O_2Hb$  and  $HHb$ ) end-tidal  $CO_2$  ( $P_{\text{ET}}CO_2$ ), heart rate (HR), stroke volume (SV), cardiac output (CO), total peripheral resistance (TPR), and thoracic electrical impedance (TI). Data are median and range. \*  $P < 0.05$  in comparison to standing before leg cross, †  $P < 0.05$  patients vs. controls.

	Standing	Leg cross	Standing
$MAP_{\text{heart}}$ (mmHg)			
Controls	84 (70-95)	90 (74-94)	86 (70-94)
Patients	58 (42-79) <sup>†</sup>	72 (52-89)*	60 (41-82) <sup>†</sup>
$MAP_{\text{mca}}$ (mmHg)			
Controls	62 (56-73)	71 (59-72)	64 (55-72)
Patients	36 (19-58) <sup>†</sup>	50 (28-73)*	39 (17-62) <sup>†</sup>
$MCA V_{\text{mean}}$ ( $cm.s^{-1}$ )			
Controls	56 (46-77)	64 (46-80)*	57 (47-72)
Patients	55 (38-77)	63 (45-80)*	57 (38-78)
$\Delta O_2Hb$ ( $\mu mol.l^{-1}$ )			
Controls	0	0.83 (-0.11-2.04)	0.69 (-0.11-0.93)
Patients	0	1.12 (0.52-3.27)*	0.46 (-0.12-0.89)
$\Delta HHb$ ( $\mu mol.l^{-1}$ )			
Controls	0	-0.33 (-0.92- 0.01)	-0.05 (-0.80- 0.45)
Patients	0	-0.53 (-2.33- 0.16)	0.07 (-0.23- 0.66)
$P_{\text{ET}}CO_2$ (mmHg)			
Controls	35 (31-38)	35 (34-42)	35 (33-40)
Patients	36 (28-39)	36 (29-40)	35 (29-39)
HR ( $beats.min^{-1}$ )			
Controls	74 (72-86)	71 (58-79) <sup>†</sup>	73 (65-83)
Patients	75 (64-97)	75 (59-92)	74 (63-95)
SV (%)			
Controls	68 (54-85)	84 (73-102)*	69 (61-92)
Patients	54 (45-59) <sup>†</sup>	62 (56-69) <sup>*†</sup>	53 (43-61) <sup>†</sup>
CO (%)			
Controls	93 (75-109)	103 (91-119)*	88 (82-114)
Patients	66 (58-79) <sup>†</sup>	72 (66-95) <sup>*†</sup>	67 (51-83) <sup>†</sup>
TPR (%)			
Controls	113 (93-126)	105 (82-117)	112 (81-124)
Patients	84 (58-115) <sup>†</sup>	95 (68-118)*	89 (65-113)
TI (Ohm)			
Controls	60 (54-80)	60 (54-78)	61 (54-80)
Patients	60 (55-64)	60 (55-64)	60 (55-64)

## Legends to Figures

### Figure 1

#### Leg crossing in a patient with pure autonomic failure

Written informed consent of the patient was obtained for the photograph. Solid box, leg crossing and open boxes, standing legs uncrossed. Leg crossing induced an instantaneous increase in arterial pressure (BP), and cerebral blood velocity (CBV) and oxygenation ( $O_2Hb$ ) with a reduction in thoracic electrical impedance (TI) indicating an acute increase in thoracic blood volume.

### Figure 2

#### 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. Arterial pressure (BP), cerebral blood velocity ( $V_{mean}$ ), oxyhemoglobin ( $O_2Hb$ ), thoracic electrical impedance (TI), end-tidal  $CO_2$  ( $P_{ET}CO_2$ ).

### Figure 3

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

Recordings obtained in 3 separate experimental runs are superimposed. Mean arterial pressure (MAP), middle cerebral artery mean blood velocity ( $V_{mean}$ ), oxyhemoglobin ( $O_2Hb$ ), thoracic electrical impedance (TI), heart rate (HR), stroke volume (SV), cardiac output (CO), total peripheral resistance (TPR), end-tidal  $CO_2$  ( $P_{ET}CO_2$ ).

**Figure 4****Cardiovascular and cerebral perfusion and oxygenation responses to leg crossing**

Solid box, leg crossing; open box, standing. *Bold lines*, patients and *thin lines*, controls (averaged responses). Effects on mean arterial pressure (MAP), middle cerebral artery mean blood velocity ( $V_{\text{mean}}$ ), oxyhemoglobin ( $\text{O}_2\text{Hb}$ ), thoracic electrical impedance (TI), heart rate (HR), stroke volume (SV), cardiac output (CO), total peripheral resistance (TPR), end-tidal  $\text{CO}_2$  ( $\text{P}_{\text{ET}}\text{CO}_2$ ).

**Figure 5****Relationship between mean arterial pressure (MAP), cardiac output (CO) and middle cerebral artery mean blood velocity ( $V_{\text{mean}}$ ) during leg crossing**

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

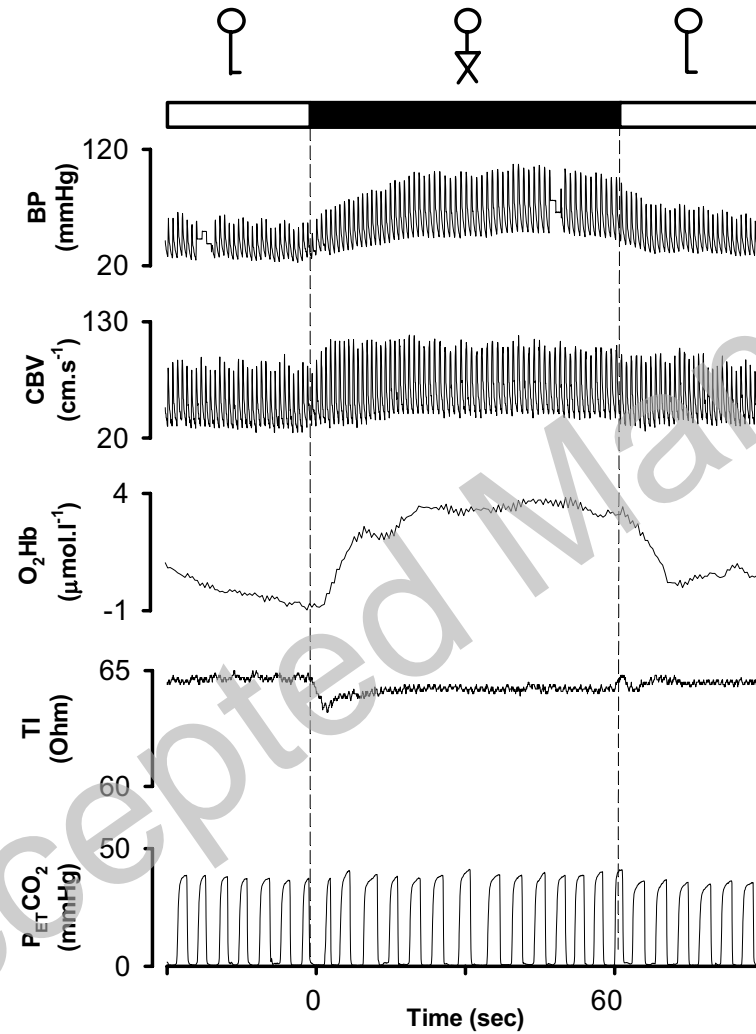


Figure 1



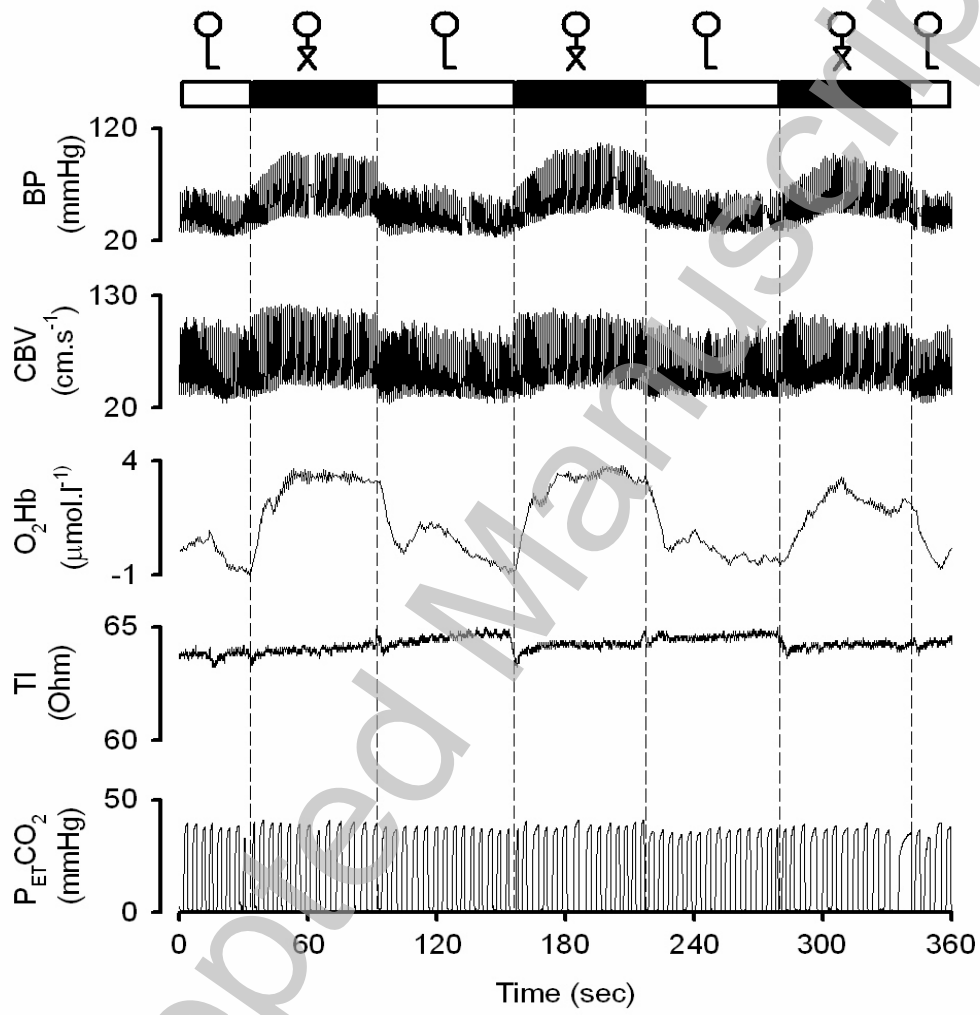


Figure 2

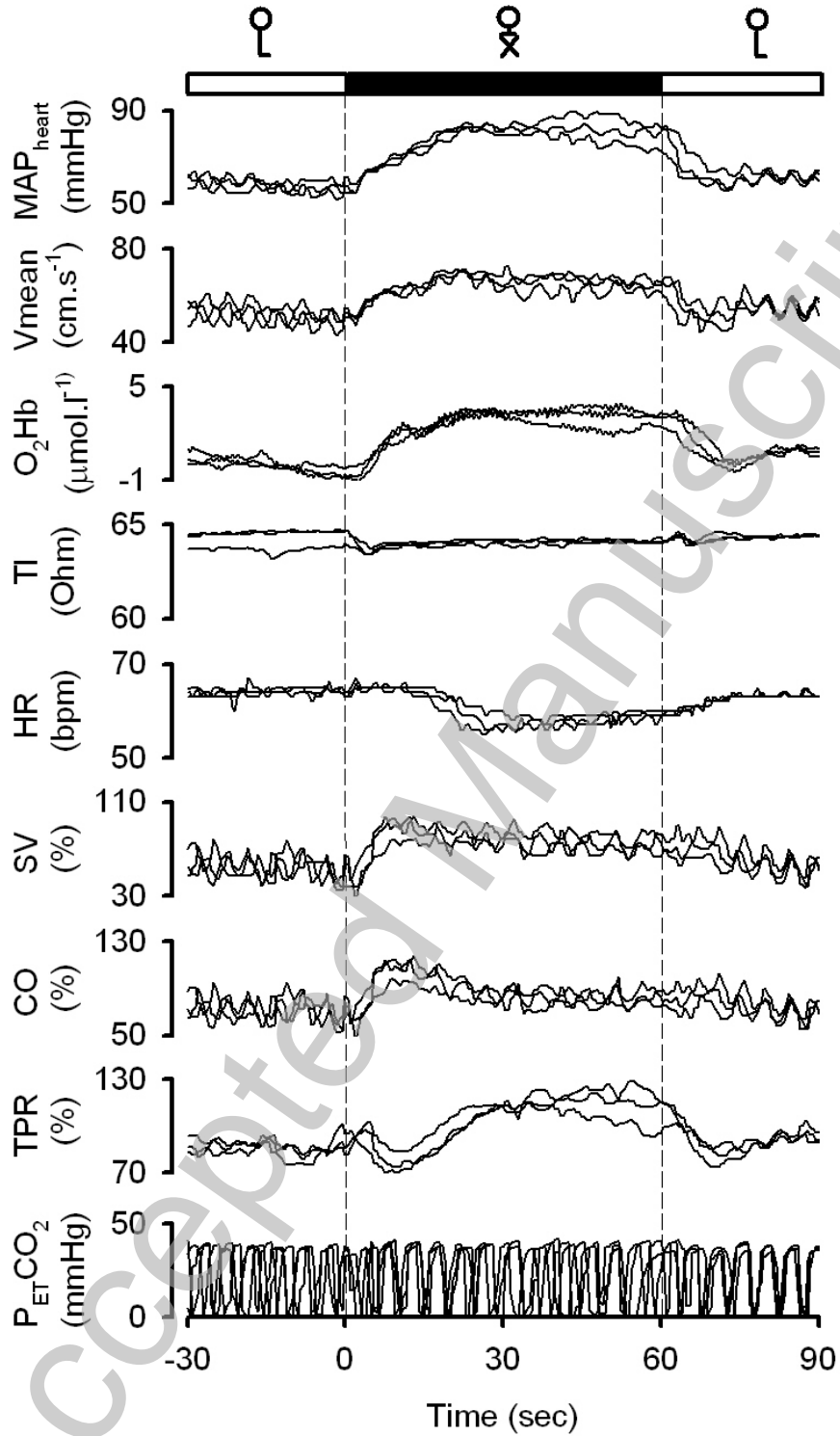


Figure 3

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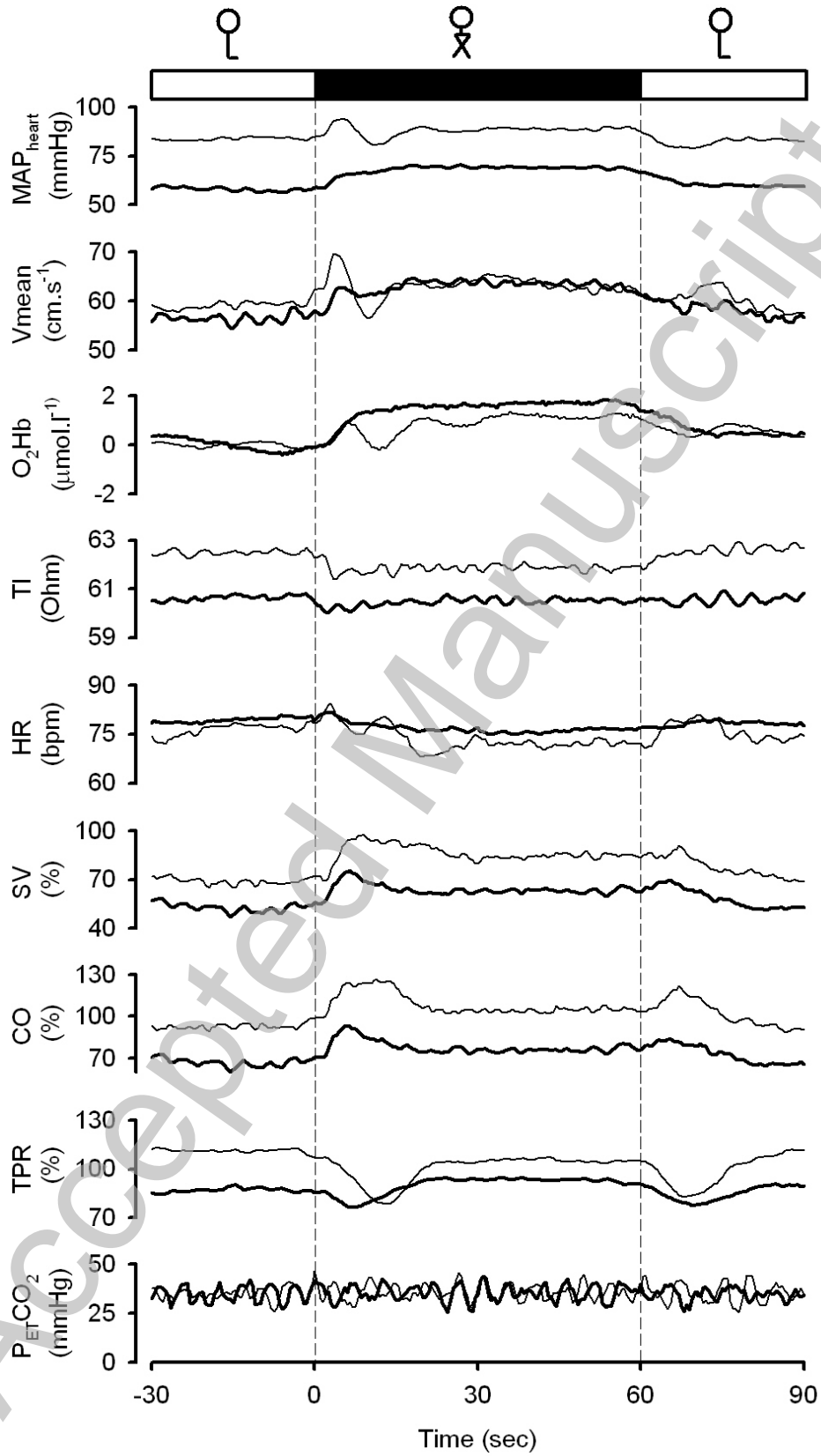


Figure 4

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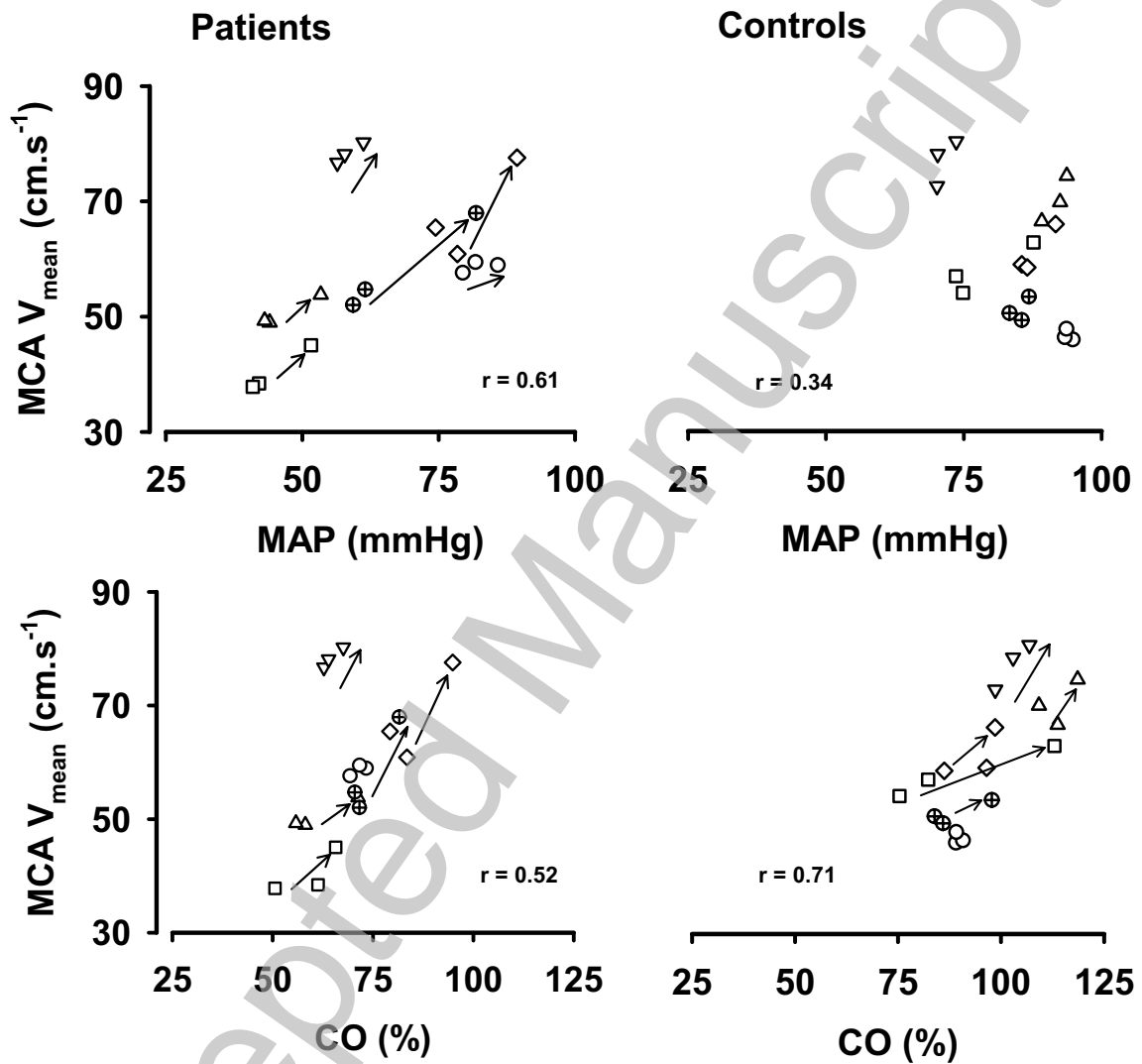


Figure 5

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