Leg crossing improves orthostatic tolerance in healthy subjects: a placebo-controlled crossover study

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Krediet, C. T. Paul, Johannes J. van Lieshout, Lysander W. J. Bogert, Rogier V. Immink, Yu-Sok Kim, and Wouter Wieling. Leg crossing improves orthostatic tolerance in healthy subjects: a placebo-controlled crossover study. Am J Physiol Heart Circ Physiol 291: H1768–H1772, 2006.—Vasovagal syncope is the most common cause of transient loss of consciousness, and recurrent vasovagal fainting has a profound impact on quality of life. Physical countermeasures are applied as a means of tertiary prevention but have so far only proven useful at the onset of a faint. This placebo-controlled crossover study tested the hypothesis that leg crossing increases orthostatic tolerance. Nine naive healthy subjects [6 females, median age 25 yr (range 20–41 yr), mean body mass index 23 (SD 2)] were subjected to passive head-up tilt combined with a graded lower body negative pressure challenge (20, 40, and 60 mmHg) determining orthostatic tolerance thrice, in randomized order: 1) control, 2) with leg crossing, and 3) with oral placebo. Blood pressure (Finometer), heart rate, and changes in thoracic blood volume (impedance), stroke volume, and cardiac output (Modelflow) were followed during orthostatic stress. Primary outcome was time to presyncope (systolic blood pressure ≤85 mmHg, heart rate ≥140 beats/min). With leg crossing, orthostatic tolerance increased from 26 ± 2 to 34 ± 2 min (placebo 23 ± 3 min, P < 0.001). During leg crossing, mean arterial pressure (81 vs. 81 mmHg) and cardiac output (95 vs. 94% supine) remained unchanged; heart rate increase was lower (13 vs. 18 beats/min; P < 0.05); stroke volume was higher (79 vs. 74% supine, P < 0.05); and there was a trend toward lower thoracic impedance. Leg crossing increases orthostatic tolerance in healthy human subjects. As a measure of prevention, it is a worthwhile addition to the management of vasovagal syncope.

Physical countermeasures such as leg crossing combined with leg, buttock, and abdominal muscle tensing (13, 15), and isometric arm exercise (1, 13) have been introduced as effective measures in aborting an impending vasovagal faint. Although these maneuvers are helpful in managing vasovagal reactions, they are only a means of tertiary prevention: containing an evoked vasovagal reaction and thus preventing loss of consciousness. As a drawback, such maneuvers are only feasible for patients who recognize (if any) prodromal symptoms, and vasovagal reactions often return after the maneuver is terminated (1, 14, 15).

Aiming for leg crossing as secondary prevention for orthostatically induced vasovagal reactions, this study investigated the hypothesis that leg crossing (i.e., without additional muscle tensing) would improve orthostatic tolerance. We chose a human model for vasovagal syncope in a randomized crossover, placebo-controlled study design and applied progressive central blood volume depletion by combining head-up tilting with incremental lower body negative pressure (LBNP) to induce presyncope in healthy subjects (4, 16).

METHODS

After approval of the Medical Ethical Committee of the Academic Medical Center of the University of Amsterdam, nine subjects [6 women, median age 25 yr (range 20–41 yr), height 176 cm (SD 12), weight 72 kg (SD 12), and body mass index 23 kg/m² (SD 2)] responded to an advertisement in a national newspaper. Except for four subjects on oral contraceptives, they used no medications. All subjects had a normal exercise tolerance. Six had fainted previously, none of them had sought medical attention for it, and none had fainted in the previous year. Standard physical examination and ECG revealed no abnormalities. All subjects received a detailed demonstration of the protocol before giving written consent.

Protocol. In a crossover design, orthostatic tolerance was challenged at the same time of the day (±15 min) on three consecutive days. The tests were carried out J) without intervention, 2) with leg crossing, and 3) with oral placebo tablet (Albochin, FNA, Dutch generic) in randomized order. One hour (±5 min) before start of the test, subjects took the placebo with 50 ml of tap water. The investigators had informed the subjects that one aim of the study was to “compare the effects of leg crossing with those of this approved medication,” that they “expected the drug to stabilize the blood pressure,” and that the subjects would thus “sustain a more profound presyncope,” and that the subjects would thus “sustain a more profound presyncope.” Aiming for leg crossing as secondary prevention for orthostatically induced vasovagal reactions, this study investigated the hypothesis that leg crossing (i.e., without additional muscle tensing) would improve orthostatic tolerance. We chose a human model for vasovagal syncope in a randomized crossover, placebo-controlled study design and applied progressive central blood volume depletion by combining head-up tilting with incremental lower body negative pressure (LBNP) to induce presyncope in healthy subjects (4, 16).

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Subjects abstained from alcohol, tobacco, and caffeine from 24 h before the first test until after the third test. From 2 h before each test,
they also abstained from any other food or liquid intake (apart from the tap water with the placebo). Before the test, the subjects practiced leg crossing supervised by one of the investigators. During the maneuver, the subjects positioned both feet flat on the footboard of the tilt table, bearing weight on both without any specific leg tensing. The manner in which they crossed the legs (right over left or vice versa) was left to the subjects’ preferences and recorded.

Tests took place in a climate-controlled room at ambient air temperature of 21–23°C. Finger blood pressure (BP, Finometer, Finapres Medical Systems) and ECG (model 78341, Hewlett-Packard) were measured continuously. The cuff was applied to the midphalanx of the left hand and placed in the midaxillary line at heart level. Thoracic impedance (TI) was monitored each 15 s (C-Guard, Dammeter) as an index of thoracic blood volume. Two pairs of electrodes were positioned with an internal distance of 5 cm behind the right sternocleidomastoid muscle, and another pair was positioned in the left midaxillary line at the level of the xiphoid process.

After a LBPN box was fitted closely on a manually operated tilt table (after a design by R. Hainsworth, Leeds, UK, modifications by F. P. de Vries, AMC Medical Technological Development) at the level of the subjects’ iliac crests, further instrumentation, and a subsequent 5-min supine baseline period, subjects were 60° head-up tilted. When testing leg crossing, this maneuver commenced 3 min after onset of tilt. Through a window in the LBPN box, the investigators verified that the maneuver was performed correctly. After 20 min of head-up tilting, increasing LBPN (20, 40, and 60 mmHg) was added stepwise, applied for 10 min at each level. The protocol ended when systolic blood pressure fell to ≤85 mmHg or if heart rate (HR) was ≥140 beats/min and subjects were tilted horizontally.

Data acquisition and analysis. Signals of blood pressure and ECG were converted from analog to digital at 100 Hz (Beatscope 1.1, TNO-BMI) for off-line analysis. Cardiac stroke volume (SV) was calculated with the use of Modelflow (Beatscope 1.1). This methodology tracks rapid changes in SV accurately during postural stress and leg crossing compared with SV determined by inert gas rebreathing and Doppler ultrasound (25, 27). Mean arterial pressure (MAP) was the integral over one heart beat, and HR was the inverse of the pulse interval. Cardiac output (CO) was SV times HR. Total peripheral resistance (TPR) was MAP divided by CO, and pulse pressure (PP) was systolic minus diastolic pressure. SV, CO, and TPR are expressed relative to supine rest.

Off-line data were printed for visual inspection of beat-to-beat results. Beat-to-beat data were digitally transformed to resampled data at 1 Hz for analysis (Beatscope 1.1a, Finapres Medical Systems).

Outcomes. The primary outcome was orthostatic tolerance, defined as time (in min) of tilting to presyncope development of symptoms, such as light-headedness, profuse perspiration, abdominal discomfort, and systolic blood pressure ≤85 mmHg or HR ≥140 beats/min. Secondary outcomes were MAP, HR, SV, CO, PP, TPR, and TI at relevant stages during the test.

Statistics. The original study design (n = 21) had a power of 70% to demonstrate an effect on the primary outcome of 4 min (α: 0.05). After interim analysis for the primary end point after five subjects had been studied, the number of subjects in the study was adjusted to nine. For the primary outcome, a value of P < 0.01 was then considered significant. For all other variables, the P value for significance remained P < 0.05.

Unless otherwise indicated, data that are considered to fit a normal distribution in the general population (i.e., hemodynamic variables and orthostatic tolerance) are expressed as means ± SE. Intraindividual differences in orthostatic tolerance in the three tested conditions were compared by paired t-tests. To control for the potential accumulated type I error, the P value for significance was adjusted to <0.005. Differences in secondary outcomes were only tested between control and leg crossing.

RESULTS

Leg crossing and orthostatic tolerance. Six subjects crossed the right over the left leg, the remaining vice versa. At the start of tilt back, all subjects met the predefined criteria for presyncope. Figure 1 compares the hemodynamic variables in the control and leg crossing test during the first 27 min of the protocol. This time frame was chosen because shortly after the 27th minute, several subjects were tilted back, and from this instant on, the scatter of the results of the remaining subjects became too large to provide for a realistic plot lacking statistical power. With the differences in tolerated tilt time per individual and per intervention accounted for, the responses for MAP, PP, and HR in the late stages are given in Fig. 2, grouped per intervention in all subjects relative to the time of start of tilt back (i.e., from 5 min before to 2 min after tilt back).

Table 1 gives the prevailing values for BP and HR measured at the start of tilt back. Within subjects, the tolerated tilt time differed with condition (no intervention vs. placebo vs. leg crossing), but BP and HR responses before tilt back were similar for each subject on 3 days (Fig. 2). With leg crossing, all subjects sustained a greater orthostatic challenge than dur-

Fig. 1. Hemodynamic variables during the first 27 min of protocols (n = 9; from 13 min, n = 8 when subject 5 was tilted back during control study). Data are averaged over 30 s. Solid circles, control; open circles, leg crossing; TI, thoracic impedance; CO, cardiac output; SV, stroke volume; PP, pulse pressure; HR, heart rate; MAP, mean arterial pressure; HUT, head-up tilt; LBPN20, 20-mmHg lower body negative pressure. Values are means ± SE. *P < 0.05, **P < 0.01.
ing control or with placebo (34 ± 2 vs. 26 ± 2 vs. 23 ± 3 min; P < 0.001). There was no significant difference in orthostatic tolerance between control and placebo (Fig. 3).

Hemodynamic effects of leg crossing. From 5 to 20 min of head-up tilting with leg crossing, MAP was not different from control (81 vs. 81 mmHg; Fig. 3), but the increase in HR compared with the supine position remained lower (+13 vs. 18 beats/min; P < 0.05) and was accompanied by a larger SV (79 vs. 74% supine; P < 0.05) with CO and TPR unchanged (CO, 95 vs. 94% supine; TPR, 122 vs. 122% supine). There was a trend toward lower TI from the onset of leg crossing (Fig. 1).

DISCUSSION

This study shows that leg crossing (without additional leg tensing) enhances orthostatic tolerance in healthy subjects. The documented increase in orthostatic tolerance likely represents a factual improvement because BP and HR at the termination of the test did not differ with and without intervention. The average improvement in tolerance of 8 min (and to placebo, 11 min) may seem minor but compares well with studies that apply the same orthostatic stress to explore therapeutics such as water ingestion [5 min (22)] and salt loading [9 (9) and 12 min (2)].

The strengths of this study are in its randomized placebo-controlled design and the repeated measurements within 50 h in an accepted model. We used naïve subjects and controlled for learning effects and circadian variation in cardiovascular regulation. We did not control for menstrual cycle or phase of oral contraception because all measurements were performed within 50 h and are, therefore, not likely to have importantly influenced our results.

To maintain orthostatic tolerance, humans need to use the muscles in the legs to prevent accumulation of blood and fluid in dependent parts of the body (18, 19), but it is unresolved how much skeletal muscle activity is needed. Therefore, it may seem unfortunate that, in this study, there is no evaluation of how much activity leg crossing without additional active muscle tensing induced. However, this study was not set out to make such estimation where the studied intervention comprised leg crossing alone. We consider any changes in leg

Table 1. Blood pressure and heart rate at presyncope

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<th>Sex</th>
<th>Tilt time, min</th>
<th>SBP, mmHg</th>
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Average of three heartbeats before start of tilt back. SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate.

Fig. 2. Hemodynamic variables from 5 min before to 2 min after tilt back (n = 9). Data are averaged over 30-s intervals. Solid circles, control; open circles, leg crossing; shaded dots, placebo. Values are means ± SE. At this stage of the protocols, there are no significant differences between the three tested conditions.

Fig. 3. Individual orthostatic tolerances expressed as time to tilt back under the three tested conditions. Values are means ± SE. NS, nonsignificant.
muscle tension to originate from direct mechanical compression (i.e., impact on and from the crossing leg) and probably also from active skeletal muscle contraction to keep balance, as stance width (which is decreased during leg crossing) is a known determinant of leg muscle activity (11).

We used Modelflow to document relative changes in SV (12), and for this purpose, the method has been validated during active and passive postural stress [against thermodilution (10) and Doppler ultrasound (27)] and leg crossing [against gas rebreathing (25)].

From previous work, it is known that, at the onset of skeletal muscle contractions in the lower body, central venous pressure rises and right atrial pressure increases (28). This causes instant reflex sympathetic withdrawal, more pronounced in the upright than in the supine position (21), with a decrease in TPR and a subsequent transient arterial baroreflex-mediated HR increase.

After some three heart beats, the translocated blood has passed through the pulmonary circulation to contribute to left ventricular SV (28). The resulting surge in CO and decrease in TPR subside, and within 1–2 min, BP, CO, and TPR return to baseline values. In addition to previous work that focused on the response during 1 (24) or 2 min (25) of leg crossing, this study documents the sustained increase in SV with reflex inhibition of HR. The trend toward a lower TI conforms to an elevated cardiac preload as a result of reduced leg venous pooling capacity. Salt loading studies show that increases in circulating volume of only 4–5% can increase orthostatic tolerance to 5–6 min in the same head-up tilt-LBNP protocol as used in the present study (20).

In an earlier supine study using LBNP, Smith et al. (23) found a stabilizing effect on orthostatic tolerance from leg contractions at 5 to 10% of maximum voluntary contraction force. In addition hereto, our study shows that very low increases in skeletal muscle tone, such as from leg crossing (with no extra voluntary force involved), have a similar effect, and with Smith et al. (23), we emphasize the importance of ensuring a relaxed state during interventions such as LBNP if valid observations are to be made.

Apart from the hemodynamic mechanism of the gained orthostatic tolerance, other factors should be taken into account. Standing with the legs crossed is likely to affect the motor programs for keeping balance by decreasing stance width (11). Via central command mechanisms, this may influence baroreflex sensitivity (6) and, subsequently, orthostatic tolerance.

In 1928, Ghrist and Brown (7) described the stabilizing hemodynamic effects of leg crossing in a patient with autonomic failure, and after systematic investigations in the 1980–1990s, leg crossing is an integrated part in the treatment of chronic orthostatic hypotension. In a recent multicenter trial (26), leg crossing as tertiary prevention for vasovagal syncope showed its clinically significant effect on syncope burden. The present study shows the efficacy of leg crossing as a secondary prevention measure. Apart from those with motor disabilities, this essentially costless therapy is feasible in all subjects, including those without prodromal symptoms.

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GRANTS

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