Initial orthostatic hypotension and cerebral blood flow regulation: effect of \(\alpha_1\)-adrenoceptor activity

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Lewis NCS, Ainslie PN, Atkinson G, Jones H, Grant EJ, Lucas SJE. Initial orthostatic hypotension and cerebral blood flow regulation: effect of \(\alpha_1\)-adrenoceptor activity. Am J Physiol Regul Integr Comp Physiol 304: R147–R154, 2013. First published November 21, 2012; doi:10.1152/ajpregu.00427.2012.—We examined the hypothesis that \(\alpha_1\)-adrenergic blockade would lead to an inability to correct initial orthostatic hypotension (IOH) and cerebral hypoperfusion, leading to symptoms of presyncope. Twelve normotensive humans (aged 25 ± 1 yr; means ± SE) attempted to complete a 3-min upright stand, 90 min after the administration of either \(\alpha_1\)-blockade (prazosin, 1 mg/20 kg body wt) or placebo. Continuous beat-to-beat measurements of middle cerebral artery velocity (MCAv; Doppler), blood pressure (finometer), heart rate, and end-tidal PCO2 were obtained. Compared with placebo, the \(\alpha_1\)-blockade reduced resting mean arterial blood pressure (MAP) (−15%; \(P < 0.01\)); MCAv remained unaltered (\(P \geq 0.28\)). Upon standing, although the absolute level of MAP was lower following \(\alpha_1\)-blockade (39 ± 10 mmHg vs. 51 ± 14 mmHg), the relative difference in IOH was negligible in both trials (mean difference in MAP: 2 ± 2 mmHg; \(P = 0.50\)). Compared with the placebo trial, the declines in MCAv and PETCO2 during IOH were greater in the \(\alpha_1\)-blockade trial by 12 ± 4 cm/s and 4.4 ± 1.3 mmHg, respectively (\(P \leq 0.01\)). Standing tolerance was markedly reduced in the \(\alpha_1\)-blockade trial (75 ± 17 s vs. 180 ± 0 s; \(P < 0.001\)). In summary, while IOH was little affected by \(\alpha_1\)-blockade, the associated decline in MCAv was greater in the blockade condition. Unlike in the placebo trial, the extent of IOH and cerebral hypoperfusion failed to recover toward baseline in the \(\alpha_1\)-blockade trial leading to presyncope. Although the development of IOH is not influenced by the \(\alpha_1\)-adrenergic receptor pathway, this pathway is critical in the recovery from IOH to prevent cerebral hypoperfusion and ultimately syncope.

cerebral blood flow; blood pressure; syncope

INITIAL ORTHOSTATIC HYPOTENSION (IOH) is defined in physiological terms as an exaggerated transient fall in blood pressure (BP) [systolic BP (SBP) >40 mmHg and/or diastolic BP (DBP) >20 mmHg] within 15 s of standing (41, 44, 50). Such IOH is commonly associated with syncope or short-lasting symptoms of presyncope (light-headedness, visual disturbances, and nausea), precipitated by insufficient cerebral perfusion (41). Although the prevalence of IOH increases with age (~20% in those >65 yr; ~30% in those >74 yr), IOH also has a reported incidence of ~4% in young adults (9). Upon standing, gravitational force causes ~0.5 to 1.0 liter of thoracic blood to pool in the lower extremities (36), leading to a reduction in venous return and a transient decrease in stroke volume (SV) and cardiac output (Q). The resultant fall in BP activates the baroreflex, resulting in an increased sympathetic outflow in attempt to restore Q and BP via an increase in heart rate (HR) and total peripheral vascular resistance (TPR) (39). Evidence indicates that the increase in TPR is more effective than the increase in Q for restoring BP during postural stress (39, 40, 42, 49). Sympathetic activation upon the vasculature is mediated predominantly via the \(\alpha_1\)-adrenergic receptor pathway (10); thus, \(\alpha_1\)-adrenergic vasoconstrictor activity has an imperative role in BP regulation during postural stress via affecting increases in TPR (7). In addition to the central sympathetic control upon the arterial vasculature, local sympathetic control involving the venoarteriolar reflex has been shown to account for 45% of the increase in TPR during standing (16, 21). Such venoarteriolar reflex is thought to involve an \(\alpha\)-adrenergic sympathetic axon reflex mechanism (15, 16, 21, 48). Nevertheless, the contribution of the \(\alpha_1\)-adrenergic sympathetic pathway in determining the extent of IOH during active standing remains to be quantified.

Near simultaneous to the decline in BP, cerebral blood flow (CBF) is also reduced upon standing (17, 32, 41). Although this decline in CBF is predominantly influenced by systemic hypotension, the decline in CBF takes place even when perfusion pressure remains within what is considered to be its autoregulatory range (17). The corrective response of cerebral autoregulation (CA) to restore CBF lags by ~10 s (53), and given that BP is not restored fully until ~30 s after standing (40), the initial stages of standing represent a critical period in which cerebral hypoperfusion and syncope may occur. Some evidence supports a role of sympathetic neural control in the regulation of dynamic CA during acute hypotension in humans (14, 30, 53). Although these previous findings provide valuable information, the stimulus used to elicit acute hypotension (i.e., thigh cuff deflation, oscillatory lower body negative pressure, and drug infusion) do not physiologically represent a normal physical challenge that humans experience daily. Therefore, the influence of \(\alpha_1\)-adrenergic vasoconstrictor activity upon CBF during active standing to elicit a normal hypertensive stress, and how it may influence the potential development of syncopal symptoms, remains to be explored.

Therefore, we aimed to explore the effect of \(\alpha_1\)-adrenoceptor blockade on the development of and recovery from IOH induced by active standing, and the concurrent regulation of...
STANDING: EFFECT OF α1-BLOCKADE

CBF. We hypothesized that α1-adrenergic blockade would exaggerate the development of IOH (i.e., the relative decline in SBP and DBP) and the associated decline in CBF, and presyncope symptoms would be more pronounced. To address this hypothesis, we used the selective α1-sympathetic receptor blocker, prazosin, as it has been shown to induce systemic peripheral arterial dilation and venodilation via this mechanism (3, 19).

METHODS

Participants. Twelve healthy normotensive volunteers (8 male; 4 female) with a mean ± SE age of 25 ± 1 yr, body mass 73 ± 3 kg, height 172 ± 1 cm, and body mass index 24 ± 3 kg/m², were recruited for this crossover experiment. This study was approved by the Human Ethics Committee of the University of Otago and conformed to the standards set by the Declaration of Helsinki. All participants completed a health-related questionnaire to ensure they met the relevant inclusion and exclusion criteria: being normotensive (systolic BP < 130 and diastolic BP < 85 mmHg); nonsmokers, no history of cardiovascular, cerebrovascular or respiratory diseases or frequent recurrent episodes of syncope and/or related symptoms; and medication-free other than the oral contraceptive pill. The majority of participants were recreationally active, typically engaging in low- (e.g., walking) and moderate- (e.g., jogging, stationary bike) intensity aerobic activities (2–3 days/wk). Female participants were tested in the early follicular phase (days 1–7) of the menstrual cycle determined by the first day of menstruation, or during menstruation of the pill withdrawal phase (at approximately days 2–7). Although the same participants in the current study were also involved in an earlier published study (24), none of the data presented here is duplicated from that study.

Experimental design. Participants attended the laboratory on three occasions, each separated by ≥36 h. The first visit consisted of familiarization with experimental equipment and protocols, along with the measurement of height and body mass. For the following two visits, participants engaged in the experimental protocol at ~0630 following an overnight stay at the laboratory to control for physical activity and diet. Participants reported to the laboratory the previous evening by 2230, ready for nocturnal sleep. Ninety minutes prior to start of the experimental protocol, inclusive of setup (0440), participants orally consumed the α1-adrenoceptor blocker, prazosin (1 mg/20 kg body mass), or an identical placebo (empty capsule). This acceptable clinical dose of prazosin has previously been used by others and has been shown to have a functional block of ~80% (20, 29). The 90 to 180 min postingestion period was appropriate for the peak activity of prazosin (18, 20). Physical activity was limited to a 10–15-m walk to the bathroom 90 min prior to the start of the experimental session (i.e., following prazosin or placebo ingestion). Participants voided their bladder and provided a urine sample. This was used to evaluate the preexperimental hydration status through the measurement of urine specific gravity (USG) using a hand-held clinical refractometer (Atago Hand Refractometer, Astra Zeneca, Osaka, Japan). USG between the placebo trial (1.027 ± 0.005 USG) and prazosin trial (1.024 ± 0.002 USG) did not differ (P = 0.81). All experimental sessions were double-blinded to the participants and researchers, apart from a research technician not otherwise involved in the study, who organized the administration of the capsules (completed in a randomized order). Experimental testing began after a 24-h abstinence from alcohol and strenuous exercise and a 12-h abstinence from caffeine, and it occurred in a climate-controlled laboratory (22–23°C).

Experimental protocol. Following instrumentation, participants completed a 20-min supine rest period. Upon instruction, participants rapidly assumed an upright standing position within 3 s. Participants were instructed to swing their legs around and off the bed and stand up in one smooth motion, using their right hand as support (to avoid disturbing the recordings of BP made with the sphygmomanometer on the left hand). To ensure ease of transition from a supine to standing position, the bed height was adjusted for the height of each individual. Participants were required to remain standing for 3 min or until the onset of presyncope. Previously defined indices for IOH associated with standing were adopted: a decrease in SBP > 40 mmHg and/or a decrease in DBP > 20 mmHg within the first 15 s of standing (25, 41, 50). Presyncope was defined by a drop in SBP below 80 mmHg for more than 10 s or at the participant’s request due to one or more subjective presyncopal symptoms becoming intolerable (feelings of dizziness, nausea, faintness, visual disturbances, hearing disturbances, and fatigue). The time of the stand was taken from the moment the participant started to rise from the supine position. Participants were instructed not to speak, to breathe normally, and remain still to reduce any influence of the skeletal muscle pump. Presyncopal symptoms were recorded using a validated questionnaire (41) immediately on the return back to the supine position. Participants were asked to rate their symptoms based upon a visual scale from 1 to 10 (with 1 being no symptoms to 10 being intolerable) for the time related to the end of the challenge (i.e., at 3 min or the point of presyncope).

Measurements. Middle cerebral artery blood flow velocity (MCAv), BP, HR, and the partial pressure end-tidal carbon dioxide (PetCO₂) were recorded continuously. Beat-to-beat blood flow velocity in the right middle cerebral artery was measured using a 2-MHz pulsed Doppler ultrasound system (DWL Doppler; Compumedics, Singen, Germany). Using previously described search methods (1, 51), we maintained the Doppler probe in position, at a fixed angle, using a commercially available fixation headframe (Marc 600; Spencer Technologies, Northborough, MA). Beat-to-beat BP was measured by finger photoplethysmography (Finapres Medical Systems, Biomedical Instruments, Amsterdam, The Netherlands), and HR was recorded via a three-lead electrocardiography (ECG; ML132, ADInstruments, Colorado Springs CO). Manual sphygmomanometer BP recordings were obtained during supine rest prior to standing, to confirm the accuracy of the finger photoplethysmography measurements. Stroke volume and Q were calculated from the BP waveform obtained from the finger photoplethysmography using the Modelflow method, incorporating age, sex, height, and weight (BeatScope 1.0 software; TNO TPD; Biomedical Instruments, Chantilly, VA). Total peripheral resistance index (TPRi) was calculated from mean arterial BP (MAP)/Q. Cerebrovascular resistance index (CVRi) was calculated as MAP/mean MCAv. Cerebrovascular conductance index (CVCi) was calculated as mean MCAv/MAP. PetCO₂ was sampled from a leak-free facemask, attached to a Y-shaped, two-way nonrebreathing valve (7900 series; Hans-Rudolph, Kansas City, MO). All data were sampled continuously at 200 Hz using an analog-digital converter (PowerLab/16SP ML795; ADInstruments) interfaced with a computer and displayed in real time during testing. Data were stored for subsequent off-line analysis using the commercially available Chart software (v7, ADInstruments).

Resting dynamic CA was assessed using transfer function analysis (TFA). Beat-to-beat MAP and mean MCAv signals recorded during supine baseline conditions were then cubic spline interpolated and resampled at 4 Hz for spectral and TFA based on the Welch algorithm. Each 5-min recording was first subdivided into five successive windows that overlapped by 50%. The data within each window were linearly detrended, passed through a Hamming window, and subjected to fast Fourier transform analysis. For TFA, the cross spectrum between MAP and mean MCAv was determined and divided by the MAP autospectrum to derive the transfer function gain, phase, and coherence indices. Spontaneous MAP and mean MCAv spectral powers, the mean value of transfer function coherence, gain, and phase were calculated in the very low (VLF, 0.02–0.07 Hz) and low (LF, 0.07–0.20 Hz) frequency ranges where CA is thought to be operant (43). To ensure that robust phase and gain estimates within the VLF and LF bands were entered for subsequent analysis, we averaged measured powers, the mean value of transfer function coherence, gain, and phase were calculated in the very low (VLF, 0.02–0.07 Hz) and low (LF, 0.07–0.20 Hz) frequency ranges where CA is thought to be operant (43). To ensure that robust phase and gain estimates within the VLF and LF bands were entered for subsequent analysis, we averaged
only those gain and phase values in which the corresponding coherence was ≥0.5. In the context of applications of this technique, impaired dynamic CA would manifest as increases in coherence and gain (11, 52) and reductions in phase (33). Conversely, strong CA would theoretically be associated with reductions in coherence and gain and increases in phase.

Data and statistical analysis. The analysis of the physiological responses during IOH is not straightforward, as the onset of IOH and the associated physiological response may both vary over time. Therefore, it is important to analyze all physiological responses relative to time elapsed during the orthostatic challenge. We adopted the summary statistics approach for analyzing this type of time-series data (2). We examined trial differences in our a priori selected summary statistics associated with IOH: baseline, time taken to reach the peak/nadir response during the first 30 s, the absolute decline from baseline for all participants from baseline. */H9251

RESULTS

Supine baseline. Compared with the placebo trial, the α1-blockade significantly reduced SBP, MAP, DBP, and CVRi, and increased CVCi; by −13 ± 4 mmHg, −14 ± 4 mmHg, −11 ± 3 mmHg, −0.23 ± 0.07 mmHg·cm·s−1, and +0.12 ± 0.03 cm·s−1/mmHg, respectively (P ≤ 0.02; Fig. 1). Although significance was not reached, TPRi was lower following the α1-blockade (13.9 ± 0.9 mmHg·l·min−1) compared with the placebo trial (15.9 ± 0.9 mmHg·l·min−1; P = 0.13). Mean MCAv, systolic MCAv (SMCAv), diastolic MCAv (DMCAv), and PETCO2 did not significantly differ between the two trials (P ≥ 0.28). Three participants were excluded from transfer function analysis due to either technical issues or they displayed coherence below 0.05; therefore, transfer function analysis was effectively conducted in nine participants. No between-trial differences in MCAv power, MAP power, or transfer function analysis metrics of gain, phase, and coherence were evident (P ≥ 0.17; n = 9; Table 1).

Initial orthostatic hypotension. All individuals (n = 12) experienced IOH in both the placebo and α1-blockade trials (Fig. 2), within 15 s of standing, with one exception in the α1-blockade trial in which one person did not reach their nadir until 16 s. The between-trial difference in the relative decline in SBP and DBP upon standing was negligible (Fig. 2), and the between-trial difference of the decline in MAP was 2 ± 2 mmHg (P = 0.50). Compared with the placebo trial, the absolute nadir for MAP and SBP was lower following α1-blockade (MAP: 51 ± 4 mmHg vs. 39 ± 3 mmHg; SBP: 80 ± 6 mmHg vs. 64 ± 4 mmHg; P ≤ 0.04; Fig. 1). The time course of the decline to nadir in SBP (9 ± 0 s), DBP (7 ± 1 s), and MAP (8 ± 0 s; Fig. 1) in the placebo condition occurred slightly sooner than in the α1-blockade trial (11 ± 1 s, 10 ± 1 s, and 11 ± 0 s, respectively; P ≤ 0.02). The increase in HR during the α1-blockade trial was greater than that seen in the placebo trial, with a mean difference of 17 ± 3 beats per

Fig. 1. A: Values are expressed as means ± SE change in mean arterial pressure (MAP), mean middle cerebral artery blood flow velocity (mean MCAv), total peripheral resistance index (TPRi), heart rate (HR), stroke volume (SV), cardiac output (Q), end-tidal CO2 (PETCO2), cerebral vascular resistance index (CVRi), and cerebral vascular conductance index (CVCi) from baseline (0) and across the first 30 s of standing. Data point after 10 s, 15 s, and 17 s represents 11, 10, and 9 participants, respectively. *α1-blockade condition significantly different from placebo condition (P ≤ 0.03). B: mean ± SE change at the end of standing for all participants from baseline. *α1-blockade condition significantly different from placebo condition (P ≤ 0.01).
minute ($P < 0.001$), and compared with the placebo trial, the time course of this increase took 4 ± 2 s longer in α1-blockade trial ($P = 0.05$; Fig. 1). The decline in SMCAv, DMCAv, mean MCAv, and $P_{ETCO_2}$ were all greater in the α1-blockade trial (placebo vs. blockade trial: −8 ± 5 cm/s vs. −26 ± 4 cm/s; −35 ± 3 cm/s vs. −43 ± 2 cm/s; −25 ± 3 cm/s vs. −37 ± 2 cm/s; and −3.5 ± 1.1 mmHg vs. −7.9 ± 1.0 mmHg, respectively; $P \leq 0.01$).

Standing tolerance. All participants successfully completed the 3-min stand in the placebo trial compared with only two participants completing the 3-min stand during the α1-blockade trial (Fig. 3A); tolerance time was reduced by 105 ± 17 s during the α1-blockade trial (Fig. 3B). Consistent with this reduced standing tolerance, overall presyncopal symptom scores (out of 70) collected at the end of the stand challenge during the α1-blockade trial (17 ± 3) were more pronounced than the placebo trial (1 ± 0; $P < 0.001$); the major symptoms experienced were dizziness, visual disturbances, fatigue, and nausea. All measured variables at the end of the stand challenge, apart from SMCAv and $P_{ETCO_2}$, were significantly different between the α1-blockade and placebo trials ($P \leq 0.03$; Fig. 1). Likewise, apart from SMCAv, the change from baseline at the end of the standing challenge was more pronounced in the α1-blockade trial compared with the placebo trial for all other measured variables (Table 2; $P \leq 0.04$). The trial difference in the decline from baseline to the end of the stand for TPRi did not reach significance; however, a trend of being 2.7 ± 1.5 mmHg·l·min$^{-1}$ more in the α1-blockade trial was evident ($P = 0.10$).

**DISCUSSION**

The current study examined the role of α1-sympathetic vasoconstriction in the regulation of CBF during and following recovery from IOH induced by active standing and the onset of syncopal symptoms. The primary new findings of this study are that the development of IOH was not exaggerated following α1-adrenergic blockade; however, the absolute level of MAP with IOH was lower following α1-blockade. Nevertheless, the associated decline in MCAv with IOH was greater. Unlike in the placebo trial, MAP failed to return toward baseline values following IOH, and a clear pressure-passive relationship between MAP and mean MCAv was evident, contributing to presyncope in all but two participants. These findings illustrate that although the development of IOH is not influenced by the α1-adrenergic receptor pathway, this reflex is critical in the recovery from IOH to prevent cerebral hypoperfusion and ultimately syncope.

**Supine rest: effect of α1-adrenergic blockade.** Oral ingestion of prazosin did not alter resting mean MCAv, despite a significant reduction (~15%) in resting MAP. Resting spontaneous transfer function gain, phase, and coherence were unaltered following the α1-blockade, providing evidence that spontaneous CA remains intact despite a static change in MAP. This finding fully supports that of Ogoh et al. (30), who suggested that CA mechanisms compensate for systemic hypotension induced by prazosin ingestion to maintain MCAv constant (in the absence of an orthostatic stress). Thus, consistent with other studies (14, 30, 38), our findings also support the notion that removal of sympathetic vasoconstrictor activity does not influence CBF regulation during supine rest.

**Effect of α1-adrenergic blockade on IOH.** Initial orthostatic hypotension is an exaggerated transient fall in SBP >40 mmHg and/or DBP >20 mmHg upon active standing. As

**Table 1. Summary of baseline (supine) spontaneous spectral and transfer function analysis**

<table>
<thead>
<tr>
<th></th>
<th>α1-Blockade</th>
<th>Placebo</th>
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<tbody>
<tr>
<td>MCAv spectral analysis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total power, (cm/s)$^2$</td>
<td>13.3 ± 2.2</td>
<td>12.9 ± 1.3</td>
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<tr>
<td>LF, (cm/s)$^2$</td>
<td>7.4 ± 1.2</td>
<td>6.9 ± 0.7</td>
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<tr>
<td>MAP spectral analysis</td>
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<tr>
<td>Total power, mmHg$^2$</td>
<td>10.4 ± 2.0</td>
<td>12.4 ± 2.9</td>
</tr>
<tr>
<td>LF, mmHg$^2$</td>
<td>7.8 ± 1.0</td>
<td>8.3 ± 1.6</td>
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<tr>
<td>Cerebral TFA</td>
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<tr>
<td>VLF coherence</td>
<td>0.5 ± 0.1</td>
<td>0.5 ± 0.1</td>
</tr>
<tr>
<td>LF coherence</td>
<td>0.7 ± 0.1</td>
<td>0.7 ± 0.1</td>
</tr>
<tr>
<td>VLF gain, cm/s/mmHg</td>
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<td>0.9 ± 0.2</td>
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<tr>
<td>LF gain, cm/s/mmHg</td>
<td>1.5 ± 0.1</td>
<td>1.3 ± 0.1</td>
</tr>
<tr>
<td>VLF phase, radians</td>
<td>0.8 ± 0.2</td>
<td>0.9 ± 0.1</td>
</tr>
<tr>
<td>LF phase, radians</td>
<td>0.5 ± 0.1</td>
<td>0.5 ± 0.05</td>
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</tbody>
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Values are expressed as means ± SE; n = 9. MCAv, middle cerebral artery velocity; MAP, mean arterial blood pressure; TFA, transfer function analysis; VLF, very low frequency; LF, low frequency.
lower limit of CA (60 mmHg), with the absolute MAP nadir being considerably lower (vs. placebo: 39 ± 10 vs. 51 ± 14 mmHg), and the duration below this threshold prior to reaching the point of nadir was longer in the α1-blockade trial. Therefore, there is the potential that the absolute decline seen in the α1-blockade trial exceeded CA capacity and is responsible for the exaggerated fall in MCAv. However, it is important to note that such specific limits of CA have not been defined within a subject population, and the brain is likely more pressure passive than originally considered (8, 27). Another important consideration is that the brain acts like a high-pass filter; for example, there is a close linear relation (high spectral coherence) between changes in pressure and flow that occur almost synchronously with no dampening (high gain) when pressure oscillations are relatively fast (less than ~10 s). However, as oscillations become slower (more than ~20 s), pressure and flow become less linearly related (13) Thus, the corrective response of CA to restore CBF lags by ~10 s (53) and is likely influenced by the magnitude of the drop in BP (27); therefore, because the BP was much lower following the α1-blockade trial, we feel that these factors explain the greater reduction in MCAv at this point.

Research has indicated that the decline in CBF during orthostatic stress is also dependent upon a decline in Q (4, 41, 45, 47); therefore, we cannot overlook the fact that the exaggerated decline in mean MCAv upon standing during the α1-adrenergic blockade trial may have been influenced by the decline seen in Q (Fig. 1). For example, we have previously reported that dynamic CA to acute supine hypotension (via bilateral thigh deflation) is impaired when pharmacologically blocking the arterial baroreflex-mediated tachycardia and consequent changes in cardiac output (31). Further, irrespective of the trial condition, the declines in MAP and MCAv upon standing that we observed were considerably greater than that

shown in Fig. 2, all individuals experienced IOH in both trials, and contrary to our hypothesis, the development of IOH (relative decline in BP) was not exaggerated following the α1-blockade. Therefore, the α1-adrenergic sympathtic pathweway does not contribute to the development of IOH during active standing. This finding supports the concept that rapid leg muscle vasodilation is the primary determinant of IOH onset (42).

Although the relative decline (magnitude) in MAP upon standing was similar between trials, the decline in mean MCAv in the α1-blockade trial was exaggerated. This finding is in agreement with Ogoh et al. (30), who found a greater decline in mean MCAv during an acute hypotensive stimulus (thigh cuff deflation) following prazosin, and provides further evidence that dynamic CA is impaired following α1-adrenergic blockade when BP is actively perturbed. Unlike Ogoh et al. (30), however, prazosin ingestion in the current study produced a ~15% reduction in supine MAP, and consequently, the range in which the absolute decline in MAP occurred was much lower in the α1-blockade trial. The traditional concept of static CA in humans suggests that CBF is maintained constant across a range of MAP between 60 and 150 mmHg (22). Indeed, the decrease (nadir) in MAP in both trials was below this so-called

<table>
<thead>
<tr>
<th>Experimental Condition</th>
<th>Placebo</th>
<th>α1-blockade</th>
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<tbody>
<tr>
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</tr>
<tr>
<td>Tolerance Time (s)</td>
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</tr>
<tr>
<td>Placebo</td>
<td>100</td>
<td>100</td>
</tr>
</tbody>
</table>

Fig. 3. A: survival proportion and number of participants left standing at a certain time point during the placebo and α1-blockade condition. Stand time was in seconds during the placebo and α1-blockade conditions. Stand time at 45, 47); therefore, we cannot overlook the fact that the exaggerated fall in MCAv. However, it is important to note that such specific limits of CA have not been defined within a subject population, and the brain is likely more pressure passive than originally considered (8, 27). Another important consideration is that the brain acts like a high-pass filter; for example, there is a close linear relation (high spectral coherence) between changes in pressure and flow that occur almost synchronously with no dampening (high gain) when pressure oscillations are relatively fast (less than ~10 s). However, as oscillations become slower (more than ~20 s), pressure and flow become less linearly related (13) Thus, the corrective response of CA to restore CBF lags by ~10 s (53) and is likely influenced by the magnitude of the drop in BP (27); therefore, because the BP was much lower following the α1-blockade trial, we feel that these factors explain the greater reduction in MCAv at this point.

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The change from baseline in the α1-blockade trial significantly different from placebo trial, P ≤ 0.04.
observed by Ogoh et al. (30) during thigh-cuff deflation to induce acute hypotension. This indicates that active standing is a more vigorous physiological challenge to assess cerebrovascular control in response to systemic hypotension. It was also intriguing to note the apparent disassociation in the assessment of cerebral perfusion regulation upon standing. The effects on spontaneous fluctuations (i.e., TFA) and stimulus-induced (i.e., IOH) manipulations in MAP, given that this approach was selectively confined to the latter. While each approach has its limitations with no universally accepted “gold standard” (51), it would appear that MAP needs to be actively forced to more reliably engage CA, and, thereby, improving its functional detection sensitivity. This can be further optimized in physiological challenges like IOH or via TFA of augmented sinusoidal MAP oscillations forced through repeated squat-stand or oscillatory lower-body negative-pressure maneuvers (13).

The effect of $\alpha_1$-adrenergic blockade on recovery from IOH. Unlike in the placebo trial, MAP failed to return toward baseline values following the onset of IOH. In agreement with others (40, 42, 49, 50), the recovery of IOH in the placebo condition was precipitated by an increase in TPRi and a well-maintained Q (the decline in SV being compensated by an increase in HR). However, in the $\alpha_1$-blockade trial, the lack of recovery in BP appears to be attributed to an inability to increase TPRi following IOH onset, resulting in a persistent attenuation in SV due to venous pooling and ultimately impairment in venous return. Although not significant, supine TPRi was 12% lower following prazosin, indicating baseline vasodilatation increased the capacity for blood pooling in the lower limbs. These findings support others (30) in highlighting the importance of the $\alpha_1$-adrenoreceptor pathway in the arterial baroreflex restoration of BP following acute hypotension, and emphasize the importance of the venous system on BP restoration.

Despite the exaggerated decline in mean MCAv with IOH in the $\alpha_1$-blockade trial, mean MCAv did recover transiently to comparable levels, as seen in the control trial within the first 30 s of standing. This recovery in mean MCAv appeared to be mediated by an increase in Q precipitated by an exaggerated increase in HR, and partial recovery of BP. Nevertheless, this recovery was short lived as mean MCAv quickly diminished (Fig. 1), and standing tolerance was substantially reduced in the $\alpha_1$-blockade trial, resulting in presyncope. This decline in mean MCAv was due to a collective fall in perfusion pressure (MAP) that was mediated via reductions in both TPRi and Q.

Interestingly, the decline in mean MCAv at the point of presyncope was predominantly influenced by the decline in DMCAv, as SMCAv was relatively maintained at presyncope. This observation is consistent with other reports of such a response during profound hypotension induced by orthostatic stress (35, 41) and pharmacological (27) interventions. We and others have previously suggested this maintenance of SMCAv is due to an increase in pulsatility flow in an attempt to preserve CBF (26, 27), due possibly to a paradoxical increase in cerebrovascular resistance (23). In agreement with a previous report (30), CVCi in the $\alpha_1$-blockade trial opposed the response seen in the placebo trial and remained elevated, reflecting a maintained cerebral vasodilation (Fig. 1). The maintenance of SMCAv may reflect that the effect of perfusion pressure upon mean MCAv was greater in the $\alpha_1$-blockade trial, but whether this increase in pulsatile flow is a result of an increase in CVRi remains questionable (23), as CVRi in $\alpha_1$-blockade trial was near baseline values (Fig. 1). Collectively, the findings in the present study further support the role of $\alpha_1$-adrenergic receptor activity in dynamic CA during active hypotension stress (31, 34).

Limitations. We measured blood flow velocity in the middle cerebral artery by transcranial Doppler (TCD) ultrasound. Previous reports have shown that MCA diameter changes little with acute hemodynamic perturbations (12), such as those elicited during the thigh-cuff release protocol (30). Therefore, and considering MCAv was unaltered following the prazosin, we are confident that TCD measures of the transient changes in MCAv reflect those of the transient changes in CBF (36a).

Perspectives and Significance

This study is the first to investigate the influence of the $\alpha_1$-adrenergic sympathetic pathway on the development of IOH and the concurrent effect on CBF during active standing—a physiologically relevant hypotensive stimulus that humans experience daily. Although the hypotensive actions of $\alpha_1$-adrenergic receptor inhibitors have been documented (5, 10, 46), the actions of $\alpha_1$-adrenergic receptor inhibition upon CBF regulation have received little attention. Ogoh et al. (30) reported that prazosin ingestion compromised CBF regulation and that there may potentially be a risk of cerebral hyperperfusion following a transient hypotensive stimulus. The findings of the current study indicate that following a more relevant
hypotensive stimulus (i.e., standing), cerebral hypoperfusion is exaggerated, increasing the risk of syncope. We acknowledge that patients with hypertension have high sympathetic nerve activity and increases in cerebrovascular resistance (28, 37) and that the actions of prazosin on the development of IOH and its influence upon CBF response in this population may differ from normotensive individuals, and thus warrants further investigation. Nevertheless, prazosin is not solely used in the treatment of hypertension; it is also used in other medical conditions, such as prostatic hyperplasia and posttraumatic stress disorder; therefore, such individuals may be at greater risk to experience syncope, with the development of IOH upon standing.

DISCLOSURES
No conflicts of interest, financial or otherwise, are declared by the authors.

AUTHOR CONTRIBUTIONS

REFERENCES


