Selective $\alpha_1$-adrenergic blockade disturbs the regional distribution of cerebral blood flow during static handgrip exercise


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Submitted 5 February 2016; accepted in final form 23 March 2016

Fernandes IA, Mattos JD, Campos MO, Machado AC, Rocha MP, Rocha NG, Vianna LC, Nobrega AC. Selective $\alpha_1$-adrenergic blockade disturbs the regional distribution of cerebral blood flow during static handgrip exercise. Am J Physiol Heart Circ Physiol 310: H1541–H1548, 2016. First published March 25, 2016; doi:10.1152/ajpheart.00125.2016.—Handgrip-induced increases in blood flow through the contralateral artery that supplies the cortical representation of the arm have been hypothesized as a consequence of neurovascular coupling and a resultant metabolic attenuation of sympathetic cerebral vasoconstriction. In contrast, sympathetic restraint, in theory, inhibits changes in perfusion of the cerebral ipsilateral blood vessels. To confirm whether sympathetic nerve activity modulates cerebral blood flow distribution during static handgrip (SHG) exercise, beat-to-beat contralateral and ipsilateral internal carotid artery blood flow (ICA; Doppler) and mean arterial pressure (MAP; Finometer) were simultaneously assessed in nine healthy men (27 ± 5 yr), both at rest and during a 2-min SHG bout (30% maximal voluntary contraction), under two experimental conditions: 1) control and 2) $\alpha_1$-adrenergic receptor blockade. End-tidal carbon dioxide (rebreathing system) was clamped throughout the study. SHG induced increases in MAP (+31.4 ± 10.7 mmHg, $P < 0.05$) and contralateral ICA blood flow (+80.9 ± 62.5 ml/min, $P < 0.05$), while no changes were observed in the ipsilateral vessel (−9.8 ± 39.3 ml/min, $P > 0.05$). The reduction in ipsilateral ICA vascular conductance (VC) was greater compared with contralateral ICA (contralateral: −0.8 ± 0.8 vs. ipsilateral: −2.6 ± 1.3 ml·min$^{-1}$·mmHg$^{-1}$, $P < 0.05$). Prazosin was effective to induce $\alpha_1$-blockade since phenylephrine-induced increases in MAP were greatly reduced ($P < 0.05$). Under $\alpha_1$-adrenergic receptor blockade, SHG evoked smaller MAP responses (+19.4 ± 9.2, $P < 0.05$) but similar increases in ICA’s blood flow (contralateral: +58.4 ± 21.5 vs. ipsilateral: +54.3 ± 46.2 ml/min, $P > 0.05$) and decreases in VC (contralateral: −0.4 ± 0.7 vs. ipsilateral: −0.4 ± 1.0 ml·min$^{-1}$·mmHg$^{-1}$, $P > 0.05$). These findings indicate a role of sympathetic nerve activity in the regulation of cerebral blood flow distribution during SHG.

NEW & NOTEWORTHY

Sympathetic nerve activity plays a role in the distribution of regional cerebral blood flow during handgrip exercise.

Voluntary muscle contraction increases neuronal activation and brain metabolism and is tightly coupled to changes in cerebral perfusion (29, 31, 37). Regional increases in blood oxygen level-dependent signal, for example, have been reported in the contralateral primary motor cortex and cerebellar nuclei and cortex in response to simple motor tasks such as static handgrip exercise (SHG) (29). Similarly, increases in blood velocity through the intracranial arteries that supply arm (17) and leg (33) cortical representations were observed during unilateral forearm and calf exercises, respectively. Despite the marked increases in arterial and cerebral perfusion pressures in response to forearm muscle contraction, no hemodynamic changes have been reported in cortical areas (29) or intracranial blood vessels (17) in the ipsilateral hemisphere of the brain. Neurovascular coupling has been suggested to be the underlying mechanism of regional hyperemia (7), whereas the brain’s capacity of buffering arterial pressure fluctuations (i.e., cerebral autoregulation) may avoid increases in ipsilateral hemispheric perfusion.

In addition to cerebral autoregulation, the adrenergic innervation of pial arteries (9) and jugular venous norepinephrine overflow (20) provide anatomical and functional support for sympathetic nerve activity in the regulation of ipsilateral hemispheric perfusion. Furthermore, sympathetic nerve activity appears to impact cerebral autoregulation because the capacity of buffering arterial pressure fluctuation is impaired after selective $\alpha_1$-adrenergic receptor (22) and stellate ganglion (38) blockades. Although the sympathetic contribution to the regulation of brain perfusion at rest remains controversial (32), under transient hypertensive conditions such as during SHG, sympathoectionization has been shown to provoke cerebral vasconstriction (4, 25, 28). Thus we hypothesize that sympathetic neural restraint prevents increases in ipsilateral hemisphere perfusion of the brain during SHG. Although a similar hypothesis has been tested in an animal model involving dynamic whole body exercise (8), it remains unknown whether these findings translate to the regulation of human brain blood flow in response to a simpler motor task.

The confirmation of this experimental hypothesis would strengthen the idea that handgrip exercise-induced increases in brain contralateral arterial blood flow may be due to neurovascular coupling and its capacity to override sympathetic vasoconstriction (11, 34). Data from our research group support the metabolic attenuation of sympathetic cerebral vasoconstriction during handgrip exercise (34). Nonetheless, this is not a universally reported finding (11). Therefore, the aim of this study was to determine the role of sympathetic nerve activity, through the selective $\alpha_1$-adrenergic receptor blockade, in the regulation of cerebral blood flow distribution during SHG. We hypothesized that selective $\alpha_1$-adrenergic receptor blockade would disturb regional cerebral perfusion, resulting in similar increases in blood flow through the contra- and ipsilateral brain; cerebral blood flow; forearm exercise; neurovascular coupling; sympathetic nerve activity

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internal carotid arteries (ICA) during SHG. To test this hypothesis, we simultaneously quantified blood flow in both the contra- and ipsilateral ICAs, at rest and during SHG, under two different experimental conditions: 1) control and 2) under selective α1-adrenergic receptor blockade. These conduit blood vessels take part in the upstream perfusion pathway of cortical areas responsible for controlling the exercising and nonexercising arms, respectively.

MATERIALS AND METHODS

Subjects. Sixteen male subjects volunteered for this study. Eligibility criteria involved 1) age between 18 and 49 yr, 2) no smoking habits, and 3) neither chronic diseases nor engagement in regular pharmacological treatment. Eligible subjects were also screened via duplex ultrasound examination of both ICAs. When the anatomical position of the carotid arterial bifurcation permitted simultaneous insonation of both the right and left ICA without any sign of turbulent or retrograde blood flow, volunteers were invited to participate in this study. Based on this criterion, only 10 healthy recreationally active men underwent the research protocol. As one subject did not complete the research protocol due to discomfort related to the breathing mask, the final analysis involved the data of nine subjects (25 ± 7 yr, 178.2 ± 6.6 cm and 72.6 ± 4.6 kg). Before their participation, subjects signed a written consent form containing a detailed written explanation of the experimental procedures. The research protocol was conducted in accordance to the Declaration of Helsinki and received the approval of the Ethical Committee for Research (CAAE: 36683814.0.0000.5243) at Fluminense Federal University.

Instrumentation. A venous catheter was inserted into the left arm antecubital vein for the drug infusion protocol. Heart rate was continuously monitored by a lead II electrocardiogram (BioAmp, MLA2540; ADInstruments, Bella Vista, NSW, Australia). Noninvasive beat-to-beat arterial pressure was recorded throughout the research protocol via finger photoplethysmography on the left hand (Finometer Pro; Finapres Medical Systems, Arnhem, The Netherlands). Validation of the absolute Finometer values was based on brachial artery blood pressure measurements obtained from the right arm using an automated sphygmomanometer (EM-759-E; Omron, Kyoto, Japan). Breathing-related changes in abdominal/thoracic circumference were monitored via a piezoelectric transducer (MLT1132 respiratory belt; ADInstruments). Continuous breath-by-breath recordings of ventilation, tidal volume, and end-tidal carbon dioxide partial pressure (PETCO2) were carried out while the subjects breathed through either a mouthpiece (wearing a nose clip) or a mask connected to a gas analyzer system (Ultima CPX; Medgraphics, St. Paul, MN). Surface electromyographic activity (EMG, BioAmp, MLA2540; ADInstruments) of both the right and left forearm was also recorded to confirm that changes in the ipsilateral ICA blood flow were not a consequence of undesired muscular activation.

Two high-resolution Doppler ultrasound systems (Vivid 7, General Electric, Horten, Norway and Logiq P5, GE Medical Systems, Milwaukee, WI) with multifrequency linear array (8–12 MHz) probes were used to simultaneously measure right and left ICA diameter and insonation angle-corrected (±60°) blood velocity spectra. Two experienced operators started the measurements asking the subjects to elevate their chin to facilitate ICA insonation. Measurements were taken 1.5 to 2.0 cm distal from the carotids bifurcation with no evidence of turbulent flow (30). Sample volumes were identified at the center of the vessels and were then adjusted to span their width. The probe location was marked on the skin of each side of the neck and did not change throughout the study. Diameters and blood velocity waveforms were continuously recorded during the last 30 s for both the baseline and SHG in each condition of the study.

Experimental setup. Eligible subjects were familiarized with the experimental protocol before any experiments were performed. The subjects were asked to abstain from caffeine and alcohol consumption as well as exercise for 24 h before the experimental visit. Upon arrival at the experimental facilities, fasted (2 h) subjects rested supine for 20 min in a dark, temperature-controlled (22–24°C), quiet room. This resting period was followed by a protocol designed to obtain the maximal voluntary contraction (MVC) in which a handgrip dynamometer was held in the dominant hand and three to five vigorous efforts were made. Each trial was separated by at least 1 min, and the MVC was defined as the highest produced force. EMG recordings were also obtained during the MVC procedures. The subjects were then outfitted with the instrument and asked to quietly rest for 10 min while the respiratory rate and depth were monitored. After this procedure, in which the eupneic levels of PETCO2 (target) were defined, the subjects were instructed to follow a metronome to breathe at a rate of 20 respiratory incursions per minute. The subjects were also provided with verbal instructions to reach tidal volume levels that corresponded to the target PETCO2. Once a consistent respiratory pattern was achieved, the target PETCO2 was maintained for the entire research protocol via a rebreathing circuit (2). Importantly, the procedures of controlling breathing rate and magnitude were only adopted to minimize the often-reported SHG-induced hyperventilation (15, 21) and then facilitate the operation of the rebreathing system. In summary, this system provides a simple mean of holding arterial blood gases constant in the face of spontaneous changes in breathing and its capacity has been reported even in conditions of maximal whole body exercise (24).

Figure 1 presents a timeline of the experimental visit. Initially, subjects rested for 3 min (baseline) and then performed a 2-min bout of SHG at 30% of the MVC. Visual feedback of the force level was provided throughout the handgrip task. While squeezing the dynamometer with the dominant hand, the subjects were instructed to avoid any other body movement. Following SHG, the subjects were allowed to rest for 15 min before ingesting prazosin, a selective α1-adrenergic receptor antagonist. In the second phase of the experimental visit, which began 170 min post-prazosin ingestion, the subjects again underwent a 3-min baseline period and a successive 2-min SHG bout. A period of time between ingestion and the beginning of the second phase was necessary to reach prazosin peak activity. The prazosin dosage (1 mg/20 kg of body wt) was based on previous research (22) reporting the efficiency of this clinical dose.

Phenylephrine challenge. Validation of these findings was dependent on the capacity of prazosin to antagonize α1-adrenergic receptors and to inhibit pressor responses resulting from their activation. The efficiency of this selective blockade was confirmed by intravenous bolus infusion of phenylephrine, a selective agonist of α1-adrenergic receptors. As the black arrows in Fig. 1 indicate, the subjects received antecubital venous injections of phenylephrine (1 µg/20 kg of body wt) before, 150 min after prazosin ingestion, and at the end of the research protocol (15 min after the last SHG bout). These procedures were performed to confirm the antagonism of the α1-adrenergic receptors. This dose of phenylephrine typically evokes arterial pressure increases ranging from 15 to 20 mmHg (22). Thus arterial

![Experimental setup](http://ajpheart.physiology.org/)

**Fig. 1.** Experimental setup. Praz, prazosin ingestion; SHG, static handgrip exercises at 30% of the MVC; PE, phenylephrine infusion.
pressure recordings were carried out during the infusions to determine the efficiency of the $\alpha_1$-adrenergic receptor blockade.

Data analysis. Raw signals were registered at a sampling rate of 1 kHz and stored for offline analysis (PowerLab 16SP hardware and LabChart 7 software; ADInstruments). The last 30-s averages were calculated, and the dependent variables were expressed as the difference between SHG and baseline unless otherwise stated. Mean ICA blood velocity was determined by a function encoded by the Doppler ultrasound systems (Vivid 7, General Electric and Logiq P5, GE Medical Systems). For ICA diameter, B-mode video signals were encoded in real time and then were captured by an USB video board (Easy cap, DC60; Leadership) and stored as digital AVI files. The analysis was initiated by uploading the AVI files to an automated edge detection and wall-tracking software (Vascular Research Tools 5; Medical Imaging Applications, Coralville, IA). Regions of interest within the optimal portions of the ICA images were identified and did not change throughout the analysis. The mean diameter was determined without the application of an R-wave gating function. ICA blood flow [blood flow = blood velocity $\times \pi \times (\text{diameter}/2)^2 \times 60$ (in ml/min)] and vascular conductance [blood flow/mean arterial pressure (in ml/min$^{-1}$-mmHg$^{-1}$)] were calculated at both the baseline and SHG. Cardiac output was derived from the arterial pressure waveform using the Modelflow method (3). Cardiac output fractional distribution (%) to both ICAs ([ICA blood flow $\times$ 100]/cardiac output) was also calculated. Total conductance was estimated by the ratio between cardiac output and mean arterial pressure (3). During the phenylephrine challenge, arterial pressure responses were determined to be the difference between the highest value obtained during infusion and the average of the baseline period. EMG recordings during MVC, baseline and SHG were rectified and low-pass filtered (50 Hz), and the average root mean square (RMS) was calculated. Baseline and SHG RMSs were normalized and presented relative to the greater RMS value obtained during the MVCs (%).

Statistics. Data are presented as the mean $\pm$ SD. Repeated-measures two-way ANOVA was performed to identify significant within-group differences for all normally distributed variables. Least significant difference post hoc analysis was conducted when a main effect was detected. t-Tests were used to detect differences between $\Delta$-values. When the assumption of normality was not met, statistical inference was obtained using equivalent nonparametric tests. Significance was accepted at the 0.05 level. Analyses were performed using the Statistical Package for Social Sciences, version 21.0 for Macintosh (SPSS, Chicago, IL).

RESULTS

Data of one subject were not included in the analysis of ICA variables (velocity, diameter, blood flow, conductance, and fractional distribution of cardiac output) because the ultrasound Doppler beams provoked signal interferences and did not allow simultaneous blood flow measurements.

Prazosin effectively antagonized $\alpha_1$-adrenergic receptors, as indicated by abrupt reductions of mean arterial pressure responses to phenylephrine at 150 min after oral ingestion ($-77 \pm 14\%$, $P < 0.05$; Fig. 2) and upon the end of the research protocol ($-64 \pm 23\%$, $P < 0.05$). Figure 2 also shows that heart rate followed the same trend and showed smaller reductions at both 150 min after oral ingestion ($-59.6 \pm 38.1\%$, $P < 0.05$) and the end of protocol ($-74.0 \pm 27.7\%$, $P < 0.05$).

Figure 3 displays both breath-by-breath PE$\text{ETO}_2$, and hand-grip force level (modified to 1-Hz sampling rate) at the last 30 s of the baseline and SHG. Breath-by-breath PE$\text{ETO}_2$, as well as the mean values available in the Table 1, demonstrated the effectiveness of the rebreathing system at clamping euclidean levels for the duration of the research protocol. Figure 3 also confirmed that mean handgrip force levels ranging from 22 to 30.4% of MVC were achieved and maintained under both experimental conditions (control 26.4 $\pm$ 2.3 vs. $\alpha_1$-adrenergic blockade 26.7 $\pm$ 2.1%, $P > 0.05$).

During the control trial, SHG provoked substantial increase in mean arterial pressure ($+31.4 \pm 10.7$ mmHg, $P < 0.05$), heart rate ($+18.1 \pm 7.4$ beats/min, $P < 0.05$), and cardiac output ($+2.0 \pm 1.0$ l/min, $P < 0.05$). Table 1 shows that SHG was also related to a small but significant reduction in total conductance ($-0.01 \pm 0.01$ l/mmHg, $P < 0.05$). Contralateral ICA blood flow ($+80.9 \pm 62.5$ ml/min, $P < 0.05$ vs. baseline and ipsilateral ICA) increased during SHG, while no change was observed in ipsilateral ICA perfusion ($-9.8 \pm 39.3$ ml/min, $P > 0.05$). Table 1 also indicates that changes in contralateral ICA blood flow were driven by increases in blood velocity ($+4.8 \pm 4.1$ cm/s, $P < 0.05$) rather than alterations in vessel diameter ($+0.01 \pm 0.02$ cm, $P > 0.05$). A greater decrease in both ipsilateral ICA vascular conductance (Table 1, contralateral: $-0.8 \pm 0.8$ vs. ipsilateral: $-2.6 \pm 1.3$ ml-min$^{-1}$-mmHg$^{-1}$, $P < 0.05$) and fractional distribution of cardiac output (contralateral: $-0.5 \pm 1.7$ vs. ipsilateral $-1.6 \pm 1.8\%$, $P < 0.05$) provided further evidence of regional changes in brain blood flow distribution (Fig. 5).

Under $\alpha_1$-adrenergic blockade, the mean arterial pressure increased in response to SHG. However, the magnitude of this response was reduced compared with the control trial (Table 1,

* doi:10.1152/ajpheart.00125.2016 • www.ajpheart.org
control: +31.4 ± 10.7 vs. α₁-adrenergic blockade: +19.4 ± 9.2 mmHg, P < 0.05). Greater increases in heart rate were also observed during SHG under α₁-adrenergic blockade (control: +18.1 ± 7.4 vs. α₁-adrenergic blockade: +24.1 ± 5.8 beats/min, P < 0.05). Cardiac output also showed similar increases during SHG compared with the control condition (2.3 ± 1.4 l/min, P < 0.05). Total conductance did not change during SHG, although it was greater when compared with the control trial (2.3 ± 1.4 l/min, P < 0.05).

In contrast, ipsilateral ICA blood flow increased during SHG under α₁-adrenergic blockade. This increase was of a similar magnitude to that observed in the contralateral ICA (ipsilateral: +54.3 ± 46.2 vs. contralateral: 58.4 ± 21.5 ml/min, P > 0.05) and was driven by changes in blood velocity (+3.2 ± 1.2 cm/s, P < 0.05 vs. baseline and control trial). Changes in blood flow distribution were also indicated via similar decreases in vascular conductance (contralateral: −0.4 ± 0.7 vs. ipsilateral: −0.4 ± 1.0 ml·min⁻¹·mmHg⁻¹, P > 0.05) and fractional distribution of cardiac output (contralateral: −0.29 ± 0.7 vs. ipsilateral: −0.34 ± 0.73%, P > 0.05) during SHG. EMG data (Table 1) demonstrated no activation of ipsilateral forearm muscle:

Table 1. Cardiovascular, respiratory, and cerebrovascular hemodynamic responses to static handgrip exercise

<table>
<thead>
<tr>
<th></th>
<th>Rest</th>
<th>SHG</th>
<th>Control</th>
<th>α₁-Adrenergic Blockade</th>
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</thead>
<tbody>
<tr>
<td></td>
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<tr>
<td>MAP, mmHg</td>
<td>73.2 ± 11.1</td>
<td>104.6 ± 19.4*</td>
<td>75.2 ± 11.3</td>
<td>94.7 ± 16.3†</td>
</tr>
<tr>
<td>Heart rate, beats/min</td>
<td>71.1 ± 9.2</td>
<td>89.2 ± 13.5*</td>
<td>75.7 ± 14.8</td>
<td>99.8 ± 17.5†</td>
</tr>
<tr>
<td>Cardiac output, l/min</td>
<td>7.5 ± 2.2</td>
<td>9.5 ± 2.2*</td>
<td>8.3 ± 1.8</td>
<td>10.5 ± 2.6*</td>
</tr>
<tr>
<td>T-conductance, l/min</td>
<td>0.11 ± 0.04</td>
<td>0.09 ± 0.03*</td>
<td>0.11 ± 0.04</td>
<td>0.12 ± 0.04†</td>
</tr>
<tr>
<td>PETCO₂, mmHg</td>
<td>39.4 ± 1.3</td>
<td>39.3 ± 1.2</td>
<td>39.5 ± 1.1</td>
<td>39.2 ± 1.4</td>
</tr>
<tr>
<td>Contralateral ICA</td>
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<tr>
<td>Diameter, cm</td>
<td>0.53 ± 0.05</td>
<td>0.54 ± 0.04</td>
<td>0.53 ± 0.04</td>
<td>0.54 ± 0.03</td>
</tr>
<tr>
<td>Velocity, cm/s</td>
<td>27.4 ± 5.0</td>
<td>32.2 ± 7.0*</td>
<td>25.6 ± 4.8</td>
<td>29.0 ± 5.8*</td>
</tr>
<tr>
<td>Blood flow, ml/min</td>
<td>362.8 ± 64.3</td>
<td>443.7 ± 93.7*</td>
<td>348.4 ± 98.4</td>
<td>406.9 ± 96.9*</td>
</tr>
<tr>
<td>VC, ml·min⁻¹·mmHg⁻¹</td>
<td>5.1 ± 1.4</td>
<td>4.3 ± 1.1</td>
<td>4.7 ± 1.9</td>
<td>4.4 ± 1.5</td>
</tr>
<tr>
<td>%Cardiac output</td>
<td>5.5 ± 2.7</td>
<td>5.0 ± 2.0</td>
<td>4.3 ± 1.0</td>
<td>4.0 ± 1.1</td>
</tr>
<tr>
<td>Ipsilateral ICA</td>
<td></td>
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<tr>
<td>Diameter, cm</td>
<td>0.52 ± 0.04</td>
<td>0.52 ± 0.04</td>
<td>0.53 ± 0.03</td>
<td>0.53 ± 0.04</td>
</tr>
<tr>
<td>Velocity, cm/s</td>
<td>29.0 ± 5.0</td>
<td>28.3 ± 4.6</td>
<td>27.0 ± 3.0</td>
<td>30.2 ± 2.9*</td>
</tr>
<tr>
<td>Blood flow, ml/min</td>
<td>375.2 ± 77.6</td>
<td>365.4 ± 79.5</td>
<td>355.7 ± 62.6</td>
<td>410.0 ± 79.9*</td>
</tr>
<tr>
<td>VC, ml·min⁻¹·mmHg⁻¹</td>
<td>5.3 ± 1.6</td>
<td>2.7 ± 0.6*</td>
<td>4.8 ± 1.4</td>
<td>4.4 ± 1.3†</td>
</tr>
<tr>
<td>%Cardiac output</td>
<td>5.6 ± 3.0</td>
<td>4.1 ± 1.5*</td>
<td>4.4 ± 0.5</td>
<td>4.0 ± 1.1</td>
</tr>
<tr>
<td>EMG, %MVC</td>
<td></td>
<td></td>
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<tr>
<td>Dominant forearm</td>
<td>1.7 ± 1.3</td>
<td>23.4 ± 17.1*</td>
<td>1.3 ± 0.6</td>
<td>21.6 ± 13.9*</td>
</tr>
<tr>
<td>Nondominant forearm</td>
<td>1.7 ± 1.0</td>
<td>2.4 ± 2.3</td>
<td>1.6 ± 0.9</td>
<td>1.7 ± 1.2</td>
</tr>
</tbody>
</table>

Values are mean ± SD. %Cardiac output, fractional distribution of the cardiac output; EMG, electromyography of forearms muscle; ICA, internal carotid artery; MAP, mean arterial pressure; PETCO₂, end-tidal carbon dioxide partial pressure; SHG, static handgrip exercise; T-conductance, total conductance; VC, vascular conductance. *P < 0.05, rest vs. SHG; †P < 0.05, control vs. α₁-adrenergic receptor blockade.
muscle during SHG under both control conditions and α₁-adrenergic blockade.

DISCUSSION

This investigation was based on the hypothesis that sympathetic neural restraint may play a role in avoiding SHG-induced perfusion in the ipsilateral hemisphere of the brain. Indeed, selective α₁-adrenergic receptor blockade resulted in changes in the cerebral blood flow distribution during SHG that were characterized by a significant increase in ipsilateral ICA blood flow. No additional changes in contralateral ICA blood flow were observed in response to SHG during α₁-adrenergic blockade. Thus these findings indicate a modulatory role of sympathetic nerve activity in the regulation of blood flow distribution to the hemisphere not involved in the motor control and the metabolic attenuation of sympathetic cerebral vasoconstriction in blood vessels that perfuse the cortical representation of the exercising arm.

Sympathetic vasoconstriction has been suggested as a protective mechanism for the brain, limiting cerebral perfusion and microcirculatory pressure during conditions of transient increases in arterial pressure (7). SHG represents a potent stimulus that evokes sympathetic activation and increases in arterial pressure (23, 29, 34); this protective mechanism may explain the lack of changes in ipsilateral ICA blood flow and the significant attenuation in its conductance. Despite the dense sympathetic innervation of the ICA territory (37), our findings do not support the hypothesis that this extracranial artery plays a modulatory role in cerebral perfusion; no significant changes were detected in its diameter. This is in agreement with the idea that cerebral resistance regulation takes place in pial arterioles (7, 9), which have been suggested as a potential target of SHG-induced sympathetic activation.

Under α₁-adrenergic receptor blockade, we found that ipsilateral ICA blood flow increased and the reduction in its conductance was attenuated during SHG. This response was similar to that observed in the contralateral ICA. These hemodynamic responses were not accompanied by changes in either PETCO₂ or left forearm muscle activation (EMG). This indicates that increases in ipsilateral ICA perfusion did not result from vascular reactivity to changes in blood gases or increased neuronal activation and brain metabolism. Thus, we believe that an attenuation of cerebrovascular tone as well as impairment in autoregulation may explain the changes observed in ipsilateral hemispheric perfusion under α₁-adrenergic receptor blockade. While cerebral autoregulation appears to be preserved during SHG (23), it has been reported that the capacity to buffer arterial pressure fluctuations is impaired during both selective α₁-adrenergic receptor (22) and stellate ganglion (38) blockades. Furthermore, it has been shown that α₁-adrenergic receptor blockade impairs cerebral autoregulation and attenuates increases in cerebral vascular tone during moderate dynamic exercise (26). This theory has also been supported by a human integrative model that estimated the manner and degree to which all mechanisms speculated to be involved in the cerebral autoregulation, such as the myogenic, cholinergic, and sympathetic responses, shape the relationship between arterial pressure and cerebral blood flow (10). Although this mathematical modeling indicated myogenic responses as the largest contributor to the pressure-flow relationship, sympathetic reflexes accounted for almost total gain and upper limit of the cerebral autoregulation (10). Therefore, the autonomic control

![Graphs showing changes in heart rate, arterial pressure, total conductance, and cardiac output during both control and α₁-adrenergic receptor blockade conditions.](http://ajpheart.physiology.org/)

Fig. 4. Changes in heart rate, arterial pressure, total conductance, and cardiac output during both control and α₁-adrenergic receptor blockade conditions. *Control vs. α₁-adrenergic receptor blockade.
of the brain vasculature seems to constitute an essential factor in the homeostatic regulation of cerebral perfusion in which constant blood flow in response to changes in arterial pressure would require active modification in vessel diameter. Thus, even considering the influence of other mechanisms on cerebral autoregulation, the increased ipsilateral hemispheric perfusion may be a consequence of an inability of the brain to buffer SHG-induced transient hypertensive responses under \(\alpha_1\)-adrenergic receptor blockade.

Despite the disturbed modulation of ipsilateral hemisphere perfusion, \(\alpha_1\)-adrenergic receptor blockade did not elicit additional increases in contralateral ICA blood flow during SHG. While this finding suggests that neurovascular coupling completely attenuated SHG-induced sympathetic cerebral vasoconstriction, which corroborates previous results from our research group (33), the smaller but nonsignificant reduction in contralateral ICA conductance also suggests lesser sympathetic restraint and increased perfusion to the contralateral brain hemisphere. This fact raises the hypothesis that increases in both exercise intensity and degree of sympathoexcitation would be related to a greater autonomic restraint to blood vessels that perfuse contra- and ipsilateral hemispheres of the brain. Thus, in this hypothetical condition, we would expect a further increase in contralateral blood flow in response to \(\alpha\)-adrenergic blockade as previously reported in humans during dynamic exercise under simultaneous \(\beta_1\)-adrenergic and unilateral stellate ganglion blockade (14).

While the aforementioned smaller reduction on contralateral hemisphere conductance gives an idea of lesser sympathetic restraint to its blood vessels, a nonsignificant smaller increase in contralateral ICA blood flow was also observed under \(\alpha_1\)-adrenergic receptor blockade. We speculate this response results from an attenuation of vasoconstrictor tone in ipsilateral hemispheric blood vessels as well as in other peripheral vascular beds. This increase in vessels conductance would disturb fractional cardiac output distribution that, instead of being preferentially driven to the contralateral hemisphere, would also increase blood supply to other cortical and peripheral regions. This mechanism is well characterized in skeletal muscle blood flow regulation (13) and was here supported by the increase in ipsilateral ICA perfusion, the smaller nonsignificant decrease in the fractional cardiac output distribution to the contralateral conduit artery, as well as the increase in total conductance during SHG under \(\alpha_1\)-adrenergic receptor blockade.

Brain functional hyperemia, in theory, results from anatomical and metabolic interactions among neurons, glial cells, and cortical penetrating arterioles (1, 12). These interactions mediate vasodilation, which may be retrogradely propagated through gap junctions between adjacent vascular smooth muscle cells. These vascular signals are then transmitted to upstream pial arterioles to promote remote vasodilation (7). We therefore speculate that contralateral ICA blood flow increased in response to SHG as consequence of a metabolic remote pial vasodilation, which attenuates sympathetic-mediated cerebrovascular resistance. This speculation is supported by the fact that increases in upstream vessel perfusion were primarily driven by changes in blood velocity.

Validation of our research findings relies on the capacity of prazosin to antagonize \(\alpha_1\)-adrenergic receptors. In fact, increases in arterial pressure in response to phenylephrine were abruptly reduced at both 150 min after oral ingestion of prazosin and at the end of the protocol. These responses were in agreement with previous findings that reported similar reductions in arterial pressure responses to phenylephrine infusion during selective \(\alpha_1\)-adrenergic blockade (22, 26). In addition, smaller but significant increases in mean arterial pressure as well as exaggerated increments in heart rate were observed in response to SHG under selective \(\alpha_1\)-adrenergic blockade, as previously reported (16, 26). This reduced response of mean arterial pressure during SHG reflects the attenuation of sympathetic vascular transduction...
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mediated by the antagonism of α1-adrenergic receptors. The greater SHG-induced increase in heart rate observed in the α1-adrenergic blockade trial, which is in accordance with previous findings (16), may be related to the arterial baroreflex resetting (27). During exercise, feedforward (central command) (36) and feedback (skeletal muscle afferents) (3) mechanisms reset baroreflex-heart rate curve operational parameters, allowing concurrent increases in the arterial pressure and heart rate. Therefore, as α1-adrenergic receptor blockade minimizes both sympathetic transduction and increases in arterial pressure, we speculate that it would result in a negative feedback from arterial baroreceptors indicating that the operating pressure is low (35). This would reflexively cause greater increases in heart rate during SHG under α1-adrenergic receptor blockade.

The smaller increases observed in SHG-induced arterial pressure were likely evoked by α2-adrenergic receptors (5), although the activation of remaining unblocked α1-receptors cannot be excluded. Whereas a selective blockade may represent a limitation, the use of prazosin is justified not only by the fact that α1-receptors are the most abundant adrenergic receptors in the brain but also by their postsynaptic nature. α2-Adrenergic receptors, in contrast, are located on the presynaptic membrane of the nerve terminal and function in a localized negative feedback loop that regulates norepinephrine release (6). Thus a nonselective α-adrenergic blockade would result in disturbances of norepinephrine release and would confound the interpretation of our results. Finally, prazosin has lipophilic characteristics, and its capacity to cross the blood-brain barrier (19) raises questions regarding the antagonism of central α1-adrenergic receptors. Although studies in humans are lacking, animal models indicate that prazosin does not suppress sympathetic outflow when administered intracerebroventricularly (18).

Conclusion. In summary, selective α1-adrenergic receptor blockade provoked disturbances in the distribution of regional cerebral blood flow that resulted in significant changes in ipsilateral hemispheric blood flow and conductance. However, the lack of change in contralateral ICA blood flow and conductance suggests that neurovascular coupling completely attenuated SHG-induced sympathetic vasoconstriction. These findings therefore suggest a role for sympathetic nerve activity in regulating regional brain perfusion during SHG.

ACKNOWLEDGMENTS

We appreciate the time and effort expended by all volunteer subjects in this study. We also thank Daniel Mansur for technical assistance during the experiments.

GRANTS

This study was supported by grants from the Brazilian National Council of Scientific and Technological Development (CNPq), the Foundation for Research Support of Rio de Janeiro (FAPERJ), Coordination for the Improvement of Higher Education Personnel (CAPES), and Brazilian Funding Agency for Studies and Projects (FINEP).

DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the author(s).

AUTHOR CONTRIBUTIONS


REFERENCES


