Acute hypoxia impairs dynamic cerebral autoregulation: results from two independent techniques

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Subudhi AW, Panerai RB, Roach RC. Acute hypoxia impairs dynamic cerebral autoregulation: results from two independent techniques. J Appl Physiol 107: 1165–1171, 2009.—We investigated the effect of acute hypoxia (AH) on dynamic cerebral autoregulation (CA) using two independent assessment techniques to clarify previous, conflicting reports. Twelve healthy volunteers (6 men, 6 women) performed six classic leg cuff tests, three breathing normoxic (FiO2 = 0.21) and three breathing hypoxic (FiO2 = 0.12) gas, using a single blinded, Latin squares design with 5-min washout between trials. Continuous measurements of middle cerebral artery blood flow velocity (CBFv; DWL Multidop X2) and radial artery blood pressure (ABP; Colin 7000) were recorded in the supine position during a single experimental session. Autoregulation index (ARI) scores were calculated using the model of Tiecks et al. (Tiecks FP, Lam AM, Aaslid R, Newell DW. Stroke 26: 1014–1019, 1995) from ABP and CBFv changes following rapid cuff deflation (cuff ARI) and from ABP to CBFv transfer function, impulse, and step responses (TFA ARI) obtained during a 4-min period prior to cuff inflation. A new measure of %CBFv recovery 4 s after peak impulse was also derived from TFA. AH reduced cuff ARI (5.65 ± 0.70 to 5.01 ± 0.96, P = 0.04), TFA ARI (3.76 ± 0.76 to 3.73 ± 0.71, P = 0.04), and %Recovery (62.2 ± 10.9% to 50.8 ± 9.9%, P = 0.03). Slight differences between TFA and cuff ARI values may be attributed to heightened sympathetic activity during cuff tests as well as differential sensitivity to low- and high-frequency components of CA. Together, results provide consistent evidence that CA is impaired with AH. In addition, these findings demonstrate the potential utility of TFA ARI and %Recovery scores for future CA investigations.

METHODS

Subjects

Following approval from the local institutional review board, 14 healthy, physically active, nonsmokers (7 men and 7 women; 24–40 yr) were recruited to obtain a sample size in accordance with previous studies (3, 18). All volunteers gave written informed consent and completed a thorough medical history and physical examination, including evaluation of retinal health, prior to participation. Subjects were included only if they were normotensive and free of illness requiring medication.

Cerebral Autoregulation (CA) acts to maintain cerebral blood flow by rapidly adjusting vessel diameter in response to changes in perfusion pressure (30). CA is impaired in pathological conditions where cerebral hypoxia occurs secondary to ischemia [e.g., stroke (7, 8), carotid artery stenosis (16, 29), and traumatic brain injury (15, 28)]. Whether CA is impaired during brief periods of arterial hypoxemia is unclear since only two conflicting reports of such stress in humans exist in the literature. Iwasaki et al. (18) found that 5 min of mild hypoxia (FiO2 = 0.15; P02 ~105 mmHg) altered CA using transfer function analysis (TFA) to evaluate beat-by-beat relationships in arterial blood pressure (ABP) and cerebral blood flow velocity (CBFv). They based their finding of mild CA impairment during hypoxia on an increased linear correlation between ABP and CBFv (coherence) and greater transmittal of ABP to CBFv amplitude (gain) across very low frequencies (0.02 to 0.07 Hz). In contrast, Ainslie et al. (3) reported no changes in very low frequency CA during two 4- to 5-min steps of more severe hypoxia (FiO2 = 0.12 and 0.10, P02 ~ 85 and 70 mmHg) using the same TFA technique. These inconsistent TFA results are difficult to reconcile, thus further study is warranted to clarify the effect of acute hypoxia on CA.

While TFA is an accepted, noninvasive method to measure dynamic CA (11, 37), it suffers from a lack of interpretation standards for simultaneously evaluating the three resulting metrics of coherence, gain, and phase shift over a wide range of frequencies (24). Theoretically, impaired CA should be associated with increased coherence, increased gain, and decreased phase shift (changes in CBFv follow ABP more passively) across low frequencies (<0.10 Hz) where autoregulation is most active (24), yet conclusions are often supported by changes in only one of the three metrics and/or within higher frequency ranges that lack sufficient power for TFA and where the influence of respiratory cycles may be a major confounder (e.g., Refs. 3, 11, 13, 14). In light of these complexities, Panerai et al. (26, 29) suggest that interpretation of TFA metrics can be facilitated by using both gain and phase shift metrics to calculate a step response that shows the speed and degree to which CBFv recovers from spontaneous fluctuations in ABP. The step response can be evaluated by a curve-fitting algorithm (34) to yield an auto regulation index (ARI) analogous to that obtainable via classic leg cuff tests (1). The resultant single ARI score thus simplifies interpretation of TFA.

Therefore, the primary objective of this study was to use the TFA ARI method to clarify the effect of acute, severe hypoxia on CA. For independent validation, leg cuff tests were performed concurrently to derive traditional cuff ARI scores. We hypothesized that acute, severe hypoxia would cause impairments in both measures of CA. As a secondary objective, we sought to compare the results of both CA measures to determine the most practical method to use in future studies.

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**Protocol**

All volunteers were instructed to refrain from eating or consuming caffeinated beverages for at least 2 h prior to a single experimental session. Subjects were instrumented to continuously monitor ABP, via a tonometer placed over the left radial artery (model 7000, Colin Medical Instruments, San Antonio, TX). This device had been previously validated using invasive measurements of radial artery pressure (19, 23). CBFVs, in the ipsilateral middle cerebral artery, was insonated through the temporal window using a 2-MHz transcranial Doppler (Multi Dop T2, DWL Electronic Systems, Singen, Germany) at depths of 44–52 mm and secured to a custom-made headset by a single, trained investigator. Subjects were studied in a supine position with their left arm abducted to avoid hydrostatic differences in blood pressure between the radial and middle cerebral arteries. In a single blinded design, medical grade normoxic (21% O₂, 79% N₂) or hypoxic (12% O₂, 88% N₂) gas was delivered under ambient pressure (623–630 mmHg; Pio₂ ~ 121 or 70 mmHg, respectively) using compressed gas tanks, a 15-liter breathing reservoir, and two-way breathing valve (Hans Rudolph, St. Louis, MO). Expired respiratory gases and volumes were analyzed using fast response O₂ (Ametek S-3A, AEI Technologies, Pittsburgh, PA) and CO₂ (Ametek CD-3A, AEI Technologies) analyzers and a heated pneumotach (Hans Rudolph). Blood oxygen saturation (SpO₂) was monitored by finger pulse oximetry (Nellcor, Nellcor N-595, Pleasanton, CA) and ECG via standard three-lead configuration (BioAmp, ADInstruments, Colorado Springs, CO). All sensors were secured in place and signal integrity was monitored continuously during the protocol. Analog signals from each instrument were integrated with a data acquisition system (Powerlab 16SP, ADInstruments) that sampled at 400 Hz throughout the experimental period. Each subject completed a total of six trials (≤10 min/trial) breathing either normoxic (3 trials) or hypoxic (3 trials) gas using a Latin squares design to assign order. Poikilocapnic hypoxia was chosen to mimic physiological responses in field/clinical settings. Subjects rested for 5 min while breathing ambient air between trials. Two assessment techniques for evaluating dynamic CA were determined by independent methods of data collection and analysis.

**Leg cuff test.** After 3 min of breathing compressed gas (normoxic or hypoxic), large pneumatic cuffs (Hokanson, Seattle, WA) placed around both thighs were inflated to 30 mmHg above systolic pressure or hypoxic), large pneumatic cuffs (Hokanson, Seattle, WA) placed indicated absent and 9 indicated perfect CA. Beat-by-beat data were extracted and resampled at 5 Hz. FFT using the Welch algorithm with a 256-point window and 40% overlap resulted in at least five segments of data. The average coherence, gain, and phase shift across these windows were evaluated in the low-frequency range of autoregulation (≤0.10 Hz) associated with cycle lengths longer than 10 s. An inverse FFT was then performed using both gain and phase to yield an impulse response in the time domain. Integration of the impulse yielded a step response representing the cumulative area under the impulse curve at a given time to accentuate differences between conditions. The first 3 s of the step response were used to fit one of Tiecks et al.’s (18) ARI models (TFA ARI). Additionally, step responses were evaluated independent of ARI curve fitting using a new index of CA given by the %CBFv recovery 4 s after the peak impulse (%Recovery). It was believed that this index would offer a quicker method to assess step responses with physiologically relevant units.

**Statistics**

Key variables of interest included ABP, CBFv, finger tip oxygen saturation, minute ventilation (Ve), and PetO₂ and PetCO₂. Paired t-tests were used to assess differences between conditions (normoxia and hypoxia) for both cuff and TFA methods. Pearson product moment correlation coefficients were calculated to evaluate the relationship between cuff and TFA methods. The degree of agreement between methods was assessed using the methods of Bland and Altman (5). Significance was accepted at P < 0.05 for TFA and ARI scores. The Holm procedure for adjusting the criterion P value was used to control for type I error across the remaining physiological comparisons. Data are presented as means ± SD.

**RESULTS**

All subjects completed the study protocol, yet two subjects’ CBFv tracings were of insufficient quality for TFA. Data from the remaining 12 subjects (6 men, 6 women, 29 ± 6 yr, 172 ± 10 cm, 68.6 ± 11.9 kg) are reported hereafter.

Resting data were averaged across the 4-min segment used for TFA analysis (Table 1). Acute hypoxia affected all variables except ABP (P = 0.70) and CBFv (P = 0.04: not significant after Holm’s adjustment). Three minutes of leg blood flow occlusion tended to increase ABP (P = 0.04) in normoxia, but not hypoxia (P = 0.12). The release of cuff pressure was associated with changes in ABP (>10 mmHg), HR, and Ve 4 s later (P < 0.01: Table 2). Cuff ARI scores in hypoxia were lower than normoxia (P = 0.04; CV = 19.2%), indicating impaired CA (Table 3). FFTs revealed increased ARI and CBFv power (P < 0.05: hypoxia vs. normoxia) across low frequencies (<0.10 Hz: Fig. 1), with TFA showing weak trends toward increased coherence and gain and decreased phase shift (P < 0.20: Fig. 2). Both TFA ARI and %Recovery in hypoxia were lower than normoxia (P = 0.04 and 0.03, respectively; Table 3 and Fig. 3), indicating impaired CA.

The relationships between cuff and TFA ARI were low, sharing only 9 and 6% of variance in normoxia and hypoxia,

<table>
<thead>
<tr>
<th>Condition</th>
<th>ABP, mmHg</th>
<th>CBFv, cm/s</th>
<th>HR, beats/min</th>
<th>Sat%</th>
<th>Ve, btps, l/min</th>
<th>RR, beats/min</th>
<th>PetO₂, mmHg</th>
<th>PetCO₂, mmHg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normoxia</td>
<td>86.5 ± 11.0</td>
<td>59.9 ± 10.1</td>
<td>54 ± 8</td>
<td>97 ± 2</td>
<td>12.0 ± 3.7</td>
<td>14.5 ± 3.3</td>
<td>84.1 ± 4.3</td>
<td>34.3 ± 2.9</td>
</tr>
<tr>
<td>Hypoxia</td>
<td>88.1 ± 14.3</td>
<td>63.6 ± 10.9</td>
<td>69 ± 10*</td>
<td>85.4 ± 2*</td>
<td>14.8 ± 3.6*</td>
<td>13.9 ± 3.6</td>
<td>42.4 ± 3.0*</td>
<td>30.7 ± 2.7*</td>
</tr>
</tbody>
</table>

Values are means ± SD (n = 12). ABP, arterial blood pressure; CBFv, velocity of cerebral blood flow; HR, heart rate, Sat, saturation; Ve, btps, ; PetCO₂ and PetO₂, end-tidal partial pressure of CO₂ and O₂, respectively. *Different from normoxia (P < 0.025).
Table 2. Physiological variables 4 s before and after cuff release

<table>
<thead>
<tr>
<th>Condition</th>
<th>Cuff Pressure, mmHg</th>
<th>ABP, mmHg</th>
<th>CBFv, cm/s</th>
<th>HR, beats/min</th>
<th>Sat%</th>
<th>VE btps, l/min</th>
<th>Pe/ETo2, mmHg</th>
<th>Pe/ETo2, mmHg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normoxia</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cuff up</td>
<td>158±15</td>
<td>94.0±14.1</td>
<td>59.3±11.0</td>
<td>57±11</td>
<td>98±2</td>
<td>14.7±4.5</td>
<td>84.2±4.4</td>
<td>33.3±2.8</td>
</tr>
<tr>
<td>Cuff down</td>
<td>1.1±0.2*</td>
<td>78.1±9.7*</td>
<td>58.6±10.7</td>
<td>73.4±9.0*</td>
<td>98±1</td>
<td>15.5±4.2*</td>
<td>84.4±4.3</td>
<td>33.3±2.4</td>
</tr>
<tr>
<td>Hypoxia</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cuff up</td>
<td>156±15</td>
<td>92.2±14.5</td>
<td>66.6±13.8</td>
<td>76±12*</td>
<td>81±5*</td>
<td>17.0±3.9*</td>
<td>42.4±3.0*</td>
<td>29.3±2.1</td>
</tr>
<tr>
<td>Cuff down</td>
<td>1.3±2.2*</td>
<td>78.3±14.0*</td>
<td>66.1±12.6</td>
<td>88±11**</td>
<td>81±5*</td>
<td>18.1±2.6*</td>
<td>42.1±2.6*</td>
<td>29.4±2.0</td>
</tr>
</tbody>
</table>

Values are means ± SD (n = 12). #Different from cuff up (P < 0.01); *Different from normoxia (P < 0.01).

respectively. Bland-Altman plots indicated differences between measurements, with identical biases toward lower TFA ARI scores in normoxia (1.28) and hypoxia (1.28). The relationship between TFA ARI and %Recovery was strong, sharing 82 and 93% of the variance in normoxia and hypoxia, respectively (Fig. 4).

DISCUSSION

This study provides the first evidence that CA is impaired during acute, severe hypoxia via two independent methods of analysis. Results help clarify previous, conflicting reports regarding effects of acute hypoxia on CA. Slight differences between TFA and cuff methods can be partially attributed to differential sensitivity to low- and high-frequency components of the overall CA response. From a practical standpoint, TFA and cuff methods should be considered for future studies since they offer minimally intrusive, quick, and sensitive alternatives to the classic cuff technique.

Effects of Hypoxia on Cerebral Autoregulation

Decreased TFA ARI and %Recovery scores provided primary evidence that CA was impaired during acute hypoxia among healthy individuals with intact CA (Table 3). Results were supported by independent assessment of classic cuff ARI data, which showed similar reductions in ARI scores during acute hypoxia in the same volunteers (Table 3). While there is currently no accepted gold standard for CA assessments, the consistency in our independent assessment techniques suggests that acute, severe hypoxia plays an important role in the modulation of CA.

Our TFA findings extend the work of Iwasaki et al. (18), performed in mild hypoxia (P1O2 ~105 mmHg), to a more severe degree of hypoxia (P1O2 ~70 mmHg), similar to that used by Ainslie et al. (3). Although methodological differences between studies (e.g., degree and length of hypoxia) make direct comparisons difficult, preliminary analysis of TFA results over the very low frequency range (VLF: 0.02 to 0.07 Hz) used by the previous authors were in agreement with those of Ainslie et al. (3), who suggested that CA was not impaired in the VLF, but in contrast to Iwasaki et al. (18), who reported altered CA. We believe that these conflicting conclusions result, in part, from inherent challenges of simultaneously assessing three TFA metrics (coherence, gain, and phase shift) over arbitrarily defined frequency ranges with insufficient statistical power.

It is important to note that our sample size was too low to detect statistically significant changes in individual TFA metrics. Post hoc power analyses revealed that 41 subjects would have been needed to detect increases in both coherence and gain and that 82 subjects would have been needed to also see a decrease in phase shift across the low-frequency range. Thus the relatively low statistical power of standard TFA may explain the lack of consistency in previous investigations and the difficulty in finding concurrent changes in all three metrics. We addressed the issue of low statistical power by basing our interpretation on the step response, which is calculated from the combination of gain and phase metrics across frequencies to bring the data back to the time domain (inverse FFT). This method decreases variance in TFA measurements, increases statistical power, and facilitates interpretation. We recommend that future studies consider this method of interpretation.

Overall, our interpretation process for TFA results involves three major steps. First, we restrict our interpretations to low frequencies (<0.10 Hz) where CA is considered to have the greatest clinical relevance (24, 25). This low-frequency range captures peak power in the respective spectra (Fig. 1) and neglects higher frequencies that have little or no spectral power, thus it facilitates interpretation by focusing on the single frequency band where CA is most active. Evaluation of spectral power graphs reveals that acute hypoxia increases low-frequency spectral power of both ABP and CBFv (Fig. 1). This finding hints toward impaired CA since greater low-frequency oscillations in ABP are associated with similar changes in CBFv, as was previously reported by Iwasaki et al. (18). Second, we evaluate each TFA metric individually. Trends toward improved linear correlations between ABP and CBFv (coherence), greater ABP to CBFv signal amplitude transmittal (gain), and reduced delay (phase shift) are considered suggestive of impaired CA. Statistical differences between normoxic and hypoxic CA are confirmed in our final
step, where TFA ARI and %Recovery scores, from impulse
and step responses, are assessed (Table 3). As stated above,
this final step enhances the statistical power of TFA.

The finding that CA value fell so quickly on exposure to
hypoxia implies that CA may be an integral component of the
systemic acute hypoxic response. Hypoxia increased heart rate
by 22.5 ± 7.4% (P < 0.01) and tended to increase CBFv by
5.1 ± 10.1% (P = 0.04; Table 1). These responses, as well as
the increase in low-frequency oscillations of ABP and CBFv,
may be mediated by heightened autonomic nervous activity
(17, 18). If left unchecked, increased cerebral perfusion could
compromise integrity of the blood-brain barrier and lead to
vasogenic cerebral edema (20, 31); however, our data are
limited to the first few minutes of hypoxic stress. Since
humans can tolerate extended periods of hypoxemia, it is
conceivable that CA exhibits a multiphase response with an
eventual return to baseline values over prolonged exposure
to hypoxia, similar to that documented with ventilation as
chemoreceptor sensitivity changes (9, 36).

The degree of hypoxia was sufficient to stimulate an 11.7 ±
14.4% increase in \( \dot{V}E \) (P = 0.01), yet because increased \( \dot{V}E \) was
explained by enlarged tidal volume, rather than greater respira-
tory frequency (Table 1), and interpretations were restricted
to frequencies below those induced by respiration (~0.20–
0.25 Hz), ventilation was not considered to have a major
influence on CA. Elevated \( \dot{V}E \) also lowered \( \text{PET}_{CO_2} \) by 11.7 ±
5.0% (P < 0.01), yet it is unlikely that reduced \( \text{PET}_{O_2} \) explained
decreased ARI scores, since previous reports have shown that
similar levels of hypocapnia had either no effect (2) or even
improved CA (4). In general, CA deteriorates as arterial CO
rises (10, 27, 37), thus even larger reductions in ARI scores
might have been expected with isocapnic hypoxia over the
same period of exposure. Future studies are needed to inves-
tigate the time course of changes in CA over prolonged periods
of isocapnic and poikilocapnic hypoxia.
ACUTE HYPOXIA IMPAIRS AUTOREGULATION

Intact autoregulation depends on coordinated effects of metabolic, myogenic, and neurogenic mechanisms (30), each of which may be affected by increased sympathetic stimulation during hypoxia (12, 32). Additional sympathetic stimulation imposed during cuff tests (26) may partially explain low degrees of shared variance (<10%) and agreement with TFA ARI scores. Low correlations between ARIs are in contrast to an earlier report (29) showing a higher degree of shared variance (56%) and agreement across a wide sample of patients with carotid artery stenosis and healthy controls. A closer evaluation of only healthy control data in the previous study (Fig. 2 in Ref. 29) shows a weaker relationship between methods, similar to the present findings in normoxia. It is thus possible that the relatively narrow range of ARI scores obtained from our small sample of healthy subjects obscured the overall relationship. Alternatively, cuff ARI and TFA ARI scores may be sensitive to different components of an integrated response to maintain CBF. Additional studies are needed to determine the relative contribution of myogenic, metabolic, and neurogenic aspects of each method.

Results also revealed a bias toward lower TFA ARI scores, but differences between resulting ARI values should not be surprising given the large discrepancy between protocols. Slow, low-amplitude, sinusoidal changes in ABP (≥10 s/cycle) across resting conditions represent steady-state responses that are distinct from large, rapid, transient changes induced by cuff deflation (typically restored in <10 s), which may evoke confounding baroreflexes and heightened levels of sympathetic activity. Since CA assessments are frequency dependent (11, 37, 38), it is likely that TFA ARI scores were more sensitive to lower frequency components of dynamic CA than cuff ARI scores. The independence of the two ARI measurement techniques gives a broader view of CA and strengthens our argument that acute hypoxia impairs overall CA.

From a practical standpoint, TFA ARI assessments offer some advantages over cuff ARI assessments because they can be performed on resting subjects with minimal intervention. In addition, Mahony et al. (21) reported that optimal cuff ARI studies need to be repeated three times with a ≥8 min rest between cuff inflations, resulting in a minimal duration of 22 min. In contrast, the TFA ARI results reported in the present study were completed on a 4-min segment of data from 6 min total time breathing hypoxic or control gases. If TFA ARI measurements would be improved by repeat measurements, longer data collection time, or other methodological steps is not known. It has also been suggested that resting fluctuations in ABP are the most physiologically representative stimuli for assessing CA (35). These advantages should be considered when dealing with ill subjects, who may be reluctant to volunteer for repeated, and potentially uncomfortable, cuff assessments. For these reasons, we feel that TFA ARI tests offer a promising tool for future CA research.

Although the single integer values obtained by ARI techniques are easier to interpret than concurrent coherence, gain, and phase shift measures given by standard TFA techniques, ARI scores do not have physiological units. Alternatively, our results show that evaluation of the step response 4 s after the initial peak yields similar information to the TFA ARI score since they are both derived from the step response (r = 0.88, 79% shared variance; Fig. 4), but with the advantage of the outcome variable being in units of %Recovery of CBFv. For example, using these scores we can say that CA under normoxic conditions effectively restores 62.3 ± 10.9% of CBFv within 4 s of a hypothetical step change in ABP. In contrast, under hypoxic conditions, CA is challenged as only 50.8 ± 9.9% of CBFv is restored within 4 s of a similar step change in ABP. These values are in contrast to the nearly full recovery of CBFv 4 s following rapid changes in ABP induced by cuff deflation (Table 2), adding further support to our argument that TFA and cuff assessments measure different frequency components associated with myogenic, metabolic, and neurogenic regulation of cerebral blood flow.

Limitations

Cerebral blood flow was assumed to be proportional to changes in CBFv. This assumption is only valid if MCA diameter is constant, but we believe it is a reasonable assumption based on direct observation of MCA diameter during arterial PCO2 manipulation and application of lower body negative pressures to −40 mmHg (33). Additionally, abso-

Fig. 3. Step responses (n = 12) from 4 min of rest in normoxia (black) and hypoxia (shaded). TFA autoregulation index (ARI) and %CBFv recovery 4 s after the peak impulse (%Recovery) at 4 s scores derived from the step response were lower in hypoxia (P = 0.04 and 0.04, respectively). Error bars represent SE 4 s after peak response.

Fig. 4. Relationship between TFA ARI and %Recovery (n = 12) in normoxia (●) and hypoxia (-). Dashed line of identity shows a tight correlation between measurements (R = 0.88, R² = 0.79), which was expected since both measurements were derived from the step response. Results suggest that %Recovery may thus offer a simple surrogate to the more analytically intensive ARI.

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lute measurements of carotid artery blood flow have been well correlated with changes in MCA CBFv during leg cuff tests (22). Studies of acute hypoxia are inherently confounded by compensatory responses that preclude the ability to measure a steady physiological state. Because cuff ARI assessments are known to exhibit large CVs, measurements were taken in triplicate and averaged for analysis (21). A Latin squares design was used to balance the order of normoxic and hypoxic trials, but residual effects of prior trials may have increased ARI CVs. Due to time limitations, extended baseline periods necessary for TFA ARI calculations were only performed once in normoxia and hypoxia, yet resulting data were sufficient to obtain at least five windows (of 256 points), which were averaged for TFA analysis. A recent study has reported that TFA ARI assessments also have large CVs of 12–13% (6). Thus future studies should consider longer evaluation periods to obtain more and larger windows for TFA analysis, or potentially even clamping PETCO2, to reduce variance due to the influence of hypocapnia on CBF.

Our results are limited to measurement of dynamic CA. Pharmacological investigations that compare static CA against TFA ARI and %Recovery techniques may give additional insight into mechanisms underlying the integrated CA response.

Last, there are no absolute standards to determine if CA is intact or impaired from a single test. Conclusions regarding CA integrity were thus based on relative changes between normoxia and hypoxia. Larger population-based studies are needed to establish better normative ranges for those with known CA impairment and healthy controls using these relatively new measures of CA.

Conclusions
Results of this study provide the first evidence that acute, severe hypoxia impairs CA when evaluated by multiple, independent techniques. While both cuff and TFA assessments were sensitive to hypoxia, they appeared to measure different aspects of hypoxic CA impairment and healthy controls using these relatively new measures of CA.

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