Attenuated cerebral vasodilatory capacity in response to hypercapnia in college-aged African Americans

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New Findings

- What is the central question of this study?
  The main purpose of this investigation is to determine whether there is a difference in cerebral vasodilatory capacity in response to rebreathing-induced hypercapnia between African Americans and Caucasian Americans.

- What is the main finding and its importance?
  College-aged African Americans have reduced cerebral vasodilatory capacity during hypercapnia when compared with Caucasian counterparts, a finding that suggests cerebral vascular dysfunction in this population. These findings may contribute to the understanding of the greater prevalence of cerebral vascular disease in this population.

African Americans (AAs) have increased risk for cardiovascular, cerebral vascular and metabolic disease, including hypertension, stroke, coronary artery disease, metabolic syndrome and type II diabetes, relative to Caucasian Americans (CAs). While it is accepted that endothelial function is impaired in AAs, less is known regarding their cerebral vasodilatory capacity in response to hypercapnia. We hypothesized that AAs have a reduction in the total range of change in cerebral blood flow velocity (CBFV) measured in the middle cerebral artery and an index of cerebral vascular conductance (CVCI) in response to changes in the partial pressure of end-tidal carbon dioxide ($P_{ET,CO_2}$) during rebreathing-induced hypercapnia when compared with CAs. Twenty-one healthy, college-aged AA (10 male) and 21 age- and sex-matched CA (10 male) subjects participated in this study. A four-parameter logistic regression was used for curve fitting the responses of CBFV and CVCI relative to changes in $P_{ET,CO_2}$. The total ranges of change in CBFV (101 ± 18 versus 69 ± 23%; P < 0.001) and CVCI (83 ± 21 versus 58 ± 21%; P < 0.001) as well as the maximal increase in CBFV (205 ± 24 versus 169 ± 24%; P < 0.001) and CVCI (188 ± 30 versus 154 ± 19%; P < 0.001) were reduced during hypercapnia in AAs relative to CAs despite a similar increase in $P_{ET,CO_2}$ (change, 15 ± 3 versus 15 ± 3 mmHg; P = 0.65). In conclusion, these data indicate that AAs have attenuated cerebral vascular capacity to respond to hypercapnia when compared with CAs.

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Introduction

African Americans (AAs) are at an increased risk for cardiovascular and metabolic disease, including hypertension, stroke, coronary artery disease, metabolic syndrome and type II diabetes, relative to Caucasian Americans (CAs). The underlying mechanisms for this increased risk remain unresolved; however, blunted
endothelial function is a major contributing factor (Perregaux et al. 2000). Endothelial dysfunction results in impaired vasodilatation in the cerebral vasculature, and thus, leads to a dysfunction in cerebral blood flow (CBF) regulation (Zimmermann & Haberl, 2003; Lavi et al. 2006; Vicenzini et al. 2007). In this regard, AAs suffer from a greater prevalence of cerebral vascular disease, including stroke, relative to CAs (Roger et al. 2011).

The cerebral circulation is tightly regulated by arterial carbon dioxide tension ($P_{aCO_2}$), with hypercapnia increasing and hypocapnia decreasing CBF (Ide et al. 2003; Willie et al. 2014). The relationship between changes in CBF and $P_{aCO_2}$ is often assessed to evaluate cerebral vascular function (Ringelstein et al. 1988; Kleiser & Widder, 1992). The cerebrovascular response to changes in CO$_2$ is diminished in some clinical conditions, including diabetes (Kadoi et al. 2003), hypertension (Lavi et al. 2006) and carotid artery disease (Ringelstein et al. 1988), and is believed to be not only a predictor but also a contributor to stroke (Gur et al. 1996; Nur et al. 2009). The increase in CBF and/or cerebral vascular conductance during hypercapnia occurs primarily through modulation of the cerebral microcirculation, and thus, is a powerful tool that provides a non-invasive index of cerebral vascular health (Ringelstein et al. 1988; Lavi et al. 2003, 2006).

We hypothesized that the cerebral vasodilatory capacity, indexed by the range of change in cerebral blood flow velocity (CBFV) and an index of cerebral vascular conductance (CVCI), as well as the maximal value of CBFV and CVCI achieved during rebreathing-induced hypercapnia, are reduced in healthy college-aged AAs relative to CAs.

Methods

Ethical approval

The Institutional Review Board at The University of Texas at Austin approved all study procedures and the consent process used in the present study. Subjects were given a verbal description of all procedures and informed of the purpose and risks involved in the study before providing their informed, written consent. The study conformed to the provisions of the Declaration of Helsinki.

Subjects

Twenty-one Caucasian Americans (CAs; 10 males) and 21 African Americans (AAs; 10 males) participated in this study (Table 1). A subject’s ethnicity was defined as AA or CA and was only accepted if both parents were AA or CA, respectively. Subjects were non-smokers, were not taking medications and were free from cardiovascular, neurological, metabolic or cognitive diseases. All studies were conducted in the morning following an overnight fast (>12 h). Subjects refrained from strenuous exercise and alcoholic beverages for 24 h prior to and refrained from consuming caffeine and food for 12 h prior to the experimental trial, which was conducted in a temperature-controlled laboratory (~24°C and 40% relative humidity).

Instrumentation and measurements

All data were collected in the supine position. Each subject was instrumented for continuous measurement of heart rate (HR) and cardiac rhythms from an electrocardiogram (HP Patient Monitor; Agilent, Santa Clara, CA, USA) interfaced with a cardiotachometer (CWE, Ardmore, PA, USA). Continuous mean arterial pressure (MAP) was recorded and monitored from a finger using the Penaz method (CNAP, Biopac Monitor 500, Bruck an der Mur, Austria). The CBFV was measured continuously using transcranial Doppler ultrasonography. The right middle cerebral artery was imaged through a 2 MHz Doppler probe (Multi-flow; DWL Elektronische Systeme, Singen, Germany) adjusted over the temporal window until a signal was identified. The probe was fixed securely in place using a head strap to prevent any slight movement of the Doppler probe. The CVCI was calculated from the ratio of CBFV to MAP. End-tidal carbon dioxide tension ($P_{ET,CO_2}$) was measured continuously using a capnograph, through a mouthpiece, during all data collection periods and was used as an index of $P_{aCO_2}$ (VitalCap Capnograph Monitor; Oridion, Needham, MA, USA).

Experimental protocol

Following instrumentation, subjects rested quietly in the supine position for 20 min. Following the resting period, subjects were fitted with a nose-clip and breathed through a mouthpiece attached to a Y-valve. One end of the Y-valve was connected to a 5 litre bag and the other end was open to room air. Subjects breathed room air for a 6 min period of baseline data collection while CBFV, MAP, HR and $P_{ET,CO_2}$ data were collected. Subjects were then exposed to a rebreathing protocol, Subjects first performed a deep inspiration and exhaled into an empty rebreathing bag via the Y-valve. The subjects continued to rebreathe for ~3 min before switching the valve for a recovery period. During the rebreathing period, arterial oxygen saturation was held constant (between 97 and 98%) by bleeding a small amount of oxygen into the rebreathing bag (Claassen et al. 2007).

Data analysis

Data for MAP, HR, CBFV and $P_{ET,CO_2}$ were collected at 125 Hz via a data-acquisition system (Biopac System,
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Santa Barbara, CA, USA) during baseline conditions. Average cerebrovascular responses (CBFV and CVCI) during baseline and rebreathing conditions were assessed on a breath-by-breath basis. The percentage change in CBFV and CVCI was employed, while the absolute change in $P_{ET, CO_2}$ was determined. A four-parameter logistic regression was employed for sigmoidal curve fitting (Kent et al. 1972; Claassen et al. 2007, 2009), as follows:

$$f(x) = y_0 - \left( \frac{a}{1 + e^{b(x-x_0)}} \right)$$

where $a$ represents the range of change in the percentage of CBFV or CVCI, $b$ is a constant that determines the overall sigmoidal property of the curve, $x_0$ is the level of $P_{ET, CO_2}$ where cerebral vasomotor reactivity for CBFV or CVCI is maximal, and $y_0$ represents the maximal value of CBFV and CVCI during hypercapnia (Fig. 1). Maximal cerebral vasomotor reactivity [CVMR (CVMR$_{max} -$ CBFV and CVMR$_{max} -$ CVCI)], which was obtained at $x = x_0$, was calculated from the first-order derivative of the following logistic function:

$$f'(x) = \frac{ab \times e^{b(x-x_0)}}{\left[1 + e^{b(x-x_0)}\right]^2}$$

In order to compare with a four-parameter logistic curve model, CVMR using linear regression of changes in CBFV and CVCI (expressed as percentages) in response to a change (D) of 9 mmHg from its baseline $P_{ET, CO_2}$ value was assessed. The $\Delta$9 mmHg was chosen because it was the highest common change in $P_{ET, CO_2}$ that all subjects achieved during hypercapnia.

In order to assess cerebral vascular function further, indices of cerebral autoregulation were assessed by transfer function analysis over a specified frequency range (very low, 0.02–0.07 Hz; low, 0.07–0.20 Hz; and high, 0.20–0.35 Hz; Zhang et al. 1998). Transfer phase, gain and coherence functions were calculated using commercially available software (DADiSP; DSP Development, Cambridge, MA, USA).

**Statistical analysis**

Statistical analyses were performed using a statistical software package (SigmaPlot 12.5; Systat Software, Inc., San Jose, CA, USA). Subject characteristics, baseline haemodynamic data, transfer function analysis data, and all parameters and estimates of CVMR from a four-parameter logistic function and linear regression were compared using Student’s two-tailed paired t-tests. A $\chi^2$ test was used for difference in sex ratio between the two groups. All significance was set at $P \leq 0.05$, and data are presented as means $\pm$ SD.

### Table 1. Subject characteristics

| Variable                        | Caucasian Americans ($n = 21$) | African Americans ($n = 21$) | P Value |
|---------------------------------|--------------------------------|-----------------------------|---------|
| Age (years)                     | $23 \pm 3$                     | $23 \pm 4$                  | 0.97    |
| Sex (male/female)               | 10/11                          | 10/11                       | 1.00    |
| Body mass index (kg m$^{-2}$)   | $23 \pm 3$                     | $24 \pm 4$                  | 0.07    |
| Height (cm)                     | $174 \pm 8$                    | $173 \pm 9$                 | 0.85    |
| Weight (kg)                     | $68 \pm 12$                    | $73 \pm 14$                 | 0.24    |

Values are means $\pm$ SD.

### Results

**Subject characteristics and haemodynamic values during baseline period**

There were no differences between groups for age, sex, body mass index, height or weight (Table 1; $P > 0.05$ for all comparisons). During the eucapnic baseline period, there were no differences between groups for HR, MAP, CBFV, $P_{ET, CO_2}$, and CVCI (Table 2; $P > 0.05$ for all comparisons).

**Cerebrovascular responses during hypercapnia**

Representative examples of the relationship between CBFV versus $P_{ET, CO_2}$ and CVCI versus $P_{ET, CO_2}$ are illustrated in Fig. 2A and B, respectively. Table 3 shows the group-averaged parameters and estimates of CVMR from the logistic and the linear regressions. Maximal CBF (CBFV, as a percentage of baseline) during hypercapnia was lower in AA relative to CA subjects (CA, 195 ± 17% versus AA, 170 ± 20%; $P < 0.001$). Likewise, maximal conductance was reduced in AAs (CA, 178 ± 17% versus AA, 153 ± 16%; $P < 0.001$). The magnitude of hypercapnia ($\Delta P_{ET, CO_2}$) induced by rebreathing was similar between groups (CA, 15 ± 3 mmHg versus AA, 15 ± 3 mmHg; $P = 0.65$).

**Curve fitting and model parameters**

The correlation coefficients ($r^2$) for logistic regression were 0.95 and 0.94 for CBFV versus $P_{ET, CO_2}$ and CVCI versus $P_{ET, CO_2}$, respectively. From Table 3, the total range of changes in CBFV ($\alpha$; as a percentage) was attenuated in AAs (CA, 101 ± 18% versus AA, 69 ± 23%; $P < 0.001$). Likewise, the total range of changes in CVCI ($\beta$; as a percentage) was reduced in AAs (CA, 83 ± 21% versus AA, 58 ± 21%; $P < 0.001$). The maximal increase in CBFV ($\gamma_a$; as a percentage) was lower in AAs (CA, 205 ± 24% versus AA, 169 ± 24%; $P < 0.001$). Likewise, the maximal increase in CVCI ($\gamma_b$; as a percentage) was lower in AAs (CA, 188 ± 28% versus AA, 154 ± 19%; $P < 0.001$). The levels of $P_{ET, CO_2}$ that exhibited the highest CO$_2$ sensitivity ($x_0$; in millimetres of mercury) were not different between

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the two groups. Group differences for $a$ and $y_0$ are shown graphically in Fig. 3A and B, respectively.

**Estimates of CVMR**

No difference in maximal CVMR for CBFV and CVCI was observed between the two groups. In linear regression, there was no significant difference in the CVMR between the two groups ($P = 0.35$ and $P = 0.82$ for group differences of CBFV versus $P_{ET,CO_2}$ and CVCI versus $P_{ET,CO_2}$, respectively).

**Transfer function analysis**

The estimates of transfer phase, gain and coherence functions are shown in Table 4. In the very low-frequency range, there was no difference in phase between CAs and AAs (CA, 0.038 ± 0.026 radians versus AA, 0.024 ± 0.030 radians; $P = 0.18$). In contrast, in the low-frequency and high-frequency ranges, the transfer phase function was lower in AAs relative to CAs ($P = 0.04$ and $P = 0.02$, respectively). Transfer gain and coherence functions in all frequency ranges were not significantly different between CAs and AAs ($P > 0.05$ for all comparisons).

**Discussion**

The present study demonstrates that cerebral vasodilatation in response to rebreathing-induced hypercapnia is attenuated in young and healthy AAs compared with CAs. The lower cerebral vasodilatory response in AAs is a novel finding and may help to explain the greater prevalence of cerebral vascular disease in this population, although the underlying mechanisms need to be investigated further.

Carbon dioxide is a potent stimulus for changes in cerebral perfusion, and the sensitivity of this unique feature of the cerebral circulation is needed to ensure an adequate nutrient and oxygen supply as well as removal of metabolic waste products from brain tissue (Ringelstein et al. 1988; Kleiser & Widder, 1992). The ability of the brain to regulate its perfusion in response to changes in $P_{aCO_2}$ is an indicator of cerebral vascular health (Ringelstein et al. 1988; Kleiser & Widder, 1992). A reduction in cerebral vasodilatation impairs the ability to provide adequate nutrient and oxygen supply to

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**Table 2. Haemodynamic values during baseline period prior to rebreathing protocol**

| Variable                  | Caucasian Americans | African Americans | $P$ Value |
|---------------------------|---------------------|-------------------|-----------|
| HR (beats min$^{-1}$)     | 57 ± 10             | 61 ± 9            | 0.15      |
| MAP (mmHg)                | 98 ± 15             | 99 ± 13           | 0.91      |
| CBFV (cm s$^{-1}$)        | 63 ± 13             | 65 ± 16           | 0.71      |
| $P_{ET,CO_2}$ (mmHg)      | 38 ± 4              | 40 ± 5            | 0.29      |
| CVCI (cm s$^{-1}$ mmHg$^{-1}$) | 0.66 ± 0.2       | 0.67 ± 0.2        | 0.89      |

Values are means ± SD. Abbreviations: CBFV, velocity of blood in the middle cerebral artery; CVCI, index of cerebral vascular conductance; HR, heart rate; MAP, mean arterial pressure; and $P_{ET,CO_2}$, partial pressure of end-tidal carbon dioxide.

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**Figure 1. Schematic representations of logistic regressions**

A logistic regression and four parameters of the velocity of blood in the middle cerebral artery (CBFV) and index of cerebral vascular conductance (CVCI) versus the partial pressure of end-tidal carbon dioxide ($P_{ET,CO_2}$) are displayed in A and B, respectively. The parameter $a$ represents the range of change in the percentage of CBFV or CVCI, $b$ is a constant that determines the overall sigmoidal property of the curve, $x_0$ is the level of $P_{ET,CO_2}$ at which cerebral vasomotor reactivity for CBFV or CVCI is maximal, and $y_0$ represents the maximal value of CBFV and CVCI during the hypercapnic rebreathing protocol.
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the cerebral microcirculation as well as to prevent fluctuations in pH status (Lavi et al. 2003, 2006). In this regard, the present findings are particularly important, given the high prevalence of a variety of diseases and conditions, including stroke, Alzheimer’s disease and cognitive dysfunction, in the AA population (Mensah et al. 2005; Melikian et al. 2007).

From the examples depicted in Fig. 2A and B, an increase in CBFV and CVCI tends to be similar until a change of \( \pm 10 \) mmHg of \( P_{ET, CO_2} \), and this tendency is reflected in the CVMR results that were the same between the two groups (Table 3). Despite the similarity in this variable, AA subjects achieved maximal CBFV and CVCI prematurely, which resulted in a plateau as the hypercapnic period continued. In other words, the maximal increase and total range of increase in CBFV and CVCI were blunted in the AA subjects. In comparison, CAs exhibited a relatively stable elevation in CBFV and CVCI. Seven AA subjects showed a complete plateau similar to Fig. 2A and B, whereas no CA subjects showed this plateau. This trend for a plateau in AAs was reflected in a higher value of \( b \), which is the curvilinear property of the regression curve. Taken together, these findings further support the hypothesis of reduced cerebral vascular function in AAs.

Cerebral autoregulation

Damage to the cerebral microcirculation as a result of impaired cerebral autoregulation may explain why the capacity of the brain vasculature to dilate in response to changes in CO\(_2\) was reduced in AAs. Cerebral autoregulation is a mechanism to protect the cerebral vasculature against changes in blood pressure and to stabilize CBF (Meel-van den Abeelen et al. 2014; Willie et al. 2014). Impaired cerebral autoregulation is associated with increased morbidity and mortality (Hu et al. 2008) and is present in patients with hypertension, ischaemic stroke, severe head injury, Parkinson’s disease and carotid artery disease (Czosnyka et al. 1996; Eames et al. 2002, 2003; Vokatch et al. 2007; Reinhard et al. 2008). Long-term dysfunction of cerebral autoregulation induces physiological alterations, including cerebral microvascular remodelling and rarefaction (Levy et al. 2008; Reinhard et al. 2008), which limits maximal cerebral vasodilatory capacity, and if present in AAs, could partly explain the present findings. The transfer estimates of phase (a reflection of the temporal shift required to align the MAP signal with the CBFV signal) were lower in AAs in the low- and high-frequency ranges (Table 4). These findings suggest impaired cerebral autoregulation (Blaber et al. 1997; Zhang et al. 1998). However, transfer estimates of gain (the relative amplitude between changes in MAP and CBFV) and coherence (the linear relationship between MAP and CBFV) were similar between AAs and CAs in all frequency ranges (Table 4). These findings suggest similar autoregulation between groups. Based on these findings, differences in cerebral autoregulation between AAs and CAs are inconclusive and warrant further investigation.

Endothelial dysfunction and CO\(_2\)-mediated pathway in the brain

Cerebral blood flow is controlled by a CO\(_2\)-mediated pathway and endothelial signals in response to shear stress as well as changes in blood pressure. Thus, endothelial dysfunction...
Table 3. Cerebrovascular response to hypercapnia and parameters from logistic model

| Variable | Caucasian Americans | African Americans | P Value |
|----------|---------------------|-------------------|---------|
| Hypercapnia |                     |                   |         |
| Maximal flow (CBFV; % of baseline) | 195 (17) | 170 (20) | <0.001 |
| Maximal conductance (CVCI; % of baseline) | 178 (17) | 153 (16) | <0.001 |
| Magnitude of hypercapnia achieved (ΔPEt, CO2; mmHg) | 15 (3) | 15 (3) | 0.65 |
| Parameters from logistic model |         |                   |         |
| Flow |                     |                   |         |
| a (%) | 101 (18) | 69 (23) | <0.001 |
| b | 0.34 (0.2) | 0.50 (0.3) | 0.06 |
| x₀ (mmHg) | 45 (5) | 44 (4) | 0.47 |
| y₀ (%) | 205 (24) | 169 (24) | <0.001 |
| Conductance |                     |                   |         |
| a (%) | 83 (21) | 58 (21) | <0.001 |
| b | 0.34 (0.2) | 0.58 (0.4) | 0.018 |
| x₀ (mmHg) | 44 (6) | 43 (4) | 0.43 |
| y₀ (%) | 188 (28) | 154 (19) | <0.001 |
| Estimates of CVMR |         |                   |         |
| Logistic regression |         |                   |         |
| CVMRmax − CBFV (% mmHg⁻¹) | 8.3 (3.8) | 7.3 (2.8) | 0.35 |
| CVMRmax − CVCI (% mmHg⁻¹) | 6.8 (3.7) | 7.1 (2.9) | 0.82 |
| Linear regression (slope mmHg⁻¹) |         |                   |         |
| CVMRmax − CBFV (% mmHg⁻¹) | 6.6 (2) | 6.1 (2) | 0.40 |
| CVMRmax − CVCI (% mmHg⁻¹) | 5.6 (2) | 5.1 (2) | 0.39 |

Values are means ± SD. Abbreviations: a, the range of change in percentage of CBFV or CVCI; b, a constant that determines the overall sigmoidal property of the curve; x₀, the level of PET, CO₂ at which cerebral vasomotor reactivity for CBFV or CVCI is maximal; and y₀, the maximal value of CBFV and CVCI during the hypercapnic rebreathing protocol; CVMRmax, the maximal cerebral vasomotor reactivity using logistic regression analysis and linear regression analysis. Other abbreviations are as for Table 2.

Dysfunction or an impaired CO₂-mediated pathway in the brain would restrict cerebral vasodilatory capacity. Nitric oxide synthase inhibition reduces basal CBF (Joshi et al. 2000) and blunts CBF in response to hypercapnia in rats (Buchanan & Phillis, 1993), primates (Thompson et al. 1996) and humans (Schmetterer et al. 1997), indicating that basal cerebral perfusion as well as the response to hypercapnia is regulated, in part, by NO. This response is reversed by internal carotid artery infusion of L-arginine, a precursor for NO synthesis, in primates (Thompson et al. 1996) and in individuals with elevated cerebral vascular risk (Zimmermann & Haberl, 2003). The effect of NO synthase inhibition is greater as PₐCO₂ increases during hypercapnia (Buchanan & Phillis, 1993), suggesting a positive correlation. Furthermore, hypertensive and diabetic patients with impaired peripheral endothelial...
function have impaired cerebral vascular responses to hypercapnia, and this impairment was abolished following administration of the exogenous NO donor sodium nitroprusside (Lavi et al. 2006). African Americans have impaired endothelial function (Perregaux et al. 2000), reduced NO bioavailability (Melikian et al. 2007) and impaired NO-dependent vasodilatation (Perregaux et al. 2000). These impairments could contribute to the reduced cerebral vasodilatory capacity in this population.

**Limitations**

The CBFV reflects CBF only if the diameter of the middle cerebral artery is constant. Previous studies (Huber & Handa, 1967; Bradac et al. 1976; Serrador et al. 2000) demonstrated that the diameter of the middle cerebral artery does not change significantly during moderate changes in arterial blood pressure and carbon dioxide tension in plasma (within the range in the present study); thus, changes in CBFV reflect changes in CBF and can be used as an index of cerebral perfusion.

We did not measure \( P_{ac,o_2} \). Instead, \( P_{et,o_2} \) was used as an index of \( P_{ac,o_2} \). However, Phan et al. (1987) and others (Whitesell et al. 1981; Yosefy et al. 2004) have demonstrated that \( P_{et,o_2} \) is correlated well with \( P_{ac,o_2} \) at rest. Moreover, Xie et al. (2006) reported that there were no differences in CVMR values between \( P_{et,o_2} \) and \( P_{ac,o_2} \) during hypercapnia. Thus, we believe that \( P_{et,o_2} \) is a valid index for representing \( P_{ac,o_2} \) during both rest and hypercapnia.

**Conclusions**

In conclusion, we observed that young, otherwise healthy African Americans had reduced cerebral vasodilatory capacity in response to the same degree of elevation in \( P_{et,o_2} \) induced by hypercapnic rebreathing when compared with their Caucasian counterparts. This finding supports the hypothesis that the cerebral vascular response is reduced in relatively young, healthy African Americans. Given that African Americans are at higher risk of cardiovascular and cerebral vascular disease, the findings indicate that reduced cardiovascular and cerebrovascular function is present at an early age in African Americans, leaving a long period of time to become progressively worse and develop into overt cardiovascular and cerebral vascular diseases and their complications with advancing age.

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**Table 4. Transfer function analysis**

| Parameter          | Caucasian Americans | African Americans | \(P\) Value |
|--------------------|---------------------|-------------------|-------------|
| Gain (cm s\(^{-1}\) mmHg\(^{-1}\)) |                     |                   |             |
| Very low           | 0.83 (0.47)         | 1.16 (0.76)       | 1.17        |
| Low                | 0.79 (0.34)         | 0.86 (0.21)       | 0.71        |
| High               | 0.61 (0.34)         | 0.51 (0.15)       | 0.20        |
| Phase (radians)    |                     |                   |             |
| Very low           | 0.37 (0.16)         | 0.43 (0.19)       | 0.39        |
| Low                | 0.54 (0.15)         | 0.47 (0.16)       | 0.13        |
| High               | 0.42 (0.12)         | 0.40 (0.11)       | 0.51        |
| Coherence          |                     |                   |             |
| Very low           |                      |                   |             |
| Low                |                      |                   |             |
| High               |                      |                   |             |

Values are means ± SD. The following three different frequency ranges were used for the transfer function analysis: very low, 0.02–0.07 Hz; low, 0.07–0.20 Hz; and high, 0.20–0.35 Hz.
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Additional information

Competing interests

None declared.

Author contributions

C.H. contributed to the study design, data analysis and data interpretation, and drafted this manuscript. K.K., M.L.H. and R.M.B. contributed to the study design, data collection, data analysis, data interpretation and editorial process of the manuscript. All authors approved the final version of this manuscript. All experiments of the present study were conducted in the Environmental and Autonomic Physiology Laboratory at The University of Texas at Austin.

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