Cerebral Autoregulation

Cerebral Autoregulation of Blood Velocity and Volumetric Flow During Steady-State Changes in Arterial Pressure

Jie Liu, Yong-Sheng Zhu, Candace Hill, Kyle Armstrong, Takashi Tarumi, Timea Hodics, Linda S. Hynan, Rong Zhang

Abstract—The validity of using transcranial Doppler measurement of cerebral blood flow velocity (CBFV) to assess cerebral autoregulation (CA) is a concern. This study measured CBFV in the middle cerebral artery using transcranial Doppler and volumetric cerebral blood flow (CBF) in the internal carotid artery (ICA) using color-coded duplex ultrasonography to assess CA during steady-state changes in mean arterial pressure (MAP). Twenty-one healthy adults participated. MAP was changed stepwise by intravenous infusion of sodium nitroprusside and phenylephrine. Changes in CBFV, CBF, cerebrovascular resistance (CVR=MAP/CBF), or cerebrovascular resistance index (CVRi=MAP/CBFV) were measured to assess CA by linear regression analysis. The relationship between changes in ICA diameter and MAP was assessed. All values were normalized as percentage changes from baseline. Drug-induced changes in MAP were from −26% to 31%. Changes in CBFV and CVRi in response to MAP were linear, and the regression slopes were similar between middle cerebral artery and ICA. However, CBF in ICA remained unchanged despite large changes in MAP. Consistently, a steeper slope of changes in CVR relative to CVRi was observed (0.991 versus 0.804; P<0.05). The ICA diameter changed inversely in response to MAP (r=−0.418; P<0.05). These findings indicate that CA can be assessed with transcranial Doppler measurements of CBFV and CVRi in middle cerebral artery. However, it is likely to be underestimated when compared with the measurements of CBF and CVR in ICA. The inverse relationship between changes in ICA diameter and MAP suggests that large cerebral arteries are involved in CA. (Hypertension. 2013;62:973-979.) ● Online Data Supplement

Key Words: blood pressure ■ carotid artery, internal ■ middle cerebral artery ■ ultrasonography, Doppler, transcranial

Cerebral autoregulation (CA) is essential to maintain a constant cerebral blood flow (CBF) in the context of changes in cerebral perfusion pressure.1 Assessment of CA reflects cerebrovascular function and has been used widely in hypertension studies and other clinical settings.2,3 Quantitative assessment of CA is challenged by the methods used for CBF measurement. Modern imaging modalities such as single-photon emission computed tomography, positron emission tomography, perfusion computed tomography, and MRI are difficult to be applied for CBF measurement in clinical studies of CA because of the cumbersome experimental conditions, the limitations of using radioactive isotopes (single-photon emission computed tomography and positron emission tomography), or other imaging contrast agents (computed tomography and MRI) for repeated measurements.4

Recently, transcranial Doppler (TCD) has been used to assess CA because of its bedside availability, noninvasiveness, and high temporal resolution in measuring changes in cerebral blood flow velocity (CBFV) in the basal cerebral arteries.5 However, because the diameter of the insonated vessels cannot be measured directly using TCD, the validity of using this technique to assess CA is based on a fundamental assumption that changes in CBFV represent changes in volumetric CBF, that is, by assuming that the diameter of basal cerebral arteries does not change significantly in the face of changes in blood pressure.5 For its importance, this assumption has been evaluated repeatedly by using a variety of imaging modalities to measure CBF and to compare with TCD measurement of CBFV during changes in arterial pressure.6,7 However, the findings so far are inconsistent.8–10 One of the major limitations of these studies is that CBF and CBFV often were not measured simultaneously or were measured with different temporal and spatial resolutions, thus making it difficult or even impossible for direct comparisons between CBF and CBFV.
measurements given the nature of spontaneous oscillations in CBF and CBFV. In this regard, an earlier study showed that during acute reduction in arterial pressure, changes in CBFV in the middle cerebral artery (MCA) measured with TCD accurately reflected changes in volumetric CBF in the internal carotid artery (ICA) measured simultaneously with electromagnetic flowmetry. However, this study was conducted only in 7 patients with cerebrovascular diseases under surgical conditions, and these observations need to be confirmed. Color-coded duplex ultrasonography (CDUS) is a noninvasively bedside available technology that has been used to measure volumetric CBF in the ICA. Similar to TCD, CDUS also has high temporal resolution. In addition, changes in CBF in the ICA most likely reflect those in the MCA and anterior cerebral artery, which are the major branches of ICA.

In this study, we simultaneously measured changes in CBFV in the MCA and ICA and CBF in the ICA to assess CA during stepwise changes in arterial pressure induced by intravenous infusion of sodium nitroprusside (SNP) and phenylephrine. We tested the hypothesis that CA could be assessed equally well based on the measurements of CBFV in the MCA and volumetric CBF in the ICA. The outcome of this study will provide significant and new information regarding the validity of using TCD to assess CA during steady-state changes in arterial pressure.

Methods

Subjects

Twenty-one healthy adults were recruited from the local community to participate in this study. Subject demographic and clinical characteristics are presented in Table S1 in the online-only Data Supplement. Subjects were screened to exclude clinical histories of stroke, carotid stenosis, major medical and psychiatric disorders, unstable heart disease, uncontrolled hypertension, and diabetes mellitus. This study conformed to the standards of the Declaration of Helsinki for medical research involving human subjects. All subjects signed the informed consent including the study protocol approved by the institutional review boards of the UT Southwestern Medical Center and Texas Health Presbyterian Hospital of Dallas.

Experimental Protocol for Changes in Arterial Pressure

Subjects were asked to refrain from high-intensity exercise, alcohol, and caffeinated beverage at least 24 hours before the experiment. Intravenous infusions of SNP and phenylephrine were used to induce stepwise changes in arterial pressure. Subjects were in the supine position throughout the experiment. After ≥20 minutes of supine rest and baseline data collection, SNP was started with an infusion rate of 0.25 μg/kg per minute and then increased incrementally by 0.25 μg/kg per minute until mean arterial pressure (MAP) was reduced by 25% from the baseline or by 20 mm Hg whichever came first. The maximum dose used was 1.00 μg/kg per minute in the present study. After SNP infusion, a time interval of ≥20 minutes was provided to allow changes in hemodynamics to recover back to baseline. Then, phenylephrine infusion was started with 0.5 μg/kg per minute and then increased incrementally by 0.5 μg/kg per minute until MAP was increased by 30% from the baseline or by 25 mm Hg, whichever came first. The maximum dose used was 1.5 μg/kg per minute in the present study. At each stage of drug infusion, after changes in pressure were stabilized (≤2 minutes for SNP and 5 minutes for phenylephrine), 3 minutes of data were collected. Of note, the numbers of the exact stages of drug infusion were different among individual subjects depending on their cardiovascular responses to SNP or phenylephrine infusion.

Data Collection

TCD was used to measure the time-averaged peak velocity from the spectral envelop of Doppler signal to represent CBFV in the MCA using the standard method (DWL Elektronische Systeme, Germany). The TCD probe was placed on the skin over the temporal bone region above the zygomatic arch. A custom-made probe holder or a headgear (Spencer Technologies) was used to prevent movement of the TCD probe during the study. Brachial arterial pressure was measured using a sphygmomanometer (Tango+, Suntech). Analog signals of CBFV waveforms, arterial pressure (Finapres, Ohmeda), ECG (GE Solar 8000M, and respiratory CO2 (Capnomard, Novametrix) were recorded continuously using a data acquisition system (Acknowledge, BIOPAC Systems). The time-averaged data of CBFV, arterial pressure, heart rate, and breath-by-breath end-tidal CO2 (ETCO2) at the baseline and during each stage of drug infusion were used for statistical analysis.

The CBFV and CBF measurements at the ipsilateral ICA including quantification of the vessel diameter (D) and the cross-sectional area [CSA=π(D/2)]2 of the ICA were performed using the CDUS method (Figure 1). For details on these measurements, please see the online-only Data Supplement. Cerebrovascular resistance index (CVRi) was estimated as MAP divided by CBF, and cerebrovascular resistance index (CVR) was estimated as MAP divided by CBFV. All of the measurements were obtained from the baseline and when blood pressure was stabilized during each stage of drug infusion.

Assessment of CA

First, CA was assessed by linear regression of percentage changes in CBFV, CBF, CVRi, or CVR (Δ%) in responses to percentage changes in MAP (Δ%) based on the pooled data from all subjects. For ΔCBFV% or ΔCBF%, a linear regression slope of 0 has been used to indicate intact autoregulation whereas a significantly increased slope indicates impaired autoregulation. Conversely, a linear regression slope of 0 for ΔCVRi% or ΔCVR% would suggest impaired autoregulation, whereas a slope of ≈1.0 indicates intact autoregulation. However, it must be acknowledged that the use of these indices to assess CA is likely to be useful only for quantification of relative changes in CA because a clear cutoff threshold for any of these indices to indicate an impaired CA has not been established.

Furthermore, CA was assessed for each individual subject by linear regression of percentage changes in CVR or CVR in the MCA and ICA in responses to percentage changes in MAP to account for the individual variability in CA and for group comparisons. Finally, multiple linear regression analysis was used to account for the influences of percentage changes in ETCO2 (Δ%) on CA: Y=A+B×ΔMAP%+ C×ΔETCO2%+ e, where Y represents ΔCBFV%, ΔCBF%, ΔCVRi%, or ΔCVR% (dependent variable), A is a constant, B is the unstandardized linear regression coefficient representing CA after adjustment for the influence from changes in ETCO2, C is the unstandardized linear regression coefficient representing cerebral vasomotor reactivity to changes in CO2, and e represents model random error. We used a similar multiple linear regression analysis to assess the influences of percentage changes in ETCO2 and MAP on the ICA diameter or CSA−1 (cerebrovascular resistance index (CVR) was estimated as MAP divided by CBF, and cerebrovascular resistance index (CVRi) was estimated as MAP divided by CBFV). All of the measurements were obtained from the baseline and when blood pressure was stabilized during each stage of drug infusion.

Statistical Analysis

We performed linear regression analysis of changes in CBFV, CBF, CVRi, or CVR in response to changes in arterial pressure using the general linear model method. For the pooled data from the whole group, we compared CA between the MCA and ICA using the regression slopes of ΔCBFV% or ΔCVRi% to ΔMAP% according to the Steiger method. In the ICA, we compared the linear regression slopes of ΔCVRi% and ΔCVR% (ie, velocity versus volumetric flow for assessment of changes in CVR) to ΔMAP% according to the Steiger method. Slopes are expressed as mean±SE. Comparisons of CA based on the individual data were performed using paired t test. A level of P<0.05 was considered statistically significant. Data were analyzed using SPSS 19 (IBM SPSS Inc, Chicago, IL).
Results

Baseline systemic and cerebral hemodynamics are presented in Table S1. Drug infusion–induced percentage changes in MAP were from −26% to 31% (65–132 mm Hg) relative to the baseline. ETCO₂ changed concomitantly associated with changes in arterial pressure ranging from −24% to 18% (24–48 mm Hg). A positive correlation was found between ΔMAP% and ΔETCO₂% ($r=0.396$; $P<0.001$).

The linear regression slopes of ΔCBFV% and ΔCVRi% to ΔMAP% were positive and similar between the MCA and ICA (ΔCBFV%: 0.239±0.065 versus 0.220±0.054; $P=0.69$; and ΔCVRi%: 0.777±0.078 versus 0.804±0.065; $P=0.09$; Figure 2A versus 2B; Figure 2D versus 2E). However, no significant changes in CBF in the ICA were observed despite large changes in MAP (the linear regression slope was small and not statistically different from zero, Figure 2C). Consequently, the slope of ΔCVR% to ΔMAP% was steeper than that of ΔCVRi% to ΔMAP% (0.991±0.062 versus 0.804±0.065; $P<0.05$; Figure 2F versus 2E), suggesting that the assessment of CA is likely to be underestimated by the measurement of CVRi instead of CVR. Notably, large individual variabilities of changes in CBFV, CBF, ICA diameter, and CSA⁻¹ were observed during changes in arterial pressure (Figures 2 and 4).

Consistently, for individual data analyses, no group difference in the linear regression slopes of ΔCVRi% to ΔMAP% was found between the MCA and ICA; however, these slopes were significantly lower than that of ΔCVR% to ΔMAP% at the ICA (0.820±0.056 versus 1.090±0.065; $P<0.01$; and 0.874±0.059 versus 1.090±0.065; $P<0.01$; Figure 3).

Multiple regression analyses showed that changes in ETCO₂ during drug infusion influenced the cerebral hemodynamics (Table S2). After controlling for changes in ETCO₂, CBFV and CVRi responses to changes in MAP were similar between the MCA and ICA, consistent with the simple linear regression results (Table S2).

Finally, at ICA, the ΔDiameter% was correlated negatively and the ΔCSA⁻¹% was correlated positively to ΔMAP% (Figure 4). Multiple linear regression analyses showed that these relationships were not influenced by changes in ETCO₂ (Table S2).

Discussion

The main findings of this study are 2-fold. First, we found that changes in CBFV and CVRi in response to changes in arterial pressure measured in the MCA using TCD were similar to those measured in the ICA using CDUS. Notably, the linear regression slopes of changes in CBFV to MAP were positive but relatively small ($\approx 0.24$) and the slopes of changes in CVRi to MAP also were positive but relatively large ($\approx 0.78$), suggesting presence of CA. However, volumetric CBF measured in the ICA, as a group average, remained unchanged despite large changes in MAP. Consistently, the linear regression slope of CVR to MAP was steeper than that of CVRi to MAP. Collectively, these findings indicate that CA can be assessed via the measurement of CBFV and CVRi in the MCA using TCD, but it is likely to be underestimated with these measures. Second, we found an inverse relationship between changes in the ICA diameter and MAP, suggesting that large cerebral arteries participate in CA in human subjects.

Autoregulation of CBFV and CBF

TCD measurement of CBFV in the MCA has been used widely to assess CA. Previous studies in healthy adults found a positive correlation between changes in CBFV and MAP with a linear slope of 0.5% to 3.0% per mm Hg within a range of MAP from $\approx 60$ to 150 mm Hg. These observations have
been interpreted to indicate that CBF could not be maintained constant in response to change in arterial pressure even with the presence of intact CA. Consistent with these prior studies, our study also showed a positive linear slope of $0.24 \Delta \text{CBFV} (\%) \cdot \Delta \text{MAP} (\%)^{-1}$, which is $0.27\%$ per mm Hg between changes in CBFV and MAP.

The new findings of the present study are that CBFV responses to changes in arterial pressure were similar between the MCA and ICA. As expected, the obtained $\Delta \text{CVRi} % - \Delta \text{MAP} %$ slopes were similar between the MCA and ICA (Figure 2D versus 2E). The slope of linear regressions between $\Delta \text{CVRi} %$ and $\Delta \text{MAP} %$ has been used to reflect CA capacity. A slope of 0 has been used to indicate absence of CA, whereas a slope of 1.0 indicates the presence of a perfect CA. Thus, assessment of CA based on the CVRi–MAP relationship would suggest that CA is $70\%$ to $80\%$ intact during steady-state changes in arterial pressure in the subjects of the present study.

However, as a group average, volumetric CBF in the ICA remained unchanged during changes in arterial pressure. Consistently, the slope of $\Delta \text{CVR} % - \Delta \text{MAP} %$ was near to 1.0, which would suggest the presence of a perfect CA. Thus, when compared with volumetric CBF or CVR measurements, the assessment of CA could have been underestimated when CBFV or CVRi was used.

There are 2 important issues related to the data interpretation that need to be discussed. First, consistent with previous studies, we found that there was a positive correlation between changes in ETCO2 and MAP. A recent study suggests that baroreflex-mediated changes in ventilation may explain changes in ETCO2 associated with transient changes in arterial pressure. Whether similar mechanism(s) would apply during steady-state changes in arterial pressure is not known, and we did not measure ventilation in this study.

Changes in ETCO2 may reflect changes in arterial CO2 which have profound effects on CBF. Previous studies of
CA used a correction coefficient of 3% to 6% changes in CBF or CBFV per mmHg change in ETCO₂ to account for the confounding effect of CO₂. This method has limitations in that either under- or overcorrections may occur because of the existence of large individual variability in cerebral vasomotor reactivity to CO₂. In this study, multiple linear regression analysis was used to account for the influences of changes in ETCO₂ on assessment of CA. As expected, the ΔCBFV%−ΔMAP% regression coefficients were reduced and the ΔCVRI% or ΔCVR%−ΔMAP% coefficients were increased after adjustment of ΔETCO₂% when compared with simple linear regressions (Figure 2 and Table S2).

Second, large intra- and intersubject variabilities of CBFV and CBF were present during changes in arterial pressure. In this study, TCD probe was kept in the same position and the insonation angle was maintained constant by using a custom-made probe holder or a headgear to reduce artifacts. Furthermore, for CBF measurement using the CDUS method, the ICA diameter was measured using a high-resolution edge-detection and echo-tracking method to reduce the confounding effect of CO₂. This method has limitations of the existence of large individual variability in cerebral vasomotor reactivity to CO₂. In this study, multiple linear regression analysis was used to account for the influences of changes in ETCO₂ on assessment of CA. As expected, the ΔCBFV%−ΔMAP% regression coefficients were reduced and the ΔCVRI% or ΔCVR%−ΔMAP% coefficients were increased after adjustment of ΔETCO₂% when compared with simple linear regressions (Figure 2 and Table S2).

Second, large intra- and intersubject variabilities of CBFV and CBF were present during changes in arterial pressure. In this study, TCD probe was kept in the same position and the insonation angle was maintained constant by using a custom-made probe holder or a headgear to reduce artifacts. Furthermore, for CBF measurement using the CDUS method, the ICA diameter was measured using a high-resolution edge-detection and echo-tracking method to reduce the confounding effect of CO₂. This method has limitations of the existence of large individual variability in cerebral vasomotor reactivity to CO₂. In this study, multiple linear regression analysis was used to account for the influences of changes in ETCO₂ on assessment of CA. As expected, the ΔCBFV%−ΔMAP% regression coefficients were reduced and the ΔCVRI% or ΔCVR%−ΔMAP% coefficients were increased after adjustment of ΔETCO₂% when compared with simple linear regressions (Figure 2 and Table S2).

Second, large intra- and intersubject variabilities of CBFV and CBF were present during changes in arterial pressure. In this study, TCD probe was kept in the same position and the insonation angle was maintained constant by using a custom-made probe holder or a headgear to reduce artifacts. Furthermore, for CBF measurement using the CDUS method, the ICA diameter was measured using a high-resolution edge-detection and echo-tracking method to reduce the confounding effect of CO₂. This method has limitations of the existence of large individual variability in cerebral vasomotor reactivity to CO₂. In this study, multiple linear regression analysis was used to account for the influences of changes in ETCO₂ on assessment of CA. As expected, the ΔCBFV%−ΔMAP% regression coefficients were reduced and the ΔCVRI% or ΔCVR%−ΔMAP% coefficients were increased after adjustment of ΔETCO₂% when compared with simple linear regressions (Figure 2 and Table S2).

Second, large intra- and intersubject variabilities of CBFV and CBF were present during changes in arterial pressure. In this study, TCD probe was kept in the same position and the insonation angle was maintained constant by using a custom-made probe holder or a headgear to reduce artifacts. Furthermore, for CBF measurement using the CDUS method, the ICA diameter was measured using a high-resolution edge-detection and echo-tracking method to reduce the confounding effect of CO₂. This method has limitations of the existence of large individual variability in cerebral vasomotor reactivity to CO₂. In this study, multiple linear regression analysis was used to account for the influences of changes in ETCO₂ on assessment of CA. As expected, the ΔCBFV%−ΔMAP% regression coefficients were reduced and the ΔCVRI% or ΔCVR%−ΔMAP% coefficients were increased after adjustment of ΔETCO₂% when compared with simple linear regressions (Figure 2 and Table S2).

Second, large intra- and intersubject variabilities of CBFV and CBF were present during changes in arterial pressure. In this study, TCD probe was kept in the same position and the insonation angle was maintained constant by using a custom-made probe holder or a headgear to reduce artifacts. Furthermore, for CBF measurement using the CDUS method, the ICA diameter was measured using a high-resolution edge-detection and echo-tracking method to reduce the confounding effect of CO₂. This method has limitations of the existence of large individual variability in cerebral vasomotor reactivity to CO₂. In this study, multiple linear regression analysis was used to account for the influences of changes in ETCO₂ on assessment of CA. As expected, the ΔCBFV%−ΔMAP% regression coefficients were reduced and the ΔCVRI% or ΔCVR%−ΔMAP% coefficients were increased after adjustment of ΔETCO₂% when compared with simple linear regressions (Figure 2 and Table S2).

Second, large intra- and intersubject variabilities of CBFV and CBF were present during changes in arterial pressure. In this study, TCD probe was kept in the same position and the insonation angle was maintained constant by using a custom-made probe holder or a headgear to reduce artifacts. Furthermore, for CBF measurement using the CDUS method, the ICA diameter was measured using a high-resolution edge-detection and echo-tracking method to reduce the confounding effect of CO₂. This method has limitations of the existence of large individual variability in cerebral vasomotor reactivity to CO₂. In this study, multiple linear regression analysis was used to account for the influences of changes in ETCO₂ on assessment of CA. As expected, the ΔCBFV%−ΔMAP% regression coefficients were reduced and the ΔCVRI% or ΔCVR%−ΔMAP% coefficients were increased after adjustment of ΔETCO₂% when compared with simple linear regressions (Figure 2 and Table S2).

Second, large intra- and intersubject variabilities of CBFV and CBF were present during changes in arterial pressure. In this study, TCD probe was kept in the same position and the insonation angle was maintained constant by using a custom-made probe holder or a headgear to reduce artifacts. Furthermore, for CBF measurement using the CDUS method, the ICA diameter was measured using a high-resolution edge-detection and echo-tracking method to reduce the confounding effect of CO₂. This method has limitations of the existence of large individual variability in cerebral vasomotor reactivity to CO₂. In this study, multiple linear regression analysis was used to account for the influences of changes in ETCO₂ on assessment of CA. As expected, the ΔCBFV%−ΔMAP% regression coefficients were reduced and the ΔCVRI% or ΔCVR%−ΔMAP% coefficients were increased after adjustment of ΔETCO₂% when compared with simple linear regressions (Figure 2 and Table S2).
cerebral arteries. However, intracarotid infusion of SNP sufficient to reduce arterial pressure does not change CBF in humans. Thus, whether or not SNAP has direct effects on the ICA diameter needs to be determined. Finally, 9 subjects in this study used antihypertensives to control their blood pressure (Table S1). It is not known whether the antihypertensives used would have different effects on the MCA CBFV or ICA CBF regulation. However, a subgroup data analysis of these subjects did not differ from those of not using antihypertensives (data not shown). Thus, all the data were pooled together in this study.

**Perspectives**

TCD has been used widely to study CA in patients with hypertension and other neurovascular diseases. However, one of the major limitations of TCD is that it can only measure CBFV in the basal cerebral arteries, and an assumption has to be made that changes in CBFV in the insonated arteries reflect changes in volumetric CBF. Thus, the validity of using TCD for assessment of CA has been a concern. In this study, we found that changes in CBFV in response to steady-state changes in arterial pressure were similar between the MCA and ICA and that the linear regression slopes between changes in CBFV (or CVR) and arterial pressure indeed could reflect characteristics of CA. However, assessment of CA using these indices obtained with TCD is likely to be underestimated when compared with the measurements of CBF or CVR in the ICA. Furthermore, we found an inverse relationship between changes in the ICA diameter and arterial pressure which suggests that large cerebral arteries are involved in CA. Given the important role of CA in understanding the control of brain perfusion, these findings have significant clinical implications for evaluation of the methodologies used for CA assessment.

**Acknowledgments**

We thank all our study participants for their willingness, time, and effort devoted to this study and all other members of our team for their excellent technical support.

**Sources of Funding**

This study was supported in part by the National Institutes of Health grants R01AG033106-01 and R01HL102457.

**Disclosures**

None.

**References**


### Novelty and Significance

**What Is New?**

- Cerebral autoregulation, a protective vascular mechanism to maintain brain blood flow constant, was assessed by measuring changes in blood flow velocity and volumetric flow simultaneously in the large cerebral arteries during stepwise changes in arterial pressure. This study demonstrates that changes in blood flow velocity in response to changes in arterial pressure are consistent among large cerebral arteries and that the large cerebral arterial arteries, such as the internal carotid artery, are involved in cerebral autoregulation in human subjects.

**What Is Relevant?**

- Study of cerebral autoregulation is fundamentally important for understanding the mechanisms of control of brain perfusion in patients with hypertension and for antihypertensive therapy.

**Summary**

Transcranial Doppler is a widely used method for studying cerebral autoregulation but has a major limitation in that it only can measure blood flow velocity in the large cerebral arteries. This study showed that changes in transcranial Doppler measured blood flow velocity in response to changes in arterial pressure indeed reflect the characteristics of cerebral autoregulation. However, assessment of cerebral autoregulation using blood flow velocity is likely to be underestimated when compared with volumetric blood flow. Furthermore, large cerebral arteries are involved in cerebral autoregulation. These novel findings are important for evaluation of the methodologies used for cerebral autoregulation assessments in clinical settings.
Cerebral Autoregulation of Blood Velocity and Volumetric Flow During Steady-State Changes in Arterial Pressure
Jie Liu, Yong-Sheng Zhu, Candace Hill, Kyle Armstrong, Takashi Tarumi, Timea Hodics, Linda S. Hynan and Rong Zhang

Hypertension. 2013;62:973-979; originally published online September 16, 2013; doi: 10.1161/HYPERTENSIONAHA.113.01867

Hypertension is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2013 American Heart Association, Inc. All rights reserved.
Print ISSN: 0194-911X. Online ISSN: 1524-4563

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://hyper.ahajournals.org/content/62/5/973

Data Supplement (unedited) at:
http://hyper.ahajournals.org/content/suppl/2013/09/16/HYPERTENSIONAHA.113.01867.DC1

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Hypertension can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Hypertension is online at:
http://hyper.ahajournals.org//subscriptions/
Cerebral Autoregulation of Blood Velocity and Volumetric Flow during Steady-State Changes in Arterial Pressure

Short title: CA measured in MCA and ICA

Jie Liu\textsuperscript{1,2,3}, Yong-Sheng Zhu\textsuperscript{1,2}; Candace Hill\textsuperscript{1}; Kyle Armstrong\textsuperscript{1}; Takashi Tarumi\textsuperscript{1,2}; Timea Hodics\textsuperscript{4}; Linda S. Hynan\textsuperscript{5}; Rong Zhang\textsuperscript{1,2,4,*}

\textsuperscript{1}Institute for Exercise and Environmental Medicine, Texas Health Presbyterian Hospital Dallas, Dallas, TX, USA
\textsuperscript{2}Department of Internal Medicine, University of Texas Southwestern Medical Center, Dallas, TX, USA
\textsuperscript{3}Department of Ultrasound Diagnostics, Tangdu Hospital, Fourth Military Medical University, Xi’an, China
\textsuperscript{4}Department of Neurology and Neurotherapeutics, University of Texas Southwestern Medical Center, Dallas, TX, USA
\textsuperscript{5}Department of Clinical Sciences and Psychiatry, University of Texas Southwestern Medical Center, Dallas, TX, USA

\textsuperscript{*}Corresponding Author:
Rong Zhang
Institute for Exercise and Environmental Medicine,
Texas Health Presbyterian Hospital Dallas,
7232 Greenville Ave, Dallas, TX 75231
Tel: (214) 345-8843
Fax: (214) 345-4618
E-mail: RongZhang@texashealth.org
SUPPLEMENTAL METHODS AND TABLES:

Color-coded duplex ultrasonography (CDUS)
A 3-12 MHz linear array transducer of a CDUS system (CX-50, Phillips Healthcare) was used for cerebral blood flow (CBF) measurements from the internal carotid artery (ICA)\(^1\). The CDUS probe was placed on the neck and the sample volume for CBF measurement in the ICA was at least 1 cm distal to the carotid bulb. A straight vessel segment with a parallel wall view was identified where the luminal diameter remained the same for a length of at least 0.5 cm to enhance the uniformity of Doppler sample volume which covered the entire vessel lumen for data acquisition (Figure 1A and 1C). At least 5 complete cardiac cycles of consecutive blood flow velocity waveforms were recorded to obtain the time-averaged peak velocity (TAPV) and the time-averaged mean velocity (TAMV) (Figure 1C). TAPV measured in the ICA was compared with that obtained in the ipsilateral middle cerebral artery using transcranial Doppler. The ICA inner diameter (the intima to intima distance between the near and far vessel walls in a perpendicular angle) was measured using a semiautomatic edge-detection and echo-tracking software to enhance the accuracy and reliability of the measurement (Figure 1A and 1B). The time-averaged vessel diameter (D) over 3 to 5 cardiac cycles was used to estimate the mean ICA cross-sectional area (CSA) with CSA = \(\pi \times (D/2)^2\), and CBF was calculated as CBF = TAMV × CSA × 60. This measurement was repeated for 3 times at baseline and each stage of drug infusion and averaged to reduce intrinsic CBF variability.\(^1\)

References for expanded materials and methods
Table S1. Subject characteristics and baseline hemodynamics

<table>
<thead>
<tr>
<th>Variables</th>
<th>Values* (n = 21)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>68 (6)</td>
</tr>
<tr>
<td>Female, No. (%)</td>
<td>12 (57%)</td>
</tr>
<tr>
<td>Height, cm</td>
<td>171 (8)</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>80 (16)</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>26.9 (4.2)</td>
</tr>
<tr>
<td><strong>Antihypertension medications</strong></td>
<td></td>
</tr>
<tr>
<td>ACE inhibitors</td>
<td>7 (33%)</td>
</tr>
<tr>
<td>Diuretics</td>
<td>4 (19%)</td>
</tr>
<tr>
<td>Calcium channel blockers</td>
<td>3 (14%)</td>
</tr>
<tr>
<td>β-blocker</td>
<td>1 (5%)</td>
</tr>
<tr>
<td>Renin inhibitor</td>
<td>1 (5%)</td>
</tr>
<tr>
<td><strong>Baseline hemodynamics</strong></td>
<td></td>
</tr>
<tr>
<td>SaO₂, %</td>
<td>96 (2)</td>
</tr>
<tr>
<td>ETCO₂, mmHg</td>
<td>40 (4)</td>
</tr>
<tr>
<td>Blood pressure, mmHg</td>
<td></td>
</tr>
<tr>
<td>Systolic BP</td>
<td>123 (16)</td>
</tr>
<tr>
<td>Diastolic BP</td>
<td>76 (10)</td>
</tr>
<tr>
<td>Mean arterial pressure</td>
<td>91 (11)</td>
</tr>
<tr>
<td>Heart rate, bpm</td>
<td>59 (9)</td>
</tr>
<tr>
<td>MCA</td>
<td></td>
</tr>
<tr>
<td>CBFV, cm/s</td>
<td>52.0 (16.6)</td>
</tr>
<tr>
<td>CVRi, mmHg·s/cm</td>
<td>1.88 (0.51)</td>
</tr>
<tr>
<td>ICA</td>
<td></td>
</tr>
<tr>
<td>CBFV, cm/s</td>
<td>38.2 (8.6)</td>
</tr>
<tr>
<td>CVRi, mmHg·s/cm</td>
<td>2.51 (0.64)</td>
</tr>
<tr>
<td>Diameter, mm</td>
<td>4.73 (0.69)</td>
</tr>
<tr>
<td>CBF, mL/min</td>
<td>233 (60)</td>
</tr>
<tr>
<td>CVR, mmHg·min/mL</td>
<td>0.42 (0.17)</td>
</tr>
</tbody>
</table>

*Values are the mean (standard deviation) or categorical variables (percentage).
ACE indicates angiotensin converting enzyme; SaO₂, arterial blood oxygen saturation; ETCO₂, end-tidal CO₂; Bp, blood pressure; bpm, beats per minute; MCA, middle cerebral artery; CBFV, cerebral blood flow velocity; CVRi, cerebrovascular resistance index; ICA, internal carotid artery; CBF, cerebral blood flow; CVR, cerebrovascular resistance.
Table S2. Multiple linear regressions of percentage changes in cerebral hemodynamics in response to percentage changes in ETCO2 and arterial pressure

<table>
<thead>
<tr>
<th>Dependent Variables (Δ%)</th>
<th>Vessels</th>
<th>Model R²</th>
<th>Independent variables* (Δ%)</th>
<th>Model parameters † (95% CI)</th>
<th>SE</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CBFV</td>
<td>MCA</td>
<td>0.247</td>
<td>ETCO₂</td>
<td>0.405 (0.166~0.643)</td>
<td>0.120</td>
<td>0.001</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>MAP</td>
<td>0.150 (0.016~0.283)</td>
<td>0.067</td>
<td>0.028</td>
</tr>
<tr>
<td></td>
<td>ICA</td>
<td>0.327</td>
<td>ETCO₂</td>
<td>0.418 (0.228~0.608)</td>
<td>0.095</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>MAP</td>
<td>0.127 (0.021~0.233)</td>
<td>0.053</td>
<td>0.019</td>
</tr>
<tr>
<td>CBF</td>
<td>ICA</td>
<td>0.119</td>
<td>ETCO₂</td>
<td>0.308 (0.124~0.491)</td>
<td>0.092</td>
<td>0.001</td>
</tr>
<tr>
<td>CVRi</td>
<td>MCA</td>
<td>0.608</td>
<td>MAP</td>
<td>0.891 (0.732~1.050)</td>
<td>0.080</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>ETCO₂</td>
<td>-0.512 (-0.796~ -0.228)</td>
<td>0.143</td>
<td>0.001</td>
</tr>
<tr>
<td></td>
<td>ICA</td>
<td>0.720</td>
<td>MAP</td>
<td>0.919 (0.792~1.046)</td>
<td>0.064</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>ETCO₂</td>
<td>-0.521 (-0.749~ -0.294)</td>
<td>0.114</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CVR</td>
<td>ICA</td>
<td>0.783</td>
<td>MAP</td>
<td>1.071 (0.943~1.198)</td>
<td>0.064</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>ETCO₂</td>
<td>-0.361 (-0.589~ -0.133)</td>
<td>0.115</td>
<td>0.002</td>
</tr>
<tr>
<td>Diameter</td>
<td>ICA</td>
<td>0.174</td>
<td>MAP</td>
<td>-0.114 (-0.169~ -0.060)</td>
<td>0.027</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CSA⁻¹</td>
<td>ICA</td>
<td>0.182</td>
<td>MAP</td>
<td>0.231 (0.124~0.339)</td>
<td>0.054</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

*Independent variable is excluded if P > 0.05; †Model parameters are unstandardized correlation coefficients. Δ% indicates percentage change relative to baseline; CI, confidence Interval; SE, standard error of the model parameter estimates; CBFV, cerebral blood flow velocity; CBF, cerebral blood flow; CVRi, cerebrovascular resistance index = MAP/CBFV; CVR, cerebrovascular resistance = MAP/CBF; CSA⁻¹, the reciprocal of cross-sectional area at internal carotid artery (ICA); MCA, middle cerebral artery; MAP, mean arterial pressure; ETCO₂, end-tidal CO₂.