Fundamental relationships between blood pressure and cerebral blood flow in humans

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1Cardiovascular Systems Laboratory, University of Otago, Wellington South, New Zealand; 2Centre for Translational Physiology, University of Otago, Wellington South, New Zealand; 3Centre for Heart, Lung and Vascular Health, School of Health and Exercise Sciences, University of British Columbia, Okanagan, Kelowna, British Columbia, Canada; and 4Graduate School of Biomedical Engineering, University of New South Wales, Sydney, New South Wales, Australia

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Tzeng YC, MacRae BA, Ainslie PN, Chan GS. Fundamental relationships between blood pressure and cerebral blood flow in humans. J Appl Physiol 117: 1037–1048, 2014. First published August 28, 2014; doi:10.1152/japplphysiol.00366.2014.—Cerebral blood flow responses to transient blood pressure challenges are frequently attributed to cerebral autoregulation (CA), yet accumulating evidence indicates vascular properties like compliance are also influential. We hypothesized that middle cerebral blood velocity (MCAv) dynamics during or following a transient blood pressure perturbation can be accurately explained by the windkessel mechanism. Eighteen volunteers underwent blood pressure manipulations, including bilateral thigh cuff deflation and sit-to-stand maneuvers under normocapnic and hypercapnic (5% CO2) conditions. Pressure-flow recordings were analyzed using a windkessel analysis approach that partitions the frequency-dependent resistance and compliance contributions to MCAv dynamics. The windkessel was typically able to explain more than 50% of the MCAv variance, as indicated by R2 values for both the flow recovery and postrecovery phase. The most consistent predictors of MCAv dynamics under the control condition were the windkessel capacitive gain and high-frequency resistive gain. However, there were significant interindividual variations in the composition of windkessel predictors. Hypercapnia consistently reduced the capacitive gain and enhanced the low-frequency (0.04–0.20 Hz) resistive gain for both thigh cuff deflation and sit-to-stand trials. These findings indicate that 1) MCAv dynamics during acute transient hypotension challenges are dominated by cerebrovascular windkessel properties independent of CA; 2) there is significant heterogeneity in windkessel properties between individuals; and 3) hemodynamic effects of hypercapnia during transient blood pressure challenges primarily reflect changes in windkessel properties rather than pure CA impairment.

effective regulation of cerebral blood flow (CBF) is a requisite for brain health and function, yet the mechanisms underlying this regulatory process are poorly understood. Unlike adipose tissue or resting muscle, brain tissue is unique due to its high basal metabolic rate, limited intrinsic energy reserves, and heavy reliance on aerobic glucose metabolism (32). These energetic traits underline the brain’s distinctive vulnerability to ischemia and highlights why stringent maintenance of perfusion stability is necessary for cerebrovascular health (40). To this end, active autoregulation of cerebral arterial resistance has gained acceptance as the foremost mechanism for optimizing CBF stability against changes in arterial blood pressure (BP) (21). For over 2 decades, cerebral autoregulation (CA) has been a focal point for a diverse range of physiological and pathophysiologic research. Unfortunately, advancing knowledge in the field has been challenging due to the lack of a quantitative gold-standard measure of CA (45).

Contemporary understanding of CA physiology has been decisively shaped by two ideas. First is the canonical view that CA is a vascular process that maintains CBF near perfectly stable across a wide range of arterial BPs (50–150 mmHg) (19). Lassen’s notion of CA has never been conclusively validated within subjects, yet it has become a popular model of CA with pervasive influence in many aspects of clinical medicine (51). Second is the idea that, rather than being a perfect buffering mechanism across all timescales, CA is a process that achieves only relative CBF control in response to dynamic BP challenges (2). In their landmark experiments, Aslaid and colleagues (3, 42) used transcranial Doppler ultrasound (TCD) to characterize the blood velocity responses in the middle cerebral artery (MCA) (MCAv; as an index of CBF) to an abrupt and transient reduction in BP in otherwise healthy individuals. Although BP and MCAv both decreased following the sudden release of thigh occlusion cuffs, the ensuing recovery of MCAv was always faster (5–10 s) than that of BP (15–20 s). This pivotal observation was attributed to active cerebral arterial vasodilatation (i.e., CA), and the explanation has become the basis of interpretation for many quantitative measures of CA function (44).

Recent data, however, indicate that common interpretations of many CA metrics are overly simplistic, since few exhibit quantitative relations to justify a common physiological basis (45). Indeed, the cerebrovasculature is a distensible organ (23–25), and analyses that account for its resistance and compliance properties can explain close to 80% of CBF variance under conditions where BP is dynamically rising (8), falling (8, 29), or oscillating at low frequencies (47). Other studies have shown that windkessel models generated surprisingly accurate hemodynamic simulations of CBF waveforms and pressure-flow transfer functions (15, 29, 52). These accuracies support the concept that dynamic cerebral pressure-flow relations are determined by the complex interplay between the mechanical properties of blood vessels and active vasomotor mechanisms, such as CA.

In light of the above, we sought to determine the extent to which the windkessel mechanism underlies a quintessential flow characteristic frequently affiliated with CA: the early CBF recovery response to transient hypotensive challenges (2). Our first objective was to test the hypothesis that cerebrovascular windkessel properties play an integral role in modulating...
MCAv dynamics following a transient hypotension stimulus. Our second objective was to explore the diversity of mechanisms underpinning these hemodynamic responses and to gain insight into interindividual response variations that are expected of phenotypically heterogeneous individuals.

To address these goals, healthy human volunteers were recruited to undergo BP manipulations using the thigh-cuff deflation (TC) (2) and sit-to-stand (STS) techniques (39). Data obtained under normocapnic conditions were compared against the hypercapnic state wherein the cerebrovasculature is vasodilated and CA is often assumed to be impaired. Pressure-flow recordings were then subjected to a novel analysis approach that partitions the individual and collective contributions of vascular resistance and compliance on CBF dynamics (8, 47). To place the findings in context of established quantification approaches, we also derived the Tiecks’ autoregulatory index (ARI) for TC and STS trials (39, 42).

METHODS

Subjects

Experiments were conducted on 18 healthy subjects (nine women; mean age 23 ± 0.67 yr) without any history of cardiovascular, respiratory, or endocrine disease. The protocol was approved by the New Zealand Central Regional Ethics Committee and conformed to guidelines established in the Declaration of Helsinki. All subjects had abstained from caffeinated products and exercise for at least 12 h prior and were advised to have a light breakfast at least 2 h before the study. Participants gave written, informed consent before participation.

Measurements

We recorded continuous three-lead electrocardiogram, noninvasive beat-to-beat BP via finger photoplethysmography (Finometer MIDI, MLE1054-V, Finapres Medical Systems), MCAv (2-MHz pulsed Doppler ultrasound, ST3 Digital Transcranial Doppler System, Spencer Technologies, Seattle, WA), and partial pressure of end-tidal CO₂ sampled from a nasal catheter (gas analyzer model ML206, ADInstruments, Colorado Springs, CO). All studies were conducted in a temperature-controlled laboratory (22–23°C) at the University of Otago. All data were monitored in real-time during experimental testing and acquired continuously at 1-kHz per channel via an analog-to-digital converter (PowerLab/16SP ML795; ADInstruments) interfaced with a Macintosh computer. Stored data were later extracted for postprocessing using LabChart 7 Pro (ADInstruments).

BP and CO₂ Manipulation

Subjects underwent a comprehensive BP manipulation protocol with oscillatory lower body negative pressure and bilateral TC in the supine position and STS maneuvers in the upright position. Each condition was completed during normocapnia (breathing room air) and a physiological state where CA is assumed to be impaired (induced via hypercapnia; 5% CO₂) (2, 54). Test condition (normocapnia vs. hypercapnia) was randomized for each method but not for the order of the test methods. This was done to minimize postural and equipment setup transitions, which pilot studies indicated was necessary to ensure subjects could comfortably complete the protocol within a single session. This study reports the data from the TC and STS trials. All test sessions began with an initial 10-min period of baseline recordings before active testing. For TC, large pneumatic cuffs were secured around both thighs and inflated to suprasystolic pressures (200 mmHg) for 3 min before rapid (<1 s) deflation and a further 3 min of monitoring. STS maneuvers were performed with the subjects initially positioned in a straight back chair with their feet flat on the floor, resting quietly for 5 min. Thereafter, subjects were instructed to stand and remain standing for a further 3 min. The arm bearing the Finometer was placed in a sling to ensure it was fixed at heart level and to minimize movement artifacts. Participants were instructed to breathe normally (i.e., avoid the Valsalva maneuver) and to minimize excessive forward flexion when standing up. Hypercapnia was achieved by asking participants to breathe a premixed gas mixture containing 5% CO₂, 21% O₂, and balanced with N₂.

Data Analysis

Windkessel model parameter estimation. Cerebral pressure-flow dynamics were characterized using a regression-based modeling approach based on the windkessel model (8, 47) (see APPENDIX for description of the model design). To quantify the extent to which dynamic changes in BP and MCAv were related to cerebral arterial resistance and compliance, data were fitted to Eq. A6 (see APPENDIX) using general linear mixed-effects models adjusted for repeated measures. For TC and STS trials, the arterial pressure and MCAv waveforms were integrated within each cardiac cycle and divided by the pulse interval. The resultant mean arterial pressure (MAP) and mean blood velocity (MCAv) time series were then resampled at 4 Hz, followed by signal decomposition and data segment selection (Fig. 1). This was done by first passing the 4-Hz time series through a 0.20-Hz low-pass filter (zero-phase eighth-order Butterworth). The very-low-frequency (VLF) component was extracted using a 20-s Hanning windowed moving average, and the low-frequency (LF) and high-frequency (HF) components were obtained by respectively subtracting the VLF trends from the 0.20-Hz signal, and the 0.20-Hz signal from 4-Hz signal. To account for delayed compliance (31), the lag corresponding to the maximum positive correlation between rate of change in MAP (dMAP/dt) and LF MCAv was determined, and the dMAP/dt was shifted to incorporate this delay.

In this study, we sought to model the flow recovery phase, which was defined as the interval between hypotension onset (i.e., t = 0, corresponding to the moment of thigh-cuff release or stand) and the point at which flow returns to the pretest baseline (trecov). To gain insight into the postrecovery phase, we also modeled the variable interval between trecov and 35 s from t = 0 (see APPENDIX for full details). For each phase of the TC and STS response, we modeled the MCAv time series as the dependent variable, and the VLF, LF, and HF MAP (MAPVLF, MAPLF, and MAPHF, respectively) and dMAP/dt as independent predictors. The conductive gains relating MAPVLF, MAPLF, and MAPHF to MCAv (GVLF, GLF, and GHF, respectively) and the capacitive gain relating dMAP/dt and MCAv were quantified as unstandardized β-coefficients. Standardized β-coefficients were also derived and systematically ranked to evaluate the relative impact of each predictor in explaining MCAv variance. Steady-state cerebrovascular conductance index (CVCi) was calculated as ratio between average MCAv and MAP.

ARI. The ARI was calculated using the methods developed by Tiecks et al. (42) and modified by Chacon et al. (7). This involved applying a second-order linear differential equation defined as:

$$\frac{dP_n}{dt} = \frac{MAP - MAP_{base}}{MAP_{base} - CCP}$$

$$x_{2n} = x_{2n-1} + \frac{(x_{1n} - 2D_n \cdot x_{2n-1})}{f \cdot T}$$

$$x_{1n} = x_{1n-1} + \frac{(dP_n - x_{2n-1})}{f \cdot T}$$

$$mV_n = MCAv_{base} \cdot (1 + dP_n - k \cdot x_{2n})$$

where dPn is the normalized change in MAP relative to the control value (MAP_{base}) adjusted for the estimated critical closing pressure (CCP = 12 mmHg), x₂ and x₁ are state variables (equal to 0 at baseline), mA is modeled mean velocity, MCAv_{base} is baseline velocity, and CCP is the critical closing pressure.
Fig. 1. Schematic illustration showing the conceptual steps involved in the mixed-effects model analysis. This representative example shows the recorded mean arterial pressure (MAP) time series following thigh-cuff deflation (TC; shaded lines; C). Corresponding MCAv data are superimposed (solid lines; C). VLF, very low frequency; LF, low frequency; HF, high frequency; dMAP/dt, rate of change in MAP; ∆, change.

MCAv, f is the sampling frequency (10 Hz), and n is the sample number. The mVn generated from 10 predefined combinations of parameters T (time constant), D (dampening factor), and k (autoregulatory gain) were fitted to the actual MCAv recording within a 35-s window to identify the best fit model associated with the minimum standard error. The unconstrained ARI ranging between 0 (absence of CA) to 9 (strongest CA) was derived via polynomial interpolation (7). According to Tiecks’ model, the ARI assigns an integer value to each of the 10 template curves (0–9). The conventional interpretation of this metric is that a value of 0 represents no CA (i.e., CBF passively follow perfusion pressure), and a value of 9 represents perfect CA (i.e., changes in perfusion pressure produces no alteration to CBF) (42).

Statistical Analysis

Groupwise estimation and comparisons of windkessel model parameters across study conditions were made using general linear mixed-effects models (20). This analytic approach has ideal statistical properties for handling missing and repeated-measures data compared with conventional regression or ANOVA analyses. Whereas conventional regression analysis requires x–y data to be reduced to summary measures before secondary analysis, mixed-effects models are implemented in one step without the loss of information concerning the precision of parameter estimates. This ensures that group average coefficients relating predictor and dependent variables and their differences across groups or conditions are weighted for precision based on the standard error of estimates. These properties confer greater power for detecting relationships and treatment effects (6).

For implementation, MCAv was entered into all models as the primary outcome variable and BP variables (i.e., MAPVLF, MAPLF, MAPHF, dMAP/dt) as continuous predictors. The primary fixed factors of interest were methods (TC, STS) and study conditions [normocapnia (control) vs. hypercapnia]. Thus differences in windkessel parameters across method and or condition can be parsimoniously evaluated by testing for two- and three-way interactions and all lower-order fixed effects (adjusted for multiple comparisons). In addition to the fixed effects, random effects terms for subject identification, intercept, and BP variables were included to enable estimates of slopes and intercepts to vary for each individual. This approach is theoretically justified because cerebral pressure-flow relations are expected to vary between individuals. In this study, the G-matrix random effects were modeled using the variance components covariance structure. Furthermore, to account for the fact that repeated measurements within individuals tend to be correlated, the R-matrix random effects were modeled using the autoregressive covariance structure. The inclusion of these terms objectively improved the model fit as determined on the basis of the Akaike information criterion (14). Given that information criterion are relative rather than absolute measures of model fit, we also derived an $R^2$ statistic for mixed-effects models (12). Expressed in percentages, the $R^2$ indicates the proportion of CBF variance that can be explained by the fixed effects terms of a given mixed-effects model.

Unless otherwise specified, all analyses were conducted separately for the flow recovery and postrecovery phases as a priori planned comparisons. All data were analyzed using software written in LabView 11 (National Instruments, Austin, TX), SPSS (IBM SPSS statistics version 19, Surrey, UK), and SAS programming packages (version 9.1.3, SAS Institute, Cary, NC). For consistency, all data and weighted parameter outputs from mixed-effects models were expressed as means ± SE. Statistical significance was set a priori at $P < 0.05$.

RESULTS

Pressure-Flow Dynamics Following TC and Standing

Baseline cardiovascular and respiratory parameters are summarized in Table 1. All subjects completed the TC trials. Sudden deflation of bilateral TC elicited an acute reduction in MAP and MCAv in all subjects. The reduction in MAP and MCAv from baseline to the nadir was 21 ± 1.0 mmHg and 13 ± 3.4 cm/s, respectively. In all subjects, MCAv recovered back to baseline levels following the onset of TC (9.8 ± 0.80 s).
before MAP recovery. Data were obtained from 17 subjects for the STS trials. Following STS, the reduction in MAP and MCAv from baseline to the nadir was 25 ± 2.2 mmHg and 15 ± 7.6 cm/s, respectively, with MCAv recovery occurring 9.8 ± 0.52 s following standing. Qualitatively, there were significant interindividual variations in the pattern of MCAv dynamics during both the flow recovery and postrecovery phases (see Figs. 1 and 2 for examples). One notable pattern was that, in 53% of subjects, MCAv recovery following standing was seen to overshoot the baseline at \( t_{\text{recovery}} \), before settling at a level around (66% of subjects) or below (24% of subjects) the baseline. In contrast BP recovery was typically slower and generally still below baseline levels at \( t_{\text{recovery}} \).

The analytic steps involved in the windkessel analysis are illustrated in Fig. 1, which shows the decomposition of BP signals into their constituent frequency components. Ingeniously, the MAPLF trend positive predictors of flow dynamics following TC were LF capacitive gain (CLF) and GHF during the flow recovery phase, and G\(_{\text{VLF}}\), C\(_{\text{LF}}\), and G\(_{\text{HF}}\) during the postrecovery phase. Similarly, the most consistent positive predictors of flow recovery after STS were C\(_{\text{LF}}\) and G\(_{\text{HF}}\). For STS, the most consistent positive predictors of postrecovery flow dynamics were G\(_{\text{HF}}\), C\(_{\text{LF}}\), and G\(_{\text{LF}}\). However, unlike the TC response, G\(_{\text{VLF}}\) was not a positive predictor of postrecovery dynamics in any subject. These results indicate that the influential determinants of flow recovery dynamics following TC are similar to those following STS, but that contrasting predictor distribution patterns are seen during the postrecovery phase.

To assess the relative importance of each BP predictor on MCAv dynamics, we analyzed and ranked the standardized \( \beta \)-coefficients. For the flow recovery phase following TC, C\(_{\text{LF}}\) was the most influential predictor of variance (0.62 ± 0.062, \( P < 0.01 \)) followed by GHF (0.29 ± 0.039, \( P < 0.01 \)). A similar pattern was observed following STS, with C\(_{\text{LF}}\) ranked

### Table 1. Baseline parameters during normocapnia (control) and hypercapnia conditions

<table>
<thead>
<tr>
<th>Variable</th>
<th>Control</th>
<th>Hypercapnia</th>
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<tbody>
<tr>
<td>HR, beats/min</td>
<td>61 ± 1.2</td>
<td>63 ± 1.3*</td>
</tr>
<tr>
<td>MCAv, cm/s</td>
<td>65 ± 3.4</td>
<td>74 ± 4.6*</td>
</tr>
<tr>
<td>MAP, mmHg</td>
<td>81 ± 2.6</td>
<td>84 ± 2.9</td>
</tr>
<tr>
<td>End-tidal ( P_{\text{CO}_2} ), Torr</td>
<td>39 ± 0.57</td>
<td>45 ± 0.73*</td>
</tr>
<tr>
<td>CVCi, cm(^{-3})mmHg(^{-1})</td>
<td>0.81 ± 0.048</td>
<td>0.90 ± 0.059*</td>
</tr>
</tbody>
</table>

Values are means ± SE. HR, heart rate; MCAv, mean middle cerebral artery blood velocity; MAP, mean blood pressure; CVCi, cerebrovascular conductance index. * \( P < 0.05 \) vs. control.

Figure 2 shows examples of model fits for two individuals, and Fig. 3 summarizes the overall \( R^2 \) values during both the flow recovery and postrecovery phases. In general, the fixed-effects terms of the windkessel model explained >50% of MCAv variance during TC and STS trials. For TC trials, the flow recovery phase was associated with a slightly better model fit compared with the postrecovery phase (\( \Delta R^2 = 15\% \)). In contrast, for STS trials, the model fit was slightly better during the postrecovery phase (\( \Delta R^2 = 11\% \)).

Analysis of the composition of explanatory variables across individuals shows that it was possible for subjects to have between one and four statistically significant positive predictors of MCAv dynamics (Fig. 4). In general, the most consistent positive predictors of flow dynamics following TC were LF capacitive gain (CLF) and GHF during the flow recovery phase, and G\(_{\text{VLF}}\), C\(_{\text{LF}}\), and G\(_{\text{HF}}\) during the postrecovery phase. Similarly, the most consistent positive predictors of flow recovery after STS were C\(_{\text{LF}}\) and G\(_{\text{HF}}\). For STS, the most consistent positive predictors of postrecovery flow dynamics were G\(_{\text{HF}}\), C\(_{\text{LF}}\), and G\(_{\text{LF}}\). However, unlike the TC response, G\(_{\text{VLF}}\) was not a positive predictor of postrecovery dynamics in any subject. These results indicate that the influential determinants of flow recovery dynamics following TC are similar to those following STS, but that contrasting predictor distribution patterns are seen during the postrecovery phase.

**Fig. 2.** Representative model analyses for two subjects during the flow recovery (left) and postrecovery (right) phases following TC (top) and sit-to-stand (STS, bottom) trials. Model fits (dotted line) are superimposed on data (solid lines). Note that MCAv clearly overshoots the baseline at \( t_{\text{recovery}} \), which corresponds to time \( t = 0 \) for the postrecovery phase.
Table 2. Predictors of MCAv dynamics following TC and STS under control condition (normocapnia)

<table>
<thead>
<tr>
<th>Parameter Estimates</th>
<th>TC Flow recovery</th>
<th>TC Postrecovery</th>
<th>STS Flow recovery</th>
<th>STS Postrecovery</th>
</tr>
</thead>
<tbody>
<tr>
<td>GVLF, cm·s⁻¹·mmHg⁻¹</td>
<td>0.19 ± 0.068†</td>
<td>0.31 ± 0.15*</td>
<td>0.81 ± 0.13†</td>
<td>−0.60 ± 0.092†</td>
</tr>
<tr>
<td>GLF, cm·s⁻¹·mmHg⁻¹</td>
<td>0.17 ± 0.11</td>
<td>−0.018 ± 0.15</td>
<td>0.023 ± 0.11</td>
<td>0.50 ± 0.072†</td>
</tr>
<tr>
<td>GHF, cm·s⁻¹·mmHg⁻¹</td>
<td>0.97 ± 0.10†</td>
<td>0.97 ± 0.15†</td>
<td>0.76 ± 0.083†</td>
<td>0.78 ± 0.060†</td>
</tr>
<tr>
<td>CLF, cm/mmHg</td>
<td>0.99 ± 0.098†</td>
<td>1.0 ± 0.15†</td>
<td>1.0 ± 0.14†</td>
<td>0.76 ± 0.060†</td>
</tr>
</tbody>
</table>

Values are means ± SE. TC, thigh-cuff deflation; STS, sit-to-stand; GVLF, very-low-frequency conductive gain; GLF, low-frequency conductive gain; GHF, high-frequency conductive gain; CLF, low-frequency capacitive gain. Statistically significant: *P < 0.05 and †P < 0.01.

the highest (0.76 ± 0.046, P < 0.01) followed by GHF (0.25 ± 0.033, P < 0.01).

In contrast, we observed divergent patterns of predictor influence during the postrecovery phase. For TC trials, the most influential predictor was GVLF (0.36 ± 0.089, P < 0.01), followed closely by CLF (0.35 ± 0.060, P < 0.01) and GHF (0.22 ± 0.031, P < 0.01). In contrast, CLF (0.48 ± 0.055, P < 0.01) and GHF (0.20 ± 0.036, P < 0.01) exerted the greatest relative influence following STS.

Effects of Hypercapnia

Hypercapnia trials were successfully conducted on all subjects. The effects of hypercapnia on spontaneous baseline cardiovascular and ventilatory parameters are shown in Table 1. Compared with the control condition, hypercapnia was associated with higher heart rate, MCAv, end-tidal PCO₂, and CVCi (Table 1). The control and hypercapnia conditions did not differ significantly on levels of MAP (Table 1).

On average, the statistically significant predictors of TC flow recovery dynamics during hypercapnia were MAPVLF, MAPLF, MAPHF, and dMAP/dr (Table 3). Likewise, the significant predictors of postrecovery flow dynamics during hypercapnia were MAPVLF, MAPLF, MAPHF, and dMAP/dr (Table 3). For STS trials, we found that MAPVLF, MAPLF, MAPHF, and dMAP/dr were all statistically significant predictors of flow recovery dynamics (Table 3). During the postrecovery phase, MAPLF, MAPHF, and dMAP/dr were all statistically significant predictors of MCAv dynamics, except for MAPVLF, which did not reach statistical significance (P = 0.13).

Goodness-of-fit analysis under the hypercapnia condition indicates that the windkessel model was typically able to explain a substantive portion of flow variance (Fig. 3) during both the flow recovery phase and postrecovery phases.

To quantify the changes in windkessel parameters with hypercapnia, we examined the two-way interactions between the BP parameter as continuous predictors and study condition as a fixed factor (Table 4). Analysis of TC trials yielded significant two-way interactions for GLF and CLF during both the flow recovery and postrecovery phases, indicating that hypercapnia was associated with an increase in mean GLF and a decrease in mean CLF during both phases of the TC trial.

Corresponding analyses of STS trials showed significant two-way interactions for GVLF, CLF, and GHF during the flow recovery phase, indicating that hypercapnia increased mean CLF and decreased mean GHF. Two-way interactions were also found for GVLF, GHF, and CLF during the flow recovery phase, consistent with an increase in GVLF and GHF, and a decrease in CLF. To determine whether the change scores associated with hypercapnia differed significantly between TC and STS trials, we tested for three-way interaction effects between condition (control vs. hypercapnia), method (TC vs. STS), and BP parameters as continuous predictors. Significant three-way interactions were found for GVLF during the flow recovery phase, and for GVLF, CLF, and GHF during the postrecovery phase.

Figure 5 shows the effects of hypercapnia on the ARI index calculated for TC and STS. The average model fit (R²) for TC trials under control and hypercapnia conditions were 53 ± 5.1 and 74 ± 4.0%, respectively. The corresponding model fits for STS trials were 68 ± 4.6 and 79 ± 3.0%, respectively. Pairwise comparisons showed that exposure to CO₂ lead to significant reductions in ARI values for both TC and STS trials. ARI values derived from TC and STS trials were not related (R² = 0.1, P = 0.21).

Fig. 3. Bar plots showing the proportion of variance explained (R²) by the windkessel models for TC and STS trials under room air conditions (shaded bars) and hypercapnia (open bars). For TC trials, the flow recovery phase was associated with a slightly better model fit compared with the postrecovery phase (ΔR² = 15%). For STS trials, the model fit (excluding MAPvLF) was slightly better during the postrecovery phase compared with the flow recovery phase (ΔR² = 11%). Hypercapnia improved the model fit for the TC postrecovery phase (ΔR² = 8%) and the STS flow recovery phase (ΔR² = 7%), but did not significantly alter the model fits for TC flow recovery and or STS power recovery phases.
Fig. 4. Distribution of statistically significant positive predictors across the subjects studied expressed as percentage of subjects. The most consistent predictors of flow dynamics following TC were LF capacitive gain ($C_L$; 100%) and HF conductive gain ($G_H$; 94%) during the flow recovery phase, and VLF conductive gain ($G_{VLF}$; 100%), $G_H$ (100%), and $C_L$ (89%) during the postrecovery phase. The most consistent predictors of STS flow recovery were $C_L$ (82%) and $G_H$ (88%). Unlike TC trials, $G_{VLF}$ for STS was not a positive predictor of postrecovery dynamics in any subjects. However, controlling for its effects, we found that LF conductive gain ($G_L$; 94%), $G_H$ (100%), and $C_L$ (77%) were all significant positive predictors. Removing the MAP$_{VLF}$ predictor from the model altered the predictor distribution slightly for $G_L$ (53%) and $C_L$ (88%).

**DISCUSSION**

This study comprises three major findings. First, we showed that the windkessel explained, on average, >80% of flow variance during the initial flow recovery phase following TC deflation and STS and continued to explain >50% of flow variance during the postrecovery phase. This finding broadly supports our hypothesis that windkessel properties play a critical role in modulating CBF responses canonically ascribed to CA. Second, we found that the composition of BP predictors, particularly during the postrecovery phase, varied dramatically between individuals, and between different modes of BP perturbation within an individual. This finding suggests that CBF responses to transient hypotensive challenges are underlain by heterogeneity in windkessel properties. Such physiological diversity may help explain why many indexes of CA impairment per se. The following discussion outlines the evidence, assumptions, and technological considerations that underpin our three main findings.

**Windkessel Modulation of Human Cerebral Pressure-Flow Relations**

The flow responses to a transient hypotensive perturbation, such as TC and standing (e.g., STS), or intravenous injections of vasodilator substances (e.g., nitroprusside) are often attributed to CA (3, 28, 38, 42, 49). Recently, our laboratory (8, 46) and others (15, 29, 52) have proposed an alternative perspective based on the windkessel. In this study, we extended our analytic approach to explore the hemodynamic basis of two CA assessment techniques (bilateral TC deflation and STS) that have gained widespread acceptance. Our principal finding was that a linear windkessel model quantitatively explains well over 50% of MCAv variance under conditions where the hemodynamic effects of CA are generally thought to dominate. These results suggest that net MCA flow likely reflects an admixture of capacitive flow ($Q_C$) (determined by the rate of change in pressure and vascular compliance) and resistive flow (determined by instantaneous pressure and vascular resistance), as well as nonlinear flow responses (arising from active processes such as CA) (8, 47). Furthermore, we observed differences in the extent to which capacitive and resistive flow contributed to net MCA flow dynamics between individuals, and between different BP perturbation modes. The heterogeneous nature of CBF dynamics alludes to previously unrecog-
Table 4. Effects of hypercapnia on windkessel model parameters

<table>
<thead>
<tr>
<th>Parameter Estimates</th>
<th>Flow recovery</th>
<th>Postrecovery</th>
<th>Flow recovery</th>
<th>Postrecovery</th>
<th>Flow recovery</th>
<th>Postrecovery</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\Delta G_{VL}$, cm·s$^{-1}$·mmHg$^{-1}$</td>
<td>0.044 ± 0.084</td>
<td>0.032 ± 0.077</td>
<td>$-0.29 \pm 0.12^*$</td>
<td>0.52 ± 0.099†</td>
<td>&lt;0.01</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>$\Delta G_{HF}$, cm·s$^{-1}$·mmHg$^{-1}$</td>
<td>0.36 ± 0.084†</td>
<td>0.39 ± 0.065†</td>
<td>0.56 ± 0.092†</td>
<td>0.089 ± 0.059</td>
<td>0.16</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>$\Delta G_{IF}$, cm·s$^{-1}$·mmHg$^{-1}$</td>
<td>0.0028 ± 0.044</td>
<td>0.0074 ± 0.031</td>
<td>$-0.024 ± 0.044$</td>
<td>0.096 ± 0.014†</td>
<td>0.95</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>$\Delta C_{LF}$, cm·mmHg</td>
<td>$-0.49 \pm 0.092^*$</td>
<td>$-0.45 \pm 0.082^*$</td>
<td>$-0.60 \pm 0.12^*$</td>
<td>$-0.29 \pm 0.075^*$</td>
<td>0.78</td>
<td>0.13</td>
</tr>
</tbody>
</table>

Values are means ± SE. All values are change scores ($\Delta$) between control and hypercapnia (5% CO$_2$) condition. Statistically significant three-way interactions indicate that the changes with hypercapnia differ between TC and STS trials. Statistically significant two-way interactions ($^*P < 0.05$ and †$P < 0.01$) indicate that parameter estimates differed between the control and hypercapnic condition. Note that changes with hypercapnia are assessed as two-way interactions because model parameters are slope estimates.

nized complexities, precluding simple approaches to physiological interpretation (45).

Two particular findings warrant specific consideration. First, we found that the composition of statistically significant predictors was highly consistent during the flow recovery phase, but varied considerably among individuals during the postrecovery phase, and between different modes of BP perturbation.

By far the most consistent predictors of flow recovery following TC and STS were $C_{LF}$ and $G_{IF}$, with the former exerting the greatest relative influence. The practical significance of $C_{LF}$ is most likely due to large dMAP/dt changes during flow recovery engaging the arterial compliance to generate $Q_C$. These results confirm the influential effects of accelerating/decelerating BP on CBF dynamics (47). On the other hand, the significance of $G_{IF}$ indicates that relations between BP and CBF are predominately linear and resistive in the higher frequency ranges, which means that linear HF dynamics are embedded in vascular responses that are often thought to purely reflect nonlinear CA. Interestingly, such resistive relations were generally absent in the VLF range, likely because flow recovery occurred relatively rapidly within time scales that do not contain these frequencies, or because of CA, which is generally thought to be most effective in the VLF range (54).

Another possibility is that the recovery of synchronized arterial vasomotion in the VLF range that is absent during arterial hypotension may occur over variable times and explain the heterogeneous role of $G_{VL}$. Nevertheless, these findings show that the linear transmission of HF resistive flow and LF $Q_C$ are the key determinants of flow recovery dynamics following both TC and STS.

Second, in contrast to the flow recovery phase, we observed clear interindividual differences in the composition and relative influence of predictors on the post-flow recovery dynamics. For TC trials, $G_{VL}$, $G_{IF}$, and $C_{LF}$ were the most consistent predictors of post-flow recovery, whereas $G_{LF}$ reached statistical significance in no more than two individuals. Among the significant predictors, $G_{VL}$ was found to have the greatest relative influence. This predictor distribution indicates that resistive flow dynamics (i.e., flow driven by instantaneous changes in MAP), particularly in the VLF range, dominates post-flow recovery, which can be expected of a dilated vascular bed. Our data do not explain the underlying causes of cerebral arterial vasodilatation, which may have occurred as a result of myogenic autoregulation in response to hypotension (i.e., CA), or reductions in CBF triggering cerebral vasodilatation via flow-dependent pathways (17). Alternatively, since metabolic feedback is thought to have a longer time constant than myogenic mechanisms, metabolic feedback may be responsible for exerting vasodilatory effects into the postrecovery phase (30).

The theory and approach presented in this paper suggests that the hemodynamic influences of windkessel vascular properties are substantial during the flow recovery phase, but may decrease during the postrecovery phase of a TC trial. This is based on our observation that, on average, the windkessel model explains less CBF variance ($R^2 \approx 15\%$) during postrecovery compared with the flow recovery phase. Such inflation of residual unexplained variance might reflect the influence of time-varying changes in vascular tone. In support of this contention, animal studies employing direct cranial windows indicate that pial arterial vasodilation can take up to $5 \text{ s}$ to initiate, and up to $30 \text{ s}$ to fully evolve after an abrupt hypotensive perturbation (18). If these latencies broadly approximate human cerebrovascular responses, then windkessel properties would be expected to dominate flow recovery dynamics, but become less influential during the postrecovery phase as CA takes place. Interestingly, the postrecovery phase following STS was associated with a slight improvement in model fit ($R^2 \approx 11\%$) compared with the flow recovery phase, further underscoring the hemodynamic distinctions between TC and STS trials.

An unexpected but important finding in this study was that $G_{VL}$ was a negative predictor of postrecovery dynamics following STS. We strongly suspect this is due to flow “overshooting” the baseline at $t_{recovery}$ (~50% of individuals), and subsequently settling below baseline levels (~24% of individuals) during the remainder of the postrecovery phase. In these cases, BP and blood flow can become inversely related because
BP is typically still recovering below the baseline at \textit{t}_{\text{recovery}}. We do not have a clear explanation for these complex dynamics, but have previously argued that any negative predictors should be excluded from the modeling analysis because they are, strictly speaking, uninterpretable in the context of the windkessel model (8). This approach would simply shift the variance explained by \( G_{\text{VLF}} \) into the lumped residual component of unexplained variance, which is potentially justified given negative predictors may be the product of physiology that our model has failed to take into account. For example, it is possible that the flow overshoot may have engaged flow-dependent vasomotor mechanisms (17) that actively reduced CBF independently of BP (43). Additionally, STS is likely to produce rapid blood drainage from the cerebral venous compartments, which may take longer to restore compared with TC, leading to MCA\textit{v} overshoot and, therefore, a negative \( G_{\text{VLF}} \) estimate. On the other hand, it can be argued that statistically controlling for the influences of \( G_{\text{VLF}} \) has helped clarify the role of the other BP predictors. We acknowledge that these considerations do not tangibly influence our conclusions, because the explanatory power of the windkessel model is relatively high (see Fig. 3), even without the MAP\textit{VLF} predictor. However, these analytic and interpretative challenges highlight the complexities of the cerebrovascular system and point to areas that require further research.

\textbf{Hypercapnia Exerts Complex Cerebral Hemodynamic Effects}

It is widely accepted that hypercapnia-mediated vasodilation impairs CA. This assumption is based on a number of experimental observations, suggesting that the cerebral circulation becomes more pressure-passive during hypercapnia. These include that hypercapnia 1) prolongs the flow recovery phase following TC during hypercapnia (2); 2) attenuates the rate of change in cerebrovascular resistance (calculated on a beat-to-beat basis) within seconds of TC (2); and 3) augments transfer function coherence and reduces the transfer function phase relationships between pressure and flow, consistent with a more pressure passive (linear) circulation (45). Our observation that the TC and STS ARI values decreased during hypercapnia is also potentially consistent with the hypothesis that hypercapnia impairs CA. However, this interpretation assumes that CA is the principal determinant of cerebral pressure-flow relationships when the high explanatory power of our model suggests that the ARI may partially reflect windkessel properties.

Our findings prompt consideration of several alternative mechanisms for how the cerebral circulation can become more pressure-passive during hypercapnia, independently of any change in active CA. In this study, we found that the windkessel model, consisting of only linear parameters, explained a significant proportion of the variance in active CA under both the control and hypercapnia conditions. Given that experimental and model simulation studies have shown that changes in steady-state windkessel properties can alter dynamic pressure-flow relationships (47, 52), the dilation of cerebral resistance arteries during hypercapnia itself can lead to accentuation of Poiseuille-type resistive flow. Our data support this possibility, because hypercapnia increased CVC\textit{i}, and mixed-effects model analysis revealed significant two-way interactions for \( G_{\text{LF}} \) with hypercapnia for the flow recovery phases following both TC and STS. Another possibility is that an increase in cerebral blood volume secondary to hypercapnia-mediated vasodilation may have reduced cerebral arterial compliance (50). This is plausible given \( C_{\text{LF}} \) decreased following all phases of the TC and standing response.

These alternative explanations do not preclude the possibility that hypercapnia also impairs CA, but our method, like many other techniques, does not permit definitive conclusions being drawn regarding the role of CA. One limitation is that there are no gold standard measures of CA and, therefore, inferences regarding CA are based on indirect assumptions. For example, CA impairment should theoretically render the cerebral circulation more pressure passive and enhance the linearity between pressure and CBF. However, pressure-flow linearity is generally thought to be an unreliable scale for CA, because it is critically dependent on the state of vascular properties, such as resistance and compliance independent of CA (52), and the magnitude of the BP input (16), which is difficult to standardize.

Another limitation is that many purported measures of CA are based on differential equation models of first order or higher that contain at least one BP derivative. Popular examples include Tiecks’ ARI, which is a second-order differential equation (42), and the transfer function models applied by Zhang et al. (52, 54), Olufsen et al. (29), and Gommer et al. (15). In each case, the models can be expressed in terms of time-invariant resistance and compliance parameters that translate to time-domain derivatives of BP. It can be argued that metrics derived from these methods are likely to reflect, to some extent, the determinstic influences of the windkessel rather than just the effects of CA in isolation. On the other hand, approaches based on nonlinear methodologies also suffer limitations. For example, it has been claimed that projection pursuit regression is ideally suited for CA quantification, even though the derived models appear to have relatively low explanatory power (41).

\textbf{Methodological Considerations}

The findings from this study need to be considered in view of several methodological considerations. First, although our findings suggest that windkessel properties are key determinants of cerebral pressure-flow dynamics, it is important to recognize that lumped parameter models cannot assess the spatial distribution of resistance and compliance in the cerebral circulation. It is generally assumed that resistance derives mainly from resistive vessels, such as the small pial arteries and arterioles, and compliance derives mainly from larger cerebral arteries, including the anterior/posterior cerebral arteries (23). However, because the arterial compartment is coupled to the capillary and venous vasculature, our model parameters may also potentially reflect the resistance and compliance properties of the capillary and venous compartments. This is certainly plausible, if the downstream capillary pressure (\( P_{\text{c}} \)) decreases (rather than remains constant) during transient hypotension. Interestingly, given the compliance and the time constants for the discharge of the capillary and venous compartments are larger than those for the arterial compartment (22), downstream compartments can theoretically operate in a lower frequency range than the arterial compartment, which may explain why \( C_{\text{LF}} \) was a significant predictor of flow
dynamics in our model. While these uncertainties do not influence the validity of our primary conclusion, which is that cerebrovascular windkessel properties are important determinants of cerebral pressure-flow dynamics (22), clarification of the spatial distribution of cerebral windkessel properties will require additional and challenging work that incorporates invasive measurements of intracranial pressure (P<sub>IC</sub>) and downstream vascular pressures at the capillaries (P<sub>C</sub>) and cerebral veins.

Second, in this study, we analyzed interpolated values from beat-to-beat BP and MCAv data rather than raw pulsatile waveforms. This was done to standardize with signals typically used for ARI calculations, but more importantly to ensure that our model is fitted to signals containing only lower frequency content (33). This is justified on the understanding that, even though the windkessel is most often used to explain the shape of pulsatile arterial waveforms (34, 35), windkessel properties are, in fact, most prominent in LFs [i.e., below cardiac frequency (34, 35)], where the central tenets of the model are most valid (33).

Third, measurements of cerebral blood velocity using TCD only reflect changes in volumetric blood flow, provided that the diameter of the insonated vessel is constant. For the MCA, this requirement has been demonstrated in a wide range of BP's (37), including those elicited during TC (2). Therefore, while we have not measured MCA volumetric flow, it seems reasonable to assume that MCAv provides a proportional and reliable surrogate of MCA blood flow during the physiological BP challenges presented in this paper. Should MCA caliber have altered under any of the conditions in this study, this would manifest as an increase in the model residuals. Indeed, our present approach does not explicitly characterize any time-varying or nonlinear determinants of cerebral hemodynamics (e.g., CA, nonlinear compliance, dynamic changes in P<sub>IC</sub>), all of which were lumped into the single-residual component of unexplained variance. The relatively strong model fits observed in this study indicate that such nonlinear contributions were generally small to modest, with only 20–30% of flow variance remaining unexplained following TC and STS. However, given that autoregulation is known to occur in the cerebrovasculature, we speculate that CA may be the dominant component of our model residuals. Future studies should attempt to partition these residual components, if the necessary intracranial measurements can be obtained in healthy volunteers. Additionally, future studies should characterize the pressure-flow dynamics we have explored in response to transient increases in BP, given the potential for asymmetric responses have previously been suggested (1).

Our fourth methodological consideration relates to the classical definition of compliance as the change in blood volume for a given unit change in BP. In this study, we measured MCAv, which means that our analysis only models the nature of flow changes that would be expected of a compliant vascular bed with frequency-dependent resistance (or more precisely impedance). Our C and G parameters are, therefore, termed capacitive and conductive gains to distinguish them from quantitative estimates of arteural conductance and compliance calculated from volumetric flow recordings. One limitation is that, while our derived windkessel parameters can be compared within individuals across different study conditions, they cannot be directly compared between individuals. However, these limitations do not affect our conclusions, which are all based on within-subject effects.

Finally, our model was parameterized to allow for differences in the amplitudinal relationships between BP and CBF according to frequency. This was based on studies of cerebral input impedance (55) and linear pressure-flow transfer function analysis showing that such differences exist (54). Nevertheless, pressure-flow relationships exhibit high interindividual variability (45), which means that our adopted frequency bands may represent suboptimal model parametrizations for some individuals. For example, in this study, we incorporated three resistance parameters for each frequency band, but only included one LF compliance parameter. A VLF compliance parameter was omitted because the differentiator function of Q<sub>s</sub> should theoretically suppress VLF and enhance LF oscillations in a relative manner (8). We also did not specify a compliance term in the HF range because resistive pressure-flow relations are known to dominate in this frequency range (52), and sensitivity analyses indicate its inclusion, on average, does not significantly improve model fits. Nevertheless, the hemodynamic effects of compliance are unlikely to have fixed-frequency demarcations, and, therefore, consideration of compliance-related flow dynamics above or below our defined LF range may improve model performance on an individual basis.

Key Implications

Arteries and veins are integral in the delicate process of blood flow regulation, yet a precise understanding of their function in many organs, such as the brain, remain elusive (44). For decades, physiologists have believed that cerebral arteries are rigid vessels incapable of passively buffering brain blood flow against changes in BP (3, 13). On reaching the cranial cavity, blood movement is thought to become predominantly longitudinal due to the maxim that cerebral arteries are intrinsically rigid (26), and that passive arterial lateral distension and relaxation are limited by the fact that the skull is, in effect, a rigid container filled with an approximately fixed volume of incompressible contents (27). Furthermore, the potential influence of cerebral venous vascular properties on CBF dynamics monitored in large basal cerebral arteries is rarely acknowledged or even considered. As such, most metrics of CBF regulation are assumed to mainly reflect the integrity of CA as an active arterial vasomotor mechanism (2, 4, 9, 10, 36, 53, 54). Recent evidence, however, suggests this paradigm may be incomplete, as few metrics of CA demonstrate statistical associations with each other to support a shared functional basis (45). For example, our laboratory has recently shown that relations between transfer function metrics (coherence, phase, gain derived from spontaneous and forced BP fluctuations), and the ARI and the rate of regulation index are either statistically unrelated, or only weakly correlated (45). Such a lack of metric convergence points to the need to consider alternative mechanistic constructs to explain cerebral pressure-flow dynamics. Here we have shown that data previously regarded as largely reflective of active arterial CA can be explained by passive windkessel properties. We also showed that significant interindividual variations exist in terms of BP predictor composition. Thus the physiological interpretation of putative CA measures, such as the rate of regulation, ARI, and transfer function analysis, are likely to be more complicated than is
current acknowledgment. Our findings suggest that, in addition to active vasomotor control, the windkessel mechanism should be regarded as a critical component of CA (8) and one that dominates flow dynamics following TC and standing.

Conclusion

According to variance explained, the windkessel mechanism is a key determinant of cerebral hemodynamics. The heterogeneity in pressure-flow relationships between individuals, and between different conditions within an individual, can be attributed to windkessel properties in addition to CA. Awareness of such complexities underpinning the integrated regulation of CBF is paramount to advancing cerebral hemodynamic measurement, interpretation, and physiological understanding.

APPENDIX

Windkessel Model Design

Our methods are based on the intracranial hydrodynamic models developed by Ursino (50), which describes the hemodynamic of the cerebrovascular system in terms of lumped resistance and compliance parameters. A full description of the model can be found elsewhere (8). Here only the principal basis of the model design and key modifications needed to address the objectives of this study are outlined. The net MCA blood flow entering the intracranial compartment \((Q_n)\) is defined as the sum of forward moving blood flow \((Q_{in})\) through resistance vessels, and \(Q_C\) representing volume expansion and discharge in compliant vessels.

\[
Q_n = Q_C + Q_{out} \quad (A1)
\]

Blood flow \(Q_{out}\) out of resistance arteries is defined as the product of arterial conductance and the perfusion pressure gradient at the level of the MCA, given as

\[
Q_{out} = G_{AI}(P_A - P_C) \quad (A2)
\]

where \(G_{AI}\) is the lumped cerebral arterial conductance, which is the inverse of resistance \((G_{AI} = 1/R)\), \(P_A\) is systemic arterial pressure, and \(P_A\)-\(P_C\) is the perfusion pressure gradient across the cerebral arterial compartment. The hemodynamic of vessels composition is described by the following equation:

\[
Q_C = C_{AI} \frac{d(P_A - P_C)}{dt} \quad (A3)
\]

where \(Q_C\) represents the blood volume change (expansion/discharge) in the vessel segment; \(C_{AI}\) is the lumped cerebral arterial compliance; \(P_C\) is governed by the combined influences of brain tissue volume; cerebrospinal fluid volume, and intracranial venous blood volume; and \(P_A\)-\(P_C\) represents the distending pressure in compliant vessels. Combining Eqs. A2 and A3 gives the total MCA flow:

\[
Q_n = C_{AI} \frac{d}{dt}(P_A - P_C) + G_{AI}(P_A - P_C) + \Delta k(t) \quad (A4)
\]

For this study, \(P_A\) was estimated from finger BP. \(P_C\) and \(P_C\) were assumed to be significantly lower than \(P_A\) and constant, although in reality they can potentially change (the implications of these assumptions are considered in the discussion under Methodological Considerations). \(G_{AI}\) and \(C_{AI}\) represent the basal (constant) cerebrovascular conductance and compliance of the vessel segment, and \(\Delta k(t)\) represents the error term. Furthermore, MCA\(v\) was used as a surrogate for MCA volumetric flow. This assumption is valid as long as the diameter of the insolated vessel remains constant. Although we did not explicitly verify this assumption, substantive data support this condition being met under the conditions of this study (37). Any time-varying changes in MCA\(v\) or dynamic changes in resistance and compliance would inflate the proportion of unexplained variance in the residual term and lead to poorer model fits. Thus the measured MCA\(v\) can be defined as:

\[
MCA_v(t) = MCA_v(t) + \Delta k(t) \quad (A5)
\]

where MCA\(v\) is the model fitted component, and \(\Delta k(t)\) is the residual component not explained by the model.

The windkessel model component (MCA\(v\)) should ideally be specified to account for known features of cerebral hemodynamic. For example, the linear transfer function between arterial pressure (input) and flow velocity (output) shows a pattern of progressively increasing gain between 0.02 and 0.20 Hz (45), indicating that the amplitudinal relationship between pressure and flow are frequency dependent. Within this range, the pressure-flow phase angle is also generally positive, consistent with flow leading BP changes. This phase lead progressively decreases towards zero as frequency increases, such that between 0.20 and 0.40 Hz, pressure and flow fluctuations are near synchronous.

Our analysis accounted for these established hemodynamic features in several ways. First, the windkessel resistance parameters were modeled separately for each of VLF (<0.04 Hz), LF (0.04–0.20 Hz), and HF (>0.20 Hz) spectral ranges to allow for the amplitudinal relationship between pressure and flow to vary across frequency. Second, \(Q_{in}\) was selectively modeled within the LF range, because the differentiator function behaves like a high-pass filter suppressing VLF but accentuating LF dynamics (8). Thus the final model can be given as:

\[
MCA_v(t) = G_{VLF} + P_{VLF}(t) + G_{LF}P_{LF}(t) + C_{LF}\frac{dP_A(t)}{dt} + G_{HF}P_{HF}(t) + k \quad (A6)
\]

where \(C_{LF}\) is the capacitive gain to the first derivative of \(P\); \(G_{VLF}\), \(G_{LF}\), and \(G_{HF}\) are the respective conductive gains to the VLF, LF, and HF components of \(B P\) \((k)\) is the constant. The general model structure described can be modified to reflect different levels of physiological complexity or serve different analytic objectives. For example, the compliance parameter can be removed to model purely resistive vessels, or the equations can be simplified to encompass only single resistance and compliance terms to model frequency-specific dynamics (47). Alternatively, extra resistance and compliance parameters can be added, although parameters should only be included if they lead to significance improvements in model performance. For example, whereas the HF resistance parameter was a significant predictor in all conditions, we found that HF compliance was a significant predictor of flow dynamics only during two of the eight model conditions [i.e., thigh-cuff deflation postrecovery phase under the control \((P = 0.0336)\) and the hypercapnic condition \((P = 0.042)\)]. Furthermore, the addition of HF compliance only improved model \(R^2\) by 0.013 (range 0.00018–0.057) across all study conditions. Therefore, our sensitivity analyses do not support the inclusion of HF compliance for the types of data examined in this study, although its potential role should always be considered when other physiological conditions are being explored.

For this exploratory exercise, we sought to explain commonly observed hemodynamic behavior that form the basis of methods that are currently applied for CA quantification. First, the typical hemodynamic response to TC is an abrupt drop in BP and MCA\(v\) within one to two heartbeats (2, 48), followed by MCA\(v\) recovery over 5–10 s, and BP recovery over 15–20 s (48). The expedient recovery of flow relative to pressure is generally attributed to active cerebral vasodilation and is the justification for using CA metrics, such as the rate of regulation index (2) and Tiecks’ ARI (42). The hemodynamic sequence of an abrupt pressure and flow reduction that is followed by...
early (compared to BP) flow recovery after standing is also commonly attributed to CA (11, 39).

Thus we sought to explicitly model the flow recovery phase, which was defined as the interval between hypotension onset (i.e., \( t = 0 \) at the moment of thigh cuff release or stand) and the point at which flow returns to the pretest baseline (\( \text{recovery} \)). In practice, not all subjects during TC showed an obvious flow recovery point. In a minority of individuals (~20–30%), flow recovery was partial in that the local maximum immediately following the flow trough clearly approached but never exceeded the pretest baseline. In these cases, \( \text{recovery} \) was defined as the local maximum immediately after the flow trough. Second, even though flow recovery duration can vary markedly between individuals, it is typical for all data within an arbitrarily defined window to be included (42). This approach implicitly assumes that pressure-flow relations within the defined window are wholly indicative of CA, despite new evidence suggesting that other factors may be equally influential. Therefore, to gain insight into the postrecovery phase, we also modeled the variable interval between \( \text{recovery} \) and 35 s from \( t = 0 \). Identification of the flow recovery and postrecovery phases was based on the low-pass filtered MCAVs signal to avoid the detection of “peaks” and “troughs” caused by momentary fluctuations related to respiration.

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DISCLOSURES

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

AUTHOR CONTRIBUTIONS


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