Contribution of arterial Windkessel in low-frequency cerebral hemodynamics during transient changes in blood pressure

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Submitted 2 December 2010; accepted in final form 2 February 2011

The Windkessel is an important component of many cardiovascular models and has been widely adopted in the study of arterial hemodynamics (2, 4, 26, 27, 38). In its most basic form, the two-element Windkessel model (Fig. 1A) characterizes the arterial bed as a lumped resistance (R) element, predominantly governed by the tone of small arteries and arterioles, and a lumped compliance (C) element, which represents the capability of elastic arteries to expand and relax in response to pressure change. Because it is practically difficult to directly quantify resistance and compliance of an entire vascular bed based on vessel calibers, the Windkessel model provides an effective means of characterizing vascular hemodynamic properties attributable to resistance and compliance from single pairs of pressure and flow measurements (2, 26, 27, 38). The importance of the Windkessel mechanism in buffering arterial pulsations is well understood and involves converting a rapid change in pressure and flow during systole into slow volume discharge during diastole to facilitate peripheral perfusion (28).

The existence of compliant cerebral arteries (19, 35) raises the possibility that the Windkessel mechanism may also play a significant role in dampening flow fluctuations caused by acute blood pressure (BP) perturbations, which may be potentially harmful to the cerebral microcirculation (20). Notwithstanding the exclusive application of the Windkessel model in the study of arterial pulse wave hemodynamics thus far (2, 26, 27, 38), a recent study (40) based on model simulation proposed that the Windkessel mechanism is relevant to low-frequency (LF) beat-to-beat modulation of cerebral blood flow (CBF) velocity (CBFv) (40). An important conclusion was that the dynamic cerebral pressure-flow relationship is not solely determined by the active adjustment of vascular tone secondary to cerebral autoregulation (CA) (9, 21, 22, 29, 34) but also by the Windkessel resistance and compliance of the cerebral vasculature. The potential contribution of Windkessel in LF cerebral hemodynamics is of great interest, given the relevance of this frequency range in physiological BP challenges (e.g., posture change) (6, 41). However, the previous investigation (40) was based on model simulation and analysis of spontaneous fluctuations rather than the empirical fitting of data to the model; therefore, to what extent the cerebral Windkessel properties contribute to dynamic BP-CBFv relationships during large induced BP changes remains undefined.

Recently, our group examined the dynamic CBFv response to transient BP changes elicited by intravenous bolus injections of phenylephrine hydrochloride (PE) and sodium nitroprusside (SNP) (34). This pharmacological technique, commonly known as the Oxford method, has been extensively used for assessing cardiac baroreflex sensitivity (33). The clear advantage of this technique is the ability to examine both transient hypertension and hypotension and to reproduce similar BP changes (~20 mmHg) across different subjects. The CBFv response to SNP-induced hypotension was also...
found to be comparable with sit-to-stand hypotension (34); thus, the method had direct relevance to physiological changes in BP. In the present study, a two-element Windkessel model of the cerebral arterial compartment was adopted (35), and a time-domain model-based analysis approach was implemented to quantitatively assess the contribution of cerebrovascular resistance and compliance in the dynamic CBFV response to drug-induced BP changes. Comparison was also made between the proposed Windkessel model (Fig. 1A) and a pure resistance model with a single resistance (Fig. 1B). Our hypothesis was that the arterial Windkessel plays an integral role in modulating CBFV during large and acute BP fluctuations. In other words, that the arterial Windkessel plays an integral role in modulating CBFV. The method had direct relevance to physiological changes in BP. In the present study, a two-element Windkessel model (Fig. 1A) and a pure resistance model with a single resistance (Fig. 1B). Our hypothesis was that the arterial Windkessel plays an integral role in modulating CBFV during large and acute BP fluctuations. In other words, that the arterial Windkessel plays an integral role in modulating CBFV.

METHODS

Subjects. A total of 14 healthy subjects were recruited (7 men and 7 women). Subjects had the following baseline characteristics (means ± SD): age, 25 ± 4 yr; height, 1.7 ± 0.1 m; weight, 62 ± 11 kg; systolic BP, 113 ± 13 mmHg; diastolic BP, 66 ± 6 mmHg; and heart rate, 62 ± 11 beats/min. This study was approved by the New Zealand Central Regional Ethics Committee and conformed with standards set by the Declaration of Helsinki. Subjects were informed of the experimental procedures and possible risks before written informed consent was obtained. Subjects on regular medication or with a known history of respiratory, cardiovascular, or endocrine disease were excluded from participation.

Measurements. ECG, noninvasive finger arterial pressure (Finometer, TNO-TPD Biomedical Instrumentation), CBFV (2-MHz pulsed Doppler ultrasound, DWL, Doppler, Sterling, VA), and respiratory PCO2 sampled from a face mask (Hans Rudolph Heated Pneumotach HR 800 and a model CD-3A gas analyzer, AEI Technologies) were acquired at 1,000 Hz via a data-acquisition unit (Powerlab/16SP ML795, AD Instruments). To obtain CBFV, the Doppler probe was secured with a headband device (Spencer Technologies) to maintain the optimal insonation position for the acquisition of middle cerebral artery (MCA) flow velocity (MCAV). Beat-to-beat heart rate, mean arterial pressure (MAP), and mean MCAV (MCAV mean) were detected from the recorded ECG, arterial BP, and MCAV waveforms, whereas breath-by-breath end-tidal PCO2 and respiratory rate were detected from the respiratory signal. All offline data processing was performed using custom written software in Matlab (Natick, MA).

Experimental protocol. All subjects abstained from caffeine-containing beverages for at least 4 h before the study. This study was conducted in the supine position in a temperature- and humidity-controlled laboratory (22–23°C). Subjects were instructed to maintain a normal breathing rate and volume to minimize changes in end-tidal PCO2 during the interventions. An initial 10-min resting period was allowed for hemodynamic stabilization. Baseline measurements of systolic and diastolic BP were performed using a manual sphygmomanometer by a trained clinical investigator (Y.-C. Tzeng). Other baseline data were obtained from the 30 s before the commencement of pharmacological challenges. Transient hypotension and hypertension were induced by intravenous bolus injections of SNP (range: 50–200 μg) and PE (range: 50–350 μg) in random order. Calibration of the finger BP device (Physiocal) was performed immediately before the drug injection but was disabled during the transient pressure changes to avoid interruption of the BP waveform by the calibration procedure, which was necessary for a complete recording of beat-to-beat MAP data within the short time frame of pressure variation (~20 s) without significant loss of data due to calibration. SNP and PE tests were spaced 10 min apart to allow for hemodynamic stabilization. Drug injections were repeated if changes in MAP were inadequate (<10 mmHg) or if changes in end-tidal PCO2 levels were large (>2.5 mmHg).

Model design and identification. The lumped Windkessel model for the cerebral arterial bed (Fig. 1A) was adapted from Ursino (35) and was previously developed to simulate the intracranial pressure (PIC) response to drug-induced BP changes. Comparison was also made between the proposed Windkessel model (Fig. 1A) and a pure resistance model with a single resistance (Fig. 1B). Our hypothesis was that the arterial Windkessel plays an integral role in modulating CBFV during large and acute BP fluctuations. In other words, the incorporation of both resistance and compliance in the Windkessel model would statistically explain a considerable portion of dynamic cerebral pressure-flow relationships in both transient episodes of hypotension and hypertension, with a much better model fit [or adjusted coefficient of determination (R²)] compared with a single-resistance model.

The following Windkessel model equation of MCAV variability (derivation given in the Appendix) consists of a model component and a time-varying residual component (Δk(t)) not explained by the model:

\[ \text{MCAV}(t) = \text{MCAV}(t) + \Delta k(t) \]

where MCAV(t) is the Windkessel model component of MCAV as a function of time t given as:

\[ \text{MCAV}(t) = C_{LV} \int \text{dP}_{A}(t)/\text{dt} + G_{VLF}P_{VLF}(t) + G_{LF}P_{LF}(t) + k \]

The conductive gains [very-low-frequency (VLF) gain (G_{VLF}) and LF gain (G_{LF})] govern the forward blood flow into the resistive vessels (R_{A3}) driven by the VLF trend and LF oscillatory components of MAP variability [VLF MAP variability (P_{VLF}) and LF MAP variability (P_{LF})]. The capacitive gain (C_{LF}) accounts for the effect of volume loading/unloading in compliant vessels (C_{AI}) driven by the derivative of MAP variability (dP_{A}/dt). For a purely resistive cerebral arterial bed, the lumped parameter model consists of R_{AI} only (Fig. 1B), and the MCAV model component is given as follows:

\[ \text{MCAV}(t) = C_{AI} \int \text{dP}_{A}(t)/\text{dt} + G_{VLF}P_{VLF}(t) + G_{LF}P_{LF}(t) + k \]
\[ MCA_V(t) = G_{\text{MAP}} P_{\text{MAP}}(t) + k \]

where \( G_{\text{MAP}} \) is the conductive gain to MAP variability.

Model fitting was performed on the pressure rising and falling ramp segments during PE and SNP bolus injection. The signal processing procedures involved in the model identification are described and explained in detail in the Appendix. The model gain parameters were estimated by fitting MCAV (represented by MCAV mean) and the various components of MAP variabilities (sampled at 4 Hz and bandlimited to <0.15 Hz, as shown in Fig. 2) to a (multiple) linear regression model, and the relative contribution of lumped vascular properties versus other time-varying factors in the MAP-MCAV relationship can be evaluated by the model goodness of fit (or \( R^2 \) value). The ratio between the variances of capacitive flow (\( G_{\text{LF}} \times x_c \)) and resistive flow (\( G_{\text{LF}} \times P_{\text{LF}} + G_{\text{VLF}} \times P_{\text{VLF}} \)) was computed and scaled to within the range of zero to one using the mathematical transformation \( f(x) = 1 - e^{-x} \) and was denoted as the capacitive flow (\( Q_c \))-to-resistive flow (\( Q_R \)) ratio (\( Q_c/Q_R \)). This ratio has a value toward one when \( Q_c \) dominates and toward zero when \( Q_R \) dominates.

Statistical analysis. All data are reported as means ± SE unless stated otherwise. \( R^2 \) (adjusted) for least-squares regression was calculated for the single-resistance and Windkessel models identified from each subject’s data. These data and the individual gain values were then treated as summary measures, explored for parity with parametric assumptions, and compared between hypertension and hypotension using paired \( t \)-tests. This summary measures approach was adopted because of the extensive data reduction and exploration procedures involved in the model identification are described and the excellent fit in both trials with the Windkessel model parameters during PE-induced hypertension and SNP-induced hypotension are shown in Table 1. End-tidal PCO2 remained the same before and during the injection of PE (34 ± 1 vs. 34 ± 1 mmHg, \( P = 0.9 \)) and SNP (36 ± 1 vs. 36 ± 1 mmHg, \( P = 0.3 \)). The breathing rate was maintained during the injection of PE (14.3 ± 0.6 breaths/min) and SNP (14.2 ± 0.7 breaths/min); thus, respiration did not contribute to the response at <0.15 Hz. No significant differences were found between PE and SNP trials in the model gains, although during PE, \( Q_c/Q_R \) tended to be higher (\( P = 0.068 \)) and a large proportion of subjects (10 of 14 subjects) had lower \( G_{\text{VLF}} \). A significant improvement in \( R^2 \) from each subject was obtained using the proposed Windkessel model compared with the single-resistance model in both trials. The Windkessel model provided a very good fit (\( R^2 > 0.9 \)) for nine subjects with PE and eight subjects with SNP; however, some variability was evident (range of \( R^2 \) from 0.68 to 1.00 for PE and from 0.38 to 0.99 for SNP). No significant correlation was found between the model \( R^2 \) and the baseline or postintervention MAP. No significant sex differences were found in any of the measures shown in Table 1.

Modeling results for two subjects are shown in Fig. 3. Note the excellent fit in both trials with the Windkessel model (\( R^2 = 0.96 \) for PE and 0.91 for SNP) compared with the single-resistance model (\( R^2 = 0.50 \) for PE and 0.25 for SNP) for the first subject (Fig. 3A), with a clear dominance of \( Q_c \). These responses contrast with the second subject (Fig. 3B), who had lower \( R^2 \) values (\( R^2 = 0.84 \) for PE and 0.75 for SNP), showed lesser improvement from the single-resistance model (\( R^2 = 0.61 \) for PE and 0.59 for SNP), and had a much larger contribution of \( Q_R \) (particularly during SNP). Of the 14 sub-
demonstrate the potential importance of arterial Windkessel in regulating the mean middle cerebral artery flow velocity; improvement, improvement of variance) during large and acute changes in BP was statistically significant in the best-fit model, R², adjusted coefficient of determination; G_MCAV, linear conductive gain; C_MCAV, low-frequency capacitive gain; G_MCAV_vl, very-low-frequency conductive gain; G_MCAV_lf, low-frequency conductive gain; Qf/Qo, capacitive flow-to-resistive flow ratio; R² improvement, improvement of R² comparing the Windkessel model to the single-resistance model. *P < 0.005, significantly different from zero.

Table 1. Comparison of MAP and MCAV mean measurements and model parameters during transient hypertension (PE) and hypotension (SNP)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Hypertension (PE)</th>
<th>Hypotension (SNP)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline MAP, mmHg</td>
<td>83 ± 3</td>
<td>81 ± 3</td>
<td>0.099</td>
</tr>
<tr>
<td>ΔMAP, mmHg</td>
<td>18 ± 1*</td>
<td>−22 ± 2*</td>
<td>0.107</td>
</tr>
<tr>
<td>Baseline MCAV mean, cm/s</td>
<td>75 ± 5</td>
<td>71 ± 5</td>
<td>0.156</td>
</tr>
<tr>
<td>ΔMCAV mean, cm/s</td>
<td>5 ± 1*</td>
<td>−6 ± 1*</td>
<td>0.292</td>
</tr>
</tbody>
</table>

Values are means ± SE. P values were determined from a paired t-test between hypertension and hypotension (for ΔMAP and ΔMCAV mean, the t-test was performed on the magnitude of change). PE, phenylephrine; SNP, sodium nitroprusside; MAP, mean arterial pressure; ΔMAP, change in MAP; MCAV mean, mean middle cerebral artery flow velocity; ΔMCAV mean, change in MCAV mean; G_MCAV, conductive gain; C_MCAV, capacitive gain; G_MCAV_vl, very-low-frequency conductive gain; G_MCAV_lf, low-frequency conductive gain; Qf/Qo, capacitive flow-to-resistive flow ratio; R² improvement, improvement of R² comparing the Windkessel model to the single-resistance model. *P < 0.005, significantly different from zero.

projects, the number of subjects with positive and significant Windkessel gains were as follows: 11 subjects for C_LF, 11 subjects for G_VL, and 4 subjects for G_LF with PE and 12 subjects for C_LF, 14 subjects for G_VL, and 8 subjects for G_LF with SNP. For the trials with nonzero C_LF in the best-fit model, the R² improvements exhibited a wide range, from 0.02 to 0.93, whereas for the five trials (3 PE and 2 SNP) with zero C_LF and nonzero G_LF and G_VL in the model, the R² improvements were generally small (<0.1 for 4 trials and 0.2 for 1 trial). The inclusion of nonzero C_LF was therefore the dominant factor for the mean R² improvement in the Windkessel model. Inclusion of negative C_LF and G_LF in the model only improved R² by an average of 0.02 for PE and 0.005 for SNP; thus, their exclusion would have minimal impact on the explanatory power of the model. Significant intersubject correlation for the two trials was found in G_VL (r = 0.74, P = 0.002) but not in C_LF (r = −0.27, P = 0.35) or G_LF (r = −0.05, P = 0.86). For those with positive C_LF, the differentiator operation of compliance introduced a delay of 1.0 ± 0.2 s and 2.1 ± 0.3 s for the PE and SNP trials, respectively.

DISCUSSION

Main findings. We adopted a novel Windkessel model-based analysis approach for assessing LV dynamics of MCAV during pharmacologically induced transient hypertension and hypotension. A substantial portion of MCAV fluctuation (80–90% of variance) during large and acute changes in BP was statistically explained by flow-buffering effects of the cerebral arterial Windkessel. Moreover, the integration of resistance and compliance in the Windkessel model was found to provide a significantly better fit to MCAV compared with the single-resistance model. Our findings are the first to empirically demonstrate the potential importance of arterial Windkessel in modulating LF cerebral hemodynamics, as previously postulated based on model simulation (40). The implication is that the transient CBFV response to pressure change represents not only the forward-travelling blood flow that directly enters the cerebral microvasculature but also volume loading in the downstream capacitive arteries. This flow-buffering effect may be crucial to the maintenance of steady microvascular flow, particularly during large and acute BP disturbances.

Implications of the cerebral Windkessel model. The regulation of CBF against rapid changes in BP (e.g., during posture change, exercise, coughing, defecation, etc.) is often termed dynamic CA (29). It is widely assumed that the flow modulation is principally achieved through counterregulatory changes in cerebral vascular tone (9, 21, 22, 34). A study by Zhang et al. (40), however, has pointed out that steady-state Windkessel properties could modulate the frequency-domain relationship between arterial pressure and CBF, such that it would not be possible to discriminate between the effects of mechanical properties (e.g., Windkessel) versus active control mechanisms (e.g., autoregulation). The present work supports this contention and by fitting empirical data to the model further demonstrated that a significant portion of MCAV response that could be explained by the mechanical properties of the cerebral vasculature (as indicated by the high model R²). While our results did not rule out the involvement of active autoregulation in the MAP-MCAV relationship during acute BP changes, they provided strong justification for arterial Windkessel as a potent mechanism of dynamic CBF modulation that should not be neglected.

The lumped parameter cardiovascular model adopted in this study is a two-element Windkessel previously used to describe the cerebral arterial compartment (35). In a later study by Ursino et al. (37), this vascular model was used to describe the lumped behaviors of the large and small pial arteries and arterioles and was incorporated within a comprehensive mathematical model of the whole cerebral vasculature that included intracranial veins, capillaries, and cerebrospinal fluid circulation. Mathematical equations of vascular compliance and autoregulatory mechanisms were developed, with several model parameters (e.g., autoregulatory gains) identified by a best-fit algorithm, while others (including the basal cerebral arterial resistance and compliance) were assigned based on physiologically realistic values. The model was able to reproduce the measured patterns of MCAV and PTC from the input MAP and arterial CO₂ pressure during a norepinephrine-induced BP rise.

The modeling work by Ursino et al. (37) illustrated the potential involvement and integration of multiple mechanisms in the regulation of intracranial hemodynamics, including both the active control of vascular tone by autoregulation and the Windkessel mechanism. The present study, on the other hand, specifically addressed how much of the arterial flow response could be directly attributed to the Windkessel mechanism, by considering only the pressure-flow dynamics in the arterial compartment. A model-based signal analysis approach was developed, which facilitates the unique determination of arterial Windkessel properties [conductance (G) and compliance (C)] from the measured pressure and flow fluctuations (26, 27). A limitation of the present approach, however, was that the various time-varying and nonlinear factors, including nonlinear compliance, active autoregulation, and changes in PTC, were lumped into a single residual component not explained by the model and, thus, could not be separately assessed.
Previously, Olufsen et al. (22) used a three-element Windkessel model to analyze pulsatile MCA\textsubscript{V} waveforms on a beat-to-beat basis and identified variations in cerebrovascular resistance during posture-induced hypotension (sit to stand). This pulsatile resistance, however, was associated with the modulation of cardiac pulse waves and, therefore, is not equivalent to our conductance parameters derived from interbeat variations in pressure and flow over a longer time frame. Our conductance parameters are thus termed $G_{\text{VLF}}$ and $G_{\text{LF}}$, to emphasize that vascular resistance (or more precisely, vascular impedance) should be interpreted with respect to their frequency bands (2, 26, 27). It is interesting to note that $G_{\text{VLF}}$ was correlated for the two trials, possibly indicating the consistency of intersubject difference in cerebral small vessel tone.

Despite the potential nonlinear behavior of vessel compliance due to dependency on pressure and diameter (14, 35), the Windkessel model with a constant capacitive gain was sufficient to provide a good fit of MCA\textsubscript{V} in most subjects, suggesting a predominantly linear pressure-volume relationship in the downstream vasculature. This could be justified by direct measurements of the pressure-volume curve of an arterial segment, which showed that within $\pm$20-mmHg change from the normal operating pressure (as in the present study), the pressure-volume relationship was essentially linear, with nonlinear behavior only becoming dominant at the very low and high ends of the pressure-volume curve (14). Nevertheless, the shifting of the operating point beyond the linear range might explain the poor fit in some subjects.

The average $C_{\text{LF}}$ from our model (neglecting zero gain values) can be translated to a compliance of 0.13 ml/mmHg (assuming a MCA\textsubscript{diameter}} of 0.3 cm), which is comparable with a physiologically realistic value (0.2 ml/mmHg) adopted in a recently developed cerebrovascular model for describing the peripheral arterial compliance downstream of the MCA (36). Given that an in vitro study (31) of flow velocity profiles showed a laminar flow pattern in the MCA resembling Poiseuille-type $Q_R$, the contribution of MCA compliance in $C_{\text{LF}}$ is likely to be insignificant. Interestingly, the same study also found a strong disturbance/deflection of flow at the first downstream bifurcation of the MCA (anterior/posterior parietal arteries), which might suggest the presence of $Q_C$. The contribution of cerebral veins to $Q_C$ was also considered (17), although this effect should only be observable under arteriolar dilatation rather than arteriolar constriction (implied by the coexistence of high $Q_C$ and negligible $Q_R$). The compliance function was found to introduce a delay (from $dP_A/dt$ to MCA\textsubscript{V}) of $\sim$1–2 s, which was attributed to the delay associated with the viscoelastic behavior of distensible vessels, as explained earlier (17, 25).

Cerebral hemodynamic responses to hypertension and hypotension. The adjusted $R^2$ values quantitatively assessed how much of the MCA\textsubscript{V} variation was statistically explained by the components of MAP via the developed model. On average,
80–90% of the MCA
response could be explained by the constant gain Windkessel model during both hypertension and hypotension. The remaining 10–20% of residual MCA variance unexplained by the model was attributed to time-varying effects, including the active adjustment of cerebralvascular tone by CA mechanisms (7, 12) and pressure-dependent compliance (14, 35). Individually, however, the model fit exhibited a wide range ($R^2$ from 0.38 to 1.00), indicating that these time-varying vascular effects, in particular, active CA, could have exerted a major influence on the MCA responses in some subjects. This highlights the degree of heterogeneity in the subjects’ CA responses (39), as shown in Fig. 3: the MCA mean variation shown in Fig. 3A is largely explained by the dP/dr-driven $Q_c$, whereas, as shown in Fig. 3B, MCA mean was initially well matched with the model response in the first 10 s of MAP fall and was then followed by a sharp fall and subsequent rise (indicated by the arrow) that could not be attributed to either pressure or dP/dr. We speculate that this was due to cerebral vascular adjustment by an active CA mechanism as BP went below a certain threshold (12), which might be subject dependent, although further studies are required to validate this possibility.

No significant differences were found in the capacitive and conductive gains between the hypertension and hypotension responses, suggesting similar vascular properties during the pressure rise and fall episodes. This contrasts our earlier finding of significantly lower conductive gain in hypertension, based on linear regression of MAP and MCA, (equivalent to the single-resistance model) (34). However, the apparent disparity between the studies needs to be considered in the context of important analytic differences that reiterate the inherent challenges of characterizing human cerebral pressure-flow relations. Previously, the pressure ramps were identified as the initial data segments where MAP was linearly rising/falling (analogous to the first 10 s of pressure fall shown in Fig. 3B) (34). The findings of a high $R^2$ value (0.87) indicated that a single-resistance model adequately describes the pressure-flow relationship within this time window. In contrast, pressure ramps were identified in this study via $P_{VLF}$ and its first derivative, which encompassed the entire BP range where active CA influences are more likely to manifest as pressure reached the trough (12). These factors likely account for the lower conductive gain and greater proportions of variance unexplained by the simple resistance model observed in this study. Nevertheless, the higher $Q_c/Q_R$ ($P < 0.07$) suggests the relative dominance of $Q_c$ versus $Q_R$ during hypertension, which indicates that cerebral arterial compliance may be more effective in counteracting transient hypertension compared with hypotension (29, 34). This differential response may relate to the intrinsic properties of the cerebral vasculature, although the precise mechanism would need to be clarified by further studies.

Methodological considerations. A major limitation of the present approach was that arterial pressure was measured at the finger but not at the MCA, and the finite resistance to flow along the arterial pathway might introduce pressure differences between the two sites (4, 7, 12). Nevertheless, a good model fit was obtainable from most subjects (mean $R^2 > 0.8$ and $R^2 > 0.9$ for 9 subjects with PE and 8 subjects with SNP), suggesting a minimal effect of site difference on the investigation of LF hemodynamics, despite the possible existence of an absolute pressure difference between the two sites. MAP measurements obtained by the finger device and the intra-arterial (brachial artery) catheter were found to be in close agreement during various dosages of PE and SNP infusion (5, 8, 10). However, as the automatic calibration (Physiocal) was disabled during the drug intervention period to obtain continuous and uninterrupted beat-to-beat BP variability, it is possible that changes in vascular tone in the finger artery could lead to an over- or underestimation of BP by the volume clamp technique, leading to a worse fit in the pressure-flow model. Nevertheless, finger and intra-arterial BP variability exhibited high concordance during transient peripheral vasomotor changes elicited by vasoactive drugs (such as PE) and various physiological challenges (8, 23). Another possible cause of poor fit was measurement artifacts associated with low finger BP, although this was unlikely a major factor given that no significant correlation was found between model $R^2$ and postintervention MAP.

The lack of MCA caliber measurement was another limitation, such that only velocity flow could be obtained but not volumetric flow. Nevertheless, the use of the MAP-MCA relationship to infer CBF regulation during dynamic BP perturbation has been a widely accepted approach (6, 9, 21, 22, 34, 40, 41). The current Windkessel model was specifically built to describe the MAP-MCA relationship, with the vascular gain parameters normalized by the MCA cross-sectional area (see Eq. 8). To account for the possibility of MCA caliber change as a confounding factor, a residual term was incorporated in the model (see Eq. 7). The good fit obtained from most subjects in the flow velocity model would suggest minimal influence of MCA caliber change and capacitive effects, consistent with the resistive behavior of MCA based on previously reported flow velocity profiles (31). However, we cannot rule out the possibility that the relatively poor fit in a small number of individuals was due to active vascular adjustment in the MCA (e.g., Fig. 3B). As explained earlier, the compliance in our Windkessel model represents the aggregate compliance of the whole peripheral arterial network downstream of the MCA; thus, it would be difficult, if not impossible, to use in vivo vessel caliber measurements to validate its presence.

Direct effects of PE and SNP on the cerebral vasculature were considered unlikely given that the blood-brain barrier normally prevents endogenous circulating catecholamines from binding to $\alpha_1$-adrenoreceptors in small cerebral vessels (1, 16, 18) and that mechanoregulation of CBF generally occurs independently of nitric oxide-mediated pathways (11, 13). In fact, our model fit also argues against direct drug effects within the study timeframe, as any alteration in vascular tone by the drug would change the slope of pressure-flow relationship over the time course of the intervention, leading to deviation from a linear model across all trials; our results clearly indicate this did not occur. Finally, the validity of constant vascular properties was based on analysis of the initial pressure rising/falling phase (as BP reached its first peak/trough) immediately caused by PE/SNP bolus injections and should not be overextrapolated to the case of continuous PE/SNP infusion, which is known to alter cerebrovascular tone via a static CA response to changes in steady-state BP (15, 40). We speculate that a sustained BP elevation over a longer period than our study
timeframe would be required to initiate a static CA adjustment.

The change in $P_{IC}$ during the intervention could also potentially affect model fit, given the distending pressure that drives $Q_A$ is $d(P_A - P_{IC})/dt$, and any noticeable influence of $P_{IC}$ on dP/dt can confound the linear relationship between dP/dt and $Q_C$. The importance of $P_{IC}$ in intracranial hemodynamics has been emphasized (37), and its inclusion in the model may provide a much more complete characterization of cerebral vasculature behavior. Future application of this model may consider the inclusion of $P_{IC}$, should this invasive intracranial measurement be feasible (e.g., the study of head injury patients). It is also important to recognize that the present findings were derived from large and acute BP changes and should not be overextrapolated to small and spontaneous variations in CBF. Spontaneous CBFV variability exhibits a high degree of local vasomotor activities potentially attributed to myogenic and metabolic factors, as evident by the low coherence with BP, particularly in the VLF band (41); this is analogous to a low $R^2$ in the MAP-MCAV model, in which case the dynamic effects of arterial Windkessel are less prominent compared with active CA.

Implications. High short-term BP variability (<10 min) has been linked with intracerebral hemorrhage (30). Without the appropriate regulatory mechanisms, large and acute BP fluctuations would be translated to unbuffered CBFV fluctuations, leading to abrupt changes in arterial wall shear stress that may contribute to an increased risk of cerebral vascular damage (20). The present results highlight that apart from the well-recognized mechanism of CBF control by autoregulatory adjustment of vascular tone, the Windkessel properties of cerebral arteries may also contribute significantly to the maintenance of steady microvascular flow, whose importance in various cerebral pathophysiological conditions warrants further investigation.

APPENDIX

Windkessel model design. A two-element Windkessel model of the cerebral arterial bed is shown in Fig. 1A. The MCA blood flow ($Q_A$) is divided into two components: $Q_E$ into $C_{AI}$ and $Q_C$ into $C_{AI}$, as follows:

$$ Q_A = Q_C + Q_R $$

(1)

$Q_R$ can be computed as follows:

$$ Q_R = G_{AI}(P_A - P_C) $$

(2)

where $G_{AI} = 1/R_{AI}$ and is the lumped cerebral arterial conductance, $P_A$ is the systemic arterial pressure, and $P_C$ is the capillary pressure. $Q_C$, despite being termed “flow,” in fact represents blood volume expansion/discharge in the capacitive vessels and can be computed as follows:

$$ Q_C = C_{AI} \frac{d(P_A - P_C)}{dt} $$

(3)

where $P_{IC}$ is governed by the combined influences of brain tissue volume, cerebrospinal fluid volume, and intracranial venous blood volume. Total MCA flow is given as follows:

$$ Q_A = C_{AI} \frac{d(P_A - P_C)}{dt} + G_{AI}(P_A - P_C) $$

(4)

In this study, $Q_A$ and $P_A$ are the variables being measured (as a function of time). $P_C$, $P_{IC}$, $C_{AI}$, and $R_{AI}$ (or $G_{AI}$) are the unknowns, and each comprises a basal (constant) and a time-varying component (denoted by $\Delta$), as follows:

$$ Q_A(t) = [C_{AI} + \Delta C_{AI}(t)] \frac{d[P_A(t) - P_{IC}(t)]}{dt} + [G_{AI} + \Delta G_{AI}(t)][P_A(t) - P_C + \Delta P_C(t)] $$

(5)

The time-varying components account for factors that lead to a deviation from linearity, such as modulation of cerebrovascular tone by active autoregulation (affects $\Delta G_{AI}$, $\Delta P_{IC}$, $\Delta P_C$, and possibly $\Delta C_{AI}$) (7, 12), and nonlinear compliance dependent on pressure and diameter (affects $\Delta C_{AI}$) (14, 35). By grouping the constant and time-varying terms into $k$ and $\Delta k$, respectively, we obtain the following:

$$ Q_A(t) = \left[ C_{AI} \frac{dP_A(t)}{dt} + G_{AI}P_A(t) + k \right] + \Delta k(t) $$

(6)

Note that $\Delta k$ may include nonlinear functions of $P_A$, if any of the time-varying terms in Eq. 5 is a function of $P_A$.

The model equation is further modified to fit MCAV and MAP signals. First, since only flow velocity is measured but not $Q_A$ (flow velocity $\times$ vessel cross-sectional area), both sides of the equation are divided by the vessel (MCA) cross-sectional area; thus, the $G$ and $C$ values are expressed as per unit area. Note that the model C depicts the overall volume change in all vessels downstream of the MCA site where flow was measured rather than the volume change of the MCA itself. Should there be any change in MCA caliber during the intervention, this would result in flow velocity variation [i.e., $\Delta k(t)$] not explained by the Windkessel model component. Second, only the frequency range of <0.15 Hz (excluding the respiratory variation) is considered, as this range is the most relevant to the effects of pharmacological intervention and regulatory mechanisms on MCAV and MAP variability (24, 41). The respiratory component was not analyzed, as it was largely mediated by stroke volume variation embedded in the pulsatile pressure and flow waveforms (32) and, thus, would contribute more toward pulsatile vascular impedance properties.

The analyzed frequency range consists of the LF (0.04–0.15 Hz) and VLF (<0.04 Hz) components, which are modeled separately for $Q_R$ to allow for the possible frequency dependency of vascular resistance/impedance (2, 26, 27). The difference in cerebral bloodflow relationships in the LF and VLF bands has been demonstrated by frequency-domain transfer function analysis (6, 41), implicating potentially frequency-dependent resistance in these spectral ranges; hence, the use of separate conductive gain parameters would seem necessary. $Q_C$, on the other hand, consists of mostly LF, as the differentiator acts like a high-pass filter, which suppresses VLF and enhances LF in a relative manner.

Based on a modification of Eq. 6, the measured MCAV variability is decomposed into the following modeled component and time-varying residual component ($\Delta k$) not explained by the model:

$$ \text{MCAV}(t) = \text{MCAV}(t) + \Delta k(t) $$

(7)

and the Windkessel model component (with constant gains) is given as follows:

$$ \text{MCAV}(t) = C_{LF} \frac{dP_A(t)}{dt} + G_{VLF}P_{VLF}(t) + G_{LF}P_{LF}(t) + k $$

(8)

where $G_{VLF}$ and $G_{LF}$ are the conductive gains to the VLF trend and LF oscillatory components of MAP variability ($P_{VLF}$ and $P_{LF}$), which govern $Q_A$ fluctuations, and $C_{LF}$ is the capacitive gain to the derivative of MAP variability ($dP_A/dt$), which reflects volume loading/unloading.

For a purely resistive cerebral arterial bed, the lumped parameter model consists of $R_{AI}$ only (Fig. 1B); thus, the total flow ($Q_A$) is
equivalent to the \( Q_x \) component (Eq. 2). The \( \text{MCAV} \) model component is given as follows:

\[
\text{MCAV}(t) = G_{\text{MAP}}P_x(t) + k
\]

where \( G_{\text{MAP}} \) is the conductive gain to MAP variability (<0.15 Hz).

**Signal processing and model identification.** The beat-to-beat time series of MAP and \( \text{MCAV} \) were detected from the recorded finger BP and MCAV waveforms and resampled at 4 Hz using a previously proposed algorithm (3). The 4-Hz variability signals were band limited to 0.15 Hz by zero-phase low-pass filtering (eight-order Butterworth). The beat-to-beat time series and corresponding filtered signals of one subject are shown in Fig. 2. The VLF trends of the filtered signals were extracted by a 20-s Hanning windowed moving average (3 dB at 0.04 Hz, with 0 delay), and the LF oscillations were obtained by subtracting the VLF trends from the 0.15-Hz signals. The VLF component of MAP (\( P_{\text{VLF}} \)) was used to identify the pressure rising (PE) and falling (SNP) ramp segments. In the detection of pressure rise, the troughs (local minima) and peaks (local maxima) in \( P_{\text{VLF}} \) were first located, and the first ramp with an amplitude (i.e., peak minus trough) of at least 10 mmHg was then identified. As the trough of \( P_{\text{VLF}} \) could sometimes occur earlier than the start of the PE infusion, the ramp onset time was more precisely located by first identifying the first derivative peak of \( P_{\text{VLF}} \) (or the point of maximum rising slope) and then searching backward in time for the closest point when the first derivative of \( P_{\text{VLF}} \) approached zero; this may either be a trough of \( P_{\text{VLF}} \) (i.e., zero crossing in the first derivative of \( P_{\text{VLF}} \)) or an inflection point (i.e., local minimum of the first derivative of \( P_{\text{VLF}} \), whose value was <50% of the first derivative peak). The end point of the pressure rise, on the other hand, would always be the detected peak of \( P_{\text{VLF}} \). The detection of pressure fall was similarly performed by applying the above technique to the negated \( P_{\text{VLF}} \). The proposed method allowed the consistent detection of both the pressure rise and fall segments within and across trials based on well-defined criteria, with an onset that always occurred after the initiation of the drug infusion.

The derivative operation of vessel compliance was modeled as an \( n \)-point first derivative filter, which differentiated the 0.15 Hz-filtered MAP to obtain \( \text{d}P_x/\text{d}t \) and introduced a time delay of \( (n - 1)/2 \) sample points. Inclusion of this delay was consistent with the viscoelastic behavior of distensible blood vessel, whose maximum/ minimum volume change in response to a step increase/decrease in transmural pressure was achieved after a certain time delay (this mechanism is also known as “delayed compliance”) (17, 25). The optimal choice of \( n \) was based on maximum correlation with the detrended LF oscillation of \( \text{MCAV} \) mean, by searching up to a delay of 5 s (\( n = 41 \)). Note that this differentiator needs to be designed with a time-domain equation that provides an exact value of the first-order derivative with respect to time (in s). For example, a five-point derivative can be designed as \( y(n) = \{x(n) - x(n - 4)/4\} + \{x(n - 1) - x(n - 3)/2\} \), where \( T \) is the sampling interval. No delay was accounted for in the resistance element, as this would depend on the pressure wave propagation time, which is in the order of milliseconds and can be neglected in LF analysis (26).

The 0.15 Hz-filtered \( \text{MCAV} \) mean (including both the VLF and LF components) was assigned as the dependent variable in the models. For the identification of the single-resistance model, linear least-squares regression was performed with 0.15 Hz-filtered MAP as the single predictor. For the identification of the Windkessel model, \( \text{MCAV} \) was fitted to \( \text{d}P_x/\text{d}t \), \( P_{\text{VLF}} \), and \( \text{d}P_{\text{PLF}}/\text{d}t \) by multiple linear least-squares regression, and the unstandardized \( \beta \)-coefficients were taken as \( C_{\text{LF}}, G_{\text{VLF}}, \) and \( G_{\text{PLF}} \). The modeling procedure started with fitting \( P_{\text{VLF}} \) to obtain the base model, and \( \text{d}P_{\text{PLF}}/\text{d}t \) and/or \( P_{\text{PLF}} \) were then added to the model if they provided an improvement of \( R^2 \) with positive and significant (\( P < 0.05 \)) \text{C}_{\text{LF}} \) and/or \( G_{\text{PLF}} \). This was based on the consideration that \( \text{d}P_x/\text{d}t \) and \( P_{\text{PLF}} \) had overlapping frequency bands; thus, either term alone might fully explain the LF oscillations in \( \text{MCAV} \). Physiologically, complete buffering of LF pressure oscillations by compliance could result in \( G_{\text{LF}} = 0 \), whereas loss of distensibility in compliance vessels (e.g., due to active constriction or passive unloading) might turn the vasculature into purely resistive; hence, \( C_{\text{LF}} = 0 \). An a priori assumption was therefore made to allow for \( G_{\text{LF}} = 0 \) or \( C_{\text{LF}} = 0 \) to avoid uninterpretable negative or nonsignificant values in the final model. It is conceivable that given the sinusoidal nature of the LF oscillations, \( \text{d}P_x/\text{d}t \) and \( P_{\text{PLF}} \) may explain part of \( \text{MCAV} \) mean fluctuations even though they represent nonlinear effects of autoregulation rather than the direct linear effect of pressure and \( \text{d}P_x/\text{d}t \) (41). However, by imposing the criteria of positive and significant gains, the chance of inappropriate fitting could be minimized. The final model parameters comprised a unique set of \( G_{\text{VLF}}, G_{\text{LF}}, \) and \( C_{\text{LF}} \) (with \( G_{\text{LF}} \) or \( C_{\text{LF}} \) assigned a value of 0 if the corresponding component was not included) that best fit the \( \text{MCAV} \) response with maximum \( R^2 \).

**GRANTS**

This work was supported by New Zealand National Heart Foundation Grant 1284 (to Y.-C. Tzeng).

**DISCLOSURES**

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

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