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Assessment of the cerebral pressure-flow relationship using psychological stress to
manipulate blood pressure

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Abstract

Recent evidence indicates that cerebral autoregulation (CA) might be more pressure-passive than previously thought. That is, cerebral blood flow, traditionally thought to be regulated independently of prevailing mean arterial pressure (MAP), might fluctuate, to some extent, as a function of MAP. However, due to limitations associated with experimental usage of pharmaceuticals to manipulate MAP and inconsistent control of arterial carbon dioxide, questions remain regarding the MAP-cerebral blood flow relationship, especially during typical daily activities that alter MAP. Therefore, the current study aimed to assess CA using a non-pharmacological acute psychological stress task to augment MAP, while at the same time controlling for end-tidal carbon dioxide ($P_{ET}CO_2$). Twenty-five healthy young adults completed a stressful task while continuous measures of MAP, middle cerebral artery blood flow velocity (MCAv), and $P_{ET}CO_2$ were recorded. Slope values obtained from hierarchical linear regression were used to assess the strength of the MAP-MCAv relationship and control for $P_{ET}CO_2$. The stress task significantly increased MAP ($p < .001$) and MCAv ($p < .001$), and decreased $P_{ET}CO_2$ ($p = .05$). For every 10mmHg task-induced increase in MAP, MCAv increased by $\approx 3.5\%$; task-induced changes in $P_{ET}CO_2$ did not appreciably change the MAP-MCAv relationship. Greater task-induced MAP responses were significantly related to decreased MAP-MCAv slope values, consistent with CA. These data support the hypothesis that CA is more pressure-passive than previously thought and provide initial evidence indicating that a pressure-passive MAP-MCAv relationship may play a role in the observed associations between MAP stress responses, stroke, and cerebrovascular disease.

Introduction

Cerebral autoregulation (CA) refers to the mechanism through which cerebral blood flow (CBF) is regulated, via adjustments in cerebrovascular resistance, during changes in arterial blood pressure. Traditionally, 'static CA' describes the relationship between mean arterial pressure (MAP) and CBF on the time scale of minutes to hours while 'dynamic CA' refers to the regulation of CBF during transient (i.e., seconds) changes in MAP (Aaslid, Lindegaard, Sorteberg, & Nornes, 1989). However, this distinction is nominal as conclusive evidence supporting a physiological basis for such a distinction does not exist, and it is possible that they represent the same CA phenomenon across the spectrum of time (Tan & Taylor, 2014). The Lassen (1959) model is the traditionally accepted model of static CA and depicts a plateau region between ≈ 50 -150 mmHg where CBF is maintained relatively constant, independent of changes in MAP. However, ensemble data used to derive the model consisted of steady-state measures of MAP and CBF from heterogeneous samples of participants, some with confounding pathology. Secondary analyses of the Lassen data (Heistad & Kontos, 1983), excluding participants with confounding pathology, and a meta-analysis of 40 experimental studies (Numan et al., 2014) of static CA indicate that regulation of CBF is more pressure-passive than previously thought; CBF varies, to some extent, as a function of changes in MAP. However, usage of vasoactive substances to manipulate MAP and override baroreflex function, and inconsistent experimental or statistical control of arterial carbon dioxide (PaCO_2) has limited interpretation regarding the within-subjects relationship between MAP and CBF (Numan et al., 2014). Within-subjects assessments of the relationship between MAP and CBF using non-pharmacological methods, controlling for PaCO_2 , are sparse.

The goal of the present study was to assess the relationship between CBF and MAP by increasing MAP using a non-pharmacological psychological stress task, similar to what an individual might encounter in daily life (Zanstra & Johnston, 2011). Transcranial Doppler (TCD) imaging was used to measure blood velocity in the left and right middle cerebral arteries (MCAv) as an index of global CBF supply to the cerebrum. Psychological stress was examined for two reasons. First, psychological stress is a common daily experience that has implications for physical health. Stress-induced blood pressure responses have been shown to prospectively predict increased risk of stroke (Everson et al., 2001) and, in cross-sectional analyses, relate to an increased number of silent infarcts and white-matter hyperintensities, markers of cerebrovascular disease (Waldstein et al., 2004). Second, psychological stress tasks, like the Paced Auditory Serial Addition Task (PASAT) used in the present study, have been shown to reliably elicit robust, sustained (e.g., minutes) increases in MAP (Ring, Burns, & Carroll, 2001) and significantly decrease baroreflex sensitivity (Fauvel et al., 2000; Lellamo et al., 1996); physiological adjustments similar to those achieved by pharmacological manipulation. Consequently, psychological stress represents a unique non-pharmacological model within which to assess the pressure-flow relationship between MAP and CBF during MAP augmentation. Based on prevailing evidence, it was hypothesized that changes in CBF would be relatively pressure-passive during psychological stress. If confirmed, not only would this provide novel support for the hypothesis that regulation of CBF is somewhat pressure-passive, but also, provide initial evidence for a possible pressure-passive mechanism that could explain the observed link between large-magnitude MAP stress responses and increased risk of stroke and cerebrovascular disease (Everson et al., 2001; Waldstein et al., 2004).

Methods

Participants and Ethical Approval

Twenty-five participants (Table 1) were recruited for the present study. Participants reported medication usage and were excluded if they reported having a history of cardiovascular or metabolic disease or had previously participated in the psychological stress protocol where blood pressure and/or heart rate was continuously measured (detailed below). All participants were required to refrain from alcohol and vigorous exercise for 12 h, caffeine for 2 h, and food and drinks other than water for 1 h before testing. Participants provided informed consent and received participation credit as part of their degree program. The study was approved by the University of Birmingham Ethics Committee.

[Insert Table 1 about here]

Experimental Design and Procedure

Each participant attended a laboratory session where they completed an acute psychological stress task. Participant's height and weight were measured and body mass index (BMI; kg/m^2) calculated on arrival to the laboratory. Participants were then asked to sit while being instrumented, following which they completed a standardized 8-min adaptation period. Physiological data was continuously recorded first during an 8-min baseline period and then during a separate 8-min Paced Auditory Serial Addition Test (Gronwall, 1977). During the baseline period, participants were asked to remain seated and rest quietly. After finishing the PASAT, participants completed a brief questionnaire immediately upon completion of the task, which required them to rate task stressfulness on a standard Likert scale ranging from 1-10 anchored by "not at all stressful" to "extremely stressful," respectively.

PASAT Stress Task

During the 8-min PASAT, participants consecutively added single digit numbers, presented via CD recording, while remembering the most recent number so that it may be added to the next number presented. Participants responded via keypad. Although continuously administered, the PASAT was composed of four 2-minute blocks where, numbers were presented at increasing speeds beginning at 2.5 seconds between each number and decreasing 0.5 seconds every two minutes. Before the task began, participants were told that their scores would be compared to others in the study (there was a scoreboard visible to the participant) and that they were being videotaped and would be subsequently analyzed by “body language experts” for signs of anxiety. Participants were instructed to look at themselves on a television screen throughout the task. An experimenter overtly scored the participant’s performance and delivered a standardized number of loud aversive noise bursts that they were informed were occasioned by wrong answers, looking away from the television screen, or hesitation. These manipulations served to enhance task stressfulness by increasing the socially evaluative and competitive elements of the task (Ginty, Phillips, Higgs, Heaney, & Carroll, 2012).

Physiological Measurements

Heart rate (HR) was measured continuously during all task phases via three-lead electrocardiography. Beat-to-beat MAP was measured during baseline and task phases of the protocol from the middle finger of the supported non-dominant hand via photoplethysmography (Finometer Pro, Finapres Medical System, Biomedical Instruments, Amsterdam, The Netherlands). MAP values were validated with measurements taken using a semi-automatic sphygmomanometer and cuff placed over the brachial artery of the dominant arm. End-tidal PCO_2 (P_{ETCO_2}) was continuously measured during baseline and task phases from a leak-free

respiratory mask connected to a gas analyzer (ML206; ADInstruments, Bella Vista, NSW, Australia). Based on established methods (Aaslid, Markwalder, & Nornes, 1982; Willie et al., 2011), CBF velocity was measured in the left and right middle cerebral arteries (MCAv) during baseline and task phases using a 2-MHz pulsed Doppler ultrasound system (Multi Dop X, DWL, Compumedics Ltd, Germany), with the probe secured and insonation angle maintained constant throughout testing using a headband device (DWL). All data were continuously sampled at 200 Hz using an analogue-digital converter (PowerLab, ADInstruments) and analyzed offline using LabChart software (Version 7, ADInstruments). Baroreflex sensitivity was measured using the sequence method (Parati, Di Rienzo, & Mancia, 2000). Briefly, systolic blood pressure (SBP) and inter-beat interval (IBI) time series data from baseline and task phases were analyzed off-line to find sequences of 3 or more consecutive beats characterized by a rise in SBP and lengthening of IBI or decrease in SBP and shortening of IBI. Linear regression was applied individually to each sequence, and only those with an $R^2 \geq .85$ were accepted. An aggregated slope of the regression lines was computed as a measure of baroreflex sensitivity.

Statistical Analysis

Analyses revealed no significant difference between right and left MCAv ($p > .05$) so, within each participant, data from the right and left middle cerebral arteries were pooled. Average MAP values for baseline and task phases were analyzed with a repeated-measures (time: baseline, task) analysis of variance (ANOVA) to confirm a significant increase in MAP by psychological stress. Individual beat-to-beat data were used to independently assess the MAP-MCAv relationship during changes (task minus baseline) in MAP during the PASAT. Linear regression analysis was carried out on individual participant data and slopes (unstandardized B-coefficient) were aggregated across participants. Absolute changes in MAP (mmHg) predicted

both absolute ($\text{cm}\cdot\text{s}^{-1}$) and relative ($\%\text{cm}\cdot\text{s}^{-1}$, hereafter referred to as %) changes in MCAv in unadjusted analyses. In controlled analyses, adjustments were made for relative ($\%\text{mmHg}$) changes in P_{ETCO_2} . Data were first analysed across the entire 8-min task period, then during each of the four 2-min blocks that comprised the task. The latter analysis was conducted because previous evidence has suggested that the physiological mechanisms (e.g., baroreflex function and vascular resistance) that govern stress responding may vary across the duration of the stressor (Durocher, Klein, & Carter, 2011; Ring et al., 2001). The distributions of slope values were normal and no violations of sphericity were indicated, so repeated-measures ANOVA (four 2-min blocks of the PASAT) was used to test for differences in slope values across the task. ANOVA and Spearman's rank correlations were used to determine if slope values differed as a function of age, sex, anthropometric measures, or baseline cardiovascular activity. To assess predictors of CA, task-induced changes in MAP and P_{ETCO_2} , two of the most well characterized regulators of CBF (Willie et al., 2011), were simultaneously entered into a multiple regression model predicting CA slope values. All data, unless specified are presented as mean \pm standard deviation and significance was operationalized as $p < .05$. Occasional discrepancies in degrees of freedom represent missing data points due to poor signal quality while measuring P_{ETCO_2} ($n=1$) and BP ($n=1$; during 1st 2-minute block of PASAT). Poor signal quality was determined based on recording physiologically implausible values.

Results

Task Stressfulness and Cardiovascular Activation

Participant ratings of task stressfulness were, on average, 7.6 ± 1.4 , indicating that the task did induce psychological stress. In response to acute psychological stress, MAP [$F(1,24) = 51.72, p < .001, \eta^2 = .68$; Figure 1A] and MCAv [$F(1,24) = 34.05, p < .001, \eta^2 = .59$; Figure 1B]

significantly increased from baseline to task. In contrast, baroreflex sensitivity [$F(1,24) = 20.94$, $p < .001$, $\eta^2 = .47$; Figure 1C] and $P_{ET}CO_2$, [$F(1,23) = 4.27$, $p = .05$, $\eta^2 = .16$; Figure 1D] significantly decreased from baseline to task.

[Insert Figure 1 about here]

Blood Pressure & Cerebral Blood Flow Velocity

For increases in MAP during psychological stress, slope values ranged from -0.7 to 7.5 %/10mmHg. The average slope was $3.5 \pm 2.2\%/10\text{mmHg}$ ($2.0 \pm 1.3 \text{ cm}\cdot\text{s}^{-1}/10\text{mmHg}$; Figure 2). Controlling for changes in $P_{ET}CO_2$ did not appreciably change the values, $3.2 \pm 2.3\%/10\text{mmHg}$ and $1.8 \pm 1.3 \text{ cm}\cdot\text{s}^{-1}/10\text{mmHg}$, for relative and absolute MAP-MCAv slope values, respectively. The MAP-MCAv relationship remained consistent throughout the task period as slope values did not significantly differ across the consecutive 2-min blocks comprising the task period [$F(3,69) = 1.20$, $p = .32$, $\eta^2 = .05$; Figure 3]. The MAP-MCAv relationship did not significantly differ as a function of sex ($F(1,23) = .017$, $p = .90$, $\eta^2 = .001$), nor did it relate to age ($r = .09$, $p = .67$), BMI ($r = .15$, $p = .48$), task stressfulness ($r = .06$, $p = .76$), or baseline cardiovascular measures of MAP ($r = -.02$, $p = .91$) or HR ($r = -.25$, $p = .23$). Overall, task-induced changes in MAP and $P_{ET}CO_2$ accounted for approximately 20% of the variance in MAP-MCAv slope values (Table 2). Task-induced increases in MAP significantly predicted smaller MAP-MCAv slope values, indicative of stronger CA (all $p \leq .038$). Task-induced increases in $P_{ET}CO_2$ were associated with larger MAP-MCAv slope values, but not at a statistically significant level (all $p \geq .07$).

[Insert Figures 2 and 3 about here]

[Insert Table 2 about here]

Discussion

The present study aimed to assess the cerebral pressure-flow relationship using psychological stress to non-pharmacologically manipulate MAP, while at the same time accounting for changes in $P_{ET}CO_2$. Results indicated that the relationship between MAP and MCAv is, to some extent, pressure-passive, even after accounting for changes $P_{ET}CO_2$. Notable inter-individual variability in the strength of CA was also evident.

The traditional view that CBF remains constant independent of steady state changes in MAP has been re-evaluated recently due to accumulating experimental evidence demonstrating a relatively pressure-passive relationship between MAP and CBF. Experimental evidence from a study using phenylephrine and nitroprusside to manipulate MAP showed that MCAv changed $\approx 8\%$ per 10 mmHg change in MAP (Lucas et al., 2010). A subsequent meta-analysis of 40 experimental studies of static CA confirmed this finding (Numan et al., 2014). However, it was noted that usage of vasoactive substances to manipulate MAP and override baroreflex function and inconsistent experimental control of $PaCO_2$ has limited the ability to draw inferences regarding the within-subjects relationship between MAP and CBF. The present study aimed to overcome these obstacles by using a non-pharmacological psychological stress task to elicit changes in MAP, while at the same time continuously measuring $P_{ET}CO_2$. The task was successful in eliciting a robust increase in MAP and MCAv. Our findings demonstrated that for every 10 mmHg change in MAP, MCAv changed on average by $\approx 3-3.5\%$; a relationship that withstood adjustment for $P_{ET}CO_2$. That such a relationship was observed using an acute psychological stress task is notable since systematic control of MAP in pharmacological studies, although necessary and experimentally rigorous, lacks validity outside the laboratory whereas an

acute psychological stress task is more similar to an experience that might be encountered in daily life (Zanstra & Johnston, 2011).

The strength of the CA varied considerably between individuals. This was not unexpected as inter-individual differences in 'static CA' have also been documented in experimental studies using pharmacological intervention to precisely manipulate MAP (Lucas et al., 2010). It stands to reason that individuals exhibiting greater task-induced increases in MAP would also exhibit greater CA (e.g., smaller slope value) since the theoretical purpose of CA is to protect the brain from harmful surges in MAP. This appeared to be the case as task-induced changes in MAP were found to be significantly associated with slope values; greater changes in MAP related to smaller slope values, indicative of a stronger CA. Task-induced changes in $P_{ET}CO_2$ were also related to slope values, but relationships did not reach statistical significance. Importantly, a notable quantity of inter-individual variability in the strength of CA remained after controlling for MAP and $P_{ET}CO_2$. So, what factors might account for the observed inter-individual differences in CA? Anatomically, the sympathetic nervous system is uniquely positioned to influence CA (Brassard, Tymko, & Ainslie, 2017a), but the extent to which sympathetic innervation moderates CA in humans is still unknown (Ainslie & Brassard, 2014). Acute psychological stress tasks, such as the one used in the current study, have been shown to elicit robust sympathetic nervous system activation indexed by increases in circulating adrenaline and noradrenaline (Brindle, Ginty, Phillips, & Carroll, 2014). Given that sympathetic activity appears to influence CA, especially in response to changes in perfusion pressure (Ainslie, 2009; Cassaglia, Griffiths, & Walker, 2008; Cassaglia, Griffiths, & Walker, 2009), it is tempting to speculate that individual differences in task-induced sympathetic activation might account for individual differences in CA. However, targeted experimental evidence is needed to

substantiate such a hypothesis. Finally, given the cognitive demands of the task used in the present study, differences in neurovascular coupling are likely to contribute, to some extent, to increases in MCAv and to the individual differences observed in CA (Filosa & Blanco, 2007).

Cut-off values indicative of impaired CA and the temporal stability of individual differences in CA are clinically relevant. A review of CA in clinical samples (Panerai, 2008) showed that a loss-of-zero MAP-MCAv slope was observed in autonomic nervous system failure, pre-mature new-borns, hypertension, and stroke. However, our data demonstrate that in healthy young adults, in response to psychological stress, a non-zero MAP-MCAv slope is also observed. It may be that a non-zero MAP-MCAv slope does not necessarily imply defective CA (Lucas et al. 2010). Rather, the individual differences in CA observed in this, and other studies, may represent a normal distribution of CA strength with some individuals exhibiting a near-zero slope and others exhibiting slope values indicative of a pressure-passive MAP-MCAv relationship. If this is the case, the temporal stability of such differences is important as individuals normally exhibiting a more pressure-passive MAP-MCAv relationship may be at greater risk for cerebrovascular events. For example, blood pressure responses to psychological stress, such as the one used in this study, have been shown to relate to stress-induced blood pressure increases outside the laboratory (Zanstra & Johnston, 2011) and remain relatively stable over the course of years (Hassellund, Flaa, Sandvik, Kjeldsen, & Rostrup, 2010), and in some cases, increase over time (Uchino, Holt-Lunstad, Bloor, & Campo, 2005; Uchino, Birmingham, & Berg, 2010). Presumably, this is due to hypertrophic remodelling of peripheral vasculature (Folkow, 1990). Cerebral autoregulation appears to be preserved with advancing age (Carey, Panerai, & Potter, 2003; Eames, Eames, Blake, Panerai, & Potter, 2003). Consequently, a scenario can be envisaged where individuals who react to psychological stress with large-

magnitude changes in MAP, or develop such a cardiovascular reactivity pattern over time, and have a relatively pressure-passive MAP-MCAv relationship may be at increased risk of cerebrovascular events. Such circumstances might explain why large-magnitude increases in MAP, provoked by psychological stress, have been related to increased risk of incident stroke (Everson et al., 2001) and a higher prevalence of cerebrovascular disease (Waldstein et al., 2004).

Several considerations must be taken into account when interpreting the results of the present study. First, changes in MCAv only represent changes in CBF to the extent that diameter of the MCA remains constant throughout the recording session (Willie et al., 2011). A strength of the current study is that no pharmacological agents were used to manipulate blood pressure so a direct effect on the diameter of the MCA due to pharmacological intervention can be ruled out. Of note, a study using a similar stress task simultaneously measured MCAv and blood flow in the carotid artery and noted simultaneous increases in blood velocity and flow in the MCA and carotid artery, respectively (Naqvi & Hyuhn, 2009). Nevertheless, some carotid artery vasodilation was noted so results must be interpreted in the context of the technical limitations of transcranial Doppler sonography. Specifically, there may indeed be some dilation of the MCA during our stress task, however, this would only act to underestimate the true effect of the increased flow since a wider diameter without any change in flow would lower velocity rather than increase it. Second, only young adults were included in the study, consequently, the results may not generalize to other older or clinical samples. Third, MAP was successfully increased by psychological stress, however, the relative contributions of psychological stress and cognitive load to increases in MCAv could not be determined within the study design. Therefore, the results should not be interpreted as CA “under stress.” Nevertheless, given that chronic stress had

been related to increased risk of disease (Cohen, Janicki-Deverts, & Miller, 2007) it would of interest to know if psychological stress (and the concurrent physiological activation) influences the extent to which CA can optimally function. For example, laboratory-based stress paradigms differ in the extent to which they activate alpha-, beta-, or mixed-adrenergic responses. Consequently, different stress paradigms may provide specific probes with which to assess the role of sympathetic activity in CA. Fourth, no measures of trait anxiety were made in the present study. Consequently, we are unable to determine whether trait-level characteristics impact resting- or stress-related CA. Finally, only increases in MAP were examined in the current study. There is evidence in humans that support hysteresis in cerebral autoregulation (Brassard et al., 2017b; Schmidt, Klingelhöfer, Perkes, & Czosnyka, 2009; Tzeng et al., 2010). That is, the relatively increased capacity of cerebrovasculature to buffer increases in blood pressure, compared to decreases in blood pressure. Although evidence exists to the contrary (Lucas et al., 2010; Numan et al., 2014), caution should be taken in generalizing these results to situations where MAP may decrease (e.g., orthostatic challenge).

Accumulating evidence indicates that the relationship between MAP and CBF is more pressure-passive than originally thought. However, usage of vasoactive substances to manipulate MAP and override baroreflex function, as well as inconsistent experimental control of arterial carbon dioxide (P_{aCO_2}) has limited the ability to draw inferences regarding the within-subjects relationship between MAP and CBF. Using acute psychological stress, similar to what an individual may experience in daily life, to increase MAP, our data show that MCA_v is indeed, to some extent, pressure-passive, independent of changes in P_{ETCO_2} . These data add support to the hypothesis that regulation of CBF is more pressure-passive than previously thought and provide initial evidence indicating that pressure-passive CA may play a role in the

observed association between MAP stress responses, stroke, and cerebrovascular disease (Everson et al., 2001; Waldstein et al., 2004).

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Conflicts of Interest: None to report

Table 1. Participant Characteristics

Variable	Mean (SD)/%
Age, years	19.80 (3.94)
Gender, %female	52.00
BMI, kg/m ²	22.46 (3.26)
PASAT Stressfulness, 1-10(extremely stressful)	7.6 (1.4)
Waist-Hip Ratio, cm	0.80 (0.04)
Baseline SBP, mmHg	106.37 (9.10)
Baseline DBP, mmHg	63.34 (6.65)
Baseline MAP, mmHg	78.69 (6.83)
Baseline HR, bpm	71.54 (9.95)
Baseline MCA _v , cm/s	57.39 (8.17)
Baseline BRS, ms/mmHg	12.67 (5.83)
Baseline P _{ET} CO ₂ , mmHg	37.46 (4.15)

Note: SD = Standard deviation, PASAT = Paced Auditory Serial

Addition Task

Table 2. Predictors of MAP-MCAv Slope Values

	β	t	p	ΔR^2
Relative (%)				
MAP Reactivity	-.476	-2.22	.038	.087
P _{ET} CO ₂ Reactivity	.411	1.917	.069	.136
Full model				.223
Absolute (cm/s)				
MAP Reactivity	-.499	-2.31	.031	.120
P _{ET} CO ₂ Reactivity	.344	1.30	.126	.095
Full model				.215

Note: Full model contained MAP and P_{ET}CO₂ reactivity measures i.e.

difference between task and baseline values

Figure 1. Task-induced changes in A) mean arterial pressure (MAP), B) middle cerebral artery (MCA_v) blood flow velocity, C) baroreflex sensitivity (BRS), and D) end-tidal partial pressure carbon dioxide (P_{ET}CO₂). * denotes significantly different from baseline ($p \leq .05$). Errors bars indicate standard error.

Figure 2. Regression lines depicting the relationship between task-induced changes in mean arterial pressure (MAP) and middle cerebral artery blood flow velocity (MCA_v). (N = 25). Black line represents average slope.

Figure 3. Mean unstandardized regression slopes for the entire psychological stress task period and each of the four 2-min blocks comprising the task. (N = 25). Error bars indicate minimum and maximum observed slopes.





