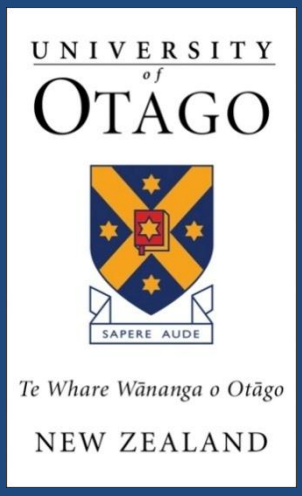

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Braid MacRae

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INTERINDIVIDUAL RELATIONSHIPS BETWEEN BLOOD PRESSURE AND CEREBRAL BLOOD FLOW VARIABILITY

STUDENT **Braid MacRae**

SUPERVISORS Dr Shieak Tzeng

SPONSORS THE SURGICAL RESEARCH TRUST

LOCATION Department of Surgery and Anaesthesia
University of Otago
Wellington

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Braid MacRae

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Supervised by: Dr. Shieak Tzeng

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Although the identification and treatment of excessively high average blood pressure dominates clinical management of chronic blood pressure disease, there is growing recognition that elevated blood pressure variability (BPV) across a wide range of timescales is associated with poorer health outcomes (e.g. stroke incidence and post-stroke outcome). These observations indicate that other aspects of blood pressure, such as BPV, are also valuable for population risk stratification. Narrowly focussing on blood pressure, however, neglects the dependence of the brain on perfusion (blood flow) rather than blood pressure *per se*. Therefore, it is conceivable that cerebral blood flow varibility (CFV) underlies the association between BPV and cerebrovascular disease.

The purpose of this study was to examine the inter-individual (population-level) relationships between BPV and CFV under conditions of normal and blunted (calcium channel blockade) cerebrovscular control. Haemodynamic data was recorded under resting conditions from 12 subjects treated with a calcium channel blocker (60 mg oral Nimodipine) and 11 subjects treated with a placebo pill. Using mathematical approaches we derived information about BPV and variability in middle cerebral artery flow velocity (i.e., CFV). The major findings were that spontaneous BPV is positively related to CFV across individuals, and treatment with a calcium channel blocker reduces both BPV and CFV despite some impairment of cerebrovascular control. These findings raise the possibility that CFV may be a explanatory factor in the association between elevated BPV and adverse cerebrovascular outcomes, and support the possibility of using CCB to improve hemodynamic stability under resting conditions.

LAY REPORT

ABSTRACT

The relationships between blood pressure variability (BPV) and cerebral blood flow variability (CFV) across individuals with intact or blunted cerebrovascular control are poorly understood. This study sought to characterize the interindividual associations between spontaneous BPV and CFV under conditions of normal and blunted (calcium channel blockade; CCB) cerebrovascular control in healthy humans. We analyzed pressure-flow velocity data from 12 subjects treated with CCB (60 mg oral Nimodipine) and 11 subjects treated with a placebo pill. Spontaneously-occurring fluctuations in mean arterial blood pressure (MAP) and middle cerebral artery flow velocity (MCAvmean; transcranial Doppler) were characterized using power spectral and transfer function analysis in the very low (0.02–0.07 Hz), low (0.07–0.20 Hz), and high (0.20–0.40 Hz) frequency ranges. Across our study sample MAP and MCAvmean power were positively correlated in all three frequency ranges both before ($R2=0.34–0.67$, all $P<0.01$) and after CCB ($R2=0.53–0.61$, all $P<0.02$). Compared to placebo, CCB reduced very low frequency MAP ($P<0.05$) and MCAvmean power ($P<0.01$), and the low frequency cross-spectral phase angle ($P<0.05$). The magnitude of change in MAP and MCAvmean power with CCB (i.e. change scores) was positively related in the very low frequency range. Collectively, these findings indicate that CFV may be an explanatory factor in the association between elevated BPV and adverse cerebrovascular outcomes, and support the possibility of using CCB to improve hemodynamic stability under resting conditions.

INTRODUCTION

Although the identification and treatment of excessively high average blood pressure dominates clinical management of chronic blood pressure disease, there is growing recognition that elevated blood pressure variability (BPV) across a wide range of timescales also predicts poorer health outcomes (12, 19, 22). Elevated short-term (minutes) and long-term (visit-to-visit) BPV have been linked to accelerated end-organ damage (25, 26), stroke incidence (24), and post-stroke complications (e.g. hemorrhagic transformation, mortality) (10). These findings suggest that other aspects of blood pressure, such as BPV, are also valuable for population risk stratification (20). However, narrowly focusing on BPV belies the dependence of vital organs such as the brain on perfusion (i.e. blood flow) rather than blood pressure per se. Because the brain has a high metabolic demand for oxygen, cerebral blood flow variability (CFV) and the integrity of flow-stabilizing mechanisms such as autoregulation may underlie the relationship between elevated BPV and end-organ disease.

Much is known about the within-individual physiology relating cerebral perfusion pressure with cerebral blood flow (4, 7, 28, 30, 34). In contrast, the extent to which CFV is determined by BPV and CA across individuals has received comparatively little attention despite population relationships being equally important from an epidemiological risk-stratification perspective. Furthermore, Matsui et al. (13) recently showed that day-by-day BPV was lower in patients treated with an angiotensin II receptor blocker/calcium channel blocker combination compared to those treated with an angiotensin II receptor blocker/diuretic combination. This raised the possibility that elevated BPV can be treated using conventional antihypertensive agents (18), although using calcium channel blockers to reduce BPV may not necessarily decrease CFV given the potential for concomitant CA impairment (29). The implications for conditions that are fundamentally due to disordered perfusion (e.g. cerebral ischemia) are that possible variability increasing hemodynamic effects may negate the benefits of reducing BPV.

In view of these considerations, the objectives of this study were twofold. First, we sought to determine the extent to which differences in CFV across individuals were determined by BPV. Second, we examined the cerebral hemodynamic effects of calcium channel blockade (CCB) on these variables and their relationships. Impairment of CA with CCB was useful in two ways in that it provided insight into both the interplay between BPV and CA in determining CFV across individuals, and the potential for CCB to be used to stabilize hemodynamic profiles. Assuming CCB would influence both BPV and CA (via direct action of CCB on peripheral and cerebral vasomotor activity), the use of a healthy cohort, over a patient cohort with established CA impairment, allowed the influence of intact CA (before blockade) and blunted CA (following

blockade) to be investigated. It is hypothesized that across individuals, spontaneous BPV will be positively related to CFV, and that CCB will reduce spontaneous CFV concomitantly to reduced BPV despite CA impairment.

MATERIALS AND METHODS

Twenty-three healthy subjects (12 females) without any history of cardiovascular, respiratory, or endocrine disease signed written informed consent before participating. All subjects had abstained from exercise and caffeinated food and beverages for at least 12 hours and were advised to have a light breakfast at least 2 hours prior to the study commencement at 0900 hours. The study was approved by the New Zealand Central Regional Ethics Committee and conformed to the standards set by the Declaration of Helsinki.

Experimental protocol

All subjects were studied in the supine position in a temperature-controlled laboratory (22–23°C). Six-minute baseline recordings were made before and ~50 min following ingestion of either 60 mg Nimodipine (n = 12, 6 female; 26 ± 5 y) or a placebo pill (n = 11, 6 female; 29 ± 9 y). The duration between recordings was based on the peak pharmacodynamic activity of Nimodipine on the cerebrovasculature (3); the placebo trials served as time controls. Subject allocation to active or placebo treatment was randomized.

Measurements

We recorded the electrocardiogram, non-invasive beat-to-beat blood pressure via finger photoplethysmography (Finometer MIDI, MLE1054-V, Finapres Medical Systems), right middle cerebral artery blood flow velocity (MCAv; 2 MHz pulsed Doppler ultrasound, ST3 Digital Transcranial Doppler System, Spencer Technologies, Seattle, USA), and partial pressure of end tidal CO_2 ($P_{ET}CO_2$) sampled from a nasal line (gas analyzer model ML206, ADInstruments, Colorado Springs, CO, USA). Recalibration of the finger blood pressure device was performed periodically before each recording to ensure accuracy of measurement, which was also verified against manual brachial artery blood pressure measurements. Data were acquired continuously at 1 kHz per channel via an analog-to-digital converter (PowerLab/16SP ML795; ADInstruments, Colorado Springs, CO, USA) interfaced with a computer, and stored for off-line analysis. From the recorded electrocardiogram, blood pressure, and MCAv waveforms, we determined the time of each R wave and beat-to-beat values for mean MCAv ($MCAv_{mean}$) and mean arterial blood pressure (MAP). Data were processed and analyzed with custom software written in LabView 11 (National Instruments, Texas, USA).

Spectral and transfer function analysis

Beat-to-beat MAP and $MCAv_{mean}$ data was subjected to fast Fourier transform analysis. The cross-spectrum between MAP and $MCAv_{mean}$ was determined and divided by the MAP auto-spectrum to derive the transfer function phase, gain, and coherence indices. In this study we used phase as our primary indicator of CA function based on previous work showing a clear linear response between phase and CA modulated across a wide range of arterial PCO_2 levels (27). Spontaneous MAP and $MCAv_{mean}$ spectral powers, and the mean value of transfer function phase, gain, and coherence were each calculated in the very low (VLF, 0.02–0.07 Hz), low (LF, 0.07–0.20 Hz), and high (HF, 0.20–0.40 Hz) frequency ranges as commonly defined (34). To account for interindividual differences in MCA diameter and potential treatment influences on MCA diameter (within-individual), transfer function gain and $MCAv_{mean}$ spectral power were assessed using normalized units defined as the beat-to-beat values divided by the mean value (17). To account for potential changes in absolute blood pressure following CCB, MAP spectral power was assessed in both absolute and normalized units. For consistency of reporting with $MCAv_{mean}$ spectral power, the normalized values were presented unless specifically stated otherwise.

Statistical analysis

Normality was assessed for all parameters using the Shapiro-Wilk test; log transformations were applied to all spectral variables and values presented are as described in the Table or Figure legends. *A-priori* defined comparisons investigating the differences in treatment effects between CCB versus placebo on hemodynamic and power spectral variables were assessed using linear mixed effects models (15, 33). For each dependent variable, the linear mixed model specified a main effect for treatment (before vs. after treatment), a main effect for group (CCB vs. placebo), and a treatment x group interaction. Statistically significant interactions indicated that the treatment response differs between the CCB and placebo groups. The effect of treatment (before vs. after treatment) on spectral parameters within each group (CCB or placebo) was defined *a priori* as comparisons of interest. These pair-wise comparisons were performed as planned using paired t-tests adjusted for multiple comparisons (Holm-Bonferroni method) to control for inflated type-1 error (21). Potential gender differences were assessed with the inclusion of gender as a fixed factor and testing for a gender x treatment x group interaction. Specific relationships defined *a priori* between spectral powers were assessed using scatter plots, Pearson's correlation coefficients, and linear regression. Given the relationship between different spectral parameters involved multiple comparisons, *P* values were also adjusted for multiple comparisons. All data were analyzed using SPSS 17 (SPSS, Chicago, IL). Unless otherwise stated in figure and table legends, all values are expressed as mean (SE) and rounded to two significant figures. Statistical significance was set *a priori* at $P \leq 0.05$.

RESULTS

Effects of calcium channel blockade on baseline parameters

Baseline cardiovascular, respiratory, and cerebrovascular variables under the conditions of this study are presented in Table 1. Significant treatment × group interactions were found for HR, $MCAv_{mean}$, and MAP indicating that CCB had treatment effects that were distinct from the placebo group. An increase in HR and reduction in $MCAv_{mean}$ were observed following CCB but not the placebo. In contrast, MAP increased following the placebo but not CCB. A clinically negligible, but statistically significant, reduction in $P_{ET}CO_2$ was observed following treatment in both groups (~1 mmHg; Table 1).

Table 1. Summary of baseline variables before and after treatment with calcium channel blockade or placebo.

	Calcium channel blockade		Placebo		Interaction
Variable	Before	After	Before	After	*P* value
HR, beats/min	64 (2.4)	71 (4.6)**	60 (1.9)	57 (1.6)	<0.01
$MCAv_{mean}$, cm/s	64 (3.4)	56 (2.4)**	65 (3.4)	65 (3.1)	<0.01
MAP, mmHg	76 (3.5)	72 (2.4)	78 (2.8)	84 (2.8)*	<0.05
$P_{ET}CO_2$, mmHg	40 (0.72)	39 (0.87)*	39 (0.82)	38 (0.71)*	0.68

HR, heart rate; $MCAv_{mean}$, mean middle cerebral artery flow velocity; MAP, mean arterial blood pressure; $P_{ET}CO_2$, end-tidal partial pressure of carbon dioxide. *P* values presented in the table are for main effects and interactions in the linear mixed model. *P<0.05 vs. before treatment, **P<0.01 vs. before treatment; paired comparisons (before vs. after) were Holm-Bonferroni corrected. Values are mean (SE).

Effects of calcium channel blockade

The influence of CCB on $MCAv_{mean}$ and MAP spectral powers for one example subject is shown in Figure 1. The treatment effects of both CCB and placebo on $MCAv_{mean}$ and MAP spectral powers are summarized in Figure 2. A reduction in $MCAv_{mean}$ spectral power was observed in the VLF range following CCB treatment that differed from the placebo effect (interaction effect P<0.01). Paired comparisons showed that CCB treatment reduced LF $MCAv_{mean}$ spectral power (versus before treatment) but the interaction effect was not significant (P=0.12). Likewise, treatment response was also statistically similar between groups (CCB and placebo) in the HF band (interaction effect P=0.14).

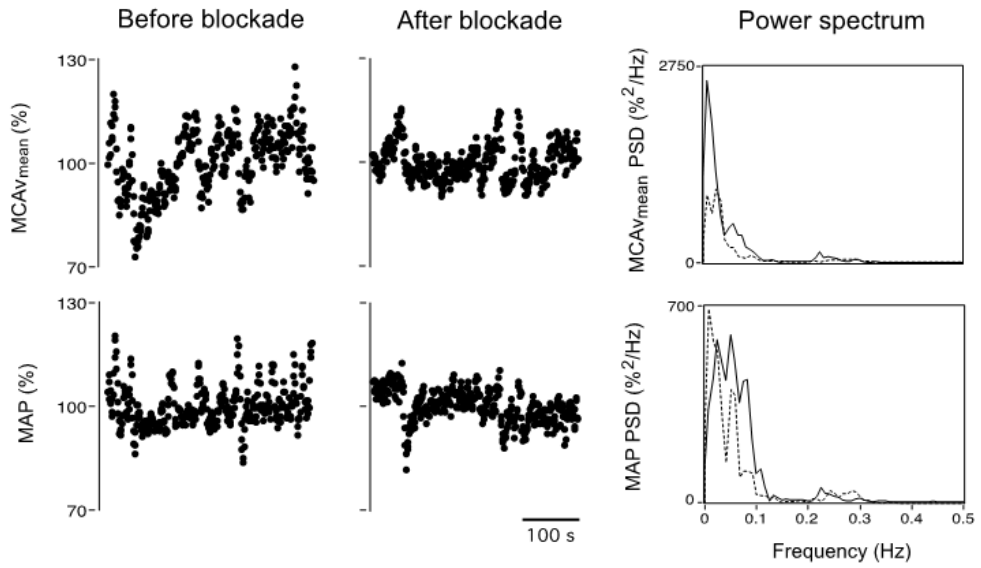

Figure 1. Data for one subject showing a pronounced reduction in the variability of mean middle cerebral artery flow velocity ($MCAv_{mean}$) and mean arterial blood pressure (MAP). For power spectral density (PSD), solid and dashed lines represent before and after calcium channel blockade, respectively.

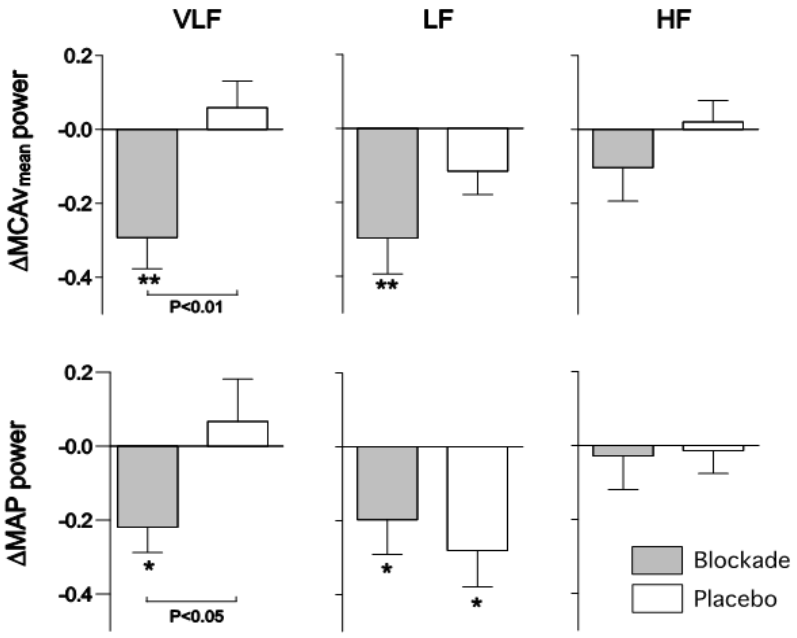

Figure 2. Changes in spectral power for mean middle cerebral artery flow velocity ($MCAv_{mean}$) and mean arterial blood pressure (MAP) following treatment with calcium channel blockade (grey bars) or placebo (white bars) for very low frequency (VLF; 0.02–0.07 Hz), low frequency (LF; 0.07–0.20 Hz), and high frequency (HF; 0.20–0.40 Hz) bands. Values are presented as log ratios (± SE), which is mathematically equivalent to differences of logarithms. *(P<0.05) and **(P<0.01) represents within-group treatment effects (before versus following treatment); horizontal bars and P values indicate significant interactions effects.

A reduction in VLF MAP power was observed following CCB but not following the placebo (interaction effect $P<0.05$). In contrast, treatment with CCB produced responses that were similar to placebo for both LF and HF MAP power (interaction effects were not significant; both $P>0.10$). The outcomes of the statistical analyses for absolute MAP power were consistent with those presented here for normalized MAP power. In support of the summary statistics for defined bands (Figure 2), the group responses plotted on a continuous spectrum illustrate that reductions in both $MCAv_{mean}$ and MAP spectral power following CCB are most evident within the VLF range (Figure 3).

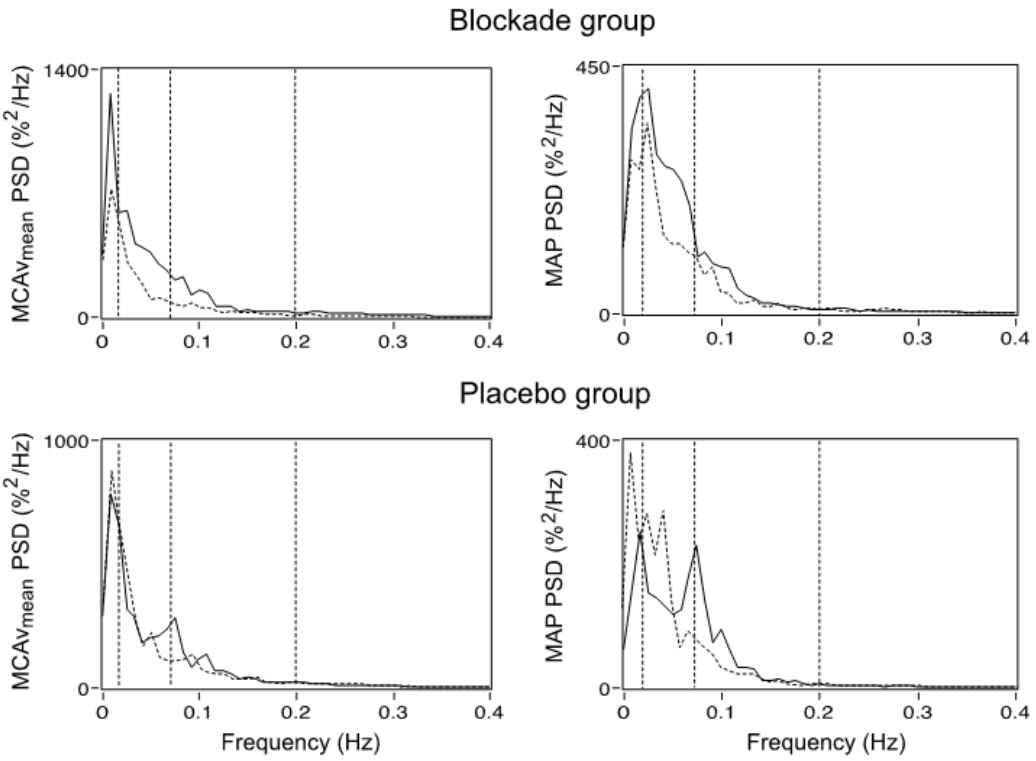

Figure 3. Power spectral density (PSD) for mean middle cerebral artery flow velocity ($MCAv_{mean}$) and mean arterial blood pressure (MAP) in the calcium channel blockade and placebo groups. Solid and dashed lines represent group median PSD before and following treatment, respectively. Dashed vertical lines illustrate boundaries of the very low frequency (VLF; 0.02–0.07 Hz), low frequency (LF; 0.07–0.20 Hz), and high frequency (HF; 0.20–0.30 Hz) bands.

The effects of CCB and placebo treatment on cross-spectral coherence, phase, and gain are presented in Table 2. VLF and LF phase were each reduced following CCB although a significant interaction effect was seen only in the LF range. Treatment responses for HF phase were similar between CCB and placebo (Table 2). Responses were invariably

similar for coherence and gain between CCB and placebo for all band definitions (VLF, LF, HF; Table 2). There were no statistically significant gender interactions for MAP and $MCAv_{mean}$ spectral power or transfer function parameters in any frequency band (all $P>0.1$).

Table 2. Summary of spontaneous transfer function analysis variables before and after treatment with calcium channel blockade or placebo.

	Calcium channel blockade		Placebo		Interaction
Variable	Before	After	Before	After	*P* value
VLF coherence, AU	0.48 (0.29)	0.52 (0.26)	0.39 (0.12)	0.46 (0.10)	0.62
LF coherence, AU	0.73 (0.22)	0.79 (0.096)	0.73 (0.15)	0.74 (0.17)	0.097
HF coherence, AU	0.78 (0.25)	0.68 (0.16)	0.74 (0.15)	0.68 (0.16)	0.96
VLF phase, radians	1.1 (0.33)	0.64 (0.34)**	1.1 (0.71)	1.0 (0.45)	0.086
LF phase, radians	0.58 (0.25)	0.46 (0.42)*	0.73 (0.30)	0.79 (0.18)	<0.05
HF phase, radians	0.0095 (0.17)	0.21 (0.26)**	0.092 (0.18)	0.21 (0.30)**	0.96
VLF gain, %/%	1.0 (0.50)	0.88 (0.50)	1.0 (0.53)	1.2 (0.66)	0.20
LF gain, %/%	1.2 (0.67)	1.1 (0.22)	1.3 (0.27)	1.4 (0.35)	0.20
HF gain, %/%	1.5 (0.55)	1.4 (0.50)	1.4 (0.50)	1.6 (0.52)	0.18
VLF gain, %/mmHg	1.3 (0.54)	1.3 (0.46)	1.2 (1.0)	1.4 (0.72)	0.99
LF gain, %/mmHg	1.7 (0.51)	1.6 (0.41)	1.8 (0.68)	1.6 (0.53)	0.54
HF gain, %/mmHg	1.8 (0.79)	1.9 (0.47)	2.1 (0.47)	2.0 (0.55)	0.63

VLF, very low frequency (0.02–0.07 Hz); LF, low frequency (0.07–0.20 Hz); HF, high frequency (0.20–0.30 Hz). AU, arbitrary units. *P* values presented in the table are for the treatment x group interaction term in the linear mixed model. *$P<0.05$ vs. before treatment, **$P<0.01$ vs. before treatment; paired comparisons (before vs. after) were Holm-Bonferroni corrected. Values are median (interquartile range).

Interindividual relationships between hemodynamic parameters

Simple linear regressions relating $MCAv_{mean}$ and MAP spectral powers before treatment (pooled) and following CCB are shown in Figure 4 for the VLF, LF, and HF bands. MAP power was a positive predictor of $MCAv_{mean}$ power in each frequency band both before treatment (R^2=0.34–0.67, all $P<0.01$) and following CCB (R^2=0.53–0.61, all $P<0.05$). Baseline MAP was unrelated to $MCAv_{mean}$ both before (R^2=0.0020, P=0.84) and following CCB (R^2=0.19, P=0.20).

To determine whether CA might also be a predictor of $MCAv_{mean}$ power, we performed multiple linear regression analyses with either phase or gain included as a covariate. Analyses showed that before treatment the combination of MAP power and gain explained approximately 73% of the variance in the VLF range (R^2=0.73), and 56% in the LF range (R^2=0.56). It was found that VLF MAP power significantly predicted VLF $MCAv_{mean}$ power (β=0.87±0.14, P<0.01), as did VLF gain (β=1.2±0.25, P<0.01). Likewise, both LF MAP power (β=0.83±0.19, P<0.01) and LF gain (β=1.0±0.29, P<0.01) significantly predicted LF $MCAv_{mean}$ power. A similar pattern of relationships was observed following CCB treatment with MAP power and gain collectively explaining 82% of the variance in the VLF range (R^2=0.82), and 74% in the LF range (R^2=0.74). VLF MAP power significantly predicted VLF $MCAv_{mean}$ power (β=0.90±0.17, P<0.01), as did VLF gain (β=1.7±0.39, P<0.01). Similarly, LF MAP power (β=0.91±0.16, P<0.01) and LF gain (β=1.7±0.50, P<0.01) both significantly predicted LF $MCAv_{mean}$ power. Ranking of the standardised β-coefficient showed that VLF and LF MAP power was always ranked higher than gain both before and after following CCB. In contrast to gain, phase was not a significant predictor of VLF or LF $MCAv_{mean}$ power under both conditions (all P>0.1).

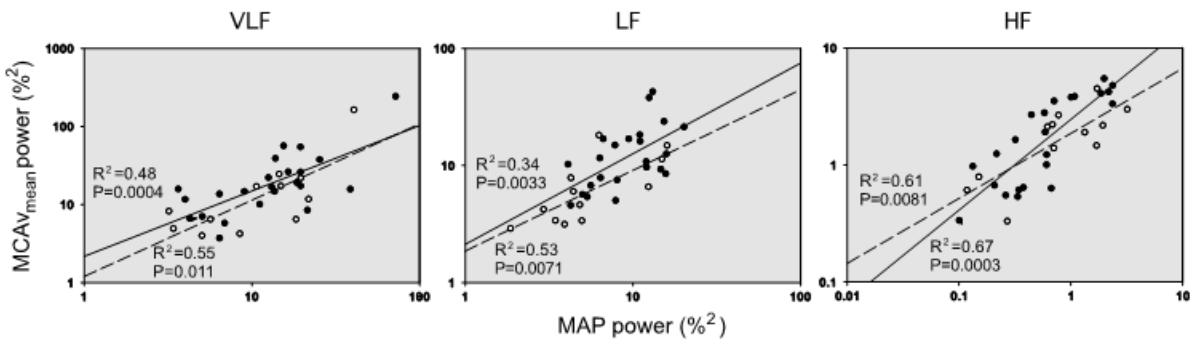

Figure 4. Relationship between the spectral powers of mean middle cerebral artery flow velocity ($MCAv_{mean}$) and mean arterial blood pressure (MAP) before and following calcium channel blockade in the very low frequency (VLF; 0.02–0.07 Hz), low frequency (LF; 0.07–0.20 Hz), and high frequency (HF; 0.20–0.30 Hz) bands. R^2 values are coefficients of determination and P values were corrected for multiple comparisons using the Holm-Bonferroni method. Black dots and solid lines represent before treatment (n=23); white dots and dashed lines represent following blockade (n=12). Before-treatment data from both blockade and placebo groups were pooled because all individuals were in an untreated state. Statistical analyses were performed on log-transformed values. However, for ease of interpretation they are shown here in raw units on log axes.

Interindividual relationships between treatment effects

Where treatment with CCB resulted in significant changes in $MCAv_{mean}$ and MAP spectral powers (VLF band; Figure 2), regression analysis was conducted to explore the relationship between these treatment effects. Following CCB, the magnitude of the reduction in MAP power was a positive predictor of $MCAv_{mean}$ power accounting for 48% of the variance (Figure 5). That is, the within-individual effects of CCB on $MCAv_{mean}$ and MAP spectral powers were positively related across individuals. To determine whether changes in CA might also be a predictor we included the change in phase with CCB treatment as an additional covariate. Results indicated that change (following CCB) in MAP power (β=0.90±0.30, P<0.01) but not change in phase (β=0.90±0.30, P=0.33) was a significant predictor of change in $MCAv_{mean}$ power (R^2=0.54). In contrast, neither the change in MAP power (β=0.60±0.29, P=0.07) or phase (β=-0.059±0.23, P=0.81) was related to change in $MCAv_{mean}$ power in the LF range.

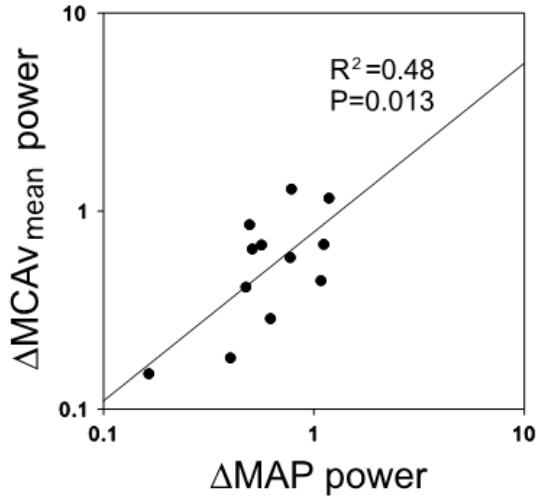

Figure 5. Within-individual changes in the spectral powers of mean middle cerebral artery flow velocity ($MCAv_{mean}$) and mean arterial blood pressure (MAP) following calcium channel blockade in the very low frequency (VLF; 0.02–0.07 Hz) band plotted across individuals. Given that spectral parameters were log transformed in the analysis presented in Figure 2, the relationship between change scores were analyzed as log ratios, which is mathematically equivalent to differences of logarithms. Values are presented here as ratios on log scales.

DISCUSSION

This study was the first to examine the interindividual relationships between BPV and CFV in a cohort of subjects with an initially intact and subsequently blunted CA. Consistent with our hypotheses we have demonstrated that in the resting state: 1) spontaneous BPV is positively related to CFV across individuals, 2) treatment with CCB reduces both BPV and CFV despite some impairment of CA, 3) these variability-dampening effects (on BPV and CFV) are predominately observed in the VLF band, and 4) in this band, the magnitude of change in BPV is positively related to the magnitude of the change in CFV.

Cerebral pressure-flow relationships

Although some proportionality between BPV and CFV might be expected between individuals, to date the exact nature and strength of these associations have not been adequately explored. Our analysis showed that CFV and BPV were positively related across all the frequency ranges studied (0.02–0.40 Hz) and that the coefficient of determination relating CFV and BPV ranged between 0.34-0.67 before and 0.53-0.61 after CCB. These findings indicate that BPV is a determinant of CFV across all frequency bands studied irrespective of whether CA is intact or blunted, and also suggest that factors other than BPV are influential. Multiple regression analysis incorporating MAP power and gain showed that both factors were positive predictors of $MCAv_{mean}$ power, indicating that on average individuals with higher BPV and poorer dynamic CA have greater CFV. However, we found that phase did not significantly predict $MCAv_{mean}$ power under any condition. This lack of convergence between two different CA metrics points to the need to confirm the relevance of CA in explaining interindividual variations in CFV in future studies using alternative measures of dynamic CA.

Clinical significance

BPV has established recognition as a prognostic indicator of certain adverse health outcomes (20). However, given that many cerebrovascular disease processes involve disordered brain perfusion, it seems that perfusion itself (i.e. CFV) could explain why individuals with high BPV are at greater risk of stroke and subsequent complications. Such a causal pathway would require BPV to be related to CFV at a population (interindividual) level, and the present study supports this latter contention.

It has previously been demonstrated that the day-by-day BPV of hypertensive individuals can be reduced with CCB (13). There is concern, however, that CCB may also impair CA, reduce cerebrovascular resistance, and enhance blood pressure transmission to vital organs such as the brain (11, 28). Similar concerns have also been raised in studies of kidney function showing that CCB enhances blood pressure transmission and accelerates the development of progressive glomerulosclerosis (6). Contrary to these concerns, we have demonstrated that CCB results in a more stable hemodynamic profile in the resting state in that, despite some CA impairment, CCB reduced both BPV and CFV. Collectively these results extend the notion that, first, elevated BPV can be treated with CCB in the resting state (13), and second, reduced CFV may partially underlie any therapeutic benefits of BPV reduction.

Long-acting dihydropyridine CCB are already recommended in both primary and secondary stroke prevention (8). CCB using agents with unique cerebrovascular

specificity such as Nicardiapine (2) and Nimodipine (32) are first-line agents for managing ischemic complications following aneurismal subarachnoid hemorrhage. For this indication, CCB has been shown to reduce the incidence of cerebrovasospasm and 'delayed' cerebral ischemia. Interestingly, CCB can improve outcome even if the vasospsam is not significantly reduced on angiography (1), raising the possibility that some of the therapeutic effect may be due to alternative mechanisms such as reduced BPV and/or CFV. Such mechanisms may also explain why relatively low doses of oral Nimodipine (e.g. 30 mg every 6 h) have been shown to improve neurological outcome in stroke (5, 14, 16).

Given the emerging interest of using CCB to explicitly treat elevated BPV, prospective clinical trials are now needed to determine whether antihypertensive agents that can reduce BPV will also have beneficial effects on end-organ perfusion variability and improve functional outcome. Our findings prompt the resolution to these questions because a number of randomized controlled trials that were designed to verify the putative neuroprotective effects of CCB in acute stroke (e.g. the INWEST trial) reported higher incidence of death and dependency in patients initially treated with high dose intravenous Nimodipine (2 mg/h) when compared to placebo (9, 31).

Methodological considerations

Inferences from this study should be made in cognizance of several important methodological considerations. Transcranial Doppler is based on measurements of cerebral blood flow velocity not volumetric flow. Because flow is a product of the vessel cross section area (πr^2) multiplied by blood velocity, the latter can only be used as a valid surrogate of volumetric flow for comparisons across individuals if the caliber of the insonated vessel is known. For this reason we have focused our results and interpretations on relative rather than absolute changes in flow velocity variability (17).

It is important to recognize that whilst transfer function analysis is widely applied for CA assessment, there is currently no accepted gold-standard CA metric (27). Recent studies show that many popular CA metrics exhibit poor convergent validity and therefore data interpretation needs to be done with an awareness of their individual strengths and limitations (27). Nevertheless, our assertion that CCB impairs CA is based on the knowledge that Nimodipine attenuates dynamic cerebral vasomotion under direct visual examination (23), and not simply on the current observation that CCB reduced LF phase.

It is also worth recognizing that the focus in this study was resting conditions. Although we found CCB results in a more stable resting hemodynamic profile, this treatment could nevertheless compromise the ability of the vasculature to respond to active blood

pressure perturbations such as during changes in body posture or physical activity. Furthermore, given the current study was performed in healthy young subjects and after acute administration of a single dose of CCB, the results should not be directly extrapolated to patients under chronic CCB treatment or to patients with cerebrovascular disease without further clinical validation. Finally, although we observed significant reductions in phase consistent with diminished CA, the average phase post CCB was still greater than zero. Thus, our findings reflect the changes associated with the blunting, not the complete abolishment, of CA.

CONCLUSIONS

Our findings show that BPV is a determinant of CFV across individuals within the 0.02–0.40 Hz frequency range whether CA is intact or blunted. These findings raise the possibility that CFV may be a potential explanatory factor in the association between elevated BPV and adverse cerebrovascular outcomes, and support the possibility of using CCB to improve hemodynamic stability under resting conditions.

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STUDENT

Name: Braid MacRae

Email: braid.macrae@otago.ac.nz

Supervisors: Dr. Shieak Tzeng

Host Department: Department of Surgery and Anaesthesia
Institution: Otago of University, Wellington
Address: PO Box 7343
Wellington 6242
New Zealand

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