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Mayer wave activity in vasodepressor carotid sinus hypersensitivity

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Aims Mayer waves are low frequency blood pressure waves, whose modulation involves central/peripheral baroreflex pathways. Although vasodepressor carotid sinus hypersensitivity (VDCSH) is a common hypotensive disorder in ageing, the mechanism of VDCSH is unknown. We hypothesize that VDCSH is due to impaired baroreflex function and that Mayer wave amplitude and oscillation frequency are therefore altered.

Methods and results Ten minutes ECG and continuous beat-to-beat blood pressure (TNO Finapres©) recordings were taken in supine position. Blood pressure variance, spectral power (0.04–0.15 Hz) and centre of frequency was examined across a number of frequency bands. Vasodepressor carotid sinus hypersensitivity was defined as 50 mmHg drop in systolic blood pressure (SBP) during carotid sinus massage. Syncope facility was used in this study. Twelve patients with VDCSH median age 72 range (50–92) were compared with 36 case–controls median age 78 range (48–88). Diastolic blood pressure variability (median SD) was significantly higher in the VDCSH 6.6 (1.9–12.9) mmHg compared with controls 4.0 (1.7–9.5) mmHg; $P < 0.05$. Mean arterial blood pressure (MAP) variability (median SD) was significantly higher in the VDCSH 6.6 (2.9–10.1) mmHg compared with controls 4.6 (2.5–9.1) mmHg; $P < 0.05$. Low frequency Mayer wave activity in MAP in VDCSH compared with controls was increased at 0.06 Hz [controls −21.7 $mmHg^2$/Hz (IQR: 30.8); VDCSH −31.5 $mmHg^2$/Hz (IQR: 72.0) $P < 0.05$] and at 0.1 Hz [controls −4.9 $mmHg^2$/Hz (IQR: 9.4); VDCSH −11.5 $mmHg^2$/Hz (IQR: 12.9) $P < 0.1$]. High frequency blood pressure fluctuations were significantly increased at 0.3 Hz in VDCSH group in SBP [controls −4.1 $mmHg^2$/Hz (IQR: 10.4); VDCSH −17.4 $mmHg^2$/Hz (IQR: 47.9) $P < 0.05$] and MAP records [controls −32.5 $mmHg^2$/Hz (IQR: 76.9); VDCSH −64.6 $mmHg^2$/Hz (IQR: 59.8) $P < 0.01$].

Conclusion Blood pressure variability in particular activity at Mayer wave frequencies was higher in VDCSH. Future work will investigate this approach as a basis for diagnosis of VDCSH, with implications for syncope and falls management.

Keywords Mayer waves • Vasodepressor carotid sinus hypersensitivity • Syncope • Falls management • Blood pressure variability

Introduction

Carotid sinus hypersensitivity (CSH) is an age-related autonomic disorder[1–3] characterized by exaggerated cardiac slowing (CICSH, cardioinhibitory carotid sinus hypersensitivity) and/or profound drops in blood pressure (VDCSH, vasodepressor carotid sinus hypersensitivity) following unilateral carotid sinus massage (CSM).[4–5] First described by Roskam,[6] CSH is now a well-established modifiable risk factor for syncope and falls in the elderly,[7] responsible for symptoms in up to 30% of older patients.[8] Cardiac pacing reduces symptoms in those with CICSH;[9] however in VDCSH, a successful treatment option remains elusive, which is further exacerbated by an incomplete understanding of its pathophysiology.

On the basis of experimental evidence, it has been postulated that CSH occurs secondary to up-regulation of α2 adrenoreceptor

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induced deafferentation of the baroreflex resulting from atherosclerosis and a reduction in carotid sinus compliance.[10] Neuropathological evidence reports a small but significant increase in neurodegenerative hyperphosphorylated Tau proteins in brainstem nuclei that regulate cardiovascular activity.[11] Polvikoski *et al.*[12] found marked α-synuclein pathology in the stellate ganglia of an elderly lady with CICSH. Growing evidence thus suggests that CSH affects the baroreflex arc in central areas; however, the manner in which this dysfunction leads to a hypersensitive response remains obscure.

In an attempt to further understand the mechanisms contributing to VDCSH, we examine Mayer wave activity as a non-invasive marker reflective of the state of the blood pressure regulation system. Mayer waves are low frequency (slower than respiration) arterial pressure oscillations, which exhibit a significant coherence with oscillations of sympathetic nerve activity.[13] They are believed to result from oscillations induced in sympathetic nerve activation of peripheral resistance vessels. Mayer waves are strongly attenuated after acute α-adrenoceptor blockade[14,15] and sino-aortic baroreceptor denervation.[16,17] These oscillations are variable in amplitude but have relatively stable intra-species frequency. In humans, this frequency is age, gender, and posture independent, centred typically ∼0.1 Hz.[18]

A number of authors have suggested that measurement of these oscillations may be used as a non-invasive tool for investigating underlying alterations in peripheral resistance regulatory mechanisms.[19–21] Studies, which simulate Mayer wave generation,[19,22,23] predict that Mayer wave amplitude increases with the gain and range of the baroreflex. Oscillation frequency decreases as afferent, efferent, and vascular response delays increase. This association between Mayer wave activity and baroreflex physiology provides an opportunity to study differences in baroreflex function in health and disease using non-invasive methods. Furthermore, the direction of Mayer activity alterations may provide insight into the manner in which the baroreflex gain and/or range is affected.

As the generation and modulation of Mayer waves involve central baroreflex pathways common to those implicated in the pathogenesis of VDCSH, we hypothesize that Mayer wave activity is altered in VDCSH. The purpose of this study was to compare Mayer wave amplitude and Mayer wave frequency in VDCSH and case–controls.

Methods

Participants

Participants were recruited prospectively from a dedicated Falls and Blackout facility in a large teaching hospital. All subjects attended for a single visit between 09.00 and 13.00 h in a temperature (23°C), comfortably lit, low-noise environment.[24] Consecutive patients (aged more than 50) with a history of recurrent syncope or unexplained falls in the previous year were recruited. All patients had full clinical assessment including CSM as part of routine cardiovascular assessment. The study had ethical approval from the local Ethics Committee.

Carotid sinus massage

Prior to CSM all subjects underwent a 10 min baseline surface electrocardiogram (ECG) and continuous beat-to-beat blood pressure (TNO Finapres©) recording. Subjects were instructed to lie supine and directed to breathe normally while measurements were taken. Following an initial 5 min cardiovascular stabilization period Physiocal© was switched off, and data were recorded for a further 5 min. Signals were sampled at 200 Hz, filtered between 0.01–100 Hz, and stored digitally on a PC for further analysis. This allowed standard baseline cardiovascular variables including heart rate (HR), systolic blood pressure (SBP), diastolic blood pressure (DBP), and mean arterial blood pressure (MAP) to be recorded. Mayer activity was derived from last 5 min of this rest period.

Following this CSM was performed. Firm longitudinal massage was applied for 5 s at the point of maximal pulsation over the carotid (usually located at the level of the upper border of the cricoid cartilage) on the right and then left sides allowing a 30 s interval between stimuli. Carotid sinus massage was performed in both supine and upright positions (head-up tilt to 70° foot plate assisted table).[5] Thus participants underwent a maximum of four episodes of CSM.

Definition of carotid sinus hypersensitivity

Vasodepressor carotid sinus hypersensitivity was defined as a drop of 50 mmHg or more in SBP and <3 s of asystole. Cardioinhibitory carotid sinus hypersensitivity was defined as asystole of 3 s or more asystole and <50 mmHg SBP vasodepressor response; mixed CSH was a combination of CCSH and VCSH.

Data analysis

All initial data processing was performed with custom written analysis software using MATLAB 6.5© (Mathworks, Inc., Natick, MA, USA). Subject data were separated into four groups according to their cardiovascular response to CSM: (i) Controls (no CSH), (ii) CICSH, (iii) VDCSH, and (iv) Mixed. Only those individuals with Normal or VDCSH responses to CSM were considered for further analysis. Data records were scored for significant noise and artefact, and excluded if noise was above an empirically derived threshold. The ECG data were screened for abnormal rhythms, and the presence of ectopic beats (data were excluded if the number of ectopics $>5\%$ total number of beats). Data records of DBP, SBP, MAP, and R–R interval were linearly detrended prior to subsequent spectral analysis.

To derive interval frequency spectra, 5-min R–R interval, SBP, DBP, and MAP recordings were analysed according to the technique described by DeBoer *et al.*[25] To account for differences in intervals on the frequency axis (arising from inter-individual differences in mean pulse interval), cubic spline interpolation was applied to resample spectra from 0 to 0.5 Hz in steps of 0.0025 Hz. Standard time domain indices of cardiovascular variability were extracted from BP and R–R series including standard deviation and interquartile range. Frequency domain variables were calculated by integration of spectral estimates within a number of standard pre-defined frequency bands.[24] Standard blood pressure variability frequency bands VLF (0.003–0.04 Hz), LF (Mayer wave band 0.04–0.15 Hz), HF (Traube–Herring band 0.15–0.4 Hz) were examined for differences between VDCSH and controls. A number of sub-bands were further examined in the LF band including LF_1 (0.04–0.07 Hz), LF_2 (0.08–0.1 Hz), LF_3 (0.1–0.012 Hz). This selection was achieved via statistical procedure whereby independent *t*-tests were applied to group ensemble averaged spectra to identify those bands, which differentiate controls and VDCSH groups. The peak power spectral density (P_i) and frequency at which this peak (fp_i) occurs were found, within bands VLF, LF_1, HF and a combined band, MF, which includes LF_2 and LF_3 bands.

Table 1 Demographics and baseline cardiovascular function in normal and vasodepressor carotid sinus hypersensitivity groups

		Control	VDCSH	Significance
Number of cases		31/36	12/15	
Age	Median (range)	72 (50–92)	78 (48–88)	NS
Height (cm)	Mean ± SD	164.3 ± 8.9	167.8 ± 10.2	NS
Weight (kg)	Mean ± SD	75.0 ± 14.4	71.2 ± 18.5	NS
SBP (mmHg)	Mean ± SD	153.1 ± 17.9	159.8 ± 16.7	NS
DBP (mmHg)	Mean ± SD	74.6 ± 11.0	76.7 ± 12.7	NS
MAP (mmHg)	Mean ± SD	103.9 ± 11.8	108.4 ± 13.1	NS
HR (b.p.m.)	Mean ± SD	67.1 ± 12.6	71.9 ± 13.3	NS
MaxRR (ms)	Median (range)	882.6 (645.2–1308.1)	841.9 (643–1130.5)	NS
Nadir SBP (mmHg)	Mean ± SD	124.2 ± 22.7	102.5 ± 19.7	$P < 0.01$
Delta SBP (mmHg)	Mean ± SD	27.4 ± 9.6	57.2 ± 8.2	$P < 0.0001$

MaxRR, maximum RR interval reached after CSM; Nadir SBP, minimum SBP reached after CSM; Delta SBP, maximum change in SBP from baseline after CSM.

Statistical analysis

SPSS© version 14 (SPSS Inc., Chicago, IL, USA) was used to process study data. All features derived in the previous sections were assessed for normality using data histograms, Normal Q–Q, detrended Normal Q–Q plots, and calculating distribution skewness, kurtosis, and Kolmogorov–Smirnov test statistics. Initial group age matching was assessed using Krushkall–Wallis non-parametric testing; height and weight were compared by one-way analysis of variance. Normally distributed variables were compared using Students *t*-tests. Non-parametric two-tailed Mann–Whitney *U* test was used to compare non-parametric data. Significance was calculated at a level of $P < 0.05$.

Results

Subjects

Eighty-one patients (44 males and 37 females) were recruited. The median age of subjects was 75 (48–92) years, mean height 165.55 ± 10.27 cm, and mean weight 73.46 ± 14.26 kg.

Carotid sinus massage response

Thirty-six (17 males and 19 females) individuals had normal CSM responses; 15 individuals displayed VDCSH (9 males and 6 females); 25 subjects had CICSH (14 males and 11 females); while five had a mixed response (four males and one females). Only data from controls and VDCSH groups were considered for further analysis. A further eight data sets (five control; three VDCSH) were excluded because of artefact and ectopic beats. Data from 31 case–controls and 12 VDCSH subjects were compared. Resting SBP, DBP, HR, and peak frequency were normally distributed; pulse intervals, RR interval, time domain measures of SBP, MAP, DBP, HR, RR variability, and centre of frequency had non-normal distributions. Age, height, weight, and baseline cardiovascular variables were similar between groups (*Table 1*). Systolic blood pressure nadir and degree of vasodepressor response following CSM were more marked in VDCSH group (*Table 1*).

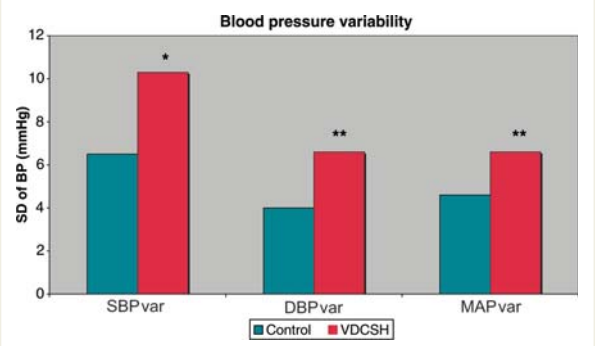

Figure 1 Comparison of time domain indices of BP variability. DBP var, SD of DBP; SBP var, SD of SBP; MAP var, SD of MAP. (*$P < 0.1$; **$P < 0.05$).

Time domain analysis of cardiovascular variability

Diastolic blood pressure and MAP variability was significantly higher in the VDCSH compared with controls [6.6 (1.9–12.9) mmHg vs. 4.0 (1.7–9.5) mmHg; $P < 0.05$ and 6.6 (2.9–10.1) mmHg vs. 4.6 (2.5–9.1) mmHg; $P < 0.05$). A trend towards increased SBP variability was noted in VDCSH (*Figure 1* and *Table 2*). Differences in time domain measures of HR, PI variability were not significant (*Table 2*).

Frequency domain analysis of cardiovascular variability

Standard VLF, LF, and HF bands of SBP, MAP, and DBP did not differ between cases and controls. A trend towards an increase in both LF (22.6%) and HF (129.6%) bands in VDCSH compared with controls was noted (*Table 3*).

On further inspection of the SBP, MAP, and DBP frequency spectral differences between control and VDCSH groups were

Table 2 Comparison of time domain indices of cardiovascular variability

Variable		Control	VDCSH	% Change	Significance
SBP var (mmHg)	Median (range)	6.5 (3.5–14.0)	10.3 (4.2–16.3)	36.9	$P = 0.07$
DBP var (mmHg)	Median (range)	4.0 (1.7–9.5)	6.6 (1.9–12.9)	39.4	$P < 0.05$
MAP var (mmHg)	Median (range)	4.6 (2.5–9.1)	6.6 (2.9–10.1)	30.3	$P < 0.05$
HR var (b.p.m.)	Median (range)	3.6 (1.1–20.1)	5.8 (1.3–14.4)	37.9	NS
PI var (ms)	Median (range)	49.2 (15.5–221.3)	79.7 (24.3–192.4)	38.3	NS

DBP var, SD of DBP; SBP var, SD of SBP; MAP var, SD of MAP; HR var, SD of HR; PI var, SD of PI.

Table 3 Comparison of standard frequency domain indices of cardiovascular variability

Variable	Band	Control	VDCSH	% Change	Significance
SBP ($mmHg^2$)	SBP_{VLF}	4.43 (IQR 6.36)	3.48 (IQR 6.09)	−21.4	NS
	SBP_{LF}	3.97 (IQR 4.47)	5.24 (IQR 11.73)	32.0	NS
	SBP_{HF}	1.58 (IQR 2.78)	2.69 (IQR 6.54)	70.3	NS
MAP ($mmHg^2$)	MAP_{VLF}	2.08 (IQR 4.52)	2.8 (IQR 4.51)	34.6	NS
	MAP_{LF}	2.18 (IQR 2.12)	2.66 (IQR 7.56)	22.0	NS
	MAP_{HF}	0.58 (IQR 1.65)	1.21 (IQR 3.93)	108.6	NS
DBP ($mmHg^2$)	DBP_{VLF}	1.34 (IQR 2.2)	1.74 (IQR 2.01)	29.9	NS
	DBP_{LF}	1.55 (IQR 2.19)	1.78 (IQR 2.24)	14.8	NS
	DBP_{HF}	0.34 (IQR 1.66)	1.06 (IQR 1.58)	211.8	NS

Subscripts VLF, LF, and HF denote standard frequency bands VLF (0.003–0.04 Hz), LF (0.04–0.15 Hz), HF (0.15–0.4 Hz).

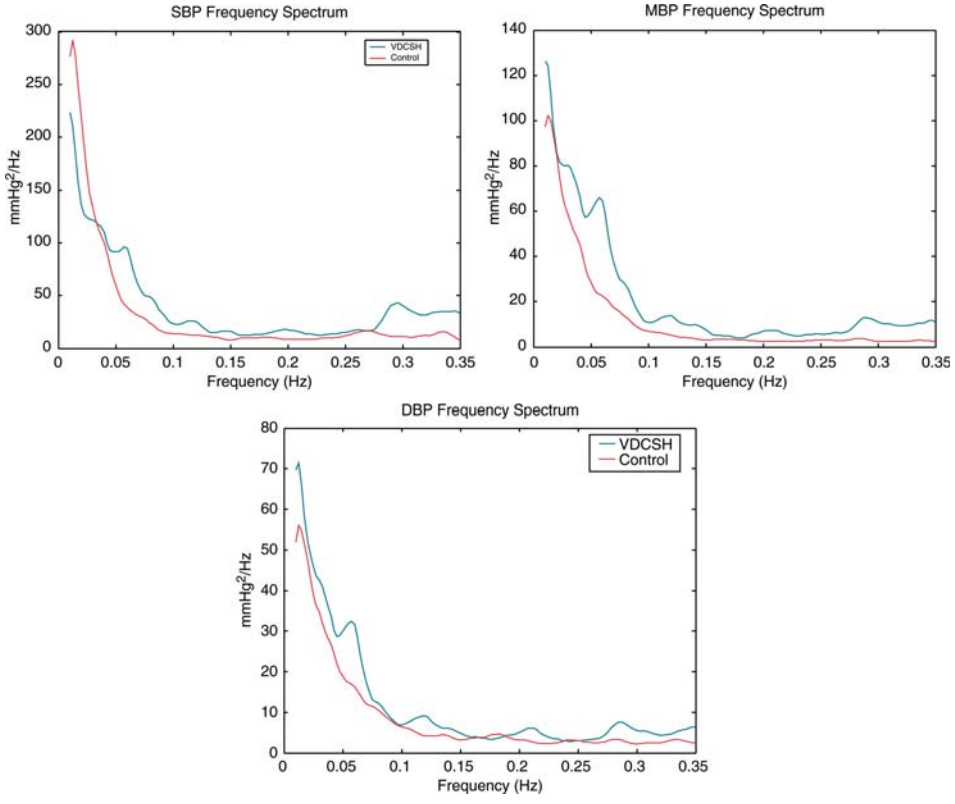

Figure 2 Comparison of ensemble average frequency spectra between vasodepressor carotid sinus hypersensitivity (VDCSH) and controls. (*A*) SBP spectra (above left), (*B*) MAP spectra (above right), (*C*) DBP spectra (below).

obvious in narrow frequency bands within the LF and HF bands (*Figure 2A–C*). Two peaks exist in the LF band ~0.06 Hz and 0.1–0.12 Hz in all three spectra in VDCSH but not in controls. A third peak in the HF band at 0.3 Hz was also noted.

Quantitative analysis indicates significant increases in LF Mayer wave activity in MAP in VDCSH compared with controls at 0.06 Hz [controls −21.7 $mmHg^2$/Hz (IQR: 30.8); VDCSH −31.5 $mmHg^2$/Hz (IQR: 72.0) $P < 0.05$]. At 0.1 Hz differences approached significance [controls −4.9 $mmHg^2$/Hz (IQR: 9.4); VDCSH −11.5 $mmHg^2$/Hz (IQR: 12.9) $P = 0.06$]. No significant differences were noted in DBP and SBP spectra (*Figure 3*).

High frequency respiratory-related blood pressure fluctuations were significantly increased at 0.3 Hz in SBP for case vs. controls [17.4 $mmHg^2$/Hz (IQR: 47.9) vs. 4.1 $mmHg^2$/Hz (IQR: 10.4) $P < 0.05$] and MAP records [32.5 $mmHg^2$/Hz (IQR: 76.9) vs. 64.6 $mmHg^2$/Hz (IQR: 59.8) $P < 0.01$]. A non-significant increase was found in DBP spectra at these frequencies (*Figure 3*).

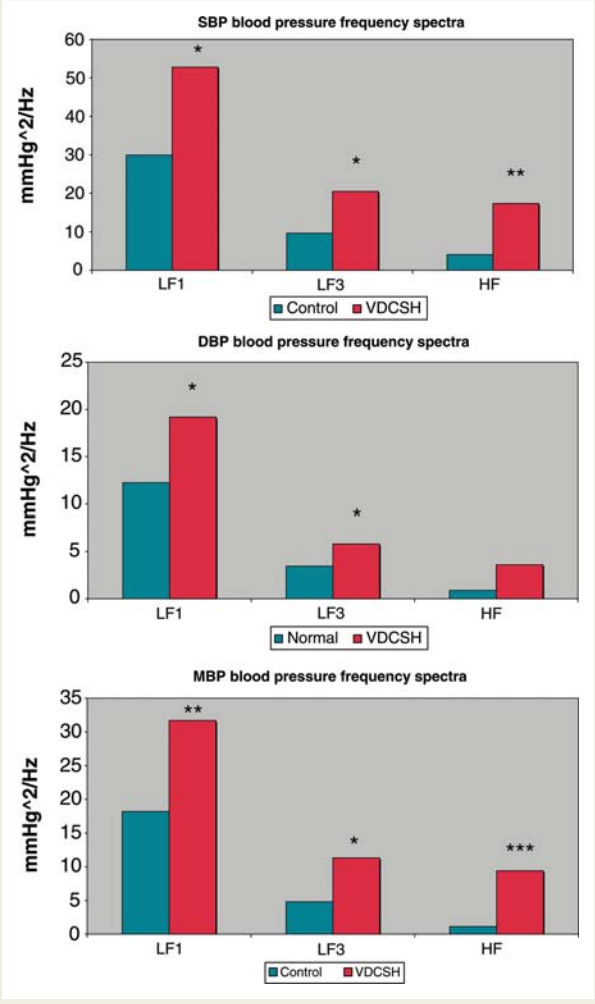

Figure 3 Comparison of frequency domain indices of BP variability. (*A*) SBP (top), (*B*) DBP (middle), (*C*) MAP (bottom). (*$P < 0.1$; **$P < 0.05$; ***$P < 0.01$).

Frequency of peaks analysis

No significant differences were found between f_P values (*Table 4*), between cases and controls. For clarity only SBP figures are shown, as trends and values for DBP and MAP were almost identical.

Discussion

Vasodepressor carotid sinus hypersensitivity is associated with significant increases in short-term blood pressure variability indices. These increases occur in two frequency bands—LF Mayer band, which is influenced strongly by baroreflex control of peripheral resistance vasculature and HF Traube–Herring band, primarily respiratory-related activity.

As far as we are aware, this is the first study investigating characteristics of short-term blood pressure fluctuations—Mayer waves in VDCSH.

A small but statistically significant increase in total DBP and MAP variability in VDCSH was detected. Increased blood pressure variability has been linked independently to end-organ damage.[26,27] Although these findings support the postulate that medullary centres maybe implicated in abnormal responses in VDCSH,[11] increases in total blood pressure variability are non-specific and could arise from a number of internal and external sources, including cardiac activity,[28] respiratory activity,[29] hypo- or hyperactive baroreflexes,[4] cognitive activation,[30] and muscle activation[24] amongst others. Wideband pressure fluctuations or increased blood pressure variance of this magnitude has been associated with blunted baroreflexes,[31] with ageing,[32] arterial stiffness,[33] in animal models with baroreflex deafferentation.[13] In such cases, increases in total blood pressure variability have been attributed to a reduced ability to modulate peripheral resistance and vascular compliance for blood pressure control in the face of internal and external disturbances.

Paradoxically increases in blood pressure variability restricted to specific Mayer wave frequency bands have been explained by an

Table 4 Comparison of the frequency of peak for systolic blood pressure for the defined frequency bands VLF, LF, MF, HF

Variable	Band	Control	VDCSH	% Change	Significance
SBP	F_{VLF}	0.037 ± 0.0025	0.035 ± 0.005	−4.1	NS
	F_{LF1}	0.0583 ± 0.0058	0.063 ± 0.006	8.8	NS
	F_{MF}	0.097 ± 0.012	0.103 ± 0.01	6.19	NS
	F_{HF}	0.288 ± 0.023	0.304 ± 0.043	5.7	NS

increase in the gain and/or range of the baroreflex.[19,22] Experimental and theoretical evidence have been provided in support of this conclusion.[13] It has been reasoned that a highly reactive baroreflex will impose strong focussed modulations upon any internal or external blood pressure fluctuations only within a narrow frequency band[13] typically ~0.1 Hz. Furthermore, the amplitude of these oscillations will be determined by the saturation and threshold properties of the baroreflex.[19] In this case, a sharp resonant peak would be expected in blood pressure spectra around the natural oscillating frequency of the feedback loop.

To draw any conclusions and make inferences regarding the nature of dysfunction in VDCSH from this finding, spectral analysis was used to further interrogate the source of the variability by decomposing the pressure fluctuations into their constituent sub-bands.

As hypothesized significant alterations in the LF Mayer band were detected indicated by a small peak in the LF bands. Such changes are consistent with alterations in the peripheral resistance-controlling arc of the baroreflex in VDCSH[13,20] and could be considered indicative of an increased gain or range of the baroreflex. However, since the frequency of this peak is at the lower end of the Mayer wave band at 0.06 Hz, some doubt still remains over whether one can definitively conclude that a hypersensitive baroreflex response exists in VDCSH. This is the first study to report possible surrogate markers for baroreflex sensitivity controlling peripheral resistance in VDCSH. In CSH, a hypersensitive response has only been observed reliably during CSM in comparison to other baroreflex sensitivity (BRS) measures. Other studies have examined BRS in CICSH only and have had contradictory results when assessing BRS using methods other than CSM in CCSS/CSH populations. Some have reported a paradoxical decrease in BRS,[34] no change in BRS,[35] whereas others have indicated an increase in BRS[36,37] It has been suggested that this discrepancy is due to differences in stimuli characteristics and protocol.[34] However, none to date has investigated the gain of the peripheral resistance feedback loop in vasodepressor form of CSH and so no parallels can be drawn here with other studies in VDCSH.

This finding is not in isolation. An increase in HF respiratory blood pressure waves was also detected. These results are consistent with altered respiratory drive in VDCSH resulting in increased tidal volume and increased intra thoracic pressure changes during respiration. Peripheral and central respiration and cardiovascular control centres are intimately linked,[38] so it is plausible that respiratory centres are also affected in CSH. Increases in cardiorespiratory variables to our knowledge have not been documented in CSH, however altered respiratory parameters including tidal and minute volume have been noted in other forms of neurocardiovascular syncope.[39] Kenny *et al.*[40] noted altered cardiorespiratory coupling during deep breathing test in a small series of patients with CICSH. Galdston and Steele[41] reported hyperpnoea in response to CSM hypothesizing that blood flow to chemoreceptors was altered. Furthermore, our findings would be in keeping with Doux and Yun's recent hypothesis, which suggests that carotid artery disease, induces maladaptation of chemoreceptors and baroreceptors in ischaemic stroke, which in turn may be responsible for autonomic mediated dysfunction in cerebral autoregulation.[42]

Unfortunately, a definite conclusion cannot be drawn into nature and direction of dysfunction in VDCSH based on these results alone. Further scientific investigation is hence warranted into (i) the nature of blood pressure variability in VDCSH to determine whether the cause is truly a hypersensitive or hyposensitive baroreflex and (ii) the role cardiorespiratory activity plays in CSH pathogenesis.

Limitations

As of any case–control study, we are limited in making any statements regarding causality in relation to VDCSH and blood pressure variability. However, biologically plausible mechanisms have been established by which VDCSH could affect blood pressure variability.[11] These mechanisms are supported by the previous studies, looking at neurogenic sources of blood pressure control in autonomic dysfunction.[38] Such levels of autonomic dysfunction have also been shown to occur in CSH by previous authors.[40] Furthermore, altered circadian blood pressure control was also noted previously in CSH.[43] Another possible limitation of our study is the lack of respiratory variable measurement. This limits our ability in drawing a definite conclusion as to the source of the detected variability especially in the HF band. However, since our significant findings were specifically found in the HF band of SBP and MAP spectra and not in the DBP records, this would support our hypothesis that these differences are respiratory related. Respiratory activity is well known to affect SBP/MAP significantly.

Conclusion

Blood pressure variability, in particular Mayer and Traube–Herring bands, was increased in VDCSH. This finding is consistent with the hypothesis that baroreflex activity is altered in VDCSH, but may also implicate cardiorespiratory centres in pathogenesis of VDCSH. Blood pressure variability thus holds the potential as a novel non-invasive marker of VDCSH, which may be related to degree of dysfunction in CSH. Further research is required to confirm the underlying physiological cause and nature of this variability.

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