INCREASED BEAT-TO-BEAT BLOOD PRESSURE VARIABILITY IS ASSOCIATED WITH IMPAIRED COGNITIVE FUNCTION

Running Head: **Continuous Blood Pressure Variability and Cognition**

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ABSTRACT

BACKGROUND

Emerging evidence has linked visit-to-visit, day-to-day and 24-hour ABPM blood pressure variability (BPV) with cognitive impairment. Few studies have, however, considered beat-to-beat BPV. This study, therefore, evaluated the relationship between beat-to-beat BPV and cognitive function among community-dwellers aged 55 years and over.

METHODS

Data was obtained from the Malaysian Elders Longitudinal Research (MELoR) study, which employed random stratified sampling from three parliamentary constituencies within the Klang Valley. Beat-to-beat blood pressure (BP) was recorded using non-invasive BP monitoring (Taskforce^{TM},CNSystems). Low frequency (LF), high frequency (HF) and low-to-high frequency (LF:HF) ratio for BPV were derived using fast Fourier transformation. Cognition was evaluated using the Montreal Cognitive Assessment (MoCA) test, and categorized into normal aging, mild impairment and moderate-to-severe impairment.

RESULTS

Data from 1140 individuals, mean age (SD) 68.48 (7.23) years, were included. Individuals with moderate-to-severe impairment had higher HF-BPV for systolic (SBP) and diastolic (DBP) blood pressure compared to individuals within the normal aging group (OR(95%CI)=2.29(1.62-3.24)) and (OR(95%CI)=1.80(1.32-2.45)), while HF-SBPV (OR(95%CI)=1.41(1.03-1.93)) but not HF-DBPV was significantly higher with mild impairment compared to normal aging after adjustments for potential confounders. Moderate-to-severe impairment was associated with significantly lower LF:HF-SBPV (OR(95%CI)=0.29(0.18-0.47)) and LF:HF-DBPV (OR(95%CI)=0.49(0.34-0.72)), while mild impairment was associated with significantly lower LF:HF-SBPV (OR(95%CI)=0.52(0.34-0.80) but not LF:HF-DBPV (OR(95%CI)=0.81(0.57-1.17), compared to normal aging with similar adjustments.

CONCLUSION

Higher HF-BPV, which indicates parasympathetic activation, and lower LF:HF-BPV, which addresses sympathovagal balance, were observed among individuals with moderate-to-severe cognitive

impairment. Future studies should determine whether BPV could be a physiological marker or modifiable risk factor for cognitive decline.

KEYWORDS
blood pressure variability; cognitive impairment; dementia, autonomic function,

INTRODUCTION

Hypertension at midlife or hypotension at later life are now recognized as risk factors for cognitive impairment.[1,2] The measurement of blood pressure (BP) to diagnose both the above conditions usually involve clinical measurements using a manual sphygmomanometer or oscillometric equipment, home-based monitoring using automated home devices and ambulatory 24-hour blood pressure monitoring (BPM) using automated wearable oscillometric devices. These commonly available BP monitoring devices, however, still provide snapshot measurements without taking into account the fact that BP varies with each heartbeat.[3] Newer technology, however, now allows for non-invasive beat-to-beat BP measurements. While this technology is now commonly used in syncope evaluation[4] and has been advocated for perioperative monitoring,[5] it has yet to be assigned a role within conventional diagnosis and monitoring processes for the management of BP in clinic settings.

In addition to providing a potentially more accurate estimation of BP by averaging a series of measurements obtained over a fixed timeframe, continuous BP measurements will also provide estimation of beat-to-beat blood pressure variability (BPV). Published studies have evaluated the relationship between BPV and cognitive function determined variations which have arisen either from visit-to-visit, day-to-day and 24-hour ABPM.[6] Increased BPV has been associated with adverse health outcomes including target organ damage, cardiovascular events and mortality.[7,8] While some studies found no association between beat-to-beat BPV and cognitive function,[9,10] others found both positive[11,12] and negative associations between beat-to-beat BPV and poorer cognitive function.[13,14] Analysis of long-term BPV within the ASPREE (Aspirin in Reducing Events in the Elderly) trial, which included over 19,000 dementia-free community-dwelling aged 70 years and above, found that increased long-term BPV was associated with a significantly increased risk of cognitive decline over three annual visits.[15] The conflicting findings from previous studies were likely to have occurred from heterogeneity

in methods of BP acquisition as well as analytical methods in existing studies evaluating BPV and cognitive function.[6]

Despite the potential of obtaining robust estimates of BPV within the same clinic visits, the role of beat-to-beat BPV remains unclear. In addition, a large number of measurements can be obtained over a short time, allowing for the use of frequency domain analyses which is usually not possible for other forms of measurements. Few studies have explored the relationship between beat-to-beat BPV and cognitive as well as other adverse health outcomes. This study was, therefore, conducted to evaluate the relationship between beat-to-beat BPV and cognitive performance among a community-dwelling population aged 55 years and over.

METHODS

Study Population

This cross-sectional study utilized data from the Malaysian Elders Longitudinal Research (MELoR) study, which recruited community-dwellers aged 55 years and over identified through stratified simple random sampling from the electoral rolls of the three neighboring parliamentary constituencies: Petaling Jaya North, Petaling Jaya South and the Pantai Valley. The age cut-off of 55 years was selected as that was the statutory retirement age in Malaysia at time the study was conceived. Details of the recruitment strategies and response rates have been published elsewhere.[16] In brief, the MELoR study excluded individuals who were bed-bound, unable to be attend hospital-based health checks, as well as individuals with advanced dementia or speech impediments who were unable to respond comprehensibly to questioning. Basic demographics and medical history were obtained during home-based computer-assisted interviews. Physiological and cognitive assessments including cognitive testing and synchronized ECG and beat-to-beat BP monitoring were obtained during hospital-based health checks.

Signal Acquisition

Five-minutes of non-invasive, continuous beat-to-beat BP measurements were recorded in the supine position with fingers cuffs using the vascular unloading method (Taskforce^{TM}, CNSystems). Participants were first asked to lie down on an examination couch and to rest for at least five minutes while the monitoring equipment was attached. Beat-to-beat measurements were calibrated to automated oscillometric arm cuff measurements. Beat-to-beat BP data were synchronized with real time ECG signals to ensure that BP measurements corresponded to individual heartbeats, and to detect artefacts.

The signals collected that were potentially contaminated with electrical power noise and artefact were converted into a network of block mathematical functions through a command-based environment. Detailed descriptions of BP signal acquisition and data analyses have been published elsewhere.[17,18] A notch filter of 50Hz was first applied to remove electromagnetic interference as a process of filtering through a self-devised MATLAB algorithm. Frequency domain power spectral analysis was conducted through fast Fourier transformation applied to noise-free data. Power spectral density (PSD) was divided into very low frequency (VLF) (0.004-0.035HZ), low frequency (LF) (0.07–0.14Hz) and high frequency (HF) (0.14– 0.35Hz) ranges. Blood pressure variability within the LF and HF ranges as well as the LF to HF ratio (LF/HF) were used for subsequent comparisons.

Cognitive Assessment

Cognitive performance was assessed with the Montreal Cognitive Assessment (MoCA) scale. The MoCA comprised the domains of executive function, naming, attention, language, abstraction, delayed recall and orientation.[19] The maximum score is 30 with a higher score indicating better cognitive function. As MoCA scores were not normally distributed, the overall study population was then categorized into three equal groups using tertile cut-offs. For ease

of interpretation, the groups were assigned labels of normal aging (total MoCA=25-30), mild impairment (total MoCA=21-24), and moderate-to-severe impairment (total MoCA=0-20).

Comorbidities

Past medical histories were established during home-based interviews. Self-reported, physician-diagnosed medical conditions were identified by asking participants, "Has a doctor ever told you that you have any of the following conditions?". Cardiac comorbidities were considered present if the participant reported any of the diagnoses of ischemic heart disease, cardiac arrhythmia, heart failure, hypertension or hypercholesterolemia. The number of cardiac comorbidities was considered the number of the above conditions reported by the individual. The maximal possible number of cardiac comorbidities was, therefore, five.

Blood Pressure Lowering Medication

Information about the use and type of blood pressure lowering medication (BPLM) was obtained by direct inspection of the medication packaging or medication list. Individual medications were then cross-checked and medications within the diuretics, calcium channel blockers antagonists (CCB), beta-adrenoreceptor blockers, alpha-adrenoreceptor blockers and angiotensin-converting enzyme inhibitors classes identified by trained pharmacists.

Depression, Anxiety and Stress

Depression, anxiety and stress were determined using the 21-item Depression, Anxiety and Stress scale (DASS-21).[20] The DASS-21 considers the three psychological domains of depression, anxiety and stress separately, with each domain evaluated with seven items rated on a four-point Likert scale. The sum total score for each domain is multiplied by two to obtain the maximum total score of 42, with a higher score indicating more severe symptoms.

Social Network

Social network was determined with the six-item Lubben Social Network Scale (LSNS-6), rated on a six-point Likert scale. A higher total indicates a stronger self-perceived social network.[21] Continuous scores indicating the extent of social network were employed for statistical analyses.

Statistical Analysis and Power Calculations

Statistical analysis was conducted using the Statistical Package for Social Science (SPSS) version 22.0 (IBM, USA). A summary table comprising means with standard deviations (SD) for continuous data and frequencies with percentages for categorical data was first presented. Univariate analysis comparing groups were conducted with analysis of variance for continuous variables and the Chi-squared test for categorical variables. Statistical comparisons were considered significant if the two-sided p-value was less than 0.05.

As BPV was non-normality distributed, it was first logarithmically transformed using $\log_{10}$. Multinomial logistic regression analyses were conducted using the frequency domain indices: $\log_{10}$ LF-BPV, $\log_{10}$ HF-BPV and $\log_{10}$ LF:HF-BPV ratio for systolic (SBPV) and diastolic (DBPV) blood pressure separately. Each BPV variable was considered as the independent variable in separate models, and cognitive function groups as dependent variables. The three cognitive groups were included as the dependent variable using dummy variables with the normal aging (total MoCA=25-30) group considered the reference category. The odd ratios (OR) with 95% confidence intervals (CI) were presented for individuals with mild and moderate-to-severe impairment, indicating the strength of association with each independent variable compared to those within the normal aging group. The OR values of above or below unity indicate increased or reduced associated risk, and statistical significance was considered present if the 95% CI did not include the unity value.

The associations are presented for first the unadjusted model, followed by five different adjustments selected from variables which were significantly different between groups in Table

1 and through clinical deduction. The models were, therefore, first adjusted for age and sex (Model 1) and then additionally adjusted for the potential mediators of years of education (Model 2), number of cardiac comorbidities and history of alcohol consumption (Model 3), depressive symptoms and social engagement (Model 4) and baseline systolic blood pressure (SBP) (Model 5). A sensitivity analysis was conducted to evaluate the interaction effect between sex and BPV and this did not influence the model. To address potential multicollinearity, only one psychosocial factor (depression) was chosen. The adjusted BPV were consequently additionally adjusted separately for BPLM including diuretics, CCB, beta-adrenoreceptor blockers and alpha-adrenoreceptor blockers to investigate the potential mediating role of BPLM in the relationship between BPV and cognitive performance.

RESULTS

Blood pressure variability and cognitive performance data were available for 1140 participants and were included in the analyses. Table 1 displays the demographic characteristics, health status, psychological well-being and BPLM according to the three MoCA groups. Differences existed for age, proportion with more than 12 years of formal education, alcohol consumption, depression scores, anxiety scores and social network engagement scores between the three groups ($p<0.05$). In terms of medical history and medications, the total number of cardiac comorbidities as well as use of CCB, beta-adrenoreceptor blockers, alpha-adrenoreceptor blockers and diuretics varied significantly across groups ($p<0.01$). Systolic and diastolic BP, however, were not significantly different between the three groups.

Compared to individuals with normal aging, individuals with both moderate-to-severe impairment and mild impairment had significantly higher $\log_{10}$ (HF-systolic blood pressure variability, SBPV) and $\log_{10}$ (HF-diastolic blood pressure variability, DBPV)(Table 2). The increased $\log_{10}$ HF-DBPV in individuals with mild impairment remained significant after

adjustment for age and sex differences (OR(95%CI)= 1.33(1.01-1.77)) but was no longer significant after additional adjustment for over 12-years of formal education suggesting that the difference in $\log_{10}$ HF-DBPV between individuals with mild impairment and normal aging is accounted by educational level. The increase in $\log_{10}$ HF-SBPV, $\log_{10}$ HF-DBPV observed in the individuals with moderate-to-severe impairment (OR(95%CI)= 2.29(1.62-3.24), (OR(95%CI)= 1.80(1.32-2.45)) as well as increased in $\log_{10}$ HF-SBPV among individuals with mild impairment (OR(95%CI)= 1.41(1.03-1.93)) compared to individuals with normal aging, remained significant after adjustment for age, sex, years of education, number of cardiac comorbidities, history of alcohol consumption and level of depression, social engagement level and SBP.

Individuals with mild impairment and moderate-to-severe impairment had lower $\log_{10}$(LF:HF-SBPV) and $\log_{10}$(LF:HF-DBPV) compared to normal aging within unadjusted analyses. The decreased $\log_{10}$LF:HF-DBPV in the mild impaired group remained significant after adjustment for age and sex (OR(95%CI)= 0.72(0.51-0.99)) but was no longer significant after additional adjustment for over 12-years of formal education. The decrease in $\log_{10}$LF:HF-SBPV and $\log_{10}$LF:HF-DBPV observed in the individuals with moderate-to-severe impairment (OR(95%CI) = 0.29(0.18-0.47), and 0.52(0.34-0.80) respectively) as well as decrease in $\log_{10}$LF:HF-SBPV in individuals with mild impairment (OR(95%CI)= 0.52(0.34-0.80)) compared to the normal aging group remained significant after adjustment for age, sex, years of education, number of cardiac comorbidities, history of alcohol consumption and depression scores, social engagement scores and SBP.

The increase in $\log_{10}$ HF-SBPV, $\log_{10}$ HF-DBPV among individuals with moderate-to-severe impairment as well as the increase in $\log_{10}$ HF-SBPV between individuals with mild impairment compared to individuals with normal aging remained significant within each model adjusted separately for diuretics, CCB, beta-adrenoreceptor blocker as well as alpha-

adrenoreceptor blocker in addition to age, sex, years of education, number of cardiac comorbidities, history of alcohol consumption and depression scores, social engagement scores and SBP (supplementary table 1). Similarly, the decrease in log_{10}LF:HF-SBPV and log_{10}LF:HF-DBPV among individuals with moderate-to-severe impairment as well as decrease in log_{10}LF:HF-SBPV in individuals with mild impairment compared to the normal aging group remained significant after adjustment for age, sex, years of education, number of cardiac comorbidities, history of alcohol consumption and depression scores, social engagement scores, SBP and BPLM in separate models for diuretics, CCB, beta-adrenoreceptor blocker and alpha-adrenoreceptor blocker. This indicates the BPLM did not influence the relationship between BPV and cognitive performance.

DISCUSSION

Increased HF-BPV but reduced LF:HF ratio derived using frequency domain analysis for both SBPV and DBPV were apparent among those who obtained 20 points or less in their MoCA test scores compared to those whose MoCA scores were 26 to 30. The differences between mild impairment and normal aging were less marked with only HF-SBPV and LF:HF-SBPV surviving adjustments for potential confounders. This indicates a dose-response relationship between continuous BPV with cognitive impairment. This study, therefore, indicates that beat-to-beat BPV is associated with cognitive impairment and further reveals the utility of frequency domain analyses within the study of BPV which differentiates between BP fluctuations within various frequency ranges. This highlights the potential of utilizing beat-to-beat BPV as a marker of cognitive performance, unveils the potential mechanisms underlying BPV in those with cognitive impairment as well as presents a potentially modifiable risk factor for cognitive impairment.

The BPV has primarily been calculated using time domain analyses as prior repeated BP measurements did not tend to produce an adequate number of measurements for frequency

domain analysis. Time domain derivation of BPV measures either simple dispersion using standard mathematical formulae to determine standard deviation or sequence of fluctuation using average real variability.[22] Beat-to-beat measurements produces one BP measurement with each heartbeat, hence yielding a large number of measurement points within a few minutes. Two minutes of clean signal, producing a minimum of 128 beats is considered adequate for frequency domain estimations.[23] With frequency domain analysis, the variation within each frequency band over a range of frequencies is demonstrated as spectral analysis.[22]

Frequency domain evaluation of fluctuations in BPV is considered a measure of the integrity of neurohumoral mechanisms involved in BP regulation[24] which may also be a simpler method potentially for detecting cognitive decline related to autonomic dysregulation.[9] Available evidence from heart rate variability analysis as well as clinical autonomic measurements suggest a positive association between autonomic dysregulation and cognitive impairment.[25,26] High frequency fluctuations in BPV reflect the changes in cardiac output observed during parasympathetic or vagal activation.[9] From this perspective, it is postulated that fluctuations in BP within the HF range is mediated by respiration which acts directly on intrathoracic vessels or indirectly through changes in stroke volume and heart rate. Decreased BP from reduced cardiac output may then lead to cerebral hypoperfusion.[27] This in turn, may lead to structural brain changes detectable on MRI imaging which may manifest as cognitive decline.[28] The mechanisms underlying hypoperfusion related cognitive impairment has been considered primarily among individuals with previous cardiovascular events and has not been explored within the general older population.

Low frequency BPV is attributed to the effect of sympathetic activity on the vasculature.[13] Other studies have suggested that reduced sympathetic control of the arterioles occurs at the early stages of dementia.[13] The lack of observed changes in LF-BPV within this study would suggest that sympathetic response is not in actual fact affected in those with cognitive

impairment. Under normal physiological conditions, however, abrupt parasympathetic stimulation suppresses sympathetic activation at rest.[29] Therefore, the assessment of BPV at the supine resting position may not be an adequate study of sympathetic activation. The physiology underlying the LF-BPV may also be influenced by HF-BPV. Hence if reduced sympathetic activation is expected with cognitive impairment, any potential reduction in LF-BPV may be offset by the sizeable increase in HF-BPV observed in this study.

Failure of feedback mechanisms, including baroreflex sensitivity, may occur if the autonomic nervous system malfunctions. The baroreflex is responsible for detecting BP changes in the carotids, cardiac chambers, and aortic arch and responding by adjusting the heart rate through vagal innervation or changing the peripheral vascular tone through sympathetic innervation. This mechanism is represented by the LF:HF BPV ratio[26]. If a reduction in the above ratio occurs, it may manifest as blunted baroreflex responses due to a lack of sympathetic drive to stimulate tachycardia in the event of a reduction in BP. Therefore, a lower LF:HF BPV ratio in this study implies potential reduction in baroreflex sensitivity, which may then lead to periods of vulnerability within the brain related to hypotensive events, which then leads to structural changes and cognitive impairment.

While cognitive decline attributed to circulatory abnormalities which may occur as the result of impaired cardiac output from systemic hemodynamic dysfunction or peripheral response dysfunction, cerebral autoregulatory abnormalities may also influence the cognition-hypoperfusion relationship.[28] Cerebral autoregulation refers to the ability of the brain to keep its blood supply constant despite fluctuations in cerebral perfusion pressure which is equivalent to the mean arterial pressure within the autoregulatory range. Therefore, should cerebral autoregulation be impaired, the brain becomes more vulnerable to the consequences of BP fluctuations and this may manifest as syncope if the disruption in blood supply is transient and restored completely or dementia if frequent or more prolonged cerebral blood flow

interruptions then leads to irreversible damage in watershed areas of the brain.[30] Blood pressure variability determined using serial arm cuff readings conducted every 10-minutes is associated with increased deep white matter hyperintensities in MRI which then correlates with cognitive impairment. Within this study, BPV is also found to correlate positively and strongly with cardiac output and ejection fraction as well as intimal medial thickness and brachial artery responsiveness within the systemic vasculature, further supporting the theory of chronic cerebral hypoperfusion.[31]

Continuous BP measurements using non-invasive techniques are just as accurate as invasive methods. It is, however, influenced by behavioral changes including postural changes and it also reflects the influence of autonomic modulation.[17] As BP signals obtained exclusively within the supine position was utilized, the absence of sympathetic stimulation which could have been induced by simple maneuvers such as standing or isometric exercises, could have led to the lack of association between LF-BPV and cognitive impairment observed in this study. Continuous BP measurements taken in the supine position, which is commonly used for beat-to-beat BPV measurements, may then be different from that obtained in the standard seated position used for snapshot BP measurements for clinical use. Cognition in this study was evaluated using the MoCA test alone. While MoCA has been widely used for the detection of mild cognitive impairment, further evaluation using additional neuropsychological evaluation should be considered. The observed relationships were thus far only evaluated cross-sectionally therefore limiting the assignment of causality, and should hence be confirmed in a future longitudinal study. Potential confounders may also not have been fully accounted for within this study.

CONCLUSION

In a community-dwelling population, individuals with moderate-to-severe cognitive impairment had increased HF-BPV but reduced LF:HF ratio for both SBPV and DBPV

compared to those with normal cognitive performance. These findings support the chronic cerebral hypoperfusion theory by pointing to the role of defective autonomic regulatory systems. Future studies should consider exploring the potential role of beat-to-beat BPV as a physiological marker or modifiable risk factor for cognitive decline using a prospective design.

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DISCLOSURE STATEMENT

No conflict of interest

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TABLE LEGENDS

Table 1. Participant Characteristics by Cognitive Performance

Table 1 showed the participants characteristics in three cognitive performance group. The significant difference is below than 0.05.

Table 2. Multivariate Analysis for Blood Pressure Variability and Cognition

Table 2 shows result from multinomial logistic regression analysis of relationship between BPV and cognitive performance by presenting the odd ratio (OR) and 95% confidence interval (CI). Bold value shows significant association is below than 0.05. The value above or below 1 indicating increased or decreased association of BPV and cognitive performance. The association was adjusted with three stages of adjustments.

INCREASED BEAT-TO-BEAT BLOOD PRESSURE VARIABILITY IS ASSOCIATED WITH IMPAIRED COGNITIVE FUNCTION

Population

Cognitive Assessment

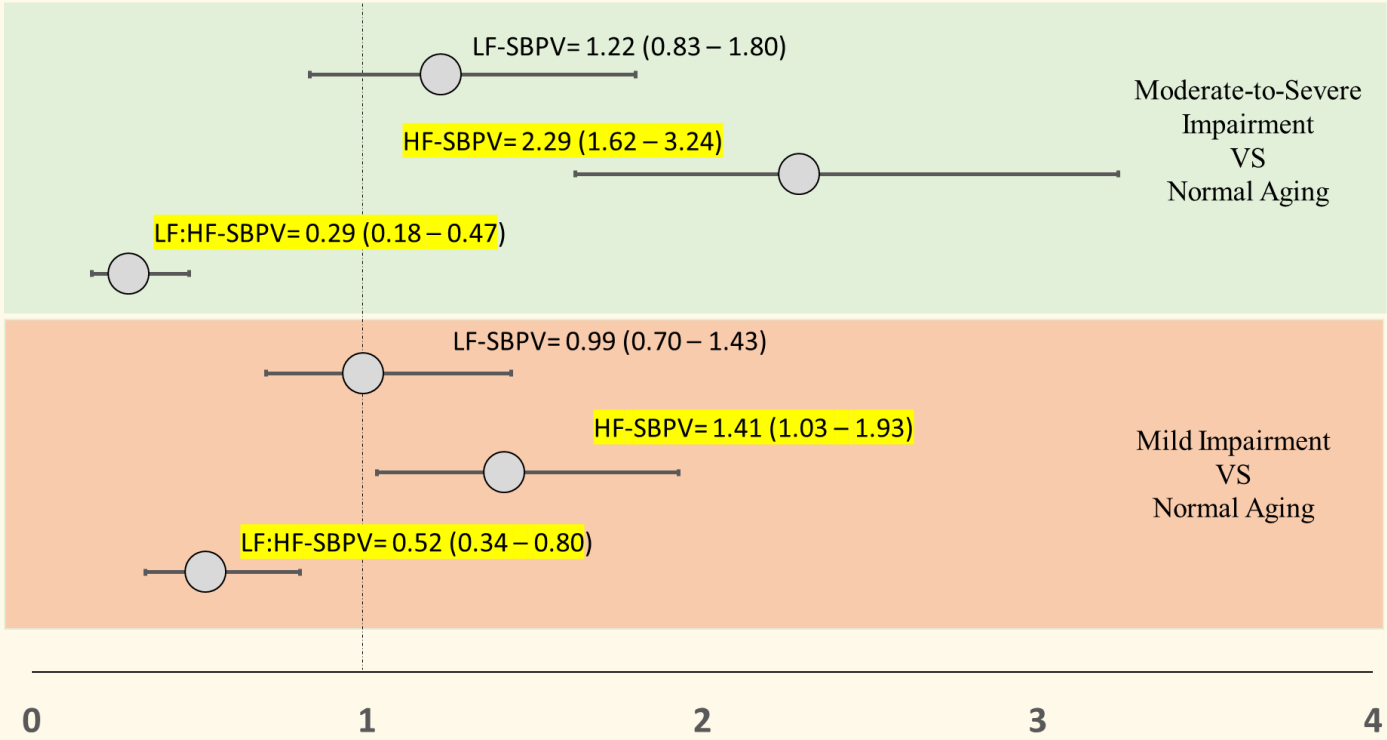
Montreal Cognitive Assessment Test (MoCA)

Blood Pressure Variability

- Low Frequency (LF)
- High Frequency (HF)
- Low-to-high Frequency (LF:HF)

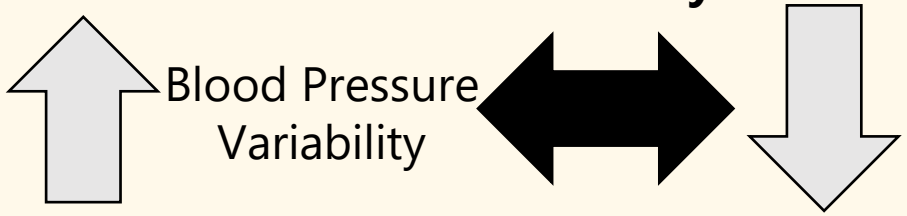
Task Force Monitor 3040i by CNSystems, Austria

Associations between Beat-to-beat BPV and Cognitive Decline



Abbreviation: LF= Low Frequency; HF = High Frequency; LF:HF= Low-to-high Frequency Ratio. Highlighted indicates P ≤ 0.05

Summary



TABLES

Table 1. Participant Characteristics by Cognitive Status

Characteristics	MoCA Tertile (MoCA Scores)			p-values
	Moderate to Severe Impairment (0-20) (N=347)	Mild Impairment (21-24) (N=351)	Normal Aging (25-30) (N=442)	
Age, mean (SD)	70.26 (8.11)	68.02 (6.83)	67.2 (6.38)	**<0.01**
Sex, n (%)				0.85
Male (ref)	147 (42.4%)	155 (44.2%)	187 (42.3%)	
Female	200 (57.6%)	196 (55.8%)	255 (57.7%)	
Years of formal education, n (%)				**<0.01**
≤ 12 years (ref)	316 (91.1%)	266 (75.8%)	195 (44.1%)	
>12 years	31 (8.9%)	85 (24.2 %)	247 (55.9%)	
No. Cardiac Comorbidities*, mean (SD)	1.73 (1.42)	1.85 (1.57)	1.50 (1.39)	**<0.01**
Smoking, n (%) (ref: no)	63 (28.6%)	92 (41.8%)	65 (29.5%)	0.66
Alcohol consumption, n (%) (ref: no)	64 (19.5%)	100 (30.5%)	164 (50.0%)	**<0.01**
Depression, mean (SD)	3.72 (5.61)	2.72 (4.79)	2.15 (3.23)	**<0.01**
Anxiety, mean (SD)	4.56 (4.71)	3.58 (3.97)	3.25 (3.89)	**<0.01**
Stress, mean (SD)	4.66 (6.47)	4.33 (5.57)	4.30 (5.10)	0.69
Social network engagement, mean (SD)	14.72 (6.77)	16.29 (5.78)	18.13 (6.22)	**<0.01**
Blood Pressure Lowering Medications, n (%), (ref: no)				
Angiotensin Converting Enzyme Inhibitors	89 (25.6%)	94 (26.8%)	99 (22.4%)	0.32
Calcium Channel Blockers	113 (32.6%)	103(29.3%)	95 (21.5%)	**0.01**
Beta-Adrenoreceptor Blocker	56 (16.1%)	59 (16.8%)	51 (11.5%)	**0.01**
Alpha-Adrenoreceptor Blocker	14 (4.0%)	18 (5.1%)	14 (3.2%)	**0.02**
Diuretics	52 (15.0%)	47 (13.4%)	19 (4.3%)	**<0.01**
Systolic Blood Pressure (mmHg), mean (SD)	114.35 (22.59)	115.05 (22.57)	114.24 (21.61)	0.87
Diastolic Blood Pressure (mmHg), mean (SD)	69.94 (16.85)	71.40 (17.42)	70.76 (15.62)	0.51

Bold indicates P<0.05, Abbreviations: SD=Standard Deviation; MoCA= Montreal Cognitive Assessment Test
*includes ischemic heart disease, cardiac arrhythmia, heart failure, hypertension and hypercholesterolaemia.

Table 2. Multivariate Analysis for Blood Pressure Variability and Cognitive Performance

Covariates	Adjustments	Vs. Normal Aging					
		Moderate to Severe Impairment			Mild Impairment		
		OR	95% CI		OR	95% CI	
			Lower	Upper		Lower	Upper
Log_{10} LF - SBPV	Unadjusted	1.09	0.76	1.56	0.97	0.70	1.36
	Adj Model 1	1.18	0.82	1.70	0.99	0.70	1.40
	Adj Model 2	1.17	0.77	1.77	1.01	0.70	1.45
	Adj Model 3	1.16	0.79	1.69	0.98	0.69	1.40
	Adj Model 4	1.21	0.82	1.78	0.99	0.69	1.42
	Adj Model 5	1.22	0.83	1.80	0.99	0.70	1.43
Log_{10} LF - DBPV	Unadjusted	1.07	0.72	1.60	1.07	0.73	1.55
	Adj Model 1	1.23	0.82	1.85	1.11	0.76	1.63
	Adj Model 2	1.15	0.76	1.76	1.10	0.74	1.63
	Adj Model 3	1.16	0.76	1.77	1.11	0.75	1.65
	Adj Model 4	1.23	0.80	1.91	1.14	0.77	1.70
	Adj Model 5	1.25	0.84	2.03	1.15	0.78	1.76
Log_{10} HF- SBPV	Unadjusted	**2.38**	**1.76**	**3.22**	**1.51**	**1.12**	**2.03**
	Adj Model 1	**2.43**	**1.79**	**3.30**	**1.53**	**1.13**	**2.06**
	Adj Model 2	**2.22**	**1.58**	**3.11**	**1.41**	**1.03**	**1.93**
	Adj Model 3	**2.25**	**1.60**	**3.17**	**1.41**	**1.03**	**1.93**
	Adj Model 4	**2.31**	**1.64**	**3.27**	**1.42**	**1.03**	**1.94**
	Adj Model 5	**2.29**	**1.62**	**3.24**	**1.41**	**1.03**	**1.93**
Log_{10} HF- DBPV	Unadjusted	**1.87**	**1.42**	**2.46**	**1.34**	**1.01**	**1.78**
	Adj Model 1	**1.83**	**1.39**	**2.41**	**1.33**	**1.01**	**1.77**
	Adj Model 2	**1.71**	**1.27**	**2.30**	1.21	0.91	1.62
	Adj Model 3	**1.75**	**1.29**	**2.36**	1.22	0.91	1.64
	Adj Model 4	**1.79**	**1.31**	**2.42**	1.23	0.92	1.65
	Adj Model 5	**1.80**	**1.32**	**2.45**	1.23	0.92	1.65
Log_{10} LF:HF- SBPV	Unadjusted	**0.23**	**0.16**	**0.35**	**0.43**	**0.29**	**0.64**
	Adj Model 1	**0.25**	**0.17**	**0.38**	**0.44**	**0.30**	**0.66**
	Adj Model 2	**0.28**	**0.18**	**0.46**	**0.51**	**0.33**	**0.77**
	Adj Model 3	**0.28**	**0.18**	**0.45**	**0.52**	**0.34**	**0.79**
	Adj Model 4	**0.29**	**0.18**	**0.46**	**0.52**	**0.34**	**0.80**
	Adj Model 5	**0.29**	**0.18**	**0.47**	**0.52**	**0.34**	**0.80**
Log_{10} LF:HF- DBPV	Unadjusted	**0.42**	**0.30**	**0.59**	**0.70**	**0.50**	**0.98**
	Adj Model 1	**0.47**	**0.33**	**0.66**	**0.72**	**0.51**	**0.99**
	Adj Model 2	**0.49**	**0.34**	**0.71**	0.50	0.56	1.15
	Adj Model 3	**0.48**	**0.33**	**0.69**	0.81	0.56	1.16
	Adj Model 4	**0.48**	**0.33**	**0.71**	0.80	0.56	1.16
	Adj Model 5	**0.49**	**0.34**	**0.72**	0.81	0.57	1.17

Bold indicates P<0.05;

Abbreviations: OR=odds ratio; CI=confidence interval; adj=adjusted; HF=high frequency; LF=low frequency; LF:HF = low frequency to high frequency ratio

Adjustment 1: adjusted for age and sex

Adjustment 2: adjustment 1+ years of education
Adjustment 3: adjustment 2+ no. cardiac comorbidities and alcohol
Adjustment 4: adjustment 3+ depression score (anxiety and stress produced similar results) and social engagement.
Adjustment 5: adjustment 4 + SBP