Quantitative Assessment of Diabetics with Various Degrees of Autonomic Neuropathy

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Keywords: Cerebral Autoregulation, Diabetics, Power Spectral Density Analysis, Cross-correlation Analysis.

Abstract: In this study, we investigate the feasibility of using power spectral density (PSD) analysis and cross-correlation function (CCF) analysis to assess the healthy subjects and diabetics with mild, moderate and severe autonomic neuropathy. Continuous cerebral blood flow velocity (CBFV) was measured using transcranial Doppler ultrasound (TCD), and continuous arterial blood pressure (ABP) was measured using Finapres device under supine, tilt-up and hyperventilation conditions. In PSD analysis, the results revealed that the autonomic nervous balance to normal subjects declined in trend from supine to hyperventilation in comparison with that of diabetics. The CCF analysis of mean ABP (MABP) and mean CBFV (MCBFV) for each group of patients was calculated in three frequency bands, i.e., very low frequency (VLF), low frequency (LF), and high frequency (HF). The maximum peak value of CCF (Max CCF) and its corresponding standard deviation and time lag were obtained. Max CCF values at LF of normal subjects and patients with diabetes without autonomic neuropathy in both supine and tilt-up positions were significantly larger than that of diabetics with autonomic neuropathy. Max CCF values gradually increased in hyperventilation at VLF from normal subjects to diabetics without autonomic neuropathy, diabetics with mild autonomic neuropathy, and diabetics with severe autonomic neuropathy.

1 INTRODUCTION

The cerebral autoregulation (CA) mechanism refers to the cerebral blood flow (CBF) tendency to retain relatively constant in the brain despite changes in mean arterial blood pressure (MABP) in the interval from 50-170 mmHg (Lassen, 1959). Over the last decade, considerable advances have been developed in the safety and accessibility of noninvasive equipment (Mitsis, 2009). A technique using a transcranial Doppler (TCD) was introduced to evaluate the dynamic response of CA in humans. Rapid drops in arterial blood pressure (ABP) caused by the release of thigh blood pressure cuffs were used as an autoregulatory stimulus. The ABP and CBF velocity (CBFV) were compared during the autoregulatory process. ABP can also be acquired noninvasively using a finger cuff device (Finapres BP monitor). A high-speed servo system in the Finapres inflates and deflates the cuff rapidly to maintain the photoplethysmographic output constant at the unloaded state. Using the autoregulatory curve made by ABP and CBFV as a model to measure whether the pressure is normal or impaired in humans, CA is more a concept rather than a physically measurable entity. Noninvasive CA assessment has been developed and studied using either static or dynamic methods. Most tests require the introduction of variations in ABP using traditional physiological or pharmacological manipulation. It is a challenge to find appropriate methods to assess CA non-invasively and reliably using simple and acceptable procedures. Recent investigations have shown that the autoregulatory dynamic response can be identified from spontaneous fluctuations in MABP and CBFV (Panerai, 2000). Some investigators assessed the dynamic relationship between spontaneous MABP and CBFV using transfer function analysis in either normal subjects or in autonomic failure patients (Blaber, 1997). Some investigators used spontaneous blood pressure changes as input signals to test CA (Chiu, 2001; 2005). Spectral and transfer function analyses of CBFV and ABP were performed using fast Fourier transform (FFT) in their experiments. However, the stationary property and time resolution are two critical problems for spectral analysis.

Chiu C., Yeh S. and Kuo Y..
Quantitative Assessment of Diabetics with Various Degrees of Autonomic Neuropathy.
DOI: 10.5220/0004230003020305
In *Proceedings of the International Conference on Bio-inspired Systems and Signal Processing* (BIOSIGNALS-2013), pages 302-305
ISBN: 978-989-8565-36-5

Another study was made to explore spontaneous beat-to-beat fluctuations in MABP and breath-by-breath variability in end-tidal CO_2 ($EtCO_2$) in continuous recordings obtained from healthy subjects at rest to estimate the dynamic influences of arterial blood pressure and CO_2 on CBFV (Panerai, 2000). The aim of this study is to investigate the feasibility of using power spectral density (PSD) analysis and cross-correlation analysis (CCF) to assess the healthy subjects and diabetics with different degrees of autonomic neuropathy.

2 METHODS

2.1 Subjects and Measurements

Four groups of subjects were recruited in this study, and shown in Table 1 (NL: normal, DM: diabetics with mild autonomic neuropathy, DAN1: diabetics with moderate autonomic neuropathy, DAN2: diabetics with severe autonomic neuropathy). The subjects in the healthy group were included only if they had no history of vascular disease, heart problems, hypertension, migraine, epilepsy, cerebral aneurysm, intra-cerebral bleeding or other pre-existing neurological conditions. None of the subjects were receiving any medication during the time of the study. CBFV was measured in the right middle cerebral artery using TCD (transcranial Doppler ultrasound, EME TC2020) in conjunction with a 5-MHz transducer fixed over the temporal bones using an elastic headband. Continuous ABP recordings were obtained through the Finapres (Ohmeda, 2300) device with the cuff attached to the middle finger of the right hand. Spontaneous ABP and CBFV were recorded simultaneously to a PC for off-line analysis. The acquisition periods were approximately 5 minutes in supine, 5 minutes in tilt-up, and 3 minutes in hyperventilation. The personal computer combined with a general purpose data acquisition board and LabVIEW environment for acquiring signals correctly was developed in our previous study (Chiu, 2001).

Table 1: Subjects recruited in this study.

	NL	DM	DAN1	DAN2
Number of subjects	M=8 F=3	M=11 F=4	M=12 F=9	M=20 F=5
Age (Mean±SD)	56.4±8.1	50.8±15.7	61.8±9.0	61.4±10

Note: M stands for male, and F for female.

The sampling rate needed to acquire the analog data from TCD and Finapres is adjustable in this system.

In the power spectral analysis of MABP and MCBFV under supine and hyperventilation, the power of high frequency (HF) and low frequency (LF) bands are calculated relatively. Then the value of LF/HF can be used to observe the sympathetic changes.

2.2 Analysis Methods

2.2.1 Power Spectral Density

The spectral analysis of blood pressure was used to explore the specific autonomic nervous system activity. Spectral analysis of arterial blood pressure and cerebral blood flow velocity signals were performed for the very low frequency range (VLF: 0-0.04 Hz), low frequency range (LF: 0.04-0.15 Hz), and high frequency range (HF: 0.15-0.4 Hz). Power spectral density was calculated as follows.

$$X(k) = \sum_{n=0}^{N-1} x(n) e^{-j\frac{2\pi}{N}kn}, k = 0,1,2,\ldots,N-1 \quad (1)$$

Where $x(n)$ is a discrete-time signal. Then the power spectral density can be calculated by:

$$S_{xx}(k) = \frac{1}{N}|X(k)|^2 = \frac{1}{N}X(k)X^*(k) \quad (2)$$

Where k is the frequency sample index and N is the number of samples. S_{xx} (k) is the power spectral density function.

2.2.2 Cross-correlation Function

Before calculating the CCF between MABP and MCBFV time series, MABP and MCBFV were normalized by using their mean values. Assume that the normalized MABP and MCBFV time series are $f(n)$ and $g(n)$, respectively. The normalized MABP and MCBFV time series can be calculated as follows.

$$f(n) = \frac{MABP - \overline{MABP}}{\sigma MABP} \quad (3)$$

Where MABP is the time series of mean arterial blood pressure for each heartbeat, $\overline{MABP}$ is mean MABP, and $\sigma MABP$ is the standard deviation of MABP.

$$g(n) = \frac{MCBFV - \overline{MCBFV}}{\sigma MCBFV} \quad (4)$$

Where MCBFV is the time series of mean arterial blood pressure for each heartbeat, $\overline{MCBFV}$ is mean MCBFV, and $\sigma MCBFV$ is the standard deviation of MABP.

$f(n)$ and $g(n)$ signals were bandpass-filtered

using a third-order digital bandpass Chebyshev filter in the VLF, LF and HF ranges before applying the CCF. Assume that the bandpass-filtered $f(n)$ and $g(n)$ time series are $\hat{f}(n)$ and $\hat{g}(n)$ respectively. The CCF between $\hat{f}(n)$ and $\hat{g}(n)$ is calculated as follows:

$$CCF_i(k) = \frac{R^i_{\hat{f}\hat{g}}(k)}{\left[R^i_{\hat{f}\hat{f}}(0)R^i_{\hat{g}\hat{g}}(0)\right]^{\frac{1}{2}}} \quad (5)$$

$$k = 0, \pm 1, \pm 2, \cdots, i\text{=1 to } N\text{-}W\text{+1}$$

$$R^i_{\hat{f}\hat{g}}(k) = \begin{cases} \frac{1}{W}\sum_{j=i}^{i+W}\hat{f}(j)\hat{g}(j+k), k = 0, 1, 2, \cdots \\ \frac{1}{W}\sum_{j=i}^{i+W}\hat{f}(j-k)\hat{g}(j), k = 0, -1, -2, \cdots \end{cases} \quad (6)$$

$$R^i_{\hat{f}\hat{f}}(0) = \frac{1}{W}\sum_{j=i}^{i+W}[\hat{f}(j)]^2 \quad R^i_{\hat{g}\hat{g}}(0) = \frac{1}{W}\sum_{j=i}^{i+W}[\hat{g}(j)]^2 \quad (7)$$

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3 RESULTS AND DISCUSSION

3.1 Power Spectral Density

The results of power spectral density analysis of MABP and MCBFV are listed in Table 2.

Table 2: The results power spectral density analysis of MABP and MCBFV (HV: hyperventilation).

Normal				
	MCBFV		MABP	
	supine	HV	supine	HV
VLF	346.5±292.7	29.7±11.9	448.2±586.7	202.1±162.9
LF	66.9±22.7	27.3±15.1	80.4±39.7	86.8±8.2
HF	80.7±29.0	70.4±38.5	23.7±11.5	40.4±46.1
Mild DAN				
	MCBFV		MABP	
	supine	HV	supine	HV
VLF	383.0±654.6	52.4±77.7	264.0±295.7	200.1±239.6
LF	63.8±67.4	22.2±11.0	52.0±54.1	49.0±42.9
HF	91.1±84.7	41.7±17.5	34.6±29.1	36.8±44.5
Moderate DAN				
	MCBFV		MABP	
	supine	HV	supine	HV
VLF	326.3±312.8	46.8±44.0	262.0±250.2	128.7±102.4
LF	50.8±38.3	34.7±32.0	32.3±35.6	26.1±21.3
HF	102.4±101.6	80.1±58.6	43.5±34.1	38.0±44.6
Severe DAN				
	MCBFV		MABP	
	supine	HV	supine	HV
VLF	149.7±128.4	40.4±45.1	173.2±190.3	218.0±235.8
LF	36.9±25.0	19.3±9.6	28.7±30.2	35.9±51.0
HF	64.7±32.4	40.2±17.2	48.7±58.1	36.3±34.8

The values of LF/HF between supine and hyperventilation are listed in Table 3. The relationship of LF/HF reflects the sympathetic activity.

Table 3: The results of LF/HF in each group.

MABP	NL	DM	DAN1	DAN2
Supine LF/HF	3.68±1.78	1.66±0.97	0.87±0.70	0.65±0.43
Tilt-up LF/HF	3.71±2.35	2.29±1.87	1.12±0.91	0.55±0.41
HV LF/HF	2.49±1.59	1.68±0.96	1.08±0.83	1.01±0.77
MCBFV	NL	DM	DAN1	DAN2
Supine LF/HF	0.91±0.43	0.66±0.26	0.59±0.25	0.67±0.57
Tilt-up LF/HF	1.01±0.54	0.63±0.34	0.45±0.2	0.38±0.31
HV LF/HF	0.41±0.19	0.56±0.26	0.41±0.15	0.49±0.17

It can be observed that the value of LF/HF with MABP in normal group during supine position is higher than that in hyperventilation, but it's lower than that in tilt-up. However, the values of diabetic groups in supine position are lower than that in hyperventilation. This result indicates the autonomic nervous balance decreases from supine to hyperventilation in normal group. It might be that when hyperventilation induces higher blood pressure, cerebral autoregulation (CA) mechanism begins to maintain blood pressure being constant and autonomic nervous balance became less active.

In diabetic groups, the value of LF/HF in hyperventilation is higher than that in supine. In the group of severe autonomic neuropathy in hyperventilation, the value of LF/HF is lower than that in supine. The difference between supine and hyperventilation in the group of severe autonomic neuropathy is more obvious than those in the other two diabetic groups. It can be speculated that autonomic neuropathy becomes more serious, the function of cerebral autoregulation (CA) tends to be more imbalance.

The values of LF/HF in CBFV during supine are higher than those in hyperventilation in all groups. Due to hyperventilation made oxygen increased in the brain, the cerebral artery diameter was increased, too. Therefore, the cerebral blood flow velocity (CBFV) becomes a slower while sympathetic activity decreasing to make CBFV increased.

3.2 Cross-correlation Function

In CCF analysis, the maximum peak value (Max CCF) of CCF, its corresponding standard deviation, and time lag were obtained. Max CCF values at LF of normal subjects and patients with different autonomic neuropathy are shown in Table 4.

It is observed that Max CCF values at LF of normal subjects and patients with diabetes without

autonomic neuropathy in both supine and tilt-up positions were significantly larger than that of diabetics with autonomic neuropathy.

Table 4: Max CCF values at LF in each group.

LF Max CCF	NL	DM	DAN1	DAN2
Supine	0.52±0.09	0.48±0.08	0.42±0.09	0.45±0.1
Tilt-up	0.6±0.13	0.59±0.13	0.46±0.08	0.48±0.16
HV	0.45±0.08	0.43±0.1	0.4±0.09	0.41±0.11

The results were especially significant in tilt-up position. It indicates that the cerebral autoregulation (CA) of normal subjects and diabetics without autonomic neuropathy is superior to that of diabetics with autonomic neuropathy.

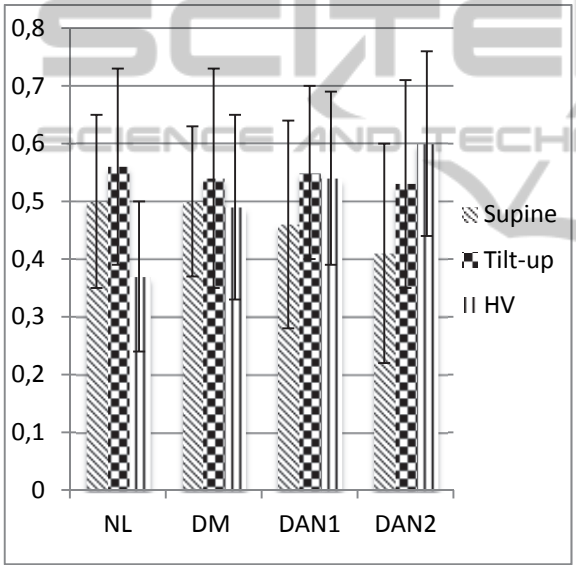

Figure 1: Comparison of Max CCF values at VLF in each group.

Max CCF values at LF of normal subjects and patients with different autonomic neuropathy are shown in Table 5.

Table 5: Max CCF values at VLF in each group.

VLF MAX CCF	NL	DM	DAN1	DAN2
Supine	0.5±0.15	0.5±0.13	0.46±0.18	0.41±0.19
Tilt-up	0.56±0.17	0.54±0.19	0.55±0.15	0.53±0.18
HV	0.56±0.13	0.49±0.16	0.54±0.15	0.6±0.16

Max CCF values gradually increased in hyperventilation at VLF from normal subjects to diabetics without autonomic neuropathy, diabetics with mild autonomic neuropathy, and diabetics with severe autonomic neuropathy shown in Figure 1. It reveals that the diabetes have worse vascular compliance in comparison with the normal subjects.

4 CONCLUSIONS

In this study, the power spectral density (PSD) analysis and cross-correlation function (CCF) analyses were applied to demonstrate hyperventilation can help us to assess the normal subjects and diabetics with various degrees autonomic neuropathy. On the contrary, the opposite results could be obtained in tilt-up position.

ACKNOWLEDGEMENTS

The authors would like to thank the National Science Council, Taiwan, R.O.C., for supporting this research under Contract No. NSC-99-2221-E-035-054-MY3.

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