Higher order crossings-based analysis to assess the effects of diabetic autonomic neuropathy on dynamic cerebral autoregulation

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Abstract

Spectral and higher order crossings (HOC) analysis of mean arterial blood pressure (MABP) and mean cerebral blood flow velocity (MCBFV) signals have been applied to evaluate the relation between diabetic autonomic neuropathy (AN) and cerebral autoregulation (CA). Results revealed low frequency (LF) power of MABP (LF_MABP: 6.54±2.06 mmHg²) and MCBFV (LF_MCBFV: 4.79±5.73 (cm/s)²) were significantly higher in healthy subjects (p<0.05). Reduced L_MABP in diabetics indicates that the sympathetic nerve modulation was impaired. A novel index, CUMUDIFF_HOC, derived from HOC estimated by MABP and MCBFV could classify severity of diabetic AN (healthy:13.44±3.59 vs. diabetics (severe autonomic neuropathy): 9.68±3.57, p<0.05). Index difference reveals disturbance in CA and provides a new insight into the effect of AN on CA.

Key words:Cerebral autoregulation, diabetes, higher order crossings (HOC), mean arterial blood pressure (MABP), mean cerebral blood flow velocity (MCBFV).
1. Introduction

Diabetes mellitus (DM) is a kind of metabolic diseases characterized by high glucose level resulting from weakness in insulin secretion, action or both. In general, glucose levels are controlled by insulin. Therefore, DM is currently considered a complex metabolic syndrome where insulin and glucose are the two major indicators. DM leads to irregular metabolism, causes disturbances in nutritional and oxygen supply of the nervous system with the consequences of autonomic neuropathy with development of cardio-vagal dysfunction, arteriosclerosis, or hypertension. Complications of both cardiovascular and nervous systems are the major risk factors for mortality of diabetics [10]. According to previous researches, DM is the most common cause of autonomic nervous dysfunctions [11]. Diabetes is one of the important risk factors to cause cerebral diseases and is a risk factor to cause stroke [37, 40]. The incidence of stroke in patients with type 2 diabetes is two- to five-fold more than that in healthy persons [17].

Many patients with diabetes have no symptoms in the early stage and are diagnosed after many years of onset of the disease. Several tests have been developed to detect autonomic nervous system dysfunction in the early onset of diabetes [35, 46, 47]. Most methods are developed for research requiring high technical skills, and are difficult to apply in clinical practice. There is a need for simple objective noninvasive approaches to assess autonomic dysfunction in diabetes for clinical practice.

Disturbance of cerebral autoregulation (CA) due to autonomic dysfunction in diabetics is one of the important factors to cause cerebral disease [21]. CA is a feedback mechanism, which maintains cerebral blood flow at a constant despite changes of blood pressure. CA acts through vasomotor effectors and CO₂ regulation that control cerebrovascular resistance (CVR) [1]. Previous study revealed that the sympathetic nervous system has a direct effect on the cerebral vasculature. Therefore, the autonomic nervous system is also an important component for cerebral flow control [13]. Static CA is a measure of the overall efficiency of the system and cerebral blood flow adjustments in response to more prolonged BP changes. Dynamic CA is the ability to maintain CBF in the face of BP changes occurring over a matter of seconds and reflects the latency of the cerebral vasoregulatory system [39]. Recent investigations have shown that the autoregulatory dynamic response can be identified from spontaneous fluctuations in mean ABP (MABP) and CBFV by using transfer function analysis in healthy subjects [9, 28, 44] or autonomic failure patients [3]. Phase analysis using time-domain based cross-correlation functions (CCF) [4, 5, 7, 29, 31, 38], spectral and transfer function analyses of CBFV and ABP [24, 45] showed the significant role of autonomic neural control on dynamic CA. But only a few studies discussed the effect of autonomic neuropathy on CA in diabetics by using spectral analysis of cerebral blood flow oscillations [22, 23].

Classifying the severity of autonomic neuropathy is usually based on autonomic reflex
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tests (heart rate responses to deep breathing, response to Valsalva maneuver, skin sympathetic response and postural blood pressure test etc.) in clinical practice. Because cerebral autoregulation is mainly controlled by autonomic nerve system, cerebral autoregulation would be affected by autonomic neuropathy. Previous studies (3,5,7,24,25,30) showed some index or approaches to assess cerebral autoregulation. However, the algorithm is more complicated, like transfer function, autoregulation index and cross-correlation function etc. Therefore, we provide a useful and simple index by assessing the relationship between blood pressure and cerebral flow velocity to assess cerebral autoregulation that can determine the presence of autonomic neuropathy in this study.

Recently, higher order crossings (HOC), a method which counts the number of zero-crossings to evaluate the degree of oscillating in time series, has been successfully applied for detection of brain injures using the EEG signal and discrimination of breath sounds [12,16]. The main purpose of this study is to detect changes of dynamic CA in diabetic patients using the HOC method for analyzing the relationship between blood pressure and cerebral blood flow velocity and evaluating possible influence of diabetic autonomic neuropathy on dynamic CA. The advantage of HOC is that crossing counts can be calculated from original data in time domain and it can help to observe some results in frequency domain. By a novel index derived from HOC, we hypothesize that (a) HOC can be used to observe fine changes between MABP and MCBFV fluctuations caused by CA and affected by diabetes and (b) HOC can be used to classify the degree of autonomic neuropathy for early detection and diagnosis in diabetics.

2. Methods

2.1 Subjects and measurement

Forty two patients with diabetes and ten healthy control subjects (57.4±8.4 years) were studied. Twenty five diabetics had mild autonomic neuropathy (67.5±8.8 years) and seventeen diabetics were diagnosed with severe autonomic neuropathy (63.7±11.0 years). The age difference in three groups is not significant (p>0.05). The determination of the presence of prominent autonomic neuropathy was based on a battery of autonomic reflex tests (more than two abnormal responses in the following tests: heart rate responses to deep breathing, response to Valsalva maneuver, skin sympathetic response and postural blood pressure test) according to the consensus conference in 1992 [34]. The diabetic patients had no stroke history among the three groups. Supine blood pressure was not different among three groups (p>0.05). The patients did not discontinue their therapy of one or two times oral intake of Sulfonylureas and Metformin per day. The healthy control subjects were included only if they had no history of cardiovascular disease, heart problems, hypertension, migraine, epilepsy, cerebral aneurysm, intracerebral bleeding, or other pre-existing neurological conditions. None of the control subjects took any medication during the period of the study. The study had been approved
by the Research Ethics Committee of Cheng-Ching General Hospital. All subjects were informed and signed consent prior to entry to the study.

2.2 Data acquisition

Continuous cerebral blood flow velocity (CBFV) was measured in the middle cerebral artery using Transcranial Doppler ultrasound (TCD, EME TC2020, Nicolet Instruments, Warwick, UK) in conjunction with a 2-MHz transducer fixed by an elastic headband over the temporal bones. Continuous arterial blood pressure recordings were obtained using the Finapres (Model 2300, Ohmeda, Englewood, CO) device with the cuff attached to the middle finger of the right hand.

In this study, MABP value was calculated for each heart beat as follows [5, 7]:

\[
MABP_i = \frac{1}{P_i - P_{i-1} + 1} \sum_{k=1}^{P_i} ABP(k)
\]

(1)

where \( ABP(\cdot) \) \( P_i \) is the arterial blood pressure pulse signal continuously acquired from Finapres. \( P_i \) is the wave-through time index in the ith pulse beat. Therefore, \( MABP_i \) is the calculated mean ABP value for the ith pulse beat. Similarly, the mean CBFV can be derived from equation (2).

\[
MCBFV_i = \frac{1}{F_{i-1} - F_i + 1} \sum_{k=F_i}^{F_{i-1}} CBFV(k)
\]

(2)

where \( CBFV(\cdot) \) is the CBFV signal continuously acquired from the TCD. \( F_i \) is the time index of the wave-through in the CBFV signal corresponding to the ith pulse beat. \( MCBFV_i \) is the mean value of CBFV for the ith pulse beat. The signals were processed before applying to analysis. In the beginning, the sampling rate to acquire the analog data of CBFV and ABP from TCD and Finapres was set to 60 Hz. The wave-peak and wave-valley of each cardiac cycle can be marked from the ABP and CBFV signals using the approach proposed in the previous study [8]. The length of signals was set to 256. Afterward, the MABP and MCBFV time series calculated by Eqs. (1) and (2). MABP and MCBFV are estimated by each heart beat in time series and the unit is time index. The sampling time was set equal to the mean heart period of each subject. Therefore, the result would not be biased.

2.3 Protocol

Subjects were studied on a tilt-table that enabled a motor-driven change from a supine to an upright position 75° within 4 seconds. Data acquisition was started after a 10-min relaxation in supine position. ABP and CBFV waveforms were recorded simultaneously at 60 Hz to PC for off-line analysis. The acquisition periods were approximately 5 minutes in both the supine and 75° head-up tilt positions. Data acquisition was performed using a general-purpose data acquisition board (NI PCI-1200, National Instruments) and acquisition program developed by LabVIEW (LabVIEW 6.0, National Instruments) [6].

2.4 Spectral analyses

We used spectral analysis 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:
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0.015-0.07 Hz), low frequency range (LF: 0.07-0.15 Hz) and high frequency range (HF: 0.15-0.4 Hz) [5, 32]. The total number of cardiac cycles for both MABP and MCBFV to compute the spectra was 256 beats.

Power spectral density $X(k)$ is calculated as follows [3, 24, 44, 45]:

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

where $x(n)$ is a discrete-time signal, $k$ is the frequency sample index and $N$ is the number of samples.

Then power spectral density is given by:

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

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

### 2.5 Higher order crossings (HOC)

The number of observed zero-crossings was determined in a finite time series oscillating after removing the mean value. This counting procedure was repeated after application of a differential filter. The filtered signal was filtered again and the number of resulting zero-crossings was determined. The resulting series of filter order (number of filtering) and zero-crossing counts at each filter stage were referred to as higher order crossings. The number of zero-crossings and normalized zero-crossing rate in discrete time can be calculated as follows [14].

1. Consider a time series $\{Z_t\}$ $t=1,2,3,...,N$.
   Define $Z_t = S_t - m$, where $S_t$ is the discrete time signal, $m$ is the mean value of $S_t$, $N$ is the length of the signal (in this study, $N$ is set to be 256 points):
   $$m = \frac{1}{N} \sum_{t=1}^{N} S_t \quad (5)$$

2. Define a binary time series $X_1,X_2,...,X_N$ by the nonlinear transformation,
   $$X_i = \begin{cases} 1, & \text{if } Z_i \geq 0 \\ 0, & \text{if } Z_i < 0 \end{cases} \quad (6)$$

3. Calculate $D(\theta) : D(\theta)$ is the number of zero-crossings of $\{Z_t\}$
   $$D(\theta) = \sum_{t=2}^{N} [X_t(\theta) - X_{t-1}(\theta)]^2 \quad (7)$$
   where $\theta$ is the filter order.

4. Normalized zero-crossing rate $G(\theta)$
   $$G(\theta) = \frac{\pi D(\theta)}{N-1} \quad \text{(unit: radius/s)} \quad (8)$$

The normalized HOC sequence converges to the highest frequency in the spectrum.

The number of zero-crossings can be used as a measure of the oscillation exhibited in the time-series. If more oscillations are present then the expected numbers of zero-crossings is higher. Conversely, fewer zero-crossings are expected when the time series is rather “smooth” and slowly varying. Moreover, normalized zero-crossing rate can be used to estimate the highest existing frequency in the signal.

To quantify the difference of zero-crossing counts between MABP and MCBFV, a linear cumulative difference index, $\text{CUMUDIFF}_{HOC}$, is constructed as follows.

1. $\text{DIFF}_{HOC}(\theta) = \text{D}_{MABP}(\theta) - \text{D}_{MCBFV}(\theta)$
2. $\text{D}_{MABP}(\theta)$: higher order zero crossing counts of signal “MABP” at filter order $\theta$.
3. $\text{D}_{MCBFV}(\theta)$: higher order zero crossing counts...
of signal “MCBFV” at filter order \( \theta \).

\[ \text{DIFF}_{\text{HOC}}(\theta) \]: difference between \( D_{\text{MABP}}(\theta) \) and \( D_{\text{MCBFV}}(\theta) \).

2. 

\[ CUMUDIFF_{\text{HOC}}(n_1,n_2) = \frac{1}{n_2-n_1+1} \sum_{\theta=n_1}^{n_2} \text{DIFF}_{\text{HOC}}(\theta) = \frac{1}{n_2-n_1+1} \sum_{\theta=n_1}^{n_2} [D_{\text{MABP}}(\theta) - D_{\text{MCBFV}}(\theta)] \]

\( CUMUDIFF_{\text{HOC}}(n_1,n_2) \): cumulative difference form index \( n_1 \) to \( n_2 \). Where \( n_2 \) is the maximal number of filtering (\( n_1 = 1 \) and \( n_2 = 20 \) in this study).

The absolute values of zero-crossing count difference (\( \text{DIFF}_{\text{HOC}} \)) between blood pressure and cerebral blood flow with increasing filter order will be compared with the frequency band.

2.6 Statistical analysis

Values in the tables and text are expressed as mean±standard deviation. All statistical analyses were performed using SPSS software (SPSS Inc., Chicago, IL). The continuous variables were analyzed by the grouped t test and the categorical variables were analyzed by the Mann-Whitney U test when appropriate [43]. The \( p \)-value is a probability, with a value ranging from zero to one. In most studies, a \( p \)-value less than 0.05 is considered as statistical significant. In this study, a \( p \)-value less than 0.05 is considered as significant in all tests.

3. Results

3.1 Time domain

The values of blood pressure and cerebral blood flow velocity are depicted in Table 1. In Table 1, supine blood pressures in three groups were not significantly different \((p>0.05)\). However, systolic, mean and diastolic arterial blood pressures \((\text{SABP}, \text{MABP}, \text{DABP})\) reveal a significant difference \((p<0.05)\) in response to head-up tilt in severe diabetics but not in mild diabetics. On the other hand, the values of systolic, mean, and diastolic cerebral blood flow velocity \((\text{SCBFV}, \text{MCBFV}, \text{DCBFV})\) were almost maintained constant in response to head-up tilt in healthy subjects. However, mean and diastolic CBFV decreased significantly \((p<0.05)\) from supine to head-up tilt position in diabetics with mild and severe autonomic neuropathy. Head-up tilt induced decrease in SABP, MABP and DABP in diabetics with severe autonomic neuropathy. It is different to the tilt induced increase or no change of blood pressure in healthy subjects.

3.2 Frequency domain

Table 2 shows group-averaged values of the power spectral analysis in blood pressure. LF power of healthy subjects in supine and head-up tilt positions was significantly higher \((p<0.05)\) than diabetics with mild and severe autonomic neuropathy. LF power of healthy subjects in MABP were significantly different in both supine and head-up tilt positions \((p<0.05)\). The LF power of SABP and MABP were significantly different in healthy subjects and diabetics. The power values in LF band increased in response to head-up tilt position. The power values in VLF and HF did not reveal a significant difference among groups. The power of LF oscillation SABP was higher than in MABP. The power of LF oscillation MABP is higher than
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Table 3 shows the resulting group-averaged values of the power spectral analysis in mean CBFV. It shows VLF and LF power of healthy subjects both in head-up tilt positions were significantly higher (p<0.05) than that of diabetics with severe autonomic neuropathy. Also, both VLF and LF power of diabetics with mild autonomic neuropathy in head-up tilt positions were significantly higher (p<0.05) than that of diabetics with severe autonomic neuropathy. On the other hand, HF power was significantly different in each group in response to head-up tilt position (p<0.05).

3.3 Higher order crossings (HOC)

Fig. 1 shows zero-crossing counts of MABP and MCBFV of typical samples in healthy subjects and diabetics. Fig. 1A is a typical example of a healthy subject in supine position where the curves of zero-crossing counts of MABP and MCBFV are converging gradually with increasing filter order. This convergent behavior of both HOC curves could be found also during head-up tilt position (Fig. 1B). In contrast, the two HOC curves of zero-crossing counts of MABP and MCBFV signals did not converge in some diabetics and remain separated. Fig. 1C and 1D shows a typical example of diabetics in supine and head-up tilt positions where the curves of zero-crossing counts of MABP and MCBFV do not converge with increasing filter order.

Fig. 2 shows the statistical results of group-averaged zero-crossing cumulative difference index ($\text{CUMUDIFF}_{\text{HOC}}$) between MABP and MCBFV by a boxplot. The y-axis represents the group-averaged value of $\text{CUMUDIFF}_{\text{HOC}}$ for each filter index from 1 to 20. Statistical differences among three groups can be distinguished significantly in supine and head-up tilt positions ($\text{CUMUDIFF}_{\text{HOC}}$ in supine position: Healthy: 13.44±3.59 vs. Diabetics (severe autonomic neuropathy): 9.68±3.57, p<0.05, Diabetics (mild autonomic neuropathy): 12.77±3.85 vs. Diabetics (severe autonomic neuropathy): 9.68±3.57, p<0.05; $\text{CUMUDIFF}_{\text{HOC}}$ in head-up tilt position: Healthy: 8.31±3.23 vs. Diabetics (mild autonomic neuropathy): 10.74±3.47, p<0.05; Healthy: 8.31±3.23 vs. Diabetics (severe autonomic neuropathy): 10.63±2.77, p<0.05). In addition, the value of $\text{CUMUDIFF}_{\text{HOC}}$ between supine and head-up tilt position was significantly different only in healthy subjects (p<0.05).

The zero-crossing rate can be estimated by the equation (7) and the results also reveal behavior similar to that in healthy subjects and diabetics. The curves of zero-crossing rate would converge at last in healthy subjects and the value indicates the highest frequency in the signal. The results reveal that the frequency of both MABP and MCBFV signal converges to around 0.4 Hz in healthy subjects and diabetics.

According to the results of zero-crossing rate in MABP and MCBFV, highest frequency is reached at 0.4 Hz after filter order 10. Fig. 3 shows the absolute change of zero-crossing count difference between MABP and MCBFV ($|\text{DIFF}_{\text{HOC}}|$) with increasing filter order. The value of $|\text{DIFF}_{\text{HOC}}|$ in index 2 was significantly higher (p<0.05) in healthy subjects than in diabetics with severe autonomic neuropathy during supine
position (Fig. 4A). After the filter order index 10, the frequency is about 0.4 Hz. With filter order index lower than 10, the frequency range is between 0 to 0.4 Hz.

The distribution of HOC MABP values of the first and second order (\(D(1)\) and \(D(2)\)) can discriminate supine and tilt position in healthy subjects (Fig. 4A) but not in diabetics (Fig. 4B and 4C). The posture change, supine to head-up tilt, caused an increase in \(D(1)\) with equal or smaller \(D(2)\) in healthy subjects. In diabetic patients, the responses were mixed and no correlation was found (Fig. 4B and 4C).

4. Discussion

4.1 Blood pressure and cerebral blood flow levels

Our study shows that the fluctuations of blood pressure (BP) and cerebral blood flow velocity (CBFV) were not different in supine position between diabetics and healthy subjects. But during orthostatic stress, MABP and MCBFV levels were lower in diabetic patients as compared to healthy subjects. This has been shown also by other investigators [5, 29]. Diabetic patients experienced a tilt induced fall in blood pressure and in cerebral blood flow greater than in the healthy subjects (Table 1). It indicates that diabetic neuropathy decreased the vasoconstrictor response of the vessels and cause orthostatic induced lower blood pressure and cerebral blood flow. Especially, all tilt induced falls of cerebral blood flow (SCBFV, MCBFV and DCFBV) are larger in the diabetic patients than in the healthy subjects.

It demonstrates that cerebral autoregulation is not functioning and fails to maintain flow at constant levels in diabetics.

Spectral analysis of blood pressure oscillations shows that \(\text{LF}_{\text{SABP}}, \text{LF}_{\text{MABP}}\) and \(\text{LF}_{\text{DABP}}\) of diabetics were significantly lower than those of healthy subjects in both supine and head-up tilt positions. High frequency blood pressure oscillations were not different. In accordance to previous study, high frequency power of blood pressure is mainly caused by the mechanical effects of respiration on the pressure gradients of large thoracic vessels and pump function of the heart [22]. Low frequency power of blood pressure is associated with sympathetic cardiovascular influence and can be used as a marker of sympathetic vasomotor tone [22] or sympathetic modulation [48]. Therefore, LF of blood pressure can reflect sympathetic vasomotor activity which had reduced in the diabetic patients.

Previous studies in healthy subjects showed upright posture induced increase of low frequency power of systolic blood pressure which is associated with increased sympathetic activity during orthostatic stress [26]. In our healthy subjects and patients, we found a trend of increase of \(\text{LF}_{\text{SABP}}, \text{LF}_{\text{MABP}}\) and \(\text{LF}_{\text{DABP}}\) power in response to head-up tilt. However, we could not find significant differences between mean values in both supine and tilt positions because we studied an older subject population which have initial lower variability and orthostatic response (aging effect) as compared to previous published data [18, 23]. This assumption is supported by other
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Researchers have found that older subjects have less increase of LF oscillations in blood pressure than younger subjects [2, 18, 27, 41] which is believed to be the result of reduced baroreflex-mediated sympathetic outflow to the vasculature [27].

4.2 Spectral analysis of cerebral blood flow

Spectral analysis of MCBFV revealed lower power of LF oscillation in cerebral blood flow during supine in diabetics as compared to healthy subjects. High frequency oscillations of cerebral blood flow were not different between diabetics and healthy subjects. Upright position increased LF_{MCBV}, which is lower in diabetics than in healthy. This might be a result of autonomic dysfunction of the cerebral vessels caused by autonomic neuropathy in the diabetic patients. It seems to be that cerebral autoregulation cannot buffer the oscillations effectively in the diabetic patients. This is also identified by other investigators that impaired cerebral autoregulation would lead less dampening of blood pressure oscillation in diabetics [25]. These demonstrate that autonomic dysfunction in diabetics is associated with dynamic cerebral autoregulation dysfunction.

4.3 HOC analysis

The main findings of HOC analysis is that the cumulative difference between blood pressure and cerebral blood flow (CUMUDIFF_{HOC}) is significantly lower in diabetics. Also the tilt induced decrease of the CUMUDIFF_{HOC} indicator is absent, perhaps due to initial low values in diabetics. The highest frequency of MABP and MCBFV determined by normalized zero-crossing rate converges to the limit of 0.4 Hz in healthy subjects and as well as in diabetics. This maximal frequency is consistent with the known maximal frequency of autonomic baroreflex control [22]. In healthy subjects, the absolute value of difference of HOC between blood pressure and cerebral blood flow (DIFF_{HOC}) rises rapidly from index 1 to index 2 with its maximum at index 2, and then it drops gradually with higher filter order. The index range around 2 represents approximately 0.05 to 0.2 Hz fluctuations and the increase might be the result of baroreflex buffering and cerebral autoregulation. In diabetics, the maximum of DIFF_{HOC} at index 2 is lower. This indicates that cerebral blood flow followed the change of blood pressure.

According to previously published data, cerebral autoregulation is more effective for low frequency than for high-frequency change in BP [23, 44]. Our results supports this assumption with higher maximum DIFF_{HOC} values in the LF range (around index 2) (Fig. 3) and higher frequency components of cerebral blood flow in the LF range in healthy subjects as compared to diabetics (Table 3). Therefore, the value of DIFF_{HOC} with increasing filter index could provide another perspective to observe the relation of MABP and MCBFV in frequency domain.

On the other hand, the zero-crossing counts in the blood pressure signal at filter order 1 and 2 are higher in diabetics than in healthy subjects. This could be because blood pressure fluctuates more rapidly and frequently than under intact baroreflex buffering. The statistical results revealed a group effect in response to head-up tilt among three groups of different severity of diabetic
neuropathy by using the cumulative linear index ($CUMUDIFF_{HOC}$). In addition, the difference between mild and severe diabetic autonomic neuropathy was also significantly different in supine posture. Since the algorithm of HOC is not so complicated compared to other approaches (such as moving correlation coefficient [33, 36] and autoregulatory index [25, 39]), the novel index, $CUMUDIFF_{HOC}$, derived from HOC could be a simple and useful way to distinguish healthy subjects from diabetics with autonomic neuropathy and classify the severity of diabetic autonomic neuropathy without tilting or autonomic reflex tests.

In Fig. 4, ($D(1),D(2)$) pair distribution of MABP response to posture change can almost distinguish between healthy subjects and patients. The posture change from supine to upright causes more oscillations in MABP which is reflected in higher $D(1)$ and $D(2)$ values. However, ($D(1),D(2)$) pair distributions in diabetics were mixed. It might be because $D(1)$ to $D(2)$ represent the low frequency band in which cerebral autoregulation is more functioning. Healthy subjects with intact cerebral autoregulation can respond to the posture change while diabetics cannot respond.

Previous studies have applied some specific approaches like chaos analysis, ARX model and transfer function to investigate cerebral autoregulation [19, 20, 30], they can identify linear and nonlinear components of cerebral autoregulation. However, these algorithms could be more complicated as compared to HOC. Recent study has shown that the index derived from higher order crossings could distinguish severity of diabetic autonomic neuropathy [42]. Moreover, in this study, we found some results based on higher order crossings can also indicate the function of cerebral dynamic in frequency domain. Due to HOC estimation is only in time domain, it does not need other transforms and some results can be observed in frequency domain in this study. An important advantage of the approach is that crossing counts are the only features that need to be stored from the original data. According to the results, it can not only satisfy with previous results but the results can be obtained and observed in a different way. In this study, the index, $CUMUDIFF_{HOC}$, is created and applied in diabetics. The index derived from HOC can distinguish severity of diabetic autonomic neuropathy efficiently and HOC can observe cerebral autoregulation in a different view. Therefore, HOC and the index can be useful and novel to be applied in diabetics.

5 Conclusion

We demonstrated that an index derived from higher order crossings analysis of blood pressure and cerebral blood flow can distinguish severity of diabetic autonomic neuropathy and observe the characteristic of cerebral autoregulation in time and frequency domain. The differences of cerebral autoregulation in diabetics and healthy subjects could be observed in another perspective by using this approach. The novel index derived from HOC analysis could be a simple and helpful indicator to improve early diagnosis and prevention of early stage diabetic autonomic neuropathy.
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Fig. 1. Zero-crossing counts of mean arterial blood pressure (MABP) and mean cerebral blood flow velocity (MCBFV) in a representative healthy subject in supine (A) and tilted position (B), and in a representative diabetic patient with mild autonomic neuropathy in supine (C) and tilted position (D), (E) is a representative diabetic patient with severe autonomic neuropathy in supine and (F) in tilted position.
Fig. 2. Boxplots of statistical results of zero-crossing count differences between MABP and MCBFV in healthy subjects, diabetics with mild AN, and diabetics with severe AN. The results are shown as average reciprocal values of difference between counts for MABP and MCBFV, $CUMUDIFF_{HOC}$, for filter range index 1 to 20.

Fig. 3. The absolute values of zero-crossing count difference ($DIFF_{HOC}$) between blood pressure and cerebral blood flow with increasing filter order in supine (A) and tilted positions (B).
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Fig. 4. \((D(1), D(2))\) pair of MABP distribution in response to head-up tilt in each group. \(D(1)\) and \(D(2)\) are first and second order, respectively.
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<td>89.33±14.59</td>
<td>86.14±17.28</td>
<td>68.52±12.47</td>
<td>65.93±15.03</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Severe</td>
<td>140.16±27.23</td>
<td>119.55±28.02</td>
<td>96.53±21.12</td>
<td>82.48±19.15</td>
<td>72.40±16.29</td>
<td>63.84±16.09</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>CBFV (cm/s)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Healthy</td>
<td>58.51±9.77</td>
<td>57.01±10.03</td>
<td>38.85±7.94</td>
<td>36.61±7.21</td>
<td>23.58±6.88</td>
<td>21.07±5.88</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mild</td>
<td>68.87±24.37</td>
<td>65.84±23.47</td>
<td>41.91±16.82</td>
<td>37.68±15.62</td>
<td>23.74±12.85</td>
<td>19.56±11.17</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Severe</td>
<td>69.99±29.04</td>
<td>65.80±26.92</td>
<td>43.19±20.32</td>
<td>37.91±18.79</td>
<td>25.08±14.95</td>
<td>20.73±13.35</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Healthy: Healthy subjects; Mild: Diabetes with mild autonomic neuropathy; Severe: Diabetes with severe autonomic neuropathy; *p < 0.05 (Severe: supine vs. tilting in systolic blood pressure), **p < 0.05 (Severe: supine vs. tilting in mean blood pressure), ***p < 0.05 (Severe: supine vs. tilting in diastolic blood pressure), !p < 0.05 (Tilting: healthy vs. severe in mean blood pressure), $p < 0.05 (Tilting: healthy vs. severe in diastolic blood pressure), @p < 0.05 (Mild: supine vs. tilting in mean cerebral blood flow), #p < 0.05 (Mild: supine vs. tilting in diastolic cerebral blood flow), ^p < 0.05 (Severe: supine vs. tilting in mean cerebral blood flow), &p < 0.05 (Severe: supine vs. tilting in diastolic cerebral blood flow).
Higher order crossings-based analysis to assess the effects of diabetic autonomic neuropathy on dynamic cerebral autoregulation.

Table 2. Group-averaged power spectrum values of blood pressure.

<table>
<thead>
<tr>
<th></th>
<th>Systolic</th>
<th></th>
<th>Mean</th>
<th></th>
<th>Diastolic</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Supine</td>
<td>Tilting</td>
<td>Supine</td>
<td>Tilting</td>
<td>Supine</td>
<td>Tilting</td>
</tr>
<tr>
<td>VLF (mmHg(^2))</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Healthy</td>
<td>26.12±17.32</td>
<td>37.46±15.43</td>
<td>13.31±8.77</td>
<td>14.32±5.57</td>
<td>7.90±5.33</td>
<td>8.45±3.54</td>
</tr>
<tr>
<td>Mild</td>
<td>32.98±38.44*</td>
<td>50.78±50.24</td>
<td>13.23±13.81</td>
<td>21.15±21.67</td>
<td>8.02±8.06</td>
<td>11.45±12.97</td>
</tr>
<tr>
<td>Severe</td>
<td>25.33±34.90</td>
<td>47.40±32.43</td>
<td>9.77±11.28**</td>
<td>20.03±13.79</td>
<td>5.82±5.08***</td>
<td>12.11±8.30</td>
</tr>
<tr>
<td>LF (mmHg(^2))</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Healthy</td>
<td>8.91±3.60@#'</td>
<td>10.30±5.45(^{\alpha})</td>
<td>6.54±2.06(\beta)γ</td>
<td>7.59±5.13(\delta)ε</td>
<td>4.05±1.75(\zeta)η</td>
<td>5.26±4.190(\kappa)</td>
</tr>
<tr>
<td>Mild</td>
<td>5.67±5.51</td>
<td>6.50±4.21</td>
<td>2.83±3.32</td>
<td>3.61±2.72</td>
<td>1.77±2.22</td>
<td>1.85±1.38</td>
</tr>
<tr>
<td>Severe</td>
<td>4.88±4.82</td>
<td>5.88±5.49</td>
<td>2.13±2.07</td>
<td>2.60±2.22</td>
<td>1.40±1.37</td>
<td>1.62±1.52</td>
</tr>
<tr>
<td>HF (mmHg(^3))</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Healthy</td>
<td>2.09±1.06</td>
<td>2.54±0.99</td>
<td>1.30±0.42</td>
<td>1.17±0.82</td>
<td>0.73±0.24</td>
<td>0.75±0.56</td>
</tr>
<tr>
<td>Mild</td>
<td>2.96±1.76</td>
<td>3.66±2.78</td>
<td>1.63±1.23</td>
<td>1.48±1.15</td>
<td>1.22±1.15(\lambda)</td>
<td>0.61±0.44</td>
</tr>
<tr>
<td>Severe</td>
<td>3.14±1.96</td>
<td>5.28±5.44</td>
<td>1.49±0.78</td>
<td>2.23±2.26</td>
<td>1.00±0.57</td>
<td>0.87±0.86</td>
</tr>
</tbody>
</table>

Healthy: Healthy subjects; Mild: Diabetes with mild autonomic neuropathy; Severe: Diabetes with severe autonomic neuropathy; VLF: very low frequency, LF: low frequency, HF: high frequency; *p<0.05 (Mild: supine vs. tilting in VLF), **p<0.05 (Severe: supine vs. tilting in VLF), *** p<0.05 (Severe: supine vs. tilting in VLF), @p<0.05 (Supine: healthy vs. mild in LF), #p<0.05 (Supine: healthy vs. severe in LF), ^p<0.05 (Tilting: healthy vs. mild in LF), \(\alpha\) p<0.05 (Tilting: healthy vs. severe in LF), \(\beta\) p<0.05 (Supine: healthy vs. mild in LF), \(\gamma\) p<0.05 (Supine: healthy vs. severe in LF), \(\delta\) p<0.05 (Tilting: healthy vs. mild in LF), \(\varepsilon\) p<0.05 (Tilting: healthy vs. severe in LF), \(\zeta\) p<0.05 (Supine: healthy vs. mild in LF), \(\eta\) p<0.05 (Supine: healthy vs. severe in LF), \(\theta\) p<0.05 (Tilting: healthy vs. mild in LF), \(\kappa\) p<0.05 (Tilting: healthy vs. severe in LF).
Table 3. Group-averaged power spectrum values of MCBFV.

<table>
<thead>
<tr>
<th>MCBFV (cm/s)</th>
<th>Supine</th>
<th></th>
<th></th>
<th>Tilting</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>VLF</td>
<td>LF</td>
<td>HF</td>
<td>VLF</td>
<td>LF</td>
</tr>
<tr>
<td>Healthy subjects</td>
<td>14.35±10.57</td>
<td>4.79±5.73@</td>
<td>1.71±0.93!</td>
<td>20.74±16.61&amp;</td>
<td>9.73±8.89&gt;</td>
</tr>
<tr>
<td>Diabetics (mild AN)</td>
<td>12.48±13.33</td>
<td>2.39±2.03#</td>
<td>2.07±1.57^</td>
<td>17.14±15.13 &lt;</td>
<td>6.25±6.92/</td>
</tr>
<tr>
<td>Diabetics (severe AN)</td>
<td>8.10±8.01</td>
<td>1.56±1.55</td>
<td>1.50±0.51*</td>
<td>10.22±12.48</td>
<td>1.94±1.27</td>
</tr>
</tbody>
</table>

!p<0.05 (Healthy: supine vs. tilting in HF), #p<0.05 (Mild: supine vs. tilting in LF), ^ p<0.05 (Mild: supine vs. tilting in HF), * p<0.05 (Severe: supine vs. tilting in HF), @ p<0.05 (supine: healthy vs. severe in LF), & p<0.05 (tilting: healthy vs. severe in VLF), < p<0.05 (tilting: mild vs. severe in VLF), > p<0.05 (tilting: healthy vs. severe in LF), / p<0.05 (tilting: mild vs. severe in LF)
Higher order crossings-based analysis to assess the effects of diabetic autonomic neuropathy on dynamic cerebral autoregulation.

基於高階交越分析法評估糖尿病神經病變對動態腦血流調控之影響

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摘要

本研究以頻譜及高階交越法分析平均血壓及平均腦血流之關係，藉以評估糖尿病神經病變對於腦血流調控之影響。結果顯示正常人平均血壓之低頻能量(LF_MABP: 6.54 ± 2.06 mmHg²)及平均腦血流(LF_MCBFV: 4.79 ± 5.73 (cm/s)²)在統計上確實高於糖尿病神經病變患者(p<0.05)，此亦可能代表糖尿病患者交感神經系統之作用較為不良。藉由高階交越法評估平均血壓及平均腦血流推導出另一新的評估指標，CUMUDIFF_HOC，可分辨出糖尿病神經病變的嚴重程度，且具統計上之意義。 (正常人: 13.44 ± 3.59 vs. 糖尿病嚴重神經病變: 9.68 ± 3.57, p<0.05)。此新的指標可顯示腦血流調控所受到的擾動外，並可以依新的方式評估神經病變對腦血流調控之影響。

關鍵詞：腦血流調控，糖尿病，高階交越，平均血壓，平均腦血流

*通訊作者