Wavelet Phase Coherence Analysis Between the Respiratory Activity and the Microcirculation: The Effects of Type 1 Diabetes

Michele Sorelli, Antonia Perrella, Piergiorgio Francia, and Leonardo Bocchi

Abstract

Microvascular perfusion is modulated by the breathing activity. However, to the authors' knowledge, no study has attempted to assess the pathological deterioration of this physiological coupling in diabetes, which is related to structural and functional alterations of the microvasculature. On this basis, a phase coherence analysis was conducted to identify a possible weakening of the time-phase relationship between the breathing rhythm and the peripheral pulse, measured with laser Doppler flowmetry. Two groups of 21 healthy subjects and 21 type 1 diabetic (T1D) patients were evaluated in this retrospective study: a significant phase coherence was detected for the area beneath the diastolic phase of the peripheral pulse (median: 0.78; IQR: 0.20), in 81.0% of the controls; however, the analysis of the T1D group highlighted a considerable loss of synchronization, with significant values obtained in only 33% of the cases (median: 0.53; IQR: 0.15). This result may yield a valuable biomarker for the detection of diabetic microangiopathy.

Keywords

Microcirculation • Diabetes • Laser Doppler flowmetry • Wavelet phase coherence

1 Introduction

The microcirculation plays a crucial function in adjusting the local blood flow rates to the spatially- and time-varying metabolic demands of the organism [1]. In this regard, the microvascular physiology is characterized by a complex array of systemic and local control pathways which regulate the tone of vascular smooth muscle cells and, thus, the regional supply of O_2 and nutrients [2]. In addition to the propagation of cardiac and respiratory-related pressure waves, the intrinsic endothelial and myogenic vasomotor mechanisms, and the extrinsic neurovascular interactions, produce oscillatory patterns in the tissue microvascular perfusion within established frequency intervals [3]. These characteristic components can be assessed noninvasively at the level of the skin by means of laser Doppler flowmetry and time-frequency analysis techniques [4].

As recently reviewed by Gutterman et al., microvascular dysfunction is recognized either as a primary causal factor or a secondary effect of a broad range of pathological conditions, including diabetes mellitus [5]. Diabetes-related hyperglycaemia has been associated with a range of biochemical and structural changes affecting the vascular endothelial and smooth muscle cells. The long-term exposure to abnormal glycaemic levels exacerbates tissue oxidative stress, which leads to a decrease in the bioavailability of vasodilator agents (namely, nitric oxide), and furthers the build-up of extracellular matrix proteins and the cross-linking of inelastic collagen fibrils, thus causing the stiffening of vascular walls [6, 7]. Arterial stiffness is deemed an independent predictor of cardiovascular events and mortality both in the diabetic and in the general population [7, 8]. In this regard, aortic pulse wave velocity (PWV) represents the current gold standard for the clinical evaluation of vascular stiffening; a significant association between PWV, diabetes duration and related complications as retinopathy, nephropathy and autonomic neuropathy is consistently reported in the literature [7, 8]. However, subtle

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vascular alterations may anticipate clinically overt pathological features [9] and may thus serve as early predictors of the above detrimental complications.

The cardiovascular system can be considered as a network of coupled cardiac, respiratory and vascular oscillators. In this respect, wavelet phase coherence [10] and dynamical Bayesian inference [11] can be respectively applied in order to detect the presence of functional interactions between these physiological processes, and to characterize their mutual strength and causality. Through this methodological approach, a weakening of the cardio-respiratory coupling (i.e. the respiratory sinus arrhythmia) has been observed in elderly subjects [12, 13]. Furthermore, an impairment of the coordination between the cardiac and the myogenic microvascular dynamics has been reported in treated essential hypertension [14]. This result appears to indicate a pathological uncoupling of the oscillatory processes underlying the normal cardiovascular function, possibly due to a persistent deterioration of the local mechanisms regulating the microvascular perfusion or to an alteration of the mechanical properties of the vascular walls. In a recent study on healthy control subjects [15], a significant degree of phase coherence has been identified between the respiratory activity and the diastolic part of the digital LDF pulse wave, accurately modeled by means of a multi-Gaussian pulse decomposition algorithm, described in [16].

The investigation of vascular alterations in type I diabetic (T1D) patients is deemed particularly important, since these subjects are not often associated with multiple metabolic comorbidities [7]. Accordingly, the aim of this study was to assess the presence of the above phase coherence parameter in a preliminary group of T1D patients: the analysis of such relationship may, indeed, lead to the identification of a clinically valuable biomarker for the early detection and monitoring of diabetes-related microvascular dysfunction.

2 Materials and Methods

The present retrospective case-control study was conducted in accordance with the guidelines of the Declaration of Helsinki: accordingly, all the participants received exhaustive information on the purpose of the research and the related procedures, and signed an informed consent form before the measurement sessions. In detail, two age-matched ($p = 0.850$, Mann-Whitney U test) and gender-matched ($p = 0.533$, Pearson's χ^2 test) groups of 21 healthy subjects (age: 26.4 ± 3.0 years, M/F: 13/8) and 21 T1D patients were compared (age: 31.4 ± 15.5 years, M/F: 11/10).

A Periflux 5000 laser Doppler flowmetry (LDF) system (Perimed, Sweden) was used to record the cutaneous microvascular perfusion on the distal phalanx of the right index finger. Furthermore, the respiratory activity was simultaneously monitored by means of a BioHarness 3 physiological monitoring telemetry device (Zephyr Technologies, US). The above signals were digitized at 250 Hz and thoroughly synchronized with a custom data acquisition software. The sessions took place in controlled thermal conditions ($T \approx 23$), after a preliminary acclimatization time of ≈10 min had passed. The measurements lasted 5 min and were performed with the test subjects in sitting position and leaning the ipsilateral forearm on a table in order to minimize the risk of movement artefacts in the perfusion data. The LDF data of microvascular perfusion were processed with an original multi-Gaussian PDA, whose implementation is thoroughly covered in [16]. The algorithm is comprised of two main building blocks: a first detection stage, which addresses the automatic recognition of the separate cardiac cycles, and the identification of systolic, dicrotic, and diastolic reference points on the LDF pulse contour; and a second modeling stage, where each peripheral pulse waveform is accurately reconstructed by means of four Gaussian components. Afterwards, the PDA extracts the overall area beneath the diastolic phase of the pulse model, A_d, as shown in (Fig. 1). At this stage, a cubic spline-interpolation of the A_d values associated with each cardiac cycle was applied in order to match the sampling time-grid of the respiratory signals. In this regard, the centroid of the diastolic phase of the waveform models was adopted in order to locate the original sample points of the feature of interest.

The phase coherence analysis between the breathing oscillatory activity and the area under the diastolic pulse contour, A_d, followed the method outlined by Tankanag et al. in [17]. Accordingly, this parameter was computed as:

$$C_\phi(f_k) = \sqrt{\langle \cos(\Delta\phi_{k,n}) \rangle^2 + \langle \sin(\Delta\phi_{k,n}) \rangle^2}, \qquad (1)$$

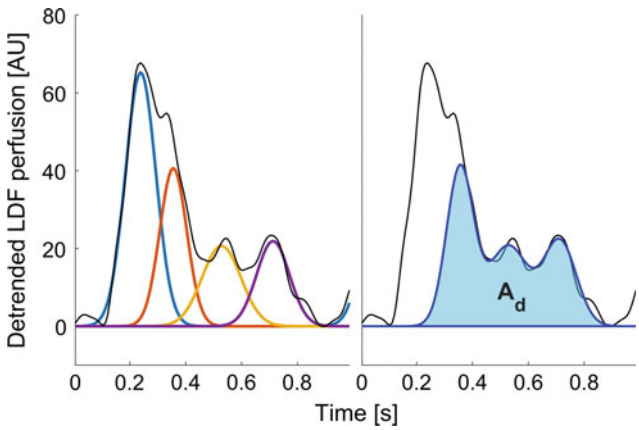

Fig. 1 Multi-Gaussian modeling of the LDF pulse and model-derived A_d feature

where $\Delta\phi_{k,n}$ is the phase lag between the components of the respiratory and A_d signals with characteristic frequency f_k at time t_n, and $\langle\cdot\rangle$ indicates time averaging. Theoretically, if two generic oscillations stay phase-locked (i.e. they are temporally coherent) throughout the analyzed time domain, then $C_\phi(f_k) = 1$; vice versa, the absence of any tendency toward the preservation of a particular phase difference would be reflected by $C_\phi(f_k) = 0$.

In this study, the extraction of the above instantaneous phase lag was performed through a wavelet transform analysis (WTA) of the breathing signal and the reconstructed time series of the resampled A_d feature; therefore, the term *wavelet phase coherence* (WPC) will be henceforth adopted. At each discrete time point, t_n, the average frequency in the nominal range of the respiratory activity, (0.145, 0.6)Hz, weighted with respect to the corresponding value of the wavelet PSD, was estimated so as to identify the instantaneous rate, f_b, of their breathing-related mode and, thus, extract the corresponding wavelet coefficients, $w_\star(t_n, f_b)$ as schematized in Fig. 2. In detail, the present WTA relied on the Morlet's mother wavelet, with central frequency $f_0 = 1$ Hz. 32 sample/octave were used to discretize the frequency axis, so as to trade-off between resolution and computational times. Moreover, only the *cone of influence* of the resulting wavelet scalograms, where the relative distortion due to boundary effects was below 1%, was considered for further analysis [18]. It is here relevant to recall how the resultant WPC values are significantly affected by the time scale of interest: WPC is, in fact, an inherently biased parameter, as it tends to increase towards the lower detectable frequencies due to the availability of fewer oscillation periods; furthermore, WPC might assume high values due to autocorrelation phenomena, even when the dynamics underlying the couple of assessed time series is actually unrelated. However, this potential source of unreliability can be accounted for by validating the $C_\phi(f_k)$ estimates against the phase coherence obtained between each original time series and a corresponding phase-randomized *surrogate* [19]. In this regard, the iterative amplitude-adjusted Fourier transform (IAAFT) method, described by Schreiber and Schmitz in [20], was applied so as to generate a set of N = 100 surrogates from each $b(t)$ and $A_d(t)$ signal, where N was selected for statistical repeatability. Afterwards, the corresponding N = 100 $C_{\phi,b,surr}(f_k)$ and $C_{\phi,A_d,surr}(f_k)$ surrogate functions were used to identify the following significance threshold:

$$T_{C_{\phi,\star,surr}}(f_k) = \overline{C}_{\phi,\star,surr}(f_k) + 2\cdot\sigma_{C_{\phi,\star,surr}}(f_k) \quad (2)$$

where $\overline{C}_{\phi,\star,surr}(f_k)$ indicates the mean WPC over the 100 surrogates, while $\sigma_{C_{\phi,\star,surr}}(f_k)$ represents its standard deviation. In detail, each assessed couple $(b(t), A_d(t))$ was considered as significantly phase-coherent at a specific frequency f_k, only if $C_{\phi,b,surr}(f_k) > T_{C_{\phi,\star,surr}}(f_k)$ held for both the breathing and A_d signals.

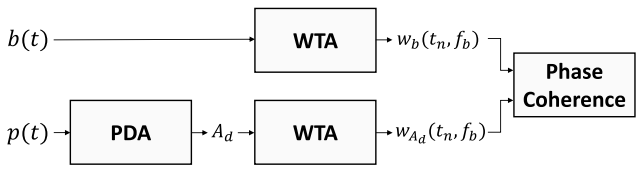

Fig. 2 Wavelet phase coherence analysis: block diagram

3 Results

In 17 out of the 21 control subjects (i.e. 81.0%), the WPC analysis identified a significant degree of phase coordination between the central breathing oscillatory process and the diastolic part of the digital LDF pulse wave (characterized by means of the area beneath its 3-Gaussian model, A_d). These significant cases were associated with a median value of the peak WPC in the nominal frequency range of the respiratory activity (0.145, 0.6)Hz of 0.78 (IQR: 0.20). Figure 3 shows a sample WPC curve obtained from one of these instances.

Conversely, the results obtained in the T1D group indicate a remarkable loss of synchronization, with significant WPC levels detected in only 8 of the 21 available cases (38.1%), for an overall median value of the peak respiratory

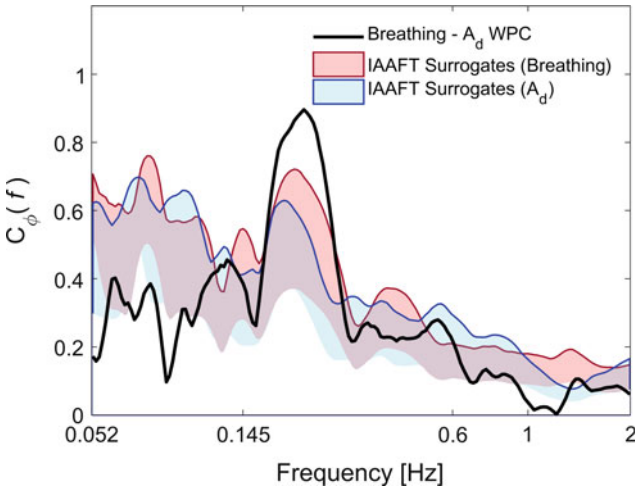

Fig. 3 Sample WPC curve between the breathing signal and the model-derived diastolic A_d feature. The upper thick colored lines depict the significance thresholds, $T_{C_{\phi,\star,surr}}(f_k)$, whereas the lower boundary of the shaded areas corresponds to the mean *surrogate* WPC

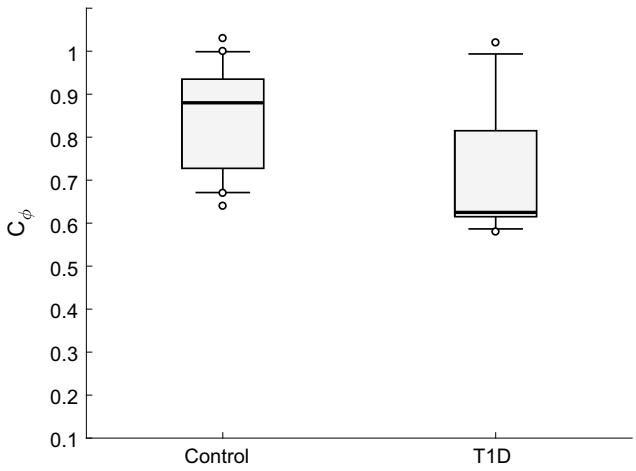

Fig. 4 Significant peak WPC values in the respiratory frequency range

Table 1 Wavelet phase coherence analysis: results

	A_d WPC	MEDIAN	IQR
Control	17/21 subjects	0.78	(0.63, 0.83)
T1D	8/21 subjects	0.53	(0.52, 0.67)

WPC of 0.53 (IQR: 0.15). The box plots of the significant WPC peaks inside the breathing frequency interval are shown in Fig. 4. Due to the non-normality of these data (preliminarily verified with the Shapiro-Wilk test), the non-parametric Mann-Whitney U test was applied to prove the statistical significance of this appreciable decrease in coherence ($p = 0.025$). Therefore, the outcome of the present study (summarized in Table 1) suggests that the proposed technique may be able to detect the subtle effects of T1D on the blood microcirculation.

Indeed, the decreased coupling highlighted in the pathological group might reflect the functional and structural vascular changes, mentioned concisely in the introductory section. However, a non-significant weaker phase coherence was nonetheless observed in 4 control subjects as well. These cases were associated with a significantly higher age (30 ± 2 years) with respect to the other healthy subjects (26 ± 3 years, $p = 0.013$): a possible effect of age would be consistent with the studies by Ticcinelli and Shiogai [13, 21], which have identified ageing as an important factor influencing the cardiovascular dynamics in healthy subjects; still, the small difference between the sample means and the low sample count preclude us from inferring a solid conclusion on this aspect.

4 Conclusion

The present study investigated the coordination between the rhythm of the breathing activity and the diastolic phase of digital LDF pulse waveforms in a group of T1D patients. Whereas a strong phase coherence with the *central* breathing function has been detected in a vast majority of the reference control subjects (81%), suggesting the presence of a physiological coupling with the microvascular perfusion, this coordination appears to be considerably weakened in the pathological group, which exhibited a significant degree of coherence only in 38.1% of the cases.

This outcome may reflect a possible subtle disruption of a breathing-related modulation of the secondary reflected waves, which arise in the circulatory tree due to the mismatch in the effective vascular impedance, encountered by the forward-travelling systolic pulse. Therefore, this study provides a preliminary indication of the suitability of the PDA-based A_d feature of the diastolic LDF pulse contour as a valuable non-invasive biomarker of T1D-related microvascular dysfunction.

Conflicts of Interest All authors have no conflict of interest to disclose in relation to the current work.

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