Journal of Biomedical Optics

BiomedicalOptics.SPIEDigitalLibrary.org

Quantifying the correlation between photoplethysmography and laser Doppler flowmetry microvascular low-frequency oscillations

Irina Mizeva
Costanzo Di Maria
Peter Frick
Sergey Podtaev
John Allen

SPIE.

Quantifying the correlation between photoplethysmography and laser Doppler flowmetry microvascular low-frequency oscillations

Irina Mizeva,[a] Costanzo Di Maria,[b,c,*] Peter Frick,[a] Sergey Podtaev,[a] and John Allen[b,c]
[a]Institute of Continuous Media Mechanics, ak Koroleva 1, Perm 614013, Russia
[b]Freeman Hospital, Regional Medical Physics Department, Microvascular Diagnostics Service, Newcastle upon Tyne, NE7 7DN, United Kingdom
[c]Newcastle University, Medical School, Institute of Cellular Medicine, Newcastle upon Tyne, NE2 4HH, United Kingdom

Abstract. Photoplethysmography (PPG) and laser Doppler flowmetry (LDF) are two recognized optical techniques that can track low-frequency perfusion changes in microcirculation. The aim of this study was to determine, in healthy subjects, the correlation between the techniques for specific low-frequency bands previously defined for microcirculation. Twelve healthy male subjects (age range 18 to 50 years) were studied, with PPG and LDF signals recorded for 20 min from their right and left index (PPG) and middle (LDF) fingers. Wavelet analysis comprised dividing the low-frequency integral wavelet spectrum (IWS) into five established physiological bands relating to cardiac, respiratory, myogenic, neurogenic, and endothelial activities. The correlation between PPG and LDF was quantified using wavelet correlation analysis and Spearman correlation analysis of the median IWS amplitude. The median wavelet correlation between signals (right-left side average) was 0.45 (cardiac), 0.49 (respiratory), 0.86 (myogenic), 0.91 (neurogenic), and 0.91 (endothelial). The correlation of IWS amplitude values (right-left side average) was statistically significant for the cardiac ($\rho = 0.64$, $p < 0.05$) and endothelial ($\rho = 0.62$, $p < 0.05$) bands. This pilot study has shown good correlation between PPG and LDF for specific physiological frequency bands. In particular, the results suggest that PPG has the potential to be a low-cost replacement for LDF for endothelial activity assessments. [DOI: 10.1117/1.JBO.20.3.037007]

Keywords: low-frequency oscillations; photoplethysmography; laser Doppler flowmetry; microcirculation; wavelet analysis.
Paper 140701RR received Oct. 24, 2014; accepted for publication Feb. 11, 2015; published online Mar. 12, 2015.

1 Introduction

The study of skin microcirculation is receiving increasing interest as recent studies have suggested that it may mirror other systemic vascular conditions.[1] Two of the main technologies that can be used to study microcirculation are laser Doppler flowmetry (LDF) and photoplethysmography (PPG).[2] The frequency characteristics of these physiological signals can be investigated using standard Fourier-based joint time-frequency analysis methods. For the analysis of signals with dynamic and irregular changes, an approach based on wavelet analysis (WA)[3] is more appropriate; this can provide a higher time resolution giving a smoother frequency spectrum (Fig. 1) and reducing artifacts.[4] Furthermore, WA does not require the signals to be stationary and it is, therefore, more widely applicable.

The use of WA has been investigated in various biomedical applications including for the analysis of the electrocardiogram.[5] Other groups have also extensively applied WA to LDF signals, demonstrating that the study of LDF low-frequency oscillations in different frequency bands can provide valuable information relative to cardiac, respiratory, myogenic, neurogenic, and endothelial activities. For example, Rossi et al.[6] demonstrated that LDF blood flow low-frequency oscillations were increased in patients with hypertension compared with normal controls and that this difference disappeared after the patients followed an average of 8-weeks hypertensive treatment. A study by Ažman-Juvan et al.[7] showed a reduction of LDF blood flow oscillatory components in patients with acute myocardial infarction as compared with healthy controls. They also showed that this reduction was more apparent in patients without reperfusion. General anesthesia was shown to reduce the amplitude of the frequency bands representative of sympathetic, myogenic, and endothelial activities.[8] The content of these frequency bands has also been demonstrated to change after physical exercise[9] and, in particular, the amplitude of the endothelial activity band was found to be increased in athletes as compared with less trained individuals.[10] Another recent study by Li et al.[11] has applied a similar method for studying prefrontal near-infrared spectroscopy signals. However, this approach has not been investigated in finger PPG signals yet.

Time-domain analysis of PPG signals has shown promising results in a variety of medical applications including detection of peripheral arterial disease,[12] the assessment of autonomic function in primary biliary cirrhosis[13] and chronic fatigue syndrome,[14] arterial aging,[15,16] and the assessment of cardiovascular functions in systemic sclerosis.[17] Our group has also demonstrated the possibility to use WA to analyze PPG signals for the quantification of cardiovascular changes in response to a deep inspiratory gasp.[18] PPG can be significantly less expensive than LDF and the technology is less sensitive to movement artifacts. Furthermore, PPG measurement systems can be

*Address all correspondence to: Costanzo Di Maria, E-mail: costanzo.dimaria@nuth.nhs.uk

1083-3668/2015/$25.00 © 2015 SPIE

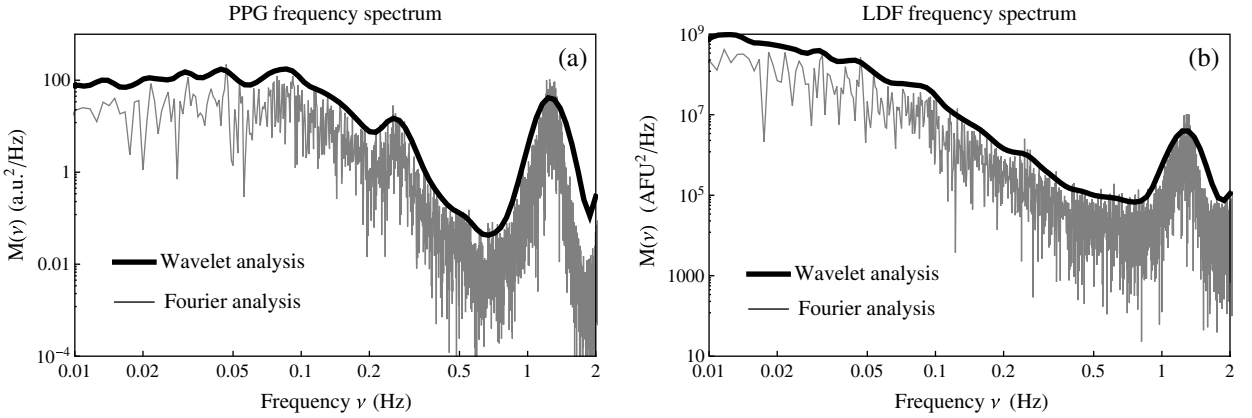

Fig. 1 Comparison of the frequency spectrum as calculated using Fourier analysis and wavelet analysis (WA) for (a) PPG and (b) LDF signals. Notice that the spectrum produced by WA is much smoother than the one obtained with Fourier analysis. Key: a.u., arbitrary units; AFU, arbitrary flux units.

miniaturized and made highly portable. Therefore, it is of interest to explore whether or not PPG low-frequency oscillations can provide useful clinical information similar to LDFs.

The aim of this study was to characterize the correlation between PPG and LDF signals in the five physiological low-frequency bands in a group of healthy adult subjects. The correlation was quantified using two different possible approaches: (1) wavelet correlation analysis, and (2) correlation analysis of the amplitude of the integral wavelet spectrum (IWS).

2 Methods

2.1 *Subjects*

Twelve healthy adult male subjects who were not on medication and who had no known history of cardiovascular disease were entered into this pilot study. All were nonsmokers. Their median age was 35 years and was within the range 18 to 50 years. This was a noninterventional and noninvasive study. All subjects gave their informed consent prior to the test.

2.2 *Measurement System*

2.2.1 *Photoplethysmography*

Bilateral PPG waveforms were measured using reflection-mode pulse pick-up probes (type 75333-5, Artema, Denmark) attached to the tissue pulp of the right and left index fingers.[19] A pair of purpose-built PPG amplifiers boosted the pulse waveforms to maximize the dynamic range of the recording system.

2.2.2 *Laser Doppler flowmetry*

A dual-channel MoorLAB LDF system (Moor Instruments Ltd., Axminster, UK) recorded the microvascular blood flux signals at the near-infrared wavelength of 780 nm. Moor Instruments MP1/7-V2 optical probes were utilized, consisting of one central transmission fiber and eight receiving fibers equally spaced within a surrounding 2-mm diameter ring. The LDF probes were attached to the pulp of the right and left middle fingers using a double-sided adhesive disc, and each LDF channel was standardized prior to the start of the study against the manufacturer's motility standard of a suspension of polystyrene microspheres in water. The LDF bandwidth limit was set to 15 kHz, and the analog outputs from the MoorLAB equipment were set with a low-pass filter with a time constant at 0.02 s.

2.3 *Measurement Procedure*

We utilized one of our standard clinical microvascular measurement protocols. Measurements were made in a microvascular measurement facility at an ambient room temperature of 23.5 (±0.5)°C with relative humidity between 30% and 50%. Subjects rested in a supine position and acclimatized in the measurement environment for at least 10 min prior to their data collection. The analog outputs of the PPG and LDF systems were connected to a multichannel analog-to-digital converter (ADC); this allowed for the PPG and LDF signals to be recorded at the same time. The ADC captured each channel to a computer at a sampling rate of 2 kHz for 20 min with the subject in the supine position. Examples of LDF and PPG recordings are shown in Fig. 2. The analog output from the PPG system was left in arbitrary units (a.u.). The output voltage of the LDF system was multiplied by 100 in order to convert the signals to arbitrary flux units (AFU), according to the instructions of the manufacturer.

2.4 *Wavelet Analysis*

The wavelet transform $W_x(\nu,\tau)$ of a signal $x(t)$ is defined in terms of an appropriate mother wavelet $\psi(t)$ as given in Eq. (1):

$$W_x(\nu,\tau) = \sqrt{\nu}\int_{-\infty}^{\infty} x(t)\psi*[\nu(t-\tau)]\mathrm{d}t, \tag{1}$$

where t is the time; τ is the time shift of the wavelet which can take any real value; ν is the oscillation frequency which can be any positive real number; and the symbol * indicates the operator of complex conjugation. The mother wavelet utilized in this study was the complex Morlet wavelet[20] [Eq. (2)]:

$$\psi(t) = e^{2\pi i t}e^{-t^2/2\sigma^2}. \tag{2}$$

The IWS was calculated by integrating the squared absolute value of the wavelet transform over a period T, as described by Eq. (3):

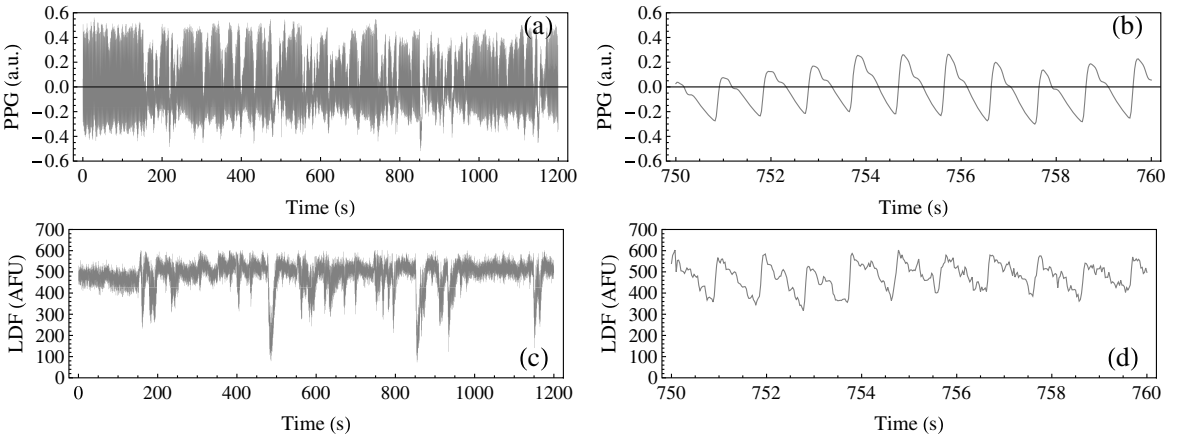

Fig. 2 Example signals: (a) full length 20-min PPG recording, and (b) 10-s excerpt PPG recording; (c) full-length 20-min LDF recording, and (d) 10-s excerpt LDF recording. All four plots are from the same recording of the same subject. Key: a.u., arbitrary units; AFU, arbitrary flux units.

$$M(\nu) = \frac{1}{T}\int_0^T |W_x(\nu,\tau)|^2 \mathrm{d}\tau. \quad (3)$$

The correlation $C_{xy}(\nu)$ between two signals $x(t)$ and $y(t)$ was also defined in terms of their wavelet transforms using Eq. (4).[21] This approach allowed the correlation between the two signals to be estimated separately for each frequency ν:

$$C_{xy}(\nu) = \frac{\int_0^T W_x(\nu,\tau)W_y^*(\nu,\tau)\mathrm{d}\tau}{\sqrt{\int_0^T |W_x(\nu,\tau)|^2\mathrm{d}\tau \int_0^T |W_y(\nu,\tau)|^2\mathrm{d}\tau}}. \quad (4)$$

The absolute value of $C_{xy}(\nu)$ is limited to the interval [0,1] and represents the strength of the correlation of the oscillations at frequency ν. The decay parameter σ plays an important role in the calculation of the wavelet correlation function (Fig. 3). Lower values of σ make it possible to obtain a smoother waveform with a sensible quantification of the correlation at the different frequencies. When the value of σ increases, the absolute value of $C_{xy}(\nu)$ becomes less and less smooth and rapid changes start to appear, which are more likely to be caused by computational artifacts rather than a real effect. In the limited case of $\sigma = \infty$, the wavelet correlation is equivalent to the function that would be obtained using Fourier analysis and the modulus of $C_{xy}(\nu)$ becomes a constant equal to 1 for any ν, without providing any significant information. In this study, we set the parameter σ to the value 1 for wavelet correlation analysis.

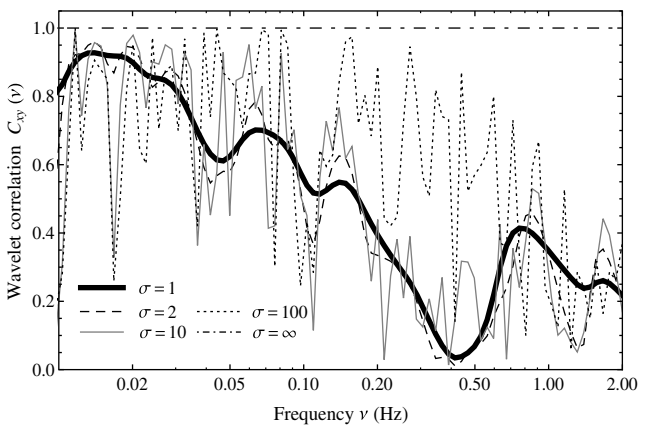

Fig. 3 Wavelet correlation $C_{xy}(\nu)$ between PPG and LDF signals. The results are shown for different values of the parameter σ of the Morlet mother wavelet. The value $\sigma = 1$ (used in our study) gave the smoothest correlation; the value $\sigma = \infty$ gives a constant correlation of 1, equating to the case when Fourier correlation is used.

2.4.1 *Definition of low-frequency physiological bands*

The low-frequency part of the wavelet spectrum was divided into five bands attributed to different physiological aspects: band I (0.6 to 2 Hz) representing cardiac activity; band II (0.145 to 0.6 Hz) representing respiratory activity; band III (0.052 to 0.145 Hz) representing myogenic activity; band IV (0.021 to 0.052 Hz) representing neurogenic activity; and band V (0.0095 to 0.021 Hz) representing endothelial activity.[7]

2.4.2 *Wavelet correlation analysis*

The wavelet correlation function [Eq. (4)] was utilized to quantify the similarity between right and left body sites separately for PPG and LDF signals and between PPG and LDF signals at the same body site separately (and also with right and left sides averaged) in the different frequency bands. Higher values of the wavelet correlation function indicate higher synchronicity between the two signals at a given frequency, independent from their possible difference in amplitude.

2.4.3 *Integral wavelet spectrum*

The amplitude of the IWS [Eq. (3)] was quantified for both PPG and LDF signals as the median value in each physiological frequency band, separately for each body site and also for the right-left average.

2.5 *Software and Statistical Analysis*

WA and all signal processing were performed in Mathematica 7 (Wolfram, Hanborough, UK). Data and statistical analyses were performed using R version 3.0.2 and the RStudio environment version 0.98.501.

Data were summarized using nonparametric statistics and the median (first quartile Q_1 to third quartile Q_3). Correlation ρ

between PPG and LDF in the amplitude of their wavelet spectrum was assessed using nonparametric Spearman correlation analysis, with a p-value less than 0.05 indicating statistical significance.

3 Results

3.1 *Wavelet Correlation Analysis*

The median IWS across all 12 subjects is shown in Fig. 4. Figure 5 shows the modulus of the wavelet correlation function across the different low-frequency bands. The median wavelet correlation between PPG and LDF signals (when right and left hands were averaged) was 0.45 for the cardiac activity, 0.49 for the respiratory activity, 0.86 for the myogenic activity, 0.91 for the neurogenic activity, and 0.91 for the endothelial activity. Right-to-left correlation of the PPG and LDF signals and single-site PPG-LDF wavelet correlations are also given in Table 1.

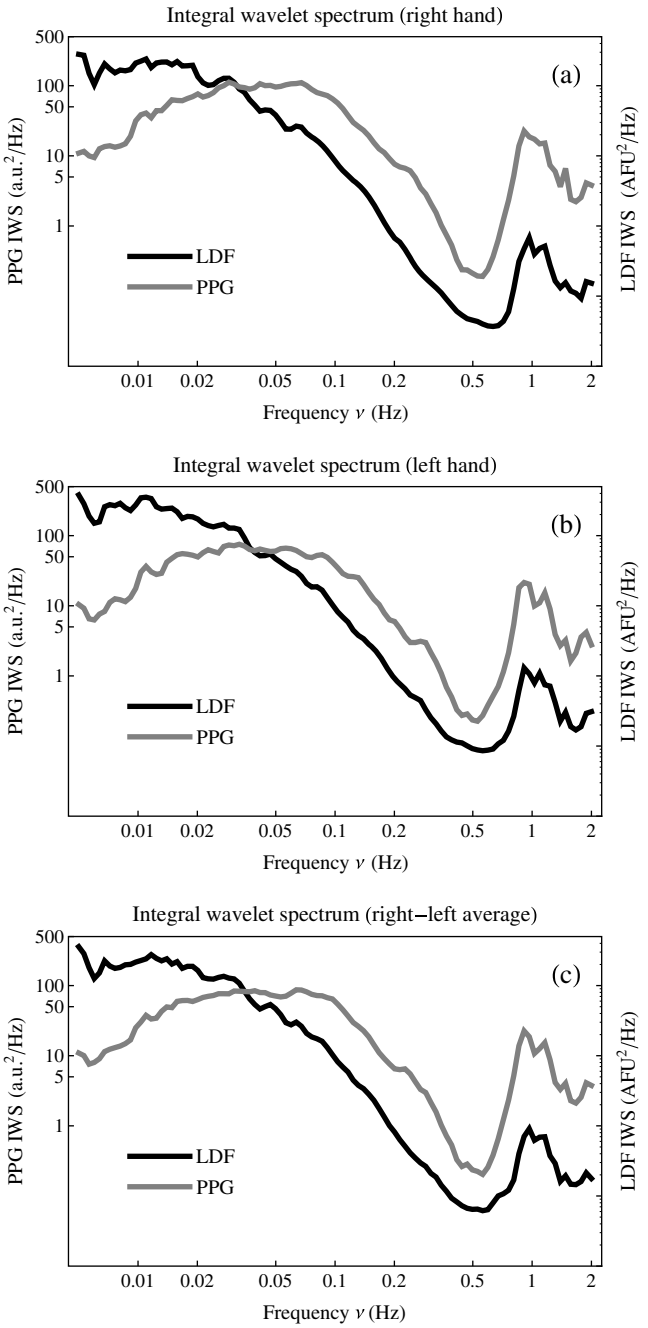

Fig. 4 Median integral wavelet spectrum (IWS) across all 12 subjects for both PPG and LDF signals. The IWS for LDF signals has been divided by a factor 10^6 in order to report it in a scale comparable with PPG. Subplot (a) is for the right hand; (b) is for the left hand; and (c) is for right and left hands averaged. Key: a.u., arbitrary units; AFU, arbitrary flux units.

3.2 *Integral Wavelet Spectrum*

The median IWS amplitude across the 12 subjects for the right-left averaged PPG signals was 21.0 a.u.^{2}/Hz for the cardiac activity band, 6.2 a.u.^{2}/Hz for the respiratory activity band, 57.6 a.u.^{2}/Hz for the myogenic activity band, 73.3 a.u.^{2}/Hz for the neurogenic activity band, and 49.3 a.u.^{2}/Hz for the endothelial activity. Separate values for each body site and also in comparison with LDF signals are given in Table 2. The correlation of IWS amplitude values (right and left sides averaged) between PPG and LDF was statistically significant for the cardiac activity ($\rho = 0.64$, $p < 0.05$) and the endothelial activity ($\rho = 0.62$, $p < 0.05$) bands. The results from Spearman correlation analysis for the other frequency bands, and also separately for each body site, are provided in Table 3 for completeness.

4 Discussion

In this pilot study, we have assessed the correlation between PPG and LDF signals in the low-frequency range using wavelet correlation analysis and Spearman correlation analysis of the IWS amplitude. Measurements were performed in a temperature- and humidity-controlled facility and following a rigorous preparation protocol, which standardized the measurement conditions across subjects. Correlations and IWS amplitudes were characterized in a group of healthy adult males and this has provided reference normative values for future studies. The low-frequency range 0.005 to 2 Hz was subdivided into five bands which are representative of different physiological activities, namely cardiac activity (band I, 0.6 to 2 Hz), respiratory activity (band II, 0.145 to 0.6 Hz), myogenic activity (band III, 0.052 to 0.145 Hz), neurogenic activity (band IV, 0.021 to 0.052 Hz), and endothelial activity (band V, 0.0095 to 0.021 Hz).[7] Wavelet correlation [Eq. (4)] was utilized to investigate the correlation of entire waveforms in the various bands. Spearman correlation analysis was utilized to assess the correlation of the amplitude of the IWS in the different bands.

Previous studies showed the possible clinical value of the information contained in these five low-frequency bands using WA of LDF forearm signals.[6–10] Other studies utilized an approach based on traditional Fourier analysis[22] and also showed promising results. The approach based on WA, however, is more widely applicable—as it does not require the signals to be stationary, it reduces the effect of possible computational artifacts, and it is, in general, less sensitive to noise. Therefore, in this work we preferred to utilize WA. Based on our previous work,[18] we used the complex Morlet mother wavelet [Eq. (2)] to perform the wavelet transform. The parameter σ was set to the value of 1 to perform wavelet correlation analysis. This setting allowed minimizing the effect of computational artifacts on the wavelet correlation function.

Wavelet correlation analysis demonstrated high correlation between right and left sites for PPG signals in all five frequency bands. For LDF signals, the right-left correlation was also high in band III (myogenic activity), band IV (neurogenic activity), and band V (endothelial activity). However, it was lower for the

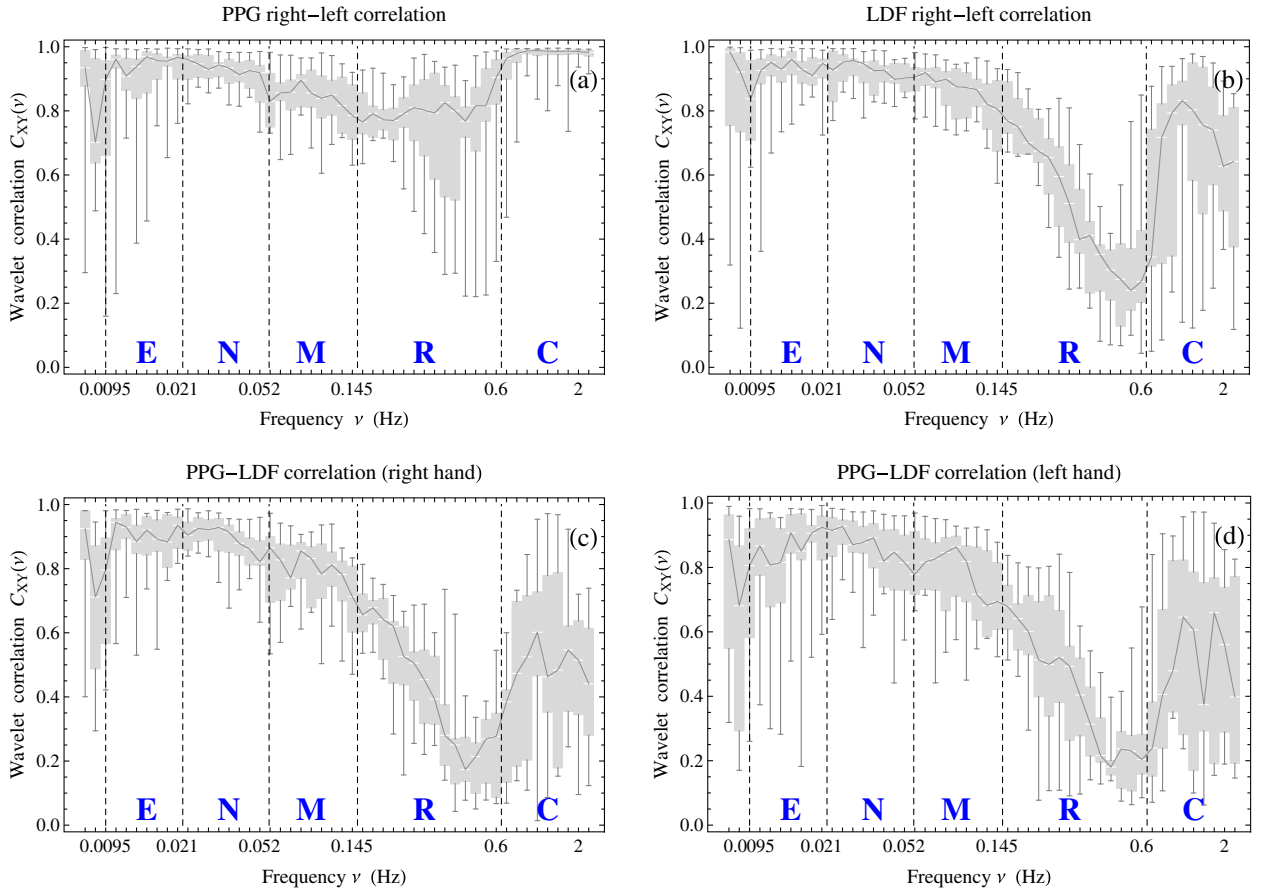

Fig. 5 Box-whisker plot for the absolute value of wavelet correlation for (a) bilateral PPG, (b) bilateral LDF, (c) PPG-LDF at the right hand, and (d) PPG-LDF at the left hand. Each box represents the central 50% of the data; whiskers extend to the entire range of the data. The frequency ranges for the five physiological bands are also highlighted: endothelial (E), neurogenic (N), myogenic (M), respiratory (R), and cardiac (C).

cardiac and respiratory activity bands (Table 1) and this may be attributed in part to a higher sensitivity to noise and movement artifacts of LDF at these frequencies. The wavelet correlation between PPG and LDF signals was high in bands III, IV, and V at both the right and left body sites (Table 1); however, this correlation decreased to below 0.5 in bands I and II and this again was possibly because of the higher sensitivity of LDF to noise in these bands.

Spearman correlation analysis for the right-left averaged spectral amplitudes showed a statistically significant correlation ($p < 0.05$) between PPG and LDF in the cardiac ($\rho = 0.64$) and endothelial ($\rho = 0.62$) bands. The correlation in the myogenic

Table 1 Values of wavelet correlation between pairs of photoplethysmography (PPG) and laser Doppler flowmetry (LDF) signals for the five physiological frequency bands. The results are reported as median (first quartile to third quartile) across the 12 subjects. PPG_r is the PPG signal taken from the right hand; PPG_l is the PPG signal taken from the left hand; LDF_r is the LDF signal taken from the right hand; LDF_l is the LDF signal taken from the left hand; PPG_{avg} is the average PPG signal from the right and left hands; LDF_{avg} is the average LDF signal from the right and left hands.

	Cardiac	Respiratory	Myogenic	Neurogenic	Endothelial
PPG_r-PPG_l	0.98 (0.95 to 0.99)	0.80 (0.71 to 0.87)	0.87 (0.80 to 0.92)	0.94 (0.90 to 0.97)	0.95 (0.89 to 0.98)
LDF_r-LDF_l	0.71 (0.37 to 0.85)	0.60 (0.38 to 0.74)	0.89 (0.82 to 0.93)	0.93 (0.89 to 0.96)	0.93 (0.89 to 0.97)
PPG_r-LDF_r	0.45 (0.28 to 0.67)	0.47 (0.33 to 0.63)	0.85 (0.65 to 0.85)	0.86 (0.74 to 0.93)	0.93 (0.89 to 0.96)
PPG_l-LDF_l	0.43 (0.24 to 0.68)	0.45 (0.27 to 0.61)	0.75 (0.84 to 0.70)	0.91 (0.87 to 0.94)	0.87 (0.74 to 0.94)
PPG_{avg}-LDF_{avg}	0.45 (0.26 to 0.70)	0.49 (0.29 to 0.67)	0.86 (0.78 to 0.92)	0.91 (0.85 to 0.95)	0.91 (0.81 to 0.95)

Table 2 Quantification of the integral wavelet spectrum (IWS) in each frequency band for both PPG and LDF at each body sites and for the right-left average. The results are reported as median (first quartile to third quartile) across the 12 subjects. PPG_l is the PPG signal taken from the right hand; PPG_l is the PPG signal taken from the left hand; LDF_r is the LDF signal taken from the right hand; LDF_l is the LDF signal taken from the left hand; PPG_{avg} is the average PPG signal from the right and left hands; LDF_{avg} is the average LDF signal from the right and left hands. a.u. is arbitrary units; AFU is arbitrary flux units.

	Cardiac	Respiratory	Myogenic	Neurogenic	Endothelial
PPG_r (a.u.^{2}/Hz)	19.5 (11.0 to 55.8)	7.3 (5.6 to 7.5)	75.1 (57.6 to 92.7)	96.9 (66.7 to 124.9)	49.5 (36.4 to 90.7)
PPG_l (a.u.^{2}/Hz)	19.7 (9.9 to 31.6)	5.3 (4.0 to 9.5)	50.2 (29.1 to 68.4)	70.0 (42.4 to 90.1)	41.5 (23.6 to 81.6)
PPG_{avg} (a.u.^{2}/Hz)	21.0 (9.5 to 39.8)	6.2 (5.2 to 8.6)	57.6 (45.5 to 84.5)	73.3 (63.5 to 102.5)	49.3 (32.2 to 83.2)
LDF_r (AFU^2/Hz) $\times 10^6$	0.9 (0.7 to 1.2)	0.6 (0.3 to 1.1)	12.1 (5.4 to 26.5)	81.3 (35.2 to 130.5)	199.7 (82.3 to 338.6)
LDF_l (AFU^2/Hz) $\times 10^6$	1.2 (1.0 to 1.7)	0.9 (0.6 to 1.5)	17.1 (6.3 to 37.3)	112.1 (49.3 to 173.8)	233.4 (116.1 to 574.2)
LDF_{avg} (AFU^2/Hz) $\times 10^6$	1.0 (0.8 to 1.3)	0.9 (0.5 to 1.1)	15.0 (5.8 to 30.0)	92.7 (45.2 to 152.0)	212.6 (108.3 to 446.6)

and neurogenic bands was medium ($\rho = 0.55$ and 0.50, respectively), but these did not reach statistical significance in this case. The correlation in the respiratory band was low ($\rho = 0.26$).

The results overall showed good correlation between PPG and LDF low-frequency oscillations and IWS amplitudes, especially in the three lowest bands related to myogenic, neurogenic, and endothelial activities. Interestingly, these findings are consistent with other results in the literature regarding the wavelet correlation between skin temperature and LDF which also reported good correlation in the myogenic, neurogenic, and endothelial frequency bands, but poor correlation for the other two higher frequency bands.[23] In this study, we have also characterized the amplitude of the IWS of PPG signals in the five low-frequency physiological bands (Table 2) and this has provided reference normative values that future studies can use for comparison with different healthy populations or different disease groups. For example, a recent study by Li et al.[11] utilized wavelet coherence to study the right-left relationship of near-infrared spectroscopy signals acquired from the forehead. This study reported decreased right-left wavelet coherence in the band attributed to myogenic activity in a group of elderly subjects with hypertension as compared with an age-matched group of elderly normotensive subjects.

Table 3 Spearman ρ correlation coefficient between PPG and LDF IWS amplitudes in the five frequency bands across the 12 subjects. PPG_r is the PPG signal taken from the right hand; PPG_l is the PPG signal taken from the left hand; LDF_r is the LDF signal taken from the right hand; LDF_l is the LDF signal taken from the left hand; PPG_{avg} is the average PPG signal from the right and left hands; LDF_{avg} is the average LDF signal from the right and left hands.

	Cardiac	Respiratory	Myogenic	Neurogenic	Endothelial
PPG_r-LDF_r	0.48	0.12	0.59[a]	0.51	0.43
PPG_l-LDF_l	0.57	0.07	0.32	0.52	0.64[a]
PPG_{avg}-LDF_{avg}	0.64[a]	0.26	0.55	0.50	0.62[a]

[a]Correlation coefficient was statistically significant ($p < 0.05$).

Our research group has a specific interest in endothelial function and its assessment, and it is encouraging that the frequency analysis for PPG and LDF gives similar information in the published spectral ranges, ultimately enabling lower-cost PPG to be exploited for this purpose.

5 Conclusions

This pilot study has shown good correlation between the low-frequency oscillations of PPG and LDF signals at the finger, especially in the frequency bands corresponding to myogenic, neurogenic, and endothelial activities. The amplitude of the PPG spectrum in each low-frequency band has also been quantified in order to provide reference normative values.

Acknowledgments

Part of the work related to the data analysis was supported by the Russian Scientific Fund (project number 14-15-00809).

References

1. L. A. Holowatz, C. S. Thompson-Torgerson, and W. L. Kenney, "The human cutaneous circulation as a model of generalized microvascular function," *J. Appl. Physiol.* **105**, 370–372 (2008).
2. J. Allen, "Photoplethysmography and its application in clinical physiological measurement," *Physiol. Meas.* **28**, R1–R39 (2007).
3. M. Holschneider, *Wavelets: An Analysis Tool*, Clarendon, Oxford (1995).
4. M. Ajab, I. A. Taj, and N. A. Khan, "Comparative analysis of variants of Gabor-Wigner transform for cross-term reduction," *Metrol. Meas. Syst.* **19**(3), 499–508 (2012).
5. P. S. Addison, "Wavelet transforms and the ECG: a review," *Physiol. Meas.* **26**, R155–R199 (2005).
6. M. Rossi et al., "Investigation of skin vasoreactivity and blood flow oscillations in hypertensive patients: effect of short-term antihypertensive treatment," *J. Hypertens.* **29**, 1569–1576 (2011).
7. K. Ažman-Juvan et al., "Skin blood flow and its oscillatory components in patients with acute myocardial infarction," *J. Vasc. Res.* **45**, 164–172 (2008).
8. S. A. Landsverk et al., "The effects of general anesthesia on human skin microcirculation evaluated by wavelet transform," *Anesth. Analg.* **105**, 1012–1019 (2007).
9. H. D. Kvernmo et al., "Spectral analysis of the laser Doppler perfusion signal in human skin before and after exercise," *Microvasc. Res.* **56**, 173–182 (1998).
10. H. D. Kvernmo, A. Stefanovska, and K. A. Kirkebøen, "Enhanced endothelial activity reflected in cutaneous blood flow oscillations of athletes," *Eur. J. Appl. Physiol.* **90**, 16–22 (2003).

11. Z. Li et al., "Wavelet coherence analysis of prefrontal oxygenation signals in elderly subjects with hypertension," *Physiol. Meas.* **35**, 777–791 (2014).
12. J. Allen et al., "A prospective comparison of bilateral photoplethysmography versus the ankle-brachial pressure index for detecting and quantifying lower limb peripheral arterial disease," *J. Vasc. Surg.* **47**, 794–802 (2008).
13. S. Stevens et al., "Microvascular optical assessment confirms the presence of peripheral autonomic dysfunction in primary biliary cirrhosis," *Liver Int.* **29**, 1467–1472 (2009).
14. J. Allen et al., "Chronic fatigue syndrome and impaired peripheral pulse characteristics on orthostasis—a new potential diagnostic biomarker," *Physiol. Meas.* **33**, 231–241 (2012).
15. D. Zheng and A. Murray, "Peripheral arterial volume distensibility: significant differences with age and blood pressure measured using an applied external pressure," *Physiol. Meas.* **32**, 499–512 (2011).
16. C. Di Maria et al., "Feasibility of monitoring vascular ageing by multisite photoplethysmography," *Comput. Cardiol.* **39**, 817–820 (2012).
17. N. D. McKay et al., "Novel photoplethysmography cardiovascular assessments in patients with Raynaud's phenomenon and systemic sclerosis: a pilot study," *Rheumatology* **53**, 1855–1863 (2014).
18. J. Allen et al., "Finger microvascular responses to deep inspiratory gasp assessed and quantified using wavelet analysis," *Physiol. Meas.* **34**, 769–779 (2013).
19. J. Allen and A. Murray, "Variability of plethysmographic peripheral pulse measurement at the ears, thumbs and toes," *IEE Proc.: Sci. Meas. Technol.* **147**, 403–407 (2000).
20. P. Goupillaud, A. Grossman, and J. Morlet, "Cycle-octave and related transforms in seismic signal analysis," *Geoexploration* **23**, 85–102 (1984).
21. E. Nesme-Ribes et al., "Wavelet analysis of the Maunder minimum as recorded in solar diameter data," *C. R. Acad. Sci. Paris* **321**(12), 525–532 (1995).
22. M. Rossi et al., "Spectral analysis of laser Doppler skin blood flow oscillations in human essential arterial hypertension," *Microvasc. Res.* **72**, 34–41 (2006).
23. S. Podtaev, M. Morozov, and P. Frick, "Wavelet-based correlation of skin temperature and blood flow oscillations," *Cardiovasc. Eng.* **8**, 185–189 (2008).

Irina Mizeva graduated from Perm State University in 2003, where she also obtained her PhD degree in mechanics in 2008. In 2012, she joined the Biomedical Group led by Prof. P. Frick and Dr. S. Podtaev at the Institute of Continuous Media Mechanics, where she currently holds a research position. Her main research interests include signal processing, wavelet analysis, the experimental study of the human microcirculation system, and MHD turbulence.

Costanzo Di Maria is a research scientist with the Regional Medical Physics Department (RMPD) of The Newcastle upon Tyne Hospitals and a research associate with the Medical School, Newcastle University. His intense research activity within the microvascular service focuses on signal processing, image analysis, and data analysis for the development of novel clinical diagnostic tools, especially utilizing optical technologies for the study of microcirculation.

Peter Frick received his diploma degree in physics from the University of Perm (1974), and his PhD degree in physics and mathematics (1981), doctor of sciences (1991). Since 1992, he has been head of the Laboratory of Physical Hydrodynamic at the Institute of Continuous Media Mechanics, Perm, Russia, and full professor at Perm State University. His main research interests include turbulence, convection, magneto-hydrodynamics, and wavelet analysis.

Sergey Podtaev works with "Control Systems Ltd," Russia—a company that specializes in the manufacture of electronic equipment for industry. He is the head of the Department of New Developments and Innovations. In 2007, he started to work on the development of new approaches in medical diagnostics. His areas of expertise include high-precision temperature measurements, low-amplitude skin temperature, and microvascular dysfunction.

John Allen is lead clinical scientist and founder of Freeman Hospital's Microvascular Diagnostics service. His key application areas include assessments in connective tissue disease, diabetes, and cardiovascular disease. He is also an honorary clinical senior lecturer with Newcastle University, publishing more than 50 peer reviewed papers and securing significant research grant and infrastructure funding relating to vascular optics. He is an accredited senior imaging scientist and fellow of The Royal Photographic Society (ASIS FRPS).