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Analysis of microvascular blood flow and oxygenation: Discrimination between two haemodynamic steady states using nonlinear measures and multiscale analysis

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ABSTRACT

Objective: This study investigates the feasibility of the use of nonlinear complexity methods as a tool to identify altered microvascular function often associated with pathological conditions. We evaluate the efficacy of multiscale nonlinear complexity methods to account for the multiple time-scales of processes modulating microvascular network perfusion.

Methods: Microvascular blood flux (BF) and oxygenation (OXY: oxyHb, deoxyHb, totalHb and SO_2%) signals were recorded simultaneously at the same site, from the skin of 15 healthy young male volunteers using combined laser Doppler fluximetry (LDF) and white light spectroscopy. Skin temperature was clamped at 33 °C prior to warming to 43 °C to generate a local thermal hyperaemia (LTH). Conventional and multiscale variants of sample entropy (SampEn) were used to quantify signal regularity and Lempel and Ziv (LZ) and effort to compress (ETC) to determine complexity.

Results: SampEn showed a decrease in entropy during LTH in BF ($p = 0.007$) and oxygenated haemoglobin (oxyHb) ($p = 0.029$). Complexity analysis using LZ and ETC also showed a significant reduction in complexity of BF (LZ, $p = 0.003$; ETC, $p = 0.002$) and oxyHb ($p < 0.001$, for both) with LTH. Multiscale complexity methods were better able to discriminate between haemodynamic states ($p < 0.001$) than conventional ones over multiple time-scales.

Conclusion: Our findings show that there is a good discrimination in complexity of both BF and oxyHb signals between two haemodynamic steady states which is consistent across multiple scales.

Significance: Complexity-based and multiscale-based analysis of BF and OXY signals can identify different microvascular functional states and thus has potential for clinical application in the prognosis and the diagnosis of pathophysiological conditions such as microvascular dysfunction observed in non-alcoholic fatty liver disease and type 2 diabetes.

1. Introduction

The maintenance of an adequate blood flow through a microvascular network, sufficient to meet the metabolic demands of the tissue, is dependent on local endothelial, metabolic, myogenic and neural vaso-mechanisms that determine vascular tone and thus temporal and spatial flow patterns within the network [1]. Recently, Frisbee et al. [2] have shown attenuation of these flow patterns using chaotic network attractor analysis in an animal model of cardio-metabolic disease. They have argued that the consequent loss of physiological information content may contribute to disease risk [3,4].

Time and frequency domain analysis and the contribution of spectral properties in frequency domains are the techniques most frequently applied to biosignals [5–7], including those derived from blood flow through the superficial dermal microvasculature [8–10]. The frequency and power of local oscillations that contribute to the total blood flow motion have been studied by many research groups [8,11,12]. They contain the cardiac (~0.6–1.6 Hz) and respiratory (~0.15–0.4 Hz) activity followed by oscillations arising from local myogenic vasomotor activity (~0.06–0.15 Hz). Two additional components that occur in lower frequencies are the neurogenic (~0.02–0.06 Hz) and endothelial (~0.0095–0.02 Hz) activity. It has been widely argued that time frequency analysis of the low frequency periodic oscillations in microvascular blood flux (BF) signals obtained

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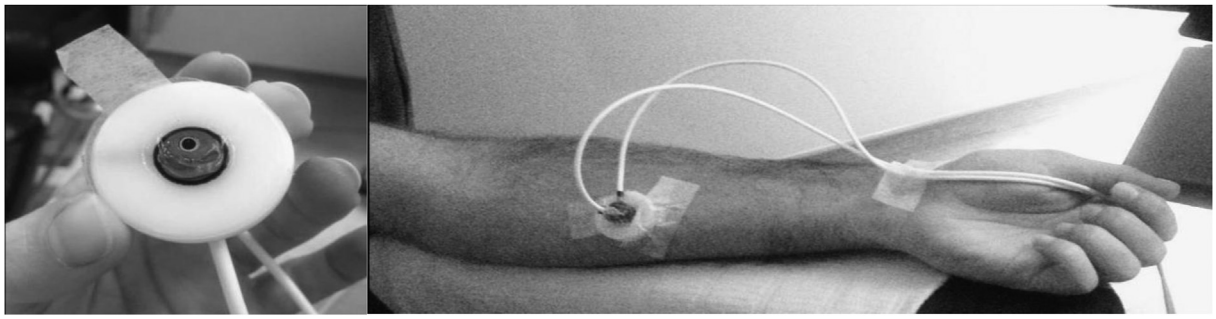

Fig. 1. The combined LDF and WLS probe inserted into a heating disc (left) and attached to the skin (right).

using for example laser Doppler fluximetry (LDF) can provide non-invasive, mechanistic information on microvascular control [8,13].

The regularity and the randomness of physiological signals has been explored using nonlinear methods such as entropy and complexity techniques, respectively, which are well suited for the analysis of short length signals such as ECG and respiratory flow signals [9,14–17]. Lempel-Ziv (LZ) complexity analysis has been applied to skin microvascular BF signals in humans [10] and in animal models [9,18], in differing haemodynamic states. These studies have demonstrated clear differences in LZ complexity between haemodynamic states. However, the relationship between the nonlinear dynamics of the BF signal and their impact on microvascular function remain to be clarified and the potential for complexity analysis as a diagnostic tool determined.

Conventional nonlinear methods have the drawback that they can only study the behaviour at one scale. Multiscale entropy algorithms have been used to quantify the complexity of the biological signals across multiple spatial and temporal scales [14,19,20]. Multiscale entropy approaches have shown good discrimination between the cardiac signals of young, elderly and subjects with heart failure [3], and multiscale LZ complexity demonstrating an 86% classification accuracy of the information content in the EEG signals of control and depressive groups [21]. Further, wavelet transform and multiscale complexity analysis of temperature signals has been used to classify risk in patients with sepsis [22]. Together these studies evidence the potential for such approaches in the characterisation of the flexibility/responsiveness of the microvasculature, particularly in individuals at risk of developing or with cardio-metabolic disease.

In this study, our aim was to investigate the information content of BF and OXY signals derived from the microvasculature in two stable haemodynamic steady states: at rest with the local skin temperature clamped at 33 °C and during vasodilation induced through local thermal hyperaemia (LTH) at 43 °C, using both conventional and multiscale techniques. The local thermal warming skin test is routinely used in clinical applications to test dilator responses [23], as other perturbation techniques such as post-occlusive reactive hyperaemia do not induce an enduring state change which was required in this study to test the efficacy of the complexity methods. Here, we first explore the changes in complexity of the microcirculatory dynamics using conventional sample entropy (SampEn), LZ and effort to compress (ETC) complexity methods. To understand the effect of scale on these nonlinear metrics and their efficacy in classifying these haemodynamic steady states the multiscale sample entropy (MSE), multiscale Lempel and Ziv (MSLZ) complexity and multiscale effort to compress (METC) methods are then evaluated.

We hypothesise that complexity-based and multiscale-based analysis of blood flux and tissue oxygenation signals derived from the skin of healthy individuals under two imposed haemodynamic steady states will enable the characterisation of the flexibility/responsiveness of a microvascular network and thus has potential for clinical application in the prognosis and the diagnosis of pathophysiological conditions.

2. Materials and methods

2.1. Study design

The study was conducted on 15 healthy male participants, age 29.2 ± 8.1y (mean ± SD). All participants were asked to refrain from caffeine-containing drinks for at least two hours before the measurement and to avoid exercise on the day of study. None of the participants were taking any medications. All measurements were made in a temperature controlled room (23.0–23.5 °C) and all participants were acclimatized for at least 20 min before measurements were taken. Measurements were made with the participant sitting comfortably in a reclining blood infusion chair with their arm supported at heart level [10]. The study was approved by Research Ethics Committee of University of Southampton and Southampton General Hospital (REC Number: SOMSEC091.10; RHMMED0992). The study was performed in accordance with standards set by the Declaration of Helsinki. All participants gave informed written consent. All data supporting this study are openly available from the University of Southampton repository at http://doi.org/10.5258/SOTON/D0343.

2.2. Acquisition of laser Doppler and OXY signals

Skin microvascular BF and oxygenation (OXY) signals were recorded simultaneously using a combined laser Doppler flowmetry and white light reflectance probe (Moor CP7-1000 blunt needle probe, Moor Instruments Ltd, Axminster, UK) using a single point 785 nm, 1 mW low power red laser light source (moorVMS-LDF2, Moor Instruments Ltd, UK) and 400–700 nm, < 6 mW white light source (moorVMS-OXY, Moor Instruments Ltd, UK). The probe was mounted in a MoorVHP1 skin heating block controlled by the MoorVMS-HEAT skin heater. Skin temperature was measured by a miniaturised negative temperature coefficient thermistor built into the heating block controlling skin warming with a precision of ± 0.1 °C and resolution of 0.1 °C. As shown in Fig. 1 the heating block and probe were placed on the ventral surface of the non-dominant forearm using a double-sided sticky O-ring, approximately 10 cm from the wrist and avoiding visible veins.

The BF and OXY recordings were obtained in two haemodynamic steady states, with the heating block clamped at 33 °C and then at 43 °C during LTH. To study the signals during these steady states, the data were divided into segments of 10 min duration. All recordings were captured at a sampling rate of 40 Hz using the manufacturer's software (MoorSoft). Fig. 2 illustrates the BF, OXY and the temperature outputs of the combined LDF/OXY probe recorded and the selection of the 10 min segments marked as grey at 33 °C and at 43 °C, respectively. These segments were selected so as to minimise any transitional effects arising during warming and to be free of movement artefacts. Data were exported to Matlab (R2016b, Mathworks, UK) for pre-processing and analysis. The truncated data could then be analysed and calculations made for: (i) the entropy and the complexity analysis and (ii) the multiscale analysis. The parameters obtained were BF in perfusion units (PU), oxygenated haemoglobin (oxyHb), deoxygenated haemoglobin