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Processing of laser Doppler flowmetry signals from healthy subjects and patients with varicose veins: Information categorisation approach based on intrinsic mode functions and entropy computation

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ABSTRACT

The diagnosis of pathologies from signal processing approaches has shown to be of importance. This can provide noninvasive information at the earliest stage. In this work, the problem of categorising – in a quantifiable manner – information content of microvascular blood flow signals recorded in healthy participants and patients with varicose veins is addressed. For this purpose, laser Doppler flowmetry (LDF) signals – that reflect microvascular blood flow – recorded both at rest and after acetylcholine (ACh) stimulation (an endothelial-dependent vasodilator) are analyzed. Each signal is processed with the empirical mode decomposition (EMD) to obtain its intrinsic mode functions (IMFs). An entropy measure of each IMFs is then computed. The results show that IMFs of LDF signals have different complexity for different physiologic/pathological states. This is true both at rest and after ACh stimulation. Thus, the proposed framework (EMD + entropy computation) may be used to gain a noninvasive understanding of LDF signals in patients with microvascular dysfunctions.

1. Introduction

Signal processing algorithms can have interesting applications in the biomedical fields or related areas [1–6]. Some of them have been used to evaluate physical activity [7,8] with the aim to prevent or diagnose cardiovascular diseases. Signals from the cardiovascular system can be divided into two groups: one group corresponds to signals reflecting the *central* cardiovascular system while the other corresponds to signals coming from the *peripheral* cardiovascular system. Data from the central cardiovascular system, as heart rate variability data, have been the subjects of many signal processing works [9–11]. By opposition, signals from the peripheral cardiovascular system are much less studied while they are of major interest for the understanding or diagnosis of pathologies such as diabetes, burns, flaps, wounds or endothelial dysfunction [12–14]. Endothelial dysfunction (inner vein lining dysfunction) of the small veins can lead to elongated and tortuous small veins (varicose veins), which is the first stage of chronic venous insufficiency (CVI). CVI can cause pain, restriction of work and leisure activities, impaired mobility and social isolation significantly affecting patients' quality of life, having venous ulceration as one of its major complications [15]. Endothelial dysfunction can be studied using the laser Doppler flowmetry (LDF) technique and a transcutaneous administration of acetylcholine (ACh) which is an endothelial-dependent vasodilator [16,17].

LDF is an established technique for a noninvasive monitoring of microvascular blood perfusion in tissue [18–20]. In LDF, the tissue under study (skin for example) is illuminated with a low–power laser light through a probe containing optical fiber light guides. In this probe one optical fiber leads the light to the tissue and another one collects the backscattered light and transmits it to a photodetector. LDF relies on the Doppler frequency shifts that appear when light is scattered by moving blood cells in the tissue. Thus, the power spectrum $P(x)$ of the photocurrent is linked to the blood cells properties present in the illuminated volume. More precisely, when the concentration of moving red blood cells is low, the first moment $\int \omega P(\omega) d\omega$ scales with the concentration of moving blood cells times their average velocity. This first moment corresponds to the LDF perfusion signals [19]; see examples in Fig. 1. Deciphering information contained in LDF signals to quantitatively evaluate the evolution of microvascular blood perfusion becomes a major scientific objective in research endeavors.

Physiologic signals, such as LDF signals, contain complex fluctuations that reflect underlying mechanisms. The analysis of the dynamical structures of these physiologic signals are of clinical interest for early diagnosis or follow-up of many pathologies [21–24].

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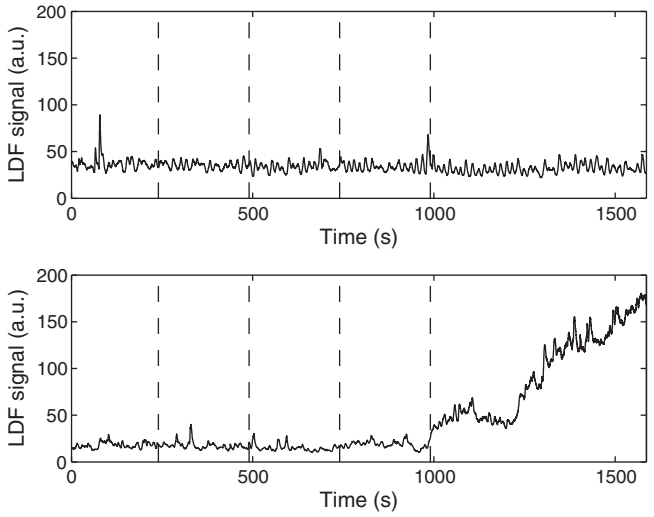

Fig. 1. Laser Doppler flowmetry (LDF) signals recorded on the leg of (a) a patient with varicose veins, (b) a healthy participant. The dotted lines correspond to the beginning of the four periods of acetylcholine stimulations by iontophoresis (see the text for details).

Our goal herein is to study if LDF signals recorded in healthy participants and patients with varicose veins present different dynamical patterns that could help in better understanding the signals themselves. For this purpose, we propose to use the empirical mode decomposition (EMD) to extract information present in the signal. EMD is a local and adaptive method that leads to intrinsic mode functions (IMFs). IMFs reveal intrinsic patterns, trends and noise. Then, for each IMF, we compute sample entropy as a descriptor related to the signal complexity. This is performed in LDF signals recorded in healthy participants and patients with varicose veins, both at rest and after ACh stimulation.

2. Proposed framework: principle and algorithm

The framework that we propose to process LDF signals is composed of two steps: (1) empirical mode decomposition of data. This first step leads to IMFs that reveal the signal patterns at different frequency bands; (2) computation of sample entropy for each IMF.

2.1. Empirical mode decomposition

EMD has been used in many fields, including biomedical [1,25]. One of the advantages of EMD is that it decomposes non stationary and nonlinear signals without requiring any *a priori* basis functions or tuning. EMD decomposes a signal into an additive set of components (IMFs). The latter reveal intrinsic patterns, trends and noise. An IMF satisfies two conditions [26]: (1) it contains the same number of extrema and zero crossings (or differ at most by one); (2) the two envelopes of an IMF (envelopes defined by its local maxima and local minima) are symmetric with respect to zero. As a result, IMFs are functions that convey the frequency and amplitude modulations. The algorithm of EMD is defined iteratively and each IMF is extracted step-by-step using a sifting process as [26]

1. (Sifting process): For a signal $X = h_0$ to process, the local maxima and minima are determined. Then, m_0 is defined as the mean of the upper and lower envelopes computed from a cubic–spline interpolation.
2. m_0 is removed from the signal, giving a first component: $h_1 = h_0 - m_0$.
3. The sifting process is iterated: h_1 takes the place of h_0. As above, a new local mean m_1 is computed and $h_2 = h_1 - m_1$.
4. The procedure is repeated k times until $h_k = h_{k-1} - m_{k-1}$ is an IMF according to the two conditions above.
5. This first IMF is designated as $c_1 = h_k$. c_1 contains the components with the highest frequencies. It is then removed from the signal as $r_1 = X - c_1$ where r_1 is a residual.
6. Steps 1–4 are repeated on the residual signal r_1 leading to IMFs c_j and residuals $r_j = r_{j-1} - c_j$, for j from 1 to n.
7. The process stops when residual r_n contains no more than three extrema.

The result of EMD is a set of IMFs c_i and the final residue r_n such as:

$$X = \sum_{i=1}^{n} c_i + r_n, \tag{1}$$

where r_n represents the trend of the original signal X. In all implementations we used the EMD toolbox available at: http://perso.ens-lyon.fr/patrick.flandrin/emd.html.

2.2. Sample entropy computation

Sample entropy (SampEn) is a modified version of approximate entropy (ApEn) [27]. ApEn gives a measure of regularity closely related to the Kolmogorov entropy [28,29]. However, ApEn depends on the time series length. Moreover, it lacks relative consistency [27]. To reduce these bias, the sample entropy has been proposed in 2000. Sample entropy is the negative natural logarithm of the conditional probability that two sequences similar for m points remain similar at the next point, where self-matches are not included in the calculation of the probability. Therefore, a lower value of sample entropy indicates more self-similarity in the time series. For the computation of sample entropy, three parameters have to be fixed: m, r, N. m is the length of sequences to be compared, r is the tolerance for accepting matches and N corresponds to the length of the time series under study: $\{u(j)\colon 1 \le j \le N\}$. First, let us define the $N - m + 1$ vectors $\mathbf{x}_m(i) = \{u(i+k) : 0 \le k \le m-1\}$ with $1 \le i \le N - m + 1$, as the vector of m data points from $u(i)$ to $u(i + m - 1)$. Sample entropy is then defined as follows [27]: $B_i^m(r)$ is first determined as $(N - m - 1)^{-1}$ times the number of vector $\mathbf{x}_m(j)$ within r of $\mathbf{x}_m(i)$, where j ranges from 1 to $N - m$ and $j \neq i$ to exclude self-matches. $B^m(r)$ is then defined as $(N-m)^{-1}\sum_{i=1}^{N-m} B_i^m(r)$. $B^m(r)$ is the probability that two sequences will match for m points. In the same way, $A_i^m(r)$ is defined as $(N - m - 1)^{-1}$ times the number of vector $\mathbf{x}_{m+1}(j)$ within r of $\mathbf{x}_{m+1}(i)$, where j ranges from 1 to $N - m$ ($j \neq i$). $A^m(r)$ is then defined as $(N-m)^{-1}\sum_{i=1}^{N-m} A_i^m(r)$. $A^m(r)$ is the probability that two sequences will match for $m + 1$ points. The sample entropy $SampEn(m, r)$ is then defined as $\lim_{N\to\infty}\{-\ln[A^m(r)/B^m(r)]\}$ which is estimated by the statistics $SampEn(m, r, N) = -\ln[A^m(r)/B^m(r)]$ [27].

3. Experiments

Seven healthy volunteers and seven patients with varicose veins (unilateral sapheno–femoral ligation and partial stripping) gave their written informed consent to participate in this study, which was approved by Southern Derbyshire NHS Ethics Committee.

All patients had isolated great saphenous vein reflux defined by duplex scanning. Similarly, for the healthy population the absence of isolated superficial venous incompetence was confirmed by duplex scanning. Participants with present or past venous ulceration, lower limb arterial disease, peripheral edema or cardiac failure, previous varicose vein history and those with major skin changes in the gaiter area were excluded.

Baseline assessments included measurements of height, weight and blood pressure. Following these, microvascular perfusion and ACh vasodilator responses in the gaiter area were measured under temperature-controlled conditions (23–24 °C) using a standard