Medical Physics Letter

Multiscale entropy of laser Doppler flowmetry signals in healthy human subjects

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Purpose: The cardiovascular system (CVS) regulation can be studied from a *central* viewpoint, through heart rate variability (HRV) data, and from a *peripheral* viewpoint, through laser Doppler flowmetry (LDF) signals. Both the central and peripheral CVSs are regulated by several interacting mechanisms, each having its own temporal scale. The central CVS has been the subject of many multiscale studies. By contrast, these studies at the level of the peripheral CVS are very recent. Among the multiscale studies performed on the central CVS data, multiscale entropy has been proven to give interesting physiological information for diagnostic purposes. However, no multiscale entropy analysis has been performed on LDF signals. The authors' goal is therefore to propose a first multiscale entropy study of LDF data recorded in healthy subjects.
Methods: The LDF signals recorded in the forearm of seven healthy subjects are processed. Their period sampling is $T=50$ ms, and coarse-graining scales from T to $23T$ are studied. Also, for validation, the algorithm is first tested on synthetic signals of known theoretical multiscale entropy.
Results: The results reveal nonmonotonic evolution of the multiscale entropy of LDF signals, with a maximum at small scales around $7T$ and a minimum at longer scales around $18T$, singling out in this way two distinctive scales where the LDF signals undergo specific changes from high to low complexity. This also marks a strong contrast with the HRV signals that usually display a monotonic increase in the evolution of the multiscale entropy.
Conclusions: Multiscale entropy of LDF signals in healthy subjects shows variation with scales. Moreover, as the variation pattern observed appears similar for all the tested signals, multiscale entropy could potentially be a useful stationary signature for LDF signals, which otherwise are probe-position and subject dependent. Further work could now be conducted to evaluate possible diagnostic purposes of the multiscale entropy of LDF signals. [DOI: 10.1118/1.3512796]

Key words: laser Doppler flowmetry, microcirculation, multiscale entropy

I. INTRODUCTION

The regulation of the cardiovascular system (CVS) can be studied from a *central* or from a *peripheral* point of view. A central viewpoint (at the heart itself) can be obtained with the heart rate variability (HRV) data. A peripheral viewpoint is given by laser Doppler flowmetry (LDF) signals.[1–6] The LDF technique allows a noninvasive and continuous monitoring of microvascular blood flow. It is therefore used for microvascular investigations and for the diagnosis and follow-up of pathologies, such as diabetes and peripheral arterial occlusive diseases (see, for example, Refs. 7–10).

Several complex biophysical processes have already been identified in the cardiovascular system (heart beats and respiration being probably the most prominent). Each of these processes comes with inherent characteristic time scales and all together also give rise to their interplays. The cardiovascular system therefore operates across multiple temporal scales. Accordingly, multiscale analyses of signals reflecting the central cardiovascular system have been conducted and have been proven to be of great interest to better understand the data and for diagnostic purposes. By contrast, multiscale analyses of LDF signals (peripheral cardiovascular system) are very recent.[11–14] Some of the works performed on the data of the central cardiovascular system have been based on the computation of the multiscale entropy.[15,16] The authors therefore studied the complexity of central cardiovascular system signals over several scales (see, for example, Refs. 15–18). However, no multiscale entropy study of LDF signals has already been carried out. Therefore, in order to bring information in this field of interest, we propose in this letter a first multiscale entropy analysis of LDF data recorded in healthy subjects at rest. Moreover, if multiscale entropy values show the same pattern for each of the signals processed, multiscale entropy could be an interesting measure to obtain a stationary signature for LDF signals, which are probeposition and subject dependent. This work is therefore a first step in the assessment of the potentialities of multiscale entropy for LDF signal analysis.

II. MEASUREMENT PROCEDURE AND SIGNAL PROCESSING METHOD

II.A. Measurement procedure

Seven subjects (29.7 ± 6.3 yr old) were enrolled in the study. Each of them gave his/her written informed consent to participate. For the measurements, the subjects were supine in a quiet room and rested for at least 10 min before the recordings started. For the measurement procedure, a laser Doppler optical fiber probe (Perimed, Stockholm, Sweden) connected to a laser Doppler flowmeter (Periflux PF5000, Perimed, Stockholm, Sweden) was positioned on the right forearm (ventral face) of the subjects. As suggested by the manufacturer, the time constant of the laser Doppler flowmeter was set to 0.2 s.[19] LDF signals were recorded in arbitrary units (a.u.) on a computer via an analog-to-digital converter (Biopac System). The sampling period was chosen equal to $T=50$ ms.

Due to the high sensitivity of the LDF technique to movements (movements of the subjects, optical fiber movements, movements of the probe head relative to the tissue, etc.), the subject has to be completely still during the acquisition. Therefore, long recordings of LDF signals are not possible. In our work, each recording lasted until 23 000 samples of data were obtained (around 19.2 min of acquisition). These 23 000 samples were then processed (see below). An example of LDF signal is shown in Fig. 1.

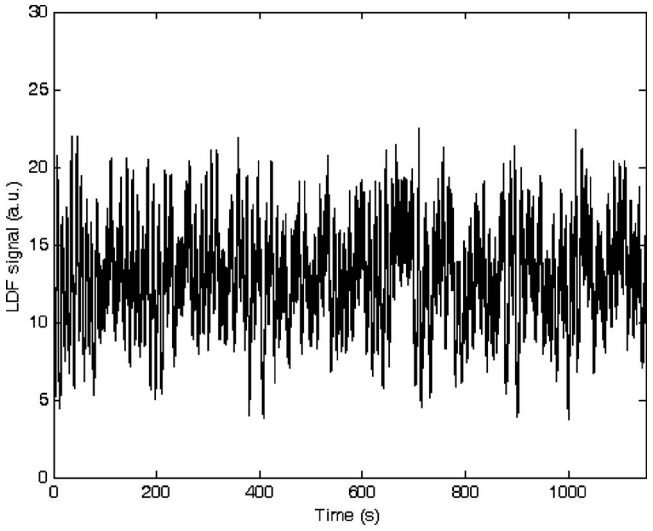

FIG. 1. LDF signal recorded during 19.16 min on the forearm of a healthy subject at rest. The sampling period is $T=50$ ms.

II.B. Signal processing method

Multiscale entropy has been proposed at the beginning of the 2000s to calculate entropy over multiple scales.[15,16] Multiscale entropy analysis is a method of measuring the complexity of finite length time series.[15,16] The algorithm relies on two main steps:

(1) For a time series $\{x_1,\ldots,x_i,\ldots,x_N\}$, a consecutive coarse-grained time series is constructed by averaging a successively increasing number of data points in nonoverlapping windows of length τ. The coarse-grained time series is calculated as

$$y_j^{(\tau)} = \frac{1}{\tau} \sum_{i=(j-1)\tau+1}^{j\tau} x_i, \tag{1}$$

where τ is the scale factor and $1 \leq j \leq N/\tau$. The length of each coarse-grained time series is N/τ.

(2) Then, the sample entropy (SampEn) is computed for each coarse-grained time series and is plotted as a function of the scale factor τ.[15,16]

SampEn is a refinement of approximate entropy (ApEn) introduced by Pincus[20–22] to quantify the regularity of finite length time series. A low value for the SampEn reflects a high degree of regularity, while a random signal has a relatively higher value of SampEn. The SampEn(m,r,N) is the negative natural logarithm of the conditional probability that a dataset of length N, having repeated itself within a tolerance r for m points, will also repeat itself for $m+1$ points, without allowing self-matches.[22] In contrast to ApEn(m,r,N) that calculates probabilities in a templatewise fashion, SampEn(m,r,N) calculates the negative logarithm of a probability associated with the time series as a whole. From its definition, contrary to ApEn, SampEn is largely independent of the record length.[22] Moreover, SampEn displays the property of relative consistency in situations where ApEn does not.[22,23] That is, if one record shows lower

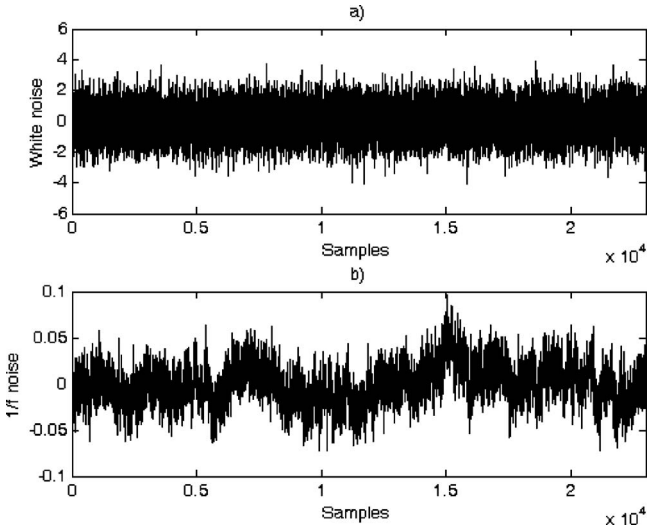

FIG. 2. (a) Gaussian white noise (mean: 0; variance: 1) of 23 000 samples. (b) $1/f$ noise of 23 000 samples.

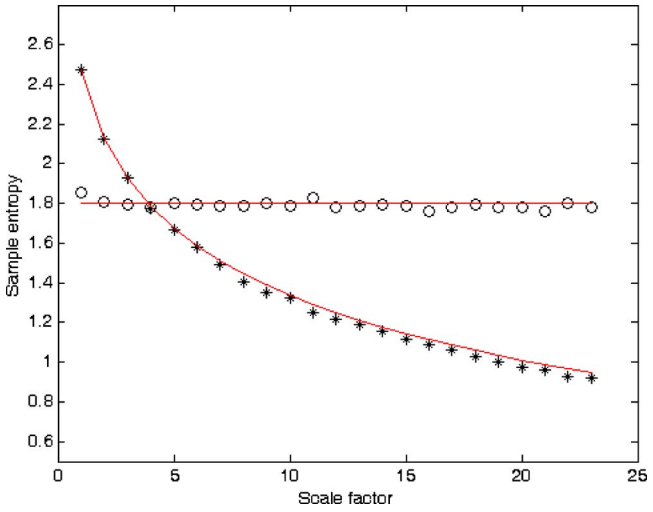

FIG. 3. Multiscale entropy values for white noise (*) and $1/f$ noise (○) time series shown in Fig. 2. The symbols "*" and "○" correspond to the numerically estimated multiscale entropy values with our implementation of multiscale entropy, whereas the lines are the numerical evaluation of analytic multiscale entropy calculation (see Ref. 16).

SampEn than another with one set of values of m and r, it also shows lower SampEn with different values.

In order to be able to compare our results to those obtained by others when processing different physiological time series, we choose for our algorithm the same parameter values as previously published (see, for example, Refs. 15–18): A pattern length $m=2$ and a similarity criterion $r=0.15\times\mathrm{SD}$ (SD is the standard deviation of the original time series). The value of the parameter r is therefore a percentage of the time series SD. This implementation corresponds to normalizing the time series (see, for example, Ref. 16). Moreover, because $N=23\,000$ in our recordings, we choose a scale factor τ going from 1 to 23 so that the shortest coarse-grained time series contains 1000 samples (see, for example, Ref. 16).

In order to test our implementation of multiscale entropy, we first apply our algorithm on simulated white (uncorrelated) and $1/f$ (long-range correlated) noises (see Fig. 2). Theoretical multiscale entropy values of white and $1/f$ noises can be found in Ref. 16.

III. RESULTS AND DISCUSSION

Figure 3 shows multiscale entropy values given by our implementation for simulated white noise and $1/f$ noise time series. From Fig. 3, we can observe that the numerically estimated multiscale entropy values and the numerical evaluation of analytic multiscale entropy calculations, for our two test synthetic signals, are close to each other. Our multiscale entropy algorithm can therefore be applied later on over LDF signals. We also note that the white noise time series possesses higher multiscale entropy values than the $1/f$ noise time series for scales below 5. However, it is the opposite for scales larger than 5. This can be explained by the fact that $1/f$ noise contains more diversity of structures across multiple scales[24,25] and is therefore, in this respect, more complex than white noise. For white noise, as the length of the windows used for coarse-graining time signal increases, the average value inside each window converges to a fixed value because no new structures exist on larger scales. Therefore, the standard deviation monotonically decreases with the scale factor, and the same is found for multiscale entropy. This reflects that white noise has information only on the shortest scales. By contrast, for $1/f$ noise, new information is revealed at all scales.[16]

The average multiscale entropy values for the LDF signals from the seven subjects are shown in Fig. 4. From this figure, we can see that the average multiscale entropy measure increases from scale factor $\tau=1$ to scale factor $\tau=7$. It then gradually decreases until scale factor $\tau=18$. These two behaviors (increase and then decrease) are observed on av-

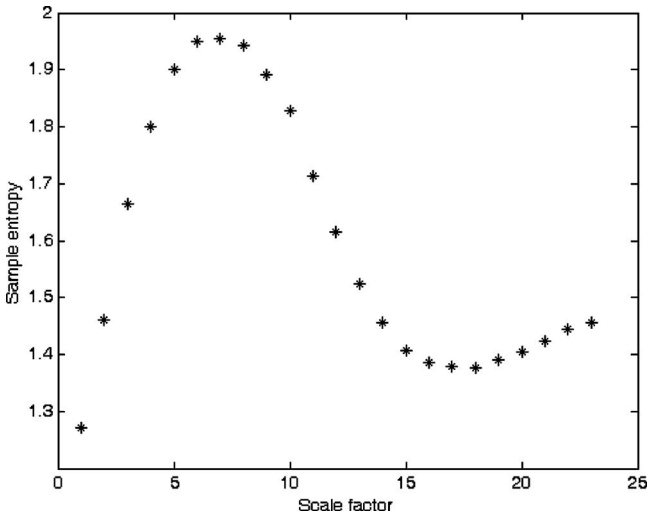

FIG. 4. Average multiscale entropy values for seven LDF signals recorded in the forearm (ventral face) of seven healthy subjects at rest. The parameters for SampEn computation are $m=2$ and $r=0.15$. The sampling period for the LDF signals is $T=50$ ms, which gives, for scale factor going from $\tau=1$ to $\tau=23$, time scales ranging from $\tau T=0.05$ s to $\tau T=1.15$ s.

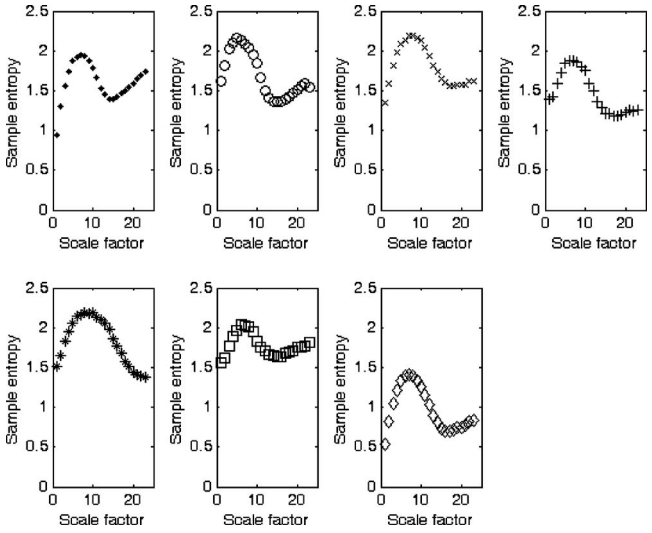

FIG. 5. Multiscale entropy values for the seven LDF signals recorded in the forearm (ventral face) of seven healthy subjects at rest. The parameters for SampEn computation are $m=2$ and $r=0.15$. The sampling period for the LDF signals is $T=50$ ms, which gives, for scale factor going from $\tau=1$ to $\tau=23$, time scales ranging from $\tau T=0.05$ s to $\tau T=1.15$ s.

erage, but also for all our signals (see Fig. 5). Finally, the average multiscale entropy progressively increases again. For scale factor $\tau=1$, corresponding to traditional SampEn, we find an average multiscale entropy equal to 1.27. This value is in accordance with the previous studies.[12] As the variation pattern observed (increase and then decrease) is the same for all our signals, multiscale entropy could potentially be a stationary signature for LDF signals, which are probe-position and subject dependent.

From a *qualitative* point of view, multiscale entropy of LDF signals (peripheral cardiovascular system) presents a marked contrast pattern compared to the one of HRV data (central cardiovascular system). Our results reveal a non-monotonic evolution of the multiscale entropy for the LDF signals. By contrast, for HRV signals from healthy subjects, the evolution observed for the multiscale entropy is usually monotonic: The multiscale entropy measure increases on small time scales (time scales smaller than one typical respiratory cycle length, which is around 3.33 s) and then stabilizes to a relatively constant value (see, for example, Refs. 15 and 16). The nonmonotonic evolution of the multiscale entropy observed for LDF signals is therefore markedly different from that of the HRV data for which multiscale entropy presents a monotonic behavior through scales.

From a *quantitative* point of view, we can note that the multiscale entropy of LDF signals emphasizes two distinctive scales where the LDF signals undergo specific changes from high to low complexity: $7T=0.35$ s and $18T=0.9$ s. As the multiscale entropy value of LDF signals is the highest around 0.35 s, we can suggest that the processes acting around this time scale have the highest irregularity. By contrast, because the multiscale entropy of LDF signals is the lowest around 0.9 s, the processes acting around this scale have the lowest irregularity. The time scale around 0.9 s is close to the period of heart beats. The regularity of this strong rhythmic activity could be the origin of the low multiscale entropy recorded around 0.9 s in the LDF signal. If the heartbeat rate changes, then we hypothesize that the distinctive scale observed around $18T$ (0.9 s) will move to another scale (a smaller or a longer scale, depending if the heartbeat rate increases or decreases). In this logic, the high multiscale entropy around 0.35 s could manifest the action in the LDF signal, on this range of temporal scales, of a very irregular underlying process, still to be identified. Now concerning long time scales above 1 s, due to the high sensitivity of the LDF technique to movements, long LDF signals (more than 30 min) are difficult to record. Therefore, with multiscale entropy studies conducted with our parameters, long scales (of the order of several seconds) seem to be difficult to obtain with LDF signals when 1000 samples are chosen as the minimum number of points for sufficient accuracy in statistical estimation of the entropy. Other works could be conducted with fewer points in the coarse-grained time series to investigate if slower biophysical processes, such as respiration or vasomotion reported in literature, could be analyzed or detected from a same limited duration of LDF recording.

These first observations of multiscale entropy on LDF signal complement those obtained recently on multiscale analyses of LDF signals.[11–14] Moreover, they also add information to the works that have been published on the (single scale) SampEn values of LDF signals.[12,26] This study is the first one dedicated to the multiscale entropy analysis of LDF signals. Experiments can now be conducted in pathological subjects to investigate how—as it is the case for the central cardiovascular system—possible diagnostic purposes could be extracted from multiscale entropy values.

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