Multifractality, sample entropy, and wavelet analyses for age-related changes in the peripheral cardiovascular system: Preliminary results

Anne Humeau[a)]
Groupe esaip, 18 rue du 8 mai 1945, BP 80022, 49180 Saint Barthélémy d'Anjou cedex, France and Laboratoire d'Ingénierie des Systèmes Automatisés (LISA), Université d'Angers, 62 Avenue Notre Dame du Lac, 49000 Angers, France

François Chapeau–Blondeau and David Rousseau
Laboratoire d'Ingénierie des Systèmes Automatisés (LISA), Université d'Angers, 62 Avenue Notre Dame du Lac, 49000 Angers, France

Pascal Rousseau, Wojciech Trzepizur, and Pierre Abraham
Laboratoire de Physiologie et d'Explorations Vasculaires, UMR CNRS 6214-INSERM 771, Centre Hospitalier Universitaire d'Angers, 49033 Angers cedex 01, France

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Using signal processing measures we evaluate the effect of aging on the peripheral cardiovascular system. Laser Doppler flowmetry (LDF) signals, reflecting the microvascular perfusion, are recorded on the forearm of 27 healthy subjects between 20–30, 40–50, or 60–70 years old. Wavelet-based representations, Hölder exponents, and sample entropy values are computed for each time series. The results indicate a possible modification of the peripheral cardiovascular system with aging. Thus, the endothelial-related metabolic activity decreases, but not significantly, with aging. Furthermore, LDF signals are more monofractal for elderly subjects than for young people for whom LDF signals are weakly multifractal: the average range of Hölder exponents computed with a parametric generalized quadratic variation based estimation method is 0.13 for subjects between 20 and 30 years old and 0.06 for subjects between 60 and 70 years old. Moreover, the average mean sample entropy value of LDF signals slightly decreases with age: it is 1.34 for subjects between 20 and 30 years old and 1.19 for subjects between 60 and 70 years old. Our results could assist in gaining knowledge on the relationship between microvascular system status and age and could also lead to a more accurate age-related nonlinear modeling. [DOI: 10.1118/1.2831909]

Key words: laser Doppler, microcirculation, aging, Hölder exponents, multifractality, sample entropy, scalogram, time-frequency representation

I. INTRODUCTION

Several signal processing studies have revealed that heart rate variability (HRV) signals and cardiac interbeat interval dynamics show less variability with aging (see for example Refs. 1–6). These alterations may be due to the reduced ability to adapt to physiological stress, degradation, and decoupling of integrated physiological regulatory systems, as well as to the loss of integrated physiologic responsiveness increasing susceptibility to injury and illness.[3,4,6] However, HRV and cardiac interbeat interval times series reflect a central view of the cardiovascular system. But what are the consequences of aging on the peripheral cardiovascular system? Are the losses of complexity and multifractality visible from a peripheral viewpoint? Is microcirculation modified with aging?

Laser Doppler flowmetry (LDF) signals allow the monitoring of microvascular blood flow and therefore provide a peripheral view of the cardiovascular system.[7] The LDF technique relies on the Doppler effect: when photons are scattered by moving erythrocytes, they are shifted in frequency. A part of the scattered light is then re-emitted from the surface. The broadening of the frequency spectrum is used to calculate an estimate of the perfusion in the tissue under study. This value is proportional to the product of the mean velocity and the concentration of red blood cells.[7] LDF measurements from the skin reflect perfusion in capillaries, arterioles, venules, and dermal vascular plexa.[8–10]

By processing LDF signals, we are interested in studying the effect of aging on the healthy peripheral cardiovascular system. Using wavelet-based representations and sample entropy computations on LDF signals, we show that the underlying processes of the microcirculation behave slightly differently between elderly healthy subjects and young healthy people. Moreover, using a parametric generalized quadratic variation based estimation method we demonstrate that LDF time series are more monofractal for elderly healthy subjects than for young healthy people for whom LDF signals are weakly multifractal.

II. METHODS

II.A. Signal acquisition

Twenty seven healthy subjects with no respiratory or cardiac failure, peripheral vascular disease, psychological disor-

der, or tremor were studied. Nine of these subjects were young (between 20 and 30 years old), nine were between 40 and 50 years old, and nine were between 60 and 70 years old. The institutionally approved study was conducted in accordance with the Declaration of Helsinki. Before their participation, all subjects were informed of the methods and procedures and gave their written consent to participate. To measure skin blood flow, a laser Doppler probe (PF408, Perimed, Stockholm, Sweden) connected to a laser Doppler flowmeter (Periflux PF5000, Perimed, Stockholm, Sweden) was positioned on the forearm (ventral face). Skin blood flow was assessed in arbitrary units and recorded on a computer via an analog-to-digital converter (Biopac System) with a sample frequency of 20 Hz. Local skin temperature was measured using a surface thermocouple probe connected to an electronic thermometer (BAT-12, Physitemp Instruments, Clifton, NJ). The surface thermocouple probe was positioned 5 cm from the laser Doppler probe. Systemic arterial blood pressure was monitored using a Finapres 2350 (Ohmeda, Englewood, CO) positioned on the second or third finger controlateral hand used for skin blood flow measurement. Recordings were performed with the subjects placed supine in a quiet room with the ambient temperature set at 24 ± 1 °C. After at least 10 min of acclimatization, skin blood flow measurement was started. No significant changes were observed for mean arterial blood pressure and for local skin temperature throughout any experiment.

II.B. Wavelet-based analyses

It has been shown that LDF signals contain, in addition to the cardiac and respiratory oscillatory activities, oscillations originating from three other processes: the myogenic (the smooth-muscle cells in the vessel walls respond continually to the changes in intravascular pressure), neurogenic, and endothelial-related metabolic activities.[9–13] The corresponding frequencies are, respectively, near to 0.1, 0.04, and 0.01 Hz for healthy humans.[9–13] In order to study the variations of these three activities with age, the frequency bands corresponding to the underlying mechanisms are analyzed. To detect the properties of LDF signals in the high (near to 0.1 Hz) and low frequencies (near to 0.01 Hz), high frequencies have to be analyzed with short windows and low frequencies with long windows. This can be achieved with a wavelet analysis,[14] which has proved to be very useful to process LDF times series (see for example Refs. 9–14), as well as other biomedical signals.[15] The idea of the continuous wavelet transform is to project a signal s on a family of zero-mean functions, the wavelets, deduced from an elementary function, called the mother wavelet, by translations and dilations. The continuous wavelet transform (CWT) of a signal s is therefore defined as

$$\mathrm{CWT}_s(a,b) = \frac{1}{\sqrt{a}} \int_{-\infty}^{+\infty} s(t)\psi\left(\frac{t-b}{a}\right) dt, \tag{1}$$

where ψ is the mother wavelet, and b and a are time and scale parameters.[16] The translation and dilation/contraction of the mother wavelet give rise to a family of basis functions. The continuous wavelet transform uses short windows at high frequencies and long windows at low frequencies.

In our work, the Morlet wavelet is chosen because the Gaussian window achieves the best time-frequency localization within the limits given by the uncertainty principle.[17] On each subject, the LDF signal taken into account for the wavelet-based analysis is resampled to 10 Hz in order to reduce the computation time, and has a length of 16 min 40 s: recordings are recommended to last at least ten times the period of the lower frequency boundary of the investigated component, but in order to ensure stationarity of the signal, should not be extended substantially beyond this time.[18] The scalogram (squared modulus of the continuous wavelet transform) is studied between 0.0095 and 0.145 Hz to obtain the characteristic frequencies corresponding to the myogenic, neurogenic, and endothelial-related metabolic activities: intervals 0.052–0.145, 0.021–0.052, and 0.0095–0.021 Hz, respectively.[12,13,19]

II.C. Hölder exponents and entropy analyses

II.C.1. Hölder exponents computation

The rapid changes in a time series are called singularities and a characterization of their strength is obtained with the Hölder exponents.[20] The Hölder exponent $h(x_0)$ of a function f at the point x_0 is the highest h value so that f is Lipschitz at x_0. There exists a constant C and a polynomial $P_n(x)$ of order n so that for all x in a neighborhood of x_0 we have[21–23]

$$|f(x) - P_n(x - x_0)| \leq C|x - x_0|^h. \tag{2}$$

Moreover, the Hausdorff dimension of the set where the Hölder exponent is equal to h is[21]

$$D(h) = \dim_H\{x|h(x) = h\}. \tag{3}$$

Monofractal signals are homogeneous: they have the same scaling properties throughout the entire signal; therefore, they are indexed by a single global exponent called the Hurst exponent, which suggests that they are stationary from the viewpoint of their local scaling properties.[24] However, multifractal signals can be decomposed into many subsets characterized by different local Hurst exponents that quantify the local singular behavior and relate the local scaling of the time series.[24] Therefore, signals are considered as multifractal when a "broad" range of Hölder exponents is found, whereas a "narrow" range implies monofractality. Multifractal signals are more complex and inhomogeneous than monofractal ones.[25,26] Recently, the computation of Hölder exponents from LDF signals recorded at rest on young healthy human subjects and comparison of their range with known mono and multifractal data has shown that LDF signals recorded on young healthy subjects are weakly multifractal.[25] Herein, each original LDF signal (sampled at 20 Hz) is processed with a parametric generalized quadratic variation based estimation method (See also http://math.cnrs.fr/imagesdesmaths/pdf2004/Cohen.pdf.)[25,27,28] We carry out the computation with the FRACLAB v2.0 tool[29] and we take into account 7895 pointwise Hölder exponents for each time series (see Figs. 1 and 2).

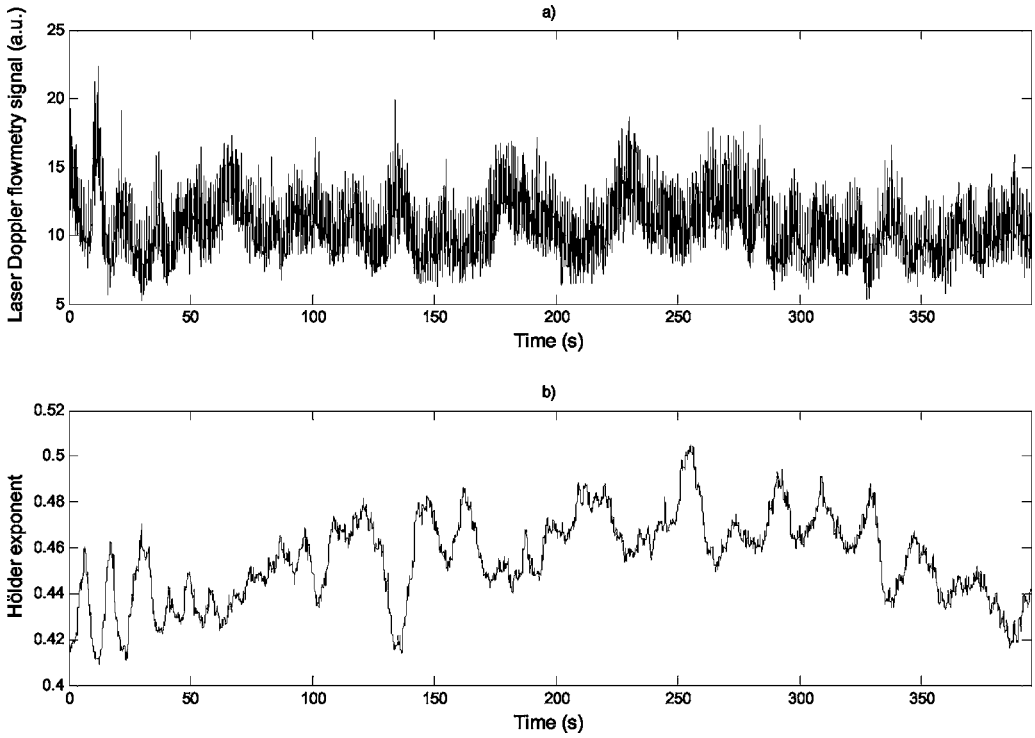

FIG. 1. (a) Skin LDF signal recorded on a healthy subject at rest (subject between 20 and 30 years old). (b) Corresponding time series of Hölder exponents.

II.C.2. Sample entropy analysis

Pincus introduced approximate entropy (ApEn) to quantify the regularity of time series (presence of similar patterns in the time series).[30,31] The more regular and predictable a time series, the lower the value of ApEn; the more random a time series, the higher the value of ApEn. ApEn can be thought of as the negative natural logarithm of the probability that sequences that are close for m points remain close for an additional point. ApEn takes a template-wise approach to calculate this average logarithmic probability. ApEn was

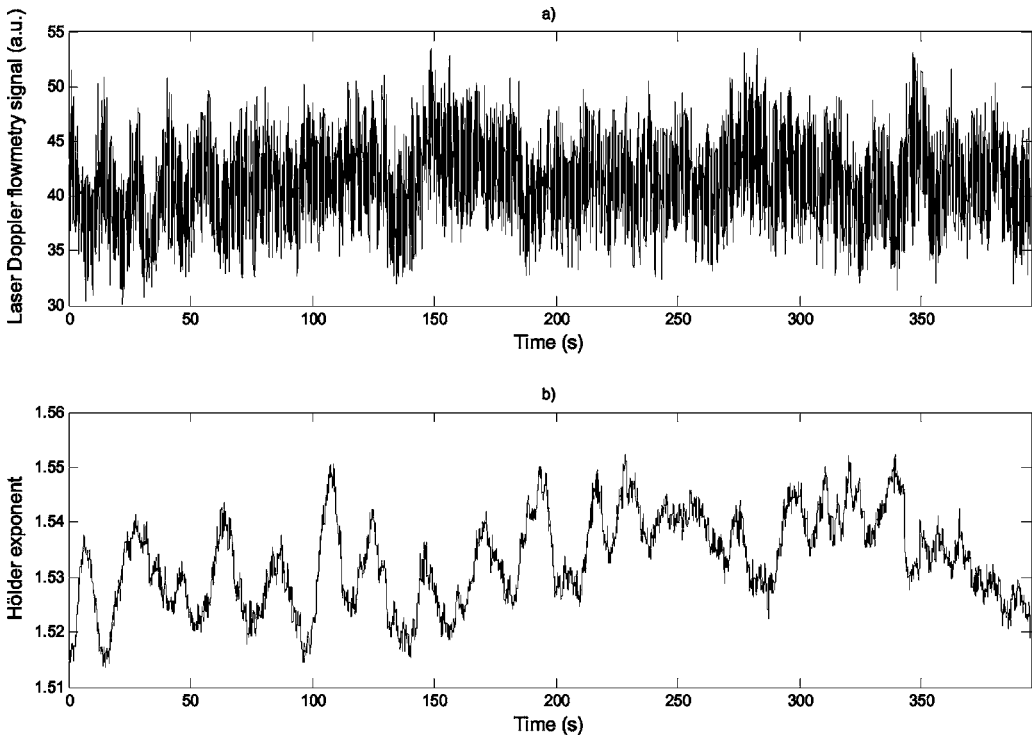

FIG. 2. (a) Skin LDF signal recorded on a healthy subject at rest (subject between 60 and 70 years old). (b) Corresponding time series of Hölder exponents.

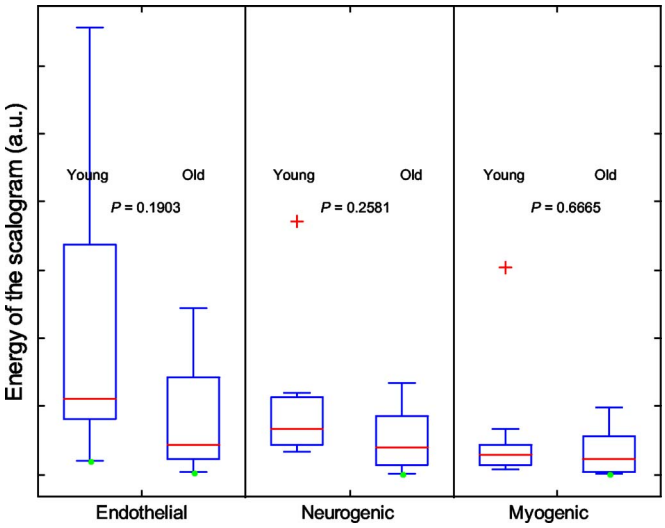

FIG. 3. Energies of the scalogram computed in each frequency band for the three populations (signals 16 min 40 s long; nine subjects for each population). The box lines represent the lower quartile, median, and upper quartile values. The whiskers (lines extending from each end of the box) show the extent of the rest of the data. Outliers are data with values beyond the ends of the whiskers. *P*-values are computed with the Mann–Whitney test.

used in numerous cardiovascular studies. However, its main drawbacks are its dependency on the record length and its lack of relative consistency.[32,33] Therefore, herein, sample entropy is used instead. The lower the value of the sample entropy, the more reproducibility in the time series. In other words, a low value for the sample entropy reflects a high degree of regularity, while a random signal has a relatively higher value of sample entropy. The sample entropy $[\mathrm{SampEn}(m,r,N)]$ 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.[32] In contrast to $\mathrm{ApEn}(m,r,N)$, which calculates probabilities in a template-wise fashion, $\mathrm{SampEn}(m,r,N)$ calculates the negative logarithm of a probability associated with the time series as a whole. Contrary to approximate entropy, sample entropy is largely independent of record length and displays relative consistency under circumstances where approximate entropy does not.[32–34]

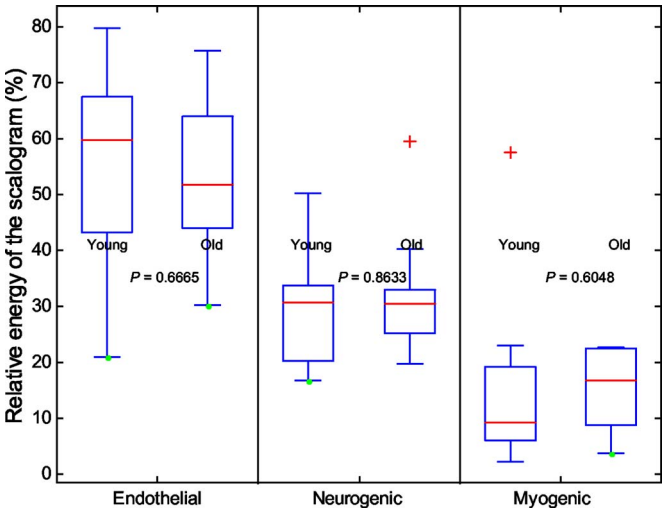

FIG. 4. Relative energies of the scalogram computed in each frequency band for the three populations (signals 16 min 40 s long; nine subjects for each population). The box lines represent the lower quartile, median, and upper quartile values. The whiskers (lines extending from each end of the box) show the extent of the rest of the data. Outliers are data with values beyond the ends of the whiskers. *P*-values are computed with the Mann–Whitney test.

TABLE I. Average value for the minimum, maximum, range, mean, and standard deviation of the Hölder exponents computed for skin LDF signals recorded on healthy subjects (average value computed over nine signals for each population). See text for the mode of computation.

Subjects	Minimum value	Maximum value	Range	Mean value	Standard deviation
20–30 years old	0.40	0.53	0.13	0.46	0.02
40–50 years old	0.87	0.96	0.09	0.91	0.01
60–70 years old	1.03	1.09	0.06	1.06	0.01

The choice of the values for m and r is critical in determining the outcome of the approximate entropy and sample entropy. The various existing rules generally lead to the use of values of r between 0.1 and 0.25 and values of m of 1 or 2 for data of length N ranging from 100 to 5000 points.[35–37] According to Wolf *et al.*[38] the number of data points should range between 10^m and 30^m. Pincus suggested that for $m=2$ and $N=1000$, r should range from 0.1 to $0.2\times$the standard deviation (SD) of the dataset.[30] On the basis of these works and others,[37,39] we choose $m=2$, $N=1000$, and $r=0.2\times\mathrm{SD}$ since it is convenient to set the tolerance r proportional to SD so as to allow measurements on datasets with different amplitudes to be compared. Equivalently, all our LDF time series (sampled at 20 Hz) are normalized to have SD=1, and are subsequently processed with the same tolerance $r=0.2$.

III. ANALYSIS AND COMPARISON

In order to compare the behavior of the myogenic, neurogenic, and endothelial-related metabolic activities with age, quantitative measures are calculated.[13,40,41] The first one is the energy of the scalogram on a given frequency band.[13,40,41] It is defined as

TABLE II. *P*-values computed with the Kruskal–Wallis test to evaluate the differences of the minimum, maximum, and mean values of the Hölder exponents between the groups of subjects.

P-value	Between the three groups of subject
Minimum values of Hölder exponents	0.0648
Maximum values of Hölder exponents	0.0980
Mean values of Hölder exponents	0.0889

TABLE III. Average value for the minimum, maximum, mean, and standard deviation of the sample entropy computed for skin LDF signals recorded on healthy subjects (average value computed over nine signals for each population). See text for the mode of computation.

Subjects	Minimum value	Maximum value	Mean value	Standard deviation
20–30 years old	0.50	1.91	1.34	0.42
40–50 years old	0.72	1.96	1.26	0.47
60–70 years old	0.88	1.87	1.19	0.35

$$E(f_1,f_2)=\frac{1}{b}\int_0^b\int_{1/f_2}^{1/f_1}\frac{1}{a^2}|CWT_s(a,b)|^2 dadb. \quad (4)$$

The results are noted as E_{Myogenic}, $E_{\text{Neurogenic}}$, and $E_{\text{Metabolic}}$ and represent the energy of the scalogram on the intervals 0.052–0.145, 0.021–0.052, and 0.0095–0.021 Hz, respectively. Moreover, in order to evaluate how the distribution of the energy among the three bands changes, we introduce the relative energy of the scalogram on a frequency band. They are noted as $E_{\text{RelativeMyogenic}}(=E_{\text{Myogenic}}/E_{\text{sum}})$, $E_{\text{RelativeNeurogenic}}(=E_{\text{Neurogenic}}/E_{\text{Sum}})$, and $E_{\text{RelativeMetabolic}}(=E_{\text{Metabolic}}/E_{\text{Sum}})$, where E_{Sum} represents $(E_{\text{Myogenic}}+E_{\text{Neurogenic}}+E_{\text{Metabolic}})$. Furthermore, the Mann–Whitney test is used to evaluate the differences between the groups of subjects. Statistical significant differences are defined as $P<0.05$.

The measures computed on the scalogram show that the energy in the frequency bands corresponding to the myogenic, neurogenic, and endothelial-related metabolic activities are lower for elderly subjects than for young people (see Fig. 3). The relative energy of the endothelial-related metabolic activity is also lower for elderly subjects than for young ones (see Fig. 4). However, we note that these differences are not statistically significant (see *P*-values in Figs. 3 and 4).

The results of the Hölder exponents and sample entropy analyses are presented in Tables I–IV and are computed as follows: for each of the 27 time series, we determine for the Hölder exponents the minimum, maximum, range, mean, and standard deviation values. Then, for each subject group, an average for the nine minimum values obtained is computed; idem for the maximum, range, mean, and standard deviation. Sample entropy is also determined for each time series. From them and for each age group, a minimum, maximum, mean, and standard deviation value is determined. The results are depicted in Tables I and III, and in Figs. 5 and 6. Moreover, the Kruskal–Wallis test is used to evaluate the differences between the groups of subjects (see Tables II and IV). Statistically significant differences are defined as $P<0.05$. The results for the Hölder exponents computed with the FRACLAB v2.0 tool[29] (see Tables I and II) show that the mean value of the exponents become higher with age (average mean value slightly higher than one for elderly subjects and near to 0.5 for young people). Furthermore, the average range of Hölder exponents becomes narrower with age: it is 0.13 for the subjects between 20 and 30 years old, and 0.06 for the elderly subjects (subjects between 60 and 70 years old). However, the statistical test shows that the differences are not significant. Moreover, the average mean value of the sample entropy (see Table III) decreases with age: it is 1.34 for the

TABLE IV. *P*-values computed with the Kruskal–Wallis test to evaluate the differences of the sample entropy values between the groups of subjects.

P-value	Between the three groups of subjects
Sample entropy values	0.7396

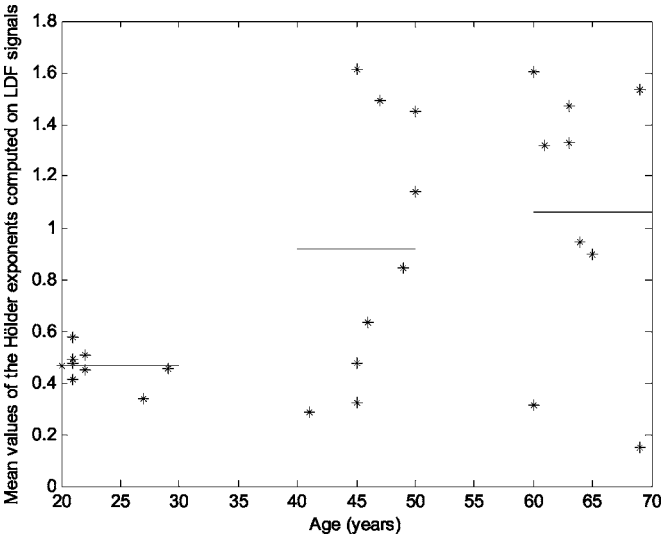

FIG. 5. Plot of the Hölder exponents mean value as a function of age with all of the subjects. A star corresponds to a subject and the lines represent the average values computed for each age group.

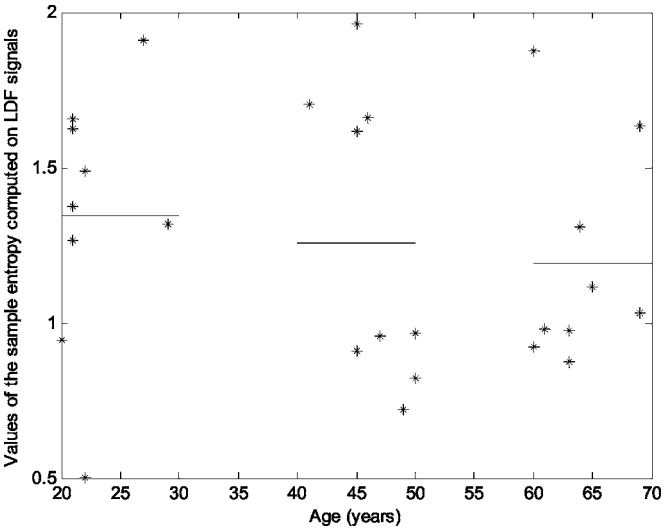

FIG. 6. Plot of the sample entropy as a function of age with all of the subjects. A star corresponds to a subject and the lines represent the average values computed for each age group.

subjects between 20 and 30 years old, and 1.19 for the elderly subjects (subjects between 60 and 70 years old). The difference found is not significant (see Table IV).

IV. DISCUSSION AND CONCLUSION

Scalograms of LDF signals have already shown to give information on the myogenic, neurogenic, and endothelial-related metabolic activities.[9–13] The present work shows that absolute and relative energies of the endothelial-related metabolic activity slightly decrease between young and elderly healthy subjects (the decrease is not statistically significant). Kvernmo *et al.* have shown that athletes have higher endothelial activity than less trained subjects.[42] They have also demonstrated a higher absolute, but lower relative, amplitude of the oscillations linked to the neurogenic activity in athletes than in controls, and a lower relative amplitude of the oscillations linked to the myogenic activity among athletes than in controls.[42] The latter conclusions mention that the neurogenic component contributes relatively less to the blood flow than the other regulators of the cutaneous blood flow in athletes than in controls, and that athletes have decreased vasomotion induced by the intrinsic activity of vascular smooth muscle cells as compared to controls. Our results show that aging leads to opposite conclusions compared to physical activity for the endothelial-related metabolic activity (see Figs. 3 and 4).

The Hölder exponents analysis also brings information on the impact of aging over the peripheral cardiovascular system. Indeed, our results show that the average range of Hölder exponents decreases with age. This means that aging leads to a loss of multifractality for the peripheral cardiovascular system. Several studies have shown that multifractality can be found in other physiological time series (heartbeat time series among others) and that some pathologies can break this property.[24,43,44] The latter conclusion can be used to distinguish healthy subjects from pathological subjects. Our results show that, for LDF signals, aging behaves in the same way as pathology for more central cardiovascular data (loss of multifractality). Moreover, our work carried out with the FRACLAB v2.0 tool[29] shows that the average mean value of Hölder exponents is higher than one for elderly subjects whereas it is lower than one for younger people. This means that LDF signals recorded on elderly healthy subjects are, on average, differentiable whereas they are not for young healthy people (Hölder exponents lower than one). Our results also show that LDF signals from young people have properties that are close to the ones of white noise (Hölder exponents near 0.5), whereas LDF signals from elderly subjects behave as $1/f$ noise (Hölder exponents near 1). These results lead to interesting interpretations if we analyze them in terms of information theory. Indeed, white noise, because it contains no redundancy, generates the most efficient or cost-effective coding of information.[45] In opposition, $1/f$ noise, which has more redundancy, represents a less efficient or more expensive coding of information. One can also think in terms of information channel, for the cardiovascular operation and regulation, from the central control to the periphery where LDF signals are recorded. Low-redundancy signals observed for young subjects would be associated with a high-quality information channel that requires no added redundancy in order to convey information reliably. In opposition, redundant signals observed for elderly subjects would be associated with a lower-quality information channel that requires added redundancy for reliable transmission of information. The comparison of our results with those of other papers dealing with more central cardiovascular data shows that aging leads to aspects that seem more complex than expected.

The sample entropy analysis conducted herein on LDF signals is related to regularity. The results show that the average mean value of the sample entropy decreases with age. As a consequence, LDF time series recorded on elderly healthy subjects are, on average, more regular than those recorded on young healthy people. However, the difference is not statistically significant.

Our work shows that there is a slight decrease of the endothelial-related metabolic activity, and a loss of multifractality and "randomness" of the healthy peripheral cardiovascular system with aging. The latter conclusions are drawn from average ranges of Hölder exponents (the latter are computed with a parametric generalized quadratic variation based estimation method) and average values of sample entropy. Several authors have shown that HRV signals and cardiac interbeat interval dynamics become less irregular with aging (see for example Refs. 1–6). Our work suggests that aging has also consequences on the healthy peripheral cardiovascular system. However, even if we find differences in energy, Hölder exponents, and sample entropy between young and old subjects, the statistical tests show that these differences are not statistically significant. Our results, therefore, may confirm the idea of Vaillancourt and Newell, who postulated that the observation of an increase or decrease in complexity with aging and disease is dependent on the nature of both the intrinsic dynamics of the system and the short-term change required to realize a local task demand.[46]

These analyses of LDF signals recorded on subjects of different ages suggest that aging can modify the peripheral cardiovascular system. Further work is now needed in order to confirm these results and to gain knowledge on the relationship between microvascular system status and age. Moreover, the preliminary findings of our work could lead to a more accurate quantification and nonlinear modeling of the peripheral cardiovascular system changes in healthy conditions in relations to age.

[a]Author to whom all correspondence should be addressed. Electronic mail: ahumeau@esaip.org; Telephone: +33(0) 2 41 96 6510; Fax: +33(0) 2 41 96 6511.

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