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Complexity analysis of the microcirculatory-blood-flow response following acupuncture stimulation

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ABSTRACT

Beat-to-beat cardiovascular variability analysis provides important information on the circulatory regulatory activities. Changes in the arterial pulse transmission or the opening condition of arteriolar openings might change the fluctuation pattern of the MBF supply, and thus change the complexity property therein. We performed complexity analysis of beat-to-beat laser Doppler flowmetry (LDF) signals to study the microcirculatory-blood-flow (MBF) response at the needled site (Hegu acupoint) following acupuncture stimulation (AS). LDF signals were measured in male healthy volunteers ($n = 29$). Each experiment involved recording a 20-minute baseline-data sequence and two sets of effects data recorded 0–20 and 50–70 min after stopping AS. Approximate-entropy (ApEn) analysis, which quantifies the unpredictability of fluctuations in a time series, was performed on each 20-minute beat-to-beat LDF data sequence. The present findings indicate that AS can not only improve the local blood supply but may also increase ApEn values and decrease MBF variability parameters. This was the first attempt to apply complexity analysis to LDF signals in order to elucidate microcirculatory responses following AS. The observed results are probably attributable to the contradictory effects on the MBF supply induced by AS, which might interfere with the microcirculatory regulatory activities so as to increase the complexity of LDF signals. The present findings could help to identify the mechanism underlying the effects of AS, might aid the development of an index for monitoring the induced microcirculatory regulatory responses, and thus provide an evidence-based connection between AS and modern physiology.

Introduction

The cardiovascular system comprises complex biophysical processes with multiple levels of regulation (Humeau et al., 2009). Beat-to-beat cardiovascular variability analysis can provide important information on the circulatory autonomic control. For example, physiological rhythms embedded in a beat-to-beat heart-rate (HR) data sequence have been used to monitor autonomic regulation in cardiovascular control (Task Force, 1996). At the microcirculatory level, it has been suggested that the microcirculatory blood flow (MBF) can be driven into the capillaries through precapillary arteriolar openings (AO) by the propelling force of the pulse pressure generated by the heartbeat and transmitted along the artery (Chen et al., 2011; Hsiu et al., 2008a, 2009a). The variability of the blood flow in arterioles has been attributed to their ability to regulate their diameter in response to external and internal changes, thereby protecting the brain against ischemia, capillary damage, and edema (Heistad and Kontos, 1983).

Acupuncture stimulation (AS), an important treatment strategy in oriental medicine, has been suggested to prevent or treat illness by adjusting autonomic functions (Jansen et al., 1989). It has also been found that AS can induce changes in microcirculatory perfusion of the skin surface around the needled site (Hsiu et al., 2011a, 2011b) or the internal organs (Tsuru and Kawakita, 2009). Laser Doppler flowmetry (LDF) is a widely-used technique to monitor the microcirculation due to its advantages of a good frequency response, ease of application, and tissue specificity, and is therefore well suited for noninvasive investigations of the microvascular responses to AS. We have previously noted that AS can increase the MBF and decrease the MBF resistance at the needled site (Chen et al., 2011; Hsiu et al., 2011a, 2011b). Differences in the induced sympathetic neural activities (SNA) between needling the Hegu acupoint and its nearby nonacupoints have also be studied by analyzing the frequency content of skin LDF signals (Hsiu et al., 2011a).

Nonlinear analysis has been suggested to provide information about the variability structure of skin blood-flow oscillations (Liao et al., 2010). Several nonlinear analysis strategies, such as fractal

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analysis (Carolan-Rees et al., 2002; Esen and Esen, 2006) and detrended fluctuation analysis (Esen et al., 2009), have been applied to MBF signals with the aim of advancing the understanding of various microvascular physiological and pathological conditions. Among various types of nonlinear analysis, the signal complexity can be evaluated by analyses of approximate entropy (ApEn) (Pincus, 1991). When applied to physiological signals, 'complexity' implies the absence of clear temporal patterns. For example, calculations of entropy values can provide information about the mechanism underlying dynamic cerebral microvascular autoregulation (Panerai, 2009). It has also been suggested that changes in microcirculatory complexity with aging and disease depend upon the type of change required to maintain function during the demands of a particular task (Vaillancourt and Newell, 2002).

The aim of the present study was to apply complexity analysis to LDF signals in order to explain the MBF response at the needled site (Hegu acupoint) following AS. One important characteristic of the present analysis was that ApEn was calculated on a beat-to-beat basis rather than the calculation being applied to the raw data. Changes in many factors that affect the pulse transmission or the AO condition, such as those in the heartbeat, arterial elastic properties, or the opening property of AO, may change the beat-to-beat MBF supply, might change the fluctuation pattern of the MBF supply, and thus change the complexity property therein. For example, many of the capillary pathways in local vascular beds are closed at any given instant, while others nearby continue to carry an active flow. The pattern of AO opening and closing over time appears random but could be dictated by induced changes in local regulatory activities (Lee and Fung, 1971), which can play an important role in maintaining a sufficient blood supply and thus the normal physiological condition of local tissues. Therefore, the present method of complexity analysis of the LDF signal may be useful for monitoring the regulatory activities of local vascular beds, and thus help in understanding the microcirculatory response following AS.

Materials and methods

Experimental setup and data acquisition

Experiments were performed on male healthy volunteers aged 20–27 years (all were students of the Department of Electrical Engineering, Yuan Ze University) and without signs or symptoms of cardiovascular or neurological disease ($n = 29$). The reason we used only male subjects and also subjects with ages within this range is to minimize the possible interference effects induced by menstrual period and different ages. The subjects were all Taiwan natives, were lightly clothed, supine, and were allowed to stabilize for at least 20 min before commencing recording. The environmental temperature was within 23–25 °C during the entire measuring period. The institutional ethics committee at Taipei City Hospital approved the study protocol, and each volunteer provided written informed consent before entering the study. Tea, coffee, alcohol, and smoking were forbidden on the day before experiments. All subjects did not exercise or consume food for at least 1 h before each experiment (Hsiu et al., 2009b, 2011a, 2011b).

The ECG and LDF signals were measured simultaneously and noninvasively (representative waveforms are shown in Fig. 1). ECG signals were measured by surface electrodes, and acquired by a preamplifier (lead II, RA-LL; 6600-series, Gould, USA). LDF (VP1 probe; MBF3, Moor Instruments, UK) was used to measure the microcirculatory flux with a time constant of 0.001 s, a cut-off frequency of 14.9 kHz and a sampling frequency of 40 Hz. The laser operating wavelength and output power were 780 nm and less than 1.6 mW, respectively. Subjects were asked to relax and breathe naturally throughout the measurement period so as to avoid motion artifacts. The signals were connected to an analog-to-digital converter card

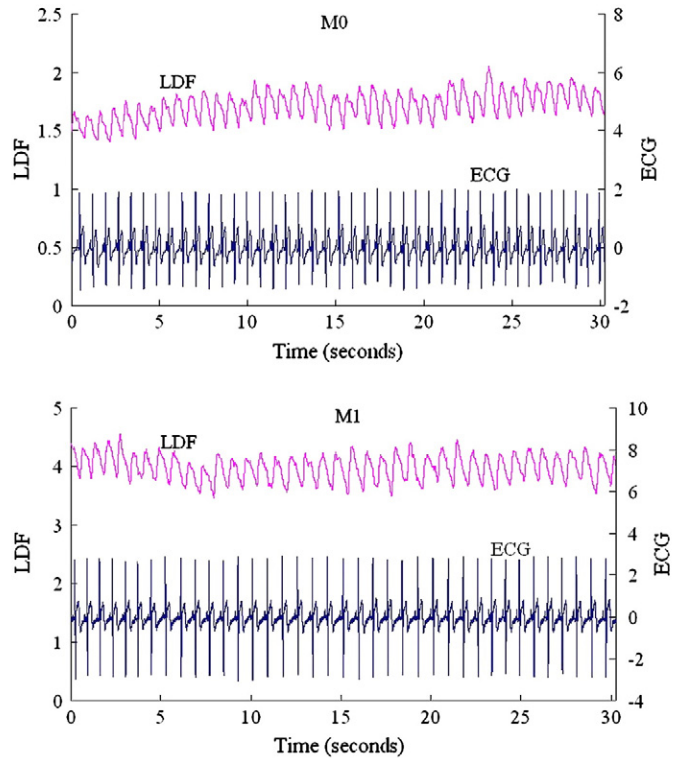

Fig. 1. Representative waveforms of ECG and LDF signals at Site 1. LDF flux and ECG are in arbitrary units. The ECG signal was filtered by a low-pass filter (with a 50 Hz cut-off to filter out the high-frequency noise) and a high-pass filter (with a 0.3 Hz cut-off to eliminate the baseline drift) to make the location of the R peak more prominent.

(PCI-9111DG, Adlink Technology, Taiwan) operating at a sampling rate of 1024 Hz (Hsiu et al., 2011a, 2011b).

The measuring sites of the LDF probes were at the left Hegu (LI4; Site 1; an acupoint located between the thumb and the index finger on the back of the hand, between the 1st and 2nd metacarpal bones, in the middle of the 2nd metacarpal bone on the radial side) and a nearby nonacupoint (Site 2; halfway between Hegu and Sanjian [LI3]) for comparison. The LDF probes were held vertically onto the skin surface by a holder with a radius of around 6 mm. The AS was performed by a qualified Chinese-Medicine doctor working in the Department of Traditional Chinese Medicine, Taipei City Hospital RenAi Branch, who has a clinical experience of about 12 years. During the measurement, the subject was supine on a measurement couch. Each assessment involved making the following recordings: the 20-minute baseline (M0) data was recorded prior to AS, after which the acupuncture needle (stainless steel needle, gauge #30, 7.5 cm in length; Chianhuei, Taiwan) was inserted into the left Hegu acupoint to a depth of around 4 mm for 20 min without applying any form of stimulation. The De-Qi feeling following AS (a special feeling, including distension of soreness or numbness, as described mutually by the subjects and the acupuncturist) was experienced in all the subjects. The needle was then withdrawn to stop AS, with the data being recorded from 0 to 20 min (M1) and from 50 to 70 min (M2) after stopping AS. In several of our previous works, 20-minute AS has been noted to be able to induce prominent MBF responses, either in healthy (Hsiu et al., 2011a) or stroke subjects (Hsiu et al., 2011b). Using AS with a shorter time might not be sufficient to induce prominent MBF response, whereas it might be difficult to remain the physiological stability of the subjects during the whole experimental periods when using AS with a longer time.

Before the baseline and after the M2 period, fundamental physiological parameters of the subject, including the heart rate (HR), systolic blood pressure (SBP), and diastolic blood pressure (DBP) were measured by a sphygmomanometer (MediGuard 150i, Rossmax, Taiwan).