Ultrasound in Med. & Biol., Vol. 41, No. 5, pp. 1320–1327, 2015

0301-5629/$ - see front matter

http://dx.doi.org/10.1016/j.ultrasmedbio.2014.12.013

● *Original Contribution*

WAVELET ENTROPY OF DOPPLER ULTRASOUND BLOOD VELOCITY FLOW WAVEFORMS DISTINGUISHES NITRIC OXIDE-MODULATED STATES

Christina E. Agnew,* Paul K. Hamilton,† Aaron J. McCann,* R. Canice McGivern,* and Gary E. McVeigh†

*Northern Ireland Regional Medical Physics Agency, Royal Group of Hospitals, Belfast, Northern Ireland; and †Centre for Experimental Medicine, Queens University Belfast, School of Medicine, Dentistry and Biomedical Sciences Institute of Clinical Science—Block A, Royal Group of Hospitals, Belfast, Northern Ireland

(*Received* 18 *April* 2014; *revised* 11 *September* 2014; *in final form* 15 *December* 2014)

Abstract—Wavelet entropy assesses the degree of order or disorder in signals and presents this complex information in a simple metric. Relative wavelet entropy assesses the similarity between the spectral distributions of two signals, again in a simple metric. Wavelet entropy is therefore potentially a very attractive tool for waveform analysis. The ability of this method to track the effects of pharmacologic modulation of vascular function on Doppler blood velocity waveforms was assessed. Waveforms were captured from ophthalmic arteries of 10 healthy subjects at baseline, after the administration of glyceryl trinitrate (GTN) and after two doses of N^G-nitro-L-arginine-methyl ester (L-NAME) to produce vasodilation and vasoconstriction, respectively. Wavelet entropy had a tendency to decrease from baseline in response to GTN, but significantly increased after the administration of L-NAME (mean: 1.60 ± 0.07 after 0.25 mg/kg and 1.72 ± 0.13 after 0.5 mg/kg vs. 1.50 ± 0.10 at baseline, $p < 0.05$). Relative wavelet entropy had a spectral distribution from increasing doses of L-NAME comparable to baseline, 0.07 ± 0.04 and 0.08 ± 0.03, respectively, whereas GTN had the most dissimilar spectral distribution compared with baseline (0.17 ± 0.08, $p = 0.002$). Wavelet entropy can detect subtle changes in Doppler blood velocity waveform structure in response to nitric-oxide-mediated changes in arteriolar smooth muscle tone. (E-mail: pk_hamilton@yahoo.co.uk) **© 2015 World Federation for Ultrasound in Medicine & Biology.**

Key Words: **Wavelet transform, Entropy, Doppler, Resistive index, Nitric oxide, Vasodilation, Vasoconstriction.**

INTRODUCTION

The earliest manifestations of cardiovascular disease appear to occur in vulnerable microvascular beds including those of the eye and kidney (Bonetti et al. 2003; Cohn et al. 2004; Feihl et al. 2006; Lockhart et al. 2009). Microvascular damage in these organs is known to predict future cardiovascular complications; therefore, a quantitative, non-invasive technique for assessing microvascular structure could have clinical utility. Changes in arterial structure and function result in characteristic changes in blood pressure and velocity waveforms (Freis et al. 1966; Kelly et al. 1989; McVeigh et al. 1999; Nicholas and O'Rourke 1997). Such waveforms are composites of incident flow waves from the heart and reflected components that arise because of mismatches in vascular impedance, or total opposition to flow presented by downstream microvascular networks. Thus, blood velocity waveforms recorded in immediate proximity to a microvascular bed should provide information about the condition of that circulation, because the microvasculature represents the primary site for wave reflection in the arterial circulation (Laurent and Boutouyrie 2007; Lockhart et al. 2009).

Time domain descriptors of flow velocity waveforms such as the resistive index (RI) (Pourcelot 1974) and pulsatility index (PI) (Gosling et al. 1971) are calculated using the maximum and minimum excursions of flow during the cardiac cycle. They are popular with clinicians because they provide a single number that in some way encapsulates data in a waveform. However, these indices are derived from less than 2% of the information contained in a waveform and fail to consistently detect changes in waveform structure (Evans et al. 1981; Lockhart et al. 2006; Polska et al. 2001; Uthoff et al. 2008). In contrast, spectral analysis techniques assess

Address correspondence to: Paul K. Hamilton, Queens University Belfast, School of Medicine, Dentistry and Biomedical Sciences, Institute of Clinical Science—Block A, Royal Group of Hospitals, Grosvenor Road, Belfast, Northern Ireland, BT12 6BA. E-mail: pk_hamilton@yahoo.co.uk

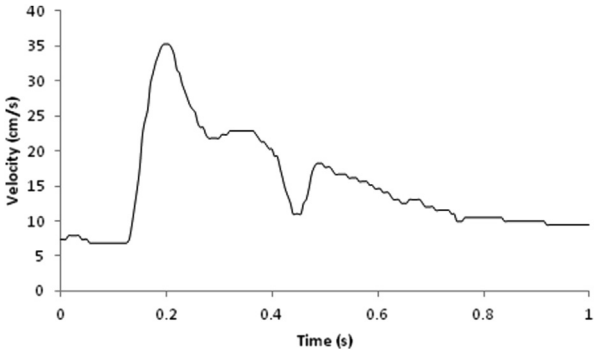

Fig. 1. Typical baseline ophthalmic artery blood velocity waveform.

signals in their totality. Of the available spectral analysis techniques, wavelet transform analysis has been established as an excellent analytical technique for studying biological, pseudo-time-stationary blood velocity waveforms (Agnew et al. 2011; Bracic and Stefanovska 1998; Guler et al. 2001; Guo et al. 1994; Kvernmo et al. 1999; Latifoglu et al. 2009; Stefanovska et al. 1999). The output from wavelet transform analysis is, however, more difficult for a non-expert to interpret than the more simplistic measures RI and PI.

A complementary approach for analyzing the spectral content of blood velocity waveforms, wavelet entropy, is presented in this work. Wavelet entropy quantifies the degree of order/disorder (complexity) in a signal from the signal's spectral content (Powell and Percival 1979; Shannon 1948). Entropy succinctly combines the signal's spectral content into a single metric and may provide an effective descriptor of the condition of the arterial vasculature. Measures of entropy have previously been implemented in analysis of heart rate and blood pressure dynamics (Lake et al. 2002; Pincus 2001; Schulz et al. 2010; Trunkvalterova et al. 2008) and in the study of the complexity of electroencephalographic waveforms (Rosso et al. 2001, 2006). The aim of this study was to investigate if measures of complexity can be used to analyze blood velocity waveforms and track the effects of changes in blood vessel function after pharmacologic manipulation.

METHODS

Subjects

Ten healthy male volunteers aged 18–26 y (mean: 22 years) were recruited for study. This data set has previously been analyzed by our group to assess the efficacy of multiple signal classification (rootMUSIC) analysis (Agnew et al. 2011). No subjects were on medication or had any history of ocular or cardiovascular disease. Written informed consent was obtained from all subjects. The study was carried out in accordance with the Declaration of Helsinki (2000) and was approved by the local research ethics committee.

Data acquisition and pre-processing

Doppler ultrasound blood velocity waveforms were captured from the ophthalmic artery (OA) by the same operator using a Philips ATL HDI 3500 ultrasound system (Advanced Technologies Laboratory, Bothwell, WA, USA) with a 12.5-MHz linear array probe and a standardized gate size of 1.5 mm. The optimum angle of insonation was selected by the operator and maintained at $<60^{\circ}$, to minimize velocity measurement errors. Maximum OA blood velocity waveforms, corrected for the corresponding Doppler angle, were extracted using HDI Laboratory software (Advanced Technologies Laboratory) with a fixed sampling frequency of 200 Hz. A typical waveform is illustrated in Figure 1. A standardized protocol was used to obtain OA blood velocity waveforms at baseline and after the administration of nitric oxide (NO)-modulating drugs, as illustrated in Figure 2.

All studies were conducted in the morning in a quiet, temperature-controlled room. The study started with a 20-minute acclimatization period, with subjects resting supine with their head supported on a pillow. Arterial blood pressure was recorded using a semi-automatic sphygmomanometer positioned on the left arm. The heart rate was continuously measured with a three-lead electrocardiograph.

The examined eye was randomly selected. During Doppler ultrasound recordings, the subject maintained gaze fixation with their non-examined eye on a point marked on the ceiling directly above their head. An initial baseline Doppler ultrasound velocity signal was recorded

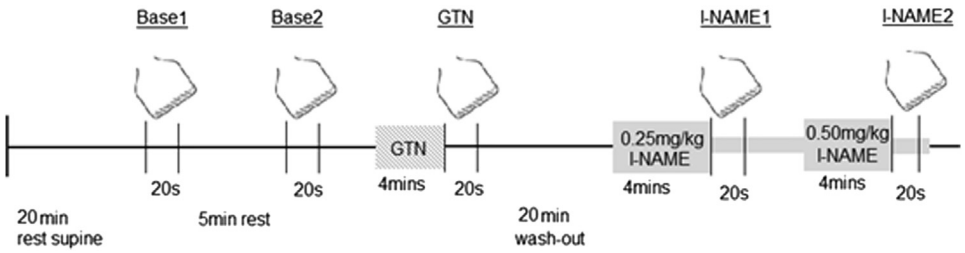

Fig. 2. Schematic diagram of study protocol. GTN = glyceryl trinitrate; LNAME = N^{G}-nitro-L-arginine-methyl ester.