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Spectral Analysis of Heart Period and Pulse Transit Time Derived from Electrocardiogram and Photoplethysmogram in Sepsis Patients

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Abstract— **Sepsis is a potentially lethal condition, and is one of the major causes of death in non-coronary intensive care units. Sepsis syndrome progresses through a number of increasingly severe stages, from systemic inflammatory response syndrome (SIRS) through sepsis, severe sepsis and septic shock. Each stage of sepsis is potentially characterized by differing autonomic nervous system responses. Spectral analysis of cardiovascular variability has been regarded as a possible non-invasive method to study this autonomic regulation, and in this study, the variabilities of heart period (RRi) and pulse transit time (PTT) derived from electrocardiogram and photoplethysmogram were investigated in three different groups: normal subjects ($n = 11$), SIRS ($n = 7$) and severe sepsis patients ($n = 16$), by computing spectral and cross-spectral measures in the low-frequency (LF) and the high-frequency (HF) ranges. SIRS and severe sepsis patients were found to have lower RRi ($p < 0.01$), augmented LF power in PTT ($p < 0.01$) and a lower RRi-PTT ratio (α_{PTT}) in the LF and HF bands ($p < 0.01$) as compared with the normal subjects, which might indicate a suppression of baroreflex-mediated autonomic control of heart rate and an increased sympathetic influence on ventricular contractility in sepsis. The results have highlighted the potential value of spectral analysis of RRi and PTT variabilities as a non-invasive tool for clinical evaluation of cardiac autonomic regulation in sepsis patients.**

I. INTRODUCTION

Sepsis syndrome is a systemic response to infection, and the most severe forms of the disease cause critical illness. It is potentially lethal; killing between 20 to 50 percent of severely affected patients, and remains the second leading cause of death in non-coronary intensive care units [1]. Due to conflicting diagnostic and monitoring questions a global estimate of 1.8 million cases per annum is likely to be a great underestimate of this syndrome, and some estimate that a more accurate total may actually approximate 18 million cases per annum [2]. Severe sepsis is usually associated with profoundly compromised hemodynamic, metabolic, and immunologic regulatory functions. It is the aggressive host response to a pathogen, rather than the pathogen itself, that is responsible for the devastating outcomes of the syndrome. Sepsis has variable severity, ranging from systemic inflammatory response syndrome (SIRS), severe sepsis, septic shock, and multiple organ dysfunction syndrome, representing increasingly severe stages of the same disease. Owing to the fact that sepsis is associated with distributive problems in blood flow [3], it is of particular interest to analyze the response of the autonomic nervous system (ANS) at different levels of sepsis syndrome severity, as both the vasculature and the heart are heavily influenced by autonomic control.

Heart period (RRi), measured by the distance between two consecutive R-waves of an electrocardiography (ECG) signal, is inversely related to heart rate, and the study of its variability in the evaluation of cardiovascular autonomic control in sepsis patients has been well documented [4], [5]. High frequency power (HF: 0.15 – 0.50 Hz) of RRi variability is believed to reflect parasympathetic modulation at respiratory frequency; while low frequency power (LF: 0.04 – 0.15 Hz) includes the combined effect of sympathetic and parasympathetic modulation, under the influence of baroreflex regulation [6].

This study also introduced the use of pulse transit time (PTT) to evaluate the autonomic regulatory function in sepsis patients. PTT, estimated as the time interval between the ECG R-wave and the arrival time of a peripheral pulse wave, is composed of pre-ejection period (PEP) and pulse wave propagation time [7]-[10]. Although the use of PTT in direct estimation of arterial blood pressure has been questioned, variations in PTT tend to be closely related to beat-to-beat blood pressure changes [7]-[9]. Previous studies have found that a substantial portion of the intra-individual PTT variation appeared to arise from changes in the PEP, which represents ventricular contractility under sympathetic influence, although the possible contribution of vascular transit time (VTT), which represents the time delay for pulse wave propagation and presumably affected by sympathetic vascular modulation, cannot be discarded [8]-[10].

In this pioneering study of PTT and RRi cross-spectrums in sepsis patients, it was hypothesized that the spectral characteristics of the PTT and RRi time series, in the LF and the HF bands, might be extensively changed in sepsis patients as a result of severe ANS disruption. This analysis was based on cardiovascular data collected from 28 patients at risk of sepsis, who presented to the Emergency Department of the Prince of Wales Hospital, Sydney from August 2006 to January 2007. A control group comprising 11 healthy subjects was used for comparative purposes.

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II. METHODS

The protocols used in this study were approved by the Prince of Wales Hospital Human Research Ethics Committee (HREC), as well as the Human Research Ethics Advisory (HREA) Panel of the University of New South Wales. Written informed consent was obtained from control subjects, informed verbal consent was obtained from individual adult patients at risk of sepsis, and verbal assent was obtained from patient's next of kin where necessary. The HREC allowed the waiver of informed written consent from sepsis patients due to both the critical illness and the benign and non-invasive nature of the study.

A. Study Samples

Sepsis group: The selection of sepsis patients relied upon convenience sampling with sequential recruitment of patients attending the Emergency Department of Prince of Wales Hospital from August 2006 to January 2007. 28 patients (13 males, 15 females) at high risk of SIRS and severe sepsis criteria as shown in Table I were enrolled into this study (SIRS = 9, severe sepsis = 19), with no exclusions based on gender or age. Patients were excluded if they presented in cardiopulmonary arrest or other clinical scenarios mandating immediate life saving treatment.

Control group: 11 healthy subjects (10 males, 1 female) were recruited into the study as controls. These subjects were free from any medication and were not allowed to consume any alcoholic beverages or caffeinated products prior to or during the measurement process. They were advised not to eat for at least 2 hours before the study or to undertake any intensive exercise within 12 hours prior.

B. Experimental Protocol

Sepsis group: Upon arrival at the Emergency Department, the patients' temperature, respiratory rate, heart rate, blood pressure, and oxygen saturation were measured. Meanwhile, arterial and venous blood gas samples, as well as the samples for routinely ordered hematology and biochemistry testing were also collected for subsequent analysis. Prior to the initiation of any intravenous interventions, the ECG and earlobe photoplethysmography (E-PPG) signals were measured and recorded from patients resting in supine position for a duration of at least 4 minutes. All patients were breathing spontaneously during the recording of signals. Thereafter, patients with a confirmed diagnosis of sepsis were treated routinely with airway management, supplemental oxygen and fluid resuscitation as required.

Control group: Control subjects were studied in a quiet dimly lit room at an ambient temperature of approximately 24°C. These subjects were instructed to rest in a supine position on a tilt table for a period of 20 minutes prior to data collection. All subjects were breathing spontaneously during the recording of ECG and E-PPG signals.

TABLE I

DIAGNOSTIC CRITERIA FOR SYSTEMIC INFLAMMATORY RESPONSE SYNDROME AND SEVERE SEPSIS [11].

Systemic Inflammatory Response Syndrome (SIRS):

- Temperature $> 38^{\circ}$C or $< 36^{\circ}$C.
- Heart rate > 90 beats per minute.
- Respiratory rate > 24 breaths per minute.
- White blood cell count $> 12000\ \mu\text{L}^{-1}$.

Severe Sepsis (SIRS Associated with Organ Dysfunctions):

- Central venous hypoxaemia $\text{ScVO}_2 < 70\%$.
- Acute oliguria (urine output < 0.5 mL kg^{-1}hr^{-1}).
- Creatinine increase > 0.5 mg/dL.
- Coagulation abnormalities (INR > 1.5 or aPTT > 60 secs).
- Thrombocytopenia (platelet count $< 100000\ \mu\text{L}^{-1}$).
- Hyperbilirubinemia (plasma total bilirubin > 4 mg/dL or 70 mmol/L).
- Hyperlactatemia (> 2 mmol/L).
- Hypotension (SBP < 90 mmHg, MAP < 70, or SBP decrease > 40 mmHg).

Abbreviations: *INR* international normalized ratio *aPTT* activated partial thromboplastin time *SBP* systolic blood pressure *MAP* mean arterial pressure.

C. Signal Processing

ECG and E-PPG signals were recorded and digitized at a sampling rate of 1 kHz using the Powerlab data acquisition system (ADInstruments, Sydney, Australia). Four-minute records free from significant corruption by artifact were selected. ECG R-waves and E-PPG troughs were identified through a custom written program in postprocessing software (Matlab, Mathworks Inc, Natick, MA). Detected R-waves and troughs were manually inspected and any existing artifacts or ectopic beats were manually replaced through linear interpolation of the beats immediately preceding and following the identified beats. Beat-to-beat PTT and RRi time series were finally low pass filtered and downsampled to evenly spaced samples at 4 Hz.

D. Spectral and Cross-Spectral Analysis

A power spectrum analysis technique based on averaging periodograms was utilized in this study to obtain smoothed power spectra. The four-minute time series of PTT and RRi were divided into five equal segments with 50% overlap (i.e., 80 seconds for each segment), before they were Hanning windowed and fast Fourier transformed into their frequency, f representations: $X_{\text{xx}}(f)$ and $X_{\text{yy}}(f)$ respectively. Auto-spectra of PTT and RRi were computed as $S_{\text{xx}}(f) = |X_{\text{xx}}(f)|^2$ and $S_{\text{yy}}(f) = |X_{\text{yy}}(f)|^2$. The cross-spectrum of PTT and RRi, $S_{\text{xy}}(f)$ was calculated from the product of $S^*_{\text{xx}}(f)$ and $S_{\text{yy}}(f)$ (where * denotes the complex conjugate).

The phase spectrum, $\theta(f)$, scaled from -180° to $+180^{\circ}$, was then estimated from $S_{\text{xy}}(f)$ as an indicator of the phase difference (lead or lag) between PTT and RRi. A negative $\theta(f)$ shows that PTT precedes RRi, and for a positive $\theta(f)$ the reverse holds. The coherence function, $\gamma^2(f)$, which holds the value between zero (i.e., RRi and PTT are totally uncorrelated) and one (perfect linear relationship between RRi and PTT), is important in the evaluation of the relationships between PTT and RRi. Within a given frequency band, $\theta(f)$ and γ^2 were obtained by averaging the corresponding values at frequencies where $\gamma^2 > 0.5$, or reporting only the values with maximum γ^2, if $\gamma^2 < 0.5$.

The spectral powers of PTT and RRi were derived from both LF (0.04 – 0.15 Hz) and HF (0.15 – 0.50 Hz) bands. Normalized low frequency power (LFn) was estimated as the ratio of LF power to the overall power spectrum, minus the very-low-frequency component (< 0.04 Hz). The representation of LF power in the form of normalized units may suppress the impact of inter-subject variation on the estimation of power spectra. In this study, the RRi-PTT ratio (α_{PTT}) was computed as the ratio of the square root of RRi to PTT spectral powers. Note that α_{PTT} was used in this study rather than the transfer function gain because α_{PTT} does not require the assumption of a direct causal relationship between RRi and PTT time series.

$$\alpha_{\mathrm{PTT}} = \sqrt{\frac{S_{\mathrm{yy(LF,HF)}}}{S_{\mathrm{xx(LF,HF)}}}} \tag{1}$$

E. Statistical Analysis

To analyze inter-subject differences at variable sepsis severity, quantitative indices of normal subjects, SIRS and severe sepsis patients were compared by performing a one-way ANOVA test. Prior to the test of means, normality and homoscedacity of the samples were checked using the Lilliefors and Bartlett tests respectively. All of the non-normal data were logarithmically transformed. When the ANOVA test results were significant, multiple comparisons of mean values were tested by unpaired Student's t-test (with Bonferroni adjustments). With $p < 0.05$ defined as statistically significant, 95% confidence intervals were calculated. For non-normal data, the geometric means and confidence intervals were reported.

III. RESULTS

Among the 39 study participants (normal = 11, SIRS = 9, and severe sepsis = 19), 5 participants (SIRS = 2 and severe sepsis = 3) were excluded from the study due to motion artifact or very low quality signals caused by poor peripheral perfusion. This led to the final inclusion of 11 normal, 7 SIRS, and 16 severe sepsis patients into the study. Table II compares the power spectra of cardiovascular signals (i.e., PTT and RRi) between normal subjects and sepsis patients (including both SIRS and severe sepsis patients) at different severity stages. Mean RRi was much lower in the sepsis patients compared with the normal subjects ($p < 0.01$), while the age of severe sepsis patients (mean age = 73 years old) was significantly greater than the other two groups ($p < 0.01$). The LF powers of PTT in SIRS and severe sepsis patients were significantly elevated ($p < 0.01$); while the LF power of RRi in severe sepsis patients was lower than the normal subjects ($p < 0.05$). By normalizing the power spectra of RRi, a significant difference was observed between the RRi LFn of SIRS and severe sepsis patients ($p < 0.01$).

In Table III, cross-spectral indices were compared between normal subjects and sepsis patients at different severity stages. The coherence in HF band was significantly lower in SIRS and severe sepsis patients relative to the normal subjects ($p < 0.01$). The α_{PTT} of both the LF and HF bands were also found to be significantly reduced in both patient groups. No significant differences in phase shifts between RRi and PTT could be observed between normal subjects and sepsis patients.

TABLE II

COMPARISON OF POWER SPECTRAL INDICES BETWEEN NORMAL SUBJECTS AND SEPSIS PATIENTS AT DIFFERENT SEVERITY STAGE

Indices	**Normal**	**SIRS**	**Severe Sepsis**
Age	30(24,35)	43(25,60)	73(67,80)††,**
Pulse Transit Time (PTT):			
Mean (sec)	0.12(0.10,0.13)	0.12(0.11,0.13)	0.13(0.12,0.14)
LF (ms^2)	3(2,4)	11(4,25)$^{\xi\xi}$	9(5,16)††
HF (ms^2)	10(7,15)	19(9,37)	28(16,49)†
LFn (%)	23(16,29)	38(25,51)	28(20,35)
Heart Period (RRi):			
Mean (sec)	1.03(0.98,1.08)	0.73(0.60,0.85)$^{\xi\xi}$	0.66(0.61,0.72)††
LF (ms^2)	718(492,1048)	306(123,762)	98(30,319)†
HF (ms^2)	747(371,1504)	84(16,434)	169(43,659)
LFn (%)	50(40,60)	77(53,101)	40(27,53)**

The symbols indicate statistically significant differences (after the Bonferroni's adjustment with $p < 0.05$ for single symbol and $p < 0.01$ for double symbols): ξ for normal vs. SIRS; † for normal vs. severe sepsis, and $*$ for SIRS vs. severe sepsis. 95% confidence intervals are stated in brackets.
Abbreviations: *LF* low frequency power *HF* high frequency power *LFn* normalized low frequency power [100 LF/(LF+HF)].

IV. DISCUSSIONS

The most significant finding of this study was a decrease in α_{PTT}, within both the LF and HF bands in sepsis patients (SIRS and severe sepsis) compared to normal individuals. In the LF band in particular, the decrease in the α_{PTT} was driven by a concomitant increase in PTT LF power and decrease in RRi LF power. The decrease in RRi variability particularly in severe sepsis was in agreement with previous research findings, and might relate to the suppression of cardiac autonomic control by the arterial baroreflex [13]-[15]. However, the effect of older age might also contribute in part to the lower RRi variability in severe sepsis patients [16]. The increase in PTT variability in sepsis patients, on the other hand, is more difficult to explain given the lack

TABLE III

COMPARISON OF CROSS-SPECTRAL INDICES BETWEEN NORMAL SUBJECTS AND SEPSIS PATIENTS AT DIFFERENT SEVERITY STAGE.

Indices	**Normal**	**SIRS**	**Severe Sepsis**
Coh. LF	0.62(0.52,0.72)	0.59(0.52,0.66)	0.58(0.55,0.60)
Coh. HF	0.73(0.70,0.76)	0.61(0.57,0.66)$^{\xi\xi}$	0.65(0.61,0.68)††
α_{PTT} LF	18(14,22)	7(3,10)$^{\xi\xi}$	5(3,6)††
α_{PTT} HF	11(6,15)	3(1,4)$^{\xi}$	4(2,6)††
Pha. LF	28(-22,78)	31(-32,94)	32(-7,71)
Pha. HF	-61(-102,-19)	23(-35,82)	-21(-53,10)

The symbols indicate statistically significant differences (after the Bonferroni's adjustment with $p < 0.05$ for single symbol and $p < 0.01$ for double symbols): ξ for normal vs. SIRS and † for normal vs. severe sepsis. 95% confidence intervals are stated in brackets.
Abbreviations: *Coh* coherence α ratio of the square root of RRi to PTT spectral powers *Pha* phase angle *LF* low frequency power *HF* high frequency power.

of prior work in this area. The LF fluctuation in PTT likely arises from the sympathetic modulation of either ventricular contractility or peripheral vascular tone, which has a major influence on PEP and VTT respectively. Other researches have found that LF diastolic blood pressure (DBP) variability tended to be lower in sepsis patients compared with normal subjects, suggesting an impaired autonomic vascular control [13]. Given the close relationship of VTT with DBP [9], an increase in LF power of VTT in sepsis patients would seem to be unlikely. Alternatively, the increase in LF power of PTT might arise from an increase in LF PEP variability, as a result of an increased dependency of ventricular contractility on cardiac sympathetic nerve stimulation in sepsis [17]. However, further studies are required to ascertain whether this is the case.

Given that PTT variability is inversely related to systolic blood pressure variability [9], [18], a possibility exists that the α_{PTT} may relate to the baroreflex gain calculated from the ratio between the spectral powers of RRi and blood pressure variability [12], and its decrease in sepsis patients may be related to impairment of the baroreflex function [15], [19]. However, the results from the cross-spectral analysis between PTT and RRi in this study do not seem to suggest a baroreflex-driven relationship in the LF range, as the change in RRi was slightly leading the change in PTT (which could only mean that an increase in heart rate was followed by an increase in blood pressure). This finding was in agreement with a previous investigation of RRi and PTT changes during paced respiration [20]. A more appropriate explanation for this decrease in α_{PTT} in sepsis patients might be a concomitant increase in sympathetic modulation of ventricular contractility (causing an increase in PTT LF power), and decrease in baroreflex-mediated autonomic modulation of RRi (causing a decrease in RRi LF power). Future work should be directed to the investigation of the physiological links between PTT and RRi variability and how they are related to cardiac autonomic tone and baroreflex control, to better understand how these techniques may be applied in clinical diagnosis of sepsis.

V. CONCLUSIONS

In this study, spectral analysis of RRi and PTT variability was performed in three different study groups, namely normal subjects, SIRS and severe sepsis patients. Both SIRS and severe sepsis patients were found to have lower RRi, augmented LF power in PTT and a lower α_{PTT} in LF and HF bands compared with normal subjects. These results highlight the potential use of spectral analysis of RRi and PTT signals as a noninvasive tool in the clinical diagnosis of sepsis syndrome. Further work is required to better understand the physiological links between the PTT and RRi variability and how they are related to the alteration in autonomic control in sepsis patients.

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