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NOTE

Segmenting cardiac-related data using sleep stages increases separation between normal subjects and apnœic patients

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Abstract

Inter-patient comparisons of cardiovascular metrics indicative of patient health have been shown to be successful in differentiating patients on a group rather than an individual level. This is in part due to the range of mental (as well as physical) activity-based variations for each patient and the difficulty assessing physical and mental activity during conscious states. In order to provide an objective scale for measuring central nervous system activity during sleep, the heart rate (RR) interval time series is divided into coarse sleep stage segments in which the $\frac{\mathrm{LF}}{\mathrm{HF}}$-ratio (the relative balance between low and high frequency power) is estimated for age and sex-matched populations of apnœic and healthy subjects. Activity-based noise is therefore reduced and a more useful comparison of heart rate variability can be made. Additionally, the spectral estimation performances of the FFT and the Lomb–Scargle periodogram (LSP), a Fourier-based technique for unevenly sampled time series are compared. Separation of patients according to condition is shown to be more pronounced when using the LSP than the FFT. Furthermore, separation is found to be most marked in slow wave sleep.

Keywords: apnœa, FFT, heart rate variability, HRV, irregular sampling, LF/HF-ratio, lomb periodogram, resampling, sleep, spectral analysis

1. Introduction

When assessing a patient's status through cardiovascular (CV) parameters such as heart rate variability (HRV) metrics, it is known that the activity level needs to be quantified both from a physical and a mental perspective (Malik and Camm 1995, Malik 1996, Bernardi *et al* 2000). Although there is no general consensus on how to measure levels of mental activity during

wakefulness because of extraneous factors (Holt 1997, Ogilvie *et al* 1989), there is a generally agreed classification of mental activity for subjects during sleep (Lavie *et al* 1999), the R&K rules (Rechtschaffen and Kales 1968).

Recent reports have shown that significant differences in HRV metrics are observed in different sleep states (Vanoli *et al* 1995). One such metric is the $\frac{\mathrm{LF}}{\mathrm{HF}}$-ratio, the relative contribution of the low frequency (LF) and high frequency (HF) components of the beat-to-beat (RR) heart rate time series (Malik and Camm 1995). This is thought to be in part due to the $\frac{\mathrm{LF}}{\mathrm{HF}}$-ratio's dependence on changes in the sympathovagal balance which occur during sleep (Lavie 1996).

In this paper, an analysis is presented of the $\frac{\mathrm{LF}}{\mathrm{HF}}$-ratio for two patient groups (one normal and one suffering from sleep apnœa). The average $\frac{\mathrm{LF}}{\mathrm{HF}}$-ratio within these states is compared for the patients within each group in order to demonstrate that segmenting the RR time series into sleep stages increases the separation of $\frac{\mathrm{LF}}{\mathrm{HF}}$-ratio values for these patient groups. Furthermore, conventional FFT techniques will be compared with Lomb–Scargle periodogram (LSP), a Fourier-based method for irregularly sampled data (Scargle 1982, Moody 1993), to demonstrate the increased accuracy of the latter technique.

2. Background

Bernardi *et al* (2000) recently demonstrated that HRV (as measured by the $\frac{\mathrm{LF}}{\mathrm{HF}}$-ratio) in conscious patients changes markedly depending on the subject's activity. Their analysis involved measuring the ECG, respiration and blood pressure of 12 healthy subjects all aged around 29 years for 5 min during a series of simple physical (verbal) and mental activities. Despite the similarity in subject physiology and physical activity (all remained in the supine position for at least 20 min prior to and during the recording), the day-time $\frac{\mathrm{LF}}{\mathrm{HF}}$-ratio had a strong dependence upon mental activity, ranging from 0.7 for controlled breathing to 3.6 for free talking. It may be argued that the changes in these values are simply an effect of changing breathing patterns (that modify the HF component). However, significant changes in both the LF component and blood pressure readings were also observed, indicating that the feedback loop to the central nervous system (CNS) was definitely affected so that the resultant change in HRV is more than just a respiratory phenomenon.

Differences in mental, as well as physical activity should therefore be minimized when comparing HRV metrics on an inter- or intra-patient basis. Since it is probably impossible to be sure whether or not even a willing subject is controlling their thought processes for a few minutes (the shortest time window for HRV metrics (Malik 1996)), this would imply that HRV is best monitored while the subject is asleep during which the level of mental activity can be more easily assessed.

Furthermore artefact in the ECG is reduced during sleep since there is less physical movement by the subject and the variation in $\frac{\mathrm{LF}}{\mathrm{HF}}$-ratio with respect to the mean value is reduced within a sleep state (Clifford *et al* 2002, Clifford 2002). (However, apnœic subjects can exhibit higher than normal levels of artefact during sleep.) Sleep stages usually last more than 5 min (Lavie 1996), the minimum required for spectral analysis of HRV (Malik and Camm 1995). Segmenting the RR time series according to sleep state basis should therefore provide data segments of sufficient length with minimal data corruption and departures from stationarity (which otherwise invalidate the use of Fourier techniques).

The standard objective scale for CNS activity during sleep was defined by Rechtschaffen and Kales (1968); a set of heuristics known as the R&K rules which are based partly on the frequency content of the electroencephalogram, the electrooculogram and the electromyogram

Table 1. $\frac{\mathrm{LF}}{\mathrm{HF}}$-ratios during wakefulness, NREM and REM sleep. N/A = not available, Norm = normal, Post-MI = a few days after myocardial infarction, CNS indicates a non-cardiac related problem. Taken from (Otzenberger *et al* 1998, Malik 1996, Vanoli *et al* 1995, Lavie *et al* 1999).

	Activity		
Condition	Awake	REM sleep	NREM sleep
Norm (Otzenberger *et al* 1998)	N/A	$2 \rightarrow 2.5$	$0.5 \rightarrow 1$
Norm (Malik 1996)	3.9	2.7	1.7
Norm (Vanoli *et al* 1995)	4.0 ± 1.4	3.1 ± 0.7	1.2 ± 0.4
CNS Problem (Lavie *et al* 1999)	N/A	$3.5 \rightarrow 5.5$	$2 \rightarrow 3.5$
Post-MI (Vanoli *et al* 1995)	2.4 ± 0.7	8.9 ± 1.6	5.1 ± 1.4

and assessed by expert observers over 30 s epochs. One of the five defined stages of sleep is termed dream or rapid eye movement (REM) sleep. Stages 1–4 (light to deep) are non-REM (NREM) sleep, in which dreaming does not occur. NREM sleep can be further broken down into drowsy sleep (stage 1), light sleep, (stages 1 and 2) and deep sleep (stages 3 and 4). When stages 3 and 4 are combined they are known as slow wave sleep (SWS). Healthy humans cycle through these sleep stages with a period of around 100 min and each sleep stage can last up to 20 min during which time the CV system undergoes few changes, with the exception of brief arousals (Lavie 1996).

When loss of consciousness occurs, the parasympathetic nervous system begins to dominate with an associated rise in HF and decrease in $\frac{\mathrm{LF}}{\mathrm{HF}}$-ratio. This trend is more marked for deeper levels of sleep (Vanoli *et al* 1995, Otzenberger *et al* 1998). Power spectral densities (PSDs) calculated from 5 min of RR interval data during wakefulness and REM sleep reveal similar spectral components and $\frac{\mathrm{LF}}{\mathrm{HF}}$-ratios (Otzenberger *et al* 1998). However, stage 2 sleep and SWS sleep exhibit elevated HF contributions (above 0.15 Hz) with $\frac{\mathrm{LF}}{\mathrm{HF}}$-ratio values around 0.5 to 1 in NREM sleep and 2 to 2.5 in REM sleep (Otzenberger *et al* 1998). In patients suffering from a simple CNS but non-cardiac related problem, Lavie *et al* (1999) found slightly elevated NREM $\frac{\mathrm{LF}}{\mathrm{HF}}$-ratio values of between 2 and 3.5 and between 3.5 and 5.5 for REM sleep.

Vanoli *et al* (1995) report that myocardial infarction (MI) generally results in a raised overall $\frac{\mathrm{LF}}{\mathrm{HF}}$-ratio during REM and NREM sleep with elevated LF and $\frac{\mathrm{LF}}{\mathrm{HF}}$-ratio (as high as 8.9) and lower HF. Values for all subjects during wakefulness in these studies (2.4 to 4.0) lie well within the range of values found during sleep (0.5 to 8.9) for the same patient population (see table 1). This demonstrates that comparisons of HRV between subjects should be performed on a sleep-stage specific basis. In this paper, the variations of the $\frac{\mathrm{LF}}{\mathrm{HF}}$-ratio during SWS, REM and NREM sleep states in both a normal healthy population and an apnœic population are investigated.

3. Methods: data selection, preprocessing and HRV metric estimation

Two test groups of data are compared in this analysis. The data for the healthy group are taken from a polysomnographic database (PSDB) (Clifford 2002) which consists of records from six males between the ages of 21 and 42, mean age 36, weighing between 65 kg and 90 kg with no known sleeping or cardiac-related problems. Subjects 01 to 06 slept for 6.5, 7.0, 3.3, 7.7, 7.5 and 7.4 h respectively. Subject 03 awoke early because of a non-health related incident. Subject 05's ECG was of too low quality to be included in the study.

The other group contains four (of a possible 16) male sleep apnœics, aged 32 to 56 (mean age 43), with weights ranging from 89 to 152 kg (mean weight 119 kg). These data are freely available as the MIT PSDB (Goldberger *et al* 2000). Each of the records in the database includes sleep stage, arousal/apnœa and ECG beat annotations. Sleep-stage annotation (and apnœa annotation if relevant) are provided for each 30 s epoch. Apnœa indices for each patient can therefore be calculated but most (if not all) records include both baseline and continuous positive airway pressure which are not indicated. A more detailed description of the database is given in Goldberger *et al* (2000).

The changes in the ECG (and hence HRV) due to sleep apnœa are complex (Clifford 2002, Goldberger *et al* 2000) and therefore sections free from apnœas are selected to ensure that the analysis is not complicated by the apnœic episodes. During such episodes a patient moves rapidly through different levels of consciousness and RR interval data are dominated by respiratory effects and often corrupted by movement artefact (Clifford 2002). Therefore only relatively low-noise ECG sections, free from apnœic events are considered. From an extensive manual review of the data patients 03, 04, 41 and 48 were chosen, with (onset, offset) indices of (2748292, 3472103), (3832987, 4393917), (3498887, 4559463) and (2756692, 3595661) respectively. The selected data segments are all longer than 30 min and contain little or no artefact.

All beat-to-beat interval times (RR tachograms) are extracted from the ECG using a standard peak detection algorithm (Pan and Tompkins 1985) and abnormal beats are removed using a timing threshold as described in Clifford *et al* (2002), which are freely available from (Goldberger *et al* 2000). The $\frac{\mathrm{LF}}{\mathrm{HF}}$-ratio is commonly calculated using the FFT applied to 5 min segments of RR interval data. Since the RR tachogram is inherently an unevenly sampled signal, and the use of the FFT implicitly assumes that the data are evenly spaced, resampling must be performed. A more appropriate PSD estimation method is the LSP (Scargle 1982, Press *et al* 1992) which evaluates the PSD on a per point basis, rather than a per-sample basis (see Clifford (2002) and Clifford and Tarassenko (2005) for further details and results from experiments on artificial data).

The RR tachogram for each patient is segmented into sections based upon sleep state (REM, NREM or SWS). A sliding 5 min window, with a 4.5 min overlap, is used to calculate the $\frac{\mathrm{LF}}{\mathrm{HF}}$-ratio value within these segments (giving a value every 30 s, the same frequency as the sleep annotations). Each subject therefore has at least 100 $\frac{\mathrm{LF}}{\mathrm{HF}}$-ratio values per sleep state.

As two expert scores are available for the normal database, a consensus labelling method is used, and a sleep score is allocated to a particular $\frac{\mathrm{LF}}{\mathrm{HF}}$-ratio if and only if

(i) both sleep experts agree on the score *and*
(ii) when there is a majority of epochs (i.e. at least six) with the same consensus score in a 5 min window (ten 30 s epochs) *and*
(iii) the $\frac{\mathrm{LF}}{\mathrm{HF}}$-ratio < 20 (since values above this are likely to be due to artefacts or sudden arousals not identified in the sleep score).

Calculations of the mean and variance of all the $\frac{\mathrm{LF}}{\mathrm{HF}}$-ratios in each of the three sleep states (SWS, REM and NREM sleep) were performed. In addition, statistical tests between the $\frac{\mathrm{LF}}{\mathrm{HF}}$-ratios for each of the sleep states were calculated for each sleep state, each spectral estimation technique and between patient groups. Note that since a sliding 5 min window with a 4.5 min overlap was used, each patient had over 100 points per sleep state and therefore statistical tests between these sections of data could demonstrate significance. Student's *t*-test (for unequal variances, assuming that change in a sleep state will affect the form of the distribution) was applied to test that the mean $\frac{\mathrm{LF}}{\mathrm{HF}}$-ratios were significantly different betwen these data sets. The F-test and the Kolmogorov–Smirnov (KS) test (Press *et al* 1992) were also applied to

Table 2. Mean $\frac{\mathrm{LF}}{\mathrm{HF}}$-ratio ($\overline{x}$) and S.D. ($\sigma$) for each of the three PSD estimation methods for normal subjects in REM sleep, NREM sleep and SWS.

	Sleep stage			
Subject	PSD method	REM $\overline{x} \pm \sigma$	NREM $\overline{x} \pm \sigma$	SWS $\overline{x} \pm \sigma$
01	LSP	3.02 ± 1.79	1.50 ± 1.21	0.62 ± 0.77
	$\mathrm{FFT_{cub}}$	6.46 ± 3.84	3.14 ± 3.57	0.83 ± 1.30
	$\mathrm{FFT_{lin}}$	6.67 ± 3.50	3.61 ± 3.48	1.10 ± 1.25
02	LSP	1.59 ± 1.71	2.07 ± 1.51	1.92 ± 1.12
	$\mathrm{FFT_{cub}}$	2.89 ± 3.12	2.76 ± 2.84	2.27 ± 1.87
	$\mathrm{FFT_{lin}}$	4.42 ± 4.59	3.80 ± 3.36	3.46 ± 2.93
03	LSP	4.63 ± 1.96	3.10 ± 2.12	1.18 ± 0.52
	$\mathrm{FFT_{cub}}$	7.94 ± 4.98	4.10 ± 4.19	1.30 ± 0.74
	$\mathrm{FFT_{lin}}$	9.44 ± 5.21	5.09 ± 4.39	1.94 ± 1.14
04	LSP	2.44 ± 1.35	1.82 ± 1.60	0.95 ± 0.40
	$\mathrm{FFT_{cub}}$	3.57 ± 3.28	2.60 ± 3.39	1.07 ± 0.68
	$\mathrm{FFT_{lin}}$	4.66 ± 4.15	3.08 ± 3.42	1.48 ± 0.96
06	LSP	5.88 ± 3.60	4.39 ± 2.91	2.39 ± 1.31
	$\mathrm{FFT_{cub}}$	6.79 ± 4.57	5.01 ± 4.19	2.53 ± 1.76
	$\mathrm{FFT_{lin}}$	8.59 ± 5.13	6.19 ± 4.48	3.65 ± 2.50

the same data. The F-test determines the probability that the variances in each distribution are significantly different (and hence variability is significantly *less* in one particular sleep state). The KS statistic is used for calculating the significance level for the probability of two data sets being drawn from different distribution functions and hence to investigate if there is a significant shift in baseline levels of stationarity between sleep states. Spreading of the distribution affects the tails of the probability distribution and may leave the median value unchanged. The KS statistic is therefore insensitive to outliers and changes in the distribution tails. It is a robust method of finding shifts (rather than spreads) in a probability distribution (especially changes in the median value). These statistical tests assume that the samples from each sleep state are drawn from normal distributions (which was confirmed by checking the kurtosis was near Gaussian) (Press *et al* 1992) and that the distributions in different states are independent; that is, the fluctuations in the $\frac{\mathrm{LF}}{\mathrm{HF}}$-ratios in SWS are not a function of the fluctuations in the $\frac{\mathrm{LF}}{\mathrm{HF}}$-ratios in REM sleep, and vice versa, but rather, they are a function of the intrinsic activity within that sleep state.

4. Results

4.1. Results on normal subjects

Table 2 presents results for the within-sleep state (SWS, REM or NREM) mean $\frac{\mathrm{LF}}{\mathrm{HF}}$-ratio ($\overline{x}$) and standard deviation (σ) for each of the three PSD estimation methods: the LSP, FFT with 7 Hz cubic spline interpolative resampling ($\mathrm{FFT_{cub}}$) and FFT with 7 Hz linear resampling ($\mathrm{FFT_{lin}}$) (see Clifford and Tarassenko (2005) for details of these algorithms).

Table 2 shows that the largest separation between the mean $\frac{\mathrm{LF}}{\mathrm{HF}}$-ratio estimates occurs between SWS and REM sleep. FFT methods, at first sight, appear to allow a greater separation between REM and deep sleep (SWS) than the LSP. However, the σ in the calculation of the sleep-stage specific means are large for FFT methods ($5.2 \geqslant \sigma \geqslant 3.1$ for REM sleep and

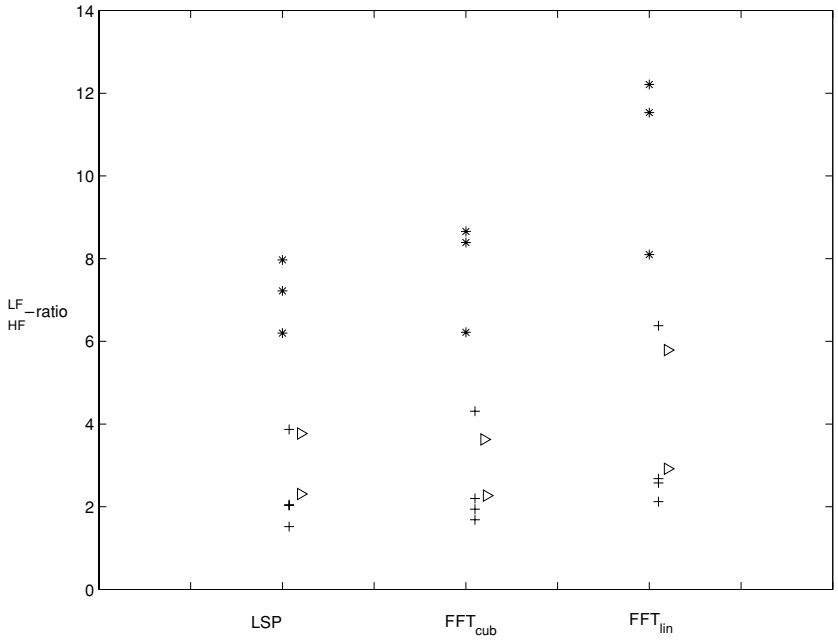

Figure 1. $\frac{\mathrm{LF}}{\mathrm{HF}}$-ratio estimates for sleep apnœic subjects (MIT PSDB) for each of the three spectral estimation methods being tested; the LSP, the FFT after cubic spline interpolation ($\mathrm{FFT_{cub}}$) and FFT after linear interpolation ($\mathrm{FFT_{lin}}$). Each patient's average $\frac{\mathrm{LF}}{\mathrm{HF}}$-ratio is given for REM sleep ($*$), NREM sleep (+) and SWS sleep ($\triangleright$) for each of the three spectral estimation methods (see text for details).

$3.6 \geqslant \sigma \geqslant 0.83$ for SWS; see table 2). In contrast to this, the σ (and hence variances) in the LSP estimates are significantly smaller.

Using the F-test, only the LSP method gave significantly different variances between NREM and REM sleep. Although it is highly likely ($P < 0.005$) that the $\frac{\mathrm{LF}}{\mathrm{HF}}$ values in REM sleep have a different distribution to those in NREM sleep for all spectral estimation techniques, only the LSP gives significantly different mean $\frac{\mathrm{LF}}{\mathrm{HF}}$-ratios for all subjects. In contrast to this, all three spectral estimation methods gave significantly different variances, means and distributions between SWS and REM sleep. No significant differences in the mean $\frac{\mathrm{LF}}{\mathrm{HF}}$-ratio values calculated by each of the three PSD methods were found between SWS and REM sleep. However, in the case of the LSP only, the KS test indicates that the distribution of $\frac{\mathrm{LF}}{\mathrm{HF}}$-ratio values is significantly different between these two states.

4.2. Results on sleep apnœic subjects

Table 3 presents the mean $\frac{\mathrm{LF}}{\mathrm{HF}}$-ratios for each of the four sleep apnœic subjects in each of the three sleep states (REM, NREM and SWS). N/A (not applicable) indicates that for the segment of data analysed the subject did not experience that particular stage of sleep. Figure 1 is a plot of the mean values from this table.

Application of the F-test, KS test and unequal *t*-test to this data reveal that in general, only the LSP method gives significantly different variances ($P < 0.05$) between NREM and REM sleep. Although the $\frac{\mathrm{LF}}{\mathrm{HF}}$ values in REM sleep have significantly different distributions to those in NREM sleep for each PSD estimation method, no significant difference exists between the mean $\frac{\mathrm{LF}}{\mathrm{HF}}$-ratios between these sleep states for any of the PSD estimation techniques

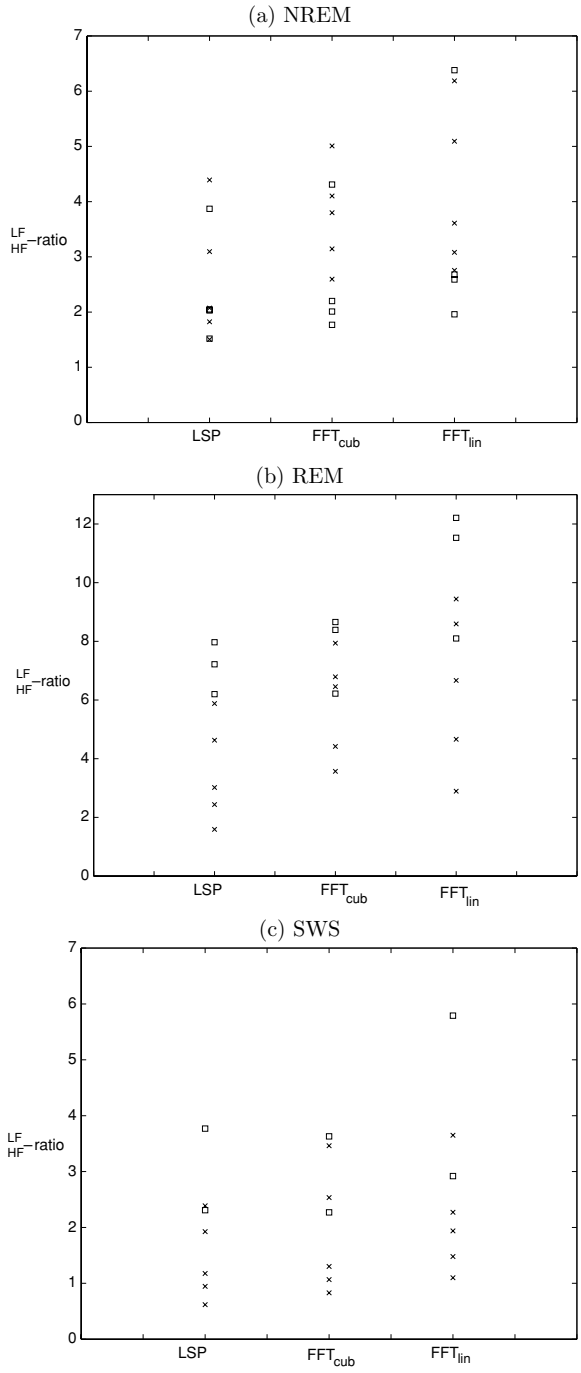

Figure 2. $\frac{\mathrm{LF}}{\mathrm{HF}}$-ratio estimates for normal subjects ($\times$) and patients suffering from sleep apnœa ($\diamond$) in (a) NREM sleep, (b) REM sleep and (c) SWS for each of the three spectral estimation methods being tested; the LSP, the FFT after cubic spline interpolation ($\mathrm{FFT}_{\mathrm{cub}}$) and FFT after linear interpolation ($\mathrm{FFT}_{\mathrm{lin}}$). Note that better patient group separation is achieved by $\frac{\mathrm{LF}}{\mathrm{HF}}$-ratio estimates using the LSP in SWS and REM sleep.

Table 3. Mean $\frac{\mathrm{LF}}{\mathrm{HF}}$-ratio ($\overline{x}$) and σ for each of the three PSD estimation methods in REM sleep, NREM sleep and SWS for sleep apnœic subjects. N/A indicates not applicable; in the segment of data analysed the subject did not experience this category of sleep.

		Sleep stage		
Subject	PSD method	REM $\overline{x} \pm \sigma$	NREM $\overline{x} \pm \sigma$	SWS $\overline{x} \pm \sigma$
03	LSP	6.20 ± 1.49	2.03 ± 1.42	2.31 ± 0.85
	$\mathrm{FFT_{cub}}$	6.22 ± 2.59	2.01 ± 1.50	2.27 ± 1.30
	$\mathrm{FFT_{lin}}$	8.10 ± 3.25	2.59 ± 1.91	2.92 ± 1.66
04	LSP	N/A	1.52 ± 0.48	N/A
	$\mathrm{FFT_{cub}}$	N/A	1.77 ± 1.11	N/A
	$\mathrm{FFT_{lin}}$	N/A	1.96 ± 1.02	N/A
41	LSP	7.22 ± 2.43	3.87 ± 1.72	3.77 ± 0.41
	$\mathrm{FFT_{cub}}$	8.39 ± 2.69	4.31 ± 2.33	3.63 ± 0.86
	$\mathrm{FFT_{lin}}$	12.21 ± 3.86	6.38 ± 3.21	5.79 ± 1.40
48	LSP	7.97 ± 2.16	2.05 ± 1.17	N/A
	$\mathrm{FFT_{cub}}$	8.66 ± 3.16	2.20 ± 1.30	N/A
	$\mathrm{FFT_{lin}}$	11.53 ± 4.14	2.68 ± 1.66	N/A

being tested. In contrast to this, there exists significantly different variances, distributions and means of the $\frac{\mathrm{LF}}{\mathrm{HF}}$-ratio between SWS and REM sleep. It should be noted that the mean FFT-based $\frac{\mathrm{LF}}{\mathrm{HF}}$-ratio values for healthy subjects and apnœic patients during sleep correspond to previously reported values by other authors using FFT-based techniques (Vanoli *et al* 1995, Otzenberger *et al* 1998). Results for the LSP are consistent with those found in simulations (Clifford and Tarassenko 2005). No intra-patient $\frac{\mathrm{LF}}{\mathrm{HF}}$-ratio variances have been previously reported.

5. Conclusions

The results from the $\frac{\mathrm{LF}}{\mathrm{HF}}$-ratio estimates for sleep apnœa sufferers and normal healthy subjects from tables 2 and 3 are compared on a per-sleep stage basis in figures 2(a)–(c) for the three spectral estimation methods: LSP, $\mathrm{FFT_{lin}}$ and $\mathrm{FFT_{cub}}$. Note that the LSP method results in a higher degree of class separation in all sleep states. SWS and REM sleep produce the largest contrasting mean and σ values of $\frac{\mathrm{LF}}{\mathrm{HF}}$-ratio. Calculation of these values using the LSP method produces a more consistent estimate (lower variances) than with either of the two FFT methods. Thus, the LSP method may allow a categorization of the state of the autonomic nervous system for patients using an HRV metric alone, provided that it is measured in SWS or REM sleep. SWS is a particularly good parameter for segmenting epochs of RR interval data for HRV studies because of the low variance in $\frac{\mathrm{LF}}{\mathrm{HF}}$-ratio values in deep sleep and is therefore the preferred sleep state to compare $\frac{\mathrm{LF}}{\mathrm{HF}}$-ratios between patients. Furthermore, artefacts tend to be less prevalent in SWS than at any other time (Lavie 1996, Clifford *et al* 2002). However, sleep apnœa severely reduces the amount of SWS a subject exhibits and so it may be necessary to compare mean $\frac{\mathrm{LF}}{\mathrm{HF}}$-ratios from REM sleep periods instead in order to have a long enough segment of data on which to make statistically viable estimates and comparisons of the $\frac{\mathrm{LF}}{\mathrm{HF}}$-ratio.

It should be noted that the number of subjects in this study was limited to just nine and a more extensive study is required to determine if these trends hold for the population in general.

However, the length of each individual recording means statistically meaningful inter-subject and inter-sleep state comparisons can be made.

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