Comparative analysis between PPG variability and HRV during non-stationary tilt table test

Eduardo Gil, Michele Orini, Raquel Bailón, José María Vergara and Pablo Laguna

***Abstract*—In this study we assessed the possibility of using the pulse rate variability (PRV) extracted from the photoplethysmography signal as an alternative measurement of the HRV signal in non-stationary conditions. The study is based on the analysis of the changes observed during tilt table test in the heart rate modulation of 17 young subjects. First, classical indices of HRV analysis were compared to indices from PRV in two–minute intervals where stationarity was assumed. Second, time–frequency (TF) analysis based on the Smooth Pseudo Wigner–Ville distribution was used to compare the time-varying spectral properties of both signals. Third, the effect of replacing HRV with PRV in the assessment of the changes of the autonomic modulation of the heart rate was considered. Classical time-invariant HRV and PRV indices were comparable, never statistically different ($p >$0.05) and highly correlated ($>$0.97). Time-frequency analysis revealed that: the TF spectra of both signals were highly correlated (0.99$\pm$0.01); the difference between the instantaneous power in LF and HF bands was small ($<10^{-3}s^{-2}$) and their temporal patterns were highly correlated (0.98$\pm$0.04 and 0.95$\pm$0.06 in LF and HF bands, respectively). Finally, the instantaneous power in LF was observed to significant increase during head-up tilting by both HRV and PRV analysis. These results support the use of the PRV analysis to assess the temporal pattern of the autonomic modulation of the heart rate, at least during tilt table test.**

***Index Terms*—PRV, HRV, tilt table test**

I. INTRODUCTION

Heart rate variability (HRV) analysis is one of the most widely used non–invasive techniques for the evaluation of the autonomic nervous system. Power spectral density of the HRV exhibits oscillations related to the parasympathetic and sympathetic activities [1]. The range between 0.04 and 0.15 Hz (low–frequency component, LF) represents both sympathetic and parasympathetic modulation, although an increase in its power is generally associated with a sympathetic activation. The range between 0.15 and 0.4 Hz (high–frequency component, HF) corresponds to parasympathetic modulation and is synchronous with the respiratory rate. Finally, the ratio between the power in LF and HF bands is an index to evaluate the sympatho–vagal balance controlling the heart rate [1].

This work was partially supported by Ministerio de Ciencia y Tecnología, FEDER under Project TEC2007-68076-C02-02/TCM and Grupo Consolidado GTC from DGA.

E. Gil, M. Orini, R. Bailón and P. Laguna are with Communications Technology Group, Aragón Institute of Engineering Research, University of Zaragoza, Zaragoza, Spain and CIBER de Bioingeniería, Biomateriales y Nanomedicina (CIBER-BBN), Instituto de Salud Carlos III (FEDER).

M. Orini is also with Department of Bioengineering, Politecnico di Milano, Milano, Italy

J.M. Vergara is with Sleep Department, Miguel Servet Children Hospital, Zaragoza, Spain and CIBER de Bioingeniería, Biomateriales y Nanomedicina (CIBER-BBN), Instituto de Salud Carlos III (FEDER).

Pulse photoplethysmography (PPG) is a simple and useful method for measuring the relative blood volume changes in the microvascular bed of peripheral tissues and evaluating peripheral circulation. Pulse photoplethysmography has been applied in many different clinical settings, including the monitoring of blood oxygen saturation, heart rate, blood pressure, cardiac output and respiration. Given its simplicity, low–cost and that it is widely used in the clinical routine, it is desirable to maximize PPG potential by exploring additional measurements which can be derived from it.

It is generally accepted that PPG can provide valuable information about the cardiovascular system. The autonomic influences on PPG signal have been analysed in several studies and recently pulse rate variability (PRV) extracted from PPG has been studied as a potential surrogate of HRV [2], [3], [4]. The difference between HRV and PPGV is the time it takes the pulse wave to travel from the heart to the finger. This time, called the pulse transit time (PTT), is tie–related to arterial compliance and blood pressure and changes beat to beat.

All the studies exploring the possibility of using PRV as an alternative measurement of HRV have been performed in stationary conditions using time–invariant analysis. However, there are many situations where significant changes in autonomic balance occur, as during orthostatic test, Valsalva maneuver, exercise stress testing and after pharmacologic interventions, which involve non–stationary processes. We focused this study on tilt table test. In this test, after head–up tilt, subjects undergo a progressive orthostatic stress and blood pressure is maintained thanks to cardiovascular regulation, which involves an increase in heart rate and a constriction of the blood vessels in the legs. This slight tachycardia and vasoconstriction are the result of sympathetic activation and vagal withdrawal. When the supine position is restored from the tilted stage, heart rate and vasoconstriction returns to previous basal values together with sympathetic tone.

The aim of this work is to evaluate the usefulness of PRV as a surrogate of HRV analysis during non–stationary conditions, in particular, during tilt table test. Traditional time–invariant analysis as well as time–frequency (TF) analysis was performed to asses whether the PRV can be used in the analysis of the autonomic modulation of heart rate in non–stationary conditions.

II. MATERIAL AND METHODS

A. Data and preprocessing

Seventeen volunteers (age 28.5$\pm$ 2.8 years, 11 males) underwent a head–up tilt table test according to the following

protocol: 4 minutes in early supine position (T_1), 5 minutes tilted head–up to an angle of 70 degrees (T_2) and 4 minutes back to later supine position (T_3), see Fig. 1. The PPG signal

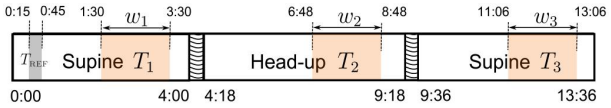

Fig. 1. Head–up tilt test protocol. Table takes 18 s for tilting during transitions, marked as lined area.

was recorded from index finger with a sampling frequency of 250 Hz, whereas standard lead V4 ECG signal was recorded with a sampling frequency of 1000 Hz. The MP 150 (BIOPAC Systems) was used to acquire both signals simultaneously. Beats from ECG and pulses from PPG were detected to generate heart and pulse rate time series. The temporal location of each R wave in the ECG (t_{E_j}) was automatically determined using the algorithm described in [5]. The PPG signal was interpolated using cubic splines to increase the resolution in time up to an equivalent sampling rate of 1000 Hz. Then, the temporal location of each pulse wave in the PPG (t_{P_j}) was detected as the maximum of the PPG signal within the interval [t_{E_j}+150 ms, $t_{\text{E}_{j+1}}$]. In addition, a PPG artefact detector [6] was applied to suppress pulses from PPG corresponding to artefacts and beat and pulse detections were manually supervised. Then, the effect of abnormal beats in both heart and pulse rate was corrected by applying a methodology based on the integral pulse frequency modulation model [7]. Heart rate and pulse rate signals, $d_{\text{HR}}(t)$ and $d_{\text{PR}}(t)$, were obtained by using a 5th order spline interpolation at 4 Hz of the inverse interval function $d_{\text{IIF}}(t_j)$:

$$d_{\text{IIF}}^{\text{ECG}}(t_j) = \frac{1}{(t_{\text{E}_j} - t_{\text{E}_{j-1}})} \quad (1)$$

$$d_{\text{IIF}}^{\text{PPG}}(t_j) = \frac{1}{(t_{\text{P}_j} - t_{\text{P}_{j-1}})}. \quad (2)$$

Finally, the HRV and PRV signals, $d_{\text{HRV}}(t)$ and $d_{\text{PRV}}(t)$, were calculated by suppressing the time–varying mean heart rate from $d_{\text{HR}}(t)$ and $d_{\text{PR}}(t)$. Mean heart rates were estimated by low–pass filtering $d_{\text{HR}}(t)$ and $d_{\text{PR}}(t)$ with a cut–off frequency of 0.03 Hz.

B. Time–invariant analysis

The Pearson's correlation coefficient, defined as:

$$\rho = \frac{C(\phi^x, \phi^y)}{\sqrt{C(\phi^x, \phi^x)C(\phi^y, \phi^y)}}, \quad x, y \in \{\text{HRV, PRV}\} \quad (3)$$

where C represents the covariance and ϕ is a general parameter derived from HRV and PRV, was used for comparison between both signals.

First, the Pearson's correlation coefficient between the variability signals, $d_{\text{HRV}}(t)$ and $d_{\text{PRV}}(t)$, $\rho_{\text{d}}^{\text{TI}}$, was calculated with $\phi^x = d_{\text{HRV}}(t)$ and $\phi^y = d_{\text{PRV}}(t)$ to evaluate their linear relationship. Then, a classical time–invariant analysis was performed in three windows (w_1, w_2 and w_3) where stationarity is assumed. These windows had a length of 2 minutes and finished 30 seconds before any transition during the tilt test, see Fig. 1. Classical time domain and frequency domain indices were estimated in each window from both HRV and PRV [1]:

- Time domain: Mean normal to normal interval (NN), standard deviation of NN intervals (SDNN), root mean–square of successive differences of adjacent NN intervals (RMSSD) and percentage of pairs of adjacent NN intervals differing by more than 50 ms (pNN50) were estimated.
- Frequency domain: Fast Fourier Transform algorithm with 2048 points was applied to $d_{\text{HRV}}(t)$ and $d_{\text{PRV}}(t)$ and the power in low frequency band (P_{LF}), high frequency band (P_{HF}) and the LF to HF ratio ($R_{\text{LF/HF}}$) were estimated.

Each index from PRV (I^{PRV}) was compared to the same index from HRV (I^{HRV}), with $I \in \{$NN, SDNN, RMSSD, pNN50, $P_{\text{LF}}, P_{\text{HF}}, R_{\text{LF/HF}}\}$. Three similarity indices were then estimated: 1) the mean and standard deviation of the difference $d_{\text{I}}^{\text{TI}} = I^{\text{PRV}} - I^{\text{HRV}}$, estimated among subjects; 2) the p–value of the Student's t–test, used to assess whether indices I^{PRV} and I^{HRV} were statistically different; 3) the Pearson's correlation coefficient between indices I^{PRV} and I^{HRV}, $\rho_{\text{I}}^{\text{TI}}$, was used to measure their linear relationship.

C. Time-varying analysis

The smoothed pseudo Wigner–Ville distribution (SPWVD) was used to estimate the time–varying spectral properties of the HRV and PRV signals. The SPWVD of signal $x(t)$ is defined as [8]:

$$S_x(t,f) = \int_{-\infty}^{\infty}\int_{-\infty}^{\infty} \phi(\tau,\nu)A_x(\tau,\nu)e^{j2\pi(t\nu - f\tau)}d\nu d\tau \quad (4)$$

$$A_x(\tau,\nu) = \int_{-\infty}^{\infty} x\left(t+\frac{\tau}{2}\right)x^*\left(t-\frac{\tau}{2}\right)e^{-j2\pi\nu t}dt \quad (5)$$

where $A_x(\tau,\nu)$ is the narrowband symmetric ambiguity function (AF) of signal $x(t)$. The kernel $\phi(\tau,\nu)$ is a 2D weighting function which performs the TF low–pass filtering necessary to suppress the interference terms which reduce the readability of the Wigner–Ville distribution. The analytical version of $d_{\text{HRV}}(t)$ and $d_{\text{PRV}}(t)$ was used in (4)–(5) in order to further reduce the interference terms [8]. We choose as kernel $\phi(\tau,\nu)$ an elliptical exponential function defined as [9]:

$$\phi(\tau,\nu;\tau_0,\nu_0) = exp\left\{-\pi\left[\left(\frac{\nu}{\nu_0}\right)^2 + \left(\frac{\tau}{\tau_0}\right)^2\right]^{\frac{1}{2}}\right\} \quad (6)$$

Parameters τ_0 and ν_0 were selected to have a frequency resolution of 0.0313 Hz and a time resolution of 15 s. Instantaneous power of HRV and PRV within each frequency band, $P_{\text{B}}^x(t)$, with $x \in \{$HRV, PRV$\}$, was obtained integrating $S_x(t,f)$ in the frequency bands $B \in \{$LF,HF$\}$. The similarity between the temporal evolution of $d_{\text{HRV}}(t)$ and $d_{\text{PRV}}(t)$ was assessed by means of three indices: 1) the Pearson's correlation coefficient of $P_{\text{B}}^{\text{x}}(t)$ and $R_{\text{LF/HF}}^{\text{x}}(t)$ estimated from HRV and PRV, $\rho_{\text{I}}^{\text{TV}}$. These indices were estimated as in (3) using $\phi \in \{P_{\text{B}}^{\text{x}}(t), R_{\text{LF/HF}}^{\text{x}}(t)\}$. 2) the difference between the instantaneous power of the two signals within each frequency

band, $d_{\text{B}}^{\text{TV}}(t) = P_{\text{B}}^{\text{PRV}}(t) - P_{\text{B}}^{\text{HRV}}(t)$. This index is used to compare the temporal evolution of the spectral content of the signals. 3) the Pearson's correlation coefficient between instantaneous spectra of the two signals, $\rho_{\text{S}}^{\text{TV}}(t)$, is estimated at every time instant t_0 as in (3) with $\phi^x = S_x(t_0, f)$. This index is used to assess whether the signals are characterized by a similar distribution of energy with frequency.

D. Physiological analysis

In this section, we assess the effect of replacing the HRV estimation from the ECG with the PRV estimation from the PPG, when the tilt table test is used to evaluate changes in the autonomic modulation of the heart rate.

In time–invariant analysis, Student's t–test was performed to compare variations of spectral indices (P_{B}^x) among windows w_1, w_2 and w_3, estimated from both HRV and PRV signals. In time–varying analysis, we quantified the statistical differences between the baseline power content $\overline{P_{\text{B}}^x}$ and the power content at t_0, $P_{\text{B}}^x(t_0)$, by iteratively performing the Student's t–test. The baseline power content $\overline{P_{\text{B}}^x}$ was estimated by averaging $P_{\text{B}}^x(t)$ in an interval T_{REF}, selected at T_1 from 15 to 45 s (see figure 1). As result of the test we obtained a time–varying p-value, $p_{\text{B}}^x(t)$, for both HRV and PRV signals.

III. RESULTS

A. Time–invariant analysis

The correlation between the variability signals, i.e. $d_{\text{HRV}}(t)$ and $d_{\text{PRV}}(t)$, $\rho_{\text{d}}^{\text{TI}}$, was 0.964±0.030 (mean ± S.D.). The mean delay of $d_{\text{PRV}}(t)$ with respect to $d_{\text{HRV}}(t)$, introduced by the pulse wave travel to the periphery, was taken into account in the estimation of parameter $\rho_{\text{d}}^{\text{TI}}$, so both signals were aligned. Table I and Fig. 2 show comparison of classical time and frequency indices derived from HRV and PRV within each analysis window. All the indices derived from PRV presented similar values to the indices derived from HRV. Statistical test proved that there were no significant differences between indices of HRV and PRV ($p > 0.05$). In addition, as shown in Table I, correlation coefficients indicated a strong correlation ($\rho_{\text{I}}^{\text{TI}} > 0.97$) for all indices but one ($R_{\text{LF/HF}}$ in w_2).

B. Time–varying analysis

The correlation between the instantaneous power in each frequency band from both signals, was $\rho_{\text{LF}}^{\text{TV}} = 0.98 \pm 0.04$, $\rho_{\text{HF}}^{\text{TV}} = 0.95 \pm 0.06$ and $\rho_{\text{LF/HF}}^{\text{TV}} = 0.97 \pm 0.03$. Global results,

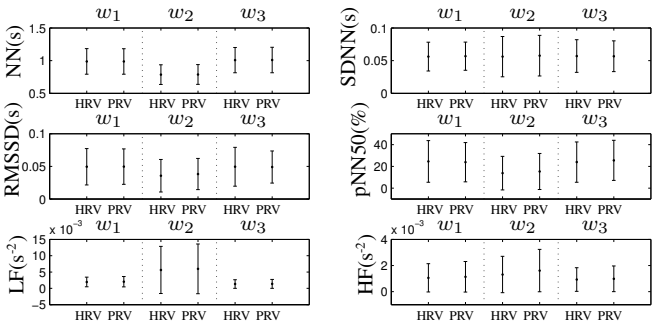

Fig. 2. Mean±SD of NN, SDNN, RMSSD, pNN50, P_{LF} and P_{HF} derived from HRV and PRV within each window w.

TABLE I
TIME–INVARIANT ANALYSIS RESULTS

Condition	Indice	difference (d_{I}^{TI})	p (T-test)	Correlation ($\rho_{\text{I}}^{\text{TI}}$)
Supine (w_1)	NN (s)	-0.00038±0.00133	0.995	1.000
	SDNN (s)	0.00064±0.00187	0.933	0.997
	RMSSD (s)	0.00026±0.00186	0.978	0.998
	pNN50 (%)	-0.68969±2.31389	0.915	0.994
	LF (s^{-2})	0.00009±0.00015	0.859	0.997
	HF (s^{-2})	0.00008±0.00013	0.840	0.996
	LF/HF (n.u.)	-0.12034±0.19607	0.845	0.996
Upright (w_2)	NN (s)	0.00116±0.00281	0.982	1.000
	SDNN (s)	0.00153±0.00256	0.886	0.997
	RMSSD (s)	0.00253±0.00195	0.765	0.998
	pNN50 (%)	1.58688±2.32206	0.774	0.992
	LF (s^{-2})	0.00033±0.00044	0.899	1.000
	HF (s^{-2})	0.0003±0.00038	0.565	0.981
	LF/HF (n.u.)	-1.51994±2.18202	0.375	0.924
Supine (w_3)	NN (s)	0.00147±0.0041	0.983	1.000
	SDNN (s)	-0.00029±0.00458	0.972	0.984
	RMSSD (s)	-0.00042±0.00841	0.965	0.970
	pNN50 (%)	1.55752±2.02452	0.807	0.994
	LF (s^{-2})	0.00004±0.00009	0.932	0.998
	HF (s^{-2})	0.00006±0.00011	0.864	0.996
	LF/HF (n.u.)	-0.10394±0.24364	0.813	0.985

obtained by averaging among subjects the similarity indices presented in section II-C, are reported in Fig. 3. In panels (a)–(b), the instantaneous power within each frequency band from HRV and PRV and the corresponding instantaneous difference are shown, respectively. Note that mean time–course of $P_{\text{B}}^{\text{HRV}}(t)$ and $P_{\text{B}}^{\text{PRV}}(t)$ presented the same temporal patterns, even if with a bias which increases during tilt. Panel (c) shows the mean trend of the instantaneous correlation $\rho_{\text{S}}^{\text{TV}}(t)$ between the power spectral density functions derived from HRV and PRV. In the same panel we report $\rho_{\text{S}}^{\text{TV}}(t)$ for the subject who presented more artefacts in the PPG signal (subject 1). It is shown that artefacts provoked an abrupt decrease in $\rho_{\text{S}}^{\text{TV}}(t)$.

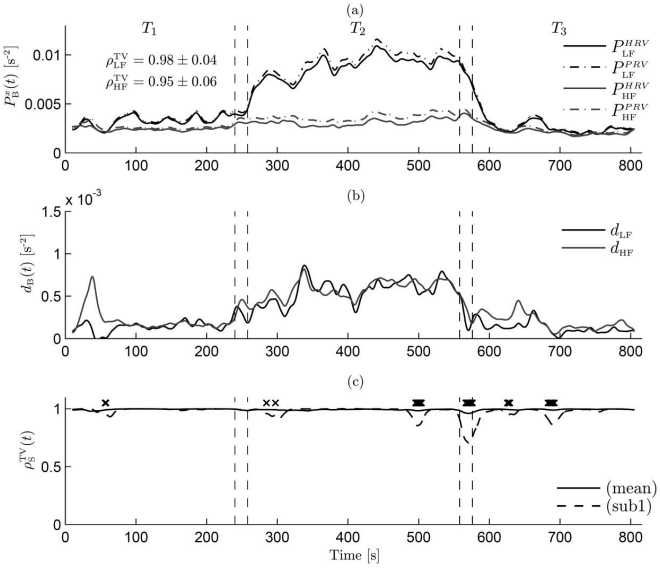

Fig. 3. Mean trend estimated by averaging among subjects. (a) $P_{\text{B}}^{\text{HRV}}(t)$ and $P_{\text{B}}^{\text{PRV}}(t)$ from HRV (continuous line) and PRV (dash–dotted line); (b) $d_{\text{B}}^{\text{TV}}(t)$ in LF band (grey line) and HF band (black line); (c) Instantaneous correlation $\rho_{\text{S}}^{\text{TV}}(t)$ between the power spectral density functions derived from HRV and from PRV (solid line). Index $\rho_{\text{S}}^{\text{TV}}(t)$ and artefacts in PPG for subject 1 are reported in dashed line and cross marks, respectively.

C. Physiological analysis results

Results of the time–invariant and time–varying analysis are reported in Table II and Fig. 4, respectively. It is shown that P_{LF} significantly increased as response to the orthostatic stress provoked by the head–up tilt. Student's t–tests presented similar results for both PRV and HRV signals.

TABLE II
TIME–INVARIANT PHYSIOLOGICAL ANALYSIS RESULTS (p VALUES)

P_{LF}^{HRV}	w_1	w_2	w_3
w_1	1	**0.047**	0.207
w_2	-	1	**0.021**
w_3	-	-	1

P_{HF}^{HRV}	w_1	w_2	w_3
w_1	1	0.569	0.7
w_2	-	1	0.352
w_3	-	-	1

P_{LF}^{PRV}	w_1	w_2	w_3
w_1	1	**0.046**	0.194
w_2	-	1	**0.02**

P_{HF}^{PRV}	w_1	w_2	w_3
w_1	1	0.342	0.677
w_2	-	1	0.184

(a) (b)

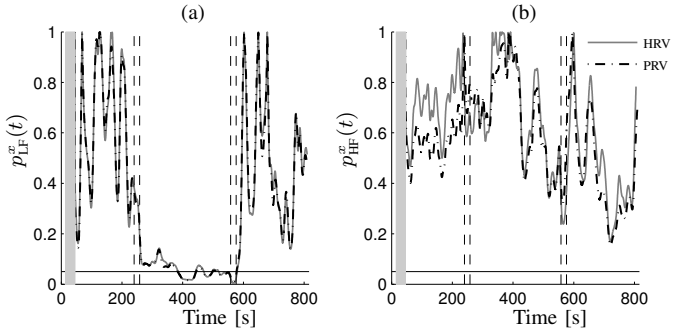

Fig. 4. Time–varying physiological analysis results. Temporal evolution of (a) the p–value $p_{LF}^{x}(t)$ and (b) $p_{HF}^{x}(t)$. Baseline values were estimated in the temporal window marked as grey area, T_{REF}.

IV. DISCUSSION AND CONCLUSION

Table I and Fig. 2 show that classical time and frequency indices derived from PRV presented similar values to the indices derived from HRV, with no statistically significant differences between them ($p > 0.05$) and strong linear correlation ($\rho_{I}^{TI} > 0.9$). Generally, during early and later supine position we observed a higher similarity between these indices than during head–up position.

During tilt table test we observed high similarity between the patterns of response of the HRV and PRV signals. The global results reported in Fig. 3 show that the instantaneous power content of the PRV is slightly higher ($d_{B}^{TV}(t) < 10^{-3}$ s^{-2}) than the instantaneous power content of the HRV signal. The temporal evolution of the similarity index $d_{B}^{TV}(t)$ was almost the same in both frequency bands. It is worth noting that during the highest non–stationary intervals (i.e. transitions where table was tilting), $d_{B}^{TV}(t)$ did not increase. Their temporal evolution was highly correlated, i.e. $P_{B}^{HRV}(t)$ and $P_{B}^{PRV}(t)$ followed the same trend. The correlation between the instantaneous spectral densities of the two signals, $\rho_{S}^{TV}(t)$, was also very high, being the temporal average of the mean and standard deviation among subjects 0.99 ± 0.01. The small decreases of $\rho_{S}^{TV}(t)$ were due to the presence of some artefacts in the PPG signal.

In both time–invariant and time–varying analysis we observed a positive bias in the measurement of spectral indices from PRV. This bias was observed to increase during head–up tilt. Our hypothesis is that this could be due to the variability introduced by PTT.

From both time–invariant and time–varying analysis we observed a statistically significant increase of the power content in LF band of HRV and PRV during head–up position. Simultaneous inspection of figures 3(a) and 4(a) reveals the transient nature of the autonomic response to orthostatic stress. It is shown that the variations in $P_{LF}(t)$ provoked changes in the temporal pattern of p–values. First, immediately after the head–up tilt, $p_{LF}^{x}(t)$ dramatically decreased; then, during T_2, $p_{LF}^{x}(t)$ continued gradually diminishing, reaching statistical significance about 2 minutes later; finally, when the supine position was restored $p_{LF}^{x}(t)$ abruptly increased to previous values. Moreover, as also shown in figure 4(a) the power content within LF band during early and later supine positions did not present any relevant difference, pointing out that recovery was fast. The power content in HF band did not present any significant change. Finally, it is worth noting that there was agreement between the physiological analysis based on HRV and PRV. This suggests that in this particular test PRV could be used as a surrogate measurement of HRV to evaluate the autonomic modulation changes of the heart rate.

It is well established that PPG measurements are quite sensitive to patient and/or probe–tissue movement artefact. Thus the presence of motion artefacts is one of the most important limitations of the use of the PRV signal as surrogate of the HRV signal.

In conclusion, our results indicate that there are some small differences in the time–varying spectral indices extracted from HRV and PRV, mainly in the respiratory band. Nevertheless, these differences were sufficiently small to suggest the use of the PRV signal as an alternative measurement of HRV signal during non–stationary conditions, at least during tilt table test.

ACKNOWLEDGMENT

This work was partially supported by: Ministerio de Ciencia y Tecnología, FEDER under Project TEC2007-68076-C02-02/TCM; and Diputación General de Aragón (DGA), Spain, through Grupos Consolidados GTC ref:T30.

REFERENCES

[1] Task Force, "Task Force of The European Society of Cardiology and The North American Society of Pacing and Electrophysiology. Heart rate variability: Standards of measurement, physiological interpretation, and clinical use," *European Heart Journal*, vol. 17, pp. 354–381, 1996.

[2] S. Lu, H. Zhao, K. Ju, K. Shin, M. Lee, K. Shelley, and K. Chon, "Can photoplethysmography variability serve as an alternative approach to obtain heart rate variability information?" *Journal of Clinical Monitoring and Computing*, vol. 22, pp. 23–29, 2008.

[3] J. Hayano, A. K. Barros, A. Kamiya, N. Ohte, and F. Yasuma, "Assessment of pulse rate variability by the method of pulse frequency demodulation," *BioMedical Engineering OnLine*, vol. 4, no. 62, 2005.

[4] K. Charlot, J. Cornolo, J. V. Brugniaux, J. P. Richalet, and A. Pichon, "Interchangeability between heart rate and photoplethysmography variabilities during sympathetic stimulations," *Physiol. Meas.*, vol. 30, pp. 1357–1369, 2009.

[5] J. P. Martinez, R. Almeida, S. Olmos, A. P. Rocha, and P. Laguna, "A wavelet-based ECG delineator: Evaluation on standard databases," *IEEE Trans. Biomed. Eng.*, vol. 51, no. 4, pp. 570–581, 2004.

[6] E. Gil, J. M. Vergara, and P. Laguna, "Detection of decreases in the amplitude fluctuation of pulse photoplethysmography signal as indication of obstructive sleep apnea syndrome in children," *Biomed. Signal Process. Control*, vol. 3, pp. 267–277, 2008, doi:10.1016/j.bspc.2007.12.002.

[7] J. Mateo and P. Laguna, "Analysis of Heart Rate Variability in the Presence of Ectopic Beats Using the Heart Timing Signal," *IEEE Trans. Biomed. Eng.*, vol. 50, no. 3, pp. 334–343, 2003.

[8] W. Martin and P. Flandrin, "Wigner-ville spectral analysis of nonstationary processes," *Acoustics, Speech and Signal Processing, IEEE Transactions on*, vol. 33, no. 6, pp. 1461–1470, 1985.

[9] M. Orini, R. Bailón, L. Mainardi, A. Mincholé, and P. Laguna, "Continuous quantification of spectral coherence using quadratic time-frequency distributions: error analysis and application," *Internat. Conf. Computers in Cardiology*, pp. 681–684, 2009.