Evidence of the Influence of Respiration on the Heart Rate Variability after Human Heart Transplantation: Role of Observation Model

G Laouini\textsuperscript{1}, A Cabasson\textsuperscript{1}, G Blain\textsuperscript{2}, P Bonizzi\textsuperscript{1}, O Meste\textsuperscript{1}, S Bermon\textsuperscript{3}

\textsuperscript{1}Laboratory I3S, UNSA-CNRS, Sophia-Antipolis, France
\textsuperscript{2}Laboratory of the Physiology of Adaptations, University of Nice Sophia-Antipolis, France
\textsuperscript{3}Monaco Institute of Sports Medicine and Surgery, Monaco, Principality of Monaco

Abstract

Studying heart transplanted patients records provide interesting data since modulation of the heart rate is not due to neural activity \cite{3}. Studying these patients reveals the so called mechanical modulation (MM) that is increased as the exercise intensity is higher. In a recent paper we have introduced the PFM model that relates the observed amplitude of the MM to the ventilation and the mean heart rate, with a set of non transplanted subjects. In this paper we use a time-frequency representation added to a t-test to show whether the HRV signal, or tachogram, contains or not power in the respiration frequency band. This approach is well adapted to the purely dynamic condition corresponding to increasing exercise. Observation models such as PFM and IPFM can be accounted in the analysis since there is no evidence of a linear interaction between observed values from the heart rate variability signal and physiological input such as the ventilation. The aforementioned models are compared regards our proposed t-test.

1. Introduction

It is well known that in stationary conditions there is a strong relation between respiration and cardiac system. Power spectral parameters of heart rate variability (HRV) represent the influence of the autonomic nervous system on the sinus node. In this paper studied if this relationship still exists in nonstationary conditions. Time frequency analysis of heart rate variability has been exploited to distinguish the neural regulation from the mechanical modulation of cardiac system. Integral pulse frequency modulation (IPFM) model has been assumed by many authors to show the relationship between the signal of modulation (m(t)) and the heart rate variability. However this model cannot be used in dynamic conditions corresponding to increasing workload exercise. To be able to use this model with our protocol we have extended it introducing a time-varying mean heart period. In \cite{5}, an alternative (PFM) model has been proposed and developed assuming dynamic conditions. We will decide which model perform the best fit with the data using a t-test in the frequency domain around the respiration frequency band.

2. Methods

2.1. ECG preprocessing

Recorded signals have been obtained from surface electrodes that produce interferences such as noise and baseline wander. So primarily to exploit all signals we must correct the disturbances caused by breathing. First we filter the signal using 500-th order high-pass finite impulse response filter in order to remove variations introduced by respiration. After using a threshold technique we demodulate the filtered signal to detect all the time occurrences of R-waves namely the $t_k$.

2.2. Statistical analysis

The coupling of respiration with the observed modulating signal is studied by comparing the power in the frequency band of respiration and the rest of the spectrum above 0.2 Hz using a student t-test. Statistical analysis has been performed in non stationary conditions in the time frequency domain. The quadratic time frequency transformation will be the spectrogram, i.e the squared short time Fourier Transform, where the power will be calculated for each time. The t-test has been applied on sets of 200 consecutive power values and shifted by one sample. Statistical significance was fixed for $p < 0.01$. In this paper, we will compare the use of the PFM and IPFM models intro-
duced for neural and mechanical modulation respectively. Both PFM and IPFM models imply a correction of the observation that relies on the corresponding assumption.

2.3. PFM model

In a recent work, the PFM model has been proposed for the generation of the R waves [5]:

\[ e_{cg}(t) = (\cos(c_1 t + a \cos(w_m t + \theta) + c_5) + 1)^{200}. \]

with \( c_5 \in [0, \pi] \)

the function \( a \cos(w_m t + \theta) \) can be considered as external modulation such as tidal volume. We assume that the maximum of \( e_{cg}(t) \) corresponds to the time occurrences of interest \( t_k \). According to results presented in [1] we have:

\[ A = \frac{T a}{\pi} \sin(f_w T \pi), \]

which establishes a relation between the magnitude \( A \) of heart rate variability and the amplitude of the modulation. Thanks to this equation, we can use the correction based on this equality to obtain the amplitude of the modulation and consequently to show the role of the observation model defined in dynamic conditions. According to results presented in [6] we retrieve the following equation:

\[
\begin{align*}
    A_{RSA}(k) &\approx a \frac{p_0(t_k)}{p_0(t_k)} \sin(\pi f_{RSA}(k)) \\
    F_{RSA}(t_k) &\approx f_{RSA}(k) p_0(t_k).
\end{align*}
\]

Assuming that \( p_0(t_k) \) is the trend of \( hp(t_k) \), \( f_{RSA}(k) \) is the frequency of respiratory sinus arrhythmia observed in \( hp(t_k) \), \( A_{RSA} \) and \( F_{RSA} \) are the magnitude and the frequency of the observed respiratory sinus arrhythmia.

2.4. Extended IPFM model

The IPFM model explains how the modulation of the autonomic system controls the heart rate, and it considers this modulation representing the influence of sympathetic and parasympathetic activity on the sino-atrial node[2]. The signal of modulation being noted \( m(t) \), the model is defined as the solution of the equation:

\[ k = \int_0^{t_k} \left( \frac{1 + m(t)}{T} \right) dt. \]  

(2)

Where \( k \) is the number of pulses generated by the model and \( t_k \) is the time corresponding to the \( k \)-th beat.

The model will sum the mean instantaneous frequency until obtaining an integer corresponding to the beat number, until the threshold is reached. In this paper we develop the dynamic IPFM model, our aim is to find a relation between the heart period and modulating signal. Assuming that between any \( t_k \) and \( t_{k+1} \) values, \( T(t) \) is equal to a constant, equation (2) can be rewritten as:

\[ I_k = \int_{t_k}^{t_{k+1}} (1 + m(t)) \, dt. \]  

(3)

\( I_k \) represents the threshold of integration which is equal to the mean of the RR intervals in the analyzing period between instants \( t_k \) and \( t_{k+1} \). Defining the modulation as:

\[ m(t) = a \cos(w_m t + \theta) \]  

(4)

And substituting equation (4) in equation (3) we obtain

\[ I_k = (t_{k+1} - t_k) + \frac{a}{w_m} [\sin(w_m t + \theta)]_{t_k}^{t_{k+1}} \]

\[ I_k = (t_{k+1} - t_k) + \frac{a}{w_m} [\sin(w_m t + \theta) - \sin(w_m t + \theta)] \]

If \( a = 0 \) then \( I_k = T_k \) with \( T_k \) is the mean instantaneous heart period between instants \( t_k \) and \( t_{k+1} \). The heart period \( hp(t_k) \) is then:

\[ hp(t_k) = t_{k+1} - t_k \]

\[ = T_k - 2 \frac{a}{w_m} [\cos(w_m t_{k+1} + t_k) + \theta) \times \sin(w_m \frac{t_{k+1} - t_k}{2})] \]  

(5)

Using the approximation:

\[ t_{k+1} = t_k + T_k \]  

(6)
We substitute (6) in (5) and get:

\[ hp(t_k) = T_k - \frac{a}{\pi f_m} \cos(\pi f_m (2t_k + T_k) + \theta) \times \sin(\pi f_m T_k) \]

From real conditions where \( f_m \) and \( T_k \) exhibit low values we have the approximation:

\[ \sin(\pi f_m T_k) \approx \pi f_m T_k \]

where \( \pi f_m T_k \) is sufficiently small. So we finally have:

\[ hp(t_k) = T_k - T_k a \cos(\pi f_m (2t_k + T_k) + \theta) \]  

(7)

\[ hp(t_k) = T_k - T_k m(t_k + \frac{T_k}{2}) \]

Assuming that in (7), \( T_k \) corresponds to \( po(t_k) \) we can retrieve the modulating signal \( m(t_k) \) (4), up to a phase \( T_k \). Note that this phase can be neglected or corrected since \( T_k \) is known. The extended IPFM model is applied to the simulated signal in fig1. The dynamic IPFM is implemented with a modulation signal \( m(t) = 0.75 \times \cos(2\pi \times 0.1 \times t) \) and a time varying mean period decreasing from 1.3 to 0.7s. From \( hp(t_k) \), the estimated mean heart period, namely \( po(t_k) \), and the variability signal are computed. These values allow the computation of the corrected observed modulation (7) in agreement with the original one, see figure 1-D. Note that the analysis of the observed modulation (figure 1-C) could lead to a wrong interpretation of a decreasing magnitude of the modulation.

3. Results

The set of subjects consists in 14 heart transplanted patients. ECGs are obtained in graded exercise, beginning initially at 20w and increased by 15w every 2 minutes. The pedalling rate was kept constant at 60 rev/min. The age of subjects was ranged from 27 to 70 years old. Transplantation time was in the range [3,171] months. Studying the heart rate variability among transplanted subjects allows us to show interesting results. The increase of magnitude of heart rate variability at the respiration frequency, during the increasing exercise, is shown in more than 50% of transplanted subjects according to the increase in the tidal volume during rising effort. Our purpose is not only to show the strong relationship between respiration and heart rate variability using time frequency analysis, but also to show the influence of the model on the observations. In order to compare the PFM and IPFM models defined in such dynamic conditions, we perform a t-test in the time-frequency domain after weighting the time-frequency plane with the two correcting models or without correction. The corresponding two dimensional weighting function is computed from either (1) or (7) depending on the selected model. When the test is applied without correction the weighting function is simply the unit function. For each time two power values are computed, one in the respiration frequency band and the second elsewhere above 0.2 Hz. This processing provides two sets of data function of time or beat index. The sets are statistically compared using a t-test in a sliding window of length equal to 200 samples. Fixing the significance value provides the threshold that should be reached to claim that the presence of power in the respiration frequency band is significative in the window. In figure 2, an example of \( hp(t_k) \), the variability signal and the trend are given. These curves will be used in the analysis and the correction. The curves stu, stupfm and stuipfm plotted in figure 3 correspond respectively to the output of the t-test without correction, with the PFM correction, with the IPFM correction of the sig-

Figure 2. (A) the heart period \( hp(t_k) \), (B) the variability of the heart period, (C) the trend \( po(t_k) \)

Figure 3. Student t-test with significance \( p < 0.01 \) from the begining to the end of exercise
nal in figure 2. The horizontal straight line corresponds to the significance level of $p < 0.01$. The presence of power in the respiration frequency band is always proved ($p < 0.01$) after the PFM correction for all patients, but it is not always true, with the same significance, using IPFM correction or without correction.

Table 1 represents the percentage of the presence of the power in the frequency band respiration, after corrections applied on the observed modulating signal, from the beginning to the end of exercise. We can see that the PFM correction always proves the strong relation between respiration and cardiac rhythm, but it is not the case for other corrections.

### 4. Discussion and conclusions

Studying HRV of transplanted subjects through the observation model presents different results according the assumed model. The difference between corrected modulations, for the same observation, can be explained by the fact that the model IPFM is adapted to modulations that are influenced by the nervous system, especially the vagal activity during exercise. In contrast to the previous model, the PFM is adapted to the mechanical modulation where the input is the tidal volume. Considering the input of the model as the signal of modulation and the output as observation, models are not linear, that’s why a good selection of the correction is crucial to reflect the reality. For example, as shown in simulation the magnitude of heart rate variability is observed with an overall decreasing function of time, that does not exist in the original input modulation. So extending the IPFM model for dynamic conditions is an important result, permitting us to perform the IPFM correction and to obtain the input that represents the influences of sympathetic and parasympathetic systems. From the results obtained during increasing exercise, IPFM model is not the best candidate to analyze the changes of HRV due to ventilation increase because it has not been developed for the mechanical modulation. In addition the variability of the heart rate at the respiration frequency is likely due to the mechanical modulation, that justify the PFM, because a questionable reinnervation has not been yet proved at present.

### References


Address for correspondence:

Ghaïlen LAOUINI
Laboratory I3S, University of Nice Sophia-Antipolis, France
Equipe BIOMED Laboratoire I3S - UNS - CNRS
Tel. +33 4 92 94 27 01 - Fax : +33 4 92 94 28 98
laouini@i3s.unice.fr