Multiscale Information Analysis of the Autonomous Nervous System during Myocardial Ischemia

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Abstract

The purpose of this study was to provide a methodology in order to characterize autonomous nervous system (ANS) changes before, during and after percutaneous transluminal coronary angioplasty (PTCA). This methodology, based on a multiscale information analysis (MIA) of the heart rate variability, has taken into account entropy rates. The study group consisted of 66 patients undergoing PTCA: 1 in the left main, 21 in the left anterior descending, 30 in the right coronary, 14 in the left circumflex arteries. The analyzed time series were: RR(t) (beat-to-beat consecutive intervals); $RR_{LF}(t)$, LF[0.04-0.15Hz]; $RR_{HF}(t)$, HF[0.15-0.4Hz]. For RR(t), results showed less regularity behavior in pre-PTCA than during PTCA and less regularity during PTCA than in post-PTCA. In $RR_{LF}(t)$ and $RR_{HF}(t)$, lower regularity was presented during PTCA than in pre-PTCA. These findings suggested that MIA was able to provide a tool allowing assessment of ANS response during PTCA.

1. Introduction

The heart rate variability (HRV) contains information of the non-linear dynamics of the cardiac control system, in this way, HRV can be used as a non-invasive diagnostic and prognostic method of cardiac pathologies [1]. A decreasing of the HRV is a clear symptom of risk increasing of suffering ventricular arrhythmias, myocardial infarction and sudden cardiac death (SCD).

Several experimental studies inferred that coronary occlusion activates afferent cardiac sympathetic nerves driving to sympathetic reflex, and can modify the activity generated by intrinsic cardiac neurons [2]. However, few studies in clinical evaluations of HRV during percutaneous transluminal coronary angioplasty (PTCA) has been reported [3,4].

The cardiac system is characterized by a high complexity, partly due that presents continuous interactions with other physiological systems. In this way, it is expected that HRV has a non-linear and non-stationary behaviour. This requires that its analysis and characterization involves techniques obtained from non-linear dynamic theory and chaos theory, which are not yet completely explored. Techniques belonging to temporal domain and frequency domain only describe the linear structure of the HRV, without being able to characterize the non-linear dynamics hidden in the generation of the heart beats.

In the present work, two algorithms were proposed and compared for the analysis of the HRV regularity in subjects undergoing percutaneous transluminal coronary angioplasty (PTCA). These algorithms were mainly based on multiscale entropy rates, using conditional entropy, applied to series with different types of normalization and quantization. For the calculus of these entropies, Shannon and Rényi definitions were taken into account. This study considered the selection of the parameters values included in those algorithms, in order to get a better characterization of HRV. The obtained indexes were statistically analyzed with the aim of setting which ones allow the occlusions to be located in their correct artery.

The purpose of the present work was to perform a multiscale information analysis (MIA) of the autonomic control of the heart, using a regularity index for the RR signal during prolonged coronary balloon occlusion, and to asses the influence of different locations of the occlusions.

2. Analyzed database

This study used the Staff-III database, obtained at Charleston Area Medical Center [5]. The subjects were undergoing elective prolonged balloon occlusion during PTCA in one of their major coronary arteries. No arrhythmic events occurred during the ECG recording. The database contains ECG recording before, during and after PTCA, acquired for each patient at rest in supine position, which constitute an appropriate model to study ischemia [6]. Nine standard leads (V1-V6, I, II, and III) were recorded (Siemens-Elema AB, Solna, Sweden) and digitized at a sampling rate of 1 kHz.

The study group consisted of 66 subjects without clinical evidence of previous myocardium infarction history. This group contains 39 males and 27 females with ages between 32.3 to 78 years (mean 61±11 years). The location of the balloon inflation were: left main artery (LM) in 1 subject, left anterior descending artery (LAD) in 21 subjects, right coronary artery (RCA) in 30 subjects and left circumflex artery (LCX) in 14 subjects.

HRV analyses were performed using RR series obtained from: 3 min of the pre-inflation ECG (pre-PTCA) record, the first (leading) 3 min of the ECG during the occlusion (PTCA_ℓ), the last (trailing) 3 min of the ECG during the occlusion (PTCA_t), and 3 min of the post-PTCA.

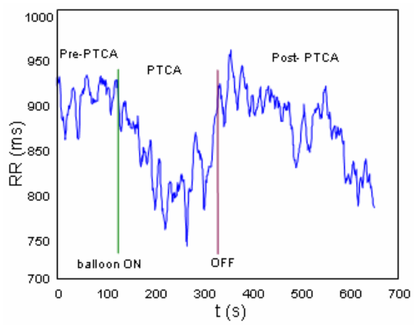


Figure 1. RR intervals during pre-PTCA, PTCA and post-PTCA.

3. Methodology

3.1. Pre-processing

Prior to MIA all RR sequences, intrinsically being non-evenly spaced data, were interpolated using cubic splines and re-sampled at 5Hz, in order to obtain uniformly sampled series (RR time series). Three sets of RR time series were considered [1]: RR(t), RR time series without band filtering; $RR_{LF}(t)$, RR time series filtered at LF band [0.04-0.15Hz]; $RR_{HF}(t)$, RR time series filtered at HF band [0.15-0.4Hz].

3.2. Measures based on entropy rates

In the present study, two algorithms based on multiscale entropy rates were proposed to asses the regularity of the RR series. These entropies, defined by conditional entropy (*CE*), were proposed as regularity index. The effect of this regularity index was studied to asses the influence of the artery occlusion in different locations.

In the *CE* definition [7], the series *X(i)* is transformed in a process with zero mean and unitary variance by means of the normalization:

$$x(i) = \frac{X(i) - av[X]}{std[X]} \qquad (1)$$

where $av[X]$ and $std[X]$ are the mean and standard deviation of the series, respectively. The series *x(i)* is spread on Q quantization regions of amplitude equal to:

$$\varepsilon = (x_{\max} - x_{\min}) / Q \qquad (2)$$

where $x_{\max} - x_{\min}$ represents the full range occupied by the process dynamics. From the quantized series $\hat{x}(i)$, a L-dimensional phase-space is reconstructed by considering $N - L + 1$ vectors $\hat{x}_L(i) = \left(\hat{x}(i), \hat{x}(i-\tau), ..., \hat{x}(i - L + \tau)\right)$ and a delay $\tau = 1$. Each vector $\hat{x}_L(i)$ represents a pattern with L consecutive samples. In this way, *CE* is defined as:

$$CE(L/L-1) = -\sum_{L-1} p_{L-1} \sum_{L/L-1} p_{L/L-1} \cdot \log p_{L/L-1} \qquad (3)$$

where p_{L-1} denotes the join probability of the pattern $\hat{x}_{L-1}(i)$ and $p_{L/L-1}$ means the conditional probability of the pattern $\hat{x}_L(i)$ of L samples given the previous L-1 samples. The *CE* obtained in (3) also can be obtained as the variation of Shannon entropy (*SH*) with respect to *L*.

$$CE(L/L-1) = E(L) - E(L-1) \qquad (4)$$

where, $E(L)$ is the *SH* of $\hat{x}_L(i)$ given by:

$$E(L) = -\sum p_L \cdot \log p_L, \quad if \ \ p_L > 0 \qquad (5)$$

CE quantifies the variation of the information necessary to specify a new state in a phase-space increased in one-dimension. Low values of *CE* are obtained when a pattern of length *L* can be predicted by a pattern of length *L*-1. If $x(i)$ samples are independent (i.e. when $x(i)$ is white noise) *CE* is constant and equal to $E(1)$ and thus only dependent on the distribution probability of the original series $x(i)$. When the series is rigorously periodic, *CE* gets zero value as soon as a new sample can be exactly predicted from the *L*-1 previous samples. To build the *L*-dimensional phase-spaces with the quantized series, *M* partitions or hypercubes ($M=Q^L$) of side length ε are obtained.

In the present work, $D_E(L)$ was proposed as index to measure the regularity. This index was defined as the difference between the entropy obtained for a phase-space of dimension *L* and the entropy obtained from a phase-space of dimension *L*-1.

$$D_E(L) = E(L) - E(L-1) \qquad (6)$$

$D_E(L)$ coincides with *CE*, given in equation (3), when $E(L)$ is calculated using *SH*. For a fixed *Q* value, the effect of parameter *L* was taking into account by analysing several values. Next, two algorithms are proposed and detailed.

Algorithm 1. This algorithm used normalized series with zero mean and unitary standard deviation (1). The amplitude range of the series was divided in equally-spaced four-regions (Q=4). $E(L)$ entropy was calculated by Shannon entropy (5) or Rényi entropy defined as:

$$Hq = \frac{1}{1-q}\log\left(\sum\left(p_L\right)^q\right), \quad if \;\; p_L > 0 \tag{7}$$

where, q is a real number, q>0 and q≠1, that determines the manner in which the probabilities are weighted. When $q \rightarrow 1$, Hq converges to SH. In the present study, q=1 denoted SH. The entropy Hq was studied considering q={0.1, 0.15, 0.25, 2, 4}.

Algorithm 2. In this algorithm the time series were not normalized. The amplitude range was divided in non-equally-spaced four-regions (Q=4), following the next criteria:

$$S_n = \begin{cases} 1 \text{ if } (1+\alpha)\mu < RR_n < \infty \\ 0 \text{ if } \quad \mu < RR_n \le (1+\alpha)\mu \\ 2 \text{ if } (1-\alpha)\mu < RR_n \le \mu \\ 3 \text{ if } \quad 0 < RR_n \le (1-\alpha)\mu \end{cases} \quad n = 1,2,\ldots,N \tag{8}$$

where μ was the mean of understudied series, N was the number of samples of the series and α was a constant to quantify the standard deviations of the series. In the present study, α was set to 0.07 [8].

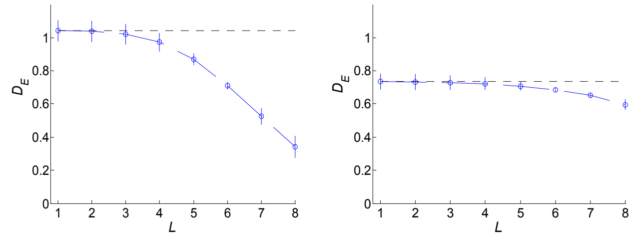
3.3. Statistical analysis

A nonparametric statistical analysis based on U Mann-Whitney test was applied to $D_E(L)$ index for different L and q. Significant differences with p-value<0.01 were taken into account in this study.

4. Results

4.1. Analysis based on entropies: random series

The two proposed algorithms were applied to 20 random series with N=1000 samples, considering only Shannon entropy (SH). Figures 2a and 2b present the mean values of $D_E(L)$ obtained applying algorithms 1 and 2, respectively. In figure 2a, it can be observed that $D_E(L)$ values diverge from their ideal values (a constant value equal to E(1)) for L>4. These results are due to the limited amount of data N taken into account for the evaluation of the probability distributions, by mean of relative frequencies [7]. However, the results obtained applying algorithm 2 were less sensitive to the increase of L (L≤8), as it is shown in figure 2b. This former algorithm permits to obtain a quasi-constant entropy $D_E(L)$, thus, only quasi-dependent on the probability distribution. These results suggest that algorithm 2 is more robust to variations of parameter L.



a) b)

Figure 2. Mean and standard deviation values of $D_E(L)$, considering Shannon entropy, obtained from 20 random series with gaussian distribution: a) algorithm 1; b) algorithm 2. Q=4 regions and N=1000 samples.

4.2. Analysis based on entropies: RR series

For the analysis of the RR series that are understudied in this work, algorithm 2 was applied since it seems to avoid the restriction given by the limited amount of data N. The parameter values L and q were statistically estimated. As example, for the RR(t) series, figure 3a shows the regularity index $D_E(L)$ which present p-values<0.01, comparing pre-PTCA and PTCA_ℓ in each artery and, as well as, in all the studied arteries (LAD +LCX +RCA +LM). Figure 3b shows a similar study when PTCA_ℓ and post-PTCA were compared.

Table 1 contains the $D_E(L)$ results of the HRV analysis in subjects undergoing PTCA. Entropy $D_E(L)$ of RR(t), when the occlusion was in LCX and RCA, takes lower values during PTCA than in pre-PTCA. This denoted more regularity and less complexity during PTCA, when q>1 for all L in LCX and 6≤L≤8 in RCA. All the arteries together and in particular LAD presented less regularity, more complexity and higher values of $D_E(L)$ during PTCA than post-PTCA, when q<0.25 and 6≤L≤7.

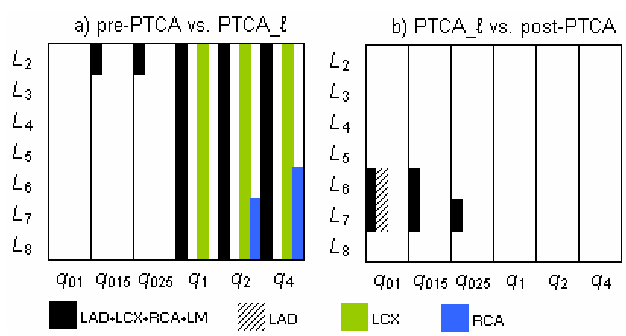


Figure 3. Index $D_E(L)$ of RR(t) with p-value<0.01 when comparing: a) pre-PTCA vs. PTCA_ℓ; b) PTCA_ℓ vs. post-PTCA.

Table 1. $D_E(L)$ analysis of HRV in subjects undergoing PTCA: p*, p-value between pre_PTCA and PTCA_ℓ; p**, p-value between pre_PTCA and PTCA_t; p#, p-value between PTCA_ℓ and post-PTCA; p##, p-value between PTCA_t and post-PTCA.

$D_E(L)$ mean±sd	L, q	pre-PTCA	PTCA_ℓ	PTCA_t	post-PTCA	p*	p**	p#	p##
Total band									
LAD	L=7,q=0.1	0.276±0.050	0.280±0.049	0.280±0.047	0.237±0.053	n.s.	n.s.	0.0076	0.0090
LCX	L=4,q=4	0.089±0.045	0.045±0.031	0.043±0.028	0.045±0.026	0.0044	0.0024	n.s.	n.s.
RCA	L=7,q=4	0.104±0.066	0.066±0.063	0.075±0.063	0.039±0.022	0.0065	n.s.	n.s.	n.s.
LAD+LCX+RCA+LM	L=7,q=0.25	0.291±0.050	0.281±0.052	0.281±0.049	0.257±0.054	n.s.	n.s.	0.0078	0.0089
LF band									
RCA	L=3,q=0.25	0.612±0.05	0.656±0.054	0.656±0.051	0.641±0.067	0.0012	0.0006	n.s.	n.s.
HF band									
LAD	L=2,q=0.25	0.976±0.081	1.041±0.079	1.057±0.076	1.043±0.087	n.s.	0.0026	n.s.	n.s.
LAD+LCX+RCA+LM	L=6,q=0.15	0.258±0.035	0.283±0.043	0.288±0.037	0.276±0.036	0.0011	0.0001	n.s.	n.s.

In LF band (RR_{LF} series) only RCA group could be characterized. Values of $D_E(L)$ were higher during PTCA than in pre-PTCA. This denoted less regularity and more complexity during PTCA, when q≤0.25 and L=3.

In HF band (RR_{HF} series) only LAD group could be described. Values of $D_E(L)$ were higher during PTCA than in pre-PTCA. This denoted less regularity and more complexity during PTCA, when q≤0.25 and L=2.

It needs to be noted that there were not significant differences between PTCA_ℓ and PTCA_t, in any of the occluded arteries that were studied in this work.

5. Conclusions

A methodology, which takes into account multiscale information analysis (MIA) of the HRV, has been proposed to study the autonomous nervous system during coronary occlusion. It has permitted to define a regularity index $D_E(L)$ based on entropy rates. This index has been able to asses the influence of an occlusion placed in different arteries and produced by PTCA.

The results suggested that MIA was able to provide a tool which allows an assessment of ANS response during PTCA. In this way, $D_E(L)$ showed an increase of complexity and a decrease of regularity of the sympatho-vagal reflex during PTCA compared with pre-PTCA in RCA, when series $RR_{LF}(t)$ were analyzed. An increase of complexity and a decrease of regularity of the vagal activity, during coronary occlusion in LAD, were observed when $D_E(L)$ was calculated in $RR_{HF}(t)$. The values of $D_E(L)$ did not present statistical significant differences between post-PTCA and during PTCA, for $RR_{LF}(t)$ and $RR_{HF}(t)$ series. This could suggest that the ischemic condition is still present during post-PTCA.

It can be concluded that the proposed regularity index was able to describe the non-linear dynamics of the HRV along PTCA procedure, associated to ischemic events.

Acknowledgements

This work was supported within the framework of the CICYT grant TEC2004-02274 and the research fellowship grant FPI BES-2005-9852 from the Spanish Government.

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