

Higuchi's Fractal Complexity of RR and QT Interval Series during Transient Myocardial Ischemia

Rudys Magrans¹, Pedro Gomis^{1,2}, Pere Caminal^{1,2}, Andreas Voss³

¹ESAI Dept, EUETIB, CREB, Universitat Politècnica de Catalunya, Barcelona, Spain

²CIBER – BBN (Bioengineering, Biomedicine and Nanomedicine), Spain

³MEB Dept, University of Applied Sciences, Jena, Germany

Abstract

Myocardial ischemia may lead to significant changes in autonomic control of heart rate (HR) affecting its variability and alter beat-to-beat ventricular repolarization periods. We hypothesized that transient myocardial ischemia affects the complex dynamics of the HR and QT. The aim of this study was to assess the RR and QT interval time series complexity using Higuchi's fractal dimension (HFD) during prolonged balloon occlusion of one of the major coronary arteries.

Eighty-five patients who underwent elective percutaneous coronary intervention procedures were selected. Patients were classified into 2 groups according to the presence of prior healed myocardial infarction (INF) ($n = 29$) or not (No_INF) ($n = 56$). RR, QT and QTc (Bazett's formula) time series were obtained from continuous ECG.

Three 3-minute stages were chosen: (1) preinflation as baseline (pre), (2) from the start of occlusion (pci), and (3) immediately post deflation (post_pci). HFD was calculated on each 3-minute stage time series to quantify the changing complexity and self-similarity of RR, QT and QTc time series (HFD RR, HFD QT and HFD QTc, respectively). Cohen's d statistics were included to measure the effect size of the procedure.

HFD values decreased significantly from baseline to pci and post_pci in the three time-series. HFD RR, 1.76 ± 0.13 vs. 1.69 ± 0.15 ($p < 0.001$, Cohen's $d = -0.64$); HFD QT, 1.90 ± 0.11 vs. 1.82 ± 0.13 ($p < 0.001$, $d = -0.67$); HFD QTc, 1.88 ± 0.09 vs. 1.83 ± 0.11 ($p < 0.01$, $d = -0.46$). The HFD reduction was greater from baseline to post_pci ($p < 0.001$, $d = -0.99$ (RR), $d = -1.02$ (QT)). HFD of QT intervals decreases during the procedure predominantly in the No_INF group.

The time series studied, related to autonomic control of HR and to the variability of ventricular repolarization, exhibit a reduced complexity provoked by transient myocardial ischemia.

1. Introduction

It has been shown that myocardial ischemia provokes different reflexes in both sympathetic and parasympathetic circuits of the autonomic nervous system (ANS) that control heart rate [1, 2]. The reaction may depend on the location of the ischemia, on the characteristics of the sensory inputs due to hypoxia, the lack of energy substrates, and local products caused by ischemia. Ventricular repolarization duration, measured by the QT interval, is closely linked to heart rate and its control system and is influenced by the ANS. However, beat-to-beat repolarization duration seem to be affected also by the ischemic effect on the channels involved in the repolarization process [3]. Fluctuations in ventricular repolarization, measured by QT interval variability, have been related with myocardial ischemia [4].

Heart rate variability (HRV) metrics by RR intervals have become the most widely used method to evaluate cardiac autonomic function. The RR intervals in healthy subjects fluctuate in a complex manner, with a non-uniform pattern. It has been associated with fractal behaviour because displays self-similar fluctuations on different orders of the temporal scale.

Temporal repolarization variability has been quantified by measuring beat-to-beat fluctuations of the QT interval either in the time or the frequency domain. However, the fractal behaviour of QT interval series is poorly understood.

Most nonlinear dynamics and fractal indices of time series require long-term recordings that are impractical in some physiological events as transient myocardial ischemia. In the present study, Higuchi's fractal dimension was used in time series obtained during 3-minute epochs.

We hypothesized that transient myocardial ischemia affects the complex dynamics of the HR and QT. The aim of this study was to assess the RR and QT interval time series complexity using Higuchi's fractal dimension (HFD) during prolonged balloon occlusion of one of the major coronary arteries.

2. Methodology

2.1. Data acquisition and population

Eighty-five patients with stable angina pectoris who underwent elective percutaneous coronary interventions (PCI), using non-perfusion balloon catheters, at the Charleston Area Medical Centre, WV, were selected (STAFF III database) [5, 6]. The study was approved by the Investigational Review Board and informed consent was obtained from each patient. Inclusion criteria: (i) no symptoms or ECG evidence of acute or recent MI; (ii) only the first occlusion procedure in every patient, to avoid the influence of recent occlusions on the ANS; (iii) occlusion duration ≥ 3 minutes.

Patients were classified into 2 groups according to the presence of prior healed myocardial infarction (INF) ($n = 29$) or not (No_INF) ($n = 56$), as indicated by the standard 12-lead ECGs using the Selvester QRS scoring system.

Continuous high resolution ECG's were acquired at 1 kHz, with $0.6\mu\text{V}$ of amplitude resolution with equipment provided by Siemens-Elena (Solna-Sweden). Nine-lead signals were stored on hard disk for post hoc analysis. For each patient, two ECG recordings were analysed: (i) a pre-inflation baseline ECG that was acquired continuously during 5 minute in the supine position before any catheter insertion in the catheterization laboratory, and (ii) the occlusion ECG recording which commenced approximately 1 minute before balloon inflation and continued during the inflation period and ended at least 3 minutes after deflation. The mean occlusion period was 4.66 ± 1.08 min.

The analyses were performed using 3-minute recordings in 3 stages: (1) pre-inflation baseline ECG, (pre), (2) from the beginning of occlusion (pci) and (3) starting immediately after balloon deflation (post). Patients where deflation period is not large enough were discarded from statistical comparisons involving this period.

2.2. Signal conditioning

QRS complex detection and waves delineation was performed using algorithm previously described [7, 8]. RR and QT intervals were extracted. In order to minimize the effect of artefacts and ectopic beats the intervals were filtered using a five-beat sliding window algorithm, rejecting any beat that deviated more than a programmed tolerance of 15% from the median of the preceding RR intervals. Then the rejected interval is replaced with an average value computed in the immediate vicinity. Percentage of beats classified as ectopic ones was 1.34 ± 2.57 of the total beats for all segments. QTc intervals were determined according to Bazzet's formula.

2.3. Higuchi's fractal dimension

Fractal behaviour displaying self-similarities across the time scale of the intervals series have been quantified using Higuchi's fractal dimension algorithm [9]. Briefly, from a given interval series (RR or QT) of N points, namely, $X=x(1), x(2), \dots, x(N)$, the technique constructs k new time series, defined as:

$$X_m^k = \{x(m), x(m+k), x(m+2k), \dots, x(m+\text{int}[(N-m)/k]k)\}, \quad (1)$$

$$m=1,2,\dots,k$$

where m is the initial time value, k is the discrete time interval between points. Then, the length $L_m(k)$ of the new sequences is computed as:

$$L_m(k) = \frac{\left\{ \sum_{i=1}^{\text{int}[(N-m)/k]} |x(m+ik) - x(m+[i-1]k)| \right\} \frac{N-1}{\text{int}[(N-m)/k]k}}{k}. \quad (2)$$

The length of the curve for the time interval k , $L(k)$, is calculated as the mean of k sets of $L_m(k)$, where $k=1,2,\dots,k_{max}$. Finally, the curve is fractal-like with dimension D if $L(k)$ is proportional to k^{-D} . D is computed from the slope of the line that fits the pairs $\{\ln(1/k); \ln(L(k))\}$. HFD was obtained as the average value from the D values computed in the range of $25 \leq k_{max} \leq 70$.

3. Results

Table 1 shows the HFD values for the 3 epochs of the PCI procedure. HFD decreased significantly throughout from baseline to pci and post_pci in the three time-series. Inferential statistics were complemented by effect size measures (Cohen's d statistic) to quantify the effect size of procedure. This effect size was moderate from baseline to pci period: HFD_RR, $d = -0.64$; HFD_QT, $d = -0.67$; HFD = -0.46 . However, the effect size was larger from baseline to post deflation stage: HFD_RR, $d = -0.99$; HFD_QT, $d = -1.02$; HFD_QTc, $d = -0.84$.

Table 1. Median (25th - 75th percentiles) of Higuchi's fractal dimension (HFD) values for RR, QT and QTc time series. Wilcoxon nonparametric rank test followed by Bonferroni's correction have been indicated as: (*) $p < 0.001$ and (+) $p < 0.01$ vs. pre.

| HFD | pre ^a | pci ^a | post ^b |
|-----|--------------------|---------------------------------|---------------------|
| RR | 1.78 (1.68 – 1.87) | 1.72 (1.59 – 1.79)* | 1.65 (1.56 – 1.76)* |
| QT | 1.94 (1.87 – 1.97) | 1.85 (1.74 – 1.93)* | 1.80 (1.72 – 1.87)* |
| QTc | 1.90 (1.83 – 1.95) | 1.84 (1.76 – 1.92) ⁺ | 1.81 (1.71 – 1.88)* |

^apre and pci, $n=85$; ^bpost, $n = 67$.

Figure 1 displays the Higuchi's fractal dimension changes in the groups with evidences of prior healed MI and without. No_INF group shows a reduction of HFD in RR and QT interval series from baseline to pci. However

these changes are not appreciated in QT interval series in the INF group. The reduction of HFD values is significant from pre inflation to post deflation stage in all interval series. Comparisons of the HFD values between groups of patients at one particular period did not show statistical significant differences.

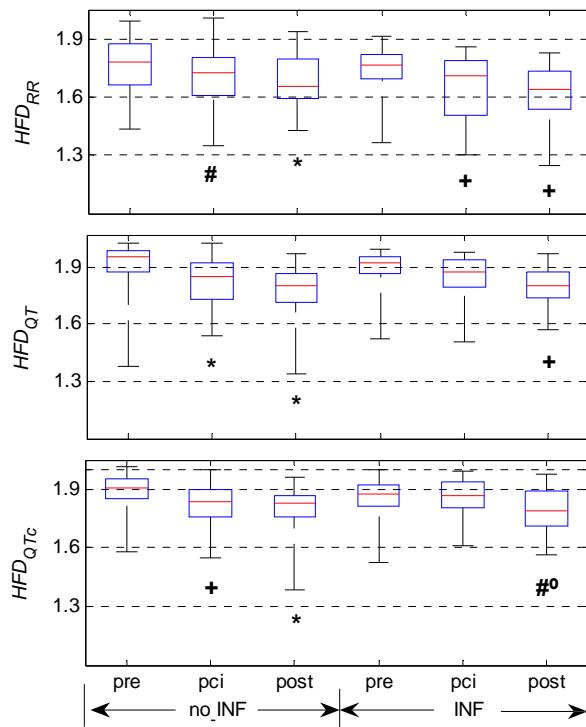


Figure 1. Box plot comparison of the HFD values in both groups of patients throughout the PCI procedure. Each box spans from the 25th to 75th percentiles, the central line is the median and the whiskers extend to the minimum and maximum values. Statistical significant differences among periods have been indicated as: * $p < 0.001$, $^+p < 0.01$, $^{\#}p < 0.05$ vs. pre-pci; $^{\#0}p < 0.01$ post_pci vs. pci.

4. Discussion

Higuchi's fractal dimension analysis of 3-minute RR and QT interval series has shown a suitable method to investigate fractal complexity changes in short-time epochs during acute myocardial ischemia episodes. The fractal dimensions of the time series have changed throughout the PCI procedure from a short or intermediate dependence during the inflation toward less dependent (or less correlated) behaviour during the post-deflation period. From a physiological standpoint such changes can be associated with sympathetic-parasympathetic reactions.

Results from RR time series agree with our previous

study [10], which has showed that heartbeat fluctuations approach to Brownian noise during post-deflation. Fractal correlation properties have been altered in several cardiac states due to changes of autonomic nervous influences [11]. Recently, we have attributed similar behaviour to sympathetic modulation predominance on the heart rate control mechanisms, presumably indicative of an adaptive role via coronary vasoconstriction, preparing the cardiovascular system for the rapid variations in heart rate, cardiac output and blood flow redistribution occurring during acute myocardial ischemia.

Several studies in humans [12] and animals [13] have revealed that an alteration of the sympathetic activity influences heterogeneity of repolarization producing a QT interval prolongation, however, slight or no QT interval changes have been observed in other studies. QT variability measured with statistic linear metrics has shown increased values of beat-to-beat repolarization variability during acute myocardial ischemia [4]. Ischemic tissue may alter the amount of channels involved in repolarization process and modify the variability of repolarization interval [3].

Using HFD analysis, QT and QTc time interval series have shown statistically significant differences between inflation and pre-inflation periods in the entire population and only in the group without previous MI. Results are difficult to interpret and further clinical studies are required to clarify the effects of ANS and ion channel activity influences on QT interval during transient myocardial ischemia.

In conclusion, fractal dimension indices measured with Higuchi's algorithm on RR and QT intervals decreased throughout the PCI procedure, probably consequence of autonomic control mechanisms of heart rate generation and regulation.

Acknowledgements

This study was supported in part by the project TEC2010-20886-C02-01 from the Spanish Ministry of Science and Innovation.

References

- [1] Malliani A, Schwartz PJ, Zanchetti A. A sympathetic reflex elicited by experimental coronary occlusion. Am J Physiol 1969;217:703-709.
- [2] Thorén PN. Activation of left ventricular receptors with nonmedullated vagal afferent fibers during occlusion of a coronary artery in the cat. Am J Cardiol 1976;37:1046-51.
- [3] Zareba W, Bayes-de Luna A. QT dynamics and variability. Annals of noninvasive electrocardiology 2005;10: 256-262.
- [4] Murabayashi T, Fetis B, Kass D, Nevo E, Gramatikov B, Berger RD. Beat-to-beat QT interval variability associated with acute myocardial ischemia. Journal of Electrocardio-

- logy 2002, 35:19-25.
- [5] Ringborn M, Pahlm O, Wagner G, Warren S, Petterson J. The absence of high-frequency QRS changes in the presence of standard electrocardiographic QRS changes of old myocardial infarction. *Am Heart J* 2001;141:573-579.
 - [6] Gomis P, Caminal P, Vallverdú M, Warren SG, Stein PK, Wagner GS. Assessment of autonomic control of the heart during transient myocardial ischemia. *Journal of electrocardiology* 2012;45:82-89.
 - [7] Martínez JP, Almeida R, Olmos S, Rocha AP, Laguna P. A wavelet-based ECG delineator: evaluation on standard databases. *IEEE Trans Biomed Eng* 2004;51:570-581.
 - [8] Pahlm O, Sörnmo L. Data processing of Exercise ECG's. *IEEE Trans Biomed Eng* 1987;34:158-165.
 - [9] Higuchi T. Approach to an irregular time series on the basis of the fractal theory. *Physica D* 1988;31:277-283.
 - [10] Magrans R, Gomis P, Caminal P, Wagner G. Multifractal and nonlinear assessment of autonomous nervous system response during transient myocardial ischemia. *Physiol Meas* 2010;31:565-580.
 - [11] Goldberger AL, Amaral LAN, Hausdorff JM, Ivanov PC, Peng CK, Stanley HE. Fractal dynamics in physiology:
- alterations with disease and aging. *PNAS* 2002;99:2466-2472.
- [12] Magnano AR, Holleran S, Ramakrishnan R, Reiffel JA, Bloomfield DM. Autonomic nervous system influences on QT interval in normal subjects. *J Am Coll Cardiol* 2002;39:1820-1826.
 - [13] Piccirillo G, Magrì D, Ogawa M, Song J, Chong VJ, Han S et al. Autonomic nervous system activity measured directly and QT interval variability in normal and pacing-induced tachycardia heart failure dogs. *J Am Coll Cardiol* 2009; 54:840-850.

Address for correspondence.

Pedro Gomis
Pau Gargallo 5,
Universitat Politècnica de Catalunya
08028 Barcelona, Spain
pedro.gomis@upc.edu