AUTOMATIC QT INTERVAL ANALYSIS IN POSTMYOCARDIAL INFARCTION PATIENTS.

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RUNNING HEAD: Automatic **QT** interval analysis in postmyocardial infarction patients

ABSTRACT

Corrected **QT** interval ($\mathbf{QT_c}$) prolongation seems to be a good marker for stratifying risk of sudden death in postmyocardial infarction patients. We have taken three groups of patients: A, postmyocardial infarction patients with malignant ventricular arrythmies (**MVA**); B, postmyocardial infarction patients without **MVA**; and C, a control group without heart disease.

QT interval has been automatically measured. We have analyzed $\mathbf{QT}, \mathbf{QT_c}, \mathbf{QTP}$ (time interval from **QRS** onset to **T** wave peak) and $\mathbf{QTP_c}$ (corrected **QTP**) in these three groups. We have found statistical differences when comparing 24 hour average $\mathbf{QT_c}$ ($\overline{\mathbf{QT_c}}$) in group A from B and C ($p < 0.01$). Also comparing the percentage of beats whose $\mathbf{QT_c}$ value is higher than some threshold, we may separate these groups ($p < 0.005$). No statistical difference was found comparing **QTP** or $\mathbf{QTP_c}$.

We have also studied **QTP** and $(\mathbf{QT} - \mathbf{QTP})$ intervals. Variations of $\mathbf{QT_c}$ in group A from B and C can be associated with changes in both intervals ($\mathbf{QT} = \mathbf{QTP} + (\mathbf{QT} - \mathbf{QTP})$). If **T** wave peak is well defined at the ECG, $(\mathbf{QT} - \mathbf{QTP})$ is a constant with each patient. In these cases it can be used to measure **QT** interval more accurately.

Heart rate variability **(HRV)** has also been analysed using the standard deviation of **RR** interval in 24 hours (Global SD index). Patients in group A show lower variability than those in groups B and C. The **HRV** together with $\mathbf{QT_c}$ improve the stratification value of this study.

1 INTRODUCTION

Cardiovascular diseases are the primary cause of death in the adult population. Half of cardiac deaths occur as sudden death. In recent years many studies have been done to show the relationship between **QT** interval and prognosis in postmyocardial infarction patients [*1-5*]. **QT** interval is the electrocardiographic representation of the ventricular depolarization and repolarization duration. It is calculated on the ECG signal (algebraic sum of every action potential of myocardial cells) as the time distance from the onset of the QRS complex to the end of the T wave. Prolonged **QT** interval may correspond to an abnormally long action potential in all cells, but it may also reflect the dispersion of action potentials, long in some zones and normal in others, which could constitute a propitious substrate for the appearance of re-entry tachycardias or ventricular arrythmies.

An abnormal $\mathbf{QT_c}$ (**QT** corrected with Bazett's formula $\mathbf{QT_c} = \mathbf{QT}/\sqrt{\mathbf{RR}}$ [*6*]) prolongation in surface could be associated with serious ventricular arrythmies, syncope and sudden death. In a previous work [*7*] we have shown how manual measurement of $\mathbf{QT_c}$ could be a marker of malignant ventricular arrythmies (**MVA**) (sustained ventricular tachycardia or ventricular fibrillation in the subacute phase of myocardial infarction).

Several automatic methods to measure **QT** interval in long-term ECG has been proposed. We have computed dynamic **QT** interval in 24 hour Holter ECG using a recently proposed algorithm [*8*]. This algorithm makes use of first derivative of the signal. We have also computed $\mathbf{QT_c}$, **QTP** (time interval from **QRS** onset to **T** wave peak) and $\mathbf{QTP_c}$ (corrected **QTP**). Corrections are performed with Bazett's formula.

In the present study three groups of patients have been selected: group A was formed by 5 postmyocardial infarction patients who presented **MVA** during or after Holter recording; group B consisted of 13 postmyocardial infarction patients without **MVA**; and group C was formed by a control group of 10 patients without heart disease.

We have considered the four previously defined intervals and we have studied their significance to stratify postmyocardial infarction patients. Also we present a discussion on **QT** and **QTP** interval measurement accuracy. Different ways to present the results have been considered. The 24 hour average interval values and the percentage of beats whose $\mathbf{QT_c}$ value is higher than some threshold has been analysed. Their statistical significance in separating patients of group A from those of B or C have been studied.

A study on the relationship between **QT**, **QTP** and (**QT** − **QTP**) intervals has been made, and criteria to obtain **QT** from **QTP** have been considered when **T** wave peak is well defined and T wave end detection is not enough precise.

Heart rate variability (**HRV**) has been reported as an index of mortality after myocardial infarction [*9*]. From the **RR** interval defined by the algorithm we can compute the heart rate variability in each patient and compare the stratification value of **QT** intervals and **HRV** in postmyocardial infarction patients. There are different methods to evaluate the **HRV** [*10*]. We have selected the global SD index (**SD(RR)**, standard deviation of **RR** interval in 24 hours) because it takes the 24 hour average as we do when we analyse the **QT** intervals.

2 METHODS

We analysed data recorded on a Holter system (ICR-6500) with a bandwith of 0.05-100 Hz (-3 dB). Holter tapes were played back on a DR tape recorder (AIWA WX808) with a bandwith of 20-16000 Hz. Tape speed of the play back system is 100 times faster than in the ICR-6500, that leads to an equivalent bandwith of 0.02-160 Hz with respect to the original ECG time scaling. These bandwiths assure that the ECG signal is recorded and played back without significant distorsion. The two leads recorded with this Holter system belong to lead V2 and V5. We visually selected one of the two channels that had the best signal to noise ratio or where **T** wave end was easier to define. Since **T** wave is abnormal after infarction, it might be better to record the 12-lead ECG to identify the one with optimal **T** wave morphology and the longest **QT** duration. In this study, due to Holter limitations, we consider only the two leads reported above.

We have analysed the previously described groups of patients A, B and C. Patients were selected in such a way that no drug therapy was administered to them previously to record the Holter ECG. This is important since anti-arrythmic drug treatment has impact on the **QT** intervals, and these induced **QT** variations would negate the value of this study where we analyse the **QT** intervals as markers to stratify risk following myocardial infarction. Same reason leaded us to reject those patients with conduction abnormalities, as bundle branch block, that prolong the **QT** interval. Patients with auricular fibrillation or with pacemaker were also rejected. All these restrictions made difficult to have a large number of patients, mostly in group A where drug treatment is administrated once the malignant ventricular arrythmy has been diagnosed. Patient ages in the

three groups range from 40 to 70, the ejection fraction in group A ranges from 36% to 40% (mean 38%) and for those in group B from 26% to 49% (mean 37%). The grade of disability according to the New York Heart Association classification is between I and II in both groups, A and B. All patients are male, excepting one in group A that is female.

Analog signals were digitized with a resolution of 12 bits, using a data acquisition system based on a Compaq Model 386/20 computer. The equivalent sampling rate was 250 samples per second. Data were stored in the computer for subsequent detailed analysis. We have applied our algorithm and present the results as 24 hour average $\mathbf{QT}, \mathbf{QT_c}, \mathbf{QTP}, \mathbf{QTP_c}$, ($\overline{\mathbf{QT}}, \overline{\mathbf{QT_c}}, \overline{\mathbf{QTP}}, \overline{\mathbf{QTP_c}}$), the $\mathbf{SD}(\mathbf{RR})$ and the percentage of beats whose parameter takes value in previously defined limits. **QT** and **RR** intervals trends in 24 hours are also available from this work.

3 ALGORITHM

To define **QT** interval we need to detect **QRS** onset and **T** wave end. Two kinds of algorithms are usually used to define **T** wave end. Some algorithms use criteria based on the signal deflection with respect to the baseline [*11-13*]. Others use criteria with respect to the differentiated signal [*13*]

The algorithm we use has recently been proposed and discussed in detail [*8*]. Here we will only note the different steps of the algorithm and for a more detailed discussion we refer to [*8*]. The algorithm is based on the differentiated ECG signal and is fast enough for 24 hour Holter ECG analysis. The algorithm is protected from noise and artifacts, and its accuracy is comparable with those of manual measurements.

The signal processing algorithm includes the following steps:

1. **Preprocessing:** A low-pass differentiator (LPD) [*8, 14*] is applied on the signal, whose transfer function is $G_1(z) = 1 - z^{-6}$. This low-pass differentiator behaves as differentiator at the ECG frequency components [*14*], and as low-pass filter at higher frequencies (Fig. 1). To avoid residual noise we also applied a successive low-pass filter [*15*] whose transfer function is $G_2(z) = (1 - z^{-8})/(1 - z^{-1})$.

   Fig. 1 shows transfer functions of the differentiator $G_1(f)$, low-pass filter $G_2(f)$, and the combination of both $G_3(f) = G_1(f) \cdot G_2(f)$.

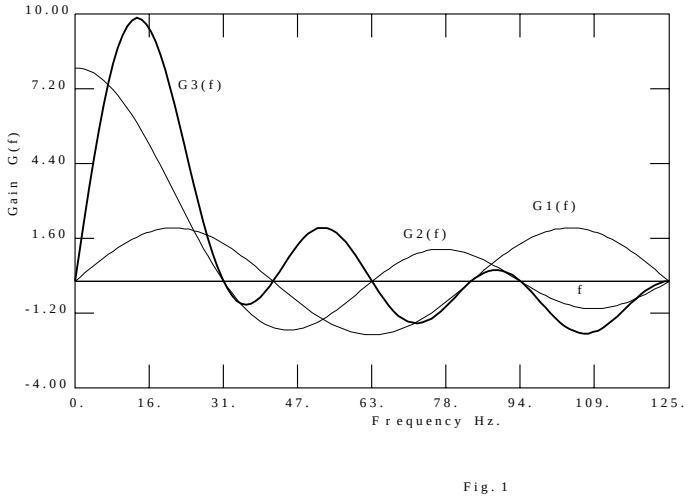

Figure 1: *Transfer functions of: Differentiator filter $G_1(f)$, low-pass filter $G_2(f)$, and combination of both $G_3(f)$.*

2. **QRS detection:** Once the signal is differentiated and filtered, a **QRS** detector is applied. It is based on an adaptive threshold [*16*], with some modifications in order to increase processing speed.

3. **QRS onset definition:** From the detected **QRS** position the algorithm looks for the **Q** wave position (or **R** wave when no **Q** wave is present) and its highest slope value. This value divided by a constant is considered as a threshold. When the differentiated ECG signal reaches this threshold value the **QRS** onset point is marked.

4. **T wave peak and end definition:** In order to define the **T** wave end point a search window is defined from **QRS** position. We again applied the low-pass filter G_2 on this window signal to attenuate remaining noise. We look for the highest slope value of the downwards side of the **T** wave (upward in inverted **T** wave). This point will be a maximum or minimum at the differentiated and low-pass filtered ECG signal in the previously defined window. We define a threshold as this slope value divided by a constant factor, that experimentally has been shown to have the best performance when it takes the value of 2. Then **T** wave end is marked when the differentiated signal reaches this threshold. From this point we define **T** wave peak as the previous zero-crossing point in the differentiated signal. At this stage we have the three point we need to define **QT** and **QTP**. Figure 2 shows different patterns of

how the algorithm performs in four different morphologies.

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Figure 2: *Patterns of four different beats and how the algorithm works. Long lines show the* **Q** *wave beginning (***QRS** *onset) and* **T** *wave end as limits of* **QT** *interval. Short lines show* **Q**, **R** *and* **T** *wave peak positions. Only* **R** *(or* **Q***) and* **T** *wave peak positions are indicated when there are just two marks.*

5. **QT values selection:** Wrong measurement could be performed when noise, PVC, or other abnormalities are present. **QT** (**QTP**) values that are out the 15% current **QT** (**QTP**) average are rejected. The remaining beats are grouped in 5 measurement sets. Beats whose **QT** (**QTP**) value is the maximum or the minimum in each set are rejected as possible wrong data (noisy or ectopic beats). If these rejected beats were not wrong no significant change occurs in the dynamic **QT** (**QTP**) behaviour.

This algorithm has been validated by hand measurements in more than 650 beats belonging to 18 different Holter tapes chosen randomly. Paper speed was 25 mm/s. On the ECG paper records a tangent to the steepest portion of the downsloping **T** wave was constructed, and the intersection of this tangent and isoelectric line was defined as the T-wave termination in the manual measures. The mean error between manual and automatic measurements results in 2.0 ms, with a standard deviation of 14.3 ms [*8*]. These values are comparable with differences between measurements done by two observers, that are described to be around 10 ms [*8,13,17*].

4 RESULTS

We have taken the previously described groups A, B and C. We have computed **QT** interval and previous **RR** interval to implement Bazett's correction ($\mathbf{QT_c} = \mathbf{QT}/\sqrt{\mathbf{RR}}$) and to evaluate the **SD**(**RR**). **QT** interval value has information on the whole repolarization time of the heart, but sometimes there is not a clear deflection that allows an accurate definition of the **T** wave end. **T** wave peak is more precisely defined [*12*] and could avoid that problem. For this reason we have also computed **QTP**, $\mathbf{QTP_c}$, ($\mathbf{QTP_c} = \mathbf{QTP}/\sqrt{\mathbf{RR}}$) to be compared with **QT** and $\mathbf{QT_c}$ values.

T wave peak is the time occurrence where there is a bigger difference between number of myocardial cells which have finished repolarization or are near the resting level potential, and those which are still at the maintained depolarization plateau or near it (Fig. 3) [*18*].

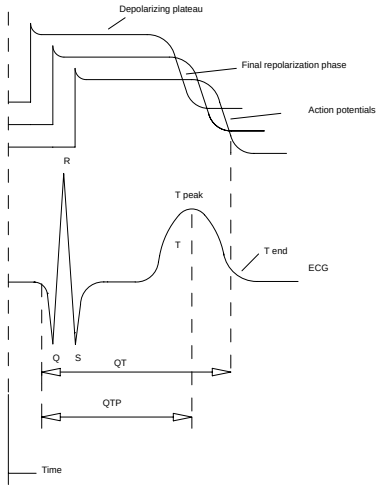

Fig. 3.

Figure 3: *Action potentials of cardiac cells. In a simplification of the complex process that generates the ECG signal we can considered that the algebraic sum of all action potentials, delayed in time from one cell to others, perform the ECG signal.* **T** *wave belongs to the final repolarization time. Note that* **T** *wave peak occurs at the time where there is a bigger difference between number of cells at the plateau region or near it and those that are already repolarized or in the final repolarization phase.*

If beat-to-beat **QT** interval variations only implies changes in the plateau region of the action potentials, we will get the same information measuring **QT** or **QTP**. But if changes occur in the final repolarization phase we will lose information about whole repolarization time when using **QTP**. To analyse that, we have measured (**QT** − **QTP**) interval in each patient as information of the final repolarization phase.

Different indexes related to **QT** intervals and **HRV** have been considered to stratify postmyocardial infarction patients. A study to analyse the performance of these indexes has been done and the prediction value for each one has been considered.

4.1 Corrected QT interval ($\mathbf{QT_c}$)

Figure 4 shows the results of 24 hour **QT** interval value in each patient of the three groups. We display the percentage of beats whose **QT** value is in successive 20 ms increment intervals. The $\overline{\mathbf{QT}}$ value and the standard deviation (SD) are also displayed for each patient. Fig 5,6 and 7 show the values of $\mathbf{QTP}, \mathbf{QT_c}$ and $\mathbf{QTP_c}$ respectively. Corrected intervals are measured in units (u) ($u = ms/\sqrt{s}$). Note that the SD of corrected intervals ($\mathbf{QT_c}, \mathbf{QTP_c}$) in 24 hours is lower than the SD of uncorrected values in groups B and C, as effect of taking into account the **RR** dependence. In group A this does not happen. This can be because of greater intrinsic **QT** variations in these patients and because the **RR** interval in these patients remains more stable than patients of groups B and C. (mean of the standard deviations of **RR** interval in 24 hour of 84 ms for these patients, compared with 115 ms and 124 ms in patients of groups B and C, respectively, as shown in table 1).

AVERAGE VALUES IN PATIENTS GROUP

		QT	QTP	QTc	QTPc	HRV
Group	**n**	$\overline{QT}\pm$ SD (ms)	$\overline{QTP}\pm$ SD (ms)	$\overline{QTc}\pm$ SD (u)	$\overline{QTPc}\pm$ SD (u)	$\overline{SD(RR)}\pm$ SD ms
A	5	374 ± 33	296 ± 34	445 ± 23	350 ± 31	84 ± 37
B	13	365 ± 21	292 ± 19	403 ± 18	322 ± 16	115 ± 27
C	10	340 ± 14	272 ± 20	402 ± 20	321 ± 25	124 ± 15
p(AB)		<0.5	<0.5	<0.005	<0.05	<0.05
p(AC)		<0.05	<0.02	<0.01	<0.1	<0.02

Table 1: *Average values and standard deviation (SD) of* $\mathbf{QT}, \mathbf{QTP}, \mathbf{QT_c}, \mathbf{QTP_c}$ *and* **HRV** *(standard deviation of RR interval* $\mathbf{SD(RR)}$ *in 24 hour as Global SD index of heart rate variability) for each group. Statistical significance using t Student test to separate group A from B (p(AB)) and from C (p(AC)) is displayed for each parameter, showing that the best one to do that is* $\mathbf{QT_c}$*. The number of patients in each group is denoted by* **n**.

In table 1 we have the average values and standard deviation of $\mathbf{QT}, \mathbf{QTP}, \mathbf{QT_c}, \mathbf{QTP_c}$ for each group of patients. We see that the best parameter to separate group A from B and C is $\overline{\mathbf{QT_c}}$, ($p < 0.01$ using t Student test). There is no difference when comparing groups B and C. We get 445 units (u) in group A and 403 u, 402 u in B and C, respectively.

On the other hand we see that differences in $\overline{\mathbf{QT_c}}$ value ($\overline{\mathbf{QT_c}} = \overline{\mathbf{QTP_c}} + \overline{(\mathbf{QT} - \mathbf{QTP})_c}$)

between A and B, and A and C (around 40 u, table 1) can be associated with the final repolarization time (differences in $\overline{(\mathbf{QT}-\mathbf{QTP})_\mathbf{c}}$ are about 10 u, table 2) and with the plateau region (differences in $\overline{\mathbf{QTP_c}}$ are about 30 u, table 1) (40-10=30 u). It means that $\mathbf{QT_c}$ variations occur by changes in both regions of the action potentials, but mostly in the depolarizing plateau (fig. 3). This explains the fact that $\overline{\mathbf{QT_c}}$ is more significant than $\overline{\mathbf{QTP_c}}$, and also the fact that $\overline{\mathbf{QTP_c}}$ had some signification to separate A from B and C ($p < 0.05$) because the 75% ($30u$ of $40u$) of the change in $\overline{\mathbf{QT_c}}$ interval between patients in A and B occurs in $\overline{\mathbf{QTP_c}}$ and only 25% ($10u$ of $40u$) occurs in $\overline{(\mathbf{QT}-\mathbf{QTP})_\mathbf{c}}$.

Regarding to figures 4 and 5, and table 2, we note that there are patients where $\overline{\mathbf{QT}}$ is not exactly equal to $\overline{\mathbf{QTP}}$ + $\overline{\mathbf{QT}-\mathbf{QTP}}$ (for example, A4 and B2). This occurs because when we evaluate **QTP** and (**QT** − **QTP**), it is necessary to reject more beats than when we evaluate **QT**, because wrong **T** wave peak definition increases the number of rejected beats with regard to those rejected when measuring only **QT** interval.

Figure 9 shows the percentage of beats whose $\mathbf{QT_c}$ value is higher than some thresholds between 400 and 500 u. We have evaluated the significance level (p) to separate group A from B and C. We obtain that each threshold considered is able to separate A from B and C. The threshold value of 440 u is the best one in sense of significance ($p < 0.005$), even better than $\overline{\mathbf{QT_c}}$.

Figure 10 shows the dynamic evolution of **QT** and **QTP** in 24 hours and how Bazett's formula corrects the **RR** dependence in the **QT** and **QTP**. This can be useful to analyse and monitor dynamic changes in the **QT** interval. Other different **QT** corrections have been proposed [*19*] but it seems that there is not a general one for all patients. The correction of **QTP** with Bazett's formula has not been applied until now. Fundamental dependence is well modelled by Bazett's correction, even in the case of **QTP**. Note (table 2 and fig. 4 and 8) that the (**QT** − **QTP**) and $(\mathbf{QT}-\mathbf{QTP})_c$ distances remains constant over time even though **QT** and **RR** change.

4.2 (QT − QTP) interval

The objective is to verify if **QT** and **QTP** have the same clinical information. To analyse that, we study the relationship between $\mathbf{QT}, \mathbf{QTP}$ and (**QT** − **QTP**) intervals.

Table 2 shows $\overline{(\mathbf{QT}-\mathbf{QTP})}$ and $\overline{(\mathbf{QT}-\mathbf{QTP})_\mathbf{c}}$ for each patient and the average in each group. We can see how these distances are not constant for all patient groups, neither $\overline{(\mathbf{QT}-\mathbf{QTP})}$ nor

AVERAGE QT-QTP IN EACH PATIENT

	AVERAGE IN EACH PATIENT				AVERAGE IN EACH GROUP	
GROUP	$\overline{QT-QTP}\pm$ SD (ms)		$\overline{(QT-QTP)c}\pm$ SD (u)		$\overline{QT-QTP}\pm$ SD (ms)	$\overline{(QT-QTP)c}\pm$ SD (u)
A	A1	72 ± 12	A1	75 ± 13	82 ± 18	90 ± 19
	A2	95 ± 32	A2	102 ± 35		
	A3	57 ± 23	A3	63 ± 27		
	A4	80 ± 21	A4	93 ± 32		
	A5	109 ± 25	A5	118 ± 30		
B	B1	79 ± 9	B1	83 ± 11	74 ± 6	78 ± 6
	B2	68 ± 18	B2	70 ± 20		
	B3	81 ± 11	B3	84 ± 13		
	B4	82 ± 12	B4	84 ± 12		
	B5	75 ± 9	B5	80 ± 10		
	B6	62 ± 6	B6	67 ± 8		
	B7	73 ± 9	B7	78 ± 11		
	B8	69 ± 7	B8	73 ± 8		
	B9	77 ± 9	B9	77 ± 9		
	B10	77 ± 20	B10	82 ± 23		
	B11	81 ± 19	B11	86 ± 22		
	B12	67 ± 10	B12	72 ± 12		
	B13	72 ± 15	B13	75 ± 16		
C	C1	89 ± 15	C1	97 ± 20	70 ± 8	77 ± 9
	C2	78 ± 24	C2	84 ± 26		
	C3	67 ± 8	C3	77 ± 11		
	C4	64 ± 7	C4	70 ± 11		
	C5	66 ± 10	C5	72 ± 14		
	C6	70 ± 17	C6	77 ± 19		
	C7	63 ± 13	C7	69 ± 16		
	C8	66 ± 10	C8	72 ± 14		
	C9	78 ± 17	C9	86 ± 20		
	C10	61 ± 20	C10	66 ± 22		

Table 2: *Mean and standard deviation (SD) of (***QT-QTP***) and* $(\mathbf{QT-QTP})_{\mathbf{c}}$ *in 24 hours for each patient in each group. On the right part we have the average value in each patient group. Note that this value is different in group A from that of group B or C, and how (***QT - QTP***) remains constant in each patient with the precision of the algorithm (14.3 ms) and the exceptions*

$\overline{(\mathbf{QT}-\mathbf{QTP})_c}$. Also these distances do not have linear dependence with $\overline{\mathbf{QT}}$ interval ($\overline{\mathbf{QT}}, \overline{\mathbf{QT_c}}$ in Fig. 4 and 6, and table 1). Groups B and C have similar values of ($\overline{\mathbf{QT}-\mathbf{QTP}}$), ($74 \pm 6$ ms and 70 ± 8 ms, respectively). These values can be considered as a constant, but different to that of Group A (82 ± 18 ms). Analogously occurs with corrected values.

We can conclude that even though **QTP** is easier to define, it loses information on repolarization time (**QT**) that cannot be recovered from **QTP** value. Then **QTP** is not suitable to study pathologies related with the whole repolarization time.

The standard deviation (SD) of ($\mathbf{QT}-\mathbf{QTP}$) in each patient has values comparable with the precision of the algorithm [*8*]. That means ($\mathbf{QT}-\mathbf{QTP}$) remains aproximately constant in each patient over time, nevertheless there are patients which ($\mathbf{QT}-\mathbf{QTP}$) has higher SD (A2, A3, A4, A5, B10, C2, C10). This occurs when the **T** wave has not a well marked maximum or minimum peak. In these cases (Fig. 11) the zero-crossing point at the differentiated signal (**T** peak point) is not precise. According with these results in patients with clear definition of **QTP**, we can express **QT** as **QTP** plus a constant

$$\mathbf{QT_i} = \mathbf{QTP_i} + \mathbf{k}$$

where **i** denotes each beat and **k** is the estimated patient constant $\mathbf{k} = \overline{\mathbf{QT}-\mathbf{QTP}}$. The estimation of **k** can be performed in a selected noise-free part of the signal where the measurement are reliable. In this way we can use **T** peak point instead of **T** end to measure **QT** interval with the advantage of a more precise definition in **T** wave peak point than in **T** wave end. To prevent possible **QTP** variations (this interval can be altered with posture over 24 hour period) periodic recalculations of the **k** constant over the 24 hour will be recommended.

4.3 Heart rate variability (HRV)

Temporal indexes to measure **HRV** [*10*] can easily be computed from the **RR** interval given by the algorithm we use. Recent works [*9*] found that patients with a reduced heart rate variability after myocardial infarction (<50 ms) have a more elevated mortality rate than those whose **HRV** is higher (>100 ms).

It seems interesting to study the **HRV** in patients analysed in this work and compare the results with those of **QT** interval. In the last column of table 1 we have the mean global SD index of **HRV** in each group and their significance to stratify postmyocardial infarction patients ($p < 0.05$).

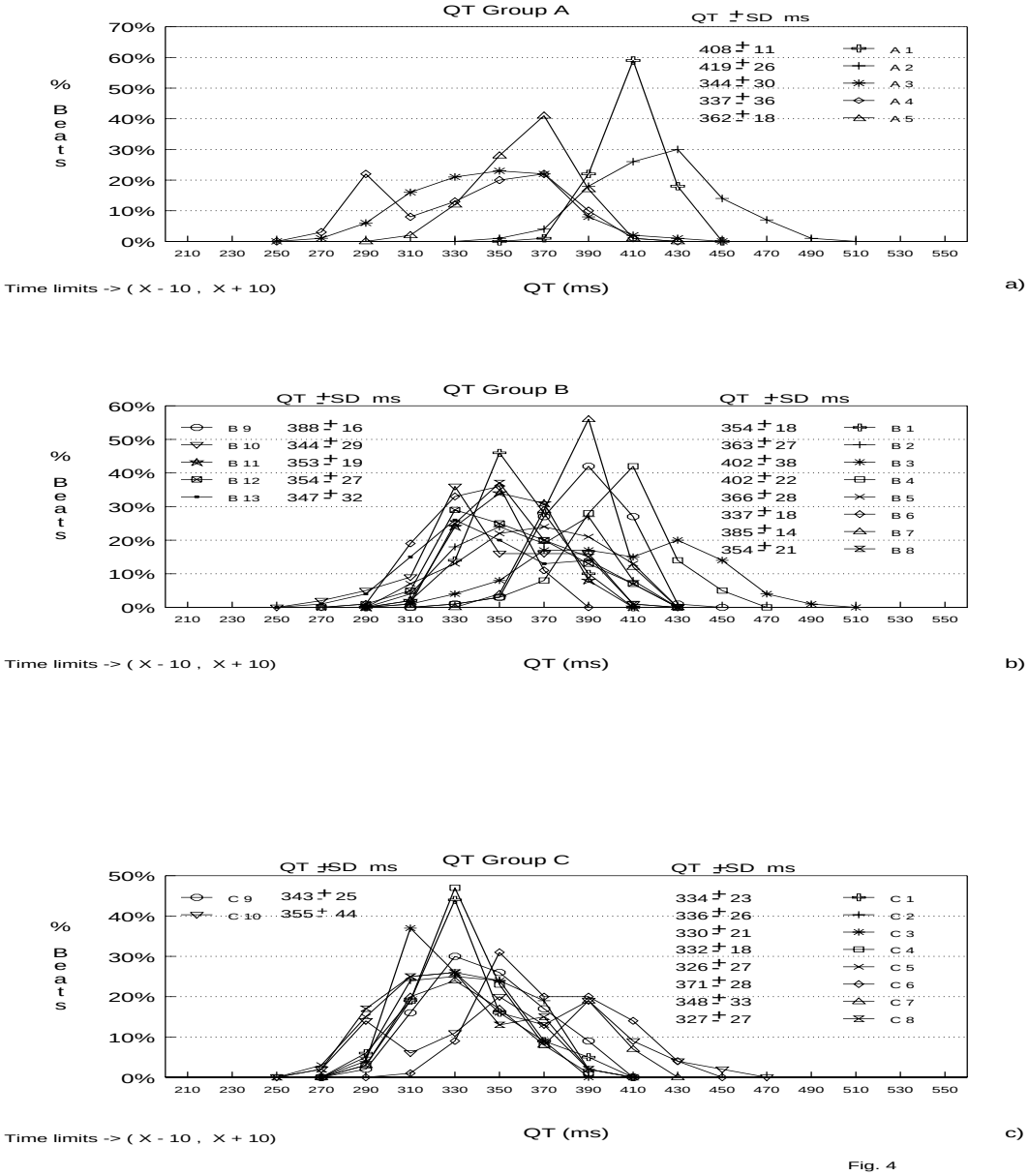

Figure 4: **QT** *interval values for 24 hour. We represent the percentage of beats whose* **QT** *value is in successive 20 ms increment intervals. These limits are denoted by the middle point interval value in ms (e. g. 210 → [200 , 220] ms). Superimposed to the graphic we have the* **QT** *average value (* $\overline{\mathbf{QT}}$ *) and the standard deviation (SD) values in 24 hour. a) Results from patients in group A, b) results from group B, and c) results from group C.*

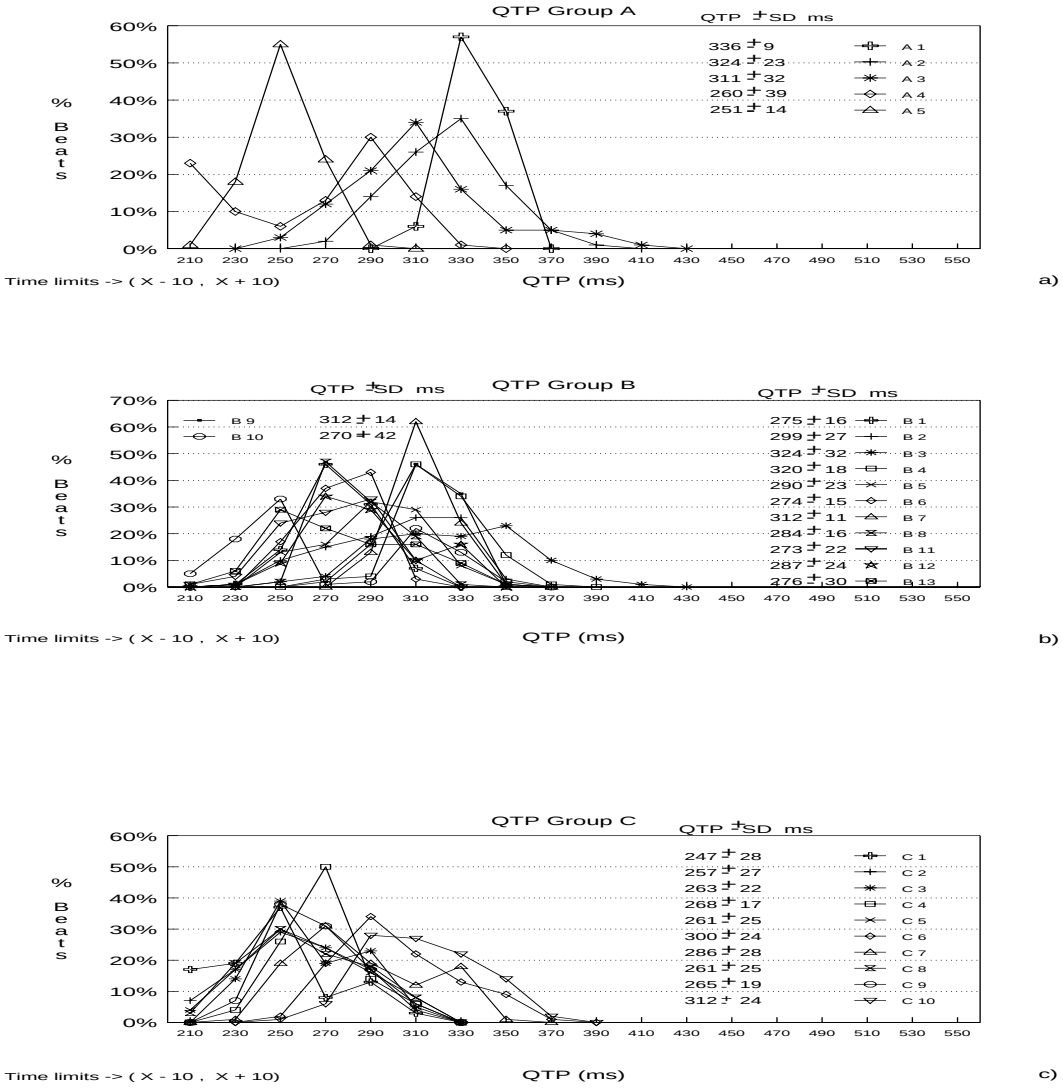

Figure 5: **QTP** *interval values for 24 hour. Same notation used in Fig. 4.*

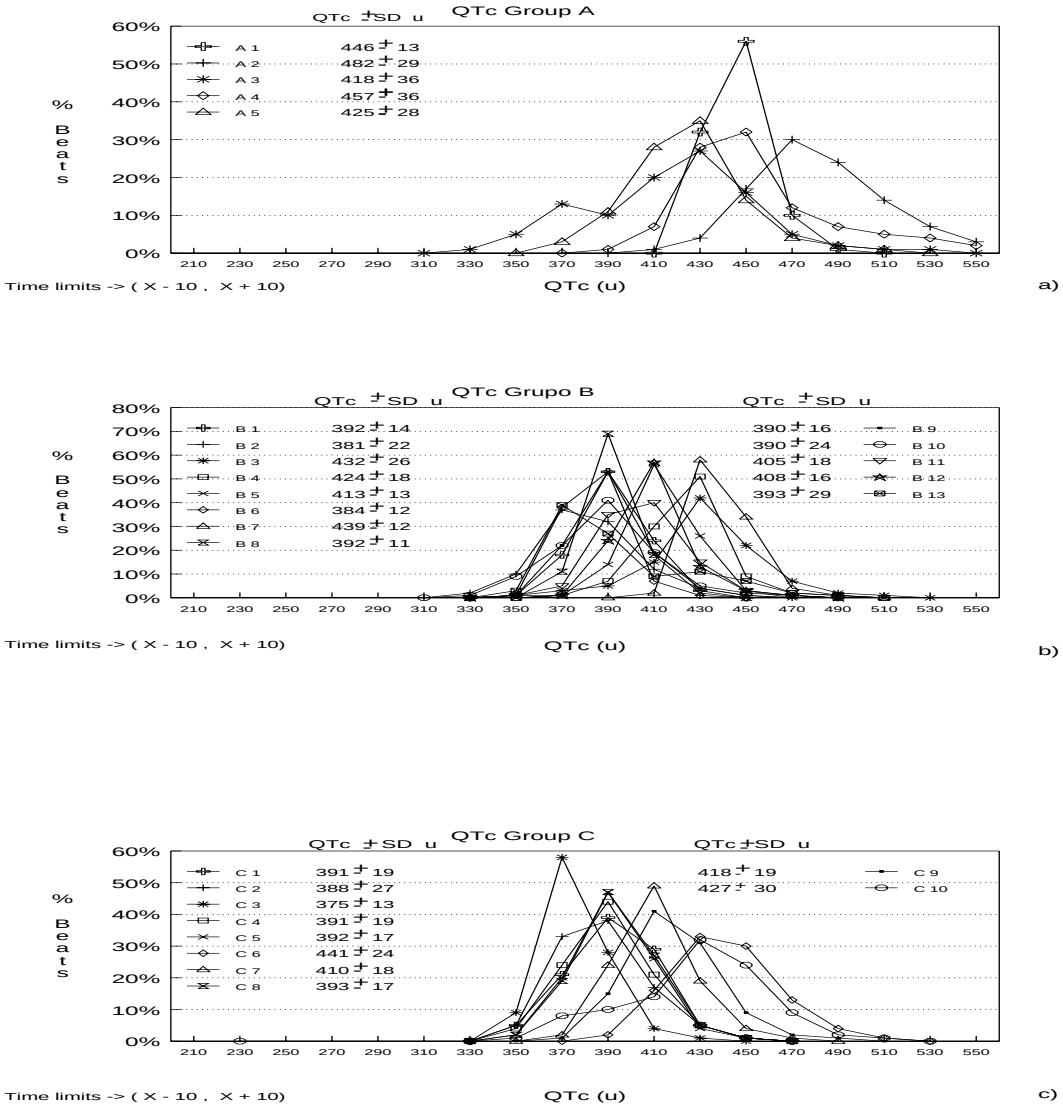

Figure 6: $\mathbf{QT_c}$ *interval values for 24 hour. Same notation used in Fig. 4.*

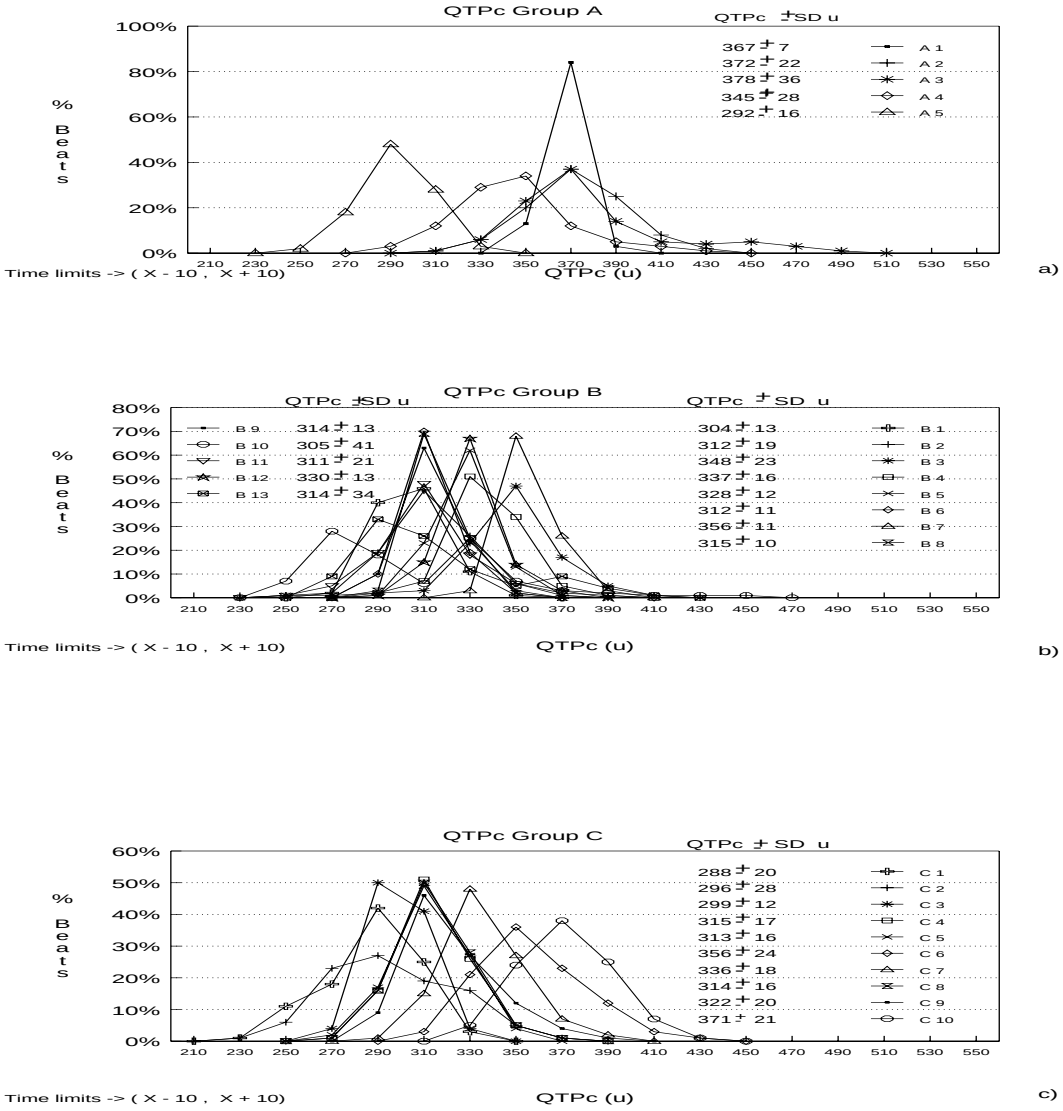

Figure 7: $\mathbf{QTP_c}$ *interval values for 24 hour. Same notation used in Fig. 4.*

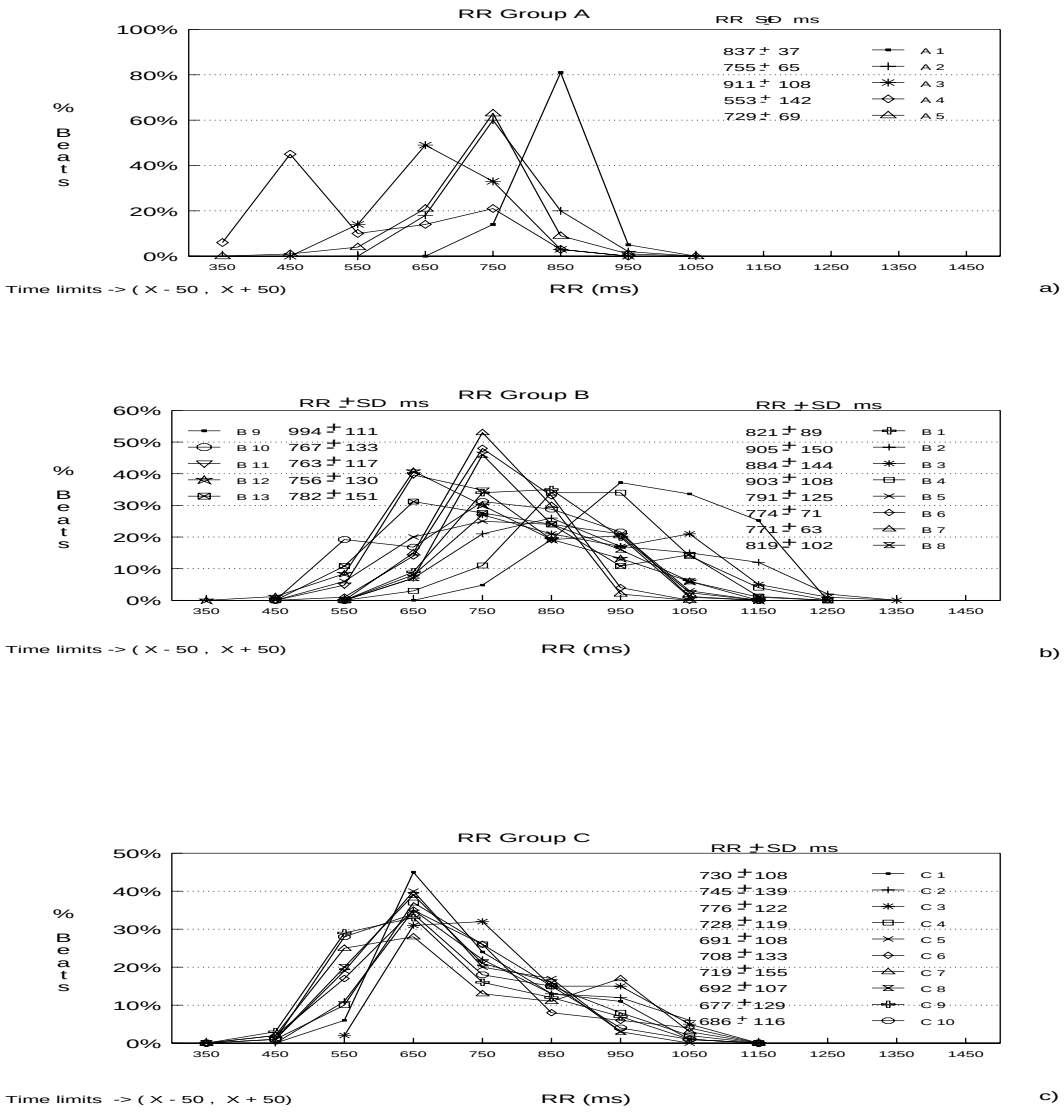

Figure 8: **RR** *interval values for 24 hour. Same notation used in Fig. 4 with 100 ms increment intervals.*

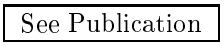

Figure 9: *Percentage of beats whose* $\mathbf{QT_c}$ *value is higher than some thresholds (500, 480, 460, 440, 420, 400 units) for each group. Numerical values with standard deviations are displayed below the graphics, and statistical differences using t Student test to separate A from B (p(AB)) and from C (p(AC)). Note that 440 u threshold is the best one to separate A from B and C.*

In fig. 8 the SD of **RR** interval is directly the **HRV** index for each patient. **HRV** is lower in postmyocardial infarction patients who are prone to develop **MVA** than in those postmyocardial infarction patients who do not develop **MVA**. These results agree with [9].

Neither $\overline{\mathbf{QT_c}}$ nor **HRV** parameters are definitive to separate these patients. Taking the combination of both indexes it may be improved the patient stratification. In case that distributions around the mean of $\overline{\mathbf{QT_c}}$ and **HRV** indexes were independent in each group, the significance level (p) is the product of significance levels (p_i) related to each index given that p is a probability. In this case, considering $\overline{\mathbf{QT_c}}$ and **HRV** to separate A from B we obtain $p < 0.005 \cdot 0.05 = 0.00025$. Analogously, comparing groups A and C, and using the threshold index.

5 DISCUSSION AND CONCLUSIONS

Several conclusions can be extracted from this study:

a) Corrected **QT** interval ($\mathbf{QT_c}$) allowed us to differentiate postmyocardial infarction patients which are prone to develop **MVA** from those who are not. $\overline{\mathbf{QT_c}}$ value and percentage of beats whose $\mathbf{QT_c}$ value is higher than 440 u have been shown to be good indexes to identify these patients. The value of this $\overline{\mathbf{QT_c}}$ index can be considered as a tendency to classify patients according to their risk of sudden cardiac death.

b) **QTP** interval loses information about whole repolarization time (**QT**) of the heart, and then it can not be considered as a good marker of pathologies related with this time period.

c) In cases where **T** wave peak is well defined we have shown that distance from this point to **T** wave end point remains constant over time. This can be used to measure **QT** interval as **QTP** interval plus a patient constant (**k**), that adds to **QTP** the repolarization time information

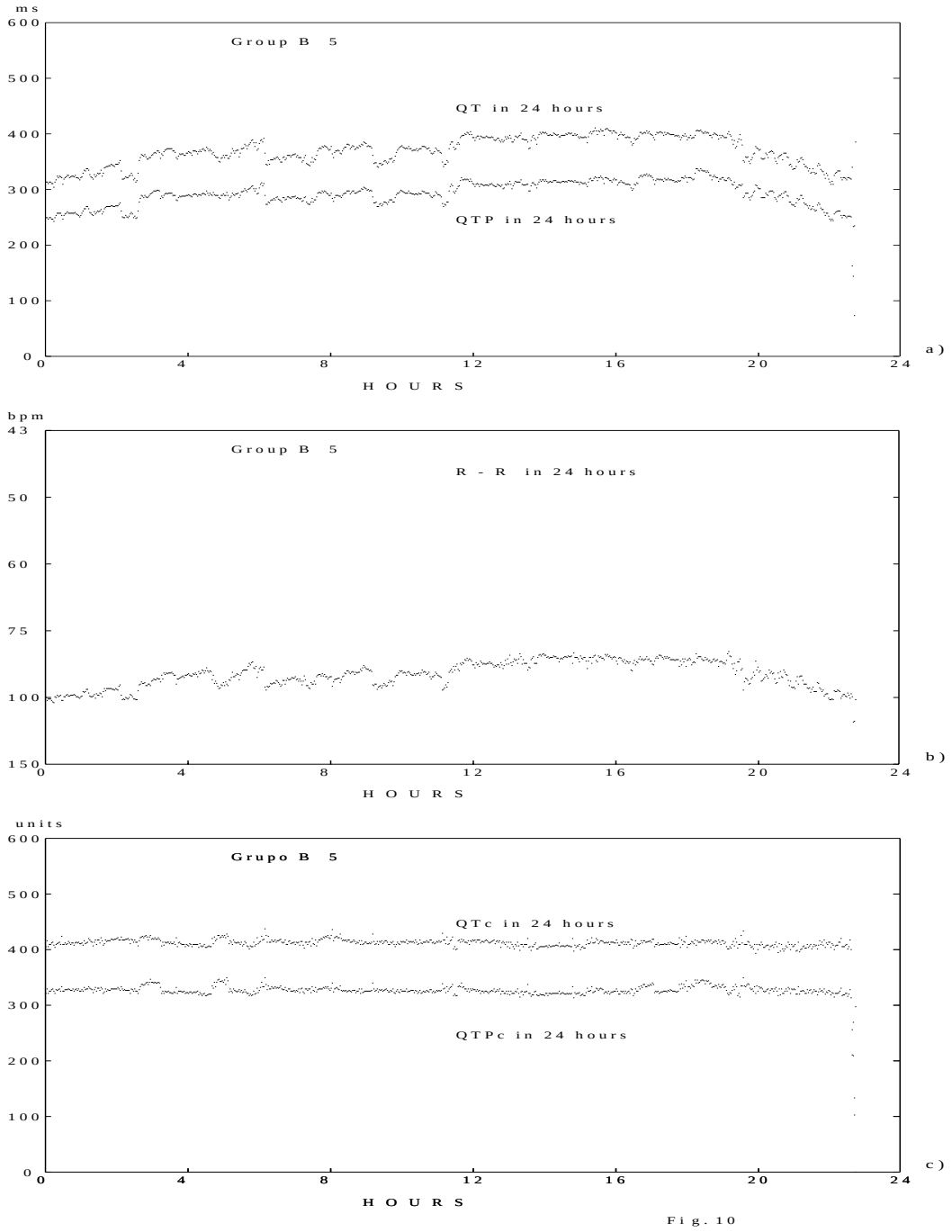

Figure 10: *Dynamic behaviour of* **QT** *values in one patient (B5) during 24 hour. a)* **QT** *and* **QTP** *evolutions, b)* **RR** *interval, expressed in beats per minute, and c)* $\mathbf{QT_c}$ *and* $\mathbf{QTP_c}$. *Each point is the average value in 36.4 s. Note how the fundamental dependence of* **QT** *and* **QTP** *with* **RR** *is well modeled by this correction.*

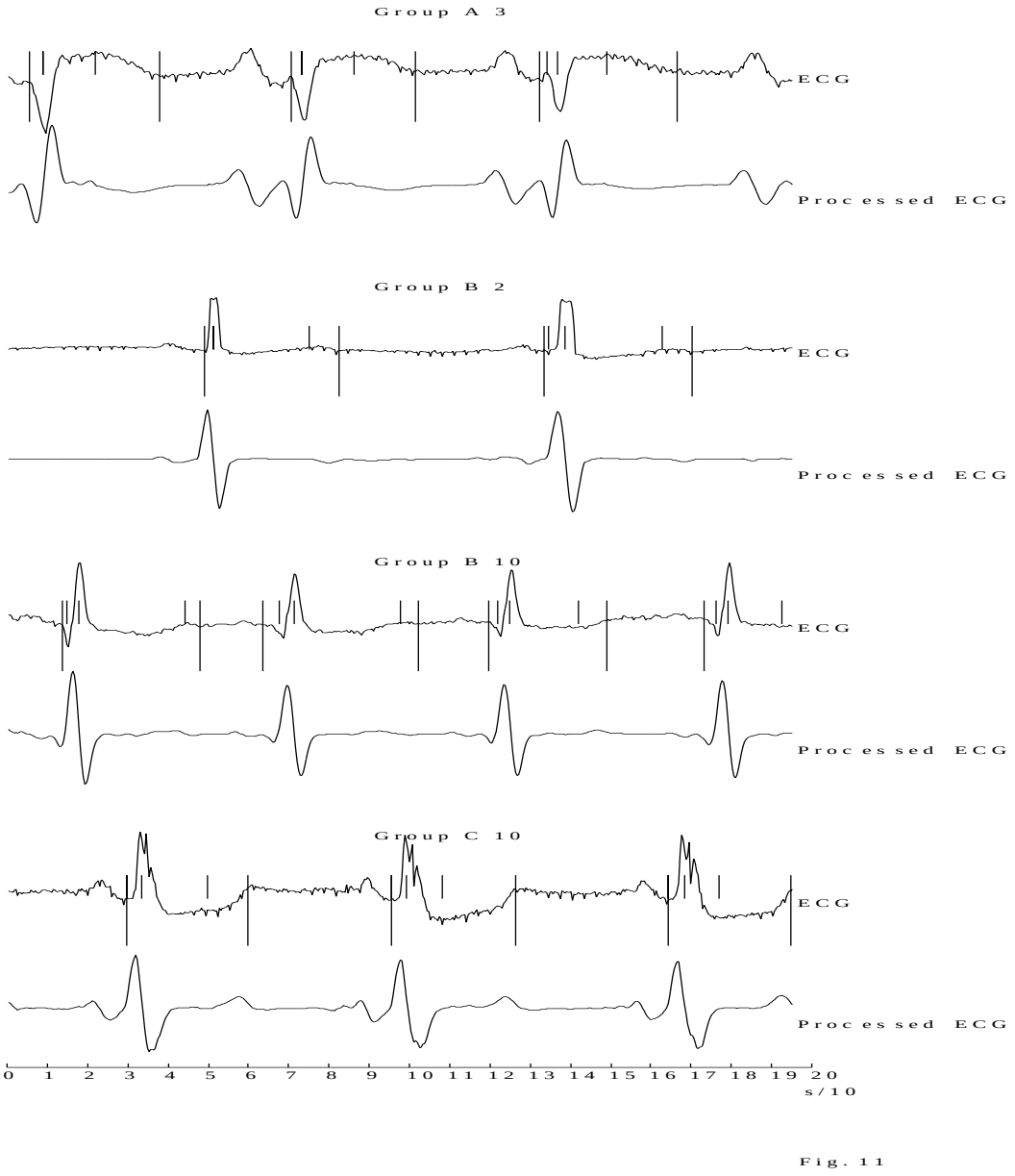

Figure 11: *Patterns of four ECG signals and their differentiated and low-pass filtered. they belong to patients (A3,B2,B10,C10). In these cases* **T** *wave has not a maximum or minimum that allows to correctly define* **T** *wave peak. Long lines show the Q wave beginning (***QRS** *onset) and* **T** *wave end as limits of* **QT** *interval. Short lines show* **Q, R** *and* **T** *wave peak positions, in this order. Note how in the differentiated signal the* **T** *peak is in a zero-flat line. This can give a big dispersion at the zero-crossing point from beat to beat.*

($\mathbf{QT} - \mathbf{QTP}$) . Then the precision and reliability of **QT** interval measured in this way becomes higher.

d) **HRV** also gives information on postmyocardial infarction patients. Its value is lower in postmyocardial infarction patients with **MVA** than in those who have not **MVA**. Combination of this index with $\mathbf{QT_c}$ may improve the patient stratification.

Two considerations could be formulated to the conclusions: Firstly the number of patients, mostly in group A, is not big enough to take definitely statistical conclusions. Data from patients of group A are difficult to obtain. More data collection in this group will be very useful to complete this study. Secondly, some patients from group A (A3, A5) have lower $\overline{\mathbf{QT_c}}$ value than other patients in groups B or C (B3, B7, C6) (Fig. 6). That means we cannot use $\overline{\mathbf{QT_c}}$ as a definitely marker, even though the study shows a clear tendency in sense of prolonged $\mathbf{QT_c}$ interval in postmyocardial infarction patients prone to develop **MVA**.

Sudden death problem is a multiparametric problem and there is not enough knowledge of what are exactly all the parameters that are related with this, or in what way they are related. This study proves that dynamic prolongations of $\mathbf{QT_c}$ interval and **HRV**, can be considered as ones of these parameters, and can help in preventing sudden cardiac death.

REFERENCES

1. **Puddu P.E., Jouve R., Torresani J. and Jouve A.** (1981) "QT interval and primary ventricular fibrillation in acute myocardial infarction". *Am. Heart J.* 101, 118-119.

2. **Puddu P.E. and Bourassa M.G.** (1986), "Prediction of sudden death from QTc interval prolongation in patients with chronic ischemic disease", *J. Electrocardiology* 19 (3), pp. 203-212.

3. **Schwartz P.J. and Wolf S.** (1978), "QT interval prolongation as predictor of sudden death in patients with myocardial infarction.", *Circulation* 57, pp. 1074-1077.

4. **Ahnve S., Lundman T. and Shoaleh-Var, M.** (1978), "The relationship between QT interval and primary ventricular fibrillation in acute myocardial infarction.", *Acta Mesd. Scand* 204, pp. 17-19.

5. **Taylor G.J., Crampton R.S., Gibson R.S., Stebbins P.T., Waldman M.T.G. and Beller G.A.** (1981), "Prolonged QT interval at onset of acute myocardial infarction in predicting early phase ventricular tachycardia". *Am. Heart J.* 102, pp. 16-24.

6. **Bazett HC.** (1920), "An analysis of the time relation of electrocardiograms", *Heart*, 7, pp. 353-370.

7. **Martí V., Bayes de Luna A., Arriola J., Songa V., Guindo J., Dominquez de las Rozas J., Marrugat J., Sanz F., Thakor N., Min Y., Caminal P. and Laguna P.** (1988), "Value of dynamic QTc in arrythmology", *in Proceedings 8th. Inter. Congr. "The New Frontiers of Arrythmies"*, Marilleva, Italy, pp. 683-691.

8. **Laguna P., Thakor N., Caminal P., Jané R. and Hyung-Ro Y.** (1990), "New algorithm for QT interval analysis in 24 hour Holter ECG: Performance and applications". *Med. & Biol. Eng. & Comput.* vol. **28**, pp. 67-73.

9. **Kleiger R.E., Miller J.P., Bigger J.T. and Moss A.J.** (1987), "Decreased heart rate variability and its association with increased mortality after myocardial infarction", *AM. J. Cardiol.*, **59** pp. 256-262.

10. **Myers G.A., Martin G.J., Magid N.M., Barnett P.S., Schaad J.W., Weiss J.S., Lesch M. and Singer D.H.** (1986), "Power spectral analysis of heart rate variability in

sudden cardiac death: Comparison to other methods" *IEEE Trans. Biomed. Eng.*, vol. BME-33, n. 12, pp. 1149-1156.

11. **Algra A., Le Brun H. and Zeelenberg C.** (1987), "An algorithm for computer measurement of QT intervals in the 24 hour ECG". *In Computers in Cardiology. IEEE Computer Society Press.*, pp. 117-119.

12. **Critelli G., Marciano F., Mazzarella M. and Migaux M.L.** (1982), "QT interval measurements of long-term ECG recordings. Application to an automatic Holter analysis system", *In Computers in Cardiology. IEEE Computer Society Press*, pp. 481-480.

13. **Pisani E., Pellegrini E., Ansuini G., Di Noto G., Rimatori C., and Russo P.** (1985), "Performance evaluation of algorithms for QT interval measurements in ambulatory ECG Recording". *In Computers in Cardiology. IEEE Computer Society Press.*, pp. 459-462.

14. **Laguna P., Thakor N., Caminal P. and Jané, R.** (1990), "Low-pass differentiators for biological signals with known spectra: Application to ECG signal processing" *IEEE Trans. Biomedical Eng.* vol. **37**, n. 4, pp. 420-424.

15. **Lynn P.A.** (1977), "Online digital filters for biological signals: some fast designs for a small computer", *Med. & Biol. Eng. & Comput.*, 15, pp. 534-540.

16. **Pan J. and Tompkins W.J.** (1985), "A real-time QRS detection algorithm", *IEEE Trans. Biomed. Eng.*, vol. BME-32, n. 3, pp. 230-236.

17. **Ahnve S.** (1985), "Errors in visual determination of corrected QT (QTc) interval during acute myocardial infarction", *J. Am Coll Cardiol.* 5, pp. 699-702.

18. **Webster J.G.** (1978), "Medical instrumentation. Application and design", *Houghton Mifflin, Boston.*

19. **Sadeh D., Shannon D.C., Abboud S., Akselrod S. and Cohen R.J.** (1987), "A new technique to determine the correlation between the QT interval and heart rate for control in sids babies". *In Computers in Cardiology. IEEE Computer Society Press.*, pp. 125-127

LIST OF SYMBOLS

- **MVA:** Malignant ventricular arrythmies
- **QT** : QT interval, distance from Q wave onset to T wave end in the QRST complex
- $\mathbf{QT_c}$: Corrected QT interval with Bazett's formula
- **QTP**: QTP interval, distance from Q wave onset to T wave peak in the QRST complex
- $\mathbf{QTP_c}$: corected QTP interval with Bazett's formula
- $\overline{\mathbf{QT}}$: Average QT interval in 24 hour
- $\overline{\mathbf{QT_c}}$: Average QT_c interval in 24 hour
- $\overline{\mathbf{QTP}}$: Average QTP interval in 24 hour
- $\overline{\mathbf{QTP_c}}$: Average QTP_c interval in 24 hour
- **RR:** RR Interval, time distance between two consecutive beats
- **HRV:** Heart rate variability as the standard deviation of RR interval in 24 hour
- **DR:** Direct recording
- **u** : Units for corrected QT intervals
- **p** : Significance level to separate two set of measures using t student test
- **SD(RR):** Standard deviation of RR interval in 24 hour