Quantification of Ventricular Repolarization Dispersion Using Digital Processing of the Surface ECG

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1. Introduction

Digital processing of electrocardiographic records was one of the first applications of signal processing on medicine (Taback et al., 1959). There are many ways to analyze and study electrical cardiac activity using the surface electrocardiogram (ECG) and nowadays a good clinical diagnostic and prevention of cardiac risk are the principal goal to be achieved (Sörnmo & Laguna, 2005).

One aim of digital processing of ECG signals has been quantification of ventricular repolarization dispersion (VRD), phenomenon which is mainly determined by heterogeneity of action potential durations (APD) in different myocardial regions (Amlie, 2000). The APD differs not only between myocytes of apex and the base of both ventricles, but those of endocardial and epicardial surfaces (transmural dispersion) and between both ventricles. Also, it was demonstrated the existence of several electrophysiologically and functionally different myocardial cells, like epicardial, endocardial and mid-myocardial M cells (Antzelevitch et al., 1999). The APD inequalities develop global and/or local voltage gradients that play an important role in the inscription of ECG T-wave morphology. In this way, we can assume that T-wave is a direct expression of ventricular repolarization (VR) inhomogeneities on surface ECG.

Experimental and clinical studies have demonstrated a relationship between VRD and severe ventricular arrhythmias (Kuo et al., 1983) (Surawicz, 1997). In addition, patients having increased VRD values have a higher risk of developing reentrant arrhythmias (Shimizu & Antzelevitch, 1998). Frequently the cardiac answer to several pathological states produces an increase of VRD; this phenomenon may develop into malignant ventricular arrhythmia (MVA) and/or sudden cardiac death (SCD). Moreover, it has been shown that the underlying mechanisms in MVA and/or SCD are cardiac re-entry, increased automation, influence of autonomic nervous system and arrhythmogenic substrates linked with cardiac pathologies. These cardiac alterations could be present in ischemia (Janse et al., 1985), hypothermia (Eagle, 1994), electrolyte imbalance (Weinberg et al., 1995), long QT syndrome (LQTS) (Priori et al., 1994), autonomic system effects (Shusterman et al., 1998) and others.

Digital processing of ECG has been proved to be useful for cardiac risk assessment, with additional advantages like its non invasive nature and direct applicability to the general population (Sörnmo & Laguna, 2005). Also, with the aim to identify high cardiac risk patients, the researchers have tried to quantify the VRD with different parameters obtained from mathematic-computational processing of the surface ECG. These parameters are based on detecting changes of T-wave intervals and T-wave morphology during cardiac pathologies, linking these changes with VRD.

Figure 1 illustrates a temporal segment of an ECG acquired in a healthy subject, which includes the representation of different waves, intervals and segments of the cardiac signal. The P-wave reflects the sequential depolarization of the right and left atria, the QRS complex (consisting of Q, R and S waves) reveals the depolarization of both ventricles, and the T-wave displays the VR. The RR interval represents the duration of a cardiac cycle. The QT interval corresponds to the time from the onset of ventricular depolarization to the offset of VR.
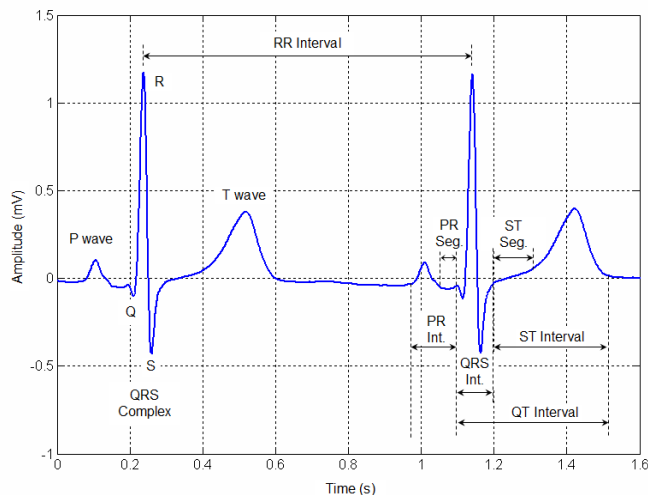

Fig. 1. Schematic representation of ECG waves, intervals and segments for a healthy subject.

In this chapter, we present a review of VRD indexes based on digital processing of ECG signals to quantify cardiac risk. The chapter is organized as follows: Section 2 explains ECG preprocessing and delineation of fiducial points. In Section 3, indexes of VRD quantification, such as: QT interval dispersion, QT interval variability and T-wave duration, are described. In Section 4, different repolarization indexes related to T-wave morphology and energy are examined, including complexity of repolarization, T-wave residuum, angle between the depolarization and repolarization dominant vectors, T-wave morphology dispersion, micro T-wave alternans, T-wave area and amplitude and T-wave spectral variability. Finally, in Section 5 conclusions are presented.

1.1 Most used abbreviations

APD (action potential duration), **C_D** (Dipolar Components), **C_{ND}** (non-dipolar components), **C_R** (complexity of repolarization), **DWT** (dyadic wavelet transform), **ECG** (electrocardiogram), **EMG** (electromyogram), **HR** (heart rate), **HRV** (heart rate variability), **HS** (healthy subject), **IL**

(isoelectric line) **MAPs** (monophasic action potentials), **PVS** (premature ventricular stimulation), **QT$_C$** (QT interval corrected), **QT$_D$** (QT interval dispersion), **QT$_V$** (QT interval variability), **SCD** (sudden cardiac death), **SVD** (singular value decomposition), **T$_{CRT}$** (total cosine R-to-T), **T$_L$** (T-wave loop), **T$_{MD}$** (T-wave morphology dispersion), **T$_{PE}$** (T-wave peak-to-end), **T$_W$** (T-wave width), **T$_{WR}$** (T-wave residuum), **T$_{WRa}$** (absolute T-wave residuum), **T$_{WRr}$** (relative T-wave residuum), **T$_{WSV}$** (T-wave spectral variance), **µT$_{WA}$** (micro T-wave alternans), **VF** (ventricular fibrillation), **VR** (ventricular repolarization) and **VRD** (ventricular repolarization dispersion).

2. ECG preprocessing

The objectives of ECG preprocessing consist on the application of several digital signal processing techniques in order to: a) attenuate the noise components present in the ECG signal, b) detect all heartbeats in the recording and, c) identify characteristics points of the ECG waves. In order to accomplish these objectives the following signal processing algorithms are used: ECG filtering, QRS complex detection and ECG delineation.

2.1 ECG filtering

Unfortunately, all ECG recordings are contaminated by different types of noise and artifacts sources (Sörnmo & Laguna, 2006) as it is illustrated in Figure 2. These noise sources are:
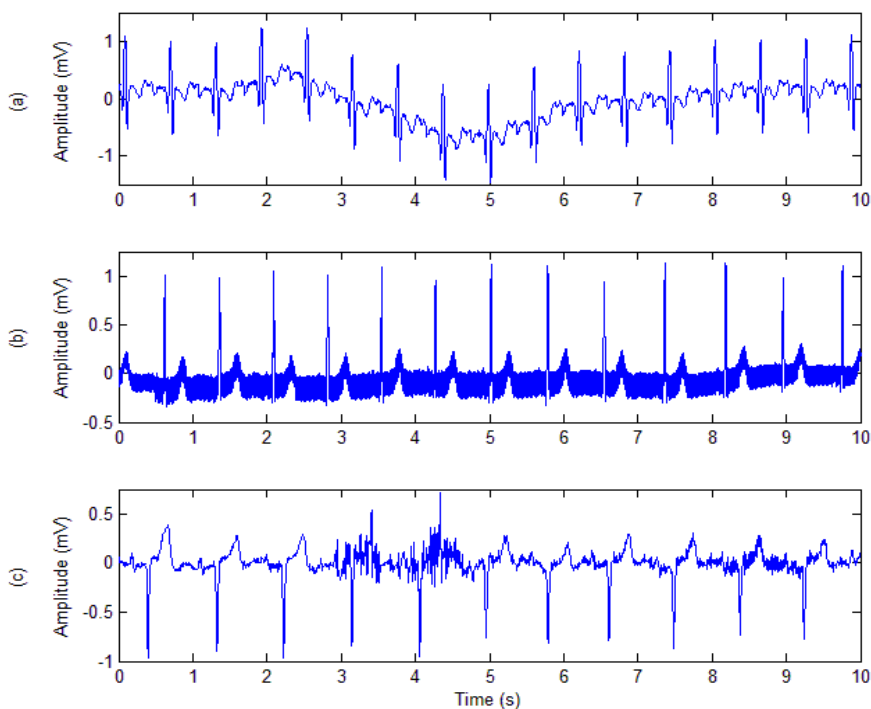

Fig. 2. Common types of noise in ECG recordings. (a) Baseline wander, (b) 50 Hz power line interference, and (c) Electromyographic noise.

a) Baseline wander is a low-frequency component in the ECG (*see Fig. 2.a*) caused by a variety of noise sources including respiration, body movements, and poor electrode contact. Its spectral content is usually confined to frequencies below 0.5 Hz. The magnitude of the baseline wander may exceed the amplitude of QRS complex by several times and it can significantly affect ECG analysis algorithms.

Different filtering techniques are employed for the removal of this low frequency noise, mainly, linear filters and polynomial fitting (Sörnmo & Laguna, 2005). In the first category, linear, time-invariant, highpass filters are used. The cut-off frequency (f_c) and phase response characteristic should be chosen to preserve the morphology of ECG signal. The value of f_c must be lower than the minimum frequency of the ECG; a choice of f_c = 0.5 Hz provides generally good results. A linear filter with time-variable cut-off frequency has been proposed for these ECG acquired during stress test (Sörnmo, 1993). Also, linear phase filters are recommended to prevent phase distortions in the ECG signal and avoid possible errors in the estimation of the wave durations and cardiac intervals. The second approach is to fit a polynomial to representative samples ("knots") of the ECG followed by the subtraction of the resultant polynomial curve. One knot must be defined for each beat, usually in the isoelectric line (IL) of PQ interval. In contrast to linear filtering, this approach requires that QRS complexes first be detected and PQ intervals are determined. After knots are located in the ECG signal, a third-order polynomial is fitted to these points (Sörnmo & Laguna, 2005).

b) Powerline interference is a common noise source in ECG recordings caused by electromagnetic fields of devices coupled to electric power system. It is characterized by a 50 or 60 Hz sinusoidal interference (*see Fig. 2.b*), which can be accompanied by its harmonics. Such narrowband noise makes difficult the further analysis of ECG record, and may affect the performance of the ECG delineation algorithms (Huhta & Webster, 1973). Various precautions may be taken during the acquisition of the ECG recording in order to minimize the level of the interference, such as shielding the leads, grounding property of the ECG system and lowering the skin-electrode impedance (Webster, 1992).

However, it may be still necessary to apply some signal processing to remove the residual powerline interference on the ECG recordings. For this purpose, simple techniques can be used such as straightforward linear bandstop or nonlinear filtering (Sörnmo & Laguna, 2005). A more advanced technique includes the amplitude and phase estimation of the interfering sinusoid in an isoelectric segment, followed by substraction of the estimated sinusoid within the entire heartbeat (Ider & Köymnen, 1995). This last technique requires a correct delineation of PQ interval.

c) Electromyographic noise is due to the electrical activity of skeletal muscles during periods of contraction. It is particularly important in ECGs recorders during ambulatory monitoring or stress tests. It can be either intermittent, e.g. due to a sudden body movement (*see Fig. 2.c*), or have more stationary noise properties, e.g during relaxation or sleep. The frequency components of electromyogram (EMG) noise considerably overlap those of the QRS complexes, making difficult their detection (Sörnmo & Laguna, 2005).

Due to the overlap spectra of both signals, EMG noise filtering is a complicated task which in several cases introduces considerable distortion in the ECG. Since the ECG is a repetitive signal, ensemble averaging is a commonly technique used for EMG noise reduction. However this technique is restricted to signal-averaged ECG analysis and can require much beats to be averaged particularly in ECG records corrupted with high levels of EMG noise (Laciar & Jané, 2001). Other different approach consists on the use of adaptive Gaussian filtering. This technique produces a time-varying lowpass filter with a variable frequency

response so that smooth segments on the ECG are subjected to considerable lowpass filtering whereas the QRS interval remains unfiltered (Talmon et al., 1986). The adaptation of the f_c of a linear lowpass filter with the slopes of the ECG has been proposed by Pinto (Pinto, 1991). Although others techniques have been proposed for EMG noise reduction, no single method has gained wide acceptance for use in clinical routine, so the muscle noise problem remains unsolved in ECG signal processing (Sörnmo & Laguna, 2005).

2.2 QRS complex detection

The following step in the ECG signal processing consists on the detection of all heartbeats in the ECG recording. Due to the QRS complex has generally greater amplitude and higher signal to noise ratio than P and T waves (*see Fig. 1*), the heartbeats identification is usually carried out with a QRS detector. Moreover, the QRS complex has a higher frequency content which can be distinguish from low frequency of P and T waves (Thakor et al., 1984). The QRS detector must be able to detect a large number of different QRS morphologies in order to be clinically useful and able to follow sudden or gradual changes of the cardiac rhythm. Consequently, the performance of any ECG automatic analysis system depends on a correct detection of all QRS complexes in the ECG record.

In the literature, it has been proposed several QRS detectors. Köhler et al., produced a rather comprehensive review of the main QRS detecting algorithms (Köhler et al., 2002). One of them, widely used, was proposed by Pan & Tompkins (Pan & Tompkins, 1985). Its implementation is simple reaching high levels of sensitivity and predictivity (both > 99.5%). Bandwidth, slope and pulse duration are the three criteria used by the algorithm. A bandpass filter keeps the spectral portion where most of the QRS energy concentrates, attenuating the P and T waves low frequency components, removing baseline slow changes or drifts and reducing 50/60 Hz line interference and EMG high frequency noise. A differentiator picks out the steep QRS edges, obviously much different that the other components smoother edges. Thereafter, the mean quadratic value of each signal sample is computed by a non-linear unit to obtain only positive values and to emphasize the QRS high frequency components. A moving window integrator adds up the areas under the quadratic signal to produce pulses and to remove short duration artifacts. Such output goes to the decision unit where each pulse is compared to the preestablished threshold singling it out or not and locating it in its proper relative temporal place. The overall output is composed of the temporal marks or spikes, each corresponding to the detected QRS complex.

2.3 ECG delineation

Since important diagnostic information is contained in the wave amplitudes and time durations of a heartbeat (*see Fig. 1*), wave delineation represents an important step in ECG processing (Sörnmo & Laguna, 2005). Basically, ECG delineation consist on the automatic determination of peaks and time limits of the cardiac waves (QRS complex, P and T-waves). Delineation algorithms usually depart from a previous QRS location and define temporal search windows before and after the QRS fiducial point to seek for the other waves. Once the search window is defined, some technique is applied to enhance the characteristic features of each wave (e.g., its frequency band) in order to find the wave peaks.

The localization of ECG wave onsets and offset is a more difficult task, as the signal amplitude is low at the wave boundaries and the noise level can be higher than the signal itself (Martinez et al., 2004). The classical definition of a wave boundary is the time instant at

which the wave crosses a certain amplitude threshold. Unfortunately, this definition is not adequate for cardiac waves delineation, particularly in ECG records corrupted with baseline wander, so it is not used in practice (Sörnmo & Laguna, 2005).

In order to solve this problem, many delineation algorithms examine the change in the slope of ECG signal to detect the wave limits. Hence, the first derivate of the signal is computed and analyzed with respect to zero crossing and extreme values. This delineation scheme is particularly appropriate to find QRS onset and offset points, due to the steep changes in the slopes of these waves (de Chazal & Celler, 1996, Daskalov & Christov, 1999).

ECG delineation is especially problematic with the estimation of T-wave end boundary, which is often characterized by a very gradual transition to the IL. The delineation of T-wave end is problematic even among cardiologists, which can exhibits differences up to 100 ms (Sörnmo & Laguna, 2005). A correct determination of this endpoint is extremely important for an accurate estimation of QT interval (*see Fig. 1*). Different algorithms have been proposed for the automatic detection of T-wave end. Xue & Reddy in 1998 compare the performance of five T-wave delineation algorithms based on: (a) the point at which the T-wave intersects the IL plus a threshold, (b) the point at which the first derivate of T-wave intersects a threshold above IL, (c) the intersection of the maximum slope of T-wave and IL, (d) the intersection of the line fitted by least squares to the maximum slope of T-wave and IL (LSI), and (e) the point at which the T-wave area reaches 90% of its total value. They conclude that LSI method has the best reproducibility (Xue & Reddy, 1998). Other ECG delineation algorithm, based on a multiresolution analysis of ECG signal using dyadic wavelet transform (DWT), has proven to be particularly adequate for a correct estimation of T-wave boundaries (Li et al., 1995, Martínez et al., 2004). This wavelet approach can be viewed as a filter bank of lowpass differentiators with varying cut-off frequencies. The wave boundaries are then found through the different decomposition levels of DWT.

3. Indexes of repolarization dispersion based on ECG durations

In this section, we present different VRD indexes obtained from ECG durations. Some of them can measure spatial heterogeneity of repolarization, such as QT dispersion, T-wave width and T-wave peak-to-end duration. Other index, like QT variability can be used to evaluate the dynamic heterogeneity of VR. Also, other spatial heterogeneity indexes, such as, T-wave amplitude, T-wave symmetry and the relationship between T-wave areas, are shortly commented.

3.1 QT interval dispersion

QT dispersion (QT_D) is defined as the arithmetic difference between the maximum and the minimum QT interval (*see Fig. 1*) or as QT interval standard deviation between all ECG-leads. QT_D was first defined on multilead recordings system (Sylven et al., 1984) and then on the standard 12-lead ECG (Cowan et al., 1988), intended to reflect the duration of the monophasic action potentials (MAPs). Thus, the QT_D measured on the 12-lead ECG aims to be a non-invasive index of VRD. The main concept proposed by Day et al., which supports the QT_D as a VRD marker, is the fact that every ECG lead picks up local activity from different heart areas and therefore differences among them directly translate into differences in APD (Day et al., 1990). In consequence QT_D quickly became popular for its non-invasive nature and calculus simplicity.

In the repolarization analysis, many studies focussed on finding a universal formula that corrected QT (QTc) for heart rate (HR) in every patient (Hodges, 1997). However, Malik et al. showed that the QTc must not be universally applied but individually (Malik, 2002). In this way, animal studies have shown that VRD does not change with HR and need not be corrected for it (Zabel et al., 1997). Also, QT_D correction in humans can be misleading since changes in this index at different HR may shows or reflects modifications in cycle length and not changes in VRD (Subramanian et al., 1999).

Later on, QT_D was studied by Day et al. in 1992 (*see Table 1*) under sinus rhythm and controlled ectopic stimulus leading to the conclusion that QT_D reflected regional variations of the cellular recovery time (Day et al., 1992).

Higham et al. (Higham et al., 1992), found a high correlation between VRD measured on MAPs basis and QT_D on both sinus rhythm and ventricular pacing. Also Zabel et al., observed that QT_D was highly correlated to ventricular recovery times and duration of MAPs in isolated rabbit hearts (Zabel et al., 1995). Later on, results were confirmed in humans, comparing QT_D from ECG 24 hs after MAPs recording, increasing accordingly QT_D and endocardic MAPs (Zabel et al., 1998b).

Zabel et al., in 32-months follow-up a prospective study including myocardial infarction (MI) patients, failed to find in QT_D a predictive value of mortality (Zabel et al., 1998a). On the other hand, Mänttäri et al., with a 6.5 years follow-up study, did find QT_D measured to T-wave peak as a predictor of SCD but not of fatal MI (Mänttäri et al., 1997).

Using a modified Langendorff-perfused rabbit heart model, Arini et al. compared QT_D measure from multilead system against the values found when the 12 standard ECG-leads were used. The obtained results supported the importance of multiple recording systems for the evaluation of QT_D and helped to understand the discrepancies found in clinical applications (Arini et al., 2000). Later, Arini et al., using an animal heart model with multiple electrode recording system, showed a differential behavior in the modulation of VRD depending on whether premature ventricular stimulation (PVS) were elicited at the right or left ventricle. They concluded that different ventricles anisotropic properties, dissimilar wall thickness and fiber orientation partially contribute to the explanation of results (Arini et al., 2001).

More controversial issues came up with Lee et al. (*see Table 1*), and Macfarlane et al. who simultaneously showed that QT_D calculated from 12-ECG leads derived from the orthogonal XYZ leads (without any regional information) was similar to that obtained from the standard ECG. Also, Kors et al. (*see Table 1*), found a high correlation between QT_D and the parameters of the T-wave loop (T_L) in the vectocardiogram, concluding that the QT_D would be more a feature of the T_L in 3D more than a local VRD phenomenon. If all the repolarization information is contained in the T_L, then the QT_D would be a result from the projection effect (Lee et al., 1998; Macfarlane et al. 1998; Kors et al., 1999).

Many technical limitations make QT_D not reliable. Great efforts have been addressed to define different ways of measurement (Hnatkova et al., 1994a) as well as to analyze their reproducibility (Macfarlane et al., 1998). Kautzner et al. tested that the greater QT intervals in leads displaying greater T-wave amplitudes. They also found a 27-33% interobserver variability for QT_D whilst a much smaller interobserver variability (2-4%) was found for QT intervals (Kautzner et al., 1994). Lead selection also affects QT_D. Hnatkova et al. analyzed in a systematic way the measurement errors derived from imperfect sets of leads. Due to the great variability found, they concluded that QT_D should be compared with a constant and standard set of leads basis (Hnatkova et al., 1994b). On the other hand, Kors & Van Herpen,

postulated a valuable criterion for lead selection based on the frontal leads dependence (Kors & var Herpen, 1998). Another technical problem concerning QT_D measurement is T-wave end delineation which was before mentioned in Section 2.3. Figure 3 shows QT_D calculated between two hypothetical ECG leads where it can be seen the dificultities to distinguish between the dispersion generated by estimation error and the real dispersion.
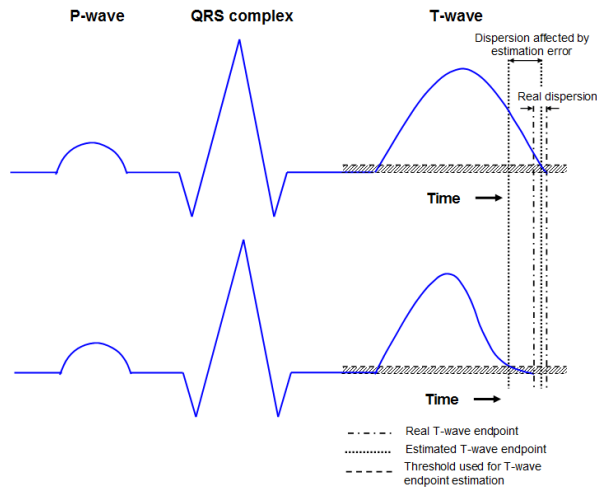

Fig. 3. Both T-waves of the same amplitude have different ends, this results in 'real dispersion' of QT intervals (vertical dashdot lines). Also, from below the threshold level (horizontal dashed lines) defined by an automatic algorithm, there are different proportions of T-waves end (vertical dot lines), this results are called 'Dispersion affected by estimation error' which is different from the 'Real dispersion'.

In spite of the technical limitations and controversies, QT_D is used in a growing number of medical applications. Examples of this are the assessment of cardiac toxicity in anesthesia (Cafiero et al., 2010) or the search of cardiac indexes in malnourished adults (Hanci et al., 2010).

3.2 QT interval variability

In order to separate the heart rate variability (HRV) from the QT variability (QT_V), the QT_V index is redefined as: $QT_{VI}=QT_V/HRV$, being this ratio related to arrhythmic events, SCD and heart failure (Berger et al., 1997, Yeragani et al., 2004). QT_{VI} reflects beat-to-beat changes of the recovery times and such variations in the refractory times can lead to reentrant arrhythmias.

In a prospective study recruiting patients referred to electrophysiological studies, the greater QT_V belonged to those who presented SCD or ventricular fibrillation (VF) (Atiga et al., 1998). Healthy subjects presented low QT_{VI} and considerable HRV, with a low average HR and a high average QT, while patients with dilated cardiopathy presented a high QT_{VI} with low QT average and low HRV with an high HR average.

In 1999, trying to get rid of the T-wave end detection, Courdec analyzed the QT abnormal components in the time-space domain by means of wavelet transform (Couderc et al., 1999) where they found LQTS patients with higher QT_V than the control patients. Burattini and

Author and year of publication	Short description	Indexes	Conditions for the evaluation of methodologies					
Day et al. (1992)	9 patients under electrophysiological study of palpitation		*CI= 300 (ms)*			*CI= 500 (ms)*		
			PSC	*VE*	*FSC*	*PSC*	*VES*	*FSC*
		AQT_D (ms)	22 ±2	80±4	23±6	18±2	87±6	18±2
Lee et al. (1998)	Conventional and derived ECGs obtain from 129 HS	QT_D (ms)	40 ±20 *(12 leads from XYZ)*			41±18 *(from 12 leads)*		
Kors et al. (1999)	1220 standard simultaneous 12 ECG leads.	QT_D (ms)	54.2±27.1 *for narrow and large T-wave loop*					
			69.5±33.5 *for wide and small T-wave loop*					
Fuller et al. (2000)	Correlation coefficients of VRD versus T-wave width (T_W) and QT_D for each lead set		Ep		BS		Pc	Op
		T_W	0.91		0.84		0.72	0.81
		QT_D	0.46		0.47		0.17	0.11

Author and year of publication	Short description	Indexes		Conditions for the evaluation of methodologies					
Arini et al. (2001)	Dispersion Variables (DV) was evaluated as a function of CI and site of stimulation in 12 in vitro rabbit hearts. *p<0.05 vs. 400ms			*CI for Stimulus RV (ms)*			*CI for Stimulus LV (ms)*		
				400	250	ERP +5	400	250	ERP +5
		DV (ms)	SDJTp	9.6± 0.88	10.2± 0.84	14.9± 0.73*	7.7± 0.55	6.2± 0.55*	11± 1.16*
			SDJTe	7.6± 0.55	8.1± 0.7	11± 0.83*	7.1± 0.52	4.6± 0.72*	11± 0.86*

AQT_D (Adjusted QT_D)= (*max*QT_D – *min*QT_D)/ √ nº of leads; *CI (Coupling interval)*; PSC (Preceding Sinus Complex); VE (Ventricular Extrasystole); FSC (Following Sinus Complex); Ep (Epicardial); BS (Body Surface); Pc (Precordial); Op (optimal); SD (Standard Deviation); JTp (J point to T-wave peak); JTe (J point to T-wave end) RV (Right Ventricle); LV (Left Ventricle); ERP (Effective Refractory Period). HS (healthy subjects)

Table 1. Some of the principal results of ECG duration indexes explained in Section 3.

Zareba, on the other hand, proposed a temporal method to measure beat-to-beat QT_V consisting on correlating T-waves with a pattern (Burattini & Zareba, 1999). This index was validated with ischemic myocardiopathy who presented a higher index than control patients. Nevertheless, no correlation with left ventricular ejection fraction (LVEF), HR, HRV and QTc were found.

Almeida et al. in 2006 postulated a parametric linear model to explore interactions between QT_V and HRV. The method was applied to simulated series and artificial ECG signals, but validated on real ECG data from healthy subjects, where it was found a 40% of QT fraction not correlated with HRV, suggesting that an important part of QT_V is not linearly driven by HRV and may contain complementary information (Almeida et al., 2006).

Recently, it was shown the relationship between QT_{VI} and cardiac sympathetic activity in hypertensive patients (Baumert et al., 2011).

3.3 T-wave duration

Fuller et al., in 2000 used isolated-perfuse canine hearts (*see Table 1*) to measure QT_D and T-wave width (T_W) from the root-mean-square (RMS) curve obtained from: the available epicardial electrograms, ECG body surface leads, standard precordial ECG leads, and optimal lead set. They induced myocardial VRD by three different ways: changing temperature, modifying the cycle length and changing activation sequence. The VRD, which was measured directly using epicardium recovery times, was compared to T_W and QT_D. VRD was strongly correlated with T_W computed from the RMS series, but not with QT_D (Fuller et al., 2000).

Arini et al., proposed that T-wave widening can result from a result of combined dispersion between apex-base and transmural APD heterogeneities. They used the addition of anthyarritmic drugs and PVS to induce increase VRD in an In Vitro rabbit heart model (*see Table 1*), concluding that VR is reflected in the ECG as a T_W widening, while index QT_D failed as risk stratification (Arini et al., 2008a).

Other studies have shown T-wave peak-to-end (T_{PE}) interval as a measure of transmural dispersion (Zareba et al., 2000), although it is difficult to associate this concept with the ECG standard, since the concept of T_{PE} is mainly associated to the ECG derived from the Wedge preparation (Antzelevitch et al., 1999). In addition, the T_{PE} can replace the T_W to measure dispersion during ischemia, since the measurement of T-wave onset is very unstable during ST-segment modifications (Arini et al., 2008b).

4. Indexes of repolarization dispersion associated to ECG-morphology

In this section, we present VRD indexes obtained from ECG morphology changes. These indexes are based on the hypothesis that morphological changes on the T-wave will appear when VRD is increased. The indexes complexity of repolarization, T-wave residuum, the total cosine R-to-T, the T-wave morphology dispersion, T-wave area and T-wave amplitude, can measure spatial heterogeneity of repolarization. Other indexes from beat-to-beat, such as micro T-wave alternans and T-wave spectral variance can measure dynamic heterogeneity of VR.

4.1 Evaluation of T-Wave morphology employing Singular Value Decomposition

The main technique used to evaluate morphological or energy changes of T-wave during increased VRD is the Singular Value Decomposition (SVD). SVD is a mathematical transformation based on the correlation between signals. In this case, SVD is applied to the eight mutually independent leads (I, II, V1-V6) and then the information is reconstructed in an optimal orthogonal space of eight pseudo-leads (S1-S8) (*see Fig. 4*). In the new space, S1 will have the maximal energy or eigenvalue ($\lambda 1$) in this direction, S2 will contain the maximal energy ($\lambda 2$) perpendicular to S1, S3 will have the maximal $\lambda 3$ perpendicular to the two first pseudo-leads and so on. S1, S2 and S3 have the 98% of total ECG energy approximately, and are named dipolar components (C_D) ($\lambda 1$, $\lambda 2$, $\lambda 3$), whereas S4-S8 have the 2% residual and are called non-dipolar components (C_{ND}). The C_D is the ECG energy represented in 3D, and shows the normal activity, but for C_D are not enough to represent pathological activity adequately, being necessaries the C_{ND}.

The Complexity of Repolarization (C_R) index is represented by the ratios between eigenvalues (Priori et al. 1997). In normality conditions, the T_L can be represented like a 3D vector with eigenvalues $\lambda1$ $\lambda2$ $\lambda3$ relative to the principal axes S_1 S_2 S_3. In general, T_L is concentrated in the $\lambda1$ and $\lambda2$ values denominated preferential plane and it can be quantified by C_R like a narrow or a rounded loop in this plane. Furthermore, the planarity can be calculated, because in a loop totally plane $\lambda3$ is equal to zero.

The ventricular gradient is the resulting vector of all the instantaneous vectors of depolarization and repolarization. Expanding this concept, it can be estimated the wavefront direction descriptor, named Total cosine R-to-R (T_{CRT}). This index was defined like the cosine of the angle formed between the dominant vectors of the VR and depolarization, measured in a 3D loop of SVD space (Acar et al., 1999). Also, the T-wave morphology dispersion (T_{MD}) index measures dissimilarities of the T-wave shapes between different leads and reconstruction vectors of the individual ECG leads and it is calculated as the average of angles among pairs of reconstruction vectors (Zabel & Malik, 2004). Finally, the T-wave residuum (T_{WR}) index was proposed by Malik et al., and estimates the non-dipolar components relative energy. The T_{WR} can be absolute (T_{WRa}) defined like C_{ND} and relative (T_{WRr}), the T_{WRa} normalized by total energy (Malik et al, 2000).
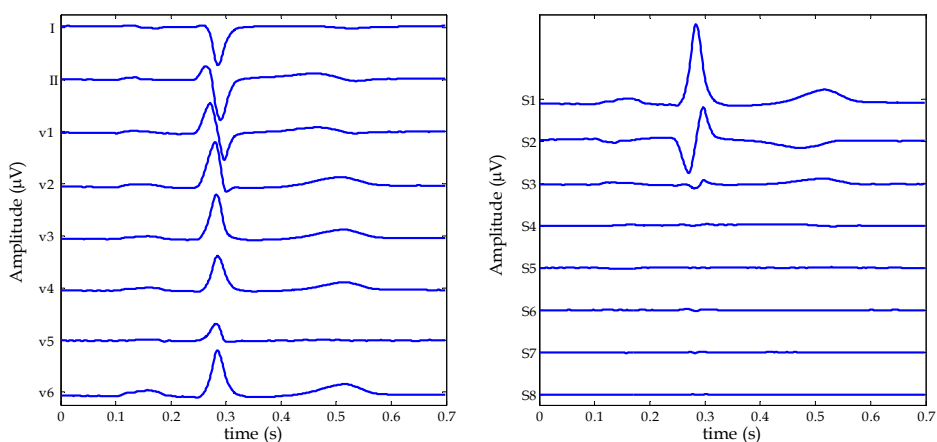

Fig. 4. Standard ECG (left panel) and pseudo-leads obtained from ECG SVD (right panel).

Badilini et al. applied the relationship between 3D T_L morphology and scalar QT_D. This analysis was applied to the XYZ ECG obtaining the normalized eigenvalues with the aim to estimate one loop narrowness parameter and two planarity parameters. They evaluated the parameters in healthy subjects (HS) and post MI and LQTS patients. The scalar measurements were significantly larger in patients with MI and LQTS than in HS but only in 3D analysis was observed a loss of planarity and an increased roundness of the T_L, differentiating MI from LQTS patients. They concluded that the spatial nature of T_L was associated to scalar interlead variability (Badilini et al., 1997).

Almost simultaneously, Priori et al. applied eigenvalues relationship to 12-lead Holter recordings (*see Table 2.*) to estimate the C_R, and compared their results against other methods that characterize QT interval. They found that the ratio of the $\lambda2$ to $\lambda1$ was more representative of C_R, being C_{R24h} the average of C_R in 24 hs. They observed that CR_{24h} was

significantly higher in LQTS than in HS. They concluded that eigenvalues relationship can be used to quantify the C_R in a non invasive way (Priori et al., 1997).

In addition to those indexes previously described, Acar et al. developed another indexes linked to T_L. They employed ECG records with HS and hypertrophic cardiomyopathy (HCM) (*see Table 2*) to calculate the conventional measures of VR and the ratios among eigenvalues. They concluded that new descriptors were more reproducible than the conventional QT interval descriptors and T_{MD} and T_{CRT} indexes were the best indexes for discrimination between groups (Acar et al., 1999).

Author and year of publication	Short description	Indexes	Conditions for the evaluations of methodologies			
Priori et al., (1997)	Were studied 36 LQTS patients and 40 control subjects.		*Normal*	*LQTS*		*Sen %*
		QTc (ms)	414±18	514±59		88
		QT_{DC} (ms)	38±9	82±37		69
		C_{R24h}	13±3	34±12		88
Acar et al., (1999)	Were employed 76 normal subjects and 63 patients with HCM. p-value of separation between normal and HCM for each index evaluated		*Normal*	*HCM*		*p- value*
		T_{MD}	10.72±4.784	41.1±26.85		2.818×10^{-18}
		T_{CRT}	0.522±0.274	-0.351±0.522		3.548×10^{-19}
		λ_2/λ_1	15.56±6.162	23.56±10.85		9.886×10^{-7}
		λ_3/λ_1	4.826±2.373	7.765±4.235		6.603×10^{-9}
Malik et al., (2000)	The study was realized with a group of 78 HS, 68 HCM, 72 DCM and 81 acute MI patients.		*Normals*	*HCM*	*DCM*	*acute MI*
		QT_D (ms)	33.6±18.3	47±19.3	37.8±21.2	57.5±25.3
			Normals vs DCM: NS, other p<0.009			
		T_{WR} (%)	0.029 ±0.031	0.067 ±0.067	0.112 ±0.154	0.186 ±0.308
			HCM vs DCM: NS, other p<0.006			
		QT_D and T_{WRr} correlation	-0.0446	0.2805	-0.1531	0.0771
			p=0.03 for HCM , other NS			
Arini et al., (2008a)	The experiments were carried out in 20 isolated rabbit hearts during PE and after DS		*Control*	*PVS*	*Control*	*DS*
		T_W (ms)	78±10.3	118.5 ±15.7	78±10.3	95.2±7.9
		SDQT (ms)	7.6±2.2	13±3.4	6.5±1.4	11.6±1.9
		θ_{PT} (º)	137±65	129±61	35±51	117±49

NS (non significant); QT_{DC} (QT dispersion corrected); SD (Standard Deviation).

Table 2. Some relevant results from ECG SVD and the comparison with another indexes

A research in which QT_D and T_{WRr} was calculated in 12-lead resting supine ECGs records corresponding to HS, HCM patients, dilated cardiomyopathy patients (DCM) and survivors of acute MI (*see Table 2.*) was carried out by Malik et al. They concluded that C_{ND} differ in clinically well-defined groups, and that QT_D is unrelated to them, so, QT_D is not a direct measure of local VRD (Malik et al., 2000).

Zabel et al., during a prospective study for risk stratification in post-MI patients evaluated C_R, T_L dispersion (T_{LD}), T_L area, T_{CRT} and T_{MD}, and where correlated with QT_D and clinical data. Zabel et al. found that T_{CRT} and T_{LD} is suitable for risk discrimination. They realized a multivariate analysis including other predictive risk stratifiers. They concluded that T-wave morphology analysis can be used in the post-MI risk estimation and in combination with other risk markers enhanced the final results (Zabel et al., 2000). Later, Zabel et al. presented a study to assess the prognostic value of the same parameters evaluated in 2000, adding the T_{WRa}, T_{WRr} and QT interval in long term survivals in US veterans with cardiovascular disease and the patients were follow up 10.4 ± 3.8 years. They showed that T_{WR} presents a significant long-term prognostic power in the population studied (Zabel et al., 2001).

The C_D and C_{ND} were analyzed by Biagetti et al., in isolated rabbit hearts model. The aim was to analyze the role of both components in the determination of T_{WR} observing that both increased significantly during PVS and after D-sotalol (DS) exposure. Despite the increase of T_{WRa}, the T_{WRr} decreased during PVS and did not change after DS. They concluded that due to the fact that C_D and C_{ND} can change simultaneously, T_{WRr} may not reflect regional heterogeneity of VR with accuracy and that C_{ND} of the 2nd half of the T-wave can be related to transmural VRD (Biagetti et al., 2004).

A study that analyzed Principal Component Analysis (PCA) parameters in relation to conduction disturbances in patients with chest pain and ECG nondiagnostic of acute MI was developed by Kesek et al. in 2004. They calculated C_R, T_{WRa} and T_{WRr} which were assessed against clinical and ECG parameters, discharge diagnosis and total mortality during 35-months follow up. They found that a T_{WRr} increased with conduction disturbances, which were associated with augmented VR inhomogeneity (Kesek et al., 2004).

Malik et al. in 2004 carried out a research in which stratified risk of arrhythmic events by mean of LVEF and HR, HRV, the slope of HR turbulence and T_{CRT} in patients who might benefit from prophylactic antiarrhytmic intervention. It was evaluated individual risk characteristics and the combinations of them. They concluded that T_{CRT} was a strongest risk stratifier that compared very favorably to LVEF and was also strongest in combination with other stratifiers like LVEF (Malik et al., 2004).

Arini et al., evaluated indexes that quantify the VRD for cardiac risk. The study was carried out in multilead ECG records from animal heart model (*see Table 2*); employing DS and PVS achieved to increment VRD. They calculated indexes from the absolute ECG summation signal (T-wave amplitude, area and width) and from the SVD of the ECG: θ_{PT} (angle between the 1st SVD axis and the VR axis), T_{WR}, T_{MD}, unnormalized T_{MD}, and T_{CRT}. They compared the results with the classical indexes based on QT and concluded that the globally increased VRD can be reflected by T_W (Arini et al., 2008a).

T-wave morphology parameters were studied in LQTS patients by Anttonen et al. in 2009. They wanted to determine if these parameters presented abnormal value in these patients and whether can be used to diagnose LQTS. They measured T_{CRT}, T_{LD} among others and concluded that patients with short QT interval and with a history of arrhythmic events presented abnormal values of T-wave morphology parameters (Anttonen et al., 2009).

4.2 Other T-wave morphology indexes

T-wave amplitude, T-wave symmetry and the relationship between T-wave areas were proposed as markers of cardiac arrhythmogenic. In ischemia, symmetry and amplitude of T-wave changes (Hartikainen, 2004) agreed with a computer model (Di Bernardo et al., 2001) in which this disease was simulated. Studies have found differences in amplitude, area and symmetry of the T-wave stress test (Langley et al., 2002), antiarrhythmic and PVS with respect to control (Arini et al., 2005).

The beat-to-beat variability of VR using QT interval (Section 3.2) approach is largely influenced by criteria used to detect T-wave end point, as was mentioned in Section 2.3. In order to solve this problem, Steinbigler et al. developed the technique of T-wave Spectral Variance (T_{WSV}) using the two dimensional Fast Fourier transform. This technique can detect dynamic changes in VR pattern either in amplitude or duration independently of the exact delineation of T-wave end (see Fig. 3). Steinbigler et al. tested T_{WSV} capacities to detect inhomogeneities of VR in retrospective way of post-MI patients with and without a history of arrhythmias (Steinbigler et al., 1998). Later on, Valverde et al., using an animal model of myocardial infarction, verified the presence of dynamic VR heterogeneity associated with chronic MI and further contributes to identify the infarcted animals (Valverde et al., 2002).

4.3 Micro T-wave alternans

The electrical T-wave alternans is defined as a variation in VR morphology on an alternate beat basis (Murda'H et al., 1997) and can be distinguished in macro and micro alternans.

Macro T-wave alternans refers to a systematic or beat to beat alteration in amplitude, width, and/or shape which can be visualized easily in surface ECG. Micro T-wave alternans (μT_{WA}) is a microscopic alteration of ST-T complex or T-wave, which are revealed through the digital processing of ECG signal (Lux & Brockmeir, 2004) showing dynamic heterogeneity of VR. Experimental and clinical evidence shows that μT_{WA} are linked to abnormal electrophysiological functions and are cardiac risk markers in patient with coronary artery disease (Ikeda et al., 2002; Nearing et al., 1991; Pires 2002; Rosenbaum et al., 1996 as cited in Lux & Brockmeir, 2004) dilated cardiomyopathy (Adachi et al., 1999 as cited in Lux & Brockmeir, 2004), myocardial hypertrophy (Kon-No et al., 2001, as cited in Lux & Brockmeir, 2004) and hypertension (Hennersdorf et al., 2001, as cited in Lux & Brockmeir, 2004). Pastore et al. measured cellular APD employing optical mapping techniques in the epicardial surfaces of guinea pigs revealing more details about μT_{WA} mechanism. They demonstrated that when HR is incremented to critical values, spatial gradients of VR can be developed by neighboring cells membrane repolarization alternating with the opposite phase. This behavior can be detected in surface ECG at microvolt levels and the heterogeneities produced are the cause of regional VRD. Also, these gradients have enough magnitude to induce unidirectional block and reentrant VF (Pastore et al., 1999).

The principal technique used to detect μT_{WA} is spectral analysis and their presence is defined by a magnitude of 1.9 µV or greater, the relationship between μT_{WA} and HR and alternans ratio (Bloomfield et al., 2002).

The spectrum depicts the frequencies at which beat-to-beat fluctuations in the amplitude of the T-wave occur. The μT_{WA} is present with a periods generally of two beats (2:1 relationship) and this appears in the spectrum at a frequency of 0.5 cycles per beat (cpb), hence, the magnitude of the peak at this frequency is a direct measure of electrical alternans allowing differentiate it from another signals occurring at other frequencies like noise or the breathing signal (Murda'H et al., 1997).

The measurement of μT_{WA} is highly dependent on HR, appearing when the HR increases above 90 beats per minutes (Bloomfield et al., 2002). The μT_{WA} measurement can be done in a non invasive way during exercise stress testing or in an invasive way during atrial stimulation with the final objective of keeping HR invariant (Constantini, 2004).

Another important feature of spectral analysis is the alternans ratio (AR), whose value represents the number of standard deviation for which the alternans magnitude exceeded the noise level (Bloomfield et al., 2002).

The significant finding was done by Adam et al. between 1981 and 1984 quantifying from a non-invasive way in dogs (*see Table 3*) μT_{WA} to determine the existence of relation between temporal variability of VR and susceptibility to VF, measured with an index called VF Threshold (VFT). The VFT was reduced inducing hypothermia, tachycardia and by coronary artery ligation (CAL). They found that when VFT was reduced, a µTWA pattern was developed. They made an index, T-wave Alternans Index (TWAI), defined as the square root of the amplitude of the power spectrum minus the noise (Adam et al., 1984) and it was called spectral method (SM).

Smith et al., in 1988 quantified the degree and statistical significance of waveform alternation present in the magnitude of the three orthogonal-lead ECG. Smith et al. reported the relationship between electrical alternans and electrical stability that was found in experimental models with dogs and clinical studies (*see Table 3*). The electrical alternans was measured with an index called Alternating Electrocardiographic Morphology Index (AEMI) and electrical stability in dog preparations was assessed via VFT measurement and in the clinical studies via programmed stimulation (Smith et al., 1988).

Nearing et al. in 1991 implemented the Complex Demodulation Method (CDM) which detected the oscillatory nature of ECG signal during μT_{WA}, modeling it like a sinusoidal signal of 0.5 cpb with phase and amplitude variable. The amplitude was estimated demodulating the 0.5 cpb signal components. They revealed that μT_{WA} is concentrated during the first half of the T-wave coinciding with the vulnerable period of cardiac cycle, linking μT_{WA} with vulnerability of VF (Nearing & Verrier, 1991).

Rosembaum et al. in 1994 tested the Smith et al. hypothesis in humans by mean of electrophysiologic studies (*see table 3*). The μT_{WA} was expressed by two indexes Cumulative Alternans Voltage (CAV) defined as the square root of the alternans peak minus the noise mean and the alternans ratio is defined like the ratio between the alternans peak minus the noise mean and the noise standard deviation. The electrophysiologic test was considered positive if sustained Ventricular Tachycardia (VT) or VF was induced after applied extra stimuli. They concluded that μT_{WA} was a significant predictor of inducible arrhythmias on electrophysiologic testing (Rosembaum et al., 1994).

The method proposed by Laguna et al. consists on applying the Karhunen-Loeve Transform (KLT) to each element of an ST-T vector. Then they calculated the Power Spectral Density (PSD) of the KLi series by the FFT during fixed periods of time. Finally the power band is estimated in those bands around the frequency where alternans appear (0.5 and 0.25cpb). The µTWA is detected when a threshold is exceed. This robust method was validated using simulated and real ECG recordings (Laguna et al., 1996).

Burattini et al. in 1997 performed a time domain Correlation Method (CM) for μT_{WA} detection and compared it with the SM using simulation data. They analyzed the ability of these methods to detect non-stationary μT_{WA} and μT_{WA} under different factors which affect

Author and year of publication	Short description	Index or indication of μT_{WA}	Conditions for the evaluations of methodologies		
Adam et al. (1984)	The experiments were performed in 20 dogs	TWAI	*Hypothermia*	*Tachycardia*	*CAL*
			(7e.) **7/7** VFT↓ p<0.03 **6/7** TWAI↑ p< 0.03	*Epicardial ECG (6 e.)* **6/6** TWAI↑ p< 0.02	*Epicardial ECG (11 e.)* **11/11** TWAI↑ p< 0.001
				Surface ECG (10 e.) **07/10** TWAI↑ p< 0.09	*Surface ECG (10 e.)* **07/10** TWAI↑ p< 0.08
Smith et al. (1988)	The experiments were performed in 10 dogs	AEMI (ST-T)	*Hypothermia*	*Transient occlusion of the LAD*	
			(10 e.) **10/10** AEMI↑ p<0.0001	*(10 e., 24 m)* **17/24** AEMI↑ p<0.002	
	23 studies to predict inducibility of VT or VF	Presence or absence of alternation	Alternation identify the inducible population with *Sen.*: 92 % and *Spec.*: 50% p< 0.05		
Rosembaum (1994)	83 patients examined to evaluate if levels of µT_WA predicted vulnerability to arrhytmia. 66 patients were follows up for 20 months		*General analysis*	*Patients follow up*	
		AR>2.5	*Sen.*: 81 %, *Spec.*: 84% p< 0.001	µT_WA and inducibility of ventricular arrhythmias, significant predictors of survival without arrhythmia p<0.001	
		CAV>10 (µV)	*Sen*: 80 %, *Spec*: 79% p< 0.003		
Nearing & Verrier (2002)	Simulated ECG and studies in 13 dogs with CAL to assess vulnerability to VF	Not specified	*Simulation Studies*	*Experimental Studies*	
			The tests present a ρ= 0,999 indicating precision in µT_WA detection	Revealed vulnerability to MI-induced VF *Sen.*: 100 %, *Spec.*:100 %	

The expression x/z means x experiments (e) or measures (m) achieve a result from z experiments or measures made in total. Abbreviations employed in the table: Sen(Sensibility), Spec (Specificity), ρ (correlation coefficient), isch. (ischemic), CAL (Coronary Artery Ligation), LAD (left anterior descendent)

Table 3. Some relevant results for TWA

real ECG records. The study proved that SM is not adequate for detecting non- stationary μT_{WA}, and while both methods are suitable to detect μT_{WA} in noise presence, with CM were obtained better results (Burattini et al., 1997). In 1999 CM was applied to ECG Holter records from LQTS patients and healthy subjects (Burattini et al., 1999).

Martínez et al. in 2000 evaluated the CDM and CM before mentioned and proposed two alternative methods, one of them was a variation of CDM called Capon Filtering Method (CFM) and the other one based on the KLT. CFM consisted on the replacement of the deterministic filter by a data dependent Capon filter. In addition, Martinez et al. proposed transform the ST- T complex by means of KLT and then apply the CFM. The evaluation of the different detectors was carried out using simulated and real data. This study concluded that CM performed worse than the other methods, which showed a similar performance, having the method that employ KLT and CFM higher computational complexity (Martinez et al., 2000).

In 2002 was proposed a new method to analyze μT_{WA} called Modified Moving Average (MMA) (*see Table 3*). This one consists on dividing the beats in even beats (A) and odd beats (B) and making a moving average for A and another for B. The μT_{WA} is determined like the maximum absolute difference between A and B MMA within the ST segment and T-wave region. They concluded that MMA is better than CDM because the MMA signal processing features are superior to CDM which can be affected by artifacts (Nearing &Verrier, 2002).

A work published in 2002 by Martínez & Olmos showed that the SM and CDM can be interpreted like a Generalized Likelihood Ratio Test (GLRT) for detection of μT_{WA} and tried to prove that Laplacian distribution is more appropriate to model the noise in μT_{WA} than Gaussian. For this they developed a Laplacian Likelihood Ratio (LLR) method which looked for estimate μT_{WA} with the maximum likelihood estimator (MLE) and detect them employing a GLRT. LLR for Laplacian noise was tested with simulated data and founding that LLR is more robust than SM and CDM but the results obtained were not as significant as was expected (Martínez & Olmos, 2002). In 2003 they employed this model with nonstationary noise obtaining similar results (Martínez & Olmos, 2003).

Monasterio & Martínez in 2009 developed a multilead scheme (MS) in which combined LLR with PCA comparing it with a single- lead (SLS) approach in which detected μT_{WA} lead by lead using Laplacian GLRT and alternans estimation is achieved with MLE (Martínez & Olmos, 2002). The MS consists on finding the eigenvectors matrix applying PCA to the output of a detrending filter which input was a data matrix, obtaining the transform leads and μT_{WA} detection is achieved applying Laplacian GLRT to them. The MS was tested with simulated data and showing better results with a lower SNR than the SLS. Moreover both methods were applied on stress ECG records in healthy and ischemic patients. With MS better results were obtained (Monasterio et al., 2009). In 2010 they presented a MS based on periodic component analysis (πCA) concluding that the new πCA MS detect most efficiently than the MS detector based on PCA, and the SLS approach (Monasterio & Martinez, 2010)

5. Conclusions

It has been proposed in the literature several indexes to quantify hetereogeneity of VR using surface ECG. These indexes could be divided into two groups: those based on ECG duration and those founded on ECG morphology. Also, in general, these indexes can be used to evaluate: a) In an individual beat simultaneously recorded leads (spatial heterogeneity) which can be calculated as: QT_D, T_W, T_{PE}, C_R, T_{CRT}, T_{MD}, T_{WR}, T-wave area and

T-wave amplitude or b) in a sequence of beats (dynamic heterogeneity) which can be calculated as: QT_V, T_{WSV} and μ_{TWA}.

The nature of the relationship between QT_D and VRD is controversial, as was showed in Fig. 3. First, due to technical issues, involving the determination of the T-wave end, the existence of U-wave and notched T-waves, as was showed in Fig. 3. Second, the problems with determining increased heterogeneity of VR using QT_D are the effects generated by the projections of T_L that have different shapes and different angles onto the axis of each ECG lead, which results in T-waves that have different amplitudes and morphologies. That is how to emerge the necessity to find indexes that allow study another aspects of VR and caracterize their anormalities, solving at the same time the problems with measures in the time-domain transforming the ECG signals to another domain obtained by SVD (*see Fig. 4*).

C_R has been evaluated in different cardiac pathologies. This index was employed using 12 standard ECG-lead and, although certain commercial equipment include it, its role in diagnostic is not well defined. In general, the T-wave morphology indexes, such as, T_{CRT}, T_{MD}, T_{WR}, T_{WSV}, have detected medium and high cardiac risk, however, the association between pathological mechanisms and these indexes still need further study.

In another sense, the T_W evaluated from RMS curve or absolute ECG summation signal, could measure apex-base or transmural VRD or both simultaneously, but it is necessary to study these parameters in different cardiac conditions. Although, T_{PE} was measured in a few clinical studies, the results are controversial. While T-wave symmetry and the relationship between T-wave areas has been proposed like cardiac risk markers (Zareba et al., 2000), its use is not widespread.

The μT_{WA} index have shown as a promising risk stratification index of SCD in some clinical populations, and as an important marker of cardiac electrical instability linking μT_{WA} with VRD and ventricular arrhythmias. Despite this, there are still technical limitations in the determination of μT_{WA} and controversy about its clinical validity under certain circumstances. On the other hand, there are a lot of techniques which detect and measure μT_{WA}, but have not been standardized the optimal times, conditions and methods for the measurement of μT_{WA}. Also , μTWA has not been evaluated in combination with other markers of SCD risk. All these aspects not covered yet, can be explored in future studies.

In conclusion, some indexes presented and evaluated in this chapter have restricted capacity to predict cardiac risk, and others have shown potential but still need to validate in medical practice. Also most of them have been evaluated in small patient populations and some of them only in animal models. Hence, in general, it should be carried out more tests for their implementation in the clinical practices. Finally, it would be important an expert consensus to unify criteria for assessment of the parameters to evaluate VRD in the same way that was done for another ECG computational techniques like late potentials in high-resolution ECG (Breithardt et al., 1991) or heart rate variability, (Heart rate variability-Standard, 1996) for which have been developed several standard documents by specialized committees.

6. Acknowledgements

7. References

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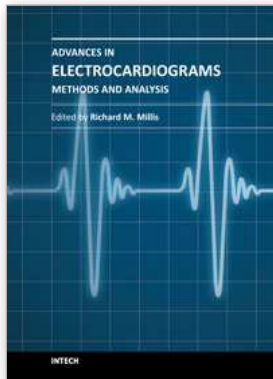
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