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T-Wave Alternans: Clinical Performance, Limitations and Analysis Methodologies

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Abstract

Accurate recognition of individuals at higher immediate risk of sudden cardiac death (SCD) is still an open question. The fortuitous nature of acute cardiovascular events just does not seem to fit the well-known model of ventricular tachycardia/fibrillation induction in a static arrhythmogenic substrate by a synchronous trigger. On the mechanism of SCD, a dynamical electrical instability would better explain the rarity of the simultaneous association of a correct trigger and an appropriate cardiac substrate. Several studies have been conducted trying to measure this cardiac electrical instability (or any valid surrogate) in an ECG beat stream. Among the current possible candidates we can number QT prolongation, QT dispersion, late potentials, T-wave alternans (TWA), and heart rate turbulence. This article reviews the particular role of TWA in the current cardiac risk stratification scenario. TWA findings are still heterogeneous, ranging from very good to nearly null prognostic performance depending on the clinical population observed and clinical protocol in use. To fill the current gaps in the TWA base of knowledge, practitioners, and researchers should better explore the technical features of the several technologies available for TWA evaluation and pay greater attention to the fact that TWA values are responsive to several factors other than medications. Information about the cellular and subcellular mechanisms of TWA is outside the scope of this article, but the reader is referred to some of the good papers available on this topic whenever this extra information could help the understanding of the concepts and facts covered herein.

Keywords

Arrhythmias, cardiac/prevention & control; death, sudden/prevention & control; defibrillators, implantable; United States/epidemiology.

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In general, most cases of sudden cardiac death (SCD) are related to coronary artery disease and dilated and hypertrophic non-ischemic cardiomyopathy[1]. Equally important are the cases of SCD reported in apparently healthy individuals. Between 1994 and 2003, in the United Kingdom, the autopsies of 453 individuals aged 15 to 81 years who died due to SDC were performed. Among this set, 269 (59.3%) of the hearts were macroscopically and microscopically normal[2].

The precise identification of individuals at higher immediate risk of SCD remains an open question. Many factors (acquired or congenital; structural, functional or genetic ones) are related to an increase in the risk of SCD; however, when considered alone, they cannot identify individuals at maximum risk. Vigorous physical activity (6 METS or more) can potentially increase the risk of acute cardiovascular events; however, the rarity of exercise-related events gives a clear indication that an additional specific cardiac substrate is necessary, according to the joint statement of the American Heart Association and the American College of Sports Medicine[3].

In other words, the apparently random nature of an acute cardiovascular event well exemplifies that the typical pathophysiological mechanism of the CSD does not seem to be a trigger in synchronism with a static arrhythmogenic substrate, so that a ventricular tachycardia (VT) or fibrillation can start. On the contrary, the electrical instability would be dynamic, which would explain the low probability of a specific trigger associated with an appropriate cardiac substrate[4].

Hence, how can the dynamics of electrical instability be measured? During the last decades, several studies have been conducted trying to measure this cardiac electrical instability (or any valid surrogate) in an ECG beat stream. These studies, in general, used two main approaches: 1) to quantify how the measured variable would be associated to the tendency toward future arrhythmias and 2) to evaluate how fast the myocardium recovers after a small electrical arrhythmia (for instance, an extra-systole) and the consequences of this fact on a future prognosis. Such approaches are similar at first glance, but this conclusion is not real. Based on the usual vocabulary of clinical arrhythmias, in which primary and secondary prevention mean, respectively, prevention before and after a cardiovascular event, one could call the first "instability primary to arrhythmia" and the second "instability secondary to arrhythmia". Among the clinical measurements of primary instability, we can mention the QT prolongation, QT dispersion, Late Potentials and T-wave alternans (TWA). The Heart Rate Turbulence, on the other hand, would be a measurement of the secondary instability group.

This review will emphasize the role of TWA in the current scenario of cardiac risk stratification. Due to the abundant literature on the subject, this review will be divided in four sections. After defining and reporting a summarized history of TWA, the second section will report its prognostic performance in different populations. As the TWA is an examination that depends essentially on technology, the third section will make considerations on a crucial aspect for the clinical performance of TWA: the available technological approaches and its consequent options of analysis and limitations. The fourth section will explore other factors that can modulate the values and influence the TWA assessments.

Definition of TWA and summarized history

The so-called TWA is an oscillation in the regular amplitude in the ST-T portion of the ECG tracing that occurs with half of the heart rate. In other words, the alterations in the ST-T amplitude repeat at every two beats, so that a pattern of amplitude with even beats and another one with odd beats can be created. For didactic purposes, we can summarize the chronological history of TWA in three distinct phases: the transition of the focus of research, from macroscopic TWA to microscopic TWA; the impact of TWA in microvolts in protocols of risk stratification and health policies; and the establishment of a solid experimental basis for the current clinical discoveries on TWA.

The macroscopic TWA (visual) has been reported since the beginning of electrocardiography[5], always associated with a poor prognosis and considered a rare finding, up to the first publication on the invisible (microscopic) TWA in 1980[6]. Since then, several groups have studied TWA and each group has done so differently. A direct consequence of this fact was the review published in 2005, listing more than 10 different technologies for its assessment[7]; however, its results were even more restricted to specific segments of the cardiologic research community. The next step - when the TWA captured the attention of clinical cardiologists, in addition to cardiology researchers - took place in the beginning of the XXI century, with the publication of evidence that the TWA would be able to reduce the mean number of implantable cardioverter defibrillators (ICD) necessary to, in fact, save a life[8].

At that time, the alternation in the duration of the action potential duration (APD-alternans) had also been intensely studied throughout the years. In 2002, evidence was obtained that the APD-alternans was the first link in a dictated progression of oscillation patterns of amplitude that were increasingly complex, up to a ventricular fibrillation (VF) during ischemia[9] and also that atrial APD-alternans had been recorded, consistently, before the transition from one atrial flutter to an atrial fibrillation[10]. Additionally, it was discovered that the TWA and APD-alternans were associated to each other in experimental studies[11], but until then, there had been no evidence that this association persisted, even in clinical contexts.

The third phase of the TWA research started with the solution of this clinical puzzle. First, it was demonstrated that patients with cardiomyopathy and inducible VT or a positive TWA test presented a more heterogeneous repolarization (in both the epicardium and the endocardium) than in those individuals without inducible VT or with a negative TWA test[12]. Later, the TWA was consistently associated to the endocardial and epicardial APD-alternans, so that a minimum number of sites with APD-alternans was always necessary for the TWA to be successfully measured on the body surface; however, the isolated APD-alternans were not always associated to TWA on the body surface[13].

Currently, the TWA presents as a valid clinical surrogate of the APD-alternans, the latter being an important marker of cardiac electrical instability. The interested reader can refer to several publications on the mechanisms of the genesis of APD-alternans and its association with the arrhythmogenic cardiac substrate[4,14-17]. These experimental fundaments aggregate value to the stratification performance through TWA in different clinical populations, which is reviewed in the following section.

Twa and cardiac risk stratification

Coronary or ischemic heart diseases

The second Multicenter Automatic Defibrillator Implantation Trial - MADIT-2 -brought convincing evidence on a decrease in mortality with the use of the ICD. Its findings showed a global decrease of 31% in the risk of mortality in post-infarction patients with left ventricular ejection fraction (LVEF) ≤ 30%, regardless of the fact whether the patients presented more advanced stages of the disease, thus defined through the NYHA functional class and level of urea nitrogen in the blood (decrease of 28-35%, regardless of the basal mortality risk in the subgroups)[18]. In 2003, the American Centers for Medicare and Medicaid Services - CMS - decided to cover the costs of the prophylactic treatment with ICD for patients of the MADIT-2 type and QRS duration > 120 ms. In 2005, the CMS decided to include all patients of the MADIT-2 type[19], but the cost-benefit was still a matter of concern and there was a clear need for a better risk stratification[20].

The evaluation of the TWA in 177 patients of the MADIT-2 type resulted in a better risk stratification performance than that of the QRS duration. Patients with a narrow QRS (QRS < 120 ms) were not free from the risk of sustained ventricular arrhythmias (SVT) during a two-year follow-up (mortality rate = 14%, similar to that of MADIT-2). On the other hand, the group of patients with normal TWA recorded only 2 deaths within the same period (actuarial mortality rate of 3.8%), whereas the set with abnormal TWA presented a hazard ratio (HR) of 4.8 (P = 0,012) for mortality due to all causes, adjusted for the duration of QRS. In MADIT-2, 18 ICD were necessary to save a life; however, when using the strategy of TWA examinations, only 7 ICD were necessary to save one life[8].

A prospective cohort study encompassing 768 ischemic patients with LVEF ≤ 35% and with no previous sustained VT (51% received ICD) gave strong evidence that the benefits of the ICD differed according to the level of the TWA, decreasing the mortality due to all causes (HR = 0.45, 95% CI = [0.27, 0.76], P = 0.003) in patients with non-negative TWA (positive or undetermined), but without decreasing the mortality in the group with negative TWA (HR = 0.85, 95% CI = [0.33,

2.20], P = 0.73). Moreover, it was also demonstrated that such findings were mostly due to the decrease in the arrhythmic mortality. Regarding the effectiveness of the ICD therapy, 9 ICD were necessary to save one life during a two-year period in patients with non-negative TWA; however, 76 ICD were necessary to save one life, during the same period of time, in the group with negative TWA[21].

After acute myocardial infarction

Regarding the capacity to predict severe arrhythmic events, in the context of preserved cardiac function after acute myocardial infarction (AMI), a Japanese prospective study (n = 1,041; 79% men) observed that the TWA showed a prognostic performance that was similar to studies in populations post-AMI with decreased LVEF. The TWA tests were carried out at least 14 days post-AMI, with 169 (17%) positive, 747 (74%) negative and 87 (9%) undetermined tests, with a general sensitivity and negative predictive value of 81% and 99.6%, respectively; the multivariate analysis showed HR = 19.7 - 95% CI= (5.5-70.4), P < 0.0001 for arrhythmic events[22].

The REFINE (Risk Estimation Following Infarction, Noninvasive Evaluation) study evaluated the prognostic performance of the autonomic tonus and/or cardiac electrical substrate evaluation in the identification of patients at higher cardiac risk soon after the AMI. In brief, no isolated parameter (TWA, heart rate turbulence, baroreflex sensitivity), in an assessment carried out 2 to 4 weeks (acute phase) after the AMI successfully predicted outcomes. The best diagnostic precision in the non-acute phase (10 to 14 weeks) after the AMI was obtained by combining the abnormal TWA and the HR turbulence, plus LVEF < 50%. This composite indicator correctly identified two thirds of all patients that suffered a heart attack, with a sensitivity of 55%, specificity of 86% and a negative predictive value of 90%. It is noteworthy the fact that the TWA measured during exercise-induced stress or in a Holter registry presented similar performance, although it had been assessed with a different technology in each case. In a multivariate analysis adjusted for age, sex, previous AMI and diabetes, the indicator comprising Holter assessment and TWA resulted in HR = 6.22 - 95% CI = (2.88 - 13.47), P < 0.001, and the combination with exercise TWA resulted in HR = 5.08 - 95% CI = (2.17 - 11.89), P < 0.001[23].

Differently from the findings of the REFINE study, another study on the TWA assessment during the period of 7 to 30 days after the AMI (n = 119) resulted in 17 (14%) undetermined, 50 (42%) positive and 52 (44%) negative tests. During a follow-up period of 3 to 23 months, the TWA presented the best prognostic value among the indicators (TWA, late potentials, ejection fraction): 14 of the 15 patients with arrhythmic events presented positive TWA, with the best sensitivity and negative predictive value among all analyzed parameters (93% and 98%, respectively; relative hazard of 16.8, P = 0.006)[24].

The TWA showed to be very efficient in risk stratification in post-AMI patients with LVEF ≤ 30%, regardless of the stage of the disease. Therefore, as a non-invasive method, it can be an important tool in the assessment of patients with ischemic disease.

Apparently healthy individuals and general population

Adults

The prevalence of TWA was assessed at rest and during physical exertion in apparently healthy group (none received permanent medication) of 48 individuals (aged 21-53 years, 29 men). Functional and structural heart diseases were excluded through the clinical history and the ECG assessment at rest and during exertion, as well as a Doppler echocardiography. Transient TWA episodes were observed in 5 individuals (10.4%). Sustained TWA was observed in 2 individuals (4.2%); however, only one (2.1%) met all criteria for positivity and none of the 48 individuals developed morbidity due to arrhythmia during the follow-up period of 12-40-months[25]. A larger study (110 healthy individuals, aged 20-75 years, 76 men) was published in the same year and 5 individuals (5%) presented a positive, 98 (89%) presented a negative and 7 (6%) presented an undetermined TWA test. Once again, no morbidity or mortality due to arrhythmia was reported during the follow-up of 32 ± 15 months[26].

Younger than 18

The TWA was assessed in 100 normal volunteers (8-17 years, with no history of heart disease, normal clinical examination and resting ECG). The excess noise hampered the adequate recording of data during exercise of 16 volunteers and the data at rest of other 24 volunteers; however, all other 76 volunteers had a negative TWA at rest. Nine volunteers (11% of the valid tests) presented sustained alternans, all of whom presented higher initial heart rates than the usual adult criteria: they varied from 120 to 158 bpm, whereas the usual threshold of initial HR is ≤ 110 bpm[27].

General population

A sub-study of the FINCAVAS (Finnish Cardiovascular Study) described the TWA assessment in a cohort of 1,037 patients (61.4% men, 58 ± 13 years), extracted from a general population, all referred to exercise stress test. The clinical indications for the exercise test included the diagnosis of coronary heart disease (46%), vulnerability to exercise-induced arrhythmia (18%), assessment of cardiac performance capacity (19%), treatment adequacy for coronary heart disease (24%), patient profile assessment before invasive surgery (13%) and evaluation after acute myocardial infarction (10%). The exercise-induced TWA, with a cutoff of 47 μV or 65 μV, was strongly predictive of SCD (RR = 2.9, P = 0.02 and RR = 7.4, P < 0.001, respectively), as well as of cardiovascular death (RR = 2.6, P = 0.01 and RR = 6.0, P < 0.001), yielding excellent negative predictive values, both close to 98%[28].

Athletes

Amateur soccer players with and without mitral valve prolapse and sedentary individuals, paired by age (three groups of 20 individuals) presented no positive TWA tests when submitted to normal protocols of exercise-induced stress[29]. TWA assessment and electrophysiology studies (EPS) were also carried out in professional athletes from several sports, both healthy ones (n = 48) and those presenting

important arrhythmias, although without arrhythmogenic pathologies (n = 52). None of the healthy athletes presented a positive test or any event during the mean follow-up of 36 months. On the other hand, 7 of the 52 (13.5%) of the athletes with arrhythmia had a positive TWA test, 5 of whom also presented a positive EPS result for VT and one a positive result for severe supraventricular tachycardia (the other refused to undergo the EPS). In the group of arrhythmic athletes, all 42 negative TWA tests were also accompanied by negative EPS results, except for one, who was specifically being treated with amiodarone. However, this individual with negative TWA/positive EPS did not present any event during the 25.3-month follow-up[30].

A recent study in athletes with ventricular arrhythmia (n = 85, 61 men) emphasized the good correlation between the TWA and the EPS results in this population. Similar numbers have been described for positive TWA tests (15 in 85, 18%) with a lower frequency of negative TWA tests (57/85, 68%) and more undetermined tests (13/85, 14%). All athletes with a positive TWA test had a positive EPS result and all athletes with a negative TWA test had a negative EPS result. No correlation was observed between the undetermined TWA and EPS results. Regarding the occurrence of events, athletes with negative TWA tests did not present any event during a mean follow-up of 30 months; however, 5 individuals with positive TWA, as well as 2 individuals with undetermined TWA tests reported events that occurred during this period[31].

TWA can become a good tool for risk stratification in normal individuals, but further studies are necessary, with samples of adequate sizes, to be able to count on reliable data concerning these populations.

Twa analytical methodologies

TWA is a type of examination that depends essentially on the used technology, as the typical oscillations of its amplitude (with a magnitude of a few 1/50 mm at a normal gain of 10 mm/mV) are beyond the physician's visual assessment. As mentioned before, there are several distinct methodologies to assess TWA. Thus, the choice of a methodology will have a direct impact on the measured values and the clinical limitations of the TWA, even if the different TWA algorithms present a similar clinical performance[23,32]. This section aims at summarizing the basic concepts, in addition to differentiating the characteristics and clinical limitations of the most relevant methodologies developed for the analysis of TWA. Therefore, we considered relevant only the two TWA analysis algorithms that are available commercially (spectral method and Modified Moving Average) and the most similar research methodologies (Complex Demodulation and Intrabeat average).

How is TWA measured? Recalling the definition of TWA, the basic concept is the frequency. When present, the TWA occurs always in the middle of the heart rate, or, in other words, at a frequency of 0.5 cycle per beat (cpb). Whenever we think about the automatic detection of TWA, this is the only available information, theoretically, as no one knows beforehand if it will be present or not, which part of the ST-T complex will show alternans or even what magnitude will the recorded alternans present. It is quite similar to turning on a stereo radio station in the car: we know the radio frequency that interests us, but we cannot predict whether there will be any relevant information in it, or just noise. Based on this distinctive characteristic of the TWA - fixed frequency - it seemed logical (or natural) the fact that the first forms of TWA analysis had been based on the tracking of this 0.5 cpb frequency. This approach is currently found in the spectral method (SM) and the complex demodulation (CM) method.

Spectral method (SM)

The SM measures T-wave fluctuations by computing differences point by point between 128 equidistant sites in the ST-T in a series of 128 consecutive aligned beats (disregarding the ectopic beats and those with noise)[33]. In other words, there are 128 tachograms similar to those used in the analysis of the HR variability. Subsequently, 128 frequency spectra are registered (thus the name of the method - SM) and their mean is calculated. The TWA value is then assessed at the frequency of 0.5 cpb (Figure1). The adaptation of this technique for human patients was first published in 1994[34]. Since then, it has been the most often used method of TWA analysis, presenting the largest range of use.

Complex demodulation (CD)

The CD method was presented at a later date than the SM[36], as an alternative algorithm. Basically, this method evaluates only the energy at the area close to the alternans frequency of 0.5 cpb, instead of calculating the fluctuations along a broad frequency band, as the SM does.

As the field of research of TWA matured, a new family of algorithms appeared, all based on the comparison of beat patterns. This approach is currently found in the Modified Moving Average and the Intrabeat Average methods.

Modified moving average (MMA)

The MMA creates, resourcefully, two patterns (models) of beats based on any sequence of valid beats (with one pattern being associated only to the even beats and another to the odd beats). To elucidate each of the beat patterns, the iterative algorithm is as follows: the differences in amplitude between the current pattern (of even or odd beats) and the next valid beat (even or odd) are measured along several equidistant sites in the ST-T complex. Each one of these differences is divided in X equal parts (where X can be 8, 16, 32 or 64) and the contribution of the current valid beat to the update of the pattern-beat is then limited to 1/X (called updating factor or limiting fraction) of the differences between model and beat (Figure 2). Finally, the TWA values are made available every 15 seconds, as the difference between the two representative patterns (and continuously updated) of the even and odd beats[37].

Intrabeat average (IBA)

The concept and the characteristics of the intrabeat average (IBA) are very similar to those presented in the MMA method. Its distinctive feature is the separation of the ST-T

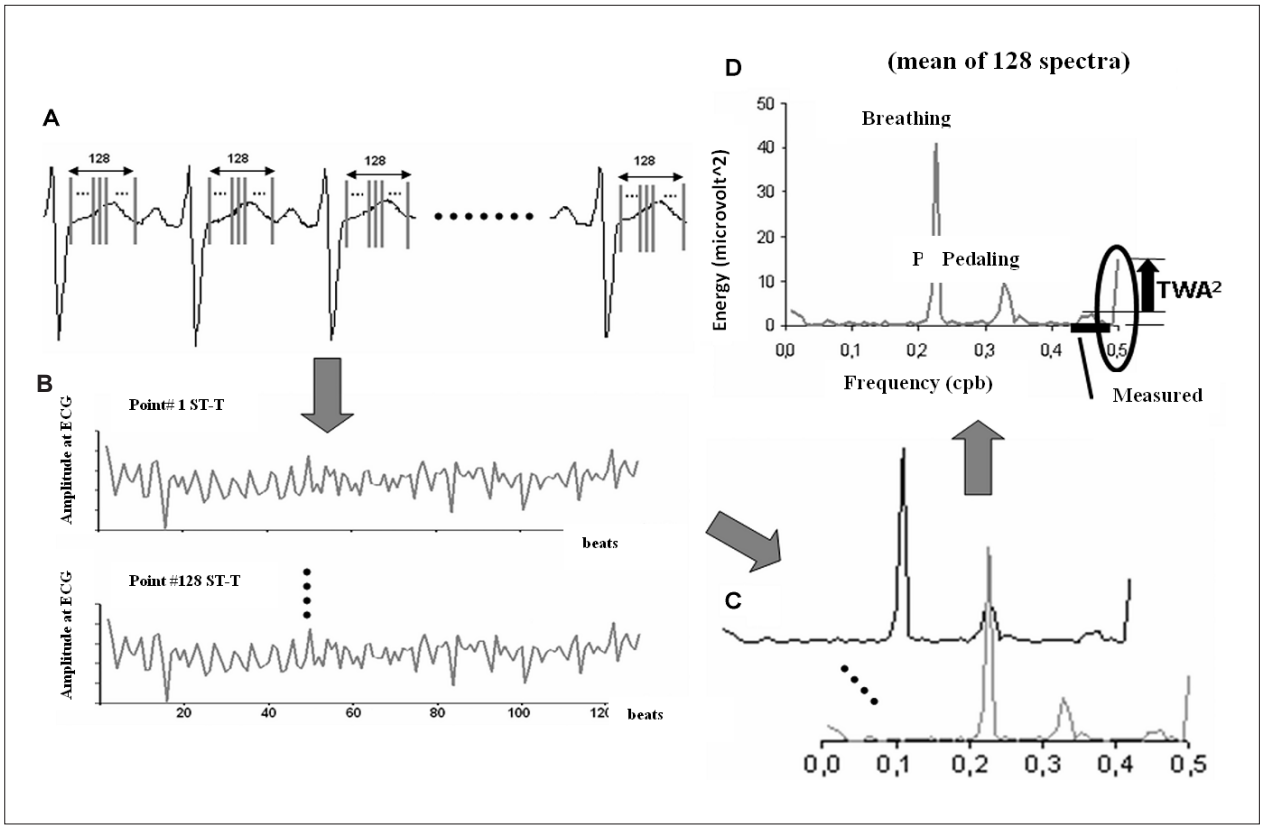

Figure 1 - The four phases of the SM methodology. A) Selection of 128 equidistant points in the ST-T complex of a series of 128 beats from the ECG. B) Graphic descriptions of the amplitude variation throughout the 128 beats from the ST-T point I to the ST-T point 128 (128 tachograms). C) Each tachogram has its spectrum calculated by Fourier Transform, in a total of 128 spectra. D) The mean of all 128 spectra is calculated to create a composite spectrum. Based on this composite spectrum, the alternans energy is calculated as the energy in 0.5 cpb minus the measured mean noise energy. The corresponding TWA amplitude is the square root of the alternans energy[35].

complex into three time intervals (T-initial to T-peak - which includes the ST segment; T-peak to T-final; T-initial to T-final) and the computation of distinct values of TWA for each one of them[39-41].

Factors that modulate TWA

Physiological and pathophysiological alterations

Initial findings obtained in Holter studies affirmed that the magnitude of the TWA responded to circadian fluctuations and physiological alterations[40,42,43]. Multivariate analyses of 24-hour ambulatory ECG, recorded in patients from the database of the ATRAMI (Autonomic Tone and Reflexes After Myocardial Infarction) trial, showed that the TWA levels > 75th percentile at 8 AM or at the maximum heart rate (around 47 μV) were related to higher chances of having a heart attack (documented VF) or arrhythmic death during the follow-up period (OR ranged from 4.2 to 7.9, depending on the lead [electrode] and the time period)[38]. Later, Stein et al[44] noticed that, on average, the higher levels of TWA accompanied the circadian cycle of increase in the risk of sudden death in patients with heart failure. Moreover, it was observed that the TWA levels > 47 μV were associated with an increased risk of SCD.

On pathological processes that affect the magnitude of the TWA, Shusterman et al[40] demonstrated an increase in the TWA magnitude preceding the spontaneous start of ventricular tachyarrhythmias (VTA). Holter records (n=59) with spontaneous VTA were selected from the database of the ESVEM (Electrophysiologic Study Versus Electrocardiographic Monitoring) clinical trial. Its results showed that the TWA magnitude increased continuously from the baseline to a peak of 25%, 10 minutes before the event. Researchers from the TOVA (Triggers of Ventricular Arrhythmias) study also verified the existence of significant TWA magnitude before the start of the arrhythmia, using electrograms[45]. Post-infarction temporal alterations in TWA during the first 6 months after the event have also been recorded, probably after ventricular remodeling post-acute myocardial infarction[46]. Eventually, the TWA at pathological levels was associated to the cardiac sympathetic denervation and accelerated sympathetic nervous activity in patients with dilated idiopathic cardiomyopathy during Iodine 123-labeled metaiodobenzylguanidine (123I-MIBG) assessment and echocardiogram[47].

Other studies investigated the effects of acute mental stress (by recalling memories that triggered anger or by doing mental arithmetics) on the TWA. Kop et al[43] concluded that this increases the TWA amplitude in patients with ICD, with documented coronary artery disease (n = 23) at lower heart rates than those in the exercise protocols currently used in the assessment of TWA[43]. Lampert et al[48] not only recorded an increase in TWA due to mental stress in patients with ICD

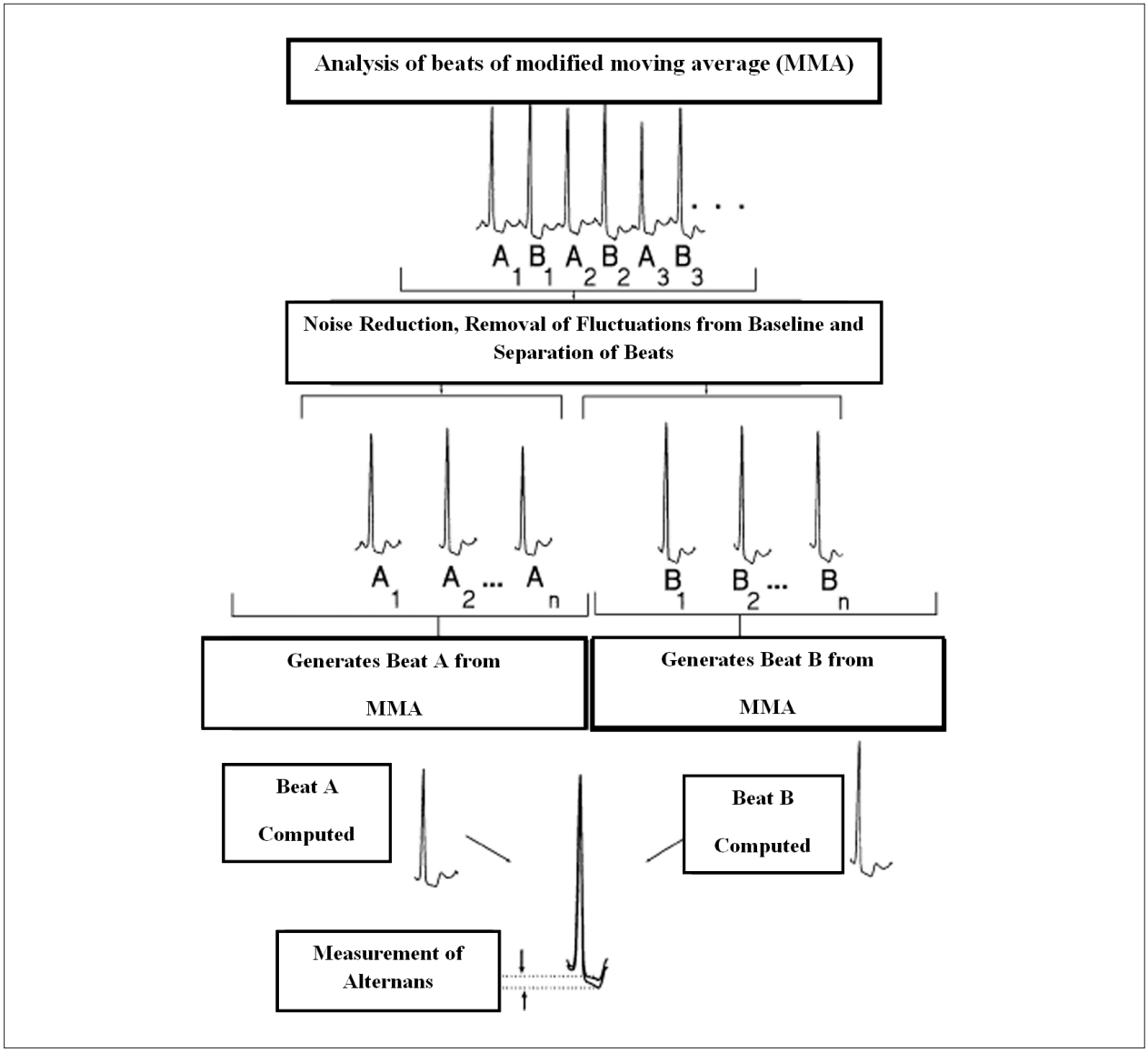

Figure 2 - Representation of the main phases of the MMA algorithm. Reproduced from Figure 1, Verrier RL, et al (2003)[38].

(n = 33), but also discovered that the TWA alterations were well correlated with alterations in HR, systolic blood pressure and catecholamine levels[48], in line with previous evidence that the mental stress alters not only the cycle length, but also the VT cessation in patients with ICD without ischemia[49].

Finally, some external influences can also affect the TWA. The spinal column stimulation (SCS) is currently used in patients with untreatable angina and it is being considered that this stimulation has an anti-arrhythmic effect on the arrhythmogenic substrate. The study of the TWA patterns to assess alterations in the arrhythmic substrate indicates that patients that originally presented high-amplitude positive TWA tests when the stimulator was off, experienced a decrease in the TWA values (although still presenting a positive TWA test) 2 hours after the SCS. Twenty-four hours after the SCS, all patients became TWA-negative. In this sample, all patients were being treated with beta-blockers and no alterations in the basal HR or atrioventricular conduction were observed in consecutive TWA tests. These findings suggest an effect of time-dependent remodeling on the arrhythmogenic substrate (evaluated by TWA), independent from the sympathetic removal[50].

Another external influence - ICD shocks during normal defibrillation tests (n = 65) - acutely increased the TWA magnitude, mediated in part by sympathetic stimulation[43]. Moreover, further studies are necessary to demonstrate whether this increase in TWA can be associated to the most common mechanism of sudden death in patients with ICD[51], i.e., the post-shock electromechanical dissociation that follows a treated VT/VF. On this subject, a key aspect to be considered is that problems in the calcium cell cycle - previously associated with the mechanical ventricular dysfunction - are strongly related to APD-alternans[4,14,15,17].

Final considerations

The prognostic role of TWA in the clinical risk stratification is becoming increasingly clearer, but still comprises a few controversies. On the one hand, the currently available literature presents strong evidence of a good prognostic performance (notably, its negative predictive value) in specific clinical populations, such as ischemic heart disease, after AMI, non-ischemic cardiomyopathy. The TWA would also be equal to, or would have a better prognostic performance than EPS in other populations (for instance, athletes with arrhythmia). On the other hand, the clinical value of the TWA assessment has yet to be further investigated regarding many of its aspects, particularly: other clinical populations of relevance (for instance, Chagas' disease) must be studied; other study protocols (for instance, comparisons between TWA in Holter and exercise- or pharmacological stress-induced TWA) must be included; the technicalities of each methodology for TWA measurement must be considered correctly in the clinical protocols to be outlined.

The next steps in the creation of new protocols and uses, in the deeper exploration of the clinical possibilities of TWA or the "filling in the current gaps" in the TWA knowledge basis follow a direction: physicians and researchers must better explore the technological characteristics of the several available technologies to assess the TWA - each one with its own strong and weak points - aware of the fact that the obtained TWA values respond to several other factors rather than medications.

Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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Study Association

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