ISHNE Lecture:

# Comparison of T wave alternans profiles of healthy subjects and patients with ICDs

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Visible T-wave alternans (TWA), actually, is not a recent finding, but it has been reported since 1909[1]. However, it is the non-visible, and much less rare, microvolt TWA that has earned a place under the spotlight because of its association with electrical disorder and elevated risk of sudden cardiac death (SCD) or arrhythmic events[2-6] as assessed in several trials, cohort studies and clinical researches: TWA in CHF[7], ALPHA[8], REFINE[9], FINCAVAS[10], Ikeda and colleagues[11] (in a collaborative cohort study) Bloomfield and colleagues[12] (in a MADIT-2 like research). In common, all these studies provided evidences of high negative predictive value of TWA regarding SCD or arrhythmic events, with low to regular positive predictive value.

Two decades of research on microvolt TWA gave rise to several different methodologies for its calculation, each one with its own strengths and weaknesses. The overall application of these methodologies in clinical research resulted in the current knowledge about microvolt TWA. Some of them had impact on delineating TWA prevalence in different clinical populations, some helped to further elucidate its mechanism, other broadened TWA analysis to new clinical protocols and settings (e.g., ambulatory ECG). Ten or more different methods can be successfully applied to measure TWA, but only two have succeeded so far in being worldwide commercially available, the Spectral Method (SM) and the Modified Moving Average (MMA).

A recent paper by Cox and colleagues[13] is the first to prospectively compare those two different TWA algorithms on the same set of patients with left ventricular systolic dysfunction (41 patients, ejection fraction 31 ± 13%), though none of them were in its commercial version. Similar clinical performances were obtained, in addition to the conclusion that “MMA amplifies TWA compared to traditional spectral analyses”. This finding calls the attention to the fact – sometimes not so obvious – that published TWA values and test results should always be considered in the light of the technical features of the method used to evaluate it. Shortly, MMA yields the maximum TWA value on the ST-T while SM returns an average value over the entire ST-T complex. For example, provided a stream of beats with T-waves of maximum alternating amplitude of 30$\mu$V and cumulative alternans voltage of 40$\mu$V over 150ms of T wave, MMA-based screening would result in a TWA value of 30$\mu$V and an SM-based test report would show nearly 4.6$\mu$V (approximately 6.5 times lower).

The choice of the TWA evaluation methodology will thus affect the quantitative aspects of any result / profile definition / classification threshold obtained or used in the research being carried out, so

which one to choose? Briefly, SM algorithm unequivocally has the wider range of applications and clinical studies published among all MTWA analysis methodologies. However, MMA approach extends TWA analysis to clinical protocols and settings not covered by the SM current implementation, such as ambulatory ECG and/or standard treadmill protocols for heart rate augmentation in ergometry.

Nieminen and colleagues[10] published in 2007 one of the largest studies on TWA research, and surely the largest study on TWA with the MMA approach, with a sample of 1037 individuals drawn from the general population eligible for ergometric evaluation, as part of the FINCAVAS trial. Their work gains on the strength of the sample size, as well as from the support staff of the associated clinical trial. On the other hand, in Brazil as well as in many other countries, treadmills are more readily used in stress tests than ergometers, which would make a direct translation of the results from Nieminen and colleagues' work a little troublesome. In our current results, we employed the MMA technology on standard treadmill protocols instead of ergometer stress testing, with clearly defined clusters of healthy subjects and patients with implanted cardio-defibrillators (ICD), the latter mostly due to secondary prevention.

This lecture aims to compare the TWA profiles of healthy subjects and patients with ICDs evaluated on standard treadmill protocols using the MMA methodology.

Apparently healthy subjects were selected, all non-smokers and not in use of any medication, to have an echocardiogram done and to perform a treadmill stress test with concomitant TWA analysis. Those which echocardiogram showed standard cavities and walls dimensions, as well as normal segmental motility, were considered eligible. Anyone with modifications in the resting ECG and inconclusive or positive stress test for ischemia was excluded. Individuals with cardio-defibrillators were recruited from outpatients being attended at the Clinical Pacing and Arrhythmia Unit and capable of performing an attenuated treadmill stress test protocol.

Both groups had the TWA analysis performed during the treadmill stress testing. The stress test protocol was selected according to the usual clinical indications in the ergometry literature: healthy volunteers working on ELLESTAD and ICD patients walking in the NAUGHTON (attenuated) protocol. In all cases, the recovery phase lasted for 6 minutes: the first two spent in slow walking and the last four at rest (in standing or sitting position at the volunteer's disclosure). We used ELLESTAD and not BRUCE since, in our experience, patients tend to achieve the peak heart rate earlier with the former protocol. Healthy patients eventually start to run at secondary stages in the ELLESTAD but not in the BRUCE protocol, and running may be a source of ECG artifacts. However, this did not affect the quality of the TWA analysis because the running phase always happened outside the heart rate range needed for successful TWA analysis (below 125 bpm according to TWA literature).

The stress test is performed with 15 leads (12 leads + Frank XYZ), with vectorcardiograms registered at rest, peak heart rate and the end of the six-minute recovery phase. The MMA algorithm yields a TWA value every 15 seconds, in each of the 15 leads, in all phases of the test (rest, exercise, recovery). Thus, one key issue is to sort the redundant information out of the relevant content. The derived comparative profile consists of 2 variables, measured twice at different times during the stress test: TWA amplitude as well as the concomitant heart rate it was registered are measured both at rest (basal value) and at peak TWA value. Statistical analyses were carried out in the SPSS package, using Chi-square or Mann-Whitney tests for comparison between groups with p values ≤ 0.05 considered significant.

Groups were not different between each other with respect to the male/female distribution (p = 0,689) but ICD patients are older on average (p < 0.001). Group I is comprised of 31 healthy volunteers (8 female, 23 male) with normal echocardiogram findings and negative stress test for ischemia, non-smokers and with no current use of medication. Group II consisted of 33 patients (10 female, 23 male) with ICD of various etiologies and optimized therapy (see Figure 1), mostly due to secondary prevention, and all sustained sinusal rhythm during the entire stress test.

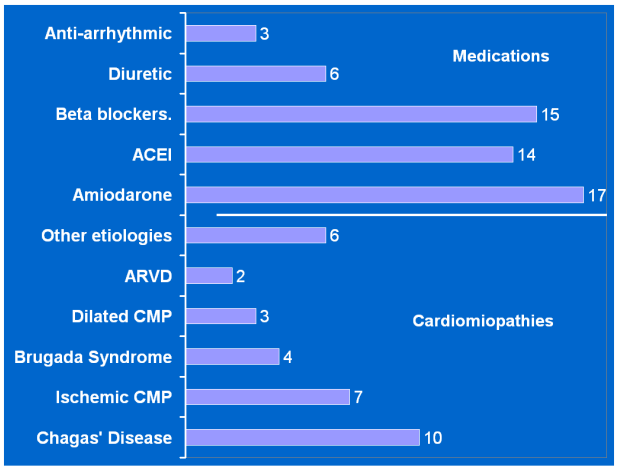


Figure 1: Background cardiomiopathies and medications in use by the secondary prevention ICD patients (data from one patient were not available).

Healthy subjects with extra-systoles (isolated or in pairs) registered during the stress test were not statistically significant from those with plain negative stress test in this sample (data not shown). Nevertheless, they were kept excluded from Group I final numbers. Our findings (Table 1) clearly show that Group I (healthy subjects) consistently showed lower TWA amplitudes at higher heart rates than Group II (secondary prevention ICD patients).

Table 1: Differences between the profiles of healthy subjects and ICD patients as depicted in the measured variables and distinctive features. All variables displayed in mean ± SD (minimum – maximum).

| Features | Group | p |
|---|---|---|

| Features | Healthy Subjects (N=31) | ICD patients (N=33) | p |
|---|---|---|---|
| Age (years) | 36 ± 9 (18 – 55) | 51 ± 17 (15 – 73) | < 0.001 |
| Max TWA @ rest (μV) | 1 ± 2 (0 – 5) | 8 ± 9 (0 – 38) | < 0.001 |
| Max TWA during test (μV) | 25 ± 13 (4 – 61) | 37 ± 20 (4 – 101) | 0.018 |
| HR @ Max TWA during test (bpm) | 117 ± 9 (92 – 127) | 88 ± 18 (55 – 126) | < 0.001 |
| HR @ rest (bpm) | 79 ± 10 (62 – 98) | 66 ± 14 (42 – 99) | < 0.001 |

Secondary prevention ICD patients and healthy subjects would clearly be opposite extremes if a quantitative scale of arrhythmogenic substrate could be created. Such a scale would probably improve our knowledge about the reasons why some extra-systoles trigger complex arrhythmias and others do not. Or why some subjects with thousands of extra-systoles in Holter records do not develop any tachycardia or fibrillation. TWA has already been reported as the first step to fibrillation towards increasingly complex oscillation patterns in the cardiac repolarization[14]. Recent studies on TWA have also collected evidence that TWA can be a surrogate for the alternans in the action potential duration, a well-known marker of increased dispersion[15].

It was expected, but it is still interesting to note, that ICD patients and healthy subjects are different entities regarding on quantitative TWA values even at rest (Figure 2). In our sample, a basal TWA amplitude threshold of 5μV was enough to correctly discriminate all healthy subjects and half of all ICD patients. In other words, 100% specificity and 50% sensibility. Our results show some overlapping between the TWA amplitude range in the two groups. On this topic, we believe that the variety of different etiologies in the ICD patients sample was a bias. For instance, some etiologies with intermittent manifestations (like Brugada) may not have a constant high arrhythmogenic substrate. Other highly focal diseases (e.g., ARVD) may have high values only in those leads who better see the arrhythmic focus. In the present state of our knowledge, these are just hypothetical thoughts who need more evidence. Nevertheless, in our sample the highest basal TWA value (38μV) was found in an ARVD patient, and it was registered in lead V1.

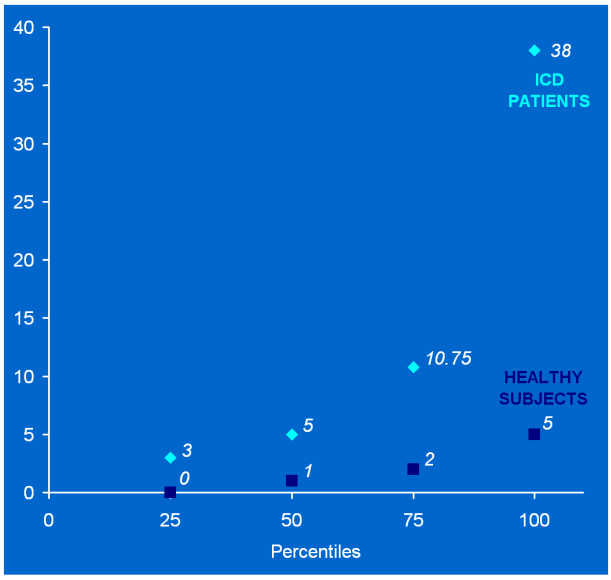


Figure 2: Percentiles of basal TWA amplitudes registered in healthy subjects and ICD patients in sinusal rhythm.

Figure 3 shows that the distinction between Group I (healthy subjects) and Group II (ICD patients) still holds at the peak TWA value registered (p = 0,018, see Table 1). The performance of a derived quantitative peak TWA threshold for discrimination between groups is noteworthy too. Selecting the 75$^{th}$ percentile (46.75$\mu$V) of the ICD patients as a cutpoint yields approximately 90% of specificity and 33% of sensibility. The mixed etiologies in the ICD group again might have acted as a bias. After all, not every etiology presented in this sample (see list in Figure 1) may have its arritmogeneity enhanced by sympathetic maneuvers like the treadmill stress test. If that is so, then not all etiologies may increase TWA values during a treadmill stress test.

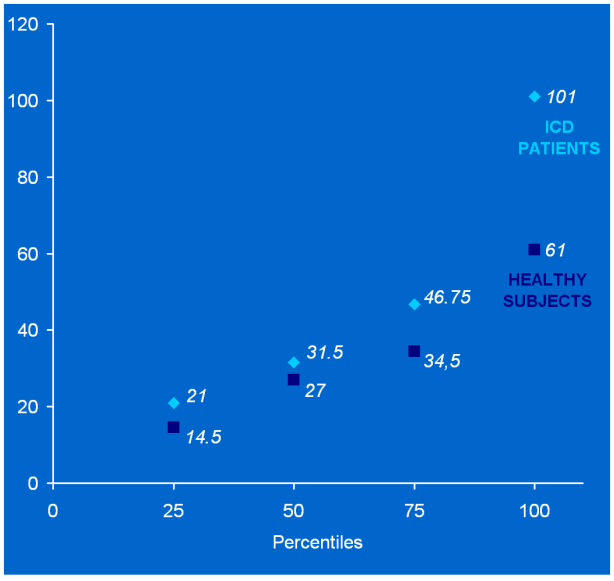


Figure 4: Percentiles of peak TWA amplitudes registered in healthy subjects and ICD patients in sinusal rhythm.

Lastly, our findings show clear evidences that the distinctions between the TWA profiles of healthy subjects and ICD patients are based not only on TWA amplitudes but also on the heart rate at which these amplitudes are registered (Figure 4). Regardless of what causes the lower heart rates in ICD patients, the association of higher TWA values at corresponding lower heart rates is always indicative of worse prognosis, according to TWA literature.

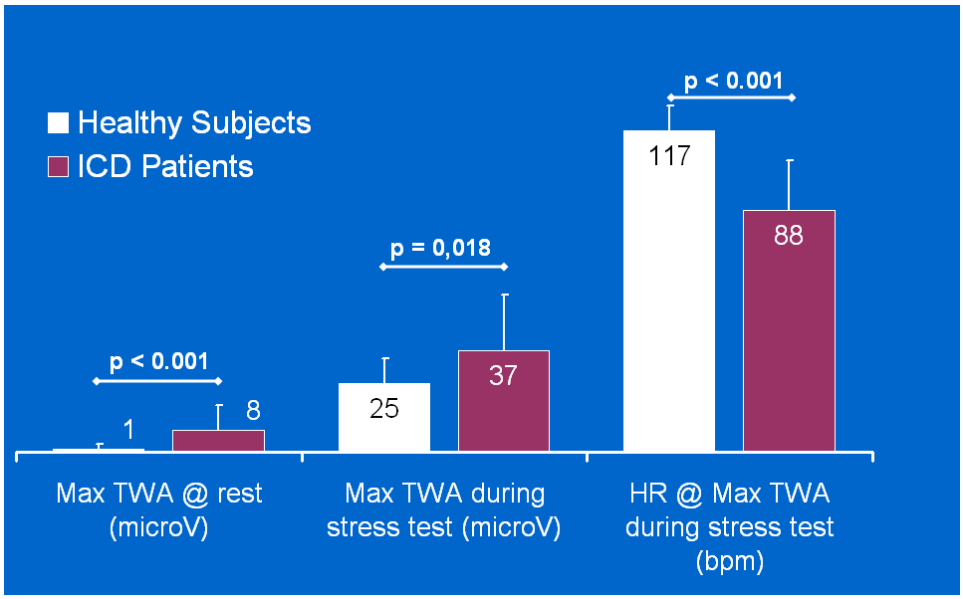


Figure 4: Comparison between healthy subjects and ICD patients showing: maximum TWA values registered at rest, peak TWA values measured during the stress test and heart rate at when the peak TWA values were registered.

In summary, our findings demonstrate a distinctive gap between TWA profiles of healthy subjects and secondary prevention ICD patients. Isolated or paired extra-systoles registered during treadmill stress test do not seem to alter the TWA profile of healthy subjects, though these results are not conclusive. The presented overlap between TWA amplitude in both groups may be due to the mixed etiologies in the ICD patients, action of drugs used in therapy, or even a possible better prognosis of ICD patients with lower TWA values. More studies are needed to clarify and delineate a possible ‘gray zone’ between the two TWA profiles of such distinct populations regarding their arrhythmogenic substrate.

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