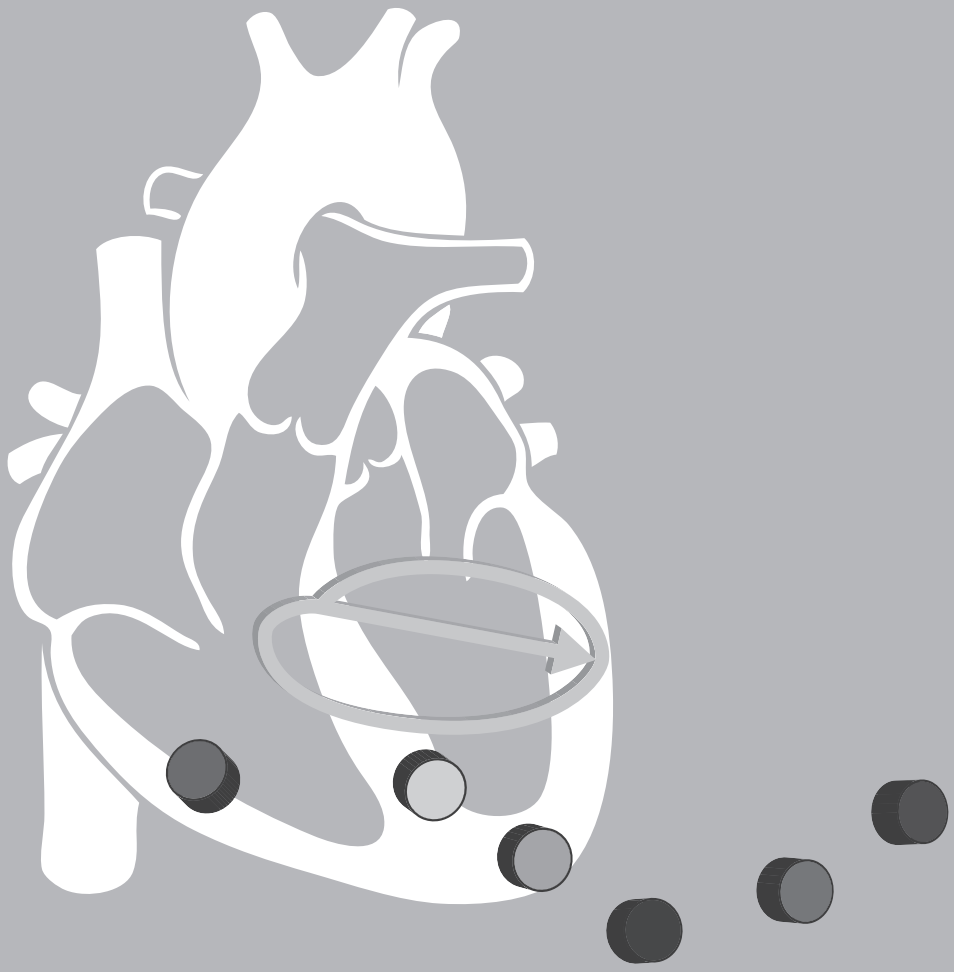

Chapter 12

Comparison of standard versus orthogonal ECG leads for T-wave alternans identification

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Abstract

Background

T-wave alternans (TWA), an electrophysiologic phenomenon associated with ventricular arrhythmias, is usually detected from selected ECG leads. TWA amplitude measured in the 12-standard and the 3-orthogonal (vectorcardiographic) leads were compared here to identify which lead system yields a more adequate detection of TWA as a noninvasive marker for cardiac vulnerability to ventricular arrhythmias.

Methods

Our adaptive match filter (AMF) was applied to exercise ECG tracings from 58 patients with an implanted cardiac defibrillator, 29 of which had ventricular tachycardia or fibrillation during follow-up (cases), while the remaining 29 were used as controls. Two kinds of TWA indexes were considered, the single-lead indexes, defined as the mean TWA amplitude over each lead (MTWAA), and lead-system indexes, defined as the mean and the maximum MTWAA values over the standard leads and over the orthogonal leads.

Results

Significantly ($P < 0.05$) higher TWA in the cases versus controls was identified only occasionally by the single-lead indexes (odds ratio: 1.0–9.9, sensitivity: 24–76%, specificity: 76–86%), and consistently by the lead-system indexes (odds ratio: 4.5–8.3, sensitivity: 57– 72%, specificity: 76%). The latter indexes also showed a significant correlation (0.65–0.83) between standard and orthogonal leads.

Conclusion

Hence, when using the AMF, TWA should be detected in all leads of a system to compute the lead-system indexes, which provide a more reliable TWA identification than single-lead indexes, and a better discrimination of patients at increased risk of cardiac instability. The standard and the orthogonal leads can be co A identification, so that TWA analysis can be limited to one-lead system.

Introduction

T-wave alternans (TWA) consists of every-otherbeat shape or amplitude alternation of the electrocardiographic (ECG) repolarization segment. A link between TWA and malignant ventricular arrhythmias[1-5] and sudden cardiac death[6-12] is generally recognized. A correct choice of the surface ECG lead systems to be used in clinical applications is fundamental for a reliable identification of TWA. Indeed, since TWA may occur as a regionally specific phenomenon[13;14], the TWA level may be lead dependent. In our previous studies[15-18] TWA measures from each orthogonal (X,Y,Z) lead were averaged, whereas Rosenbaum *et al.* preferred TWA identification from the vector magnitude[1;6;19]. Other authors performed their analysis on the precordial leads only[7;20-22], on the 12 standard leads[12;23], or even on 15 leads (12 standard and three orthogonal)[3;8;24-26]. Examples of TWA identification from other combinations of leads are also present in the literature[27;28].

The present study was designed to identify the ECG lead system, either the 12 standard or the three orthogonal, which provides the best noninvasive marker for cardiac vulnerability to ventricular arrhythmias when using our adaptive match filter method for TWA identification.[15]
To this aim, 16-lead (12 standard, three orthogonal, and the vector magnitude) exercise ECG tracings from 58 patients with a cardiac defibrillator implanted (ICD) for primary prevention were analyzed. Among these patients, 29 had ventricular tachycardia or fibrillation during follow-up (cases), while the remaining 29 were used as control group (controls). Our ICD population was used as a whole when comparing TWA quantification from different leads, whereas the two subgroups were contrasted when evaluating each lead system ability to discriminate cases from controls. Both ICD patients groups are known to show increased levels of TWA compared to healthy subjects[26].

Methods

Study Population

Our study population consisted of 58 subjects from the Leiden University Medical Center (The Netherlands) collection of routine clinical data from patients with an ICD for primary prevention because of a depressed left ventricular ejection

fraction (LVEF < 0.35). All patients were receiving standard care, which included periodic visits to the outpatient clinic, amongst others, to assess validity by bicycle ergometry. Average duration of the clinical follow-up was four years. The bicycle ergometer test consisted of an approximately 10-minute bicycle test during which the workload was incremented every minute by 10% of his/her expected maximal exercise capacity. The test was considered valid if heart rate was within the 95–110 bpm range for at least one minute during the exercise phase. During follow-up, patients were classified as either "cases" if developing ventricular tachycardia or ventricular fibrillation (treated with antitachycardia pacing and/or shock therapy), or "controls" (no device therapy during follow-up). Several patients had more than one exercise test during the follow-up period. Case patients exercise tests were excluded when a major cardiac event (infarction, VT ablation, CABG) occurred between the exercise test and the moment of VT/VF. If more than one exercise test remained available for analysis, the one closest in time (either before or after) to the VT/VF episode was selected. In control patients with more than one suitable exercise test, the earliest available one was selected.

Twenty-nine controls and 29 cases, matched for age, gender, body mass index, LVEF, coronary-artery-disease location, cardiomyopathy etiology, NYHA functional classes, and medication at the time of exercise tests (Table 1), were retrospectively selected for the present observational study on TWA. Investigators were blinded to TWA levels when matching was performed.

ECG Recordings

During the bicycle ergometer test, an 8-lead (I, II, V1 to V6) exercise ECG recording was obtained from each patient using the GE CASE 8000 recorder (sampling frequency: 500 Hz; resolution: 4.88 μV/LSB). Leads III, aVR, aVL, aVF, X, Y, Z, and the vector magnitude (VM) were obtained using well-known transformations[29-32]. Consequently, a 16-lead ECG tracing was available for each patient.

T-Wave Alternans Identification

TWA was identified using our heart-rate adaptive match filter (AMF) method[15], a technique previously tested and prospectively validated in both clinical and simulated settings[15-17;33-37]. Our AMF was applied to each one of the 16 leads available for each patient independently. Windows of 16 consecutive heart beats

were recursively (every 2 seconds) analyzed after being preprocessed for noise and baseline removal, and for noisy and ectopic beats replacement[33;35]. ECG windows with more than one replaced beat were rejected. Eventually, ECG windows characterized by stable heart rate (NN standard deviation, in seconds, less than 10% of mean NN, in seconds) were submitted to our AMF, which provided a sinusoidal

TABLE 1. Clinical Parameters Relative to the Entire ICD Population, and for Cases and Controls. Reported Values: Mean ± Standard Deviation or Number of Occurrences

	Overall (n = 58)	Cases (n = 29)	Controls (n = 29)	P
General				
Age (years)	59.3 ± 11.2	60.4 ± 12.2	58.2 ± 10.9	NS
Gender (male)	46	23	23	NS
BMI (Kg/m2)	27 ±4	26 ±4	27 ±3	NS
LVEF (%)	29 ± 9%	28 ± 12%	29 ± 6%	NS
CRT-D	32	16	16	NS
Follow-up (years)	4.2 ± 1.8	4.6 ± 176	3.9 ± 1.8	NS
CAD location				
RCA	2	1	1	NS
LCA	21	10	11	NS
RCA, LCA	5	2	3	NS
RCA, LCx	2	2	0	NS
LCA, LCx	5	3	2	NS
RCA, LCx, LCA	9	4	5	NS
None	14	7	7	NS
Etiology				
Ischemic	44	22	22	NS
Nonischemic	14	7	7	NS
NYHA functional class				
I-II	43	21	22	NS
III-IV	15	8	7	NS
Medication at exercise test				
Beta-blocker	54	27	27	NS
ACE inhibitor / AT antagonist	54	27	27	NS
Diuretics for CHF	43	24	19	NS
Statins	47	24	23	NS
Amiodarone	9	6	3	NS

ACE = angiotensin converting enzyme; AT = angiotensin; BMI = body mass index; LVEF = left ventricular ejection fraction; CAD = coronary artery disease; CHF = congestive heart failure; LCx = Circumflex; CRT-D = cardiac resynchronization therapy with defibrillator; LCA = left coronary artery; NS = not statistically significant; NYHA = New York Heart Association; RCA = right coronary artery.

signal whose amplitude represents an estimate of the TWA amplitude (TWAA, μV) characterizing the input ECG. TWAA values detected from all the accepted 16- beat windows of a single-lead 10-min ECG recording were averaged (MTWAA, μV) to provide an overall characterization of the lead.

Two kinds of TWA indexes were considered: the single-lead indexes, directly represented by the MTWAA values in leads I to III, V1 to V6, aVR, aVL, aVF, X, Y, and Z; and lead-system indexes, represented by the mean and the maximum values of MTWAA (mean MTWAA and max MTWAA, respectively) over the standard leads, over the precordial leads (often considered the most representative among the standard[38]), and over the orthogonal leads, and by the MTWAA value in the VM tracing.

T-Wave Amplitude Quantification

Since it has been hypothesized[39;40] a possible dependency of TWA amplitude on T-wave amplitude (TA, here defined as the difference between the maximum and the minimum ECG amplitude throughout the ST segment), the TA values obtained from all the single-lead 16-beat ECG windows accepted for TWA analysis were averaged (MTA, μV) to provide an overall estimate of T-wave amplitude in one lead.

Analysis of T-wave Alternans Dependency on T-wave Amplitude

Interpatients analysis of TWA dependency on TA was evaluated by computing, for each lead, the correlation coefficient (see Statistics) between the MTWAA and MTA distributions over the 58 ICD patients.

Interleads analysis of TWA dependency on TA was evaluated by first computing, for each lead, the mean values of MTWAA and MTA parameters over the ICD population, and then computing the correlation coefficient for the mean MTWAA versus mean MTA distribution over the 15 leads (12 standard and three orthogonal).

Statistics

To be independent of normal distributions, nonparametric tests were used to perform comparisons among quantities. The Kruskal–Wallis test was used to perform the one-way ANOVA test to evaluate if, when considering the entire ICD population, MTWAA, and MTA parameters distributions over the leads of a

specific system were characterized by the same median value. Information about which pairs of leads had different median values was obtained using the multiple comparison procedure. Comparisons between the distributions of continuous clinical parameters, TWA indexes and TA values over the two groups of patients were performed using the Wilcoxon rank-sum test for equal medians. Differences in the binary parameters distributions between the two groups were evaluated

TABLE 2. Single-Lead and Lead-System TWA Indexes for the Entire ICD Population, and for Cases and Controls. P-Value Refers to Cases versus Controls

Single lead analysis:	**Overall (n = 58)**	**Cases (n = 29)**	**Controls (n = 29)**	**P**
MTWAA (μV) 12 Standard leads				
I	12 ±6	12 ±6	12 ±7	NS
II	24 ± 15	28 ± 18	20 ± 10	0.0349
III	25 ± 18	30 ± 22	21 ± 11	NS
V1	17 ± 12	21 ± 15	13 ± 6	0.0171
V2	21 ± 13	25 ± 14	17 ± 10	0.0059
V3	26 ± 21	32 ± 27	20 ± 10	NS
V4	22 ± 13	26 ± 16	18 ±9	NS
V5	19 ± 13	22 ± 16	16 ±6	NS
V6	17 ±9	19 ± 12	15 ±6	NS
aVR	15 ±9	17 ± 10	13 ±7	NS
aVL	16 ± 15	20 ± 20	13 ± 7	0.0406
aVF	23 ± 11	25 ± 11	20 ± 11	NS
MTWAA (μV) 3 orthogonal leads				
X	14 ±9	16 ± 11	11 ±5	NS
Y	20 ± 10	22 ±9	17 ± 9	0.0216
Z	16 ± 10	20 ± 12	12 ± 5	0.0004
Lead-system analysis:				
12 standard leads				
Mean MTWAA (μV)	19 ±8	22 ±9	16 ± 5	0.0013
Max MTWAA (μV)	33 ± 20	41 ± 23	25 ± 11	0.0001
6 precordial leads				
Mean MTWAA (μV)	20 ± 11	23 ± 13	17 ± 6	0.0164
Max MTWAA (μV)	31 ± 20	39 ± 24	24 ± 10	0.0009
3 orthogonal leads				
Mean MTWAA (μV)	16 ±7	19 ±8	15 ± 4	0.0124
Max MTWAA (μV)	22 ± 11	26 ± 12	19 ± 9	0.0125
vector magnitude				
MTWAA (μV)	17 ± 12	20 ± 15	15 ±9	NS

MTWAA = mean T-wave alternans amplitude; NS = not statistically significant; TWA = T-wave alternans.

using the chi-square test. Agreement between two parameter distributions was evaluated by computing the correlation coefficient (r) and the regression line that best interpolates the data in the least-squares sense. The statistical significance level was set at 5%.

To evaluate the effect of high levels of TWA on the risk of developing VT/VF, the odds ratio (OR), based on logistic regression models, as well as the sensitivity (Se) and specificity (Sp) were used. No previous studies were available to provide, for each lead, the minimum risky TWAA levels. Thus, the controls were used to define such thresholds as the 75th percentile of the MTWAA distributions and of the mean and max MTWAA distributions, for the single-lead analysis and the lead system analysis, respectively.

TABLE 3. Single-Lead MTA Values for the Entire ICD Population, and for Cases and Controls. P-Value Refers to Cases versus Controls.

MTA (μV)	Overall (n = 58)	Cases (n = 29)	Controls (n = 29)	P
12 Standard leads				
I	171 ± 94	148 ± 63	194 ± 114	NS
II	418 ± 202	399 ± 189	438 ± 216	NS
III	406 ± 233	389 ± 190	423 ± 271	NS
V1	316 ± 209	335 ± 182	298 ± 235	NS
V2	538 ± 327	578 ± 329	497 ± 325	NS
V3	605 ± 339	619 ± 332	591 ± 350	NS
V4	505 ± 262	506 ± 280	503 ± 261	NS
V5	388 ± 211	377 ± 196	400 ± 228	NS
V6	315 ± 187	306 ± 182	323 ± 195	NS
aVR	255 ± 118	232 ± 116	278 ± 117	NS
aVL	230 ± 140	221 ± 97	238 ± 174	NS
aVF	405 ± 210	381 ± 178	429 ± 239	NS
3 Orthogonal leads				
X	281 ± 143	267 ± 129	295 ± 157	NS
Y	357 ± 178	341 ± 166	374 ± 191	NS
Z	357 ± 237	391 ± 216	324 ± 257	NS

MTA = mean T-wave amplitude; NS = not statistically significant.

TABLE 4. Interpatients Analysis of T-Wave Alternans. Dependency on T-Wave Amplitude.

	r(MTWAA vs. MTA)	P
12 Standard leads		
I	0.39	$<10^{-2}$
II	0.28	<0.05
III	0.39	$<10^{-2}$
V1	0.36	$<10^{-2}$
V2	0.45	$<10^{-3}$
V3	0.48	$<10^{-3}$
V4	0.51	$<10^{-4}$
V5	0.49	$<10^{-3}$
V6	0.51	$<10^{-4}$
aVR	0.28	<0.05
aVL	0.39	$<10^{-2}$
aVF	0.30	<0.05
3 Orthogonal leads		
X	0.43	$<10^{-3}$
Y	0.21	NS
Z	0.42	$<10^{-2}$

MTWA = mean T-wave alternans amplitude; MTA = mean T-wave amplitude; NS = not statistically significant; r = correlation coefficient.

Results

The single-lead TWA indexes and the TA parameters for the entire ICD population and for the cases and controls are reported in Table 2 and Table 3, respectively. Some significant differences were detectable among the 12 standard leads ($P < 10^{-14}$) as well as among the three orthogonal leads ($P < 10^{-4}$), even though it was not possible to identify a specific lead characterized by the highest or the lowest MTWAA values, compared to all the other leads of the same system. Instead, MTA analysis showed that some significant differences were detectable among the standard leads ($P < 10^{-15}$) but not among the orthogonal leads. Eventually, the analysis of TWA dependency on TA highlighted a weak ($0.21 \leq r \leq 0.51$, with $P < 0.05$ in all cases but for lead Y) interpatients association between MTWAA and MTA (Table 4), whose mean values over the 58 ICD patients were instead linked by a strong ($r = 0.85$, $P < 10^{-3}$; Fig. 1) interleads association. Moreover, though MTWAA measured in a specific lead was consistently greater in the cases than in controls, statistically significant increments of MTWAA were detected only in four (II, V1, V2, and aVL) of the 12 standard leads, and in two (Y and Z) of the three orthogonal

leads. No significant differences were observed between TA values relative to the same leads in the two ICD populations groups (Table 3).

TABLE 5. MTWAA Thresholds over which Positive T-Wave Alternans (+) is Detected, with Corresponding Odds Ratio (OR), Sensitivity (Se), and Specificity (Sp) Values for each Single Lead and Lead System. P refers to Cases+ versus Controls+.

	MTWAA threshold (μV)	Cases+ (n = 29)	Controls+ (n = 29)	OR	Se	Sp	P
Single lead analysis							
MTWAA (μV) 12 Standard leads							
I	14	7	7	1	24%	76%	NS
II	23	13	7	2.6	45%	76%	NS
III	28	13	7	2.6	45%	76%	NS
V1	16	13	6	3.1	45%	79%	NS
V2	22	17	7	4.5	59%	76%	<0.01
V3	25	13	7	2.6	45%	76%	NS
V4	23	12	7	2.2	41%	76%	NS
V5	21	8	7	1.2	28%	76%	NS
V6	18	9	7	1.4	31%	76%	NS
aVR	15	12	7	2.2	41%	76%	NS
aVL	17	12	7	2.2	41%	76%	NS
aVF	24	13	7	2.6	45%	76%	NS
MTWAA (μV) 3 Orthogonal leads							
X	14	10	4	3.3	34%	86%	NS
Y	20	17	7	4.5	59%	76%	<0.01
Z	13	22	7	9.9	76%	76%	<0.005
Lead-system analysis:							
12 standard leads							
Mean MTWAA (μV)	17	19	7	6.0	66%	76%	<0.005
Max MTWAA (μV)	31	21	7	8.3	72%	76%	<0.005
6 precordial leads							
Mean MTWAA (μV)	21	9	5	2.2	31%	83%	NS
Max MTWAA (μV)	30	17	5	6.8	59%	83%	<0.005
3 orthogonal leads							
Mean MTWAA (μV)	17	17	7	4.5	57%	76%	<0.01
Max MTWAA (μV)	22	18	7	5.1	62%	76%	<0.005
Vector magnitude							
MTWAA (μV)	17	16	6	4.7	55%	76%	<0.01

MTWAA = mean T-wave amplitude; NS = not statistically significant.

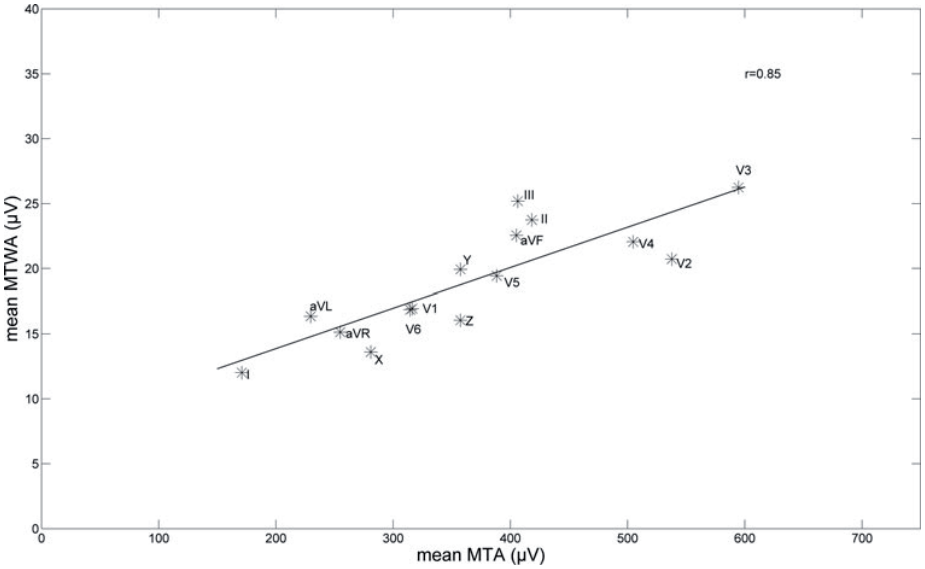

FIGURE 1. Regression line ('r': correlation coefficient) representing the interleads association between the mean MTWAA and mean MTA distributions over 15 leads (I–III, V1–V6, aVR, aVL and aVF, X,Y, and Z).

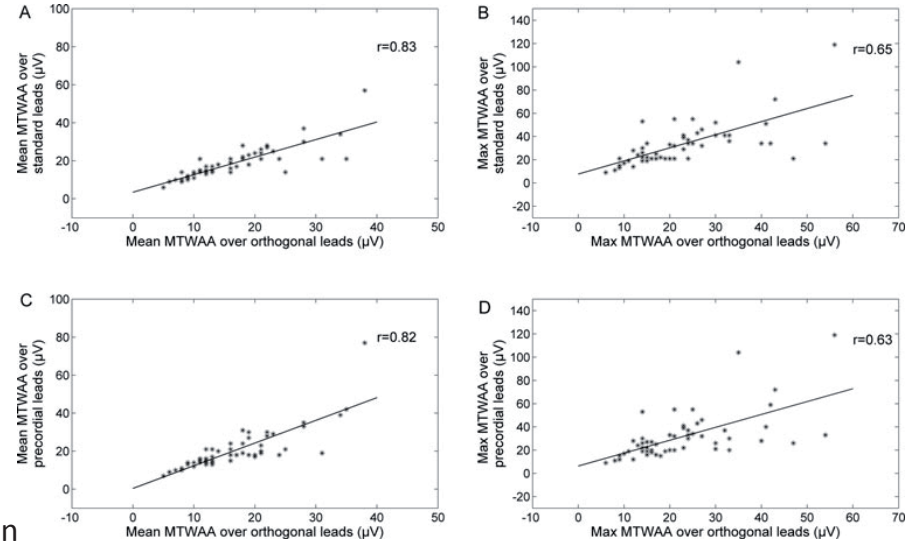

FIGURE 2. Representation of mean and max MTWAA values over the standard versus the orthogonal leads (panels A and B), and over the precordial versus orthogonal leads (panels C and D) for 58 ICD patients (*). Correlation coefficient ('r') and regression line slope and intercept were 0.83 ($P < 10^{-14}$), 0.92, and 3.48 μV, respectively, for panel A; 0.65 ($P < 10^{-7}$), 1.13, and 7.65 μV, respectively, for panel B; 0.82 ($P < 10^{-14}$), 1.19, and 0.42 μV, respectively, for panel C; and 0.63 ($P < 10^{-6}$), 1.11, and 6.31 μV, respectively, for panel D.

When comparing standard versus orthogonal leads TWA indexes, no significant difference were found in terms of mean MTWAA (standard: 19 ± 8 μV, orthogonal: 16 ± 7 μV, P > 0.05; Table 2), whereas max MTWAA was significantly higher in the former than in the latter leads (standard: 33 ± 20 μV, orthogonal: 22 ± 11 μV, P = 0.0002; Table 2). Moreover, the mean and max MTWAA values detected in the standard leads are significantly dependent of the mean and max MTWAA values detected in the orthogonal leads, respectively (mean values r = 0.83, $P < 10^{-14}$, Fig. 2A, maximum values r = 0.65, $P < 10^{-7}$, Fig. 2B). When using the precordial leads only, these, compared to the orthogonal, showed significantly higher values of both mean MTWAA (precordial: 20 ± 11 μV, orthogonal: 16 ± 7 μV, P = 0.0264; Table 2) and max MTWAA (precordial: 31 ± 20 μV, orthogonal: 22 ± 11 μV, P = 0.0028; Table 2). Correlation values between the mean and max MTWAA values provided by the two-lead systems were 0.82 ($P < 10^{-14}$; Fig. 2C) and 0.63 ($P < 10^{-6}$; Fig. 2D), respectively. The VM provided values of MTWAA (17 ± 12 μV) comparable to the mean MTWAA over the standard and the orthogonal leads, but significantly lower than the mean MTWAA over the precordial leads (P = 0.0188) and all max MTWAA values (P < 0.05). Significant correlations were also found between the MTWAA values detected in the VM and the mean and max MTWAA values over the standard (mean MTWAA: r = 0.67, $P < 10^{-7}$, Fig. 3A; max MTWAA: r = 0.55, $P < 10^{-5}$, Fig. 3B), the precordial (mean MTWAA: r = 0.65, $P < 10^{-7}$, Fig. 3C; max MTWAA: r = 0.57, $P < 10^{-5}$, Fig. 3D), and the orthogonal (mean MTWAA: r = 0.78, $P < 10^{-12}$, Fig. 3E; max MTWAA: r = 0.80, P < 10-^{13}, Fig. 3F) leads. Both mean and max MTWAA values in the standard, precordial, and orthogonal leads were significantly higher in the cases than in the controls (Table 2). Instead, the VM provided MTWAA values which did not differ significantly. Eventually, significant higher occurrences of positive TWA among cases compared to controls, associated to higher OR and better Se and Sp, were obtained only in leads V2, Y, and Z, when performing the single-lead analysis, and in all but one case (six precordial leads, mean MTWAA indexes) when performing the lead-system analysis (Table 5).

Discussion

The possible existence of an optimal lead or lead system for TWA identification has long been matter of debate[6]. Electrocardiographic TWA is a reflection of intracardiac cellular alternans, whose spatial distribution from the endocardium to

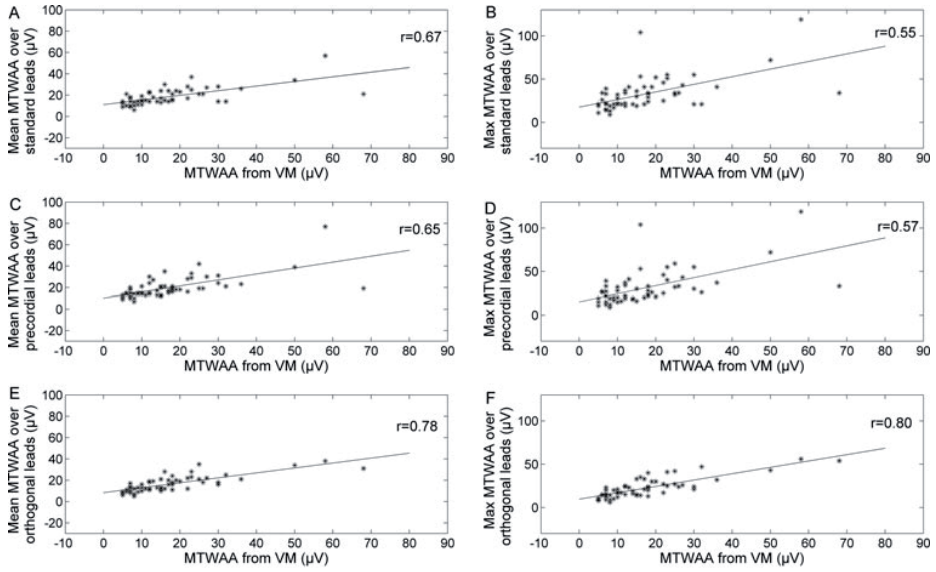

FIGURE 3. Representation of mean and max MTWAA values over the standard (panels A and B), the precordial (panels C and D) and the orthogonal (panels E and E) leads versus MTWAA from the VM (panels A and B) for 58 ICD patients (*). Correlation coefficient ('r') and regression line slope and intercept were 0.67 ($P < 10^{-7}$), 0.99, and −1.16 μV, respectively, for panel A; r = 0.55, ($P < 10^{-5}$), 0.35, and 5.79 μV, respectively, for panel B; 0.65 ($P<10^{-7}$), 0.75, and 2.32 μV, respectively, for panel C; 0.57 ($P < 10^{-5}$), 0.35, and 6.37 μV, respectively, for panel D; 0.78 ($P < 10^{-12}$), 1.32, and −4.24 μV, respectively, for panel E; and 0.80 ($P < 10^{-13}$), 0.88, and −2.34 μV, respectively, for panel F.

epicardium and from the apex to base of the heart widely varies among patients and afflicting diseases[38;41]. Consequently, the optimal lead for TWA identification is subject-dependent. Moreover, measurements from a single lead are more likely affected by noise and artifacts, which may hamper a correct TWA characterization[35]. Thus, TWA has usually been identified in more than one lead, not necessarily all belonging to the same system. During the 1990s, when the spectral method was proposed as the first automatic technique for TWA identification, the amount of computations required was significant for those years technology, so that the VM was generally used.1 The VM, indeed, has the double advantage of representing a cleaner version the orthogonal leads while requiring the same computational efforts of a single ECG lead. Later on, when computers became more powerful, more and more leads[7;20–22;27;28] have been used for TWA identification. In 2002, Bloomfield *et al.*[24] proposed to analyze all 16 leads (12 standard, three orthogonal, and a VM) independently, and to classify TWA as positive when TWA amplitude was greater or equal to 1.9 μV and, simultaneously, the alternans ratio (the spectral

method noise test) was greater or equal to three for more than a minute in any of the three orthogonal leads, or in at least two adjacent precordial leads, or in the VM. This approach, which requires the use of the spectral method as TWA identification technique, has been later on widely adopted[3,8,25,42].
In 2005, Verrier *et al.* proposed the methodological guidelines for ambulatory ECG-based TWA analysis by means of the modified moving average method[38], and indicated the unipolar precordial lead configuration as optimum. In addition, the true precordial leads were considered desirable when analyzing TWA in patients with myocardial ischemia or scar tissue, whereas limb leads as well as precordial leads were recommended for patients affected by the long QT syndrome or by other diseases that do not lead to specific regional changes in myocardial electrical properties. No specific guidelines have been previously proposed for our AMF-based TWA identification procedure[15,34].

Since both the 12 standard leads and the three orthogonal leads were conceived to provide a complete view of the heart from different angles and show excellent diagnostic agreement[43], the present study investigated if one of the two systems allows a better TWA identification by our AMF[33–35] and a better discrimination of patients at increased risk of major arrhythmic events. To this aim, exercise ECG recordings of 58 ICD patients, half of which showing VT/VF events during the follow up, were analyzed. The AMF was applied to 16-beat ECG windows, which were short enough to satisfy the heart-rate stability condition, and long enough to allow a correct filtering procedure. Eventually, the T-wave amplitude, from which TWA was hypothesized[39;40] to be dependent of, was considered as a covariate and as an index of the signal-to-noise ratio.

Analysis of the 15 single-lead TWA indexes (Table 2) highlighted some significant differences among leads. The leads showing higher TWA were also characterized by higher T-wave amplitude, but were not the most powerful in detecting significant increments of TWA among the cases. Indeed, significantly higher TWA among the cases than among the controls was only detected in leads II, V1, V2, Y, and Z, without a concomitant increase of the T-wave amplitude (Table 3). These leads, which may be considered optimal for TWA identification in the present study, are not necessarily optimal in the presence of other diseases or when using different TWA identification techniques. For example, Leino *et al.* [44], when analyzing TWA

with the modified moving average method[45] in all precordial leads from the Finnish Cardiovascular Study[46] patients, found that maximum TWAmonitored from lead V5 is the strongest predictor of cardiovascular mortality and sudden cardiac death during routine exercise testing. In a study on patients undergoing angioplasty, Nearing *et al.*[14] found that the precordial leads were superior to lead II or orthogonal leads for TWA identification by mean of the complex demodulation method[47].

The lead system TWA indexes, characterizing TWA with one TWA value for the standard leads and one TWA value for the orthogonal leads, highlighted some TWA amplitude differences between the two subgroups of ICD patients better than the single-lead TWA indexes, but did not provide insights on the spatial localization of TWA in the heart. The mean MTWAA index, previously used in[15–17], was contrasted here with the max MTWAA index, used in[12;26]. Both indexes were able to identify significantly higher TWA in the cases than in the controls (Table 2), with correlation of standard versus orthogonal being higher for the mean MTWAA ($r = 0.83$) than for the max MTWAA ($r = 0.65$). Since standard and orthogonal leads provide a different representation of the same physical phenomenon, a high correlation was expected. Still, max MTWAA may be more affected by noise, whereas mean MTWAA reduces the noise and provides a more robust TWA estimation. On the other hand, max MTWAA is more likely able to detect short and transient episodes of TWA which may be present during dynamic ECG recordings, and would remain hidden by the averaging procedure.

The existence of a significant correlation between corresponding lead-system indexes from the standard and the orthogonal leads indicates that the two lead systems can be considered equivalent for TWA identification. Use of the only precordial leads among the standard, as suggested in several studies[7;14;20–22], halved the number of computations without a significant change in the results. Eventually, the MTWAA from the VM was the only lead-system index which was not able to discriminate between cases and controls (Table 2), and provided correlation values with the mean and max MTWAA which were lower for the standard and precordial leads ($0.55 \leq r \leq 0.67$) than for the orthogonal leads ($0.78 \leq r \leq 0.80$). This may be due to the fact that the spatial orientation of the heart vector is not represented in the VM. When VM remains reasonable constant but the spatial

orientation alternates, the amplitudes in several ECG leads will alternate too, depending on the projection of the heart vector alterations on the leads.

The analysis of OR, Se, and Sp values confirmed the finding that, when analyzing TWA with the AMF, lead-system indexes should be preferred over the single-lead indexes (Table 5), the latter being only occasionally able to detect significant differences between the cases and the controls. Among the lead-system indexes, the max MTWAA was found to be superior to the mean MTWAA. Eventually, analysis over the standard leads was a little more performing than over orthogonal leads (Table 5).

In conclusion, when identifying TWA by means of the AMF-based method, TWA should be detected in all leads belonging to a system (standard or orthogonal). In our ICD population, the lead system TWA indexes provide a more reliable TWA identification than single-lead MTWAA indexes, and should be preferred for discrimination of patients at increased risk of cardiac instability. Eventually, the standard and the orthogonal leads provide equivalent TWA identification, so that TWA analysis can be limited to either one of these systems of leads.

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