

# Apicobasal gradient of left ventricular myocardial edema underlies transient T-wave inversion and QT interval prolongation (Wellens' ECG pattern) in Tako-Tsubo cardiomyopathy

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**BACKGROUND** Tako-Tsubo cardiomyopathy (TTC) presents with chest pain, ST-segment elevation followed by T-wave inversion and QT interval prolongation (Wellens' electrocardiographic [ECG] pattern), and left ventricular dysfunction, which may mimic an acute coronary syndrome.

**OBJECTIVE** To assess the pathophysiologic basis of the Wellens' ECG pattern in TTC by characterization of underlying myocardial changes by using cardiac magnetic resonance (CMR).

**METHODS** The study population included 20 consecutive patients with TTC (95% women; mean age  $65.3 \pm 10.4$  years) who underwent CMR studies both in the initial phase and after 3-month follow-up by using a protocol that included cine images, T2-weighted sequences for myocardial edema, and post-contrast sequences for late gadolinium enhancement. Quantitative ECG indices of repolarization, such as maximal amplitude of negative T waves, sum of the amplitudes of negative T waves, and maximum corrected QT interval (QTc max), were correlated to CMR findings.

**RESULTS** At the time of initial CMR study, there was a significant linear correlation between the apicobasal ratio of T2-weighted signal intensity for myocardial edema and the maximal amplitude of negative T waves ( $\rho = 0.498$ ;  $P = .02$ ), sum of the amplitudes of negative T waves ( $\rho = 0.483$ ;  $P = .03$ ), and maximum corrected QT interval ( $\rho = 0.520$ ;  $P = .02$ ). Repolarization indices were

unrelated to either late gadolinium enhancement or quantitative cine parameters. Wellens' ECG abnormalities and myocardial edema showed a parallel time course of development and resolution on initial and follow-up CMR studies.

**CONCLUSIONS** Our study results show that the ischemic-like Wellens' ECG pattern in TTC coincides and quantitatively correlates with the apicobasal gradient of myocardial edema as evidenced by using CMR. Dynamic negative T waves and QTc prolongation are likely to reflect the edema-induced transient inhomogeneity and dispersion of repolarization between apical and basal left ventricular regions.

**KEYWORDS** Tako-Tsubo cardiomyopathy; Cardiac magnetic resonance; Myocardial edema; T-wave inversion; Wellens' ECG pattern

**ABBREVIATIONS** CMR = cardiac magnetic resonance; ECG = electrocardiographic; IR = inversion recovery; LGE = late gadolinium enhancement; LV = left ventricular; NTWm = maximal voltage amplitude of negative T waves; NTWs = sum of the amplitudes of negative T waves; QTc max = maximal corrected QT interval; SD = standard deviation; SI = signal intensity; SWT = systolic wall thickening; TTC = Tako-Tsubo cardiomyopathy

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## Introduction

The Wellens' electrocardiographic (ECG) pattern, characterized by transient T-wave inversion in the anterior precordial leads and QT interval prolongation, was originally reported in the setting of acute coronary syndrome due to subocclusion of the proximal left anterior descending coronary artery.<sup>1</sup> The prognostic meaning of this ECG pattern was regarded as unfavorable because of the high incidence of

recurrent ischemic symptoms and impending acute myocardial infarction.<sup>1,2</sup> The development, dynamic changes, and resolution of the Wellens' ECG pattern was subsequently observed in a variety of other conditions, all characterized by a reversible left ventricular (LV) dysfunction (stunned myocardium), either ischemic or nonischemic, including Tako-Tsubo cardiomyopathy (TTC).<sup>3-8</sup>

TTC is a cardiovascular condition precipitated by emotional triggers that mimics acute coronary syndrome because of its acute clinical presentation with chest pain, ST-segment elevation followed by Wellens' ECG pattern, myocardial enzymatic release, and LV mid-apical wall motion abnormalities (so-called apical ballooning) in the absence of significant coronary

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artery lesions on angiography.<sup>7,8</sup> Affected patients usually survive, showing restoration of previous cardiovascular status with ECG normalization and recovery of ventricular function within approximately 1 month.<sup>7</sup>

The pathobiologic and electrogenetic mechanisms of the Wellens' ECG repolarization abnormalities in TTC remain to be elucidated. The aim of the present study was to investigate the pathophysiologic basis of the transient Wellens' ECG pattern in a consecutive series of patients with TTC by cardiac magnetic resonance (CMR) characterization of underlying myocardial tissue changes and correlation of ECG repolarization abnormalities to morphofunctional CMR findings.

## Methods

### Study population

Between September 2010 and May 2011, we prospectively studied 20 consecutive patients who were admitted at the Division of Cardiology of the University of Padua with a diagnosis of TTC according to the Mayo Clinic criteria.<sup>8</sup> Patients with atrial fibrillation and standard contraindications to both CMR and gadolinium administration were excluded.<sup>9</sup>

### Clinical evaluation

Clinical data regarding history (including coronary risk factors and possible emotional triggers), physical examination, serum troponin I level, 12-lead ECG, echocardiography, coronary angiography, and CMR were collected for each patient.

Serum troponin I levels were measured every 6 hours until a peak level was confirmed. All patients underwent  $\geq 3$  serial echocardiographic studies on admission, during hospitalization, and at 3-month follow-up to evaluate the evolving pattern of LV ballooning and systolic function over the time. On admission, all patients underwent coronary angiography and LV angiography, including at least 5 different projections of the left coronary artery and 2 of the right coronary artery. Each patient gave written informed consent to participate in the study.

### Electrocardiographic evaluation

Twelve-lead electrocardiography was performed on admission and every day until hospital discharge. The ECG was recorded with standard protocol (at the setting of 10 mm/mV, 25 mm/s) in the supine position during quiet respiration. Standard measurements included heart rate; rhythm; PR interval; QRS axis, voltage, and duration; ST-T-wave abnormalities and pathological Q waves.

The following quantitative ECG indices of ventricular repolarization were calculated: (1) maximal voltage amplitude of negative T waves (NTWm), defined as the maximum depth of negative T waves under the isoelectric line and expressed in millivolts (in leads V<sub>2</sub>-V<sub>6</sub>, L<sub>1</sub>, L<sub>2</sub>, aVL, or aVF); (2) sum of the amplitudes of negative T waves (NTWs), defined as the sum of the depth of negative T waves under the isoelectric line (excluding leads V<sub>1</sub>, aVR, and L<sub>3</sub>)<sup>10</sup>; and

(3) the maximal corrected QT interval (QTc max), defined as the prolongation of QT interval corrected for heart rate according to Bazett's formula and expressed in milliseconds.

All ECG measurements were analyzed by 2 electrophysiologists (A.Z., F.M.) blinded to clinical and CMR data. In case of disagreement, a third physician (D.C.) was consulted.

### Cardiac magnetic resonance evaluation

All patients were examined during the hospital admission and after 3-month follow-up. The cardiac magnetic resonance imaging protocol was performed as described in online Supplemental Methods and included cine images, T2-weighted sequences, first-pass perfusion, and delayed post-contrast sequences for late gadolinium enhancement (LGE) assessment. Fifteen healthy volunteers (asymptomatic, with negative family history, and no clinical evidence of heart disease) underwent CMR according to the same protocol and served as control subjects.

The presence or absence of myocardial edema was quantified and coded dichotomously (with signal intensity (SI)  $\geq 2$ SD compared with that of the skeletal muscle).<sup>11,12</sup> Myocardial edema was assessed by SI quantification accordingly to a previously reported gray-scale technique for the evaluation of tissue changes.<sup>13,14</sup>

Myocardial LGE was assessed by SI quantification as for edema evaluation. The presence or absence of myocardial LGE was coded dichotomously and LGE extent measured using SI quantification similarly to myocardial edema.

Mean SI values obtained in the initial CMR for basal, medium, and apical segments on both T2-weighted images and post-contrast sequences were compared with those recorded at follow-up and those of the reference control group.

The images of CMR were evaluated and analyzed independently by 3 observers (M.P.M., F.C., M.D.L.) blinded to clinical and procedural characteristics.

### Comparison of ECG and CMR findings

The comparison between ECG abnormalities and CMR parameters was made on the ECG tracings recorded at the time of CMR studies. Quantitative values of ECG repolarization indices (NTWm, NTWs, and QTc max) were related to findings of cine CMR sequences (systolic wall thickening [SWT] apicobasal ratio and wall motion score index), T2-weighted sequences (T2 apicobasal SI ratio, positive T2 segments, and T2 area), and T1-weighted inversion recovery (IR) post-contrast sequences (LGE apicobasal SI ratio, LGE positive segments, and LGE area).

### Statistical analysis

Continuous variables with no/mild skew were presented as mean  $\pm$  standard deviation (SD). Discrete variables were summarized as frequencies and percentages. The distribution of the data was analyzed by using the 1-sample Shapiro-Wilk test. Categorical variables were compared by using the  $\chi^2$  test or Fisher exact test as appropriate. Continuous data were

**Table 1** Clinical characteristics of the patient population (n = 20)

Characteristics	Values
Age (y)	65.3 ± 10.4
Sex: Woman	19 (95)
Clinical history	
Hypertension	14 (70)
Dyslipidemia	1
Family history of CAD	0
Current smoking	0
Diabetes mellitus	4 (20)
Depression/anxiety	8 (40)
Previous history of cancer	7 (35)
Stressful event reported	
Emotional stressor	12 (60)
Physical stressor	3 (15)
Clinical presentation	
Chest pain or discomfort	17 (85)
Dyspnea	3 (15)
Atrial fibrillation	2 (10)
Echocardiographic findings	
LV EF (%)	45 ± 8
Mitral regurgitation	12 (60)
LV hypertrophy	11 (55)
Midventricular obstruction	2 (10)
Coronary and LV angiographic findings	
LV EF (%)	40 ± 4
LV EDV (mL/m <sup>2</sup> )	72 ± 15
Dynamic LV obstruction	2 (10)
Absence of coronary artery disease	16 (80)
Nonobstructive coronary lesions (<50%)	4 (20)
Peak troponin I (μg/L)	3.2 ± 2.4
Duration of hospitalization (days)	8 ± 2

Values are given as mean ± SD and number (percentage).

CAD = coronary artery disease; EDV = end-diastolic volume; EF = ejection fraction; LV = left ventricular.

compared by using the 2-tailed paired or unpaired *t* test (for normally distributed data sets) or by using the Mann-Whitney *U* test or Wilcoxon test (for skewed variables). Bivariate correlations were assessed by using the Spearman coefficient ( $\rho$ ). A *P* value of <.05 was considered statistically significant. The intraobserver and interobserver reproducibility of CMR measurements were evaluated by using the coefficient of variation and intraclass correlation coefficient (ICC).<sup>15</sup> Data were analyzed with SPSS version 18.0 (SPSS Inc, Chicago, IL).

## Results

### Clinical characteristics

The patient population included 20 patients (19 women [95%]; mean age 65.3 ± 10.4 years) whose baseline clinical characteristics are summarized in Table 1. During a mean hospitalization of 8 ± 2 days, no deaths were observed. On admission, 2 patients presented with atrial fibrillation, which either converted spontaneously to sinus rhythm in few hours in one patient or was interrupted by electrical cardioversion on the second day in the other patient. All study patients showed sinus rhythm at the time of the initial CMR. Echocardiographic LV ejection fraction was 45% ± 8% at admission, 57% ± 6% on day 3–4, and 66% ± 5% at follow-up.

### ECG findings

Prevalence of ST-segment elevation, T-wave inversion, and abnormal Q waves on admission, at the time of the initial CMR, and during follow-up are shown in Supplemental Figure 1.

On admission, ST-segment elevation (1.5 ± 1.0 mm) was recorded in 16 (80%) patients and was associated with negative T waves in 9 (45%) (Table 2). At the time of the initial CMR (within 73 ± 6 hours), all 20 patients showed negative T waves in the precordial leads, which extended to limb leads in 15 (75%).

NTWm ranged from 0.2 to 1.7 mV (mean value 0.7 ± 0.5 mV) and was recorded in lead V<sub>4</sub> in 16 patients (80%), in lead V<sub>3</sub> in 3 (15%), and in lead V<sub>5</sub> in 1 (5%). NTWs ranged from 4 to 59 mV (mean value 23 ± 18 mV). QTc max ranged from 474 to 563 ms (mean 507 ± 43 ms).

Dynamics of negative T waves and QTc interval during the first week after symptoms onset is shown in Figure 1. In all patients, negative T waves, maximal depth of negative T wave, and maximal prolongation of QTc peaked at day 3–4 (Figure 2), decreased progressively during the following days and returned to the baseline at 3-month follow-up.

### CMR findings

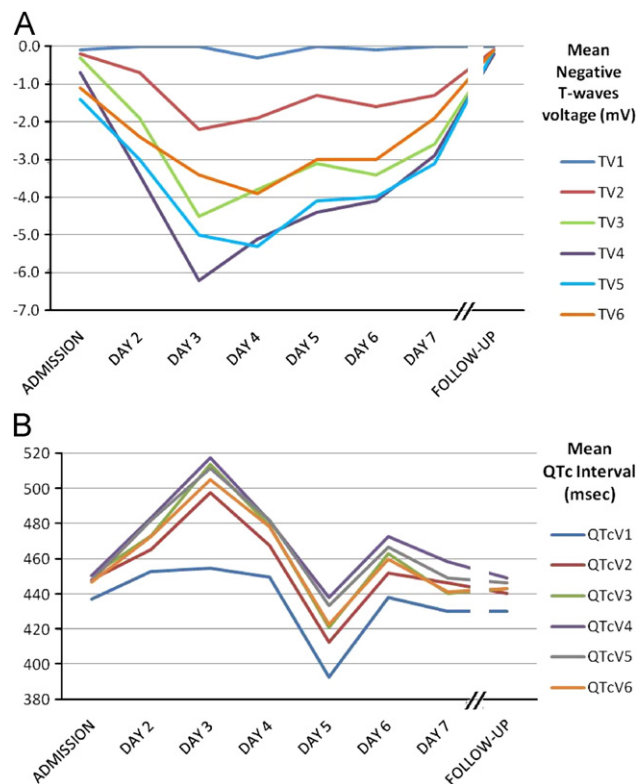
The median time delay between hospital admission and CMR was 71 ± 8 hours. The characteristics of the initial and follow-up CMR are summarized in Table 3. In the initial phase of TTC, all patients showed a reduction in ejection

**Table 2** Characteristics of ECG on admission and on initial and follow-up CMR studies

Characteristics	Admission	Initial CMR	Follow-Up
Symptoms to ECG	10.4 ± 17.6 h	73 ± 6 h	87 ± 9 days
Heart rate (beats/min)	85 ± 16	85 ± 16	85 ± 16
PR interval (ms)	152 ± 34	152 ± 34	152 ± 34
QRS duration (ms)	91 ± 16	91 ± 16	91 ± 16
QTc max (ms)	450 ± 42	507 ± 43	421 ± 29
ST-segment elevation (≥ 1 mm)	16 (80)	2 (10)	1 (5)
Maximum ST-segment elevation	1.5 ± 1.0	1.5 ± 0	1.0 ± 0
Negative T waves (≥ -1 mm)	9 (45)	20 (100)	0
Pathological Q waves	5 (25)	2 (10)	0

Values are given as mean ± SD and number (percentage).

CMR = cardiac magnetic resonance; ECG = electrocardiogram; QTc max = maximal corrected QT interval.



**Figure 1** Dynamics of negative T-wave voltage and corrected QT (QTc) interval in leads V<sub>1</sub>-V<sub>6</sub> over the first week following admission.

fraction ( $44.2\% \pm 2.6\%$ ) because of ipokinesia/akinesia of the apical and/or midventricular segments, as demonstrated by a reduced SWT (Table 3). On T2-weighted sequences, all patients showed transmural myocardial edema with the highest SI in the apical segments and lowest SI in the basal segments, with an apicobasal ratio of  $1.51 \pm 0.22$  (Table 3).

No patients showed myocardial perfusion abnormalities on first-pass sequences.

On delayed post-contrast sequences, when using an SI threshold of 5SD above the mean of remote myocardium to define significant enhancement, none of the patients had evidence of LGE. When using an SI threshold of 2SD, LGE was demonstrated in 8 patients (40%), with an apicobasal ratio of  $1.43 \pm 0.2$ .

Compared with T2-weighted images, post-contrast sequences showed fewer segments with an increased SI ( $6.0 \pm 3.9$  vs  $7.4 \pm 2.6$ ) and smaller extent of area ( $37\% \pm 12\%$  vs  $46\% \pm 13\%$ ).

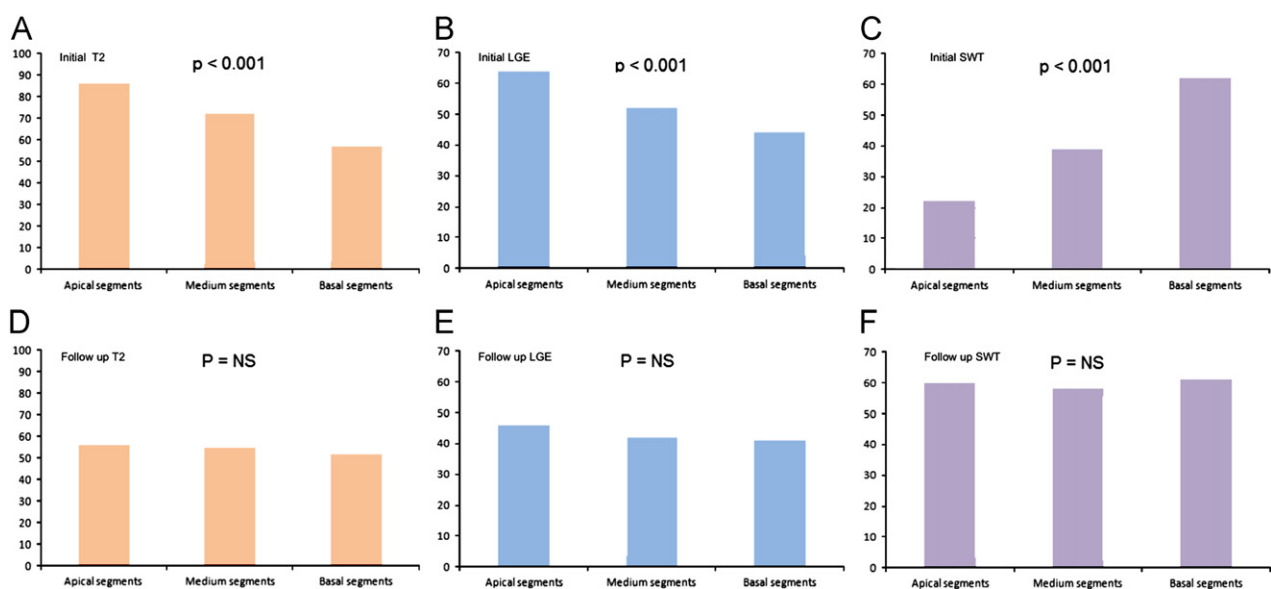
Both tissue characterization and functional parameters normalized on follow-up CMR. The SI on T2-weighted images decreased in the LV-apical segments (from  $86 \pm 19$  to  $56 \pm 11$ ;  $P < .001$ ) and in the LV-medium segments (from  $72 \pm 12$  to  $54 \pm 10$ ;  $P < .001$ ) while remained unchanged in LV-basal segments ( $57 \pm 10$  vs  $51 \pm 9$ ;  $P > .5$ ) (Figure 2A and 2D). A similar trend was found for both LGE (Figures 3B and 3E) and SWT (Figure 2C and 2F).

The SI values of T2-weighted and T1-weighted IR post-contrast sequences obtained on follow-up CMR overlap those of the control group ( $P = .4$ ). No right ventricular abnormalities were found in the initial and follow-up CMR.

The analysis of measurement variability by coefficient of variation and intraclass correlation coefficient methods showed a good inter- and intraobserver reproducibility (see online Supplemental Tables 1–4).

### Correlation between ECG and CMR findings

The analysis of ECG repolarization indices and CMR findings showed a statistically significant linear correlation



**Figure 2** Dynamics of tissue characterization and functional cardiac magnetic resonance (CMR) parameters for basal, medium, and apical left ventricular segments. The initial CMR shows a significant apicobasal gradient of signal intensity (SI) both in T2-weighted (A) and in T1-weighted inversion recovery post-contrast sequences (with SI threshold for late gadolinium enhancement [LGE]  $\geq 2SD$ ) (B) and a reverse gradient of contractility impairment expressed as systolic wall thickening (SWT) (C). All parameters normalize during follow-up (D-F).

**Table 3** Left ventricular morphofunctional features on initial and follow-up CMR studies

Characteristics	Initial CMR	Follow-Up CMR	P
Cine sequences			
LV EF (%)	44.2 ± 2.6	61.7 ± 0.5	<.001
LV EDV (mL)	93.3 ± 7.2	79.7 ± 4.7	.055
LV ESV (mL)	51.7 ± 3.5	30.3 ± 1.5	<.001
SWT (%)			
Apical	22 ± 17	60 ± 5	<.001
Medium	39 ± 15	58 ± 4	<.001
Basal	62 ± 18	61 ± 6	NS
Apicobasal ratio	0.33 ± 0.27	1.01 ± 0.06	<.001
Pericardial effusion	5 (25)	0	.047
Pleural effusion	1 (5)	0	NS
Wall motion score index	2.2 ± 0.3	3.9 ± 0.2	<.001
T2-weighted sequences (edema)			
Apical SI	86 ± 19	56 ± 11	<.001
Medium SI	72 ± 12	54 ± 10	<.001
Basal SI	57 ± 10	51 ± 9	NS
Apicobasal SI ratio	1.51 ± 0.22	1.08 ± 0.05	<.001
Segments with increased SI	7.4 ± 2.6	0	<.001
Percentage of edema area	46 ± 13	0	<.001
Post-contrast sequences (LGE)			
Apical SI	64 ± 25	46 ± 13	<.001
Medium SI	53 ± 10	42 ± 8	<.001
Basal SI	44 ± 7	41 ± 5	NS
Apicobasal SI ratio	1.43 ± 0.20	1.11 ± 0.04	<.001
Segments with increased SI	6.0 ± 3.9	0	<.001
Percentage of LGE area	37 ± 12	0	<.001
Thrombi	2 (10)	0	NS

Values are given as mean ± SD and number (percentage).

CMR = cardiac magnetic resonance; EDV = end-diastolic volume; EF = ejection fraction; ESV = end-systolic volume; LGE = late gadolinium enhancement; LV = left ventricular; SI = signal intensity; SWT = systolic wall thickening.

of the apicobasal ratio of T2-weighted SI with ECG repolarization indices such as NTWm ( $\rho = 0.498$ ;  $P = .02$ ) (Figures 3A), NTWs ( $\rho = 0.483$ ;  $P = .03$ ) (Figures 3B), and QTc max ( $\rho = 0.520$ ;  $P = .02$ ). Representative cases of relationship between T wave and myocardial edema as evidenced by T2 sequences are shown in Figure 4 and online Supplemental Figure 2.

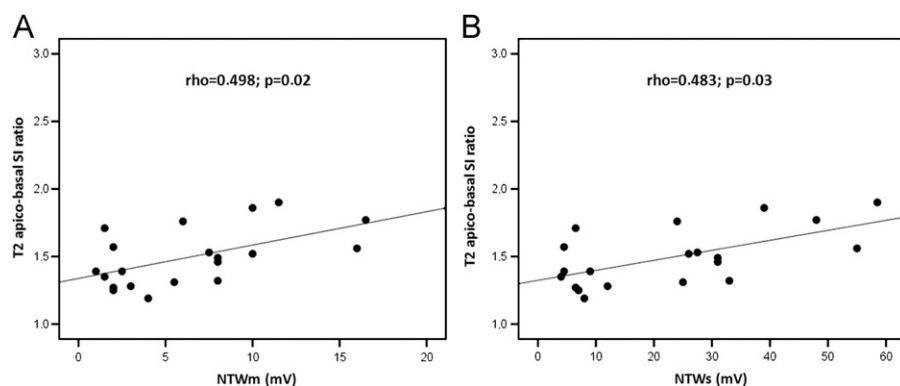
There was no statistically significant correlation between the apicobasal ratio of LGE ( $\geq 2SD$ ) on T1-weighted IR post-contrast sequences and NTWm ( $\rho = 0.376$ ;  $P = .1$ ),

NTWs ( $\rho = 0.290$ ;  $P = .215$ ), or QTc max ( $\rho = 0.280$ ;  $P = .2$ ) (Table 4).

The ECG repolarization parameters were unrelated to the apicobasal ratio of SWT, wall motion score index, and number of segments with increased T2-weighted SI.

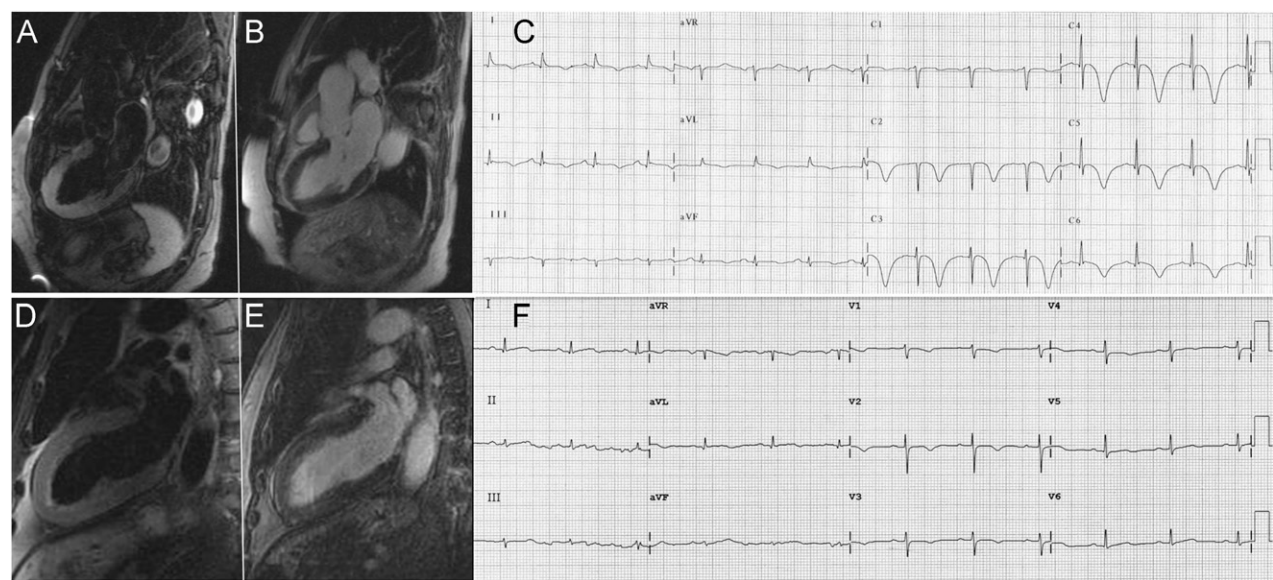
## Discussion

The present study was designed to investigate the pathophysiologic basis of Wellen's ECG pattern in TTC by using



**Figure 3** Correlation between T2 apicobasal signal intensity (SI) ratio and electrocardiographic repolarization indices, that is, the maximal amplitude of negative T waves (NTWm) (A) and the sum of amplitudes of negative T waves (NTWs) (B).





**Figure 4** Representative cases of Tako-Tsubo cardiomyopathy encompassing the spectrum of electrocardiographic repolarization abnormalities and myocardial edema. Patient 3 (*top*): Two-chamber view showing mid-apical edema with an apicobasal gradient of 1.72 in T2-weighted sequences (**A**) and late gadolinium enhancement (LGE)  $\geq 2SD$  with an apicobasal gradient of 1.59 in T1-weighted inversion recovery post-contrast sequences (**B**). Twelve-lead electrocardiogram showing deep negative T waves (NTWm = 1.3 mV, NTWs = 4.9 mV, QTc max = 590 ms) (**C**). Patient 18 (*bottom*): Two-chamber view showing mid-apical edema with an apicobasal gradient of 1.31 in T2-weighted sequences (**D**) and LGE  $\geq 2SD$  with an apicobasal gradient of 1.20 in T1-weighted inversion recovery post-contrast sequences (**E**). Twelve-lead electrocardiogram showing small negative T waves (NTWm = 0.2 mV, NTWs = 0.5 mV, QTc max = 510 ms) (**F**).

serial CMR studies. We found that (1) there was a strong correlation between quantitative ECG indices of ventricular repolarization and the degree of the apicobasal gradient of SI on T2-weighted images for myocardial edema; (2) the Wellen's ECG pattern was unrelated to either myocardial enhancement on T1-weighted IR post-contrast sequences or quantitative cine CMR parameters such as apicobasal mean SWT and wall motion index; (3) there was a parallel time course of development and resolution of ventricular repolarization abnormalities and LV myocardial edema on the initial and follow-up CMR. These findings suggest that dynamic Wellen's ECG changes of TTC reflect the underlying

asymmetric apicobasal distribution of transient LV myocardial edema.

**Previous studies on myocardial edema by CMR**  
See online Supplemental Discussion.

**Myocardial edema in TTC**  
Our results confirm those from previous clinical studies showing that myocardial edema is associated with transient LV dysfunction in TTC.<sup>16,17</sup> All our patients had an apicobasal gradient of myocardial edema as demonstrated

**Table 4** Correlation between initial CMR and ECG findings\*

	NTWm		NTWs		QTc max	
	$\rho$	$P$	$\rho$	$P$	$\rho$	$P$
Cine CMR parameters						
SWT apicobasal SI ratio	-0.022	.9	-0.033	.16	-0.412	.08
Wall motion score index	0.073	.8	-0.007	.97	0.374	.12
T2 parameters						
T2 apicobasal SI ratio	0.498	.02	0.483	.03	0.520	.02
Positive T2 segments	-0.098	.7	-0.124	.6	-0.060	.8
Area	0.034	.9	-0.024	.929	0.169	.5
LGE parameters						
LGE apicobasal SI ratio	0.376	.10	0.290	.215	0.280	.2
LGE segments	0.246	.3	0.084	.757	-0.204	.5
Area	0.347	.3	0.313	.3	0.274	.4

CMR = cardiac magnetic resonance; ECG = electrocardiographic; LGE = late gadolinium enhancement; NTWm = maximal voltage of inverted T waves observed in lead V<sub>2</sub>-V<sub>6</sub>, L<sub>1</sub>, L<sub>2</sub>, aVL, or aVF; NTWs = sum of the amplitudes of negative T waves; QTc max = maximal corrected QT interval; SI = signal intensity; SWT = systolic wall thickening.  
\*ECG recorded at the time of CMR study.

by T2-weighted myocardial hyperintensity higher in mid-apical than in basal LV segments. According to previous studies,<sup>17–19</sup> we never observed the presence of myocardial LGE on post-contrast sequences, defined as the increase of SI >5SD than that of remote myocardium; however, we found LV myocardial enhancement  $\geq 2$ SD in 8 (40%) patients. These findings are in keeping with those of the study by Rolf et al, which demonstrated in one third of patients with TTC the presence of gadolinium hyperintensity lower than that observed in myocardial infarction or acute myocarditis.<sup>19</sup> Of importance, in our study this “low-intensity” LGE showed an apicobasal distribution and disappeared on follow-up similarly to T2-weighted SI, suggesting that it was a reversible “myocardial edema-related post-contrast myocardial enhancement.” This interpretation is supported by experimental data showing that a delayed washout of gadolinium may be caused not only by permanent myocardial necrosis/fibrosis but also by increased interstitial water content such that associated with transient myocardial edema.<sup>20</sup>

### Myocardial edema and Wellens’ ECG pattern

Although the Wellens’ ECG pattern was originally related to atherosclerotic subocclusion of the left anterior descending, it was subsequently observed in other conditions characterized by a reversible LV dysfunction (stunned myocardium), by either ischemic or nonischemic causes, including TTC.<sup>3,21–23</sup> The pathophysiologic mechanism underlying the Wellens’ ECG pattern in all these conditions, whose common denominator is transient LV impaired contractility, remains to be elucidated.

Vago et al<sup>24</sup> reported transient deep T-wave inversion in the precordial leads of a 30-year-old professional soccer player who suffered a blunted chest trauma. The ECG abnormalities were associated with hypokinesia and hyperintensity enhancement of the myocardium on T2-weighted sequences for myocardial edema in the LV inferior apical septum.

Migliore et al<sup>3</sup> described 4 patients with both Wellens’ ECG pattern and reversible LV systolic dysfunction from a variety of conditions such as myocardial bridge, coronary dissection, cholecystitis, or TTC. During the initial phase, T-wave inversion and QTc interval prolongation coincided with CMR demonstration of myocardial edema; a control CMR, performed after 6–8 weeks of follow-up, showed a resolution of both ECG repolarization abnormalities and myocardial edema. Based on the coincidence of development and resolution, the hypothesis that transient myocardial edema underlies dynamic Wellens’ ECG pattern, regardless of the causative mechanism, was advanced.

The results of the present study confirm that the dynamic T-wave inversion/QT-interval prolongation and myocardial edema have a parallel time course and extend previous observations by showing that quantitative ECG indices of ventricular repolarization abnormalities (i.e., NTWm, NTWs, and QTc max) significantly correlated with the

severity of the apicobasal gradient of myocardial edema in patients with TTC. These findings provide further evidence in favor of a cause-effect relationship between LV myocardial edema and Wellens’ ECG repolarization abnormalities in TTC.

It should be recognized that our ECG-CMR correlation study demonstrated a clinical association between Wellens’ repolarization abnormalities and myocardial edema, as evidenced by the apicobasal SI gradient on T2-weighted images. The association was based on indirect evidences such as the significant correlation of magnitude of the T-wave inversion developing in the acute phase with the extent of the apicobasal ratio of T2-weighted SI as well as the parallel time course of development and resolution of ventricular repolarization abnormalities and LV myocardial edema on the initial and follow-up CMR. Further experimental electrophysiologic studies are needed to provide direct proof that local repolarization abnormalities actually exist in the edematous myocardium.

### Pathogenesis of T-wave inversion

Although the mechanism of T-wave inversion in TTC remains to be established, we can speculate that interstitial edema creates intramyocardial repolarization inhomogeneity, either transmural (i.e., between endocardial and epicardial layers) or regional (i.e., from LV apex to base). In this regard, it is noteworthy that in all patients, T-wave inversion was associated with transient prolongation of the QTc interval, which reflected a delayed and dispersed ventricular repolarization.

The potential electrogenetic role of craniocaudal asymmetry of myocardial repolarization induced by the apicobasal gradient of myocardial edema is of particular interest, given that a series of past experimental studies supported the concept of apicobasal differences in the time course of repolarization as a basis for normal T-wave morphology. In 1978, Noble and Cohen<sup>25</sup> showed that the action potential duration is longer at the “base” than at the “apex” of the sheep ventricles. The theory of “apicobasal dispersion of repolarization” underlying normal T-wave polarity dominated the medical literature until the 1990s when it was replaced by the concept of “transmural dispersion of repolarization.”<sup>26,27</sup> According to our study results, the hypothesis that myocardial edema of TTC, predominantly involving mid-apical LV regions, may transiently invert the physiologic apicobasal gradient of ventricular repolarization, accounting for diffuse inversion of T-waves, is attractive. The fact that the apicobasal repolarization inhomogeneity plays a role in the electrogenesis of the Wellens’ ECG pattern in TTC is indirectly supported by the observation that uncommon morphologic patterns of TTC, characterized by apical sparing (so-called apical sparing variants), most often are not associated with dynamic T-wave inversion, which are typically observed in the common disease form.<sup>28</sup>

It is also noteworthy that giant negative T waves observed in patients affected by the “apical” form of hypertrophic

cardiomyopathy correlate with the degree of craniocaudal asymmetry of myocardial hypertrophy, which, by analogy with TTC, may result in an apicobasal dispersion of repolarization.

<sup>10</sup>Limb leads sample across the craniocaudal axis of the heart and are more likely to detect an apicobasal dispersion of repolarization, whereas precordial leads, because of their radial direction toward the center of the heart, view the electrical field across the ventricular wall and are expected to better record transmural potential gradient. Accordingly, our findings that largest negative T waves with longest QT interval were predominantly observed in precordial leads rather than in limb leads may suggest that the transmural dispersion of repolarization can also play an important role in the electrogenesis of T-wave/QT interval abnormalities in TTC. However, no patients showed heterogeneity of the transmural (epi-endocardial) distribution of SI on T2-weighted images for myocardium edema in all LV segments at the initial phase of TTC.

## Conclusions

Our study results suggest that the apicobasal gradient of LV myocardial edema underlies the Wellens' ECG pattern occurring in the setting of TTC. Unlike irreversible lesion of myocardial infarction, which is characterized by the coexistence of hyperintensity on T2-weighted sequences and LGE on post-contrast sequences, the isolated myocardial edema observed in our patients with TTC with Wellens' ECG abnormalities predicted reversible LV dysfunction and benign outcome. The demonstration of a cause-effect relationship between myocardial edema and Wellens' repolarization abnormalities provides a key for clinical diagnosis and management of patients presenting acutely with "ischemic-like" T-wave inversion/QTc interval prolongation and LV dysfunction. In this context, CMR can provide significant diagnostic and prognostic additional values.

## Appendix A

### Supplementary Information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.hrthm.2012.09.004.

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