

# Myocardial edema underlies dynamic T-wave inversion (Wellens' ECG pattern) in patients with reversible left ventricular dysfunction

Federico Migliore, MD,\* Alessandro Zorzi, MD,\* Martina Perazzolo Marra, MD, PhD,\* Cristina Basso, MD, PhD,<sup>†</sup> Francesco Corbetti, MD,<sup>‡</sup> Manuel De Lazzari, MD,\* Giuseppe Tarantini, MD, PhD,\* Paolo Buja, MD, PhD,\* Carmelo Lacognata, MD,<sup>‡</sup> Gaetano Thiene, MD,<sup>†</sup> Domenico Corrado, MD, PhD,\* Sabino Iliceto, MD,\*

From the \*Department of Cardiac, Thoracic, and Vascular Sciences, <sup>†</sup>Department of Medico-Diagnostic Sciences and Special Therapies, and <sup>‡</sup>Department of Radiology, Padova, Italy.

**BACKGROUND** The Wellens' electrocardiogram (ECG) pattern of dynamic T-wave inversion in the anterior leads is observed in clinical conditions characterized by reversible left ventricular (LV) dysfunction (stunned myocardium), either ischemic or nonischemic. The pathophysiologic basis of this ECG pattern remains to be elucidated.

**OBJECTIVE** The purpose of this study was to report the contrast-enhanced cardiac magnetic resonance (CE-CMR) findings in 4 cases of Wellens' ECG pattern associated with transient LV dysfunction from a variety of clinical conditions such as myocardial bridge, coronary artery dissection, cholecystitis, and takotsubo syndrome.

**METHODS** All patients underwent CE-CMR at the time of acute clinical manifestations and after 6 to 8 weeks of follow-up to assess the presence and dynamics of LV myocardial changes.

**RESULTS** In all patients, the Wellens' ECG abnormalities were associated with increased signal intensity of the LV myocardium on T2-weighted sequences suggesting myocardial edema, in the

absence of late enhancement on postcontrast sequences. Repolarization abnormalities and myocardial edema had a parallel time course with persistence beyond recovery of mechanical abnormalities. T-wave inversion was associated with transient prolongation of the QTc interval in all cases.

**CONCLUSION** The study results suggest that myocardial edema rather than systolic dysfunction underlies the Wellens' ECG pattern, regardless of the causative mechanism.

**KEYWORDS** Contrast enhanced-cardiac magnetic resonance; Myocardial edema; Wellens' syndrome; T-wave inversion

**ABBREVIATIONS** CE-CMR = contrast-enhanced cardiac magnetic resonance; ECG = electrocardiogram; LAD = left anterior descending coronary artery; LGE = late gadolinium enhancement; LV = left ventricular; LVEF = left ventricular ejection fraction; TnI = troponin I

(Heart Rhythm 2011;8:1629–1634) © 2011 Heart Rhythm Society. All rights reserved.

## Introduction

Wellens' syndrome is characterized by dynamic symmetric T-wave inversion in the precordial leads and QTc prolongation (Wellens' electrocardiogram [ECG] pattern) in the setting of acute coronary syndrome caused by atherosclerotic subocclusion of the left anterior descending coronary artery (LAD). This clinical scenario was regarded as unfavorable in the prerevascularization era due to the high incidence of recurrent ischemic symptoms and impending myocardial infarction.<sup>1</sup> In the modern era, the development of transient, prominent inverted T-waves in the precordial leads after an acute coronary event has been interpreted as an ECG marker of ischemia-induced, reversible myocardial

dysfunction.<sup>2–6</sup> Moreover, the Wellens' ECG pattern has been recently described in other conditions unrelated to atherosclerotic disease of the LAD, such as takotsubo syndrome, LAD vasospasm, and intracranial bleedings.<sup>7–9</sup> The pathophysiologic basis of this ECG pattern remains to be elucidated. Contrast-enhanced cardiac magnetic resonance (CE-CMR) has recently emerged as a powerful tool that can noninvasively identify irreversible myocardial injury by late gadolinium enhancement (LGE) and myocardial inflammation by the presence of edema on T2-weighted images.<sup>10–14</sup> We report 4 cases whose common denominator was the ECG pattern of dynamic deep anterior T-wave inversion and QT interval prolongation (Wellens' pattern) associated with negligible troponin I (TnI) release and transient left ventricular (LV) dysfunction. Coronary angiography showed that this clinical syndrome was caused by a variety of conditions other than the atherosclerotic LAD subocclusion originally reported by Wellens.<sup>1</sup> All patients underwent

**Address reprint requests and correspondence:** Dr. Domenico Corrado, Department of Cardiac Thoracic and Vascular Sciences, University of Padua Medical School, Via N. Giustiniani 2 35121 Padova, Italy. E-mail address: domenico.corrado@unipd.it. (Received February 25, 2011; accepted April 30, 2011.)

CE-CMR at the time of acute clinical manifestations and after 6 to 8 weeks of follow-up to assess the presence and dynamics of ventricular myocardial changes.

Cardiac magnetic resonance was performed using a 1.5-Tesla scanner (Magnetom Avanto, Siemens Medical Solutions, Erlangen, Germany). Ventricular function was assessed by cine images that were acquired using true fast imaging with steady-state precession sequence (true FISP) cine loops in sequential short-axis and transverse long-axis views. Visualization of myocardial edema was performed using T2-weighted short tau-inversion recovery sequences. On T2-weighted images, myocardial edema was considered present when the signal intensity of the myocardium was  $>2$  SD of the mean signal intensity of the remote region or pectoral muscle.<sup>15</sup> After intravenous administration of contrast agent (gadobenate dimeglumine, Multihance, Bracco, 0.2 mmol/kg of body weight), 2-dimensional segmented fast low-angle shot inversion recovery sequences were acquired after at least 10 minutes in the same views of cine images. Late gadolinium enhancement was considered present when the signal intensity of hyperenhanced myocardium was  $>5$  SD above the mean signal intensity of remote myocardium.<sup>16</sup>

### Patient 1

A 78-year-old man was admitted for acute chest pain. The ECG on admission showed ST-segment elevation in V1-V5 leads. Repeated ECGs during the subsequent days revealed deep T-wave inversion in L1, L2, L3, aVF, and from V1 to V6 leads, in association with QTc prolongation (QTc = 510 ms) (Figure 1A). On cardiac catheterization, myocardial bridge of the second tract of LAD (Figures 2A and 2B) and apical hypokinesia with normal ejection fraction of the LV were observed. Two days after admission, CE-CMR showed no wall motion abnormalities and the presence of myocardial edema in the LV midapical anterior segments and apex by T2 weighted sequences (Figure 3A) in the absence of LGE. The peak TnI was 3.05  $\mu\text{g/l}$ . At the time of discharge (6 days after the admission), echocardiography confirmed complete resolution of the systolic dysfunction but T-wave inversion was still present on ECG. After 6 weeks of follow-up, ECG was completely normal (Figure 1E) and CE-CMR did not show myocardial edema (Figure 3E).

### Patient 2

An 86-year-old woman was admitted for acute chest pain with evidence of ST-segment elevation in V2-V3 leads. Cardiac catheterization with coronary angiography demonstrated apical LV akinesia and subocclusion of the LAD due to spontaneous dissection (Figure 2C), subsequently confirmed by coronary computed tomography (Figure 2D). The coronary dissection was successfully treated with percutaneous coronary angioplasty and stent implantation. Afterward, T-wave inversion in L1, L2, L3, aVF, and V2 to V6 leads, associated with QTc prolongation (QTc = 560 ms) did appear (Figure 1B). The peak TnI was 3.8  $\mu\text{g/l}$ . Three

days after admission, CE-CMR showed LV apical hypokinesia with myocardial edema in the LV midapical anterior, the apex, and inferior segments in the absence of LGE (Figure 3B). At discharge (7 days after the admission), inverted T-waves in precordial leads were still evident without residual echocardiographic LV systolic dysfunction, either global or segmental. After 8 weeks of follow-up, ECG did not show any repolarization abnormality (Figure 1F) and control CE-CMR revealed no edema (Figure 3F).

### Patient 3

An 81-year-old woman was admitted for acute cholecystitis. The ECG on admission showed T-wave inversion in L1, L2, L3, aVL, aVF, and V2 to V6 leads, associated with QTc prolongation (QTc = 560 ms). (Figure 1C). A mild TnI increase was observed (2.01  $\mu\text{g/l}$ ). Cardiac catheterization with coronary angiography revealed mild LV systolic dysfunction (left ventricular ejection fraction [LVEF] = 52%) with midseptal and apical hypokinesia, in the absence of coronary artery disease. A CE-CMR performed 2 days later showed no wall motion abnormalities and revealed the presence of myocardial edema in the LV midapical, inferoseptal, and anterolateral segments and in the apex without evidence of LGE, thus excluding myocardial infarction (Figure 3C). An ECG performed 7 days later showed persistent T-wave inversion with no regional systolic dysfunction at echocardiography. After 6 weeks, neither ECG repolarization abnormalities (Figure 1G) nor edema on control CE-CMR (Figure 3G) were detected.

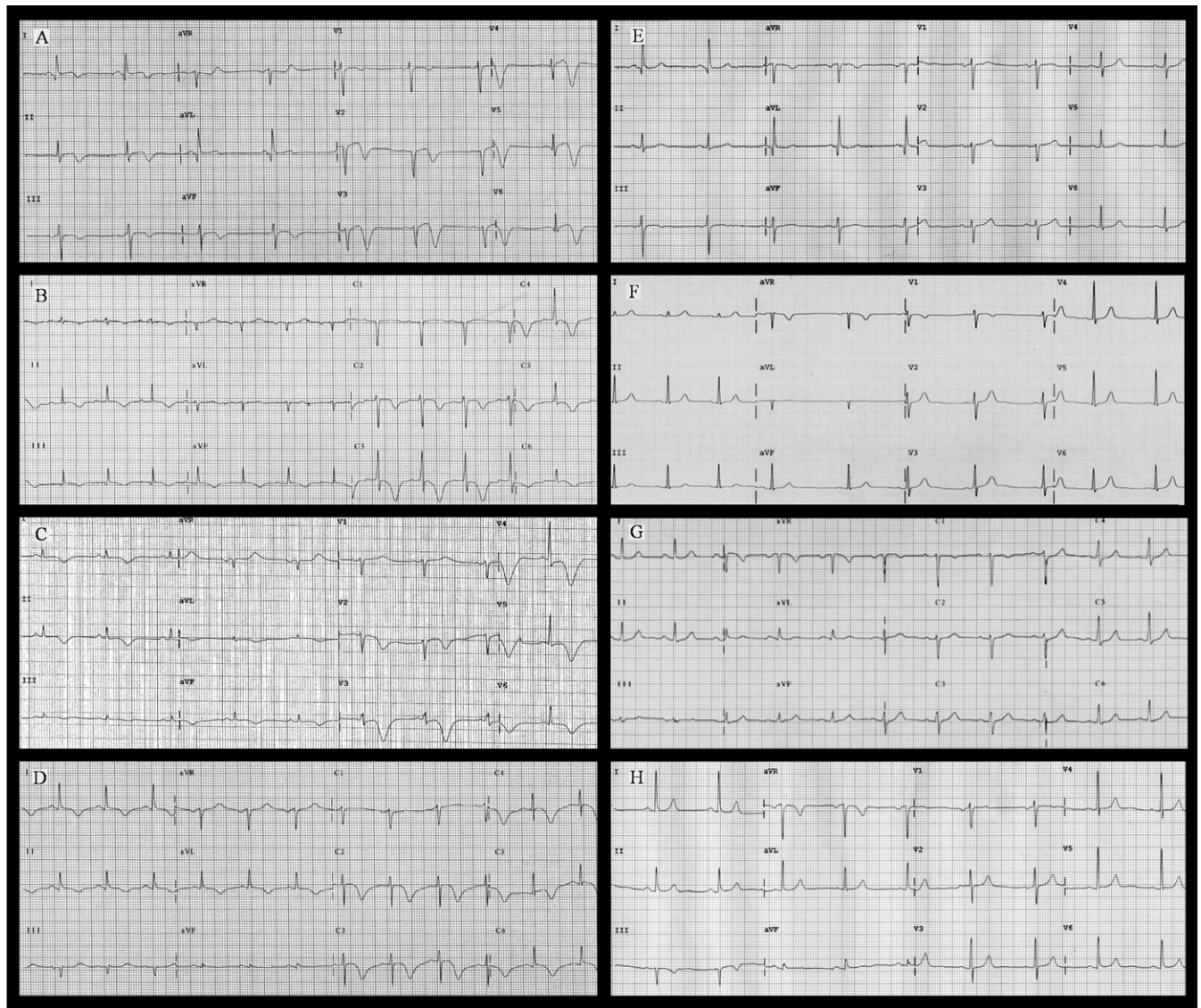
### Patient 4

A 62-year-old woman was admitted for acute chest pain associated with diaphoresis after an emotional stress. The ECG showed ST-segment elevation in V1-V6 leads. Emergent cardiac catheterization showed apical and midwall akinesia, with basal hyperkinesia and moderate LV systolic dysfunction (LVEF 45%), in the absence of coronary artery disease. A diagnosis of takotsubo syndrome was made. Over the following days, diffuse T-wave inversion with QTc prolongation (QTc = 580 ms) was observed (Figure 1D) with a peak TnI of 2.3  $\mu\text{g/l}$ . CMR performed 5 days after admission revealed LV midapical hypokinesia and mild dilatation associated with myocardial edema in the LV midapical inferoseptal and anterolateral segments and the apex without LGE (Figure 3D). Seven days later, ECG and echocardiogram demonstrated persistent negative T-wave in the presence of a normal LV global (LVEF = 57%) and regional systolic function. After 6 weeks, the ECG was completely normal (Figure 1H), and no edema was observed at CE-CMR (Figure 3H).

### Discussion

According to its original description, the Wellens' syndrome is characterized by: (1) a 12-lead ECG pattern of dynamic deep T-wave inversion usually localized in the anteroseptal leads, but occasionally extending to inferolateral leads (Wellens' ECG pattern) and (2) a subocclusion of



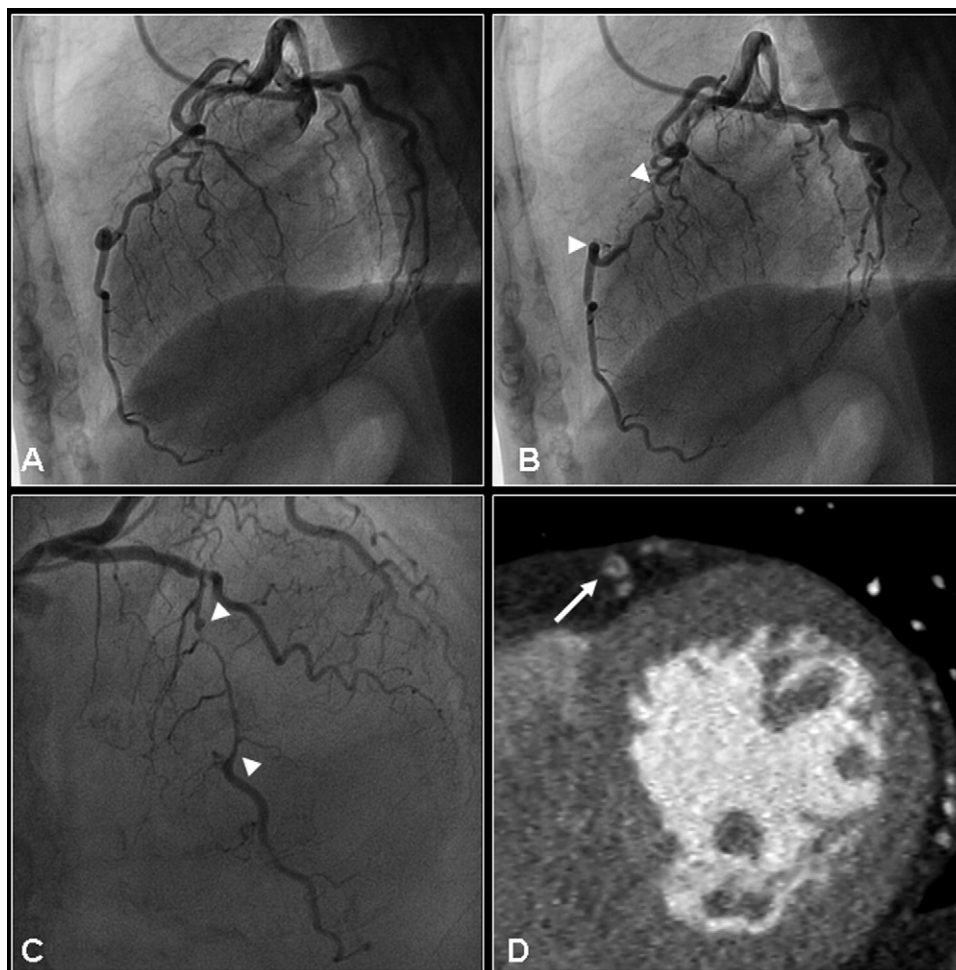


**Figure 1** Electrocardiographic findings during the acute phase (A–D) and follow-up (E–H). Twelve-lead ECG from patient 1, recorded 3 days after symptom onset, showing T-wave inversion in L1, L2, L3, aVF, and from V1 to V6 leads, in association with QTc prolongation (QTc = 510 ms). **A:** Twelve-lead ECG from patient 2, obtained 4 days after admission, showing T-wave inversion in L2, L3, aVF, and V2 to V6 leads, associated with QTc prolongation (QTc = 560 ms). **B:** Twelve-lead ECG from patient 3, on hospital admission, showing T-wave inversion in L1, L2, L3, aVL, aVF, and V2 to V6 leads, associated with QTc prolongation (QTc = 560 ms). **C:** Twelve-lead ECG from patient 4, recorded 3 days after admission, showing T-wave inversion in leads L1, L2, aVL, and V2 to V6 and QTc prolongation (QTc = 580 ms). **D:** Twelve-lead ECGs during follow-up showing complete resolution of repolarization abnormalities in all cases (E–H). ECG = electrocardiogram.

LAD.<sup>1</sup> Although the Wellens' ECG pattern was originally related to atherosclerotic subocclusion of the LAD, it was subsequently observed in other conditions characterized by a reversible LV dysfunction (stunned myocardium), by either ischemic or nonischemic causes, including takotsubo syndrome and intracranial bleeding.<sup>1,7–9</sup> However, the pathophysiologic mechanism linking the Wellens' ECG pattern and the mechanical impairment of myocardial contractility common to these conditions remains elusive. The Wellens' ECG pattern with deep T-wave inversion in the precordial leads has been recently reported in a 30-year-old professional soccer player who suffered a blunted chest trauma. The ECG abnormalities were associated with mild regional hypokinesis in the inferior region of the apical

septal segment of the LV on cine CE-CMR and increased enhancement of the myocardium, suggesting myocardial edema on T2-weighted fast suppressed short inversion recovery turbo spin echo sequences. It is noteworthy that a control CE-CMR performed at the time of disappearance of ECG repolarization abnormalities showed coincident resolution of LV wall motion abnormalities and myocardial edema.<sup>12</sup> This report prompted us to describe 4 additional patients with a Wellens' ECG pattern and reversible LV systolic dysfunction from a variety of conditions who underwent CE-CMR both at the time of acute clinical manifestations and after 6 to 8 weeks of follow-up.

Our findings confirmed and extended previous observations by showing that myocardial edema rather than systolic



**Figure 2** Cardiac catheterization and computed tomography findings. Coronary angiography of patient 1 showing a normal lumen of the middle segment of the left anterior descending coronary artery in the end-diastolic phase (A), and its dynamic compression (milking effect phenomenon) in the end-systolic phase (arrowheads) (B). Coronary angiography of patient 2 demonstrating a subocclusion of the left anterior descending coronary artery due to spontaneous dissection (arrowheads) (C), which is confirmed by coronary computed tomography showing the dissection flap with a false lumen (arrow) (D).

dysfunction underlies ECG repolarization abnormalities (Wellens' pattern), regardless of the causative mechanism: ischemic in patients 1 and 2 and nonischemic in patients 3 (cholecystitis) and 4 (takotsubo syndrome).

The mechanism underlying LV myocardium edema in patient 3 with acute cholecystitis remains speculative. In animal models, the distension of gallbladder and/or common bile duct has been associated with a reduction of coronary blood flow due to a reflexive coronary vasoconstriction.<sup>17</sup> On the other hand, intensive pain resulting from acute cholecystitis could be a trigger of a takotsubo cardiomyopathy, through activation of the sympathoadrenergic system.<sup>18</sup>

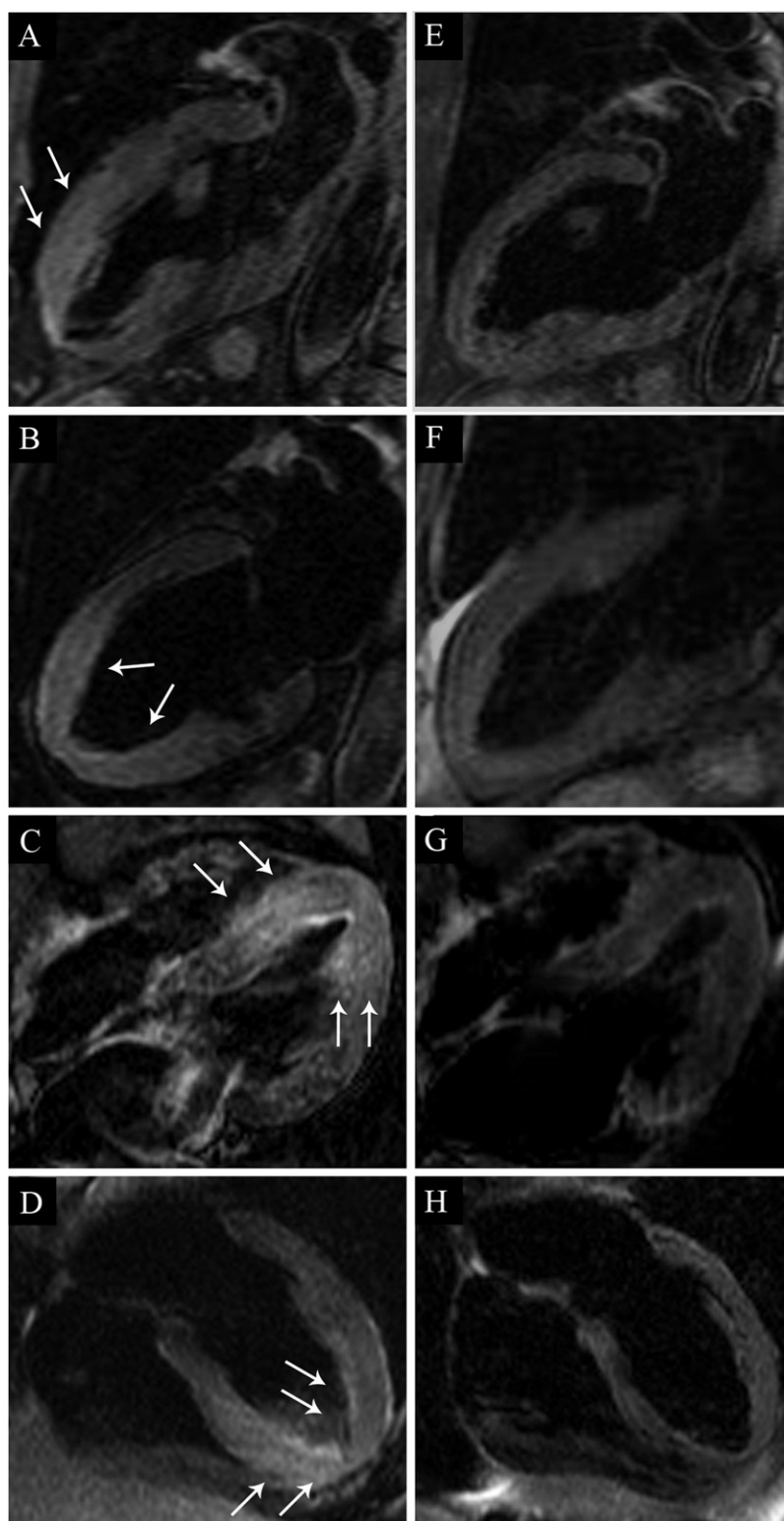
The analysis of T-wave inversion, transient LV myocardial dysfunction, and myocardial edema dynamics showed that repolarization abnormalities and myocardial edema had a parallel time course with their persistence beyond recovery of mechanical abnormalities. The small number of study patients did not allow assessment of a correlation between amount of LV myocardium edema and extent of T-wave inversion.

At 6 to 8 weeks of follow-up, all patients were asymptomatic with complete resolution of ECG repolarization abnormalities, and edema was no longer present on control CE-CMR.

These findings offer an alternative explanation to the traditional concept that Wellens' pattern is the result of reversible LV wall motion abnormalities<sup>2-6</sup> by suggesting a previously unrecognized cause-effect relationship between repolarization abnormalities and LV myocardial edema. Although the underlying pathophysiological mechanism remains to be established, we can speculate that interstitial edema creates intramyocardial repolarization inhomogeneity, either transmural (between endocardial and epicardial layers) or regional (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 ventricular repolarization.

Our results provide a new and unifying pathogenetic hypothesis of the Wellens' ECG pattern occurring in the setting of different clinical conditions all characterized by transient myocardial edema and may have significant im-





**Figure 3** Cardiac magnetic resonance T2-weighted sequences for myocardial edema during acute phase (A–D) and follow-up (E–H). Two-chamber view from patient 1 showing myocardial edema in the left ventricular midapical anterior segments and the apex (arrows) (A). Two-chamber view from patient 2 showing myocardial edema in the left ventricular midapical anterior, the apex, and inferior segments (arrows) (B). Four-chamber view from patient 3 showing myocardial edema in the left ventricular midapical inferoseptal and anterolateral segments and the apex (arrows) (C). Four-chamber view from patient 4 showing myocardial edema in the left ventricular midapical inferoseptal and anterolateral segments and the apex (arrows) (D). T2-weighted sequences on CE-CMR follow-up showing disappearance of left ventricular myocardium edema in all cases (E–H). CE-CMR = contrast-enhanced cardiac magnetic resonance.

plications for focused management strategies, including anti-inflammatory therapy.

Unlike irreversible myocardial lesion of myocardial infarction, which is characterized by the coexistence of hyperintensity on T2-weighted and LGE sequences,<sup>14</sup> reversible myocardial damage in our patients with transient LV dysfunction and T-wave inversion manifested as isolated myocardial edema in the absence of LGE. Although this finding suggests that CE-CMR may be of both diagnostic and prognostic value in patients with T-wave inversion, its accuracy in predicting patient clinical outcome remains to be evaluated by larger studies.

## References

- De Zwaan C, Bar FW, Wellens HJ. Characteristic electrocardiographic pattern indicating a critical stenosis high in left anterior descending coronary artery in patients admitted because of impending myocardial infarction. *Am Heart J* 1982;103:730–736.
- Braunwald E, Kloner RA. The stunned myocardium: prolonged, postischemic ventricular dysfunction. *Circulation* 1982;66:146–149.
- Renkin J, Wijns W, Ladha Z, Col J. Reversal of segmental hypokinesia by coronary angioplasty in patients with unstable angina, persistent T wave inversion and left anterior descending coronary artery stenosis. Additional evidence for myocardial stunning in humans. *Circulation* 1990;82:913–921.
- Hirota Y, Kita Y, Tsuji R, et al. Prominent negative T waves with QT prolongation indicate reperfusion injury and myocardial stunning. *J Cardiol* 1992;22:325–340.
- Agetsuma H, Hirai M, Hirayama H, et al. Transient giant negative T wave in acute myocardial infarction predicts R wave recovery and preservation of left ventricular function. *Heart* 1996;75:229–234.
- Sgarbossa EB, Meyer PM, Pinski SL, et al. Negative T waves shortly after ST-elevation acute myocardial infarction are a powerful marker for improved survival rate. *Am Heart J* 2000;140:385–394.
- Kurisu S, Inoue I, Kawagoe T, et al. Time course of electrocardiographic changes in patients with takotsubo syndrome. Comparison with acute myocardial infarction with minimal enzymatic release. *Circ J* 2004;68:77–81.
- Pascale P, Quartenoud B, Stauffer JC. Isolated large inverted T wave in pulmonary edema due to hypertensive crisis: a novel electrocardiographic phenomenon mimicking ischemia? *Clin Res Cardiol* 2007;96:288–294.
- Sclarovsky S, Nikus K. The electrocardiographic paradox of takotsubo cardiomyopathy comparison with acute ischemic syndrome and consideration of molecular biology and electrophysiology to understand the electrical-mechanical mismatching. *J Electrocardiol* 2010;43:173–176.
- Raman SV, Simonetti OP, Winner MW 3rd, Dickerson JA, He X, Mazzaferri EL Jr, Ambrosio G. Cardiac magnetic resonance with edema imaging identifies myocardium at risk and predicts worse outcome in patients with non-ST segment elevation acute coronary syndrome. *J Am Coll Cardiol* 2010;55:2480–2488.
- Bucciarelli-Ducci C, Denes P, Holly TA, Wu E. Pseudo Wellens T-waves in patients with suspected myocardial infarction: how cardiac magnetic resonance imaging can help the diagnosis. *Int J Cardiol* 2008;128:68–71.
- Vago H, Toth A, Apor A, Maurovich-Horvat P, Toth M, Merkely B. Cardiac contusion in a professional soccer player: visualization of acute and late pathological changes in the myocardium with magnetic resonance imaging. *Circulation* 2010;121:2456–2461.
- Tarantini G, Ramondo A, Iliceto S. Aborted myocardial infarction: a clinical-magnetic resonance correlation. *Heart* 2005;91:24–25.
- Perazzolo Marra M, Lima JA, Iliceto S. MRI in acute myocardial infarction. *Eur Heart J* 2011;32:284–293.
- Masci P, Ganame P, Strata E, et al. Myocardial salvage by CMR correlates with LV remodelling and early ST-Segment resolution in acute myocardial infarction. *J Am Coll Cardiol Img* 2010;3:45–51.
- Bondarenko O, Beek AM, Hofman MB, et al. Standardizing the definition of hyperenhancement in the quantitative assessment of infarct size and myocardial viability using delayed contrast-enhanced CMR. *J Cardiovasc Magn Reson* 2005;7:481–485.
- Molinari C, Grossini E, Mary DASG, Vacca G. Effect of distension of the gallbladder on plasma renin activity in anesthetized pigs. *Circulation* 2000;101:2539–2545.
- Nef HM, Möllmann H, Hilpert P, et al. Sympathoadrenergic overstimulation in takotsubo cardiomyopathy triggered by physical and emotional stress. *Int J Cardiol* 2008;130:266–268.