Cardiac and non-cardiac causes of T-wave inversion in the precordial leads in adult subjects: A Dutch case series and review of the literature

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Abstract

AIM: To describe the electrocardiographic (ECG) phenomena characterized by T-wave inversion in the precordial leads in adults and to highlight its differential diagnosis.

METHODS: A retrospective chart review of 8 adult patients who were admitted with ECG T-wave inversion in the anterior chest leads with or without prolongation of corrected QT (QTc) interval. They had different clinical conditions. Each patient underwent appropriate clinical assessment including investigation for myocardial involvement. Single and multimodality non-invasive, semi-invasive and invasive diagnostic approach were used to ascertain the diagnosis. The diagnostic assessment included biochemical investigation, cardiac and abdominal ultrasound, cerebral and chest computed tomography, nuclear medicine and coronary angiography.

RESULTS: Eight adult subjects (5 females) with a mean age of 66 years (range 51 to 82) are analyzed. The etiology of T-wave inversion in the precordial leads were diverse. On admission, all patients had normal blood pressure and the ECG showed sinus rhythm. Five patients showed marked prolongation of the QTc interval. The longest QTc interval (639 ms) was found in the patient with pheochromocytoma. Giant T-wave inversion (≥ 10 mm) was found in pheochromocytoma followed by electroconvulsive therapy and finally ischemic heart disease. The deepest T-wave was measured in lead V3 (5 ×). In 3 patients presented with mild T-wave inversion (patients 1, 5 and 4 mm), the QTc interval was not prolonged (432, 409 and 424 msec), respectively.

CONCLUSION: T-wave inversion associated with or without QTc prolongation requires meticulous history taking, physical examination and tailored diagnostic approach.
modalities to reach rapid and correct diagnosis to establish appropriate therapeutic intervention.

**Key words**: T-wave inversion; Coronary angiography; Pulmonary computed tomography angiography; Magnetic resonance imaging; Differential diagnosis

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Core tip: Myriad of clinical conditions have been described in association with T-wave inversion in the anterior precordial leads. T-wave inversion associated with or without corrected QT prolongation may be encountered in a variety of clinical conditions. In the reversible (dynamic) types such as vascular coronary, cerebral and pulmonary disorders; metabolic disturbances and acute adrenergic stress cardiomyopathy; resolution of T-wave inversion may occur after days, weeks, months or years following the index event. Tailored diagnostic approach should be conducted avoiding overuse of diagnostic methods. Specific tailored therapeutic interventions were undertaken when high index of clinical suspicion was raised towards certain disease entity.


**INTRODUCTION**

T-wave inversion is found in 1% of patients admitted to the coronary care unit[1] and in 14% of patients presented with unstable angina[2]. It has been stated that T-wave inversion in right precordial leads is relatively rare (0.5%) in the general population and not associated with adverse outcome[3]. The tendency to inversion of T-wave declines with increasing age. Normally in females, the T-wave in V₃ may be shallowly inverted. But in adult males, it is considered pathologic if the T-wave is inverted in V₃ or V₄[4]. The T-wave in V₃ may be inverted normally at any age and in V₃ it is sometimes normally negative[5].

Generally, the T-waves are negative in leads aVR, V₁ and V₃. Giant T-wave inversion in the precordial leads are seen in different pathologies, such as anterior myocardial wall ischemia in patients with acute coronary syndrome, apical hypertrophic cardiomyopathy, cerebral and pulmonary disorders and post-pacing or tachycardia states.

The definite diagnosis in the presence of inverted T-wave can usually be assessed by meticulous history taking including family history of sudden cardiac death or arrhythmias, physical examination as well as appropriate non-invasive, semi-invasive or invasive diagnostic investigations. This current review, will focus on T-wave inversion in the anterior chest wall leads and discuss its differential diagnosis with emphasis on the non-coronary non-cardiac disorders.

Diagnostic approach should be tailored according to the clinical presentation, medical and family history. We present a Dutch case series of eight patients with T-wave inversion in the precordial leads due to different etiologies and the literature is briefly reviewed.

**MATERIALS AND METHODS**

The study was reviewed and approved by the Hospital Group Twente, Institutional Review Board. All study participants provided verbal informed consent.

Eight representative adult patients were identified and evaluated. In all patients, physical examination, electrocardiography and transthoracic echocardiography (TTE) were routinely performed. When necessary for adequate clarification of the clinical presentation, tailored diagnostic methods were undertaken in the individual patient at the clinician’s discretion (TTE, n = 8; coronary angiography “coronary angiography (CAG),” n = 7; magnetic resonance imaging “magnetic resonance imaging (MRI),” n = 3; perfusion-ventilation scan, n = 2; computed tomography “computed tomography (CT) abdomen, n = 1; CT brain, n = 1; CT thoracic aorta, n = 1; Iodine-metaiodobenzylguanidine (MIBG) scan, n = 1 and DOPA- positron emission tomography (PET), n = 1].

**Diagnostic criteria**

The diagnostic criteria included presentation with T-wave inversion in the anterior chest leads on the admission ECG.

**Definitions**

**Electrocardiography**: The admission ECGs were analyzed using standard criteria for measurements of T-wave axis, T-wave amplitude and QT interval. ECGs were analyzed for the presence of Left ventricular hypertrophy (LVH) using the Sokolow criteria[6].

**T-wave negativity**: was defined as a voltage of giant negative T-wave ≥ 10 mm in any of the leads[7-9], deep ≥ 5 mm[8] and mild 1-3 mm[9].

**Corrected QT prolongation**: Corrected QT (QTc) interval for heart rate was performed in V₃ and was defined as QTc > 450 msec. according to Bazett[10] and Ahnve[11].

Measured serum biomarkers were creatine kinase and cardiac troponin T.
Transthoracic echocardiography: Left ventricular (LV) wall thickness as well as septal thickness were measured according to the established standards and guidelines of the American College of Cardiology/American Heart Association/European Society of Cardiology. LVH was defined as a LV wall thickness > 13 mm.

Radionuclide studies: Radionuclide imaging and positron emission tomography: One patient (patient 7) underwent $^{123}$I-MIBG and dihydroxyphenylalanine-Positron Emission tomography (DOPA-PET) scanning. In 2 patients, pulmonary perfusion/ventilation scintigraphy were performed.

Computed tomography: Abdominal, cerebral and thoracic aorta CT scanning were performed in one patient each. Pulmonary computed tomography angiography (PCTA) was performed in one patient. Coronary angiography contrast angiography was performed in standard views via the femoral approach.

Follow-up: Follow-up was obtained by direct contact with patients, their physicians or by chart review.

Statistical analysis
No statistical data are available.

RESULTS
A total of 8 adult patients presented with chest pain and negative T-wave in the anterior chest wall leads on the admission ECG were identified (Figures 1-8).

Clinical features
On presentation, the blood pressure was normal in all patients and all were in sinus rhythm (Table 1). Cerebral pathology was excluded by the absence of neurological signs. No neurological deficits were found.

All patients had on physical examination no neurological abnormalities. One patient known with a previous transient ischemic attack showed a complete recovery. Of the 8 patients, one presented with normal rest ECG, three with chest pain, one with palpitation, one with fatigue, one with left abdominal pain and psychomotor agitation and one with out-of-hospital cardiac arrest (OHCA).

None of the patients, except one (patient 8)
Corrected QT prolongation
Corrected QT prolongation defined as QTc > 450 msec. measured in lead V2. The corrected QT interval exceeded 450 ms in 5 (452-639) with a mean of 530 ms and it was not prolonged in 3 (409, 424 and 432 ms) of the patients. The amplitude of the inverted T-wave varied significantly with the maximum negative T-wave amplitude ranging from one to 20 mm. A gradual complete resolution of the T-wave inversion and QT prolongation occurred in 5 of the patients.

Other ECG findings were as follow: two patients (patients 2 and 3) showed first degree AV block, one patient (patient 8) revealed microvolt in the standard and limb leads, negative T wave in I and
aVL in 2 patients (patients 4 and 7), negative T wave in leads I, II, III, aVL and aVF in (patients 1 and 3), negative T wave in II, III and aVF without (patient 5) or with (patient 6) ST segment depression.

**Serum biomarkers**
Cardiac troponin T were assessed. Myocardial infarction was ruled out in 7 patients. One (patient 2) with non ST elevation myocardial infarction (NSTEMI) showed typical biomarker rise and fall course with markedly elevation of troponin level. Mild elevation of troponin value was found in 4 patients (patients 3, 4, 5 and 7). No elevation was detected in 3 patients (patients 1, 6 and 8).
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**Figure 6** Patient 6. An electrocardiographic (ECG) tracing, showing voltage criteria for left ventricular hypertrophy with ST depression and negative T wave in the precordial and inferior leads V3-6, of a 52-year female patient with non-obstructive hypertrophic cardiomyopathy (thickness of septum 20 mm and posterior wall of 24 mm without septal anterior movement or obstruction of outflow tract). Normal coronary arteries were found on coronary angiography. She refused genetic counseling and invasive intervention. She was treated medically with beta blocker.

**Figure 7** Patient 7. A: An electrocardiographic (ECG) tracing, showing giant T wave inversion in the precordial leads V2-6, of a 76-year Caucasian male with a past medical history of an old inferior myocardial infarction, percutaneous coronary intervention of the right coronary artery (RCA) and left anterior descending coronary artery, acutely presented with left abdominal pain, psychomotor unrest, diaphoresis and blood pressure difference between the right and left arm. Acute aortic dissection was excluded as well as recurrent MI. Coronary angiography frame of (B) the left coronary artery and (C) the RCA depicting no significant stenosis of the arterial tree. Serum cardiac markers were slightly elevated. Echocardiographic (hypokinesia of the mid and apical regions and hyperkinesia of the basal segments) findings and (D) ventriculography (apical ballooning) were all compatible with Takotsubo cardiomyopathy; E: Base line ECG. The abdominal ultrasound and (F) CT demonstrated a pheochromocytoma in the left adrenal region which was confirmed with 123I-MIBG scan and dihydroxyphenylalanine-Positron Emission tomography and proved by pathological results. Plasma and urine metanephrin and normetanephrin were highly elevated. After removal of the hormonally active tumor, the patient became symptom free and the ECG normalized. The medical treatment continued including calcium reentry blocker, beta blocker, aspirin, angiotensin converting enzyme inhibitor, statin and an α-blocker.
Pulmonary computed tomography angiography

Abdominal CT scan was performed in one patient (patient 7). Tailored individual diagnostic investigation was performed. In 2 patients (patients 3 and 4), pulmonary perfusion/ventilation scintigraphy were performed and pulmonary embolism was ruled out.

Computed tomography

Abdominal CT scan was performed in one which revealed an abdominal mass in the left adrenal region, a CT scan of the thoracic aorta excluding acute aortic dissection (patient 7) and brain CT scan in another (patient 4) showing mild atrophy and minimal ischemic changes.

Radionuclide imaging and positron emission tomography

One patient (patient 7) underwent $^{123}$I-MIBG scan and DOPA-PET scanning. This revealed MIBG uptake in the left adrenal region and a solitary lesion was detected at the left adrenal area with central necrosis.
with DOPA-PET scanning.

**Coronary angiography**
Seven patients underwent selective contrast angiography which revealed non-obstructive coronary artery disease in one patient and normal coronary arterial tree in 6 patients.

**Follow-up:** Follow-up was obtained by direct contact with patients, general practitioner, their physicians or by chart review.

**DISCUSSION**
In middle-aged subjects, T-wave inversion in the precordial leads is relatively rare in the general population occurring in 0.5% (54/10899) of the subjects. T-wave inversion in the anterior chest wall leads is relatively common in children and adolescents but infrequently found in healthy adults and is considered as "normal variants". This pattern is more common in young females and young adults (1%-3%) (14,15). The prevalence was associated with gender difference, which was higher (0.9%) in women than in men (0.1%) (31).

**Primary and secondary T-wave abnormalities**
Primary T-wave abnormalities (ischemia or injury) are due to alterations in myocardial cellular electrophysiology and secondary T-wave abnormalities

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**Table 1 Demographic features, clinical presentations, diagnostic modalities and management**

<table>
<thead>
<tr>
<th>Case/ gender/ age</th>
<th>Clinical presentation</th>
<th>ECG (5R) T-wave inversion</th>
<th>QTc (msec)</th>
<th>Associated disorders</th>
<th>TTE</th>
<th>Diagnostic modalities</th>
<th>Management</th>
<th>Condition</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-F51</td>
<td>Palpitation</td>
<td>15 mm in V2-6</td>
<td>452</td>
<td>AVNRT Depression</td>
<td>TTE</td>
<td>CAG</td>
<td>MM</td>
<td>Post-ECT, TTC (electrical stress)</td>
</tr>
<tr>
<td>2-F82</td>
<td>Chest pain</td>
<td>10 mm in V2-6</td>
<td>484</td>
<td>Mild AS PG 18 mmHg</td>
<td>TTE</td>
<td>MM</td>
<td>NSTEMI</td>
<td></td>
</tr>
<tr>
<td>3-F72</td>
<td>Abnormal rest ECG</td>
<td>5 mm in V1-4</td>
<td>553</td>
<td>PAF 2011</td>
<td>TTE</td>
<td>CAG, MRI</td>
<td>MM</td>
<td>TTC (emotional stress, spouse died 2 wk earlier)</td>
</tr>
<tr>
<td>4-F69</td>
<td>Inter-scapular pain</td>
<td>9 mm in V2-6</td>
<td>520</td>
<td>TIA 2010</td>
<td>TTE</td>
<td>MM</td>
<td>Undetermined</td>
<td></td>
</tr>
<tr>
<td>5-M55</td>
<td>Chest pain</td>
<td>1 mm in V1-3</td>
<td>432</td>
<td>Dilated hypokinesis</td>
<td>TTE</td>
<td>CAG</td>
<td>MM</td>
<td>Pulmonary embolism</td>
</tr>
<tr>
<td>6-F52</td>
<td>Fatigue</td>
<td>5 mm in V1-4</td>
<td>409</td>
<td>-</td>
<td>TTE</td>
<td>CAG</td>
<td>MM</td>
<td>HCM</td>
</tr>
<tr>
<td>7-M76</td>
<td>Left abdominal pain</td>
<td>20 mm in V1-4</td>
<td>639</td>
<td>IMI 1990</td>
<td>TTE</td>
<td>Apical hypokinesis</td>
<td>MM</td>
<td>TTC, (Pheochromocytoma)</td>
</tr>
<tr>
<td></td>
<td>and psychomotor</td>
<td></td>
<td></td>
<td>PCI RCA 1990 and 2004</td>
<td>CAG</td>
<td>CT thoracic aorta</td>
<td>MM, AAD</td>
<td>Refused ICD implantation</td>
</tr>
<tr>
<td></td>
<td>agitation</td>
<td></td>
<td></td>
<td>PCI LAD 1991</td>
<td></td>
<td>Ultrasound abdomen</td>
<td></td>
<td>Advise to refrain from strenuous exercise</td>
</tr>
<tr>
<td>8-M73</td>
<td>VF, OHCA</td>
<td>Epsilon V3-4 mm in V1-6</td>
<td>424</td>
<td>Negative family history</td>
<td>TTE</td>
<td>Apical hypokinesis</td>
<td>MM</td>
<td>ARVC/D</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>RV dilatation</td>
<td>CAG</td>
<td>Genetic counseling</td>
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</tbody>
</table>

AAD: Antiarrhythmic drug; ARVC/D: Arrhythmogenic right ventricular cardiomyopathy/dysplasia; AS: Aortic valvular stenosis; AVNRT: Atrioventricular nodal reentry tachycardia; BB: Beta blocker; CAD: Coronary artery disease; CAG: Coronary angiography; ECT: Electroconvulsive therapy; MM: Medical management; CRB: Calcium reentry blocker; CT: Computed tomography; ePAP: Estimated pulmonary artery pressure; F: Female; HCM: Hypertrophic cardiomyopathy; IMI: Inferior myocardial infarction; LAD: Left anterior descending coronary artery; LVH: Left ventricular hypertrophy; M: Male; MRI: Magnetic resonance imaging; NSTEMI: Non ST elevation myocardial infarction; OHCA: Out of hospital cardiac arrest; PAF: Persistent atrial fibrillation; PCI: Percutaneous coronary intervention; PCTA: Pulmonary computed tomography angiography; PET-CT: Positron emission tomography-computed tomography; PG: Peak gradient; PV scan: Perfusion-ventilation scan; RCA: Right coronary artery; RV: Right ventricle; SR: Sinus rhythm; TIA: Transient ischemic attack; TTC: Takotsubo cardiomyopathy; TTE: Transthoracic echocardiography; VF: Ventricular fibrillation; ECG: Electrocardiographic.
(bundle branch block or ventricular hypertrophy) are subsequent to alterations of sequence of ventricular activation.

**Differential diagnosis of T-wave inversion**

In the 1960s of last century, Jacobson and Schrire described the differential diagnosis of T-wave inversion that included heart block, ischemic heart disease, bradycardia, right ventricular hypertrophy, right bundle branch block, metabolic disturbances, changes during diagnostic coronary angiography and cerebral disturbances[40]. Nowadays, the current differential diagnosis of T-waves inversion has expanded including, besides the abovementioned citations of Jacobson and Schrire, LV anterior wall ischemia, acute central nervous system disorders, acute adrenergic stress (Takotsubo cardiomyopathy “TTC”)[17,18], pulmonary edema[19,20], antihypertensive drug effects[21], pulmonary embolism[22], cardiac memory secondary to transient tachycardia[8], post-ventricular pacing states[23], idiopathic[24] or in relation to cocaine use[25,26]. In a recent review, reversible or permanent inverted T-waves were found in 38% of patients with congenital coronary artery-ventricular multiple micro-fistulas (MMFs)[27]. Hence, congenital MMFs may be included in the differential diagnosis of anterior chest wall T-wave inversion.

**Transient and permanent T-wave inversion**

Transient T-wave inversion may occur in the following conditions: Acute coronary syndrome[1], cardiac memory T-wave inversion[8,21], cardiogenic non-ischemic pulmonary edema[19], gastroenteritis[28], post-maxillofacial surgery[29], subarachnoid hemorrhage[30], electroconvulsive therapy[31,33], Takotsubo cardiomyopathy[18,34], pheochromocytoma[35] and indeterminate origin[25]. On the other hand, permanent T-wave inversion may accompany a variety of disorders associated with LV or RV cardiomyopathy such as apical hypertrophic cardiomyopathy (AHCMD)[4,7,36,37] and arrhythmogenic right ventricular cardiomyopathy/ dysplasia[38-41].

**Non-coronary cardiac and non-cardiac disorders**

Several non-coronary cardiac and non-cardiac disorders have been associated with the development of T-wave inversion. Among the Non-coronary cardiac disorders: are pericarditis, myocarditis, cardiac metastasis, athletic heart syndrome, AhCM[41], hypertrophic cardiomyopathy[37], post-tachycardia and right ventricular pacing (cardiac memory)[8,23].

**Prognosis**

In the middle-aged population, inverted T-wave in the right precordial leads V1-3 was associated with good prognosis in contrast to inverted T-wave in leads other than V1-3 which predicted adverse outcomes such as increased risk of hospitalization due to congestive heart failure and coronary artery disease[31]. Fisch et al[42], stated that inverted shallow asymmetric T-wave with the descending limb longer than the abruptly ascending limb seen in middle-aged women are not associated with cardiac disease.

**Non-coronary non-cardiac disorders**

Non-coronary non-cardiac disorders (T-wave wide asymmetric and associated with prolonged QT interval) include severe brain injury (subarachnoid hemorrhage “SAH”, intracranial hemorrhage)[30,43], traumatic head injury, maxillofacial surgery[29], bilateral carotid endarterectomy, after vagotomy, cocaine abuse[44], flecainide use[21], pheochromocytoma[45] and gastrointestinal emergencies (perforated ulcer, acute pancreatitis and acute cholecystitis)[38,46-49].

**Transient T-wave inversion**

Acute coronary syndrome[41]: T-wave inversion in the precordial leads have been reported since 1982 as narrow, sharp, and symmetrical waves; the so called “coronary type” reflecting high-grade stenosis of the proximal left anterior descending coronary artery due to regional delay in ventricular repolarization as generally found in ischemic heart disease[50,51]. In this condition, T-wave inversion may persist for days or weeks.

Cardiac memory pattern: Memory T wave was first presented by Chatterjee et al[42], in 1969 in 94% of patients with intermittent right ventricular pacing. Transient T-wave inversion occurring after conversion to sinus rhythm from tachycardia or artificial pacing which is caused by abnormal ventricular activation. This pattern of transient T-wave inversion in the precordial leads is associated with tall T-wave in leads I and aVL and are common in patients with permanent pacemakers or ensue after recovery from ventricular or supraventricular tachycardia[23]. It is a diagnosis of exclusion. This pattern of T-wave inversion in RV pacing is caused by dysynchronous LV activation and involvement of potassium ion channels are postulated to be the key issues in its pathogenesis[53].

**Electroconvulsive therapy:** ECT may induce ECG changes with simultaneous echocardiographic regional wall motion abnormalities especially when arterial blood pressure and heart rate are markedly elevated[54]. It has been reported that transient T wave inversion Occurs in 4% of the patients undergoing ECT[55]. Transient T-wave inversion, not associated with cardiac abnormalities, has been reported due to increased sympathetic stimulation associated with ECT[31,32]. Conversely, Tuininga reported two cases of T-wave inversion following ECT with significant obstructive coronary artery disease requiring anti-anginal therapy and percutaneous coronary intervention[33]. It was recommended that further investigation to rule out significant coronary...
artery disease should be performed especially in patients with cardiovascular risk factors. Moreover, transient T-wave inversion has been reported after electroconvulsive therapy but not following transthoracic direct current electrical cardioversion for treatment of atrial fibrillation\textsuperscript{[50]}. In representative case (patient 1), the findings of CAG and cardiac MRI were normal.

**Cardiac sarcoidosis:** Cardiac sarcoidosis (CS) is a systemic inflammatory disease with unknown etiology characterized with non-caseating granulomas in multiple organ systems and may be associated with negative T-wave in the anterior precordial leads.

**Subarachnoid hemorrhage:** In the 1960s, electrocardiographic changes mimicking myocardial ischemia and infarction associated with spontaneous intracranial hemorrhage have been reported\textsuperscript{[57]}. Reversible T-wave abnormalities accompanied with prolongation of QT interval were found in 32\% of patients with SAH\textsuperscript{[30]}. ECG changes and arrhythmias occurred within the first 48 h after SAH\textsuperscript{[43,58]}. The postulated pathogenesis is cardiomyocytolysis due to excessive sympathetic stimulation. Possible mechanisms\textsuperscript{[30]} are autonomic neural stimulation from the hypothalamus and elevated levels of circulating catecholamine. The care of patients with subarachnoid hemorrhage has improved dramatically over the last few decades. These gains are the result of improved microsurgical, endovascular, and medical management techniques. This intensive management subjects patients to multiple radiographic studies and thus increased radiation exposure. Thus, tailored diagnostic modalities are required for early and correct establishment of the diagnosis. This to avoid over exposure to ionizing radiation and other invasive procedures. T-wave abnormalities in patients suffering SAH are subsequent to TTC secondary to elevated levels of circulating catecholamine and excessive sympathetic stimulation\textsuperscript{[29]}.

**Pulmonary embolism:** Acute pulmonary embolism may occasionally result in reversible deep T-wave inversion with QT interval prolongation\textsuperscript{[59]}. T-wave inversion associated with PE was first described in 1938 by Love et al\textsuperscript{[60]}. T-wave inversion in the precordial leads have been noticed in a moderate-size PE\textsuperscript{[61]}, partially occlusive\textsuperscript{[22]} and non-occlusive\textsuperscript{[22]} PE. Precordial T-wave inversion was the most common abnormal ECG finding (68\%), this anterior wall ischemic pattern was found in 85\% of massive PE and in 19\% of mild–moderate PE followed by S1 Q3 T3 pattern detected in 54\% of the patients\textsuperscript{[62]}. The proposed mechanisms include RV strain and decreased perfusion of LV anterior wall caused by hypotension consequent to pulmonary embolism\textsuperscript{[63]}. The above mentioned findings were present in the patient with PE (patient 5).

Diagnostic workup for T-wave inversion should always focus on the most likely causes and patient individually tailored diagnostic program should be followed. This to avoid and to limit unnecessary radiation exposure including diagnostic invasive cardiac catheterization.

**Pulmonary edema:** T wave inversion in the precordial leads has rarely been reported: Possible postulated mechanisms are: an acute rise in the cardiac sympathetic tone either via an increased sympathetic discharge from the central nervous system or through subendocardial ischemia due to elevated wall stress, high end-diastolic pressure and decreased coronary arterial blood flow and the electrical heterogeneity in the ventricular wall\textsuperscript{[19]}.

**Pheochromocytomas:** Pheochromocytomas are catecholamine secreting tumours that arise from the chromaffin cells of the adrenal gland. Biochemical diagnosis is established by measuring plasma free metanephrins or nor-metanephrin levels. Localization of the tumour is reached by performing computed tomography or magnetic resonance imaging scans and specifically using metaiodobenzylguanidine scan. The latter is considered the gold standard. Finally, it is confirmed by histopathologic examination\textsuperscript{[64]}.

Occasionally, pheochromocytoma may resemble acute coronary syndrome\textsuperscript{[35,65]}. Pheochromocytoma-related cardiomyopathy has incidentally been reported with inverted takotsubo contractile pattern\textsuperscript{[46]}. In patient No. 7, diagnosed with pheochromocytoma (Figure 7F) presented with chest pain and psychomotor agitation, showed periodic fluctuations of blood pressure and ECG abnormalities mimicking acute coronary syndrome (Figure 7A) without significant obstructive coronary artery disease (CAD) on his CAG (Figure 7B and C). Pheochromocytomas are rare neuroendocrine tumours with a highly variable clinical presentation but most commonly presenting with bouts of headaches, sweating, palpitation and hypertension. Imaging techniques such as CT or MRI and functional assessments using \textsuperscript{123}I-MIBG are applied to localize biochemically active tumors. In our patient (patient 7), full recovery occurred after left adrenalectomy was successfully performed in an academic hospital. The deepest T-wave inversion (Figure 7A) was found in this patient.

**Takotsubo cardiomyopathy:** TTC in relation to neurohormonal active adrenal tumor pheochromocytoma or after pulmonary resection for bilateral non-small cell lung neoplasms has rarely been reported\textsuperscript{[45,46]}. TTC accounts for 2\% of total hospital admissions for suspected acute coronary syndrome\textsuperscript{[67]}. It Accounts for approximately 1\% of admissions for suspected acute myocardial infarction in Japan\textsuperscript{[68]}. Satoh et al\textsuperscript{[69]} and Dote and
associates first described this syndrome in Japanese patients\(^\text{[70]}\). In 2001, Tsuchihashi et al.\(^\text{[17]}\) reported on cardiomyopathy with apical ballooning mimicking acute myocardial infarction (MI) without obstructive epicardial CAD, 97% of patients demonstrated T-wave inversion in the precordial leads with female predominance (86%). They observed that in 70% of the subjects there was a preceding heavy psychological or physical stress\(^\text{[17]}\). While the pathogenesis of TTC is not fully understood and remains to be elucidated, several hypotheses, including multivessel epicardial coronary artery spasm, storm of catecholamine excess and coronary microvascular disorder have been proposed\(^\text{[17,71,72]}\). In a comparison between patients with acute MI and heart failure and patients admitted with a LV systolic dysfunction after sudden emotional stress (95% female subject), Wittstein et al.\(^\text{[73]}\), found CAD in only 5% in the latter group with significantly higher plasma catecholamine levels suggesting a relation between an exaggerated sympathetic stimulation and transient LV dysfunction\(^\text{[18]}\). The following criteria are required for establishing the diagnosis TTC: transient LV systolic dysfunction frequently emerging following a stressful trigger, not associated with significant obstructive CAD, novel ECG changes with ST-segment elevation or T-wave inversion usually accompanied with slightly elevation of cardiac markers and no signs of myocarditis and pheochromocytoma\(^\text{[73-75]}\). Occasionally, in the hyperacute phase of TTC, transient J wave may precede T-wave inversion\(^\text{[75]}\). Diagnostic work-up may include history, ECG, echocardiography, CAG, ventriculography and less frequent Cardiac magnetic resonance imaging\(^\text{[76]}\). Cardiac MRI has been useful to differentiate stress TTC from anterior ST-Elevation MI with segmental wall necrosis, by absence of late enhancement in the former condition on delayed image sequence. Other pivotal MRI findings for the diagnosis of TTC are diffuse edema of the left ventricle at a later stage may be associated with akinesia or hypokinesia and absence of perfusion defects\(^\text{[34]}\). Furthermore, T2-weighted MRI delineated the ECG characterizations (dynamic negative T waves and QTc prolongation) in TTC, resembling the ischemic-like Wellens’ ECG pattern, correlating with the apicobasal gradient of myocardial edema, reflecting the edema-induced transient apicobasal inhomogeneity\(^\text{[77]}\). Recently, positron emission tomography computed tomography has been used to differentiate takotsubo cardiomyopathy TTC from acute coronary syndrome\(^\text{[78]}\). TTC may occur subsequent to aneurysmal subarachnoid hemorrhage\(^\text{[79]}\). The relation between TTC and SAH is well known. Many reports have shown the reversible pattern of T-wave inversion associated with SAH\(^\text{[29,70]}\).

Athletic heart: In 1899, Henschen\(^\text{[80]}\) described cardiac enlargement in cross-country skiers. Several ECG changes have been observed in athletes engaged in high intensity dynamic endurance sport activities which may mimic pathological and structural heart diseases. Among others, T-wave inversion in the precordial leads and relative bradycardia were reported\(^\text{[81]}\). Echocardiographic features of athletic left ventricular hypertrophy may include mild concentric LVH, mild LV dilatation, normal diastolic filling and normal systolic function\(^\text{[82]}\). It is important to distinguish between physiological adaptive ECG changes and pathological ECG abnormalities to prevent unnecessary distress \(^\text{[83,84]}\). Regression of LVH occurs when athletes decide to decondition. Some authors consider this adaptation of endurance sports athletic heart as pathologic since LVH regresses on cessation of endurance training in a similar response to a successful treatment of aortic stenosis or arterial hypertension\(^\text{[85]}\).

Permanent T-wave inversion
Arrhythmogenic right ventricular hypertrophy was first described by Dalla Volta et al.\(^\text{[86]}\) in 1961 in Italy and it was brought comprehensively under attention by Frank et al.\(^\text{[87]}\) in 1978. They reported individuals with extending fibro-fatty non-ischemic changes of the right ventricle. Sudden death may be the first sign of disease\(^\text{[88]}\). Prevalence is 1/5000 individuals\(^\text{[89]}\). They have an autosomal dominant or recessive mode of inheritance with incomplete penetrance. ARVC/D affects mainly the right ventricular myocardium characterized with progressive fibro-fatty replacement and infiltration of the RV myocardium and is considered a major cause of sudden arrhythmic death. Recently, involvement of the left ventricle at a later stage may be associated with severe manifestation and carry a worse prognosis\(^\text{[90]}\). It has been suggested by Gallo et al.\(^\text{[91]}\) and others for the implementation of a broader term as arrhythmogenic cardiomyopathy (AC)\(^\text{[91,92]}\). In AC, two major criteria or one major and 2 minor criteria are required to establish the diagnosis\(^\text{[38]}\). T wave inversion may be the first presentation\(^\text{[3]}\). Recently, in 2010, the revised task force criteria and guidelines for the clinical diagnosis of AC have been updated and T-wave inversion in the right precordial leads V1-3 or beyond was upgraded to a major criterion, in subjects > 14 years of age in the absence of complete right bundle branch block\(^\text{[93]}\), as was found in patient No. 8. The 12-lead ECG demonstrated abnormal changes in 90% of the cases with T-wave inversion in V1-3 and sometimes across V6 as the most common finding\(^\text{[89]}\). Right precordial T-wave inversions were present in 48%-85% of suspected subjects and Epsilon wave (terminal notch in the QRS complex due to slowed intraventricular conduction) was found in 8%-33% of patients with AC\(^\text{[38-40]}\) as was the case in patient No. 8. In subjects with AC, global and or regional dysfunction and structural alterations may be detected by echocardiography,
Angiography, radionuclide scintigraphy or MRI. Cardiac MRI has a high negative predictive value with sensitivity of 100% and specificity of 87%.[94] Mutations in the genes responsible for coding of connecting proteins, called desmosomes are the culprit. In the Dutch population, a founder mutation of p.Arg79X in plakophilin-2 (PKP2) gene with the same desmosome gene mutation in AC has been described.[95] Analysis of DNA in patient No. 8, showed a mutation of plakophilin-2 gene (12486C>A Tyr 616X). Rarely, cardiac sarcoidosis may mimic AC.[96]

Apical hypertrophic cardiomyopathy[4,7,36,37]: It is also called (Yamaguchi syndrome) and is considered a rare variant of hypertrophic cardiomyopathy. In the majority of cases (93%) of AHCM, negative T-wave in the precordial leads is the most frequent finding.[7] Its prevalence (15%) in Japan is high in comparison to the United States (3%)[95] and in Europe (<5%)[98]. Giant negative T-wave exceeding 10 mm is found in 47% of patients with AHCM.[7]. Typical findings were first described by Sakamoto in 1976[99] and Yamaguchi et al[100] in 1979. In the retrospective study of Eriksson et al[7], T-wave inversion was found in (98/105) 93% of the patients. Apical wall thickness of 15 mm was based on TTE or MRI measurements. The T-wave inversion is permanent without tendency for recovery. The permanent ECG features of AHCM are among others giant negative T waves in the precordial leads, ST depression and negative U waves in II, III, aVF, V4-V6, a prolonged QTc and tallest R wave in V4; however, these permanent features may vary over time.[101]

Awareness of the differential diagnosis of T-wave inversion in the precordial leads will help trainees and physicians to discern different entities and will prevent some patients from undergoing unnecessary invasive investigations and procedures. Tailored individual diagnostic investigation was performed and specific diagnostic tools were undertaken when high index of clinical suspicion was raised towards a certain disease entity.

COMMENTS

Background
Myriad of clinical conditions have been described in association with T-wave inversion in the precordial leads. T-wave inversion associated with or without corrected QT prolongation may be encountered in a variety of clinical conditions.

Research frontiers
In patients with T-wave inversion in the precordial leads, tailored diagnostic approach should be conducted avoiding overuse of diagnostic methods. Specific tailored diagnostic modalities and directed therapeutic interventions may be undertaken when high index of clinical suspicion is raised towards certain disease entity.

Innovations and breakthroughs
This study is a retrospective analysis of patients presented with T-wave inversion in the anterior chest leads. The T-wave inversion may be accompanied with or without QTc prolongation. Classification has been made into reversible and irreversible types to facilitate its differential diagnostic approach.

Applications
Awareness of the differential diagnosis of T-wave inversion in the precordial leads will help trainees and physicians to discern different entities and will prevent some patients from undergoing unnecessary invasive investigations and procedures.

Peer-review
In this paper, authors report the various clinical conditions of patients with T wave inversion in the anterior chest wall leads. This review article is interesting and very educational.

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