Review

Takotsubo cardiomyopathy: The challenging diagnosis in clinical routine

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ARTICLE INFO

ABSTRACT

Takotsubo cardiomyopathy is rapidly reversible heart failure syndrome that usually mimics the symptoms of acute myocardial infarction with the characteristic regional wall-motion abnormalities (classically with a virtual apical ballooning caused by hypokinetic or akinetic apical or midventricular myocardium and hypercontraction of the basal segments) and absence of obstructive coronary artery disease. TC is usually associated with identifiable emotional, psychological or physical stress event and most commonly appears in postmenopausal women. The certain pathophysiological mechanism remains unknown. However, the central hypothesis is supported by the excess of catecholamines and hyperactivity of nervous system. In the last decades the frequency of the TC diagnosis is increasing rapidly but at the initial presentation the diagnosis remains challenging due to the close similarities between TC and ST elevation myocardial infarction clinical presentations that consider TC as an important part of differential diagnosis in acute coronary syndrome.

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1. Introduction

Takotsubo cardiomyopathy (TC), also referred as stress cardiomyopathy [1], broken heart syndrome [2] or apical ballooning syndrome [3], is an acute but rapidly reversible heart failure syndrome [4–6] characterized by distinctive left ventricular (LV) contraction pattern. TC is usually associated with identifiable emotional, psychological or physical stress and mimics the symptoms of acute myocardial infarction with the characteristic

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regional wall-motion abnormalities (RWMA), classically with a virtual apical ballooning caused by hypokinetic or akinetic apical or midventricular myocardium and hypercontraction of the basal segments [5,7] followed by the absence of obstructive coronary artery disease [8]. The term "stress cardiomyopathy" was firstly used in 1980 by Ceblin and Hirch, who described sudden death in 11 patients without any evidence of CAD in autopsy results. In 1990 Sato et al. in Japan were the first who used the term "Takotsubo cardiomyopathy" to describe the reversible acute heart failure syndrome which, because of LV shape during systole, appeared to have similarities with Japanese octopus trapping pot with a round bottom and narrow neck. In the last decades the frequency of the TC diagnosis is increasing rapidly but at the initial presentation the diagnosis remains challenging due to the close similarities between TC and ST-segment elevation myocardial infarction (STEMI) clinical presentations that consider TC as an important part of differential diagnosis in acute coronary syndrome.

In this article we review the relevant literature regarding TC, focusing on pathophysiology, diagnosis, management and prognosis of this disease.

2. Epidemiology

The precise incidence of TC cannot be evaluated due to a lack of consensus on the diagnostic criteria. Nevertheless, recent studies have estimated that this condition probably accounts for approximately 1–2% of all patients with suspected acute myocardial infarction [9].

The recent studies revealed that TC is a unique cardiomyopathy that usually develops in postmenopausal women. Sharkey et al. prospectively assessed 136 consecutive TC patients and confirmed that TC predominantly appears in postmenopausal (mean age, 68 ± 13 years) women (96%) while the occurrence in younger group is relatively rare (10% in <50 years group) [10].

3. Classification

According to a basis of ballooning pattern TC is classified into four groups [11] (Table 1): Takotsubo type, reverse Takotsubo, mid ventricular type and localized type. However, recent studies reported TC with right ventricular involvement that should be classified separately due to the extreme clinical manifestation [12,13]. RV RWMA were reported in 26% of TC patients, when the most affected RV segments were the apico-lateral (89%), the antero-lateral (67%) and the inferior segment (67%) [12].

Table 1 – Classification of Takotsubo cardiomyopathy according to a basis of ballooning pattern.

1. Takotsubo type: apical akinesia and basal hypercontraction;
2. Reverse takotsubo: basal akinesia and apical hypercontraction;
3. Mid ventricular type: mid ventricular ballooning and basal/apical hypercontraction
4. Localized type: any other segmental ballooning when Takotsubo-like LV dysfunction is present.

4. Pathophysiology

4.1. Catecholamine excess and hyperactivity of sympathetic nervous system

Hyperactivity of sympathetic nervous system is recognized to have an important role in TC. The onset of TC is usually followed by the precipitation of physical or psychological stress. As the example can be the earthquakes in Japan when the higher TC incidence was noticed [14]. Sharkey et al. prospectively assessed 136 consecutive patients with TC during the period of 2001–2008 and identified that significant stressful event (within 12 h) was observed in the majority of patients (89%, n = 121). These events were regarded as emotional mediated (47%), usually involving anger or frustration (n = 10), financial or employment problems (n = 7), loss of the important person (n = 18), interpersonal conflict (n = 14) and panic or anxiety (n = 15) or alternatively due to a physical trigger (42%), most commonly acute non cardiac illness involving malignancy (n = 36) and medical/surgical procedures or diagnostic tests (n = 9) [10].

According to the existing literature serum catecholamine levels are 2–3 times higher in TC patients 1–2 days after initial symptoms than in MI patients with the evidence of heart failure and 20 times higher than in normal adults. Furthermore, epinephrine concentration remains elevated and reaches myocardial infarction level only after 7–9 days [7]. Studies have also reported that there might be a mechanism based on 2 overarching principles [15]. Firstly, it is observed the importance of apical-basal gradients of β-adrenergic receptors (βARs) and sympathetic innervation in mammalian LV, where apex contains the highest βAR and the lowest sympathetic nerve density. The presence of ventricular βAR gradient results in increased apical responsiveness to catecholamines predominantly epinephrine [16]. Secondly, epinephrine, at high levels can have negative inotropic impact and trigger a switch from intracellular trafficking, from G_s (stimulatory) protein to G_i (inhibitory) protein signaling through the β_{2AR}. This negative inotropic affect is greatest in apex where the density of βARs is highest [16] (Fig. 1). Paur et al. created a rat model in witch high intravenous epinephrine bolus produced characteristic reversible apical ballooning followed with basal hypercontractility and was prevented by G_i protein inactivation with pertussis toxin pretreatment [15]. These observations support the hypothesis that regional differences in β_2AR could explain the myocardial response to increased catecholamine circulation seen in TC [16].

4.2. Genetic predisposition

Some authors suggested genetic predisposition due to a reported familial association, nevertheless no genetic studies supported genetic basis of this disorder [17].

4.3. Transient epicardial coronary artery spasm

Some investigators suggested the hypothesis of transient epicardial coronary artery spasm leading to a transient myocardial stunning without any lasting injury. The hypothesis was supported by evidence of the coronary spasm that was induced by hyperventilation and provocative tests using
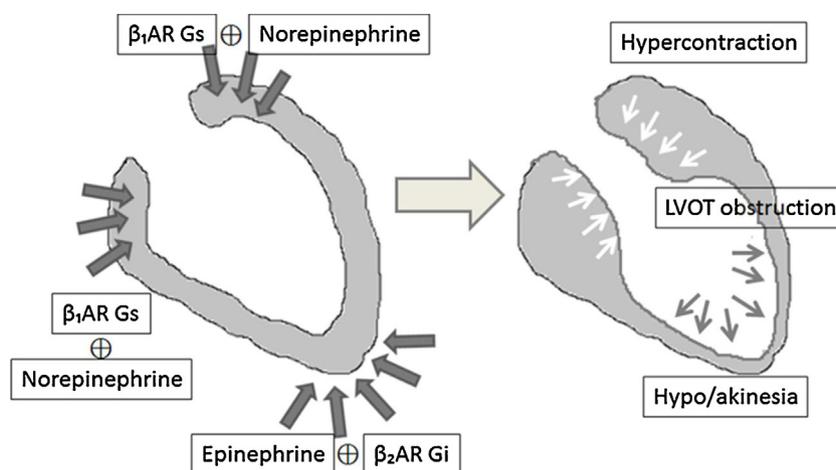
Fig. 1 – Schematic representation of the regional differences in response to catecholamine excess and hyperactivity of the sympathetic nervous system.

ergonovine or acetylcholine infusions [18,19]. However, this hypothesis is not strong enough because coronary spasm developed only for 28% of the patients [6] and the territory of hypo/akinesia of the LV usually develops beyond the single coronary artery.

4.4. Transient coronary artery occlusion/reperfusion episodes

Some investigators observed that transients LV dysfunction can be caused by atheromatous ruptured plaque that is not clearly visible on coronary angiography [20], while the TC animal model has failed to support this hypothesis [21].

4.5. Microvascular spasm due to excessive catecholamine

Reduction of parameters, that indicates myocardial perfusion, such as TIMI (Thrombolysis in Myocardial Infarction) frame count [22] or myocardial perfusion imaging [23], is observed in the majority of TC cases. However the recent studies on microvascular circulation are limited and conflicting.

4.6. Myocardial stunning due to microvascular dysfunction

It is well known that myocardial stunning is caused by the local impairment of fatty acid metabolism. Kurisu et al. used rest thallium-201 and iodine-123 dual-isotope myocardial single photon emission computed tomography (SPECT) and found that the metabolism of fatty acid was more severely impaired than myocardial perfusion in the akinetic regions during the early phase of TC [24].

4.7. Oxidative stress response to excess catecholamine

Recent studies suggest that oxidative stress in response to excess of catecholamines may be the underlying mechanism of LV dysfunction in TC [25]. However, due to the lack of evidence it is not yet clear how oxygen free radicals are

released: directly in response to increased concentration of catecholamines, as a result of catecholamines provoked microvascular changes or as a result of myocyte injury caused by various other mechanisms.

4.8. Smaller LV size predisposing to LV outflow tract (LVOT) obstruction with excess catecholamine

It is observed that dynamic LVOT may cause the rapid increase of LV intracavity pressure and dilatation of the LV apex [26], however the variant forms of TC cannot be explained on this hypothesis alone.

4.9. Relative deficiency of estrogen

TC is described as a syndrome that most commonly appears in postmenopausal women. This statement led to a theory that hormone factors such as estrogen deficiency may be responsible for the development of TC. Ueyama et al. showed that ovariectomized rats were more prone to a stress and demonstrated higher increase of the heart rate and reduction in LV function comparing to the rats that had estradiol supplementation [27]. It raises the theory that postmenopausal women lose the protective effect of estrogens which make them more prone to the excess of circulating catecholamines.

4.10. Infective agent such as a viral illness

Infiltration by mononuclear lymphocytes and macrophages are usually observed in histological examination of TC patients, nevertheless, no infective agent has been successfully isolated from TC patients [7,28].

5. Clinical manifestation and diagnosis

The diagnosis of TC remains challenging due to the close similarities to the acute coronary syndrome. There are no worldwide valid criteria for the TC diagnosis yet. In 2004, the

diagnostic criteria of TC by the Mayo Clinic, which have been modified in 2008 [8] and are widely used for the diagnosis of TC (Table 2), were proposed. However, these criteria have some limitations. Firstly, atypical forms may have RWMA beyond the area of single coronary artery. Secondly, often occurs in patients with stable CAD where obstructive CAD may be present but not causing TC. Thirdly, reversible LV dysfunction related to intracranial bleeding or pheochromocytoma has a similar pattern to TC and can also share the similar pathophysiological mechanism [29].

6. Symptoms

Clinical presentation in most TC patients is indistinguishable from an acute coronary syndrome. Commonly the clinical presentation is angina-like chest pain at rest (68%) and dyspnea (17%) while syncope and out-of-hospital cardiac arrest is rare [6,30]. Hemodynamic compromise is rare, but mild to moderate congestive heart failure is reported frequently. Despite hypotension, that is common in TC patients, due to the dynamic LV outflow tract obstruction and reduction of stroke volume, cardiogenic shock is reported as a rare complication (1.5%) [6,30].

7. Electrocardiography

The classical abnormality on electrocardiogram (ECG) is ST segment elevation mimicking acute STEMI in about 70–80% of cases [6,30], accompanied by T wave abnormalities (64%) [6,30], transient pathological Q wave (32%) [6,30], reduction of the R wave amplitude or absence R wave in anterior chest leads, new bundle-branch block and QTc interval prolongation [18]. The ECG cannot reliably diagnose TC, but it is reported that the magnitude of ST shift is usually less pronounced in comparison to STEMI [31]. Also, the recent studies described a new and simple ECG criterion to differentiate TC from acute anterior STEMI. It was reported that ST elevation ≥1 mm in at least one of the leads V3–V5 without ST elevation in lead V1 identified TC with a sensitivity of 74.2% and a specificity of 80.6% [32].

Table 2 – Mayo clinic criteria for the clinical diagnosis of takotsubo cardiomyopathy.

1. Typical LV contraction pattern: transient hypokinesia, akinesis or dyskinesia in the LV mid segments with or without apical involvement accompanied with hypercontraction in the basal segments; RWMA that extend beyond a single coronary artery vascular distribution; stressful trigger is usually but not always present;
2. Absence of obstructive CAD or angiographic evidence of acute plaque rupture;
3. Newly developed ECG abnormalities (ST segment elevation and/or T-wave inversion) or modest elevation in cardiac troponin;
4. Absence of recent head trauma, intracranial hemorrhage, pheochromocytoma, myocarditis or hypertrophic cardiomyopathy.

LV, left ventricle; RWMA, regional wall motion abnormalities; CAD, coronary artery disease; ECG, electrocardiography.

8. Cardiac enzymes

Usually the modest rise in cardiac biomarkers (including the troponin) is observed, although the magnitude of increase in the biomarkers is lower in comparison with STEMI [6,30].

9. Coronary angiography and noninvasive cardiac imaging

The characteristic feature of TC is the absence of obstructive CAD or acute plaque rupture on coronary angiography [6] while the coronary artery disease may coexist by the prevalence in the population at risk. It should not be forgotten that the important limitation of coronary angiogram remains the early resolution of thrombus at the site of ruptured LAD plaque that cannot be excluded [20].

TC is usually recognized by the distinctive LV contraction pattern. Typical TC is described as the akinesia/hypokinesia of the apical midventricular segments and hyperkinesia of the basal segments. For this typical contraction pattern TC is also known as apical ballooning syndrome [3]. Nevertheless, there are reported various other contraction patterns of TC as mentioned previously. As the important criteria is the expansion of RWMA that typically extends beyond of the distribution of any single coronary artery [8]. Transthoracic echocardiography is helpful in initial investigation to evaluate RWMA and LV dysfunction [29]. The evaluation of the true anatomic apex can be demanding due to the bad condition of the acutely ill patient. The initial diagnosis of TC in most cases is made in catheterization laboratory where the coronary angiography and ventriculography is performed in order to exclude acute coronary syndrome [8]. Nevertheless, the precise evaluation of systolic LV function and possible LV outflow tract obstruction is necessary. According to the recent studies the mean of LV ejection fraction (LVEF) is ranging from 20% to 49% at the initial presentation of TC and over a period of days to weeks the dramatic improvement of the LV function (the mean LVEF 60–76%) is observed for the majority of patients [6,30]. However, echocardiography is not a sufficient tool to make a proper differential diagnosis of TC. Cardiac magnetic resonance imaging (MRI) becomes widely acceptable to differentiate TC from other troponin positive chest pain associated causes when obstructive CAD is absent [29] (Fig. 2). Characteristic sign of TC in cardiac MRI is the absence of late gadolinium contrast enhancement [33]. It is known that gadolinium release into interstitial space of damaged myocardium and is very sensitive in conditions with severe LV dysfunction such as STEMI or myocarditis. There is a lack of data to explain why such extended LV impairment with positive troponin is not causing the late enhancement in cardiac MRI, hence it supports the hypothesis of myocardial stunning [29].

10. Management

Since is difficult to distinguish TC from STEMI at the initial presentation, the immediate treatment is likely to be based on the management of classical acute anterior STEMI with continuous ECG monitoring and administration of aspirin,
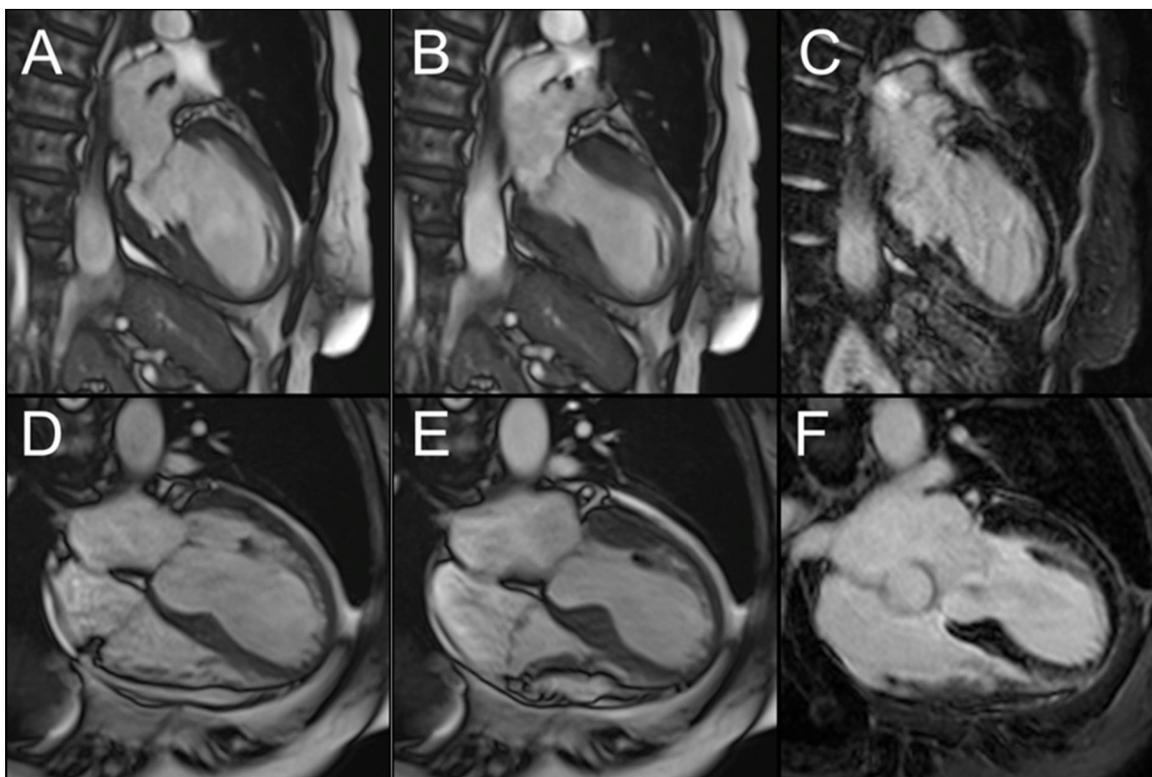
Fig. 2 – Illustrative case: a 71-year-old woman was administered to the hospital due to acute typical chest pain lasting for 2 h. It was known that the patient experienced the acute emotional stress, the severe disease of close relative, 2 h before beginning of the chest pain. In the emergency room, ST-segment elevation and T-wave inversion in V1–V3 derivations, elevated level of troponin and reduced left ventricle ejection fraction due to the regional wall motion abnormalities (apical hypo/akinesis accompanied by basal hyperkinesia) were observed. The preliminary diagnosis of ST-segment elevation myocardial infarction was made; however, no obstructive coronary artery disease in the invasive coronary angiography was found. The cause of acute heart failure was differentiated between myocarditis and Takotsubo cardiomyopathy. Cardiac magnetic resonance imaging (Siemens Aera 1.5 T) with gadolinium late enhancement was therefore performed. It showed regional contraction abnormalities of middle and apical segments of the left ventricle (diastolic images: A and D; systolic images: B and E). However, late enhancement images showed no evidence of myocardial inflammation, scar, or infarction (C and F). The diagnosis of Takotsubo cardiomyopathy was confirmed.

intravenous heparin, ACE inhibitors and β-blockers. When the diagnosis of TC is made the administration of aspirin can be discontinued if there is no coexisting coronary atherosclerosis. The quick diagnosis of TC is necessary to prevent potentially dangerous thrombolysis in these hospitals where the primary angioplasty cannot be available while in acute phase of TC low molecular weight heparin might be useful due to the increased possibility of clot formation in apex. The recent data does not give the recommendations for the optimal treatment of TC due to the lack of knowledge in pathophysiology. Nevertheless, according the new pathophysiology hypothesis, the use of β-blockers is highly recommended due to the possible excess of catecholamines [5]. There is a supportive data that combination of α- and β-adrenoreceptor blockers may be more favorable if it is accepted due to a clinical condition of the patient [34,35]. β-Blockers are also recommended when the LV outflow track obstruction due to the hyperdynamic basal contraction is present [36].

Congestive heart failure is reported as the most common complication of TC. It occurs in approximately 20% of patients

[6] especially when the RV dysfunction is involved [13,37]. Diuretics are well established to treat congestive heart failure and might be useful in these patients.

As the studies suggest, hypotension may be often present in the acute phase of TC [38] as a primary hypotension due to the LV dysfunction or a secondary one, when LVOT obstruction and systolic anterior motion of the mitral valve is occurs. In order to administer the appropriate treatment the underlying cause should be immediately found. It is recommended to treat LV dysfunction with the insertion of IABP rather than inotropes that may worsen the condition by [1] adding to the existing excess of catecholamines and/or [2] increasing LVOT obstruction [38]. For the reducing of the dynamic LVOT obstruction, basal hypercontractility and increasing of LV cavity size, intravenous fluid with short acting β-blockers should be cautiously administered [38]. And when the suggested therapy is contraindicated, the peripheral vasoconstrictor phenylephrine may be affective alternatively by increasing the afterload and LV cavity size [36] while the vasodilators, such as nitrates that are usually administered for acute coronary artery

syndrome patients, theoretically should worsen the condition by increasing LVOT obstruction and should therefore be avoided in patients with confirmed TC.

Various arrhythmias are rarely observed as complications of TC however, prolongation of QT interval or torsades de pointes may occur [39]. There are no data for any specific treatment of these arrhythmias. As previously reported, the inotropic drugs are not recommended due to catecholamine excess [26,40,41]. Atrial and ventricular arrhythmias may occur but ventricular tachycardia and fibrillation is reported as a very rare complication. The use of magnesium might be beneficial for TC patients due to its mechanism to inhibit the secretion of catecholamines from the adrenal medulla [36].

There are other drugs that might be useful in TC: anxiolytic drugs (when severe emotional stress is a trigger of TC [36]), α-adrenergic blockers such as clonidine (for the hemodynamic improvement and reduction of the need of opioids [36]); however, due to a lack of evidence, all other therapies are not supported in every TC patient.

Prasad et al. is empirically recommending the chronic β-blockers and ACE inhibitors with the aim of recurrent episode reduction [8]. It becomes more important due to uncertain diagnosis on the discharge day, while these drugs are usually administered for nonreversible LV dysfunction and renin angiotensin system can be discontinued once the complete recovery of systolic function is observed. Also the annual clinical follow-up is recommended for better understanding the course and prognosis of the disease.

11. Prognosis

TC is rapidly reversible acute heart failure as reported previously, however in-hospital mortality rate of TC is 1.2–4.2% [6,42]. Brinjikji et al. identified 24,701 patients of TC and documented that male patients had higher mortality rate comparing to female patients (8.4% vs. 3.6%, $P < 0.0001$) [42]. The higher mortality rate in male patients was explained by higher incidence of underlying critical illness in male patients (36.6% vs. 26.8%, $P < 0.0001$), average mortality rate among these patients was 12.1% (19.9% in male patients and 10.8% in female patients) [42]. The most commonly reported complications of TC (reported in 19–34.5% of TC cases) are severe heart failure, intra-aortic balloon pump (IABP) placement, ventricular fibrillation/cardiac arrest, pulmonary edema, and cardiogenic shock, while other complications including cerebrovascular accidents, thrombus, pneumothorax and ventricular septal defects are rare [6,42].

For the majority of patients who survive the initial acute stage of the disease, LV function starts improving in the first few days, and complete recovery is seen within a few months [30]. Overall, the long-term survival is similar to that of the general age-matched population [43]. The recurrence is possible, however experienced only by 3.5–10% of the patients [6,43].

12. Concluding remarks

TC is distinctive reversible cardiomyopathy that mimics an acute coronary syndrome and should be considered as a differential diagnosis for the patients with characteristic RWMA of the LV (classically with a virtual apical ballooning caused by hypokinetic or akinetic apical or midventricular myocardium and hypercontraction of the basal segments) and absence of obstructive CAD. TC is usually associated with identifiable emotional, psychological or physical stress event and most commonly appears in postmenopausal women. The certain pathophysiological mechanism remains unknown. However, the central hypothesis is supported by the excess of catecholamines and hyperactivity of nervous system while the hypothesis is challenged by the sexual disparity. Thus, despite recent clinical studies and variety of pathophysiological theories, TC remains challenging in the daily clinical routine and requires further investigations that could explain the development, the course and the possible management of this disease.

Conflict of interest statement

The authors declare no conflicts of interest.

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