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Anxiety trait in patients with stress-induced cardiomyopathy: a case–control study

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Abstract

Background Stress-induced Tako-tsubo cardiomyopathy (TTC) is an acute cardiac syndrome, mimics ST elevation myocardial infarction (STEMI), largely confined to postmenopausal women, frequently precipitated by a stressful event. The pathogenesis of TTC is still unknown. Some authors hypothesized a possible connection between TTC and anxiety disease, but no previous study analyzed the relationship between anxiety trait and TTC. This study sought to assess the potential role of anxiety trait in the development and clinical course of TTC.

Methods We included in the present prospective case–control study 50 consecutive patients admitted to our Hospital with a diagnosis of TTC according to the Mayo Clinic criteria. Fifty control patients with anterior STEMI matched for clinical characteristics such as age, gender, and hypertension were selected. During the hospitalization, all patients were asked to complete the Spielberger Trait Anxiety Inventory (STAI) scale for measuring self-reported trait anxiety (Trait-A). Outcome measures at follow-up were death, TTC recurrence, and rehospitalization.

Results The mean value of STAI scale was 46 ± 12 in TTC patients and 45 ± 14 in STEMI patients ($p = 0.815$). High-anxiety trait (STAI scale value ≥ 40) was documented in 30 (60%) TTC patients and in 26 (52%) STEMI patients ($p = 0.387$). At multivariate analysis, predictors of

TTC were lower peak creatine kinase value (HR 0.999; 95% CI 0.998–0.999; $p = 0.018$) and an antecedent stressful trigger event (HR 45.487; 95% CI 6.471–319.759; $p = 0.001$), but anxiety trait was not. There were no differences in outcome measures between TTC patients with or without high-anxiety trait.

Conclusion In TTC patients, high-anxiety trait is a common finding but it is not significantly more frequent than in patients with STEMI. Moreover, a high-anxiety trait seems to be neither associated with a worse clinical outcome nor a predictor of TTC. Our study do not support the routine evaluation of anxiety trait in patients with TTC.

Keywords Stress-induced Tako-tsubo cardiomyopathy · Anxiety trait · Coronary artery disease

Introduction

Stress-induced cardiomyopathy or Tako-tsubo cardiomyopathy (TTC) or transient left ventricular ballooning syndrome is a clinical condition largely confined to postmenopausal women, frequently precipitated by a stressful event. TTC mimics a ST segment elevation acute myocardial infarction (STEMI), and it is associated with a reversible regional dysfunction of the left ventricle without angiographic evidence of obstructive atherosclerosis of epicardial coronary arteries [1–6].

The pathogenesis of TTC is still unknown but the main hypothesis indicates the central role of activation of sympathetic nervous system (SNS) and catecholamine surge induced by mental or physical stress [2, 7].

Previous studies highlighted anxiety disorders are thought to involve a dysregulation of neurotransmitter systems with particular regard to noradrenaline, serotonin,

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γ -aminobutyric acid, dopamine, and cholecystokinin [8–10]. In light of these suggestions, some authors hypothesized possible connection between TTC and anxiety disorders [11]. No previous study analyzed specifically the relationship between anxiety trait and TTC.

We sought to assess the potential role of anxiety trait in the development and the clinical course of stress cardiomyopathy comparing TTC patients with patients admitted for STEMI.

Materials and methods

The present study was a prospective case–control study conducted from April 2005 to January 2009. Eligible case patients included consecutive subjects admitted to our Hospital with a diagnosis of TTC, who met all the four diagnostic criteria: (1) transient hypokinesia, akinesia or dyskinesia of the left ventricular mid segments with or without apical involvement; the regional wall-motion abnormalities extend beyond a single epicardial vascular distribution; a stressful trigger is often, but not always present; (2) new ECG abnormalities (either ST-segment or T-wave inversion) or modest elevation in cardiac troponin; (3) absence of obstructive CAD or angiographic evidence of plaque rupture; (4) absence of pheochromocytoma, myocarditis, hypertrophic cardiomyopathy [2]. The control group consisted of patients admitted in the same period for anterior STEMI [12]. Subsequent to enrollment of case, eligible control patients with the same gender, age, and history of hypertension were matched individually to each case patient [13].

After coronary angiography, and coronary revascularization if indicated, all TTC and STEMI patients were admitted to the coronary care unit and monitored for ECG and cardiac enzyme changes. ECG was performed at admission and at 6 h, then every 24 h until hospital discharge. Two-dimensional, Doppler and color echocardiographic evaluations were performed at admission and every 2 days until hospital discharge.

Patients were asked to complete the Spielberger State-Trait Anxiety Inventory (STAI) trait anxiety scale to measure anxiety symptoms before hospital discharge when they were medically stable. The STAI is a scale for measuring self-reported trait anxiety (Trait-A). Differently from State anxiety (State-A) that is the emotional status evoked by a condition, which is transitory, lasting for minutes, hours, or days, Trait-A refers to relatively enduring individual differences in anxiety proneness (i.e., diathesis of emotional vulnerability, which accounts for differences between people in the tendency to perceive stressful situations as dangerous or threatening). Of note, Trait-A scores remain essentially unchanged before and

after external stress. A cut-off value of 40 for Trait-A score has been used to dichotomize patients into low- and high-anxiety groups [14, 15].

Informed consent was obtained from all the cases and the controls. The study was approved by the local ethics committee.

After hospital discharge, patients were asked to return to our outpatient clinic for follow-up evaluation at 6 months and then annually thereafter. Patients who failed to show up at scheduled visits were contacted by telephone interview.

Primary end-point was the percentage of patients with high-anxiety trait (STAI scale value ≥ 40).

Major events were defined as death, recurrence of STEMI or TTC, and rehospitalization for any cause. Antecedent stressful trigger event was defined as an occurrence that produced short-term physiological changes that may lead directly to the onset of acute cardiovascular disease [16].

The study was designed on the following basis: the primary end-point rate in TTC patients will be higher than in the control group. We assumed the primary end-point would occur in 52% TTC patients and in 26% STEMI patients [14]. The planned enrollment of 50 patients for each group provides 90% power of detecting the primary end-point.

Continuous data are expressed as mean \pm standard deviation, and categorical data as proportions (%). Baseline data were compared by means of the Chi-square test for categorical variables and unpaired *t* test for continuous variables. Forward stepwise Cox multiple logistic regression analysis was used to identify independent predictors of TTC in the overall population of patients with suspected anterior STEMI. Variables tested in the model were age, gender, systolic blood pressure, diabetes mellitus, hypercholesterolemia, smoke, comorbidity, stressful trigger event, clinical presentation, ejection fraction at admission, systolic blood pressure, Troponin I at admission, peak creatine kinase-mb, total creatine kinase peak, high-anxiety trait. Differences in major events were assessed by exact log-rank test. Hazard ratios (HR) and 95% confidence intervals (CI) were calculated. Statistical significance was defined as *p* value < 0.05 . Statistical analysis was performed with SPSS 16 (SPSS, Inc., Chicago, IL, USA).

Results

Fifty patients with TTC and 50 patients with STEMI were included in the study. The baseline characteristics of the two matched groups are summarized in Table 1. Patients with TTC showed lower incidence of diabetes mellitus, lower value of cardiac enzymes peak, higher presence of an

Table 1 Baseline characteristics and clinical findings of patients with Stress cardiomyopathy, of patients with ST elevation myocardial infarction and of Stress cardiomyopathy patients divided in high- and low-anxiety trait groups (STAI Trait-A ≥ 40)

	Stress cardiomyopathy (n = 50)	ST elevation myocardial infarction (n = 50)	p value	Stress cardiomyopathy		p value
				High-anxiety trait group (n = 30)	Low-anxiety trait group (n = 16)	
Age (years)*	73 \pm 9	73 \pm 9	1	71 \pm 9	76 \pm 8	0.091
Female*	47 (94%)	47 (94%)	1	29 (97%)	15 (94%)	0.644
Hypertension*	27 (54%)	27 (54%)	1	17 (57%)	7 (44%)	0.404
Previous myocardial infarction (or Stress cardiomyopathy)	3 (6%)	3 (6%)	1	3 (10%)	0 (0%)	0.191
Diabetes mellitus	2 (4%)	9 (18%)	0.025	1 (3%)	1 (6%)	0.644
Hypercholesterolemia	14 (28%)	19 (38%)	0.288	11 (37%)	3 (19%)	0.202
Smoke	14 (28%)	7 (14%)	0.086	8 (27%)	5 (31%)	0.742
Familiar history of coronary artery disease	6 (12%)	3 (6%)	0.295	6 (20%)	0 (0%)	0.055
Comorbidity	35 (71%)	30 (60%)	0.231	22 (73%)	10 (63%)	0.447
Previous coronary artery bypass graft	0 (0%)	1 (2%)	0.315	0 (0%)	0 (0%)	
Previous percutaneous coronary intervention	0 (0%)	4 (8%)	0.039	0 (0%)	0 (0%)	
Clinical presentation						
Chest pain	35 (70%)	49 (98%)	0.004	23 (77%)	10 (62%)	0.883
Dyspnea	4 (8%)	1 (2%)		2 (7%)	2 (13%)	
Syncope	2 (4%)	0 (0%)		1 (3%)	1 (6%)	
Other symptoms	9 (18%)	0 (0%)		4 (13%)	3 (19%)	
Stressful trigger event	40 (80%)	4 (8%)	0.000	23 (77%)	14 (86%)	0.378
Ejection fraction at admission	37 \pm 9	36 \pm 8	0.415	38 \pm 9	39 \pm 9	0.841
Ejection fraction at discharge	48 \pm 11	43 \pm 9	0.048	48 \pm 10	51 \pm 15	0.344
Systolic blood pressure (mmHg)	122 \pm 23	122 \pm 24	0.988	124 \pm 24	123 \pm 21	0.873
Diastolic blood pressure (mmHg)	72 \pm 16	71 \pm 14	0.855	71 \pm 16	75 \pm 16	0.506
Heart rate (bpm)	77 \pm 15	74 \pm 14	0.426	75 \pm 16	79 \pm 15	0.390
Troponin I at admission (ng/mL)	6 \pm 10	52 \pm 90	0.001	6 \pm 12	5 \pm 6	0.710
Peak troponin I (ng/mL)	8 \pm 11	184 \pm 385	0.003	9 \pm 13	7 \pm 6	0.635
Peak creatine kinase-mb (UI/L)	25 \pm 43	927 \pm 1439	0.000	27 \pm 50	12 \pm 10	0.305
Peak creatine kinase (UI/L)	358 \pm 451	1614 \pm 1667	0.000	291 \pm 302	348 \pm 348	0.596
Intra-aortic balloon pump	1 (2%)	5 (11%)	0.068	1 (3%)	0 (0%)	0.460
Shock	0 (0%)	2 (4%)	0.153	4 (14%)	2 (13%)	0.966
Dual antiplatelet therapy at discharge	6 (13%)	46 (94%)	0.000	22 (76%)	13 (87%)	0.400
Beta-blockers at discharge	37 (77%)	32 (65%)	0.320	18 (62%)	5 (33%)	0.070
ACEI at discharge	25 (52%)	38 (78%)	0.009	1 (3%)	2 (13%)	0.218
ARBS at discharge	3 (6%)	1 (2%)	0.307	15 (52%)	5 (33%)	0.246
Statin at discharge	21 (44%)	43 (88%)	0.000	3 (10%)	1 (7%)	0.687
Calcium channel blockers at discharge	5 (10%)	1 (2%)	0.092	1 (3%)	0 (0%)	0.460
Level of instruction						
Primary school	18 (55%)	27 (66%)	0.090	15 (63%)	3 (33%)	0.292
Secondary school	7 (21%)	6 (14%)		4 (17%)	3 (33%)	
High school	5 (15%)	8 (19%)		3 (13%)	2 (23%)	
Degree	3 (9%)	0 (0%)		2 (7%)	1 (11%)	
STAI Trait-A scale value	46 \pm 12	45 \pm 14	0.815	52 \pm 9	33 \pm 5	–
High-anxiety trait (STAI scale value ≥ 40)	30 (60%)	26 (52%)	0.387	–	–	–

ACEI inhibitors of Angiotensin-converting enzyme, ARBs angiotensin receptor blockers

* According to case-control matching

Table 2 Clinical outcomes at follow-up

	Stress cardiomyopathy (<i>n</i> = 50)	ST elevation myocardial infarction (<i>n</i> = 50)	<i>p</i> value (log-rank test)	Stress cardiomyopathy		<i>p</i> value
				High-anxiety trait group (<i>n</i> = 30)	Low-anxiety trait group (<i>n</i> = 16)	
Follow-up time (months)	11 ± 11	25 ± 19	0.001	12 ± 10	11 ± 12	0.748
Death	2 (4%)	2 (4%)	0.443	0 (0%)	0 (0%)	1
Re MI o TTC	1 (2%)	2 (4%)	0.455	0 (0%)	1 (6%)	0.166
Chest pain	8 (16%)	15 (30%)	0.083	7 (23%)	1 (6%)	0.145
NYHA classification >2	4 (8%)	6 (12%)	0.526	1 (3%)	3 (19%)	0.207
Rehospitalization	13 (26%)	20 (40%)	0.094	7 (23%)	5 (31%)	0.560
Cardiac rehospitalization	10 (20%)	13 (26%)	0.087	6 (20%)	4 (25%)	0.695
Major event*	15 (30%)	21 (42%)	0.034	7 (23%)	5 (31%)	0.560

MI myocardial infarction, TTC Tako-tsubo Cardiomyopathy, NYHA New York Heart Association

* Major event is defined as: death, recurrence of MI or TTC, and rehospitalization for any cause

antecedent stressful trigger event, and higher degree of left ventricular systolic function recovery at discharge than patients with STEMI. The main clinical presentation in TTC was chest pain (70%), but also dyspnea (8%), syncope (4%), malaise or other symptoms (18%) were found, while in STEMI chest pain was the clinical presentation in 98% of patients. Four patients with TTC and two with STEMI were unable to perform STAI trait-A test for cognitive disease or for denial to complete the test. The mean value of STAI scale was 46 ± 12 in TTC patients and 45 ± 14 in STEMI patients ($p = 0.815$). High-anxiety trait (STAI Trait-A scale value ≥ 40) was documented in 30 (60%) TTC patients and in 26 (52%) STEMI patients ($p = 0.387$). At multivariate analysis of the 100 patients, predictors of TTC were lower peak creatine kinase value (HR 0.999; 95% CI 0.998–0.999; $p = 0.018$) and an antecedent stressful trigger event (HR 45.487; 95% CI 6.471–319.759; $p = 0.001$), but anxiety trait was not. The follow-up rate was 100%. Follow-up data showed a lower rate of major events in TTC patients (30%) than in STEMI patients (42%; $p = 0.034$) and a trend toward a lower rate of cardiac and all causes rehospitalizations in TTC patients ($p = 0.087$ and $p = 0.094$, respectively; Table 2). The only patient with recurrence of TTC had a low-anxiety trait (value 33) while both patients with recurrence of STEMI had a high-anxiety trait (value 63 and 66).

TTC patients were divided into high- ($n = 30$) and low- ($n = 16$) anxiety trait groups. There were no differences in baseline characteristics and in outcome measures between the two groups (Tables 1, 2). Patients with TTC were also analyzed according to the presence ($n = 40$) or the absence ($n = 10$) of antecedent stressful trigger event. Antecedent stressful trigger events that occurred in TTC patients are specified in Table 3. Patients with a stressful trigger event showed a similar high-anxiety trait rate as compared to those without (58% vs. 70%; $p = 0.659$), and a lower

Table 3 Antecedent stressful trigger event in Stress cardiomyopathy patients

Patients (<i>n</i> = 50)	
Stress present	40 (80%)
Psychological stress	23 (58%)
Violent argument	6
Death of relative, friend or pet	3
Fear/sorrow	8
Husband hospitalization	
Grandson car incidence	
Daughter's splitting-up	
Anniversary of the death of daughter	
Departure of sons for holidays	
Diagnosis of disease of a relative	
Unknown	6
Physical Stress	17 (43%)
Physical exercise	2
Medical or surgical procedures	5
Anesthesia induction	
Dental extraction	
Corneal transplantation	
Cholecystectomy	
Onset of diseases	5
Epilepsy	
Atrial fibrillation	
Chronic obstructive pulmonary disease	
Flu	
Other	5
Accidental fall	
Bone fracture	

instruction level rather than patients without stressful trigger event ($p = 0.010$). Moreover, there was no difference in outcome measures between TTC patients with and without antecedent stressful event (Table 4).

Table 4 Baseline characteristics and clinical findings of patients with Stress cardiomyopathy with and without stressful event in the clinical history

	Stress cardiomyopathy (<i>n</i> = 50)		<i>p</i> value
	Patients with stressful trigger event (<i>n</i> = 40)	Patients without stressful trigger event (<i>n</i> = 10)	
Age (years)	73 ± 9	72 ± 10	0.662
Female	38 (95%)	9 (90%)	0.552
Hypertension	21 (53%)	6 (60%)	0.670
Diabetes mellitus	2 (5%)	0 (0%)	0.470
Hypercholesterolemia	11 (27%)	3 (30%)	0.875
Smoke	10 (25%)	4 (40%)	0.345
Familiar history of coronary artery disease	5 (13%)	1 (10%)	0.828
Comorbidity	27 (68%)	9 (90%)	0.156
Previous stress cardiomyopathy	3 (8%)	0 (0%)	0.372
Clinical presentation			
Chest pain	30 (75%)	5 (50%)	0.181
Dyspnea	2 (5%)	2 (20%)	
Syncope	2 (5%)	0 (0%)	
Other symptoms	6 (15%)	3 (30%)	
Intra-aortic balloon pump	1 (3%)	0 (0%)	
Dual antiplatelet therapy at discharge	5 (13%)	1 (10%)	0.788
Beta-blockers at discharge	30 (79%)	7 (70%)	0.549
ACE Inhibitors at discharge	18 (47%)	7 (70%)	0.202
ARBS at discharge	3 (8%)	0 (0%)	0.359
Statin at discharge	18 (47%)	3 (30%)	0.325
Calcium channel blockers at discharge	5 (13%)	0 (0%)	0.226
Level of instruction			
Primary school	17 (68%)	1 (13%)	0.010
Secondary school	3 (12%)	4 (48%)	
High school	4 (16%)	1 (13%)	
Degree	1 (4%)	2 (26%)	
Ejection fraction at admission	37 ± 9	40 ± 10	0.430
Ejection fraction at discharge	48 ± 12	52 ± 10	0.463
Systolic blood pressure (mmHg)	125 ± 24	115 ± 15	0.240
Diastolic blood pressure (mmHg)	72 ± 16	70 ± 16	0.675
Heart rate (bpm)	78 ± 14	70 ± 16	0.140
Troponin I at admission (ng/mL)	5 ± 7	9 ± 19	0.378
Troponin I peak (ng/mL)	7 ± 8	11 ± 18	0.368
Creatin kinase-mb (UI/L)	22 ± 44	36 ± 40	0.415
Creatin kinase (UI/L)	272 ± 255	667 ± 794	0.013
STAI Trait-A scale value	46 ± 13	46 ± 8	0.937
High-anxiety trait (STAI scale value ≥40)	23 (58%)	7 (70%)	0.659
Follow-up clinical outcomes			
Follow-up time (months)	13 ± 12	7 ± 4	0.116
Death	1 (3%)	1 (10%)	0.279
Recurrence of TTC	1 (3%)	0 (0%)	0.627
Chest pain	6 (15%)	2 (20%)	0.620
NYHA classification >2	2 (5%)	2 (20%)	0.072
Rehospitalization	11 (28%)	2 (20%)	0.716
Cardiac rehospitalization	8 (20%)	2 (20%)	0.909
Major event	12 (30%)	3 (30%)	1

ACEI inhibitors of Angiotensin-converting enzyme, ARBs angiotensin receptor blockers, NYHA New York Heart Association

* Major event is defined as: death, recurrence of TTC or rehospitalization for any cause

Discussion

The main findings emerged from this study were the following: (1) in TTC patients a high-anxiety trait is a common finding; (2) high-anxiety trait prevalence in TTC patients was not significantly higher as compared with STEMI patients and anxiety trait was not a predictor of TTC in patients presenting with chest pain or dyspnea with suspected anterior STEMI; (3) a high-anxiety trait seems not to be associated with the worse clinical outcome in TTC; (4) the role of antecedent stressful trigger event still remain an important clinical feature of TTC, and it is independent from patient's anxiety trait.

The physiopathological mechanism of TTC is still unknown. Previous studies reported very high levels of catecholamine at TTC presentation, which remained elevate until 7–9 days [15]. The most likely mechanism involves the central role of SNS and catecholamine surge induced by mental or physical stress, that in patients with individual susceptibility may lead to microvascular spasm, or left ventricular outflow tract obstruction, or direct myocyte injury, or metabolic disorders such as abnormalities in free fatty acid metabolism and glucose uptake leading to myocardial stunning [2, 16, 17].

Anxiety is a negative emotion characterized by perceived inability to predict, control, or gain the preferred result when confronted with a threat coming from internal or external sources and can be real or imagined. Anxiety exists on a continuum from normal to pathological condition [18].

The precise mechanisms underlying the pathogenesis of anxiety remain unclear. Previous studies demonstrated pathological alteration in cardiac autonomic tone involving either increased sympathetic stimulation, or impaired vagal control in anxiety patients [19, 20]. The key role of serotonin system dysregulation in anxiety development has been demonstrated to involve the serotonin-1A (5-HT_{1A}) subtype receptor [20]. The role of catecholamines, in particular of noradrenaline, is less clear. Substantial evidence supports the hypothesis of a disturbed noradrenergic neurotransmission (adrenergic receptors α 1, α 2, β 1, β 2) contributing to anxiety symptoms [21–24]. Previous studies highlighted increase noradrenaline release, receptors dysregulation or dysregulation of the brain noradrenergic system in patients with anxiety disease [8, 9]. Moreover, catecholamines receptors down-regulation may occur in such condition, due to the chronic overactivity of central norepinephrine in anxiety patients [25].

The diagnosis of a psychiatric disease, as anxiety or depression, increase the risk of cardiac and all causes mortality in patients affected by heart diseases [14, 26], thus anxiety trait may be considered a cardiovascular risk factor [27]. A possible relationship between TTC and

anxiety trait has been hypothesized but never assessed in prospective clinical studies [11].

Our study failed to show a correlation between anxiety trait and TTC. TTC clinical course seems not to be influenced by anxiety, since clinical outcomes were similar between patients with and without high-anxiety trait, and STAI Trait-A test result was not a predictor of any clinical event at follow-up.

In light of these results, it seems that typical catecholamines alteration of anxiety disease, through increased release or by receptor dysregulation, is not a risk factor or a predictive clinical condition of TTC development. Conversely, a single acute stressful trigger event, associated with sudden and rapid surge of catecholamines levels, can induce stress cardiomyopathy. Thus, we hypothesized that TTC patients might be able to respond in an abnormal way to an abrupt rise of catecholamines levels rather than to their absolute basal levels.

A history of antecedent stressful event, emotional or physical, was described in the majority of TTC patients [7]. Acute stress triggers myocardial ischemia, promotes arrhythmogenesis, stimulates platelet aggregation, and increases blood viscosity through hemoconcentration [28, 29]. SNS stimulation produced from acute stress leads to a variety of effects, ranging from heart rate and blood pressure rise to direct effects on coronary vascular endothelium [30].

Protection against triggers, through stress reduction training or by anticipation of possible stress events, may provide a further rationale for daily therapy to limit anger and anxiety. Although selective serotonin reuptake inhibitors has been previously proposed [30], our study does not support the use of anxiety therapy to avoid TTC onset or recurrence.

Study limitations

Our results must be evaluated in light of some study limitation. First, the sample size may constitute an issue. However, TTC is considered a rare syndrome, and 50 individuals are a relevant study population in relation to the prevalence of the analyzed syndrome and may provide clinically useful information. To our knowledge, this is the very first report of anxiety trait in patients with TTC. No data are available regarding anxiety status influence on the acute phase course of tako-tsubo cardiomyopathy. There are also few data about anxiety trait in patients with STEMI, i.e., a much more prevalent clinical condition. Second, our analysis might have suffered from the limitations of case–control study. However, it is well known that this kind of analysis is ideal for rare diseases such as stress cardiomyopathy. We cannot exclude the limited power of a single evaluation of the Spielberger scale in exploring the

complexity of anxiety disorder. Third, it is unknown if a longer follow-up would provide further information about TTC natural history. Finally, all the enrolled patients belong to the same country and it is unknown if people living in different countries may potentially respond and cope with stressful situations differently.

In conclusion, in TTC patients high-anxiety trait is a common finding but it is not significantly more frequent than in patients with STEMI. Moreover, a high-anxiety trait seems to be neither associated with a worse clinical outcome or a predictor of TTC. Our study do not support the routine evaluation of anxiety trait in patients with TTC.

Conflict of interest No conflict of interest to disclose.

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