Occurrence of Takotsubo cardiomyopathy and use of antidepressants

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ARTICLE INFO

Article history:
Received 13 March 2014
Accepted 2 April 2014
Available online 13 April 2014

Keywords:
Takotsubo cardiomyopathy
Depression
Selective serotonin reuptake inhibitors

Takotsubo cardiomyopathy (TTC), also known as stress-induced cardiomyopathy, is a peculiar reversible cardiovascular disease (CVD) that may mimic an acute coronary syndrome, often affecting post-menopausal women after a stressful event.

The prevalence ranges between 1.7 and 2.2% in patients admitted with chest pain for suspected acute coronary syndrome [1,2]. Proposed pathophysiological mechanisms include: catecholamine cardiotoxicity, microvascular dysfunction and coronary artery spasm [3,4]. Major depression and comorbid anxiety disorders have been associated with elevated sympathetic activity and diminished reuptake of norepinephrine, which may be responsible for prolonged cardiac sympathetic stimulation [5].

As suggested by Ziegelstein et al. [6], the double impact effect of disproportional high catecholamine responses and increased cardiac sympathetic sensitivity may place depressed patients at higher risk for developing TTC when exposed to stressful situations.

Several case reports [7–11] have suggested that the use of SSRIs (in both therapeutic and over dosage scenarios) is associated with TCC, potentially by increasing norepinephrine levels in neuronal tissue via reuptake inhibition.

This retrospective descriptive study consisted of 78 patients who met the Modified Mayo criteria [12]: 1) akinesia or dyskinesia of the apical and/or midventricular segments of the left ventricle with regional wall motion abnormalities extending beyond the distribution of a single epicardial vessel, 2) absence of obstructive coronary artery disease, 3) new electrocardiographic abnormalities, and 4) absence of pheochromocytomas/myocarditis.

The diagnosis of depression and anxiety was made based on clinical criteria by a primary care physician or psychiatrist before being admitted to the hospital. The diagnosis of anxiety included generalized anxiety disorder, panic disorder, post-traumatic stress disorder and social phobia.

Clinical outcomes were assessed during the hospital admission and within 6 months after the index event, as follows: in hospital death (all cause-mortality), inpatient acute heart failure (HF), length of stay, and left ventricular ejection fraction (LVEF) determined by 2-D echocardiogram.

Chi-squared and paired *t*-tests were used to assess statistical differences in categorical and continuous variables, respectively. A two-tailed $P < 0.05$ was considered statistical significant. Cox-proportional hazard model was constructed to evaluate mortality. All analyses were performed employing SPSS v 19.0, Chicago IL. This study was approved by the hospital's institutional review board.

Baseline characteristics of the study population as well as by SSRI use are reported in Tables 1 and 2 respectively. SSRIs use was strongly associated with all-cause mortality during index hospital admission (OR 7.6; 95% CI 1.1–50.3; $P = 0.016$). Mean LVEF on admission in patients taking SSRIs was 36.3 ± 11.4% and for patients not taking SSRIs was 36.7 ± 11.0%. Repeated echocardiogram within 6-months revealed statistically significant recovery of LVEF in each group ($P < 0.05$ for both comparisons) with a relatively lower LVEF in patients taking SSRIs (Fig. 1, $P = 0.01$). (See Table 3.)

Mean LVEF on admission for patients without depression was 36.4 ± 11.2% and for patients with depression was 37.2 ± 10.6%. Repeated LVEF within 6-months revealed statistically significant recovery of LVEF in each group ($P < 0.05$ for both comparisons), although patients with depression had relatively lower LVEF compared to patients without depression (Fig. 2, $P = 0.02$). The survival curve (Fig. 3) showed that SSRIs patients had lower survival rate compared with patients not taking SSRIs ($P = 0.04$).

In this study, the prevalence of depression and anxiety (21% and 31%, respectively) was consistent with previous reports [4,13,14] which reported a prevalence ranging between 20 and 40%. Several authors

Table 1
Baseline clinical characteristics of the study population ($n = 78$).

Characteristic	Value
Age, years (mean)	68
Female	69 (87%)
Coronary risk factors	
Hypertension	54 (70%)
Hyperlipidemia	34 (44%)
Diabetes mellitus	14 (18%)
Current Smoker	28 (36%)
Clinical presentation	
Chest pain	50 (64.1%)
Pre-/peri-/postmedical/surgical procedure	3 (4%)
Stressful event reported	
Emotional stressor	20 (26%)
Strenuous exercise activity before the event	2 (2.6%)
Substance abuse/suicide attempt/panic attack	3 (3.9%)
Depression	16 (20.5%)
Anxiety	24 (30%)
Troponin upon admission (ng/ml)	2.41
Peak troponin during hospitalization (ng/ml)	5.16
Electrocardiographic changes at presentation	
ST elevation	26 (33%)
T-wave inversion	29 (37%)
Nonspecific ST-T wave changes	47 (60)
High-degree atrioventricular block	1 (1.3%)
Asystole	1 (1.3%)
Chronic/paroxysmal atrial fibrillation	5 (6.4%)
LV ejection fraction	
Initial ejection fraction (%)	36.6% ±11
Follow-up ejection fraction (%)	53% ±9
Medications on admission	
SSRI	15 (19.2%)
SNRI	2 (2.6%)
TCA	1 (1.3%)
SARI	3 (3.8%)
Benzodiazepines	23 (30%)

SSRI — selective serotonin reuptake inhibitors; SNRI — serotonin and norepinephrine reuptake inhibitors; TCA — tricyclic antidepressant; SARI — serotonin antagonist/reuptake inhibitors.

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Table 2
Baseline clinical characteristics of SSRI/non-SSRI groups.

Characteristic	SSRIs patients ($n = 15$)	Non-SSRIs patients ($n = 63$)	P value
Age (years), mean	61.5	68.3	NS
Female (%)	13 (86.7%)	56 (88.9%)	NS
LOS (length of stay, days)	6.73	5.36	NS
Cardiovascular risk factors			
Hypertension	10 (66.7%)	44 (68.25%)	NS
Hyperlipidemia	8 (53%)	26 (41.2%)	NS
Diabetes mellitus	3 (20%)	11 (17.4%)	NS
Current smoker	8 (53%)	20 (31.7%)	NS
Depression	13 (86.7%)	3 (4.7%)	<0.001
Anxiety	6 (40%)	18 (28.6%)	NS
Clinical presentation			
Chest pain	10 (66.7%)	40 (63.5%)	NS
In hospital heart failure	3 (20%)	13 (20.6%)	NS
In hospital death	3 (20%)	2 (3.2%)	0.016
Stressful event identified	12 (80%)	55 (87.3%)	
Emotional stressor	4 (26.7%)	16 (25.4%)	NS
Troponin I upon admission (ng/ml)	2.95	2.26	NS
Peak troponins I during hospitalization (ng/ml)	8.81	4.28	NS
Electrocardiographic changes at presentation			
ST elevation	5 (33.3%)	21 (33.3%)	NS
T-wave inversion	7 (46.7%)	22 (34.9%)	NS
Nonspecific ST-T wave changes	9 (60%)	38 (60.3%)	NS
High-degree atrioventricular block	0	1 (1.6%)	–
Asystole	0	1 (1.6%)	–
Chronic/paroxysmal atrial fibrillation	1 (6.6%)	4 (6.5%)	NS
Left ventricular ejection fraction			
Initial ejection fraction (%) mean ± SD	36.3% ± 11.4	36.7 ± 11.0	NS
Medications on admission	SSRIs patients ($n = 15$)	Non-SSRIs patients ($n = 63$)	
SSRI	15	0	
SNRI	1 (6.6%)	1 (1.6%)	
TCA	0	1 (1.6%)	
SARI	1	2 (3.2%)	
Benzodiazepines	6 (40%)	17 (26.9%)	
Beta Blockers on admission	12 (80%)	52 (82.5%)	
Angiotensin-converting enzyme inhibitors or angiotensin receptor Blockers on admission	8 (53%)	30 (47.6%)	
Statin on admission	11 (73%)	41 (65%)	
Aspirin on admission	14 (93.3%)	55 (87.3%)	

SSRI — selective serotonin reuptake inhibitors; SNRI — serotonin and norepinephrine reuptake inhibitors; TCA — tricyclic antidepressant; SARI — serotonin antagonist/reuptake inhibitors.
NS = nonstatistically significant.

have already described depression as being more prevalent in patients with CVD than in the general population and independently associated with a poor prognosis [15–18]. Psychiatric comorbidities, such as depression and anxiety, may play an important role in TTC, given its high frequency among these patients. Several mechanisms have been proposed associating mood disorders with TCC [6,19,20].

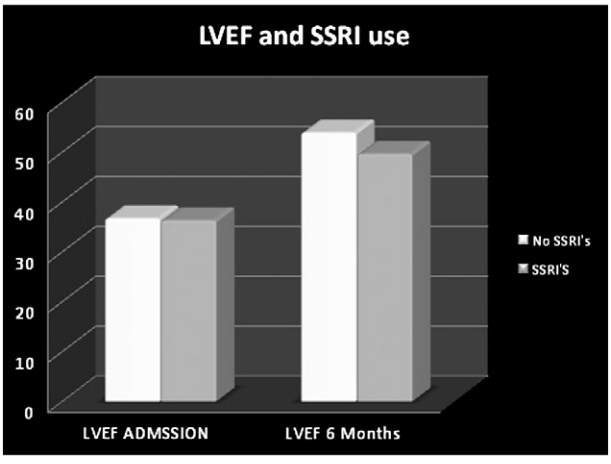

Fig. 1. Mean LVEF on admission and at 6 months in patients taking SSRIs versus not taking SSRIs.

Patients with mood disorders may mount an exaggerated norepinephrine response to emotional stress and have unusually high cardiac sympathetic activity [21]. Barton et al. [22] showed patients with major depressive disorder have reduced cardiac neuronal norepinephrine reuptake and persistence of norepinephrine in the synaptic space which could lead to increased cardiac sympathetic response.

Table 3
Preceding stressful events.

Events	No.(%) of participants (total $n = 78$)
Emotional stressors	
Death or illness of a relative/friend/pet	6 (7.7%)
Interpersonal conflict	5 (6.4%)
Panic/fear/anxiety (emotional stress)	5 (6.4%)
Job issues	2 (2.6%)
Bad news	1 (1.3%)
Other	2 (2.6%)
Physical stressors	
Perisurgical or postsurgical	4 (5.1)
Acute respiratory failure (chronic obstructive pulmonary disease exacerbation)	7 (8.9%)
Infection	8 (10.2%)
Strenuous activity	2 (2.6%)
Stroke	2 (2.6%)
Seizure	3 (3.8%)
Near drowning	1 (1.3%)
Other	9 (11.5%)
No identifiable stressors	18 (23.1%)