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ABSTRACT

BACKGROUND: Stress-induced or Tako-Tsubo Cardiomyopathy (TTC) is a rare acute cardiac syndrome characterized by transient left ventricular (LV) dysfunction of uncertain aetiology and outcome. PURPOSE: This study sought to assess the long-term outcome of TTC patients. METHODS: One-hundred and sixteen consecutive patients were prospectively included in the study and observed at long-term follow-up. Primary endpoints were: death, TTC recurrence and hospitalization from any cause. RESULTS: Mean initial LV ejection fraction (EF) at admission was 36±9%. Two patients died during hospitalization due to refractory heart failure. All patients who were discharged alive but 1 showed complete LV functional recovery. At follow-up (2.0±1.3 years), only 64 (55%) patients were asymptomatic. Rehospitalization rate was high (25%) with chest pain (n=6) and dyspnea (n=5) as the most common causes. Only 2 patients had a recurrence of TTC. Eleven patients died (7 from cardiovascular cause). There was no significant difference in mortality (12% vs 7%; p=0.284) and in the other clinical events between patients with and without severe LV dysfunction at presentation (LV EF ≤ 35%). Mortality observed in TTC patients was compared to age and gender specific mortality of the general population using the standardized mortality ratio (SMR) method. The SMR resulted 3.40 (95% CI 1.83-6.34) in TTC population. The only independent predictor of death at Cox analysis was Charlson comorbidity index (HR 1.786; p=0.0001), but initial LV dysfunction degree was not. CONCLUSION: The recurrence of TTC is rare, while recurrences of chest pain or dyspnea are common in TTC patients and frequently lead to hospital readmission. Long-term mortality is higher as compared with the control general population and at least in part related to patient's comorbidities. Initial LV dysfunction severity seems not to impact long-term event rates.

Key words: tako-tsubo cardiomyopathy; acute coronary syndrome; stress; outcome.

INTRODUCTION

Stress-induced or Tako-Tsubo cardiomyopathy (TTC) is a relatively rare acute cardiac syndrome, largely confined to female gender and often associated with a stressful event, that may mimic a ST-elevation acute myocardial infarction (STEMI). Chest pain or dyspnea, ischemic electrocardiographic changes, transient left ventricular (LV) dysfunction and limited release of cardiac injury markers, in the absence of epicardial coronary artery disease (CAD) characterize TTC acute phase.[1-6] In the majority of cases, transient LV dysfunction, which is myocardial stunning related, involves the LV apical segments and has a full recovery within few weeks. Direct and indirect catecholamine-induced myocardial injury has been indicated as the main and more likely pathogenetic mechanism.[1-3, 7] The long-term optimal management and outcome of this cardiac syndrome are unknown. This study sought to evaluate the long-term clinical outcome of TTC patients.

METHODS

Participants. We prospectively enrolled patients admitted to the 5 hospitals of our urban area, who met all the 4 currently accepted diagnostic criteria for TTC: (1) transient hypokinesis, akinesis or diskinesis of the LV 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 thrombosis or plaque rupture; (4) absence of pheochromocytoma, myocarditis, hypertrophic cardiomyopathy.[1] The study was approved by the Careggi Hospital Ethic Committee (approval number 0028728) and all patients provided informed consent.

Design. Prospective, multicentre, observational registry.

Measurements. All patients were admitted to the cardiac care unit after coronary angiography. Currently recommended treatments for acute coronary syndromes, with therapy directed at relieving myocardial ischemia and preventing thrombotic complications, were provided to TTC patients. For

each patients, the Charlson score Index,[8] that represent the most studied and valuated comorbidity index, was calculated.

The clinical definition of *cardiogenic shock* was sustained hypotension (systolic blood pressure <90 mm Hg for at least 30 minutes) and a reduced cardiac index (<2.2 L/min per m^2) in the presence of elevated pulmonary capillary occlusion pressure (>15 mm Hg) and tissue hypoxia, including oliguria, clouded sensorium, and cool, mottled extremities.

Outcomes. LV function was evaluated in all patients by two-dimensional echocardiography at admission and at discharge. Following discharge, patients were asked to return to our outpatient clinic for follow-up evaluation at 1 and 6 months, and annually thereafter. All other possible information derived from hospital readmission, or by the referring physician, relatives or municipality live registries were collected. Primary endpoints were: death, TTC recurrence and rehospitalization for any cause. Sudden death was defined as an unexpected death that occurs within 1 hour after symptom onset, with or without pre-existing stable clinical conditions. Cardiovascular death was defined as sudden death or death caused by reinfarction, heart failure, arrhythmia, or fatal vascular disease including stroke. The cause of death was assigned by the event adjudication committee consensus. At follow-up visit, *dyspnea* was classified according to the New York Heart Association (NYHA) functional classification system (from Class I = no limitation of physical activity to Class IV = unable to carry out any physical activity without dyspnea).

Statistical analysis. Continuous data are expressed as mean ± standard deviation, and categorical data as proportions (%). Data were compared by means of the χ^2 test for categorical variables and unpaired *t* test for continuous variables. Cox proportional-hazards multivariate regression analysis was used to identify independent predictors of death among TTC patients. Hazard ratios (HR) and 95% confidence intervals (CI) were calculated. Furthermore, the multivariate Cox model was used to compare the mortality observed in TTC series (females only) with the mortality observed in women with STEMI admitted to the same hospitals and included in a contemporary prospective registry,[9] adjusting for age and risk factors and the presence of shock at hospital arrival. Finally,

mortality observed in TTC and in STEMI patients were compared to age and gender specific mortality of the general population of the same area using the standardized mortality ratio (SMR) method.[10] A value of $p<0.05$ was considered significant. Statistical analyses were performed with SPSS 11.5 (SPSS Inc., Chicago, Illinois, USA) and STATA 9 (StataCorp. College Station, Texas, USA).

RESULTS

Baseline characteristics. From July 2003 to March 2008, among 3882 patients (1077 women) hospitalized for acute myocardial infarction, 116 patients with TTC were included in the Registry. Among TTC patients, an emotional or a physical stressful event was detected in 45 (39%) and 34 (29%) patients, respectively. Baseline clinical, electrocardiographic and echocardiographic findings are reported in Table 1. Urgent angiography showed no significant CAD in patients with TTC. In particular, 92 patients (79%) had truly normal coronary arteries, whereas 24 (21%) had ≤50% coronary stenosis. Poor distal run-off was observed in 27 patients (23%), whereas no patient showed coronary calcification or ectasic CAD. Associated comorbidities were detected in 94 patients; of these chronic obstructive pulmonary disease was the more frequent (n=20; Table 1). Mean LV ejection fraction (EF) at admission was 36±9%. All patients with TTC who were discharged alive but 1 showed complete LV functional recovery (LV EF>50%) during follow-up**.** The only patient who failed to recover a normal LV function had a pre-existing hypertension-related LV hypertrophy with mild systolic dysfunction. Mean interval time from admission to LV functional recovery was 8±7 days.

Outcomes. Table 2 summarizes in-hospital and long-term clinical outcomes. Two patients died during hospitalization due to refractory heart failure. The first patient who died in-hospital was a 85-year old woman with a traumatic femoral fracture and chronic obstructive pulmonary disease who developed chest pain and the classic clinical features of TTC confirmed by angiography. LV dysfunction was severe (EF 30%) and associated with moderate to severe functional mitral regurgitation. This patient developed refractory cardiogenic shock that did not improve with

inotropic drugs or balloon pump and the patient died 24 hours after TTC diagnosis. The second patient who died in-hospital was a 80-years old woman with myasthenia gravis that after TTC presentation developed cardiac and respiratory failure that did not improve with intubation and inotropic agents and the patient died 4 days after hospital admission.

The other in-hospital complications were: unfatal heart failure, cardiogenic shock, cardiac arrhythmias, LV thrombosis, functional mitral regurgitation and LV outflow tract obstruction. Long-term follow-up rate was 100%; follow-up length was 2.0±1.3 years. Two thirds of patients (n=78) had a survival free from major adverse events; of these, 64 (55%) were truly asymptomatic, while 14 (12%) had chest pain episodes. One third of patients (n=38) experienced a major adverse event. There were 11 deaths (9%; Table 3). Seven (6%) deaths were classified as cardiovascular: 2 patients died during the index hospitalization from refractory heart failure; 2 patients had fatal ischemic strokes; and 3 patients had an out-of-hospital sudden death (2 of them were on beta-blockers therapy). TTC recurrence was excluded in the 2 patients with fatal ischemic strokes. Four deaths were considered non cardiovascular and were due to chronic obstructive pulmonary disease (n=2), pneumonia (n=1), and sepsis (n=1). There was no significant difference in mortality (p=0.284) and in the other clinical events between patients with an initial LV EF ≤35% and those with a LV EF > 35% (after excluding the 2 patients who died during hospitalization the out-of-hospital mortality rates were 9% and 7%; p=0.694). Two patients experienced TTC recurrence during follow-up. The first patient was a 64-year old woman who had the fist episode of TTC in June 2005 following confrontation and argument with the neighbours. She completely recovered LV function and was asymptomatic for 3 years with calcium-channel blockers therapy. However, in 2008 following a new quarrel with the neighbours she presented again a classic TTC episode. The second patient with TTC recurrence was a 66-year old woman smoker with hypertension who developed a TTC episode after a burglary at her home. She recovered completely, but one year after she developed a new TTC episode while she was waiting for an uterus surgery. Fifteen patients had a rehospitalization that was classified as cardiovascular (chest pain [n=6], dyspnea [n=4], heart

failure, atrial fibrillation, hypertensive state, and TTC recurrences). There were also 13 cases of non cardiovascular rehospitalization, mainly related to comorbidities. Six patients had hospital admission due to COPD exacerbation. No outcome difference was observed between patient with and without an antecedent stressful event before the index episode. By Cox analysis, the only independent predictor of death was Charlson comorbidity index (HR 1.786 [95%CI: 1.299-2.456]; p=0.0001), but initial LV dysfunction degree was not. The SMR in patients with TTC was 3.40 (95%CI 1.83-6.34). The SMR in patients with STEMI admitted to the same hospitals in the same period and included in a contemporary prospective registry [9] was 5.17 (95%CI 4.19-6.37). The adjusted HR of TTC cases versus STEMI patients was 0.48 (95% CI 0.25-0.94; p=0.016).

Effect of beta-blockers recommendation. There was no significant difference in all the baseline characteristics between patient with (n=81) and without (n=35) beta-blockers recommended at discharge. A lower but not significant mortality was observed at long-term follow-up in patients with beta-blockers recommended at discharge as compared with those without (Table 2). However, patients with beta-blockers showed a trend towards a higher rehospitalization rate, mainly driven by non cardiovascular rehospitalizations (Table 2). One patient treated with beta-blockers experienced TTC recurrence.

DISCUSSION

Few but important findings related to the natural history of stress-induced or TTC emerge from the analysis of the reported data: 1) TTC recurrence is rare; 2) recurrences of chest pain and dyspnea are common in these patients and lead to frequent rehospitalizations, 3) TTC mortality rate is higher than the expected mortality in the general population, 4) long-term mortality in TTC seems to be not influenced by the initial LV dysfunction severity.

Previous TTC outcome data derived mainly from retrospective study with small populations and limited periods of observation. In our prospective Registry, almost all of the patients admitted to hospital for TTC (98.3%) were discharged alive and presented complete LV functional recovery

within few days or weeks. TTC recurrence was documented in only 2 patients (1.7%). This percentage is relatively low as compared with previous reports.[5-6] However, recurrence of any type of chest pain (either typical or atypical) and/or dyspnea were frequently presented by patients who suffered TTC and generated challenging differential diagnoses. The electrocardiographic and echocardiographic findings and cardiac injury marker evaluations were crucial to detect or rule out the TTC recurrence. As expected by the advanced age of these patients, rehospitalizations were common and mainly related to comorbidities.

The analysis of the SMR revealed that TTC patients are 3 times more likely to die when compared with the general population. This finding must be confirmed in larger study population. However, TTC seems to be associated with a long-term survival rate that is intermediate between the one of the general population and the one of patients with STEMI.[4] Comorbidity (Charlson Index) was the only predictor of mortality in the TTC population, and we can speculate that the observed mortality excess may be at least in part related to the associated diseases. After discharge, the incidence of sudden death (2.6%) was not negligible and it merits further consideration. At the present time there is no data available to recommend proper preventive strategies beside an accurate patient follow-up, an aggressive treatment of cardiovascular risk factors and an optimal management of comorbidities.

Interestingly, the severity of initial LV dysfunction seems not to impact long-term survival, since LV fully recovers in almost all of the patients. However, severe LV dysfunction, especially when associated with functional mitral regurgitation, has been identified as a potent predictor of hazardous clinical manifestations, including pulmonary edema and cardiogenic shock in the TTC acute phase.[11]

Beta-blockers therapy that is actually recommended in the majority of TTC, given the hypothesis of a cathecholamine-induced myocardial injury, seems not to completely prevent the recurrence of TTC; in fact, one patient had a TTC recurrence during beta-blockers therapy. Moreover, 63 of the enrolled patients had a previous hypertension and 17 of them were tacking beta-blockers at the time

of the index event. Thus, we can conclude that further data are needed to establish the value of beta-blockers therapy during long-term follow-up after TTC. On the other hand, the in-hospital use of beta-blockers in patients with LV dysfunction and LV outflow tract obstruction is mandatory.[12]

Study limitations. Our results must be evaluated in the light of some study limitations. First, true TTC natural history should include syndrome recurrence in patients with subclinical presentation as well as in patients with out of hospital sudden death. Unfortunately, autopsy data of patients who died suddenly were not available. Second, even if it seems unlikely, we can not exclude the contribution of atherosclerotic CAD development to the higher mortality rate of TTC as compared with the one of the general population. In fact, endothelial dysfunction, that constitute the first step of atherosclerosis, has been suggested to be present in TTC.[2] Finally, due to the nonrandomized nature of the study data on beta-blockers therapy are not conclusive and are only hypothesis generating.

Conclusions. The recurrence of TTC is rare, while recurrences of chest pain or dyspnea are common in TTC patients and lead to frequent rehospitalizations. Long-term mortality is higher as compared with the control general population and at least in part related to patient's comorbidities. Initial LV dysfunction severity seems not to impact long-term event rates.

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TABLE 1. Baseline characteristics of study patients

Variable	Tako-tsubo Cardiomyopathy (n=116)	With antecedent stress		
		Yes n=79	No n=37	p value
Age (years)	73±10	74±8	73±9	0.850
Female gender	106 (91%)	73 (92%)	33 (89%)	0.565
Hypertension	63 (54%)	43 (54%)	20 (54%)	0.970
Diabetes mellitus	10 (9%)	7 (9%)	3 (8%)	0.893
Dyslipidemia	35 (30%)	24 (30%)	11 (30%)	0.943
Smokers	28 (24%)	17 (21%)	11 (30%)	0.335
Antecedent stressful event	79 (69%)	79 (100%)	0 (0%)	0.001
Associated disorders*	94 (81%)	62 (78%)	32 (86%)	0.163
Chest pain at presentation	85 (72%)	59 (75%)	26 (70%)	0.883
ST-segment elevation at presentation	70 (60%)	53 (67%)	18 (49%)	0.104
Left ventricular ejection fraction at admission (%)	36±9	37±9	35±10	0.358
Left ventricular apical dysfunction	106 (91%)	71 (90%)	35 (94%)	0.713
Peak serum creatine kinase value (U/L; median-IQ)	310 ± 376	282 ± 298	371 ± 508	0.269
Killip class III or IV	20 (17%)	13 (16%)	7 (19%)	0.107
Therapy recommended at discharge	81 (70%)	53 (67%)	28 (76%)	0.555
Beta-blockers	83 (72%)	57 (72%)	26 (70%)	0.256
ACE-Inhibitors	51 (44%)	39 (51%)	12 (32%)	0.067
Statins	10 (9%)	8 (10%)	2 (5%)	0.378
Calcium channel blockers				

*Chronic obstructive pulmonary disease (20)	Chronic renal insufficiency (5)	Chronic anemia (2)
Atrial fibrillation (12)	Chronic Hepatitis (4)	Still's disease (1)
Cancer (11)	Sjögren disease (3)	Epilepsy (1)
TIA/Stroke (9)	Valvular disease (3)	Allergy (1)
Thyroid disease (9)	Myasthenia gravis (2)	Sclerodermia (1)
Anxiety/depression (8)	Gastric ulcer (2)	

TABLE 2. In-hospital and long-term follow-up clinical outcomes.

	Tako-tsubo Cardiomyopathy (n=116)	Beta-blockers at discharge Yes (n=81)	No (n=35)	p value
In-hospital follow-up				
Death	2 (2%)	1 (1%)	1 (1%)	0.514
Heart failure	20 (17%)	14 (17%)	6 (17%)	0.985
Cardiogenic shock	6 (5%)	4 (5%)	2 (6%)	0.862
Atrial fibrillation	7 (6%)	4 (5%)	3 (8%)	0.450
Ventricular arrhythmia	1 (1%)	1 (1%)	0 (0%)	0.999
Left ventricular thrombosis	2 (2%)	1 (1%)	1 (3%)	0.537
Severe mitral regurgitation	18 (16%)	14 (17%)	4 (11%)	0.424
Left ventricular outflow tract obstruction	4 (3%)	4 (5%)	0 (0%)	0.001
Long-term follow-up				
Follow-up length (months)	24±15	22±14	27±16	0.131
Death	11 (9%)	6 (8%)	5 (14%)	0.264
cardiovascular	7 (6%)	3 (4%)	4 (11%)	0.108
non cardiovascular	4 (3%)	3 (4%)	1 (1%)	0.818
Tako-tsubo cardiomyopathy recurrence	2 (2%)	1 (1%)	1 (3%)	0.514
NYHA classification	1.6±0.8	1.5±0.8	1.9±0.8	0.005
Rehospitalization	28 (25%)	23 (32%)	5 (15%)	0.071
cardiovascular	15 (13%)	10 (12%)	5 (15%)	0.775
non cardiovascular	13 (12%)	11 (14%)	2 (6%)	0.217
Atypical chest pain	16 (14%)	13 (16%)	3 (8%)	0.382

NYHA: New York Heart Association

TABLE 3: Characteristics of patients who died.

	1	2	3	4	5	6	7	8	9	10	11
Age (years)	85	80	72	83	89	73	77	76	82	68	81
Female gender	+	+	+	+	+	0	+	+	+	+	+
Hypertension	0	0	0	+	0	+	+	0	+	0	+
Associated disorders	COPD	Myasthenia gravis	Previous Stroke	0	Previous Stroke, PAF	Previous Stroke	COPD, Thyroid disease	COPD, Thyroid disease	Previous Stroke, PAF	CRI	COPD, CRI
Stressful event before TTC	Traumatic femoral fracture	UNK	None	Fear for surgery	Trauma	None	COPD exacerbation	None	Death of a relative	Starting dialysis	Nose bleed
Mitral regurgitation grade	+++	+	++	+	++	+	+	+	++	+++	++
ST-segment elevation	+	+	+	0	0	0	+	+	+	0	0
Peak serum CK value U/L	101	255	67	68	247	2572	91	245	766	30	406
LVEF at admission (%)	30	40	35	40	40	25	30	15	28	30	40
LVEF at discharge (%)	-	-	55	50	45	55	60	60	37	48	40
LVEF at last FU (%)	30	48	55	55	60	55	60	58	50	53	57
Time of death (days)	1	4	121	200	210	295	426	541	563	570	769
Cause of death	Acute HF	HF and RF	SD	Sepsis	Pneumonia	Stroke	COPD	SD	Stroke	SD	COPD
Stressful event before death	NA	NA	Severe disability	0	0	UNK	0	0	UNK	Symptomatic PAD	UNK

UNK: unknown; NA: not applicable; LV EF: left ventricular ejection fraction; CK: creatine kinase; COPD: chronic obstructive pulmonary disease; HF: heart failure; RF: Respiratory failure; TTC: Tako-tsubo Cardiomyopathy; SD: sudden death; FU: follow-up, PAF: Parossistic atrial fibrillation, CRI: Chronic renal insufficiency, PAD: Peripheral artery disease