

Takotsubo Syndrome: Is This a Common Occurrence in Elderly Females after Hip Fracture?

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ABSTRACT

Background: The prevalence of Takotsubo syndrome in hip fracture is not known. **Methods:** Hip fracture patients were evaluated in a multidisciplinary unit. Patients with ECG abnormalities and increased troponin I values at the time of hospital admission were included in the study. Follow-up was clinical at 30 days and by telephonic interview at one year. **Results:** Between October 1st 2011 to September 30th 2016, 51 of 1506 patients had preoperative evidence of myocardial damage. Eight, all females, fulfilled the Mayo criteria for Takotsubo syndrome, six had no coronary lesions. Hip surgery was uneventful, and all eight were alive at thirty days, and seven of these were still alive after one year. Forty-three patients had myocardial infarction: mortality at thirty days and one year were 11% and 44% ($p < 0.0001$, Student's t-test; log-rank test). **Conclusion:** At least 15% of patients with hip fracture and preoperative myocardial damage had Takotsubo syndrome. They were all elderly females. Contrary to myocardial infarction, Takotsubo syndrome has a favourable long term prognosis.

Keywords: Takotsubo syndrome, hip-fracture, ischemic heart disease

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INTRODUCTION

In elderly patients with hip fracture, 10% to 30% may present with peri-operative myocardial infarction [1, 2]. It is not widely appreciated that, in about one-third of patients, myocardial damage occurs before rather than after surgery [1-3]. Takotsubo syndrome is characterized by acute left ventricular wall motion abnormalities, often leading to severe left ventricular systolic dysfunction. Females in their seventh or eighth decade of life, are more frequently affected [4-6]. Clinical presentation may range from mild symptoms to pulmonary oedema and cardiogenic shock [7, 8].

Electrocardiographic (ECG) abnormalities in precordial leads and transient apical and mid-ventricular akinesia/dyskinesia, often with typical "apical ballooning", are hallmarks of the syndrome. Coronary angiography usually is normal [9, 10]. Acute emotional or physical stress often precede the onset of symptoms [11]. Several conditions such as severe acute medical diseases, surgery or severe trauma are common triggers

of stress cardiomyopathy [5, 12], however, at present only a few cases have been reported in association with hip fracture [13]. ECG abnormalities and biomarkers elevation may allow a generic diagnosis of myocardial damage, however, without echocardiography Takotsubo syndrome may be missed.

The study aimed to investigate the prevalence of Takotsubo syndrome in patients with hip fracture and evidence of myocardial damage before hip-fracture surgery. Additionally, a second objective was to assess whether patients with stress cardiomyopathy have a different prognosis in comparison to patients with preoperative myocardial infarction.

METHODS

The records of 1506 patients with hip-fracture, admitted consecutively to the Hip-Fracture Unit of Azienda Ospedaliera Universitaria Careggi, Florence, Italy, in the period October 1st 2011 to September 30th 2016, were evaluated.

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All patients, on admission, had an electrocardiogram and troponin assay. In those with a troponin value > 0.5 $\mu\text{g/L}$, bed-side echocardiography was performed within twelve hours of hospitalization. Informed consent was obtained from all patients included in the study. The study was approved by the Italian Health Ministry (RF-2010-2316600) and Regione Toscana. All patients whose records showed that they met the criteria of myocardial infarction according to the Third Universal Definition of Myocardial Infarction [14] e.g. troponin increase in the presence of ECG or echocardiographic abnormalities suggesting myocardial ischemia were included in the study.

Patients aged < 70 years, with recent myocardial infarction occurring less than thirty days before trauma, renal failure indicated by a creatinine clearance of < 20 ml/min, and active neoplastic disease, were excluded from the study. According to these inclusion and exclusion criteria, fifty-one patients were enrolled in the study. Eight of these patients had wall motion abnormalities, as shown by transthoracic echocardiogram, fulfilling the Mayo clinic criteria for Takotsubo syndrome [15]. Coronary angiography was scheduled for each of these eight patients to confirm the clinical diagnosis. None of the other forty-three patients underwent coronary angiography before hip surgery. All patients included in the study received 100 mg aspirin (Bayer, Germany) daily, titrated bisoprolol (Sandoz, Germany) on a starting dose of 1.25 mg twice daily, 40 mg atorvastatin (Pfizer, Germany) and when hemodynamic conditions and kidney function allowed, a starting dose of 2.5mg ramipril (Ramipril Ratiopharm-TEVA group Germany) on a starting dose of 25-50 mg losartan (Losartan Teva, Germany).

All patients were seen in the outpatient department, thirty days after surgery. At one year post-surgery, a properly adapted questionnaire outcome measures were evaluated by telephone. Patients, or their relatives if a death had occurred, were questioned as to their current clinical condition, whether they had required further hospitalization and the date and cause of death of non-survivors.

Statistical analysis was performed using SPSS 18.0 (Chicago, IL, USA) statistical software. Continuous variables were expressed as the mean and standard deviation [Mean(SD)] and differences between the groups were evaluated using the Student *t*-test (two-tailed).

Categorical variables were compared using the χ^2 test or the Fisher exact test (two-tailed). Continuous

variables were compared between the groups using the Student *t*-test (two-tailed). Survival analysis was performed using two-tailed Kaplan-Meier curves. Differences between groups were compared using the Log-Rank test.

The significance level was set at a value = 0.05

■ RESULTS

The mean (SD) age of the fifty-one patients included in the study was 85 (9.1) years. Thirty-six were female.

In eight of these patients, all female, with a mean (SD) age of 84.7 (7.6) years, the mean(SD) troponin I values were 1.96 (1.67) mg/L. All eight patients had ECG and left ventricular wall motion abnormalities that fulfilled the Mayo clinic criteria for Takotsubo syndrome. They had a history of medical treated arterial hypertension; none had a clinical history suggesting the presence of pheochromocytoma. Furthermore, a diagnosis of myocarditis was considered unlikely considering their age. One suffered from moderate aortic stenosis (aortic valve area 1.2 cm^2 calculated with continuity equation), and another had thrombocytosis treated with oncocar-bide. None had a history of coronary heart disease.

Three patients had chest pain within twenty-four hours post-trauma, and one developed pulmonary oedema while waiting for the induction of anaesthesia. Another had two episodes of supraventricular arrhythmia.

In three asymptomatic patients, ECG and echocardiographic abnormalities, as well troponin increase, were detected during preoperative clinical evaluation. In five out of eight patients electrocardiogram showed at least 1 mm ST-segment elevation in adjacent precordial leads. In the other three, deep T wave inversions were observed in the same electrocardiographic leads. All eight patients had apical “ballooning” with severely decreased left ventricular function. ECG and echocardiographic characteristics of these patients are given in Table 1.

Six patients coronary had angiography to confirm a diagnosis of Takotsubo syndrome,

One patient refused an examination and another, considering her aged of ninety-six years, clinical criteria were considered sufficiently diagnostic. No significant coronary lesions were demonstrated in the six patients who underwent angiography. Hip-surgery was performed under general anaesthesia, on average

Table 1. Clinical characteristics of patients with stress cardiomyopathy after hip fracture

Fracture	Age	ECG	Echocardiogram at diagnosis	Echocardiogram at discharge	Troponin I peak $\mu\text{g/L}$	ASA risk	Day from diagnosis to hip surgery
Left hip fracture	90	ST-segment elevation V2-V4	Severe apical hypokinesia LVEF = 30% AVA 1,2 cm ²	LBB related septal asynchrony LVEF = 50%	1.14	4	6
Extracapsular left hip fracture	76	ST-segment elevation V1- V3	Severe apical hypokinesia LVEF = 38%	Improvement of segmental wall motion LVEF= 47%	0.52	3	7
Right hip fracture	75	Incomplete LBB ST-elevation V2-V4	Anterolateral hypokinesia, and apical septal hypokinesia LVEF = 29%	Normalization of LVWM LVEF = 63%	5.53	3	11
Left hip fracture	88	ST-elevation V2-V6, D3, avF	Apical akinesia, anterior hypokinesia LVEF = 45%	Normalization of LVWM LVEF = 55%	2.73	3	4
Right hip fracture	84	Mild ST elevation V2-V5	Akinesia of anterior septum and apex LVEF= 35%,	Normalization of LVWM LVEF =58%	1.53	3	3
Right per trochanteric fracture	86	Negative T waves V2-V5	Apical akinesia LVEF =35%	Normalization of LVWM LVEF= 53%	3.43	3	14
Left hip fracture	89	Negative T waves V3-V6, D3, avF	Apical akinesia LVEF= 32%	Improvement of LVWM LVEF= 48%	0.53	3	5
Right femur neck fracture	89	Negative T waves V2-V5	Apical ballooning LVEF =40%	Normalization of LVWM LVEF= 58%	0.51	3	5

LVWM = left ventricular wall motion, LVEF = left ventricular ejection fraction

6.4 days after admission to the hospital. The delay was needed to stabilize clinical conditions in patients with severe left ventricular dysfunction. Five patients were treated by the reduction and synthesis of the fracture, three with a hip prosthesis. None had postoperative complications and were discharged to rehabilitation services. Echocardiogram was repeated in the eight patients after hip surgery but before discharge. A significant improvement of left ventricular wall motion abnormalities was found in all patients. Mean (SD) left ventricular ejection fraction at discharge was 54 (5.2)% vs. 35.5 (5)% at the time of admission ($p < 0.001$ Student's t-test). The eight patients were alive and attended the "thirty days" post-discharge follow-up. One died of pneumonia-induced respiratory failure at one-year post-discharge.

Table 2 lists the clinical characteristics of the other forty-one patients diagnosed with myocardial infarction before surgery. Fifteen were males, mean (SD) age was 86.7 (7.9) years not significantly different from patients with Takotsubo syndrome ($p = 0.2$).

Only one patient presented with an ST-segment elevation. Surgery was performed after hemodynamic stabilization. Mean(SD) time from admission to surgery was 3.7 (2.5) days.

Twenty-two patients had a history of coronary artery disease, and eleven had previous surgical or percutaneous revascularization in comparison to zero in the Takotsubo syndrome group (respectively $p = 0.007$ and $p = 0.01$). At the time of admission, left ventricular ejection fraction was significantly lower in patients with Takotsubo syndrome ($p < 0.0001$) while mean peak troponin values were higher in patients with myocardial infarction ($p < 0.0001$).

Other comorbidities and risk factors were not significantly more frequent in patients with myocardial infarction in comparison to Takotsubo syndrome.

Patients with preoperative myocardial infarction were treated with medical therapy, as reported in the methods section. Thirty-two underwent surgery under general anaesthesia, without relevant complications

Table 2. Clinical characteristics of patients with preoperative myocardial infarction in comparison to those with stress cardiomyopathy

	Preoperative Myocardial infarction (n=43)	Stress Cardiomyopathy (n=8)	p
Gender (F/M)	28/15	8/0	0.08
Age (years) (mean-SD)	86.7 (7.9)	84.7 (7.6)	0.20
Coronary heart disease	22	0	0.007
Diabetes	24	2	0.14
Hypertension	33	8	0.09
Dementia	10	1	0.6
Peripheral vascular disease	13	1	0.4
Need for RB transfusion	15	5	0.23
Double antiplatelet drug	7	0	0.5
Atrial fibrillation	14	1	0.4
Oral anticoagulation	11	1	0.4
Admission LVEF (%) (mean-SD)	45.8 (6.3)	35.5 (5.3)	0.0001
Troponin I peak µg/L (mean-SD)	12.7 (4.8)	1.96 (1.8)	0.0001
Thirty-day mortality	5	0	0.5
One-year mortality	19	1	0.12
Cause of death			
Non-cardiac	5	1	0.25
Cardiac	15	0	

in the first twenty-four hours, post-admission. Three patients died during hospitalization, one patient due to refractory heart failure, the other two patients died suddenly, probably due to malignant ventricular arrhythmias, though this can not be verified as patients were not ECG monitored at the time of death. Ventricular fibrillation and respectively asystole were recorded when firstly assisted. CPR was unsuccessful. The overall mortality was 11% at thirty days and 44% at one year (log-rank test $p < 0.0001$). Fifteen patients died due to cardiac causes in the follow-up period.

■ DISCUSSION

Limited data exist on patients with acute myocardial infarction diagnosed at the time of hospital admission after hip fracture [1-3, 16]. In most of these studies, the diagnosis was made in patients with an increase in troponin levels above the 95th percentile of reference values. There are few reports, including electrocardiographic and echocardiographic findings. Thiagarajah et al. (2011) reported a longer time to hip surgery, on average, six days from trauma, in twenty-five patients with hip fracture and preoperative myocardial infarction [1]. Mortality was 28% at thirty days. Other extensive retrospective studies reported thirty days and one-year mortality close to 15% and 40% respectively

[2, 3, 16]. Our data confirm that preoperative myocardial infarction is associated with a poor prognosis both at thirty days post operatively and one year. To allow clinical stabilization, it is our opinion that surgery should be delayed in patients with rising troponin levels which suggests ongoing ischemic damage, and in those who develop severe left ventricular dysfunction. Hemodynamic monitoring during general anaesthesia may limit further myocardial injury. Moreover, careful management of fluids and blood is recommended. However, at present, no clear indications for time to surgery are reported in existing guidelines.

Takotsubo syndrome, described variously as a transient left ventricular apical ballooning syndrome, stress-induced cardiomyopathy, “broken heart syndrome,” or ampulla-shaped cardiomyopathy, is a reversible cardiomyopathy triggered by acute psychological or physical stress that mimics acute myocardial infarction [7, 8]. This syndrome is more likely to occur in women and is more frequent in the seventh and eighth decade of life. Relevant emotional stress, such as accidents, deaths, quarrels and other life-changing events, preceded the syndrome in 14–38% of reported cases. Health-related triggers such as acute medical diseases or surgery are associated with the syndrome in 17–70% of patients [5, 11]. Chest pain and dyspnoea are the more frequent onset symptoms in Takotsubo cardiomyopathy. Oc-

asionally cardiogenic shock, syncope, ventricular arrhythmias and cardiac arrest may occur. Electrocardiogram usually shows ST-segment elevation in precordial and lateral leads followed by T wave inversion. Increase of troponin levels is generally limited. Left ventricular wall motion abnormalities of the apical segment of the left ventricle and the hyperkinesis of the basal segment are the more frequent abnormalities observed at echocardiogram. Significant coronary artery stenosis, $\geq 50\%$, are not detected by coronary angiography.

Several pathophysiological have been hypothesized. Currently, catecholamine-induced cardiotoxicity is considered the more probable cause of Takotsubo syndrome [16]. According to the hypothesis of stunned neurogenic myocardium, the first cause of the Takotsubo cardiomyopathy could be neurogenic, due to precipitant, sudden, severe and unexpected emotional distress [17-19]. Coronary angiography should be performed to confirm the clinical diagnosis [20]. The recently developed InterTAK Diagnostic Score, based on clinical features and ECG, may allow to predict the probability of Takotsubo syndrome and to distinguish it from acute coronary syndromes (ACS) [21].

Although formerly considered a transient phenomenon with an overall favourable long-term prognosis, recent studies suggest that functional abnormalities may persist up to and beyond twelve months post-diagnosis [22]. Moreover, long-term outcomes may be related to a stress factor favouring Takotsubo syndrome. In a recent study, Ghabri et al. [23] reported a higher mortality rate in patients in whom Takotsubo syndrome was related to physical stress, such as medical conditions or procedures, neurologic disorders or physical activities, in comparison to patients without identifiable triggers [23].

At present, only a few cases of Takotsubo syndrome have been reported in trauma patients, including patients with hip fracture [13, 24, 25]. Despite the National Confidential Enquiry into Peri-operative Deaths Report's recommendations [26], an echocardiogram is rarely performed in patients with hip fracture. Missing characteristic left ventricular wall motion abnormalities may lead to a severe underestimation of the syndrome.

In the present study, Takotsubo syndrome was diagnosed in eight elderly females, which accounted for 0.05% of the whole population aged > 70 years referred for hip fracture, and 15% of patients with preoperative troponin increase. Six coronary angiographies allowed confirmation of the clinical diagnosis.

The study reports a population never described before in patients with hip fracture. Time to surgery has been highly variable in patients with Takotsubo syndrome since there were no recommendations or guidelines to follow. All patients had severe left ventricular dysfunction at the time of hospital admission with clinical signs of low output and pulmonary congestion. Therefore surgery was planned after hemodynamic stabilization and in the absence of significant complications. The overall small number of patients with Takotsubo syndrome does not allow definitive conclusions to be drawn. Nevertheless, long-term prognosis in these patients does appear significantly better than in patients with myocardial infarction.

■ CONCLUSION

Data from the present study confirm that myocardial infarction, diagnosed at the time of hospital admission, is associated with higher mortality in patients undergoing surgery for hip fracture. In acute coronary syndromes, interventional treatment before hip surgery may be related to a very high risk of bleeding in the site of the fracture, and at present no indication exists about preoperative invasive strategy in patients who need urgent non-cardiac surgery. Moreover, delay in the treatment of proximal fractures of the femur is associated with a low probability of functional recovery and with increased risk of early complications and death. Correct and early recognition of Takotsubo syndrome has particular relevance in patients who need urgent non-cardiac surgery. Segmental wall motion abnormalities are transient.

Moreover, these patients had no significant epicardial coronary stenosis. These findings are associated with an acceptable surgical risk within a few days after the onset of symptoms. According to the data obtained in the present study, the prognosis in Takotsubo patients after hip fracture is significantly more favourable than in patients with peri-operative myocardial infarction. All eight patients were alive at thirty days, and seven of these patients survived to the one-year follow-up after hip surgery. Whether coronary angiography is needed in patients whose clinical presentation suggests stress cardiomyopathy syndrome requires to be evaluated by a more extensive multicentre study.

■ CONFLICT OF INTEREST

None to declare.

■ REFERENCES

- Thiagarajah S, Fenton A, Sivardeen Z, Stanley D. The management and mortality of patients undergoing hip fracture surgery following recent acute myocardial infarction *Acta Orthop. Belg.* 2011; 77: 626-31.
- Gupta BP, Huddleston JM, Kirkland LL, et al. Clinical Presentation and Outcome of Perioperative Myocardial Infarction in Very Elderly Following Hip Fracture Surgery *J Hosp Med.* 2012; 7:713-6.
- Hietala P, Strandberg M, Strandberg N et al. Peri-operative myocardial infarctions are common and often unrecognized in patients undergoing hip fracture surgery. *J Trauma Acute Care Surg* 2013;74:1087-91.
- Gianni M, Dentali F, Grandi AM et al. Apical ballooning syndrome or Takotsubo cardiomyopathy: a systematic review. *Eur Heart J*, 2006;7:1523-9.
- Lyon AR, Bossone E, Schneider B et al. Current state of knowledge on Takotsubo syndrome: a Position Statement from the Taskforce on Takotsubo Syndrome of the Heart Failure Association of the European Society of Cardiology. *Eur J Heart Fail* 2016;18:8-27.
- Ghadri JR, Wittstein IS, Prasad A et al. International Expert Consensus Document on Takotsubo Syndrome (Part I): Clinical Characteristics, Diagnostic Criteria, and Pathophysiology *E Heart J* 2018;39:2032-46.
- Desmet WJ, Adriaenssens BF, Dens JA. Apical ballooning of the left ventricle: first series in white patients. *Heart.* 2003;89(9):1027-31.
- Tsuchihashi K, Ueshima K, Uchida T et al. Transient left ventricular apical ballooning without coronary artery stenosis: a novel heart syndrome mimicking acute myocardial infarction. *Angina Pectoris-Myocardial Infarction Investigations in Japan J Am Coll Cardiol*, 2001;38:11-8
- Prasad A, Lerman A, Rihal CS Apical ballooning syndrome (Tako-Tsubo or stress cardiomyopathy): a mimic of acute myocardial infarction *Am Heart J.* 2008; 155: 408-17
- Watanabe H, Kodama M, Okura Y, et al. Impact of earthquakes on Tako-tsubo cardiomyopathy. *JAMA*, 2005; 294:305-7.
- Donohue D, Movahed M. Clinical characteristics, demographics and prognosis of transient left ventricular apical ballooning syndrome. *Heart Fail Rev.* 2005;10:311-6.
- Pilgrim TM, Wyss TR. Takotsubo cardiomyopathy or transient left ventricular apical ballooning syndrome: a systematic review. *Int J Cardiol.* 2008;124:283-92.
- Rostagno C, Cammilli A, Di Cristo AL et al. Acute coronary syndromes with significant troponin increase in patients with hip fracture prior to surgical repair: differential diagnosis and clinical implications" in *Intern Emerg Med.* 2016;11:219-24.
- Thygesen K, Alpert JS, Jaffe AS, et al. The Writing Group on behalf of the Joint ESC/ACCF/AHA/WHF Task Force for the Universal Definition of Myocardial Infarction. Third Universal Definition of Myocardial Infarction *Circulation* 2012;126:2020-35.
- Bybee KA, Kara T, Prasad A, et al. Systematic review: transient left ventricular apical ballooning: a syndrome that mimics ST-segment elevation myocardial infarction. *Ann Intern, Med.* 2004;141(11):858-65.
- Spurrier E, Wordsworth D, Martin S, et al. Troponin T in hip fracture patients: Prognostic significance for mortality at one year. *Hip Int.* 2011; 21:757-61.
- Nef HF, Mollmann H, Akashi HY, Hamm CW Mechanisms of stress (Takotsubo) cardiomyopathy. *Nat Rev Cardiol.* 2010;7:187-93.
- Merli E, Sutcliffe S, Gori M, Sutherland GG. Tako-Tsubo cardiomyopathy: new insights into the possible underlying pathophysiology. *Eur J Echocardiogr.* 2006;7:53-61.
- Tranter MH, Wright PT, Sikkil MB, Lyon, AR. Takotsubo cardiomyopathy: the pathophysiology. *Heart Fail Clin.* 2013;9:187-196.
- Wittstein IS, Thiemann DR, Lima JAC et al. Neurohumoral features of myocardial stunning due to sudden emotional stress. *N Engl J Med.* 2005; 352:539-548.
- Ghadri JR, Wittstein IS, Prasad A, et al. International Expert Consensus Document on Takotsubo Syndrome (Part II): Diagnostic Workup, Outcome, and Management *Eur Heart J.* 2018;39:2047-62.
- Scally C, Rudd A, Mezincescu A et al. Persistent Long-Term Structural, Functional, and Metabolic Changes After Stress-Induce (Takotsubo) Cardiomyopathy *Circulation.* 2018; 137:1039-48.
- Ghadri JR, Kato K, Cammann VL et al. Long-Term Prognosis of Patient With Takotsubo Syndrome *J Am Coll Cardiol.* 2018; Aug 21;72(8):874-882.
- Vergez M, Pirracchio R, Mateo J, Payen D, Cholley B Tako Tsubo cardiomyopathy in a patient with multiple trauma. *Resuscitation* 2009;80: 1074-7.
- Krpata DM, Barksdale M jr. Trauma induced left ventricular apical ballooning syndrome in a 15-year-old: a rare case of Tako-Tsubo cardiomyopathy. *J Pediatr Surg.* 2013;48: 876-9.
- The National Confidential Enquiry into Peri-operative Deaths Report 2001. Changing the way we operate [<http://www.ncepod.org.uk/2001cwo.htm>]