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Typical takotsubo cardiomyopathy in suspected ST elevation myocardial infarction patients admitted for primary percutaneous coronary intervention

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ABSTRACT

Aim: Takotsubo cardiomyopathy (TCM) is increasingly being recognised in patients admitted with suspected acute coronary syndrome, as access to angiography and echocardiography is much quicker than before. We aimed to analyse the prevalence of typical TCM in patients admitted for primary percutaneous coronary intervention (PPCI) with suspected ST elevation myocardial infarction (STEMI) to a single tertiary centre in United Kingdom.

Methods: All patients admitted to our unit with suspected STEMI from September 2009 to November 2011 were included for analysis.

Results: Of the 1875 patients admitted, 17 patients (all female) with mean age of 69 ± 11.9 yrs were identified to have clinical features of typical TCM, thus giving an overall prevalence of 0.9% in PPCI admissions (3.2% prevalence in women). The admission ECG showed ST elevation in 14 patients (82%) and 3 had LBBB (18%). In the 16 patients who had raised hs Troponin (normal range <14), the mean level was 921 ± 668 (median 778, range 110 to 2550) ng/L. Two patients survived cardiac arrest and one had apical thrombus on presentation. Left ventricular function was severely impaired ($EF \leq 30\%$) in 2 patients, whilst it was moderately impaired ($EF 31-50\%$) in others. During a mean follow-up period of 22 ± 7 months (range 8–36 months), there was no mortality or recurrence.

Conclusion: This is the first observational study to report the prevalence of typical TCM in patients admitted for PPCI in “real-world” practice. Though this condition is not benign during the acute episode, there is a good survival outcome if managed appropriately during the acute phase.

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1. Introduction

Takotsubo cardiomyopathy (TCM) is a reversible cardiomyopathy, occurring predominantly in post-menopausal women mostly due to emotional or physical stress, but occasionally due to unknown reasons [1–3]. Typically, patients present with chest pain and ST elevation or T wave inversion on their electrocardiogram (ECG) mimicking acute coronary syndrome, but with normal coronary arteries or non-flow limiting disease. One of the cardinal features of TCM is that the LV dysfunction extends beyond a single coronary territory. The wall motion abnormalities typically involve akinesia of the apex of the left ventricle with hyperkinesia of the base of the heart. Variant forms of left ventricular dysfunction have been reported, including wall-motion abnormalities such as mid-ventricular ballooning with sparing of the basal and apical segments, or inverted Takotsubo, where the apex is spared with basal wall abnormalities [4].

The prevalence among patients with symptoms suggestive of acute coronary syndrome is 1.0–2.5%, with almost 90% of cases being in post-menopausal women [4,5]. Overall, in patients suspected of ST elevation myocardial infarction (STEMI), the prevalence is 2%, but this included patients who were admitted for both pharmacological and mechanical reperfusion [5]. However, there is no “real-world” observational data about the prevalence of typical TCM in patients admitted for primary percutaneous coronary intervention (PPCI) for STEMI. We therefore analysed our database to identify patients with typical TCM who were admitted to our unit with suspected STEMI for PPCI and followed them up.

2. Methods

Primary PCI for STEMI in our unit started in September 2009 and we included all patients who were admitted with suspected STEMI for PPCI from September 2009 to November 2011 (inclusive). Our PPCI service is 24/7 service covering a catchment population of 1.6 million in east of England, which is predominantly a white Caucasian population. Activation of the STEMI pathway in our centre involves the PPCI team (consultant cardiologist, specialist registrar, cardiac catheter

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lab nurse, radiographer and physiologist) being called in when the paramedics or doctors in the emergency department of our referring hospitals (six in total) make the diagnosis of STEMI. The patients are brought to our centre and assessed by the PPCI team and further management such as coronary angiography, PCI, echocardiography and/or non-cardiac investigations are planned immediately.

We retrospectively analysed the echocardiogram and/or left ventriculogram of those patients who did not undergo PPCI to identify patients with typical left ventricular (LV) features of apical akinesia with basal hyperkinesia. In those patients who had echocardiography, they were performed within 12 h of admission. The inclusion criteria to identify TCM were patients presenting with chest pain, ECG abnormalities of ST elevation or LBBB, the absence of significant coronary disease with no artery having >50% stenosis on coronary angiography and the typical regional wall motion abnormalities described above with full recovery of LV function in follow-up echocardiography. The other echocardiographic parameters assessed include LV ejection fraction (LVEF), right ventricular (RV) function, mitral regurgitation and left ventricular outflow tract peak velocity. The LVEF was assessed using 2-dimensional Simpson's method. Their follow-up echocardiography reports were obtained from our hospital and in some cases from their respective district general hospitals. Clinical records of those who fulfilled the above criteria were reviewed to obtain baseline and clinical characteristics of patients. Their discharge medications were also reviewed from their discharge summaries. Mortality data were obtained from the National Health Service (NHS) Spine Summary Care Record (SCR) database, which is a centralised database that gets updated on a weekly basis. This was obtained using automatic flagging for date of death with the unique NHS number available for individual patients, which meant 100% mortality follow-up data.

3. Results

During the study period, 1875 patients were admitted to our unit with suspected STEMI for PPCI. Except for 20 patients, all others ($n = 1855$) underwent coronary angiography and 1471 patients proceeded on to have PPCI. Of those who did not undergo PPCI ($n = 404$), 30 patients did not have documented assessment of LV function (either by echocardiography or left ventriculography) during their index admission and they were excluded from this analysis. On reviewing the echocardiogram and/or left ventriculogram of other 374 patients, we identified 22 patients (3 m, 19 f) with LV features of typical TCM. Out of this, 17 patients had complete recovery of their LV function on follow-up echocardiography and they were diagnosed to have TCM and included for analysis. This accounts for 0.9% of typical TCM in all patients admitted for PPCI (17/1845) and 4.5% (17/374) in those who did not undergo PPCI. All 17 patients were female and their mean age was 70 ± 10.7 yrs (median 66, range 56–94 yrs). The flow chart used in the study to identify TCM is shown in Fig. 1. The prevalence of typical TCM in female patients admitted for PPCI was at 3.2% (17/540), while prevalence in men was zero, as shown in Fig. 2. The baseline and clinical characteristics of all 17 patients are shown in Table 1.

The admission ECG showed ST elevation in 14 patients (82%) and 3 had LBBB (18%). High sensitivity troponin levels were high (normal value <14 ng/L) in all, except one patient. In those who had positive troponin, the mean level was 921 ± 668 (median 778, range 110 to 2550) ng/L. Normal smooth coronary arteries were noted in 11 patients (64.7%) and 6 (35.3%) had mild atheromatous coronary artery disease. Two patients had cardiac arrest prior to hospital admission with successful resuscitation (patient No: 6 in Table 1 had VF arrest and patient No: 8 had PEA arrest). The one patient who had cardiac arrest had LVEF of 20% and had significantly impaired right ventricular function. This patient was managed with insertion of intra-aortic balloon pump (IABP) along with supportive therapy. The IABP was removed after 3 days when the LVEF started to improve.

Patients admitted with suspected STEMI

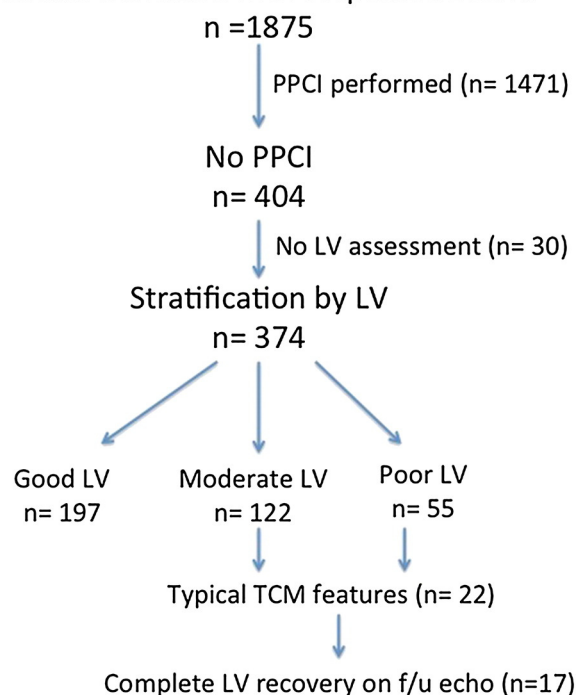


Fig. 1. Flow chart to identify TCM patients in our study. (STEMI – ST segment elevation MI, PPCI – primary percutaneous coronary intervention, LV – left ventricle, f/u – follow up).

The mean LV ejection fraction (EF) was $40.1 \pm 8\%$ ranging from 20 to 50% (median 40%). Apical thrombus was noted in one patient and therefore she was anti-coagulated with warfarin. On repeat echocardiography after 3 months, the thrombus disappeared and the LV function normalised for this patient. Therefore warfarin was discontinued after this. The echocardiographic parameters of the patients are shown in Table 2. The follow-up echocardiogram was performed within 3 months of their index admission in 15 patients. In the other 2 patients, the follow-up echocardiogram was performed between 3 and 6 months (delayed for non-clinical reasons). All of them had complete LV recovery.

Aspirin, beta-blocker, angiotensin converter enzyme inhibitor (ACE-I) or angiotensin receptor blocker (ARB) was prescribed to 13 (76.5%), 13 (76.5%) and 15 (88.2%) patients respectively on their discharge (Table 1). During a follow-up period of 22 ± 7 months (range 8–36 months), all 17 patients were alive with no recurrence of TCM.

4. Discussion

To the best of our knowledge, this is the first observational study in English literature to report the prevalence of typical TCM in patients admitted for primary PCI for STEMI in “real-world”. Our centre is a high volume cardiac unit in United Kingdom with a large catchment population of 1.6 million people. Patients with suspected STEMI are brought to our centre by 2 pathways – one, direct to our centre by the paramedics and the other by referral from emergency department from one of our 6 referring hospitals, thus reflecting the contemporary practice at present time. The decision to perform angiography and other investigations is made immediately by senior medical staff on patients' arrival. Once decision is made, angiography is performed within 30 min of arrival in most patients.

According to a systematic review by Gianni et al, the prevalence of this condition in suspected STEMI population was 2%, but this included patients who were admitted for both pharmacological and mechanical reperfusion [5]. There are few limitations in identifying patients with TCM in patients who had ST elevation who underwent pharmacological reperfusion therapy. The coronary angiogram for these patients would

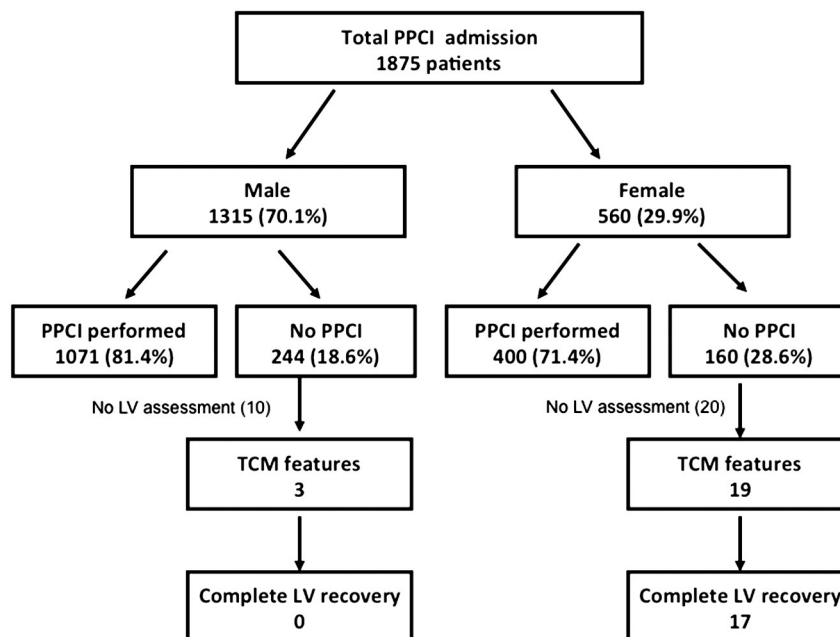


Fig. 2. Gender based flow chart to identify prevalence of TCM in both genders. (PPCI – primary percutaneous coronary intervention).

have been performed few days after reperfusion therapy and may have shown non-flow limiting lesion in their coronary arteries. This might have led to the diagnosis of TCM in few patients. The caveat to this is they might well have had thrombus in their coronary artery during the index presentation with no significant underlying stenosis. Reperfusion therapy during admission would have cleared the thrombus and re-canalised the culprit artery (for example, a large “wrap-around” LAD), which would appear as non-significant flow limiting lesion in coronary angiography. These patients would have been included in the TCM group leading to over-estimation of TCM in these studies. With the introduction of primary percutaneous coronary intervention (PPCI) for STEMI patients, coronary angiography is performed immediately after the diagnosis of STEMI is made on the ECG and this will identify patients with coronary thrombus immediately and avoid over-diagnosing TCM.

Even though initial reports about TCM were from Japan, it has subsequently been reported from many countries around the world, few of which were from Europe [6–12]. Of all the series from Europe, a single

centre from Switzerland had the largest number of TCM patients ($n = 46$) over a three-year period [11]. In this series, the prevalence of TCM was 1.7% in ACS patient with the delay in angiogram of up to 48 h after symptom onset. Emotional or physical stress was noted in 61% of the patient, compared to 55% in our series. ST segment elevation was noted only in 39% of the patient, while our series had 82%. Typical apical ballooning pattern was noted in 81% of their patient, while our study only included the apical TCM. Follow-up echocardiography was performed only in 36 patients (88%) in the Swiss series, whereas we included complete LV recovery as one of the criteria for diagnosing TCM as per the Mayo clinic criteria [13], which states “reversible” or “transient” regional wall motion abnormalities as described before. If we include all patients who had typical TCM features in index presentation without strict LV function recovery as diagnostic criteria, the prevalence rate would be 1.2%. There was no cardiac mortality in both studies over a prolonged follow-up period. In another recent series from Italy, the prevalence of TCM was 1.2% in all patients admitted with acute myocardial infarction (including patients with STEMI and non-STEMI) [12]. The

Table 1

Clinical characteristics of all 17 patients with typical Takotsubo cardiomyopathy.

Patient	Age (yrs)/sex	Admission ECG	Precipitating factor	Ethnicity	Diabetes	Hypertension	Hs Trop (ng/l)	LV EF (%)	Aspirin	Beta-blocker	ACE-I/ARB	F/U period (months)
1	74/F	Anterior STEMI	Post op	Caucasian	0	+	530	40	0	0	+	36
2	94/F	Anterior STEMI	Fracture wrist	Caucasian	0	+	110	40	+	+	+	35
3	57/F	Infero-lateral STEMI	Argument at home	Caucasian	0	0	2230	45	+	+	+	32
4	56/F	Anterior STEMI	Family stress	Caucasian	0	0	2550	45	+	+	+	23
5	71/F	Lateral STEMI	Funeral of close cousin	Caucasian	0	0	410	35	0	+	+	22
6	57/F	Ant-lateral STEMI	Unknown	Caucasian	0	+	1322	20	+	+	+	19
7	66/F	LBBB	Unknown	Caucasian	0	0	224	50	+	0	0	19
8	64/F	LBBB	Unknown	Asian	0	0	805	35	0	0	0	19
9	67/F	Ant-lateral STEMI	Missed flight	Caucasian	0	0	877	45	0	+	+	12
10	82/F	Lateral STEMI	Recent bereavement	Caucasian	0	0	750	48	+	0	+	8
11	77/F	Lateral STEMI	Family stress	Caucasian	0	+	850	35	+	+	+	22
12	65/F	Lateral STEMI	Unknown	Caucasian	0	+	606	48	+	+	+	19
13	80/F	Ant-lateral STEMI	Unknown	Afro-Caribbean	0	0	570	49	+	+	+	22
14	83/F	Lateral STEMI	Unknown	Caucasian	0	+	1190	40	+	+	+	24
15	62/F	LBBB	Unknown	Caucasian	0	+	8	35	+	+	+	19
16	65/F	Lateral STEMI	Unknown	Caucasian	0	+	484	46	+	+	+	16
17	62/F	Lateral STEMI	Chest infection	Caucasian	+	0	1220	30	+	+	+	21

Ant – anterior, F/U – follow-up, Hs Trop – high sensitivity troponin (normal value <14 ng/l), Inf – inferior, LBBB – left bundle branch block, LVEF – left ventricular ejection fraction, STEMI – ST elevation myocardial infarction.

Table 2
Echocardiographic features of TCM patients in our study (n = 17).

Severely impaired LV	2 (11.8%)
Moderately impaired LV	15 (88.2%)
RV impairment	2 (11.8%)
Mitral regurgitation	
None	13 (76.5%)
Mild	3 (17.6%)
Moderate	1 (5.9%)
LVOT peak velocity	
<1 m/s	6 (35.3%)
>1 m/s	9 (52.9%)
>2 m/s	2 (11.8%)
Apical thrombus	1 (5.9%)

mean time delay from admission to coronary angiography was 10 ± 11 h compared to our patients who had their coronary angiogram within 30 min of their admission. Also, our patients were admitted via primary PCI pathway activation, which meant a shorter call (for help) to angiography time. Complication rates were higher in our study with two patients suffering a cardiac arrest, compared to none in the above study. Cardiac arrest in TCM is controversial, as it is difficult to differentiate if the cardiac arrest is a cause or consequence of TCM. In our study, both patients who had cardiac arrest were not found to have any other diagnosis to precipitate the cardiac arrest. So one would assume that these were related primarily to the TCM than as a cause of TCM.

In those patients who were included in the large multi-centre randomised Harmonizing Outcomes with Revascularization and Stents in Acute Myocardial Infarction (HORIZONS-AMI) study comparing bivalirudin with glycoprotein IIb/IIIa inhibitors and heparin in STEMI patients undergoing PPCI, the prevalence of TCM was reported as 0.45% [14]. However, these are selected patients and do not represent the real-world patients admitted for PPCI in STEMI. This may be the reason for the low incidence in this study, compared to the published observational data. Our results of 0.9% prevalence of TCM falls in between the above two studies, which probably reflects the “real-world” prevalence of TCM in patients admitted with STEMI at the present time.

TCM occurred more commonly in women in our study, which is similar to the latest studies mentioned above [11,12]. There are 2 possible explanations for this: firstly, this may be related to the hormonal imbalance which frequently occurs in post-menopausal women. Alternatively this could be explained by the fact that men who develop the syndrome are more likely to die suddenly and thus do not survive till diagnosis.

The one patient who had cardiac arrest and severely impaired LV function in our study appears to have an extreme form of this condition. She also had severely impaired RV function which confirms the previous report by Haghi et al. that RV involvement is an indication of extreme form of this condition [15]. The previous study also showed that pleural effusion was more common in TCM patients with RV involvement (67% vs 8%, $p < 0.001$) and was predictive of RV dysfunction. Significant or bilateral pleural effusions were seen exclusively in patients with RV dysfunction [15].

5. Limitation

The main limitation of our study to identify TCM patients is the lack of cardiac MRI (CMR) imaging for these patients. Though echocardiogram or left ventriculogram identifies the typical regional wall motion abnormalities of TCM, CMR can be extremely useful in helping differentiate TCM from different types of cardiomyopathy as well as myocarditis. Early CMR is crucial as most of the imaging findings are usually present in the first 24–48 h followed by a complete recovery within days. Late gadolinium enhancement (LGE) is usually absent, in contrast to other causes of myocardial damage such as myocardial infarction or severe LV dysfunction due to myocarditis [16].

In all the previous studies and in our study, there were few patients with mild to moderate atheroma noted in their coronary arteries.

However, none of the studies including ours used intracoronary diagnostic imaging tools to ascertain the nature of atheroma. It is well recognised that plaque rupture is extremely difficult to identify with conventional 2-dimensional angiography in certain situations. Intracoronary imaging such as intravascular ultrasound (IVUS) or optical coherence tomography (OCT) would be able to identify ruptured plaque and would differentiate from TCM in certain patients.

Also, our study only looked at the prevalence of typical TCM, whereas other variants such as inverted and mid-wall TCM have been reported previously.

6. Conclusion

This first observational study of typical TCM in STEMI patients admitted for PPCI to a single large tertiary centre showed an overall prevalence of 0.9% with 3.2% prevalence in the female population. Further reports of this condition with the early use of cardiac MRI and intravascular imaging techniques during coronary angiography in doubtful situation are needed to confirm this finding. Though TCM is not benign during the acute episode, there is a good long-term survival outcome if managed appropriately during the acute phase.

Learning points

- No current data available about prevalence of TCM in “real-world” PPCI admissions for STEMI.
- 0.9% prevalence in patients admitted for PPCI in a single high volume UK centre.
- Prevalence of 3.2% in women admitted for PPCI.
- TCM is not a benign condition during acute presentation.
- Good long-term survival outcome if managed appropriately.

Conflict of interests

We declare that we participated in the authoring of this paper and have seen and approved the final version. We also declare that there is no conflict of interest.

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