

Takotsubo cardiomyopathy associated with epinephrine use: A systematic review and meta-analysis



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ABSTRACT

Background: Takotsubo cardiomyopathy is a syndrome of transient cardiac dysfunction that is frequently associated with sudden emotional or physical stress. Epinephrine use has been implicated in precipitating Takotsubo cardiomyopathy in multiple case reports and case series. We sought to systematically review the current English literature on this association.

Methods: We searched relevant articles on Takotsubo cardiomyopathy associated with epinephrine administration and extracted data on demographic characteristics, clinical features, investigations and clinical outcomes.

Results: We identified total of 41 cases from 36 articles. The mean age of presentation was (47.07 ± 15.73) years with strong female preponderance (83%, $P = 0.0001$). The most common symptom at presentation was chest pain (82%). Mean peak troponin I level was (7.12 ± 11.22) ng/ml. The most common EKG abnormality was ST elevation, seen in 40% of patients. The most common finding on echocardiography was apical hypokinesis, seen in 48.78% cases. Patients younger than 45 were less likely to have apical cardiomyopathy ($n = 5/20$, 25%) compared to patients with age >45 ($n = 14/21$, 66%, p value 0.001, OR 0.17). The most common route of administration of epinephrine was intravenous (65.85%). All patients except one survived with complete recovery of systolic function reported in most cases within an average of 14.7 days.

Conclusion: Exposure to epinephrine in clinical practice can trigger Takotsubo cardiomyopathy, which is rapidly reversible with good prognosis in most cases. This review further supports the notion that both exogenous and endogenous catecholamines are associated with the pathogenesis of Takotsubo cardiomyopathy.

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1. Introduction

Takotsubo cardiomyopathy (TC), also known as stress cardiomyopathy (SC), is a syndrome characterized by profound but rapidly reversible systolic dysfunction that is often precipitated by acute emotional or physical stress [1]. This disorder was initially reported in Japan in 1991, when authors found the shape of an affected left ventricle (LV) seemed to resemble a Takotsubo, or a Japanese octopus pot [2]. The syndrome clinically resembles acute coronary syndrome, with elevated cardiac markers, EKG changes, reversible LV dysfunction but almost always reveals normal coronary arteries on coronary angiography (CA) [3]. Several hypotheses have been proposed regarding its pathogenesis, however catecholamine-induced microvascular dysfunction that leads to myocardial stunning and toxicity are currently the most widely accepted [4,5]. This hypothesis is supported by two clinical observations of patients with stress cardiomyopathy. First, plasma catecholamine levels are significantly elevated in stress cardiomyopathy than similar patients

with acute myocardial infarction due to plaque rupture [2]. Second, endomyocardial biopsy specimens of patients diagnosed with TC show mononuclear infiltration and contraction band necrosis, a form of myocyte injury seen in clinical states of catecholamine excess [2]. Epinephrine is widely used for the management of cardiac arrest, hypotension, cardiogenic shock and anaphylaxis. If catecholamines are the causative factor in Takotsubo cardiomyopathy, it is quite plausible that exogenous catecholamine administration may provoke this condition, and indeed has been described in case reports. The purpose of the present study was to expand the current understanding on the association of exogenous catecholamine administration and TC by performing a systematic review and analysis of the English literature.

2. Materials and methods

2.1. Search strategy

A systematic electronic search of MEDLINE (via PubMed), EMBASE, clinicaltrials.gov and the Cochrane library was performed for case reports, case series and systematic reviews on stress cardiomyopathy secondary to epinephrine use from inception until June 18, 2016. The search was performed using two broad search themes "stress cardiomyopathy" and "epinephrine" (Supplementary file 1). These themes were combined using

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boolean operator “AND”. We also performed a hand search of references from included articles to identify additional publications. Only the articles written on human subjects and in English language were included.

2.2. Eligibility criteria

1. Age over 18
2. Reports in English delineating use of epinephrine
3. Development of stress cardiomyopathy according to revised Mayo Clinic criteria [6].

Screening of articles for eligibility was performed by two authors (SN, NT). Conflicts during the screening process were resolved by third author (SL). Data extraction was performed by four authors (SN, SL, NT, SG). Data extracted included demographic variables, clinical presentation, investigations, and outcomes. Categorical variables are expressed as percentage and continuous variables as mean \pm SD. Associations among categorical variables were calculated utilizing multinomial and binomial logistic regression wherever applicable. The data analysis was performed by DRP. Statistical analysis was carried out using Microsoft Excel 2010 (Microsoft Corporation, Redmond, VA) and Stata 13.1 (Stata Corporation, College Station, TX).

3. Results

We identified 41 patients with stress cardiomyopathy associated with epinephrine use from 36 articles (Fig. 1). The demographic variables, clinical presentation, investigations and outcomes were abstracted (Supplementary file 2). The mean age of presentation was (47.07 ± 15.73 years) with strong female preponderance ($n = 34$, 83% $P = 0.0001$). The most common symptom at presentation was chest pain ($n = 28$, 82%). Mean peak troponin I level was (7.12 ± 11.22 ng/ml). The most common electrocardiogram (EKG) abnormality was ST elevation, which was seen in 40% of patients. The other common EKG abnormalities were T wave abnormalities (22.5%) and ST depression (12.5%).

Cardiac catheterization was performed on all patients and revealed normal coronaries in all (100%). The mean ejection fraction on initial transthoracic echocardiogram was ($33.68 \pm 10.73\%$), and was normal ($>50\%$) in 2 patients (4.8%). The most commonly described echocardiogram wall motion abnormalities were seen in the apex, reported in 48.78% cases. Basal and midventricular abnormalities were reported in 31.71% and 19.51% cases respectively. Patients younger than 45 were less likely to have apical cardiomyopathy ($n = 5/20$, 25%) compared to patients with age >45 ($n = 14/21$, 66%, p value 0.001, OR 0.17). Anaphylaxis was the most common indication for use ($n = 14$, 34.1%) followed by intraoperative/surgical ($n = 9$, 21.9%). The most common route of epinephrine use was intravenous (65.85%) followed by intranasal (12.2%). There was no significant relationship between type of TC and route of epinephrine use ($p = 0.46$). In the 28 records that reported dose of epinephrine administered, mean dose was 2.85 mg. The most common complication in those records that mention clinical course was cardiogenic shock ($n = 10/32$, 31%). Acute pulmonary edema occurred in seven patients (22%). There was no significant correlation between type of TC and the associated complications (p value >0.05). Vasopressors were administered to treat Takotsubo complications in ten patients, nine of whom were suffering from cardiogenic shock. Dobutamine was the vasopressor chosen most frequently (40%). Outcome was reported in 41 cases, with all patients except one reporting survival with complete recovery (97.5%). The mean interval for recovery of systolic function was 14.73 ± 18.47 days. One patient died from cardiogenic shock leading to disseminated intravascular coagulation, multiorgan failure and death, and that patient had received additional epinephrine for treatment of Takotsubo-related cardiogenic shock.

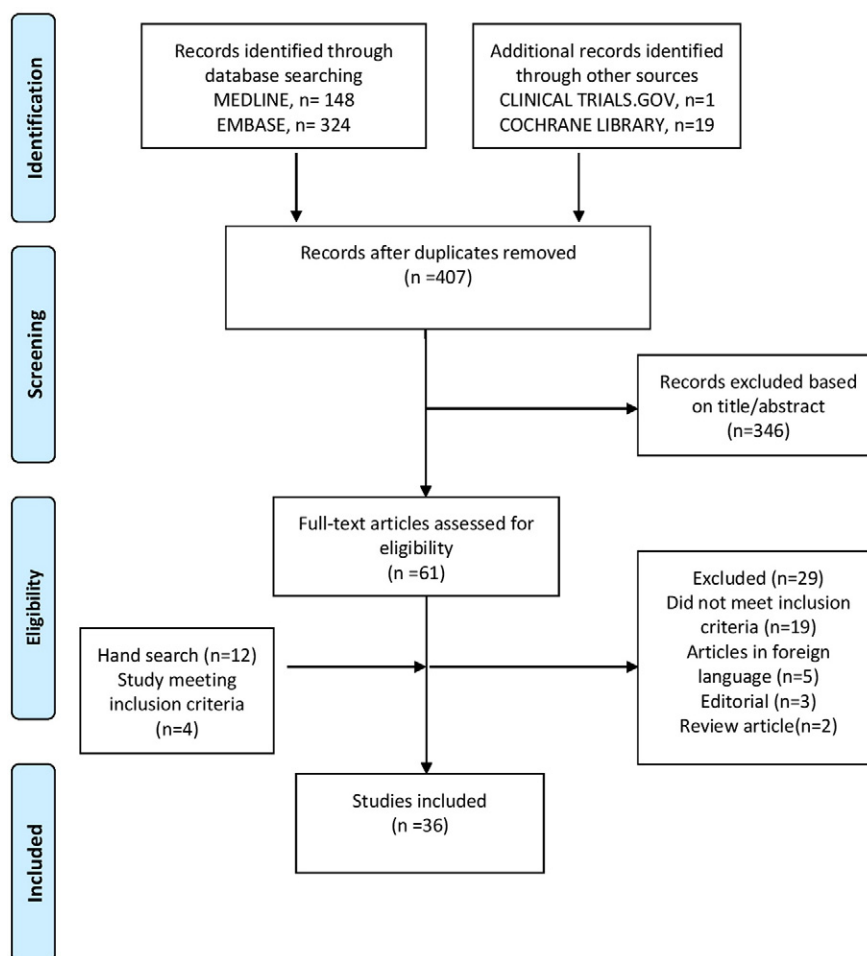


Fig. 1. Flow chart describing systematic search and study selection process.

4. Discussion

Our review found that reports of **TC related to epinephrine use** affected a population that was relatively **younger** than what is commonly reported in large registry databases. We identified an average age of **47 years**, with 14 patients under 40 years of age. Other reviews of TC have described populations with average age of 66. Our cohort was predominantly **female (83%)**, in line with most other reviews of TC induced by endogenous catecholamines [4,7] which supports the hypothesis of the **important influences that sex hormones** might have on the myocardial response to the various triggers of TC [8]. The most common clinical presentation in our review was **chest pain** ($n = 28, 82\%$). Two patients developed **shortness of breath** after epinephrine administration [11,12], one developed **nausea** [13] and three were already intubated before epinephrine administration [14,15,16]. This is consistent with typical presentation of TC where patients most commonly present with acute chest symptoms [1,3].

In our review, mean peak troponin I level was (7.12 ± 11.22 ng/ml) with mean similar to the usual cohort of patients with TC [1]. One patient had normal troponin level but met modified Mayo criteria for TC and hence was included in our review [17]. The **most common EKG abnormality was ST elevation in 40%**. This was in keeping with the findings of the international Takotsubo registry [1], in which ST elevation was present 43% of the time. In our review, the **mean ejection fraction on initial transthoracic echocardiogram was ($33.68 \pm 10.73\%$)** which was somewhat lower than what was reported in the registry (41.1%) [1]. The coronary catheterization findings showed **normal coronaries** in all patients **100%**, similar to the low rate of epicardial coronary disease reported in the Takotsubo registry (15.3%). **Cardiogenic shock** was reported in nearly a **third (31%)** of the patients in our group, quite a bit higher than the 9.9% seen in the registry data [1]. Intravenous epinephrine was responsible for the majority of our cases (65.8%), but it should be noted that **standard anaphylaxis treatment doses still brought on this condition in four patients**, suggesting that there may be some genetic predisposition to the TC response in those patients. **Prognosis was very good** in our cohort with **only one death (2%)**, similar to the registry data (4% mortality reported).

Historically, TC was characterized by hypokinesia, akinesia or dyskinesia of midventricular and/or apical parts of the left ventricle, associated with hyperkinesia of basal segments and hence was also known as **"apical ballooning syndrome"**. **Newer variants** were eventually reported including **midventricular dyskinesia** with normo- or **hyperkinesia** of the **apex** and **base** (called **"midventricular ballooning variant"**), a basal dyskinesia with normo- or hyperkinesia of the midventricular and/or apical segments of the left ventricle (termed **"basal ballooning variant"** or **"inverse/reverse TC"**), and a **focal dyskinesia of any segment** of the left ventricle (**"focal variant"**) [1,9,10]. In our review, the most common type of cardiomyopathy was **apical in 48.78%** cases. The focal variant was not identified in our review. Compared to the usual cohort of patients with TC, basal and midventricular variants were far more common in our review [1]. Interestingly, patients with age <45 were statistically less likely to have apical variant cardiomyopathy compared to patients with age >45.

We limited our review to English-language publications, and therefore may not have captured important features of this disorder not seen in the English-language literature. Since this is a relatively newly described disorder, it is quite possible that a significant number of cases that were subclinical may have gone unreported, and the subset we have identified were simply the most extreme or unusual cases identified. This may explain the skew to a younger age distribution in our review. The Modified Mayo criteria stipulates exclusion of myocarditis and pheochromocytoma, which were not specifically commented on in any of our cases, but are quite rare and would be extremely unlikely to produce similar episodic symptoms immediately after exposure to epinephrine. Finally, we were dependent on the case descriptions in the literature to understand the patient outcomes, since there was no

standard reporting criteria. Therefore we cannot determine whether recovery occurred more quickly, or whether there were recurrences or long-term sequelae.

5. Conclusion

Although uncommon, use of **epinephrine at doses often used in routine clinical practice has been associated with Takotsubo cardiomyopathy**. Overall, TC induced by exogenous catecholamines appears to have a **good prognosis** with **complete recovery** in most cases. Healthcare providers who use epinephrine should be aware of this association, and should be vigilant to identify it in female patients with chest pain, hypotension or dyspnea following administration of epinephrine. Physicians caring for these patients should remember that **cardiogenic shock from TC can sometimes produce an outflow tract obstruction if the apex is involved**, and this can be **worsened** with continued administration of additional **vasopressors** [7]. Takotsubo cases should be submitted to a registry with standardized reporting so that more data may better guide future interventions.

Supplementary data to this article can be found online at doi:10.1016/j.ijcard.2016.11.266.

Conflict of interest

All the authors have no conflict of interest.

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