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Clinical Characterization of Pharmacologically Induced Takotsubo Syndrome: Implications for Treatment and Mechanisms

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Abstract

Background: Takotsubo Syndrome (TS) is characterized by sudden localized left ventricular (LV) dysfunction and clinical features suggesting an acute coronary syndrome. It occurs more in women and is frequently associated with emotional or physical stress. Pharmacologically induced TS (PITS) has been reported but a comprehensive characterization has not been performed. Such a characterization could provide insight into mechanisms and treatment of spontaneous TS.

Methods: Local cases were combined with literature review of PITS cases. For each case, sex, age, presentation, presumed causal agent, electrocardiographic features, ejection fraction (EF), LV contraction abnormalities, and outcome were compiled.

Results: One hundred and one patients (89% female) were identified. Augmented beta adrenergic response accounted for 81% of PITS which includes epinephrine (EPI) alone (32%) or in combination with other catecholamines (5%), dobutamine (DOB) (17%), or any other beta-adrenergic enhancing agent (27%). Primary vasoconstrictors triggered 7% of PITS. Inappropriate administration (dosage or route) caused 24% of PITS but 47% of PITS due to EPI. All DOB induced PITS involved stress echocardiography. ST segment elevation (41%) was common. Apical ballooning occurred in 61%. The mean EF was 32 ± 11%. 36% developed transient congestive heart failure (CHF) and 32% required hemodynamic support. Mortality was infrequent (1%).

Conclusion: Spontaneous TS and PITS are similar entities likely occurring by the same general mechanism; increased stimulation of myocardial beta receptors. PITS was frequently associated with severe LV dysfunction and CHF. The female myocardium seems more susceptible to spontaneous TS and PITS. PITS provoking agents may facilitate spontaneous TS under appropriate conditions.

Keywords

Takotsubo syndrome, Stress cardiomyopathy, Iatrogenic, Catecholamine toxicity

Abbreviations

5-FU: 5-fluorouracil; AMP: amphetamine; CHF: congestive heart failure; DES: desvenlafaxine; DEX: dexamphetamine; DOB: dobutamine; DUL: duloxetine; EF: ejection fraction; EPH: ephedrine; EPI: epinephrine; IABP: Intra-aortic balloon pump; LV: left ventricular; MIL: milnacipran; NOR: nortriptyline; PITS: pharmacologically induced Takotsubo Syndrome; SNRI: serotonin norepinephrine reuptake inhibitor; STEMI: ST segment elevation myocardial infarction; TS: Takotsubo Syndrome; TCA: tricyclic antidepressant; VEN: venlafaxine

Introduction

Takotsubo Syndrome (TS) typically follows emotional or physical stress and is characterized by transient, and sometimes profound, LV dysfunction in the setting of clinical features suggesting an acute coronary syndrome [1-5]. The coronary arteries are free of obstructive disease and frequently entirely normal [1-5]. The vast majority of TS occurs in females, particularly post-menopausal females [1-5]. While typically an apical phenomenon, an inverted form of the syndrome is described whereby the apex is relatively spared and contraction abnormalities effect the proximal or mid portions of the left ventricle [1-5].

Though the etiology of TS is unknown, the finding of high circulating catecholamine levels [6,7] and the frequent occurrence of a preceding stressful event, has implicated catecholamines as a contributing factor [1-7]. Reports of transient LV dysfunction following accidental intravenous epinephrine (EPI) overdose [8] or use of dobutamine (DOB) [8], further implicates catecholamines as a contributor to the genesis of this syndrome. If pharmacologically induced TS (PITS) is similar to naturally occurring TS, PITS could provide valuable insight understanding TS. This investigation characterizes PITS and discusses implications this has on spontaneous TS which could help define the future care of TS patients.

Methods

Medical records from all patients presenting to Aspirus Hospital or Clinics for urgent or follow-up care with a diagnosis of TS over the past 10 years were reviewed to determine if they fit the diagnosis of TS according to the modified Mayo Clinic criteria [1]. During this analysis we encountered 86 patients that met TS diagnostic criteria, 3 of these patients developed TS following EPI and were classified as PITS. A Medline and Google search was then performed for additional cases of PITS. Initial keywords included; TS, iatrogenic, EPI, DOB, dopamine, beta-agonist, stress cardiomyopathy, catecholamines. The bibliography

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of each manuscript obtained was also reviewed for additional cases. This generated additional key words such as; duloxetine, tricyclic antidepressants, venlafaxine, desvenlafaxine, albuterol, and terbutaline which were also crossed referenced with TS. To include a case in our analysis we required the author to have concluded that the event was due to the administered agent and used the term "TS", "stress cardiomyopathy", or "catecholamine toxicity" to explain the clinical picture. If cases did not meet these criteria or if obstructive coronary disease was noted on reported angiography, they were rejected from investigation. Although we attempted to include all cases fitting these criteria, we recognize it is unlikely we captured every reported case of PITS. Clinical characteristics of each patient with PITS were obtained including, sex, presenting symptoms, electrocardiographic findings, ejection fraction, LV contraction abnormalities, and ultimate outcome. Ejection fraction was reported in a majority of cases. For cases in which it was not reported but included systolic and diastolic images in the case report, we calculated the ejection fraction to the nearest 5% using planimetry. The LV contraction pattern was broadly classified as apical, when there was pronounced apical involvement or non-apical (regional or inverted TS) where contraction abnormalities spared the apex. Electrocardiographic findings were grouped by the presence or absence of ST segment elevation concerning for myocardial infarction (STEMI).

The presumed causal pharmacologic agent responsible for PITS and the circumstances of each event were compiled. We also determined whether the causal agent was appropriately administered, or whether there was error of administration route, or intentional or unintentional overdose. Though we recognize that some cases of reversible LV dysfunction following cocaine use could well represent PITS [9-11], we elected to exclude these cases. Cocaine's cardiovascular effects are complex and have been reviewed in detail elsewhere [12]. Chest pain with LV dysfunction resembling TS has been associated with anaphylaxis (Kounis syndrome) [13,14]. We included those patients in this case series if the symptoms of TS were not initially present but occurred during the course of anaphylaxis treatment following administration of agents associated with PITS in non-anaphylactic settings and the author concluded that the treatment may have caused the clinical LV dysfunction. There are reports of TS following anesthesia for major and minor procedures [15,16]. Because these could represent spontaneous TS due to procedural stress, we omitted procedural case reports from our analysis unless the agent suspected of causing the TS had been associated with PITS under non-anesthetic settings and cardiac abnormalities were not present until the agent was administered. We also required the case authors to have concluded that PITS was a possible explanation for the observed events.

Results

One hundred and one cases of PITS were identified. Three cases of PITS were observed locally and the clinical summary presented as follows:

Case 1

LS were a 49 year old female undergoing right shoulder arthroscopy. Eighteen milligrams of EPI were inadvertently injected into the intravenous line instead of into the saline irrigation line. The patient became hypertensive, tachycardic, and complained of chest pain. Intravenous metoprolol and hydralazine were administered. Despite this she became unresponsive, was intubated, and urgently transferred to the emergency room. Upon arrival she was found to be in shock and vasopressors were started. Echocardiogram showed a markedly reduced left ventricular ejection fraction. Cardiac catheterization demonstrated normal coronary arteries and an ejection fraction of 30% in a pattern consistent with inverted TS. An intra-aortic balloon pump was placed; she stabilized and was rapidly weaned off vasopressors. Her echocardiogram showed normal LV contractility 2 days later.

Case 2

BC was a 76 year old female having outpatient varicose vein sclerotherapy with a solution that contained lidocaine with EPI. Post procedure she developed chest pain and was admitted for observation. ECG was non-specific and labs showed mild troponin elevation. Catheterization showed normal coronary arteries and apical TS with EF of 30%. Two days later her echocardiogram revealed normal LV function.

Case 3

KW was an 18 year old female with chronic poly-substance abuse brought to the emergency room after being found unresponsive. She had a slow idio-ventricular rhythm, no obtainable blood pressure, and cardiopulmonary resuscitation was instituted. Two ampules of EPI were given and a blood pressure of 90/60 mm/Hg was established. Echocardiogram in the emergency room following resuscitation was normal. Troponin I level the following morning was mildly elevated and a repeat echocardiogram showed severe LV dysfunction. Catheterization demonstrated normal coronary arteries and apical TS with an ejection fraction of 20%. She had complete recovery of her cardiac and neurologic status.

In addition to the above 3 cases, 98 additional cases were obtained from literature search [8,14,15,17-92]. Cases were broadly divided by the mechanism through which the inducing agents produce an adrenergic response, primary vasoconstriction, or whose possible mechanism of action related to PITS is difficult to discern. Table 1 summarizes the agents believed to have caused PITS based upon this classification. EPI was the agent most frequently associated with PITS accounting for 32% of the cases by itself and another 5% in combination with other catecholamines. This was followed by dobutamine which accounted for 17% of the cases, all following standard dobutamine stress echocardiography.

Although most PITS followed administration of direct beta agonists, several cases followed hyper-adrenergic states created via other mechanisms. Some cases followed amphetamine, dexamphetamine, ephedrine, or pseudoephedrine use, which increase tissue levels of catecholamines by augmenting release of nor-EPI from nerve terminals [93]. The psychotropic drugs duloxetine, venlafaxine, desvenlafaxine and tricyclic antidepressants increase tissue catecholamine levels by inhibiting nor-epinephrine reuptake [94,95]. Phosphodiesterase inhibitors increase levels of the second messenger cyclic AMP thus augmenting adrenergic responses [96].

Table 1: Summary of agents causing PITS.

# Of PITS patients (N, %)	101, 100%	references
Direct Adrenergic Agonist	58, 57%	
EPI	32, 32%	[8,14,15,17-34]
DOB	17, 17%	[8,42-54]
EPI +other catecholamine	6, 5%	[35-40]
Any other catecholamine	3, 3%	[41,55-56]
Indirect Adrenergic Agonist	18, 18%	
AMP, DEX	2, 2%	[57,58]
EPH, Pseudo-EPH	3, 3%	[59-61]
SNRI (DUL, VEN, DES, MIL)	12, 12%	[62-68]
TCA (NOR)	1, 1%	[69]
Phosphodiesterase Inhibitors	3, 3%	
Anagrelide	2, 2%	[70,71]
Dipyridamole	1, 1%	[72]
Up-regulation of beta receptors	3, 3%	
Thyroid hormone	2, 2%	[73,74]
Abrupt metoprolol withdrawal	1, 1%	[75]
Vasoconstrictors	7, 7%	
Phenylephedrine	2, 2%	[76,77]
Ergot alkaloids	3, 3%	[78-80]
Oxymetazoline	1, 1%	[81]
Zolmitriptan	1, 1%	[82]
Unknown Mechanism	12, 12%	
5-FU	6, 5%	[83-87]
Sodium tetradecyl sulfate	1, 1%	[88]
Sunitinub	1, 1%	[89]
Combretastatin	2, 2%	[90]
Pazopanib	1, 1%	[91]
Lumuracofxib	1, 1%	[92]

5-FU: 5-5fluorouracil; AMP: Amphetamine; DES: Desvenlafaxine; DEX: Dexamphetamine; DOB: Dobutamine; DUL: Duloxetine; EPH: Ephedrine; Epi: Epinephrine; MIL: Milnacipran; NOR: Nortriptyline; SNRI: Serotonin Nor-epinephrine Reuptake Inhibitors; TCA: Tricyclic Antidepressant; VEN: Venlafaxine

Table 2: Summary of clinical characteristics of PITS patients.

# of PITS patients	101
Sex (% female)	89%
Age in years (mean, range)	52 ± 19, 16-85
Resulted from dosing error or overdose	24%
Catheterization performed	84%
LV Ejection fraction %	32 ± 11
Any hemodynamic support Vasopressors IABP Intravenous fluid	32% 12% 12% 8%
Congestive heart failure	36%
LV dysfunction pattern Apical balloon Non apical (regional or inverted) Not reported	 61% 35% 4%
Presented as STEMI	41%
Survived PITS	99%
Normalized LV function (in survivors)	100%

IABP: Intra-aortic balloon pump; LV: left ventricle; PITS: pharmacologically induced takotsubo syndrome; STEMI: ST-elevation myocardial infarction

Up-regulation of beta receptor density is observed with chronic beta blocker therapy [75] and hyperthyroidism [97]. In total 81% of all PITS cases were due to agents which augment adrenergic tone directly or indirectly.

Note in table 1 that 19% of PITS cases followed administration of agents which have no direct beta adrenergic effect. Seven percent of PITS was associated with primary vasoconstrictors, either via alpha receptor agonism (phenylephrine, oxymetazoline) or non-adrenergic receptor mediated vasoconstriction (ergot alkaloids, zolmitriptan). The remaining 12% of cases in table 1 were due mostly to chemotherapeutic agents with complex mechanisms of action.

Clinical characteristics of the PITS patients are summarized in table 2. Note that 89% of cases were in females. Also note that severe cardiac compromise was frequent with a mean EF of 32 ± 11%. CHF (36%) and need for hemodynamic support (32%) was common. Note 61% of PITS presented with typical apical involvement. We found no correlation between the severity of illness or the requirement for hemodynamic support between apical and non-apical (inverted or regional) presentations of PITS. Mortality was rare (1 patient) and ejection fraction of all survivors eventually normalized. This normalization could occur rapidly. Though the time course was not typically mentioned in the literature, we found each of the 3 cases of PITS from our institution normalized their EF by the second day.

Most cases of PITS occurred following proper use of the agent per standard clinical practice. This was especially true with DOB whereby all associated cases resulted from standard protocol DOB stress echocardiograms. Although only 24% of all PITS was due to inappropriate dosing (administration route and/or dosage), EPI was overwhelmingly the most common medication to be given erroneously and within the EPI subgroup 47% of PITS involved inappropriate dosing.

Discussion

Our investigation shows PITS shares many of the characteristics associated with spontaneous TS (Table 2). Like spontaneous TS, the majority of patients with PITS were female, presented with symptoms mimicking an acute coronary syndrome, and recovered completely despite severe LV dysfunction and cardiac compromise at onset. Finally the LV wall motion abnormalities noted with PITS, like spontaneous TS, usually do not correspond to a typical coronary artery distribution.

We did find some differences between PITS and TS. The average age of our patients (52 ± 11) was considerably younger than that typically reported for spontaneous TS [1-4] and thus it is likely to consist of a higher percentage of pre-menopausal women compared to spontaneous TS. Additionally we noted a higher percentage of the patients with PITS had a non-apical LV dysfunction pattern (35%) compared to what is typically reported for TS [4]. The significance, if any, of this finding is unclear but could be due to differing effects of estrogen levels in PITS compared to spontaneous TS. More research is needed on this topic.

The present observation allows us to draw insight into pathophysiologic mechanisms involved in TS. Most of the agents observed to cause PITS in our review were either catecholamines themselves or augmented catecholamine response, leading to enhanced beta receptor activation (Table 1). This is supportive of the excessive catecholamine hypothesis as a primary factor leading to TS [5]. Although some catecholamines can cause large vessel and/or small vessel spasm producing myocardial ischemia, we feel that our findings support a direct effect upon the myocardium as being the likely mechanism for most PITS. Dobutamine, terbutaline, and albuterol and isoproterenol are beta agonists which act directly upon myocardial beta receptors but also produce vasodilatory effects. These agents combined accounted for 19% of the PITS we observed. Additionally, the wall motion abnormalities in most cases of PITS, like spontaneous TS, does not correspond to a typical coronary artery distribution; thus making large vessel coronary spasm a less viable explanation. However, the finding of a few cases of PITS attributed to purely vasospastic agents devoid of beta agonism raises the possibility that some PITS may have a vasospastic cause. In this regard PITS is also similar to spontaneous TS in which the primary mechanism is thought to be hyper stimulation of beta-receptors on the cardiomyocytes while vasospasm remains a possible cause in a subgroup of cases [2].

Like spontaneous TS we observed a female predominance in PITS. Since most of the cases of PITS were due to administered catecholamines and not dependent upon intrinsic sympathetic activity, our findings suggest the female predilection in spontaneous TS may result from increased myocardial sensitivity to catecholamines at the cellular level rather than increased sympathetic nerve tone.

We noted a very low mortality of PITS despite severe LV dysfunction and frequent occurrence of shock and CHF. We believe this is due to the transient nature of the syndrome. We were especially impressed at how rapidly the LV dysfunction normalized in our 3 local cases. Whether the cardiac abnormalities with PITS generally resolve faster than TS is unclear from our study. We also found patients with PITS had a low incidence of comorbidities and were younger. This may have resulted in increased ability to compensate for hemodynamic instability.

We suspect PITS exists as a spectrum of presentations with only the most dramatic cases being recognized and reported. Consequently this series of cases likely underrepresents the true prevalence of PITS with many cases being unrecognized due to less blatant presentations or misclassified due to occurrence at a time when there was less appreciation for the existence of TS. This is especially evident from review of older case reports. Although not included in our cases series, we found numerous reports of myocardial infarctions in mostly female patients with normal coronary arteries following use of albuterol [98], salbutamol [99,100], ephedrine [101], pseudoephedrine [102], tricyclic antidepressants [103-107], and the weight loss agent sibutramine [108], a combined norepinephrine and serotonin reuptake inhibitor. We believe that many, if not most of these cases were unrecognized variants of PITS. Indeed sibutramine was eventually removed from the market because of an increased risk of non-fatal myocardial infarctions in patients with cardiovascular disease discovered in the SCOUT study [109]. Though the nature of these infarctions was not elucidated, it is tempting to speculate that some of these events represent unrecognized PITS rather than acute coronary syndromes. Similarly it seems possible that many cases of myocardial infarction associated with anaphylaxis (Kounis Syndrome) [14,18] are actually cases of PITS due to the epinephrine used to treat the anaphylaxis.

Implications

If pharmacologic agents can independently precipitate TS, it seems reasonable that they can synergistically facilitate spontaneous TS in at risk individuals during hyper-adrenergic situations which

would otherwise have been benign. Spontaneous TS has been known to occur in the post-operative period and may result from the hyper-adrenergic state created by the pain and other stress of the event. In this setting, agents which heighten catecholamine effects could place certain patients at risk for TS. The pain reliever tramadol, which inhibits norepinephrine reuptake [110], could potentially be one such agent. Overdoses of tramadol have been associated with myocardial dysfunction consistent with catecholamine toxicity [110] and cases of post-operative TS have been reported in patients in which tramadol was part of pain management [111,112]. Similarly, susceptible patients receiving antidepressant agents which inhibit catecholamine reuptake may also be more prone to develop spontaneous TS under stressful conditions. Since recurrent TS is not uncommon and PITS and typical TS are likely similar entities, in patients with a history of TS it seems prudent to avoid use of agents known to provoke PITS.

Summary

Spontaneous TS and PITS are similar in that they occur predominately in females, have a similar clinical course, frequently involve adrenergic stimulation, and exhibit non-occlusive coronary disease. Differences are noted in that PITS has a younger mean age and a higher incidence of inverted or regional pattern of LV dysfunction. Despite these differences, we believe that naturally occurring TS and PITS likely share similar mechanisms propagated by increased stimulation of myocardial beta receptors in most cases. The frequency of PITS is likely underappreciated. Agents producing PITS could potentially facilitate spontaneous TS under appropriate conditions and may be contributing to the observed increased incidence of TS. It is prudent to avoid PITS inciting agents in any patient who has experienced an episode of spontaneous TS.

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