

## Research Article

### Stress (Takotsubo) Cardiomyopathy in Poisoned Patients

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#### Abstract

**Purpose:** Stress or Takotsubo Cardiomyopathy (TTC) is occasionally described after poisoning, but epidemiologic data are still lacking. We decided to describe the TTC echocardiographic patterns in a toxicological intensive care unit.

**Methods:** Monocentric retrospective study.

**Results:** During 42 months, 973 consecutive patients were admitted and five patients (0.5%) had TTC pattern on echocardiography, typical in 80%. TTC occurred mainly after cardiotoxicant ingestion. Stress cardiomyopathy was associated with poisoning with beta-blockers (n=2), olanzapine (n=1) and chloroquine (n=1) in the multivariate analysis and only in the univariate analysis with venlafaxine (n=1) and tramadol (n=1). Median LVEF was 20%. All TTC patients experienced shock and had more frequently pulmonary edema than the control group. TTC occurrence was significantly associated with mortality (40% versus 6%; OR=10; CI 1.7-61; p=0.01) but this association was not significant in multivariate analysis. Mechanisms are herein hypothesized: catecholamine (endogenous or exogenous) cardiotoxicity, metabolism disturbances (including fatty acid cardiac metabolism), neurological impairment or direct toxicological damage such as myocarditis.

**Conclusion:** TTC echocardiographic patterns mainly caused by cardiotoxicant are rarely reported in poisoned patients (0.5 percent) but can significantly lead to death. Pathophysiology of the causative specific or non specific involved mechanism seems multifactorial.

**Keywords:** Cardiomyopathy; Critical illness; Drug; Myocarditis; Poisoning; Takotsubo

#### Introduction

Stress or Takotsubo Cardiomyopathy (TTC) is a particular transient Left Ventricular (LV) dysfunction of acute onset. Although the epicardial coronary arteries are normal, TTC mimics an acute coronary syndrome (chest pain, ECG abnormalities and elevated

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cardiac enzymes). The typical TTC is also called the LV apical ballooning syndrome. The shape of the LV looks like a Japanese fishing pot used for trapping octopuses, with a round bottom and a narrow neck. Although a fairly rare disease with unknown etiology, some diagnoses criteria have been proposed [1]. Among the hypotheses are: catecholamine-induced myocardial stunning, LV Outflow-Tract (LVOT) obstruction frequently linked with an emotional or physical stress prior to cardiac symptoms. Many clinical situations have been associated with TTC often by the catecholamine-induced way [2]. Several drugs act directly or indirectly as adrenergic agents. Some other drugs can induce catecholamine rise while taken in excess (cf discussion). As a matter of fact, poisoned patients can be exposed to such a stress cardiomyopathy. We wanted to analyze the prevalence of TTC in a series of poisoned patients.

#### Patients and Methods

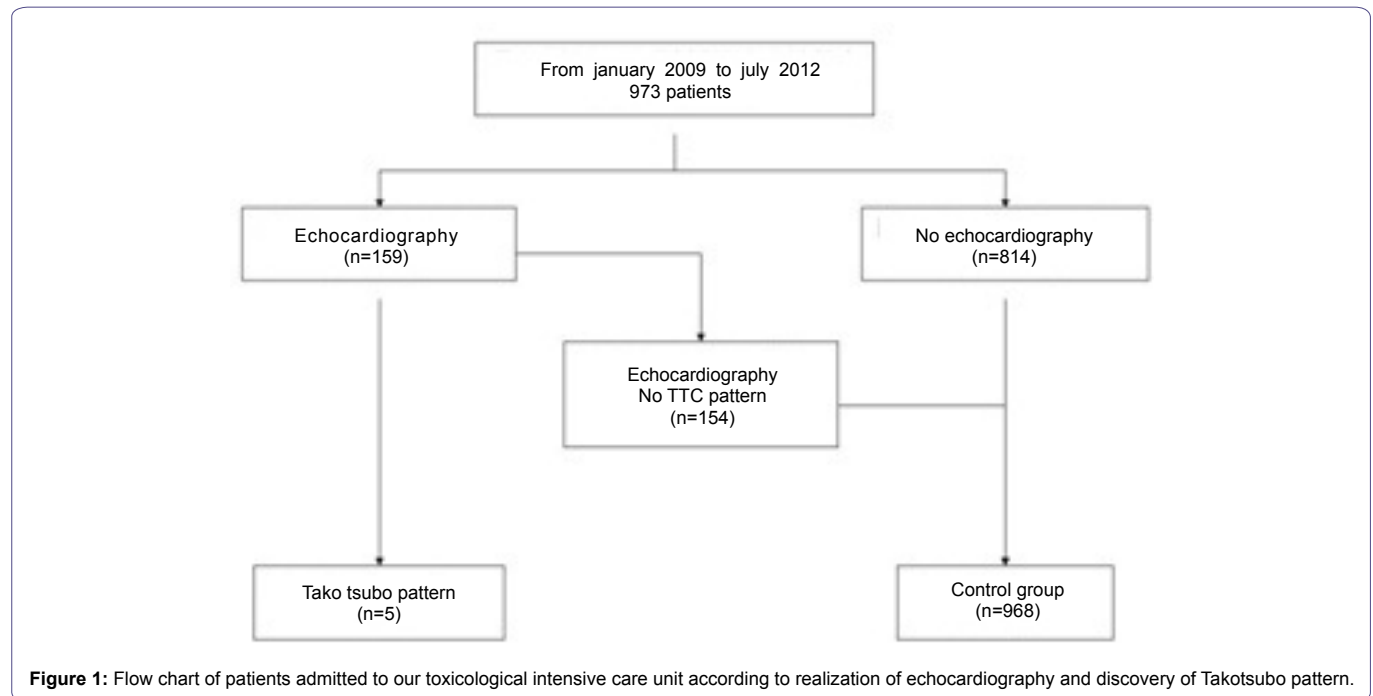
Every consecutive patient admitted for poisoning in our toxicological Intensive Care Unit (ICU) was included from January 2009 to June 2012. Every patient report was reviewed in order to check for TTC and mortality in a retrospective fashion. Every echocardiography detailing wall motion abnormality was reviewed. Either typical or atypical TTC pattern was included, even if the entire criterion were not gathered [1]. Demographic data were extensively reviewed during the period from January 2010 to July 2011 including time from intoxication, drug toxicant, presentation (hemodynamic instability, Glasgow coma scale, and respiratory distress), management (catecholamine infusion, mechanical ventilation, toxicological management, antimicrobial therapy) and time course. Patients consent was waived. The study was approved by Ethical committee and is in accordance with the Declaration of Helsinki.

#### Statistical Analysis

Data are expressed as median and 25-75 percentiles for continuous variables and number (percent) for binary variables. We used StatView 5.0 for the statistical analysis. Qualitative values are compared with chi-2 tests and quantitative values with Mann-Whitney tests as appropriate. A multivariate analysis by logistic regression was performed with different significant values during the univariate analysis for occurrence of TTC and mortality. A p value<0.05 was considered significant.

#### Results

During 42 months, 973 patients were admitted for poisoning in our ICU. During that period of time, 159 echocardiographies were performed and reported in the patient's chart. Echocardiography was performed by intensivists as soon as cardiac symptoms occurred. It seemed improbable that patients develop TTC without any clinical symptoms. TTC echocardiographic pattern was reported in only 5 patients. Subsequently, 968 patients were classified not to have TTC and constituted the control group and 448 of them were extensively reviewed from January 2010 to July 2011 (Figure 1). The prevalence was then estimated at 0.5%. The differences between TTC and control patients are reported in table 1.



	TTC (n=5)	Control (n=968)	p
Age (years)	45 (43; 55)	43 (31; 54)	0.7
Sex female	4 (80%)	524 (54%)	0.04
SAPS2 [3]	67 (59; 71)	36 (23; 50)	0.002
GCS	3 (3; 5)	8 (4; 14)	0.02
Cardiac arrest	1 (20%)	17/448 (4%)	0.06
Cardiotoxicant	3 (60%)	104/448 (23%)	0.04
betablocker	2 (40%)	55/448 (11%)	0.045
chloroquine	1 (20%)	7/448 (2%)	0.002
venlafaxine	1 (20%)	13/448 (3%)	0.03
Shock	5 (100%)	104/448 (23%)	<0.0001
typical	4 (80%)	-	
Troponin Ic (µg/L)	5 (1; 15)	0.03 (0.01; 5)	0.01
BNP (ng/mL)	2300 (2000; 3000)	57 (10; 390)	0.001
LVEF (%)	20 (15; 30)	60 (50; 65)	<0.0001
ECLS	3 (60%)	22 (2%)	<0.0001
Membrane stabilizing effect	1 (20%)	NA	
Murray score [4]	4 (2; 4)	0 (0; 1)	0.002
PaO2/FiO2 (mmHg)	185 (125; 279)	365 (246; 450)	0.03
MV	5 (100%)	233/448 (52%)	0.03
MV duration (days)	6 (4; 15)	2 (2; 4)	0.01
LOS ICU (days)	20 (4; 23)	3 (2; 4)	0.008
mortality	2 (40%)	60 (6%)	0.002

**Table 1:** Demographic data in patients with TTC or without (control).

BNP: Brain Natriuretic Peptide; ECLS: Extracorporeal Life Support; GCS: Glasgow Coma Scale; LOS ICU: Length of Stay in the Intensive Care Unit; LVEF: Left Ventricular Ejection Fraction; MV: Mechanical Ventilation; NA: Non Available; SAPS2: Simplified Acute Physiology Score 2; TTC: Takotsubo Cardiomyopathy

In the TTC group, cardiac impairment was severe with a median LVEF of 20% measured in 80% under inotropes and necessitated extracorporeal life support in 3 patients [5]. Non survivors had the highest levels of troponin Ic (15 and 45µg/L). In the control group, troponin or BNP were rarely performed or abnormal but echocardiography showed in about 10% severe global LV impairment (LVEF<40%) without wall motion abnormality (cardiomyopathy associated with sepsis, inflammatory response, or negative inotropic properties of the toxicant).

## Cases Description

The first patient ingested propranolol, angiotensin receptors antagonists and benzodiazepines in a suicidal attempt. She developed a typical TTC and survived after eight days of extracorporeal life support.

The second patient was found unconscious across empty blisters of propranolol, venlafaxine and tramadol. Because of the past history of myocardial infarction, he was the only one patient for who an

angiography was performed. No coronary artery abnormality could explain the cardiogenic shock with typical TTC pattern and the patient deceased after 3 days of extracorporeal life support.

The third patient has already been reported [6]. After massive intoxication with chloroquine, the patient experienced inverted TTC pattern requiring extracorporeal life support, multi-organ failure and deceased after 5 days on extracorporeal life support.

A fourth patient ingested his antiretroviral therapy along with benzodiazepines in a suicidal attempt. He developed cardiogenic shock for four days with minimal enzymatic release, typical TTC pattern with complete recovery on the tenth day.

The last patient self-injected a very high dose of insulin and ingested benzodiazepines in a suicidal attempt. She was rescued lately with indosable low blood glucose and severe encephalopathy. Typical TTC pattern improved after 5 days under Dobutamine.

### Univariate and Multivariate Analyses

As pictured in table 1, patients with TTC pattern had more complicated course, including more often shock and altered ventilation (decreased oxygenation and altered thoracic radiography [4]) resulting in worse outcome. In different models, only poisoning with beta-blockers, chloroquine and olanzapine remained associated with occurrence of TTC. Poisoning with tramadol or venlafaxine tend to be associated with the occurrence of TTC, however, it did not reach the statistical significance (p=0.07). TTC was associated with a tenfold increase in mortality (OR 10; CI 1.7-61; p=0.01) but this association

estimated as echocardiography was rarely performed and reported. However, it is improbable that TTC may occur without any symptoms and many fast normal echocardiographies may have not been reported in the patient's chart. As a result, the true frequency may not be so different than less than one percent. This prevalence is 3 times less than the prevalence found in a general ICU with more severe patients [2]. This could be explained by the mechanisms leading to TTC. The precise TTC's mechanism is unclear. Comprehensive reviews of TTC in the ICU propose entangled mechanisms in the critically ill patient with a preponderant catecholamine cardiotoxicity and neurological impairment [2,7]. Though, reversible myocardial dysfunction is a very common entity and frequently seen in different critical care settings [8].

As regards to the toxicological aspects, many clinical situations have been associated with TTC pattern including drug withdrawal, poisonings with either direct or non direct sympathomimetic substances. To our knowledge, no systematic study has evaluated the frequency and mechanisms in this setting. We report TTC described in the literature after poisoning with non direct sympathomimetic substances in table 2 [9-24].

Many of the substances previously reported in the literature may result in norepinephrine storm by their pharmacological effects: adrenergic amines reuptake inhibitors known as the serotonin syndrome. Additional myocardial infarctions with normal coronary arteries were encountered [25,26]. Other pesticides (organophosphorus) have been showed to induce cardiac impairment with an association between acetylcholine and an

References	Number of cases	toxic	Dose (mg)	Typical /inverted	Outcome
Partridge SJ [9]	1	Venlafaxine and paroxetine	1987 360	inverted	alive
Kawabata M [10]	1	Imipramine and amantadine	?	typical	alive
Oomura M [11]	1	Neuroleptics and benzodiazepines	?	typical	alive
Fangio P [12]	1	Venlafaxine	5500	inverted	alive
De Roocke S [13]	1	Nortriptyline	?	typical	alive
Lin CC [14]	1	Carbamates pesticide and pyrethroids	?	Typical	alive
Christoph M [15]	1	Venlafaxine	overdose	typical	alive
Trohman RG [16]	1	Duloxetine			
Rotondi F [17]	1	Duloxetine			
Selke KJ [18]	1	Duloxetine	overdose	typical	alive
Forman MB [19]	1	Milnacipran	overdose	typical	alive
Grunwald MR [20]	9 (1 case + review)	Fluorouracil	Loading dose	typical	7 alive / 2 dead
Neil CJ [21]	6	Venlafaxine and desvenlafaxine			
Tominaga K [22]	1	Gliphosate	90 mL	typical	alive
Romanò M [23]	1	Risperidone, barbiturates, and benzodiazepines	?	typical	alive
Kitami M [24]	1	Lithium	overdose	Typical	alive

**Table 2:** References regarding TTC pattern and poisoning with non-direct sympathomimetic agents.

was no more significant while introducing severity parameters such as the Simplified Acute Physiology Score 2 (SAPS2) [3].

### Discussion

In a retrospective study evaluating the frequency of TTC echocardiographic patterns in poisoned patients, we found a prevalence of 0.5 percent. The frequency may have been under

endogenous catecholamine rise [27]. The case reports with imipramine, amantadine and neuroleptics had concomitant malignant syndrome with increased plasma catecholamines level [10,11]. Another case report of TTC pattern was related to lithium poisoning (chronic with peak lithium level of 2.9mEq/L) [24]. Here again, plasma norepinephrine increase secondary to lithium poisoning was supposed to play a major role in TTC occurrence.

However, in this case report, probable seizures would be more realistically the triggering event for TTC [4].

Several hypotheses could be suggested to understand the relationships between poisoning and TTC pattern. Myocardial ischemia is the first challenging mechanism proposed to explain TTC. The only inverted TTC pattern in our series could hardly be explained by coronary stenosis in a young female without coronary disease risk factor [4]. A coronary angiography ruled out an acute coronary syndrome in only one of our patients but a coronary thrombosis seemed very improbable for all other patients. Although a possible demand/supply mismatch leading to myocardial stunning cannot be ruled out [1]. Female predominance was significant in patient with TTC pattern when compared to patients without, in our study. The role of estrogens in the genesis of TTC is still a hypothesis [2]. Metabolism dysfunctions were advocated as potential mechanism leading to TTC, including fatty acid metabolism [28]. As a matter of fact, the normal heart's major source of energy, fatty acid metabolism can be impaired in calcium channel antagonist or beta-blocker poisoning. Hyperinsulinaemia/euglycaemia therapy can improve carbohydrate uptake of the heart. The management of such poisonings has been extensively reviewed but the role of that therapy to decrease TTC induced by fatty acid metabolism disturbance remains a hypothesis [29].

In relation to epinephrine, TTC has been attributed to a molecular switch from G(s) to G(i) protein in the transduction pathway following catecholamine receptor stimulation [30]. Here, catecholamine storm resulting from both chloroquine or venlafaxine poisoning and its management based on epinephrine or dobutamine infusion may have played a significant role. TTC were not significantly associated with the global poisoning with cardio toxicant but specifically with beta-blockers, chloroquine and venlafaxine. A significant association was also found with tramadol and olanzapine. This significant association is debatable because of the rarity of poisoning with such medications in the control group. The association was still significant in multivariate analysis for beta-blockers, chloroquine, and olanzapine.

However, in a French review of pharmacovigilance, an association was found between many drugs and development of cardiomyopathy [31]. Interestingly, serotonergic (fluvoxamine but not venlafaxine) and tricyclic antidepressants were associated with a 10 fold increased risk of dilated cardiomyopathy by several proposed mechanisms: atropinic and quinidine like effects, reuptake of adrenergic amines disturbance or direct myocardial depression. Clozapine-induced myocarditis has been theoretically calculated at about 1% of the prescriptions [32] and linked with a 15 fold increased risk of dilated cardiomyopathy with a probable class effect with olanzapine. One of the last medical class involved in the pharmacovigilance study is antiretroviral therapy with a 5 fold increased risk by possible mitochondrial toxicity. Furthermore, fluorouracil is a well known provider of cardiac disturbances and has been suggested to be the cause of 9 TTC in the literature [20].

An intriguing iatrogenic cardiotoxicity is myocarditis which is known for fluorouracil, clozapine and different other drugs [20,32-34]. Such a mechanism is excluded from the definition of TTC. However, typical TTC have already been told induced by biopsy proven myocarditis [35]. The role of any drug in the development of myocarditis-induced TTC is unknown.

Membrane stabilizing effect was found on the ECG only once in our series (the third patient). This was reversible after administration of molar bicarbonates (750mL) but cardiogenic shock still developed [4]. Segmental wall motion abnormalities were completely different from those with severe membrane stabilizing effect. We hypothesized that sodium channel blockade that lead to intra ventricular conduction disturbance could not induce any of the TTC patterns.

Cardiac involvement is frequently associated with neurological impairment in the ICU [2]. Hypoglycemic encephalopathy or chloroquine-induced seizures may have represented an additional neurological trigger to two of our TTC patterns. Sepsis has been advocated as a possible trigger of TTC. This seems improbable in our series in which inflammatory markers, bacteriological finding or antimicrobial therapy were not associated with TTC pattern. Finally, a non-specific mechanism including endogenous catecholamine surge or exogenous perfusion seems as probable as a toxicological specific cardiac impairment.

## Prognosis

TTC was never a benign phenomenon. Every patient presented with cardiogenic shock and a significant association was found with impaired oxygenation with diffuse pulmonary infiltrate. This may be due to associated cardiac pulmonary edema that led to prolongation of the mechanical ventilation. However TTC was not independently associated with death in the multivariate analysis making TTC rather an indicator of disease severity. Severe arrhythmias including sudden death are known complications of TTC [1] even when drug-induced [20]. However, although sudden death is consistently increased during psychotropic treatment, TTC is exceptionally proposed as the cause of arrhythmia [33].

An interesting finding of our series is an increased risk of TTC in beta-blocker poisoning making prevention of TTC by this medication more than questionable [23] unless LVOT obstruction is patent [36].

## Limitations

Many limitations must be pointed out. First, all the criteria were not mandatory and thus it is impossible to affirm actual TTC instead of any transient wall motion abnormality. As TTC is still an imprecise entity without firm diagnostic criteria, we believe that over diagnosis were possible but with similar transient left ventricular impairment of unknown origin (stress cardiomyopathy). Secondly, as a retrospective study, no systematic cardiac investigation was performed but as clinically appropriate. Though, echocardiographies were occasionally performed. We did not report psychiatric disease and its treatment. However, it is associated with increased risk of cardiac events, and long-term cardiac death [37]. The specific role of psychiatric condition and its treatment, and TTC occurrence is to be further explored, indeed the subject of this preliminary study. Finally, the poisoned patients represent a very vague entity with various toxicants and complications, several ways of cardiotoxicity making definitive evaluation of the frequency and mechanisms of TTC debatable.

## Conclusion

Stress (Takotsubo) cardiomyopathy is an infrequent entity in poisoned patients (0.5%). It may be triggered by (either exogenous or endogenous) catecholamine cardio toxicity, metabolism disturbance, neurological impairment or direct toxicological insult such as possible myocarditis. Although associated with more severe disease,

shock and mechanical ventilation, TTC was not significantly associated with death in the multivariate analysis.

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