Am J Cardiovasc Dis 2023;13(6):354-362
www.AJCD.us /ISSN:2160-200X/AJCD0153426

Review Article

Takotsubo cardiomyopathy following scorpion envenomation: a literature review

Mabrouk Bahloul, Sana Kharrat, Karama Bouchaala, Kamilia Chtara, Mounir Bouaziz

Department of Intensive Care, Habib Bourguiba University Hospital, Sfax University, Sfax, Tunisia

Received September 14, 2023; Accepted December 10, 2023; Epub December 15, 2023; Published December 30, 2023

Abstract: Background: Takotsubo syndrome is comparable to microvascular acute coronary syndrome. It may partly share the same pathophysiology debated during scorpion envenomation (SE), with an adrenergic storm, without myocardial infarction due to the absence of coronary artery stenosis. Takotsubo cardiomyopathy can help to better understand the pathophysiology of cardiac involvement during scorpion envenomation. However, Takotsubo syndrome seems to be underestimated in the literature in patients suffering from cardiac failure following SE. Methods: In this review, we aimed to detail all described cases, the mechanism, and outcomes of scorpion envenomation complicated by Takotsubo cardiomyopathy. We used the PubMed database by using the following keywords in MeSH research: scorpion envenomation, Takotsubo cardiomyopathy, and Takotsubo syndrome. Results: The literature analysis showed the existence of only four cases of confirmed Takotsubo cardiomyopathy following severe SE. All four patients developed a transient reversible left ventricular systolic dysfunction in the absence of coronary artery disease, following a positive history of scorpion envenomation. A cardiac MRI was performed in all cases, showing a ballooning in the left ventricle associated with a left ventricular ejection fraction in all cases. All patients were improved under symptomatic treatment, and complete recovery of the wall motion was observed. Conclusion: Takotsubo syndrome, although not often reported in the literature in severe SE, can represent an effective hypothesis explaining the pathophysiology of cardiac involvement during SE. In severe scorpion envenomation, multiple mechanisms exist and can explain the development of Takotsubo syndrome. Its management is based on oxygen, with invasive or non-invasive ventilator support in patients with respiratory failure and/or cardiogenic shock. Beta-blockers, mineralocorticoid receptor antagonists, and diuretics are usually used in Takotsubo syndrome. However, in severe scorpion envenomation, all reported cases of Takotsubo cardiomyopathy are associated with cardiogenic shock and acute pulmonary edema. As a consequence, we advise the use of Dobutamine since it has already been confirmed that cardiac dysfunction following scorpion envenomation improves well and safely under Dobutamine infusion.

Keywords: Takotsubo cardiomyopathy, scorpion, adrenergic myocarditis, catecholamine, Dobutamine

Introduction

Scorpion envenomation (SE) is a common intoxication in tropical and subtropical areas, leading to intensive care admission [1]. The severity of the clinical manifestation is due essentially to the cardio-respiratory impairment. Indeed, cardiorespiratory manifestations, mainly cardiogenic shock and acute pulmonary edema, represent the main causes of death after SE [2]. Their mechanism remains unclear, and multiple conclusions are discussed and reported in the literature [2]. Moreover, the nature of SE-related cardiomyopathy is still the subject of much debate. Indeed, at least three mechanisms, namely adrenergic myocarditis, toxic myocarditis, and myocardial ischemia, have been discussed and debated in the literature [3]. However, it is well-established that the significant discharge of catecholamines plays a fundamental role in the genesis of systolic dysfunction of the left ventricle (LV) during SE [4].

Takotsubo cardiomyopathy is characterized by transient systolic dysfunction manifested by ballooning of the apex or by disturbances in the kinetics of the basal or focal median segments of the left ventricle in the absence of obstructive coronary artery disease [5, 6]. This syndrome, exceptionally reported in the literature,

can help to better understand the pathophysiology of cardiac involvement during SE [7, 8]. In fact, Takotsubo syndrome is comparable to microvascular acute coronary syndrome [5, 6]. It may partly share the same pathophysiology debated during SE, with adrenergic storm [3], without myocardial infarction due to the absence of coronary artery stenosis [9]. In fact, experimental studies have shown that severe scorpion envenomation leads to a significant increase (30-40-fold) in plasma epinephrine and norepinephrine levels [10, 11].

Takotsubo syndrome has many physiopathological mechanism similarities with scorpion-related cardiomyopathy (discharge of catecholamines and microvascular arterial dysfunction, all-motion abnormalities, reversible heart failure); nevertheless, it is rarely described in this specific condition.

In this review, we aimed to detail all described cases, the mechanism, and outcomes of scorpion envenomation complicated by Takotsubo cardiomyopathy. We used the PubMed database by using the following keywords in MeSH research: scorpion envenomation, Takotsubo cardiomyopathy, and Takotsubo syndrome.

In this review, Takotsubo cardiomyopathy due to scorpion envenomation is defined as transient reversible left ventricular systolic dysfunction associated with electrocardiographic changes and minimal cardiac enzyme release in the absence of coronary artery disease and of myocarditis or pheochromocytoma [5, 6] following a positive history of scorpion envenomation.

Based on the diagnostic standards for the International Expert Consensus Document on Takotsubo Syndrome [5], Takotsubo cardiomyopathy was positively diagnosed in all included individuals [5]. The clinical presentation, ST-segment abnormalities seen in the ECG, cardiac biomarker levels, echocardiography results, and the CMR images are all taken into consideration by these criteria [5].

Results

The search in the PubMed and Medline databases using the identified keywords showed that a total of 10 articles were published on this subject [7, 8, 12-19]. However, according to our criteria and to the Revised Mayo Clinic Criteria [20], only three publications [7, 8, 13] reported a confirmed clinical case of Takotsubo cardiomyopathy due to scorpion envenomation. A total of four patients were described to have Takotsubo cardiomyopathy following scorpion envenomation. Three cases are reported by two Tunisian critical care teams [7, 13] and one by a Brazilian emergency team [8].

All reported patients are young (ages ranging from 7 to 45 years) without any history of cardiac or coronary disease. They were admitted to an emergency department and/or ICU for severe scorpion envenomation (Grade III) by a scorpion of the *Androctonus australis* species [7, 13] or *Tityus serrulatus* species [8]. All patients exhibited signs of respiratory distress due to cardiogenic pulmonary edema. Biological findings showed a high level of troponin I in all cases and a high value of B-type natriuretic peptide (NT-proBNP) in three patients [7, 8]. The electrocardiographic study showed sinus tachycardia associated with ST-segment changes in all cases. The echocardiography was done for all patients showing a systolic left ventricular dysfunction with important hypokinesia and a left ventricle ejection fraction (LVEF) ranging from 26% to 35%. A cardiac magnetic resonance (CMR) was performed in all patients, showing an apical ballooning in the left ventricle in one case [8] and basal ballooning of the left ventricle in the three other cases [7, 13].

All patients were treated with oxygen therapy. Furosemide was administered for one patient [8], Dobutamine infusion was used in three patients [7, 13], and CPAP and/or invasive mechanical ventilation was used in three patients [7, 13]. A repeat echocardiography examination was performed for all patients, showing a full recovery of systolic dysfunction. All the patients improved well and were discharged 4 to 6 days after hospital admission.

A second CMR performed for two patients (after seven months [8] and four weeks [7]) showed a complete recovery of the wall motion in the two patients. For the two other patients [7, 13], MRI was not repeated due to logistic reasons.

All clinical and para-clinical characteristics of all included patients were detailed in the Supplementary File. **Table 1** summarizes all

Table 1. Details of Takotsubo cardiomyopathy following scorpion envenomation cases

Reference	Age	Scorpion	Clinical presentation	Electrocardiogram	Cardiac biomarkers	Echocardiography	Cardiac magnetic resonance	Chest X-ray	Outcome
Miranda et al. [8]. Brazil/2015	7 years	Tityus serrulatus	Vomiting/sweating Respiratory distress	Sinus tachycardia ST elevation in anteroseptal and lateral leads	Troponin I: 10.89 µg/L NT-proBNP: 10003 pg/L	Systolic left ventricular Dysfunction Apical hypokinesia LVEF of 26%	Apical ballooning of LV	Pulmonary edema	Improved/ Complete recovery of systolic dysfunction
Abroug et al. [7]. Tunisia/2018	36 years	Androctonus australis	Cardiogenic shock Respiratory failure	Tachycardia ST depression in anteroseptal leads	Troponin I: 3.4 ng/mL NT-proBNP: 3430 pg/ml	Systolic dysfunction LVEF 30%	Basal ballooning of the right and left ventricle	Pulmonary edema	Improved
Abroug et al. [7]. Tunisia/2018	45 years	Androctonus australis	Altered level of consciousness Cardiogenic shock Respiratory failure	Tachycardia ST depression in anteroseptal precordial leads	Troponin I: 3.1 ng/ml NT-proBNP: 6270 pg/ml	Systolic dysfunction LVEF 35%	Basal ballooning	Pulmonary edema Bilateral alveolar infiltrates	Improved Recovery of systolic dysfunction
Ben Jemaa et al. [13]. Tunisia/2021	26 years	Androctonus Australis	Cardiogenic shock Respiratory failure	Tachycardia ST depression in anteroseptal precordial leads	Troponin I: 2.9 ng/ml	Systolic dysfunction LVEF 33% Hypokinesis of the basal and mid segments	Basal ballooning	Bilateral alveolar infiltrates	Improved

clinical and para-clinical characteristics of all included patients.

Discussion

This review reports four cases of confirmed Takotsubo cardiomyopathy following severe scorpion envenomation. In fact, all four patients developed a transient reversible left ventricular systolic dysfunction associated with electrocardiographic changes and minimal cardiac enzyme release in the absence of coronary artery disease, following a positive history of scorpion envenomation. A cardiac MRI was performed in all cases, showing a ballooning in the left ventricle associated with a left ventricular ejection fraction in all cases. All patients were improved under symptomatic treatment, and complete recovery of the wall motion was observed in all cases.

Scorpion envenomation represents a big health problem in tropical and subtropical regions. Cardio-respiratory complications, mainly cardiogenic shock and pulmonary edema, are the leading causes of death after scorpion envenomation [1, 14].

The venom of scorpions contains various low-weight peptides known as neurotoxins. These peptides are more commonly associated with the Buthoids (one family, Buthidae) than with the chactoides (the other five families), the venoms of which are less harmful to humans [14, 21]. These toxins are tiny, basic proteins of around 65 amino-acids that selectively affect mammals and invertebrates. The main harmful effects of scorpion venom are on the neuromuscular and cardiovascular systems. The release of catecholamines and vasoactive peptides has been proposed as the primary mechanism of myocarditis associated with scorpion envenomation [21-23]. Actually, the neurotoxins found in scorpion venom have an impact on voltage-gated sodium (Na) and potassium (K) channels, which causes neuronal excitement and the release of a significant amount of norepinephrine, epinephrine, and acetylcholine from the adrenal medulla and sympathetic and parasympathetic nerve endings [23].

Although cardiac dysfunction is well-documented in severe cases of SE [1-3, 14], the mechanism of acute heart failure has been extensively debated. Indeed, adrenergic myocarditis, toxic myocarditis, and myocardial ischemia represent the three most detailed mechanisms that explain the cardiac dysfunction in this specific condition [1, 4, 9, 12]. However, Takotsubo syndrome, although not often reported in the literature in this specific condition, can represent an effective hypothesis explaining the pathophysiology of cardiac involvement during SE [7, 8]. In fact, Takotsubo syndrome may partly share the same pathophysiology debated during SE, with adrenergic storm [3], without myocardial infarction [9]. As a consequence, we think that Takotsubo syndrome is underestimated in the literature in patients suffering from cardiac failure following scorpion envenomation.

Clinical studies in favor of a diagnosis of Takotsubo syndrome following SE

In the literature, there are many published studies supporting the hypothesis of Takotsubo syndrome in patients suffering from cardiac failure following scorpion envenomation. Indeed, in a previous study, including six young patients (ages ranging from 4 to 29 years) suffering from severe scorpion envenomation, it was reported that there is evidence of myocardial damage, confirmed by electrocardiography and echocardiography in all patients [9]. Myocardial perfusion scintigraphy, coupled with radionuclide ventriculography performed for all patients, showed myocardial hypoperfusion in all cases [9]. Moreover, control investigations obtained in two patients showed considerable improvement in the wall motion and in myocardial perfusion. Segments with improved wall motion showed great improvement in regional perfusion. In this study [9], the investigators concluded that there is evidence of myocardial hypoperfusion in severe scorpion sting patients due to coronary vasoconstriction in young patients without any history of coronary disease. In the afore-mentioned study [9], coronary vasoconstriction after scorpion envenomation was explained by a direct vasoconstrictive effect of different substances (e.g., catecholamines) in the coronary arteries [9, 14, 21], and/or endothelial dysfunction. In fact, the release of high levels of cytokines (IL-1 alpha, IL-6, IL-10, TNF-alpha, and IL1-beta) following severe scorpion envenomation leads to microvascular injury or vasospastic responses in the coronary arteries [9, 14, 21] and may explain

coronary vasospasm and myocardial hypoperfusion.

The same results were also reported by Cupo P *et al.* [24] in 12 children (1-12 years old) admitted for severe *Tityus serrulatus* envenomation. In the latter study [24], the contribution of myocardial ischemia to the left ventricular dysfunction in SE was explored by using 99mTc-Sestamibi myocardial perfusion scintigraphy (MPS). The investigators found that all patients exhibited myocardial perfusion defects associated with systolic dysfunction. The investigators concluded that their results strongly support the participation of transitory myocardial ischemia in the mechanism of acute cardiac dysfunction caused by severe scorpion envenomation. The same conclusion was reported by Figueiredo AB *et al.* [25] in a study including 15 patients. In the latter study [25], the investigators found that myocardial perfusion abnormalities are common in scorpion envenomation. They also found a good correlation between the localization of perfusion abnormalities and contractile dysfunction. Moreover, recovery of contractility was correlated with the reversibility of perfusion defects. These findings suggest the participation of myocardial perfusion abnormalities in the pathophysiology of this form of acute ventricular failure.

All patients included in the last three studies [9, 24, 25] meet all the criteria of Takotsubo cardiomyopathy. In fact, all included patients (33 patients) developed a transient reversible left ventricular systolic dysfunction associated with electrocardiographic changes, minimal cardiac enzyme release, and transient myocardial hypoperfusion in the absence of coronary artery disease (young patients in all cases) following a positive history of scorpion envenomation.

On the other hand, in one combined hemodynamic and Echo-Doppler study including nine consecutive patients, Abroug *et al.* [26] found that the left ventricle was hypokinetic in all patients. Moreover, left ventricular systolic function evolved toward normalization within six days, preceded by full clinical recovery. Furthermore, reversible hypokinesia and decrease of left ventricular ejection fraction (EF) and fractional shortening (FS) are frequently reported in the majority of cases of severe scorpion envenomation [27]. All these changes in left ventricular ejection fraction (EF) and fractional shortening (FS) can be explained by a Takotsubo cardiomyopathy secondary to severe scorpion envenomation.

Finally, two studies [28, 29] explored histopathological findings in the autopsy of the patients following severe scorpion envenomation; the most observed abnormalities were interstitial edema [28, 29], dilation of chambers [28, 29], inflammatory infiltrates such as polymorphonuclear cells, and eosinophils [29] were the histopathological findings. These histological findings are usually observed in Takotsubo syndrome [30, 31].

Mechanisms of Takotsubo syndrome following SE

Although reported more than three decades ago [32], the exact pathophysiological mechanism of Takotsubo cardiomyopathy remains not fully understood. Its pathophysiology varies, including microvascular spasms of coronary arteries and myocardial perfusion disturbance due to microcirculatory dysfunction [33]. In severe scorpion envenomation, multiple mechanisms exist and can explain the development of Takotsubo syndrome.

Catecholamine storm: Endogenous adrenergic over-release is the most established theory for the pathogenesis of Takotsubo syndrome [33]. In severe scorpion envenomation, like in cases of sudden surprising stress and subarachnoid hemorrhage [34], a 30-40-fold rise in plasma epinephrine and norepinephrine levels was found [10, 11]. This leads to left ventricular dysfunction. In fact, a catecholamine storm leads to microvascular spasms of coronary arteries and microvascular dysfunction, which may have a toxic effect and can reduce myocyte viability [33].

Inflammatory mechanisms and cytokine storms: Severe scorpion envenomation is associated with the release of pro-inflammatory cytokines [35, 36]. In fact, Fukuhara YDM *et al.* [36] have shown that TNFalpha, IL-1β, IL-6, and IL-8 levels were significantly high in severe cases of SE. Moreover, the levels of these cytokines were positively correlated with the severity of envenomation and the presence of cardiac dysfunction [2, 35, 36]. The cytokine release leads to endothelial injuries, microvascular injuries, and/or vasospastic responses in the coronary

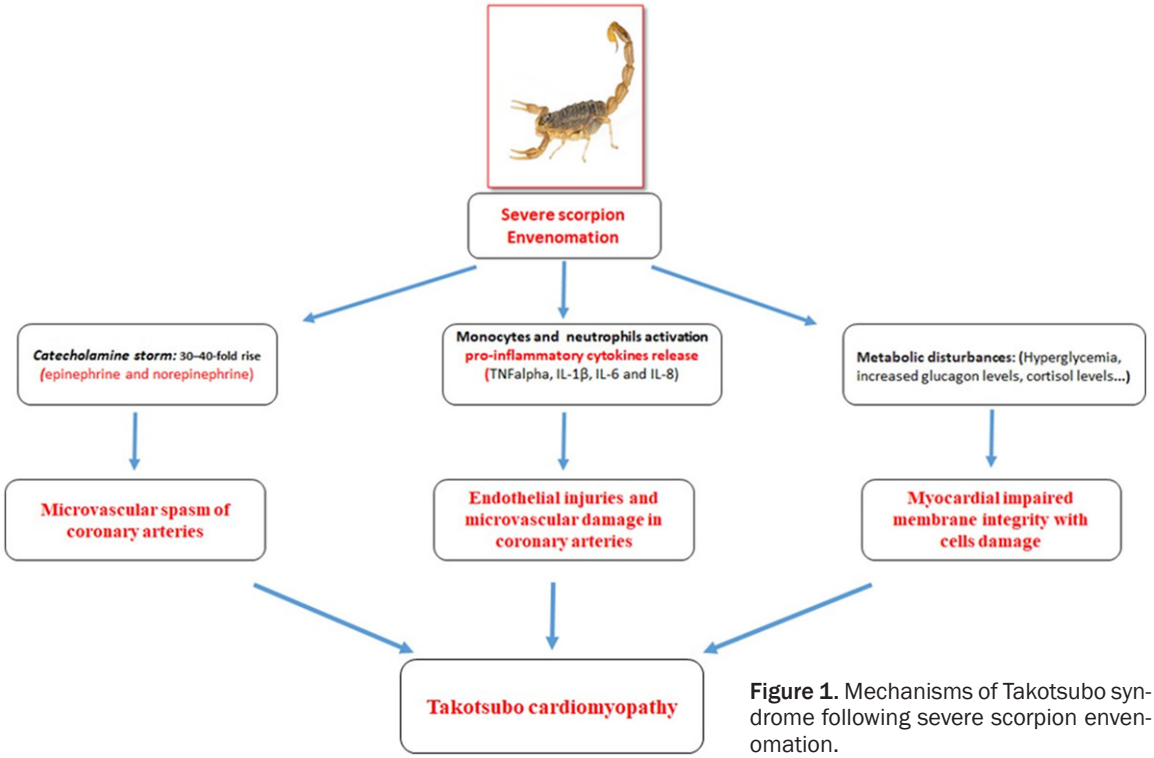

Figure 1. Mechanisms of Takotsubo syndrome following severe scorpion envenomation.

arteries [37, 38]. As a consequence, cytokine storms worsen the microvascular damage observed in coronary arteries, leading to myocardial oxygenation disturbance [37, 38].

Metabolic disturbances: Hyperglycemia is often observed in severe scorpion-envenomed patients, and its correlation with the severity of clinical manifestation is well-established. It is due to a massive release of catecholamines, increased glucagon levels, cortisol levels, and either decreased insulin levels or insulin resistance [39]. These hormonal changes lead to lipolysis and an increase in free fatty acids [40]. These hormonal changes induce myocardial impaired membrane integrity with cell damage, disturbances in calcium movement, and arrhythmia [41]. Second, hyperglycemia leads to an increase in vivo platelet activation with a massive release of thromboglobulin, leading to myocardial ischemia and dysfunction [41]. The last mechanism is the effect that hyperglycemia can lead to endothelin-1 liberation by cardiomyocytes. This leads to intracellular calcium accumulation and a disturbance in myocardial contractility [42].

Figure 1 summarizes all mechanisms implicated in Takotsubo cardiomyopathy following severe SE.

Management of Takotsubo syndrome following SE

The management of acute heart failure after Takotsubo cardiomyopathy is determined by the standard international guidelines, comprising oxygen and respiratory support, beta-blockers, mineralocorticoid receptor antagonists, and diuretics [6, 33, 43]. However, in severe scorpion envenomation, all reported cases of Takotsubo cardiomyopathy are associated with cardiogenic shock and acute pulmonary edema [7, 8, 13]. Oxygen, with invasive or non-invasive ventilator support in patients with respiratory failure and/or cardiogenic shock, is recommended to improve the clinical status of severe myocardial failure and pulmonary edema [3]. On the other hand, we advise the use of Dobutamine with a mean dose of 5-10 μg/kg per minute since it has already been confirmed that cardiac dysfunction following scorpion envenomation improves well and safely under Dobutamine infusion [7, 8, 13, 44-46].

We summarize that Takotsubo syndrome is underestimated in the literature in patients suffering from cardiac failure following scorpion envenomation. In fact, many patients included in previously reported studies [9, 24-31] who meet all the criteria of Takotsubo cardiomyopa-

thy are not classified as Takotsubo cardiomyopathy. Indeed, most included patients developed transient reversible left ventricular systolic dysfunction associated with electrocardiographic changes, minimal cardiac enzyme release, and transient myocardial hypoperfusion in the absence of coronary artery disease (young patients in all cases). However, all these studies suffer from an incomplete cardiac exploration. In the current study, only four patients were described to have Takotsubo cardiomyopathy following scorpion envenomation [7, 8, 13]. Takotsubo syndrome may be explained by the same pathophysiology debated during SE, with adrenergic storm [3], without myocardial infarction [9]. As a consequence, we think that the most significant limitation of this review is the small number of included patients, due to the under-estimation of this complication in severe scorpion envenomation.

Conclusion

Takotsubo syndrome, although not often reported in the literature in severe SE, can represent an effective hypothesis explaining the pathophysiology of cardiac involvement during SE. In severe scorpion envenomation, multiple mechanisms exist and can explain the development of Takotsubo syndrome. Its management is based on oxygen, with invasive or non-invasive ventilator support in patients with respiratory failure and/or cardiogenic shock. On the other hand, we advise the use of Dobutamine with a mean dose of 5-10 μg/kg per minute since it has already been confirmed that cardiac dysfunction following scorpion envenomation improves well and safely under Dobutamine infusion.

Disclosure of conflict of interest

None.

Address correspondence to: Mabrouk Bahloul, Department of Intensive Care, Habib Bourguiba University Hospital, Sfax University, 3029 Sfax, Tunisia. Tel: +216-98-698267; Fax: +216-74-243427; E-mail: bahloulmab@yahoo.fr

References

[1] Bouaziz M, Bahloul M, Kallel H, Samet M, Ksibi H, Dammak H, Ahmed MN, Chtara K, Chelly H, Hamida CB and Rekik N. Epidemiological, clinical characteristics and outcome of severe scorpion envenomation in South Tunisia: multivariate analysis of 951 cases. Toxicon 2008; 52: 918-26.

[2] Bahloul M, Chabchoub I, Chaari A, Chtara K, Kallel H, Dammak H, Ksibi H, Chelly H, Rekik N, Ben Hamida C and Bouaziz M. Scorpion envenomation among children: clinical manifestations and outcome (analysis of 685 cases). Am J Trop Med Hyg 2010; 83: 1084-92.

[3] Bahloul M, Kallel H, Rekik N, Ben Hamida C, Chelly H and Bouaziz M. Cardiovascular dysfunction following severe scorpion envenomation. Mechanisms and physiopathology. Presse Med 2005; 34: 115-20.

[4] Bahloul M, Regaieg K, Chabchoub I, Kammoun M, Chtara K and Bouaziz M. Severe scorpion envenomation: pathophysiology and the role of inflammation in multiple organ failure. Med Sante Trop 2017; 27: 214-221.

[5] Ghadri JR, Wittstein IS, Prasad A, Sharkey S, Dote K, Akashi YJ, Cammann VL, Crea F, Galiuto L, Desmet W, Yoshida T, Manfredini R, Eitel I, Kosuge M, Nef HM, Deshmukh A, Lerman A, Bossone E, Citro R, Ueyama T, Corrado D, Kurisu S, Ruschitzka F, Winchester D, Lyon AR, Omerovic E, Bax JJ, Meimoun P, Tarantini G, Rihal C, Y-Hassan S, Migliore F, Horowitz JD, Shimokawa H, Lüscher TF and Templin C. International expert consensus document on takotsubo syndrome (Part I): clinical characteristics, diagnostic criteria, and pathophysiology. Eur Heart J 2018; 39: 2032-2046.

[6] Ghadri JR, Wittstein IS, Prasad A, Sharkey S, Dote K, Akashi YJ, Cammann VL, Crea F, Galiuto L, Desmet W, Yoshida T, Manfredini R, Eitel I, Kosuge M, Nef HM, Deshmukh A, Lerman A, Bossone E, Citro R, Ueyama T, Corrado D, Kurisu S, Ruschitzka F, Winchester D, Lyon AR, Omerovic E, Bax JJ, Meimoun P, Tarantini G, Rihal C, Y-Hassan S, Migliore F, Horowitz JD, Shimokawa H, Lüscher TF and Templin C. International expert consensus document on takotsubo syndrome (Part II): diagnostic workup, outcome, and management. Eur Heart J 2018; 39: 2047-2062.

[7] Abroug F, Ouanes I, Maatouk M, Golli M and Ouanes-Besbes L. Inverted Takotsubo syndrome in Androctonus australis scorpion envenomation. Clin Toxicol (Phila) 2018; 56: 381-383.

[8] Miranda CH, Braggion-Santos MF, Schmidt A, Pazin-Filho A and Cupo P. The first description of cardiac magnetic resonance findings in a severe scorpion envenomation: is it a stress-induced (Takotsubo) cardiomyopathy like? Am J Emerg Med 2015; 33: 862, e5-7.

[9] Bahloul M, Ben Hamida C, Chtourou K, Ksibi H, Dammak H, Kallel H, Chaari A, Chelly H, Guermazi F, Rekik N and Bouaziz M. Evidence of myocardial ischaemia in severe scorpion envenomation. Myocardial perfusion scintigraphy study. Intensive Care Med 2004; 30: 461-7.
[10] Zeghal K, Sahnoun Z, Guinot M, Richer C and Giudicelli JF. Characterization and mechanisms of the cardiovascular and haemodynamic alterations induced by scorpion venom in rats. Fundam Clin Pharmacol 2000; 14: 351-61.
[11] Nouira S, Elatrous S, Besbes L, Boukef R, Devaux C, Aubrey N, Elayeb M and Abroug F. Neurohormonal activation in severe scorpion envenomation: correlation with hemodynamics and circulating toxin. Toxicol Appl Pharmacol 2005; 208: 111-6.
[12] Mishra AK, George AA, John KJ, Arun Kumar P, Dasari M, Afraz Pasha M and Hadley M. Takotsubo cardiomyopathy following envenomation: an updated review. World J Cardiol 2023; 15: 33-44.
[13] Ben Jemaa A, Bahloul M, Kallel H, Turki O, Dlela M and Bouaziz M. Inverted Takotsubo syndrome due to severe scorpion envenomation: report of one case. Med Trop Sante Int 2021; 1: PWX0-M245.
[14] Abroug F, Ouanes-Besbes L, Tilouche N and Elatrous S. Scorpion envenomation: state of the art. Intensive Care Med 2020; 46: 401-410.
[15] Abroug F, Ouanes-Besbes L and Bouchoucha S. Scorpion envenomation: from a neglected to a helpful disease? Intensive Care Med 2019; 45: 72-74.
[16] Madias JE. Scorpion envenomation cardiomyopathy: a promising model for Takotsubo syndrome. Clin Toxicol (Phila) 2015; 53: 787.
[17] Abroug F, Souheil E, Ouanes I, Dachraoui F, Fekih-Hassen M and Ouanes Besbes L. Scorpion-related cardiomyopathy: clinical characteristics, pathophysiology, and treatment. Clin Toxicol (Phila) 2015; 53: 511-8.
[18] Miranda CH, Braggion-Santos MF, Schmidt A, Pazin Filho A and Cupo P. Evolution of the electrocardiogram QRS complexes voltage in scorpion envenomation-induced Takotsubo syndrome. Am J Emerg Med 2015; 33: 837-8.
[19] Madias JE. Voltage attenuation of the electrocardiogram QRS complexes in a patient with "scorpion envenomation"-induced Takotsubo syndrome. Am J Emerg Med 2015; 33: 838.
[20] Sahu KK, Mishra AK and Lal A. Newer insights into Takotsubo cardiomyopathy. Am J Med 2020; 133: e318.
[21] Bahloul M, Chaari A, Dammak H, Samet M, Chtara K, Chelly H, Ben Hamida C, Kallel H and Bouaziz M. Pulmonary edema following scorpion envenomation: mechanisms, clinical manifestations, diagnosis and treatment. Int J Cardiol 2013; 162: 86-91.
[22] Amr ZS, Abu Baker MA, Al-Saraireh M and Warrell DA. Scorpions and scorpion sting envenoming (scorpionism) in the Arab Countries of the Middle East. Toxicon 2021; 191: 83-103.
[23] Gwee MC, Nirthanan S, Khoo HE, Gopalakrishnakone P, Kini RM and Cheah LS. Autonomic effects of some scorpion venoms and toxins. Clin Exp Pharmacol Physiol 2002; 29: 795-801.
[24] Cupo P, Figueiredo AB, Filho AP, Pintya AO, Tavares Júnior GA, Caligaris F, Marin-Neto JA, Hering SE and Simões MV. Acute left ventricular dysfunction of severe scorpion envenomation is related to myocardial perfusion disturbance. Int J Cardiol 2007; 116: 98-106.
[25] Figueiredo AB, Cupo P, Pintya AO, Caligaris F, Marin-Neto JA, Hering SE and Simões MV. Assessment of myocardial perfusion and function in victims of scorpion envenomation using gated-SPECT. Arq Bras Cardiol 2010; 94: 444-51.
[26] Abroug F, Ayari M, Nouira S, Gamra H, Boujdaria R, Elatrous S, Ben Farhat M and Bouchoucha S. Assessment of left ventricular function in severe scorpion envenomation: combined hemodynamic and echo-Doppler study. Intensive Care Med 1995; 21: 629-35.
[27] Fereidooni R, Shirzadi S, Ayatizadeh SH, Bahloul M, Tavangar A, Zomorodian SA, Roshanshad A and Ardekani A. Scorpion envenomation-associated myocarditis: a systematic review. PLoS Negl Trop Dis 2023; 17: e0011219.
[28] Amaral CF, de Rezende NA and Freire-Maia L. Acute pulmonary edema after Tityus serrulatus scorpion sting in children. Am J Cardiol 1993; 71: 242-5.
[29] Cupo P, Jurca M, Azeedo-Marques MM, Oliveira JS and Hering SE. Severe scorpion envenomation in Brazil. Clinical, laboratory and anatomopathological aspects. Rev Inst Med Trop Sao Paulo 1994; 36: 67-76.
[30] Kołodzińska A, Czarzasta K, Szczepankiewicz B, Budnik M, Główczyńska R, Fojt A, Ilczuk T, Krasuski K, Borodzicz S, Cudnoch-Jędrzejewska A, Górnicka B and Opolski G. Isoprenaline induced Takotsubo syndrome: histopathological analyses of female rat hearts. Cardiol J 2022; 29: 105-114.
[31] Grassi S, Campuzano O, Cazzato F, Coll M, Puggioni A, Zedda M, Arena V, Iglesias A, Sarquella-Brugada G, Pinchi V, Brugada R and Oliva A. Postmortem diagnosis of Takotsubo syndrome

on autoptic findings: is it reliable? A systematic review. Cardiovasc Pathol 2023; 65: 107543.
[32] Sato TH, Uchida T and Dote KMI. Tako-tsubo-like left ventricular dysfunction due to multivessel coronary spasm. In: Kodama K, Haze K, Hori M, editors. Clinical Aspect of Myocardial Injury: From Ischemia to Heart Failure. Tokyo, Japan: Kagakuhyoronsha Publishing Co; 1990. pp. 56-64.
[33] Singh T, Khan H, Gamble DT, Scally C, Newby DE and Dawson D. Takotsubo syndrome: pathophysiology, emerging concepts, and clinical implications. Circulation 2022; 145: 1002-1019.
[34] Mizutani K, Shioya A, Hirose Y, Saito R and Yamada S. Serious takotsubo cardiomyopathy: an autopsy case presenting severe irreversible myocardial damage after frequent episodes of recurrence. Diagn Pathol 2020; 15: 90.
[35] Petricevich VL. Scorpion venom and the inflammatory response. Mediators Inflamm 2010; 2010: 903295.
[36] Fukuhara YD, Reis ML, Dellalibera-Joviliano R, Cunha FQ and Donadi EA. Increased plasma levels of IL-1β, IL-6, IL-8, IL-10 and TNF-α in patients moderately or severely envenomed by Tityus serrulatus scorpion sting. Toxicon 2003; 41: 49-55.
[37] Kadokami T, Shimokawa H, Fukumoto Y, Ito A, Takayanagi T, Egashira K and Takeshita A. Coronary artery spasm does not depend on the intracellular calcium store but is substantially mediated by the protein kinase C-mediated pathway in a swine model with interleukin-1 beta in vivo. Circulation 1996; 94: 190-6.
[38] Klemm P, Warner TD, Hohlfeld T, Corder R and Vane JR. Endothelin 1 mediates ex vivo coronary vasoconstriction caused by exogenous and endogenous cytokines. Proc Natl Acad Sci U S A 1995; 92: 2691-5.
[39] Bahloul M, Turki O, Chaari A and Bouaziz M. Incidence, mechanisms and impact outcome of hyperglycaemia in severe scorpion-envenomed patients. Ther Adv Endocrinol Metab 2018; 9: 199-208.
[40] Clarke RS, Johnston H and Sheridan B. The influence of anaesthesia and surgery on plasma cortisol, insulin and free fatty acids. Br J Anaesth 1970; 42: 295-9.
[41] Owald GA, Smith CC, Delamothe AP, Betteridge DJ and Yudkin JS. Raised concentrations of glucose and adrenaline and increased in vivo platelet activation after myocardial infarction. Br Heart J 1988; 59: 663-71.
[42] Verma S, Maitland A, Weisel RD, Li SH, Fedak PW, Pomroy NC, Mickle DA, Li RK, Ko L and Rao V. Hyperglycemia exaggerates ischemia-reperfusion-induced cardiomyocyte injury: reversal with endothelin antagonism. J Thorac Cardiovasc Surg 2002; 123: 1120-4.
[43] Matta AG and Carrié D. Epidemiology, pathophysiology, diagnosis, and principles of management of Takotsubo cardiomyopathy: a review. Med Sci Monit 2023; 29: e939020.
[44] Bouaziz M, Ben Hamida C, Chelly H, Bahloul M and Kallel H. Dobutamine in the treatment of severe scorpion envenoming. Toxicon 2020; 182: 54-58.
[45] Elatrous S, Nouira S, Besbes-Ouanes L, Boussarsar M, Boukef R, Marghli S and Abroug F. Dobutamine in severe scorpion envenomation: effects on standard hemodynamics, right ventricular performance, and tissue oxygenation. Chest 1999; 116: 748-53.
[46] Abroug F, Ouanes-Besbes L and Elatrous S. Should dobutamine be used in severe scorpion envenomation. Clin Toxicol (Phila) 2015; 53: 584.

Supplementary File

Case-series

The search in the PubMed and Medline databases using the identified keywords showed that a total of 10 articles were published on this subject [1-10]. However, according to our criteria used and according to the Revised Mayo Clinic Criteria [11], only three publications [1, 2, 4] reported a confirmed clinical case of Takotsubo cardiomyopathy due to scorpion envenomation. A total of four patients were described to have Takotsubo cardiomyopathy following scorpion envenomation. Three cases are reported by two Tunisian critical care teams [1, 4] and one by a Brazilian emergency team [2].

The first case was published by Miranda CH *et al.* in Brazil [2] in 2015. The case reports a 7-year-old boy admitted to the emergency department for severe scorpion envenomation by a scorpion of the *Tityus serrulatus* species. The patient was admitted to the emergency department with pain in the site of the sting associated with systemic manifestation (vomiting and sweating) and respiratory distress due to cardiogenic pulmonary edema. The systolic arterial blood pressure was at 137 mmHg, the diastolic arterial blood pressure was at 100 mmHg, and the heart rate was 119 beats per minute. Biological findings showed a high level of troponin I (10.89 µg/L) and a high value of B-type natriuretic peptide (NT-proBNP) at 10003 pg/mL. An electrocardiogram (ECG) was performed, showing sinus tachycardia associated with ST-segment elevation in V1 to V2, V3, DI, and aVL leads. The echocardiography showed a systolic left ventricular dysfunction with important hypokinesia in the apical region and left ventricle ejection fraction (LVEF) of 26%. The patient was treated with furosemide intravenously and oxygen therapy. A cardiac magnetic resonance (CMR) was performed, showing an apical ballooning in the left ventricle associated with a left ventricular ejection fraction (LVEF) of 29%. The patient was well-improved and was discharged 6 days after hospital admission. A second Echocardiography performed 6 days later showed a full recovery of the systolic dysfunction. Moreover, the second CMR performed after 7 months showed a complete recovery of the wall motion in the apical region.

The diagnosis of Takotsubo cardiomyopathy was retained on clinical presentation; ST-segment abnormalities were observed in the electrocardiogram, cardiac biomarker levels, echocardiography findings, and CMR images.

The second case was reported by Abroug *et al.* (Tunisia) in 2018 [1]. The case reports A 36-year-old woman admitted to the ICU for severe scorpion envenomation (Grade III) by a scorpion of the *Androctonus australis* species. A clinical examination showed that she had a cardiogenic shock associated with respiratory failure due to pulmonary edema (with bilateral alveolar infiltrates present on the chest X-ray). The ECG showed tachycardia with ST depression in V1 to V4 leads. Troponin and NT pro-BNP level peaks were high (3.4 ng/ml and 3430 pg/ml, respectively). Echocardiography found a systolic dysfunction with a low LVEF at 30%, without any wall motion abnormalities or mitral regurgitation. Cardiac magnetic resonance imaging (MRI) performed on the day of admission showed a basal ballooning of the left and right ventricles. She was treated by oxygen and CPAP, and the Dobutamine infusion was started to treat the cardiogenic shock. She was well-improved and discharged five days later. A second cardiac MRI (performed 4 weeks later) was normal.

The third case was reported by Abroug *et al.* (Tunisia) in 2018 [1]. The case reports a 45-year-old woman with no cardiac history admitted to ICU for severe scorpion envenomation (7 hours following a scorpion sting) by a scorpion of the *Androctonus australis* species. She presented clinical signs of respiratory failure (respiratory rate at 34 c/min and SaO2 on air: 84%) due to pulmonary edema (with bilateral alveolar infiltrates present on the chest X-ray). Moreover, she presented clinical signs of cardiogenic shock with SBP at 79 mmHg, DSB at 54 mmHg, and heart rate at 126 b/min. She underwent tracheal intubation and mechanical ventilation, and Dobutamine infusion was started. The ECG showed tachycardia with ST depression in the antero-septal precordial leads. Troponin and NT pro-BNP level peaks were high (3.1 ng/ml and 6270 pg/ml, respectively). Echocardiography revealed a systolic dysfunction with an LVEF at 35%. Cardiac MRI performed 24 hours after the scorpion sting showed a basal balloon-

ing. The patient was well-improved under treatment (Dobutamine infusion and mechanical ventilation). She was discharged four days following the ICU admission with a normal LV function on repeat echocardiography examination. MRI was not repeated in this case due to logistic reasons.

The fourth, and last, case was by Ben Jemaa *et al.* (Tunisia) in 2021 [4]. The case reports a 26-year-old man with no cardiac history admitted to ICU for severe scorpion envenomation by a scorpion of the *Androctonus australis* species. He presented clinical signs of respiratory failure due to pulmonary edema (with bilateral alveolar infiltrates present on the chest X-ray) and cardiogenic shock (SBP at 80 mmHg, DSB at 40 mmHg, and heart rate at 120 b/min). The ECG showed tachycardia with ST depression in the V2 to V5 precordial leads. Troponin level peaks were high at 2.9 ng/ml. Echocardiography revealed a systolic dysfunction with an LVEF at 33% with a relative hypokinesis of the basal and mid segments. The cardiac MRI performed 24 hours after the scorpion sting showed a basal ballooning. The patient was treated with Dobutamine infusion and oxygen therapy. He was discharged six days after ICU admission with a normal LV function on repeat echocardiography examination. MRI was not repeated in this case due to logistic reasons.

References

[1] Abroug F, Ouanes I, Maatouk M, Golli M and Ouanes-Besbes L. Inverted Takotsubo syndrome in Androctonus australis scorpion envenomation. Clin Toxicol (Phila) 2018; 56: 381-383.

[2] Miranda CH, Braggion-Santos MF, Schmidt A, Pazin-Filho A and Cupo P. The first description of cardiac magnetic resonance findings in a severe scorpion envenomation: is it a stress-induced (Takotsubo) cardiomyopathy like? Am J Emerg Med 2015; 33: 862, e5-7.

[3] Mishra AK, George AA, John KJ, Arun Kumar P, Dasari M, Afraz Pasha M and Hadley M. Takotsubo cardiomyopathy following envenomation: an updated review. World J Cardiol 2023; 15: 33-44.

[4] Ben Jemaa A, Bahloul M, Kallel H, Turki O, Dlela M and Bouaziz M. Inverted Takotsubo syndrome due to severe scorpion envenomation: report of one case. Med Trop Sante Int 2021; 1: PWX0-M245.

[5] Abroug F, Ouanes-Besbes L, Tilouche N and Elatrous S. Scorpion envenomation: state of the art. Intensive Care Med 2020; 46: 401-410.

[6] Abroug F, Ouanes-Besbes L and Bouchoucha S. Scorpion envenomation: from a neglected to a helpful disease? Intensive Care Med 2019; 45: 72-74.

[7] Madias JE. Scorpion envenomation cardiomyopathy: a promising model for Takotsubo syndrome. Clin Toxicol (Phila) 2015; 53: 787.

[8] Abroug F, Souheil E, Ouanes I, Dachraoui F, Fekih-Hassen M and Ouanes Besbes L. Scorpion-related cardiomyopathy: clinical characteristics, pathophysiology, and treatment. Clin Toxicol (Phila) 2015; 53: 511-8.

[9] Miranda CH, Braggion-Santos MF, Schmidt A, Pazin Filho A and Cupo P. Evolution of the electrocardiogram QRS complexes voltage in scorpion envenomation-induced Takotsubo syndrome. Am J Emerg Med 2015; 33: 837-8.

[10] Madias JE. Voltage attenuation of the electrocardiogram QRS complexes in a patient with "scorpion envenomation"-induced Takotsubo syndrome. Am J Emerg Med 2015; 33: 838.

[11] Sahu KK, Mishra AK and Lal A. Newer insights into Takotsubo cardiomyopathy. Am J Med 2020; 133: e318.