Clinical update on scorpion envenoming

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ABSTRACT

Scorpion stings are currently the leading cause of venom-related injury to humans in Brazil and are a significant public health problem globally. Only scorpions of the Tityus genus are of medical importance in Brazil, and Tityus serrulatus is responsible for the most serious envenomations and deaths. The toxic effects of scorpion envenomation are due to a massive release of sympathetic and parasympathetic neurotransmitters; the severity is related to cardiac and hemodynamic changes, with cardiogenic shock and pulmonary edema contributing to the main causes of death. The pathophysiology of cardiac involvement has been discussed for decades and has been attributed to adrenergic discharge and a possible toxic effect of venom on the myocardium, while acute pulmonary edema may have a cardiogenic and/or non-cardiogenic origin. Currently, the clinical data point to catecholamine excess as the cause for reversible scorpion cardiomyopathy. These data include electrocardiographic changes, profiling of cardiac enzymes and troponin I, echocardiographic data with global or regional left ventricle dysfunction, and myocardial perfusion alterations compatible with spasm in the coronary microcirculation. Furthermore, recent data on cardiac magnetic resonance imaging findings, which are similar to those observed for stress-induced cardiomyopathy, have also been linked to catecholamine excess. The efficiency of antivenom serum treatment is controversial in the literature. Our experience in Brazil is that the management of patients with systemic manifestations of scorpion stings is based on three approaches, all of which are extremely important. These include symptomatic treatment, antivenom serum, and cardiorespiratory support.

Keywords: Tityus serrulatus. Antivenom. Heart failure. Scorpion envenoming.

INTRODUCTION

As observed in other parts of the world, scorpion stings are a serious public health problem in Brazil, not only because of their high incidence in certain regions, but also because of their potential to induce severe (sometimes fatal) signs and symptoms, especially in children[1][2][3][4][5].

Globally, approximately 1,500 scorpion species belonging to 18 families have been described. However, only 30 are considered dangerous to man, with 29 of them belonging to the family Buthidae. Only 11 account for serious/fatal envenoming, including scorpions of the genus Androctonus and Buthus in North Africa, Leiurus in the Middle East, Tityus in South America, Centruroides in North and Central America, Mesobuthus in Asia (especially in India), and Parabuthus in South Africa[1][2].

In Brazil, medically important scorpions belong to Tityus genus; the major envenoming-related species are T. serrulatus and T. bahiensis in the Southeast, T. stigmurus in the Northeast, and T. obscursus (paraensis) in the North (Figure 1)[3]. Most stings involve mild envenoming, while more serious envenoming is caused by T. serrulatus[3][4][5].

Since the early 2000’s, the number of scorpion envenoming cases in Brazil has increased, with 12,552 notifications in 2000 and 64,027 in 2012. The number of deaths also increased from 13 to 89 during this period. The mean national lethality rate was 0.16% (0.06-0.22). Starting in 2004, these cases exceeded those of snakebites (32,000 against 28,000) and in 2014, these values were approximately 78,200 against 24,359[5][6].

PHYSIOPATHOLOGY OF ENVENOMING

The venom of Buthidae family scorpions contains several low-molecular weight proteins (neurotoxins) that act mainly on two classes of ion channels: the sodium (Na+) and potassium (K+) voltage-gated channels[6][7]. These channels conduct the electrical impulse in most excitable tissues, promoting permeability to ions, which initiates the action potential. Alpha and beta toxins act on Na+ channels at two pharmacologically distinct sites: alpha toxins bind to receptor site-4 and inhibit channel inactivation while the beta toxins bind receptor-type 3 and enhance activation of the channel upon subsequent depolarization. Toxins acting on K+ channels physically block them, and prevent ionic conduction, thus prolonging the action potential. Therefore, the Na+ and K+ channel toxins synergize to cause intense and prolonged depolarization, leading to neuronal excitation. This in turn stimulates postganglionic nerve endings of the sympathetic and parasympathetic nervous system and of the adrenal medulla, inducing the release of acetylcholine, adrenaline, and noradrenaline. These mediators act rapidly after the sting to initiate a chain of events that...
represents scorpion envenoming, triggering the onset of clinical manifestations in practically all systems of the organism\(^{(4)}\)\(^{(7)}\).

Recent animal and human studies have identified other mediators in the physiopathology of scorpion envenoming, such as interleukins, tumor necrosis factor (TNF), platelet activating factor (PAF), and activation of the complement system\(^{(8)}\)\(^{(9)}\)\(^{(10)}\)\(^{(11)}\) and of substances such as endothelin-1 and neuropeptide Y, which may contribute to the seriousness of the case\(^{(12)}\)\(^{(13)}\).

**CLINICAL SIGNS AND SYMPTOMS**

**Local**

Erythema and discrete edema are usually observed at the sting site, and the point of inoculation is usually difficult to locate (Figure 2 and Figure 3). Piloerection, diaphoresis, and chills may be localized to the site or to the entire limb that is involved.

Local pain is practically immediate, of varying intensity ranging from mild to very intense or unbearable, depending mainly on individual sensitivity, and at times irradiating to the root of the limbs. It is characterized by tingling, burning, or stinging.

Regardless of the severity of envenoming, pain and paresthesia may persist at the site or at the affected limb for several days.

**Systemic**

The initial clinical manifestations are mainly due to venom-induced cholinergic and adrenergic effects\(^{(3)}\)\(^{(4)}\)\(^{(14)}\)\(^{(15)}\)\(^{(16)}\)\(^{(17)}\).

Acetylcholine release induces myosis, bradycardia, cardiac arrhythmias, arterial hypotension, increased lachrymal, nasal, salivary, pancreatic, gastric and bronchial secretions, diaphoresis, tremors, piloerection and muscle spasms, and increases blood amylase levels.

Manifestations secondary to catecholamine release include mydriasis, cardiac arrhythmias, tachycardia, arterial hypertension, acute pulmonary edema (APE), cardiac failure, and shock. Adrenergic firing leads to hyperglycemia and leukocytosis and contributes to hypopotassemia.
Patient signs and symptoms are variable; the established clinical picture depends on the quantity of mediators released, and on the relative contribution of acetylcholine or adrenaline, which are often antagonistic. Symptoms usually start with more transitory parasympathetic activation. Severity, however, is generally determined by the long-lasting effects of high catecholamine concentrations in the cardiovascular system\(^{(4)}\)\(^{(15)}\)\(^{(16)}\)\(^{(17)}\).

Majority of the species of the Buthidae family induce similar reactions, except for *Tityus obscurus* in Brazil\(^{(18)}\)\(^{(19)}\)\(^{(20)}\), *Centruroides*\(^{(21)}\), and *Parabuthus*\(^{(22)}\), which also induce neurological manifestations. Signs and symptoms reported in envenoming caused by *T. obscurus* in some regions of Pará (Santarém) involve myoclonus (a sensation of an electric shock throughout the body), dysmetria, dysarthria, ataxia, paresthesias and hyperreflexia, compatible with acute cerebellar syndrome with abnormal muscle movements, in addition to rhabdomyolysis and acute renal failure\(^{(19)}\)\(^{(20)}\).

**CLASSIFICATION OF SERIOUSNESS**

For therapeutic and prognostic guidance, envenoming is classified as mild, moderate and serious according to the intensity of the initial symptoms\(^{(4)}\)\(^{(14)}\)\(^{(15)}\)\(^{(16)}\).

**Mild**

Presence of only local manifestations: mild nausea, agitation, and tachycardia may be present, and are related to pain. These represent the great majority of envenoming episodes.

**Moderate**

In addition to local symptoms, some of the following low-intensity systemic manifestations may occur: diaphoresis, nausea, vomiting episodes, tachycardia, tachypnea, agitation, and arterial hypertension.

**Serious**

Systemic manifestations are evident and intense: numerous vomiting episodes, excessive salivation, profuse diaphoresis, hypothermia, tachydyspnea, bronchorrhea, tachy or bradyarythmias, arterial hyper- or hypotension, alternating agitation and prostration, and, rarely, muscle spasms and convulsions. Progression to cardiac failure, APE, shock and death may occur. The local pain is usually masked by the above signs and symptoms, and may later reappear with the improvement of signs and symptoms. Convulsions related to hypoxia or to arterial hypertension and ischemic cerebrovascular accidents have also been described and are quite rare\(^{(23)}\)\(^{(24)}\).

The severity of envenoming usually manifests within the first two hours after the sting, i.e., a patient is in a serious condition since the beginning, with the early occurrence of numerous vomiting episodes (a premonitory sign of seriousness) and with progression to systemic manifestations. In the most serious cases, when intense catecholamine release occurs, there is early cardiac aggression.

**COMPLICATIONS OF SCORPION ENVENOMING**

Envenoming severity is related to the cardiac and hemodynamic changes triggered, with cardiogenic shock and APE being the major causes of death\(^{(4)}\)\(^{(14)}\)\(^{(15)}\)\(^{(16)}\)\(^{(17)}\)\(^{(25)}\)\(^{(26)}\)\(^{(27)}\). Physiopathology of cardiac involvement and the etiology of the APE in scorpion haves been debated since 1980s\(^{(28)}\)\(^{(29)}\).
Cardiac involvement, usually reversible within the first week post-sting, has been mainly attributed to the adrenergic firing induced by the scorpion toxin. Catecholamine-mediated cardiac damage seems to be multifactorial and may be attributed to the relative hypoxia caused by the increase in heart rate, or by coronary spasm and vasoconstriction of the microcirculation, in addition to a direct toxic effect of these mediators on myocardial cells through the increase in intracellular calcium\(^{4(4)(25)(26)(27)(28)(29)(30)(33)}\). Elevated levels of proinflammatory cytokines and the neuropeptides endothelin-1 and neuropeptide Y (these in experimental animals) detected in scorpion envenoming may also potentiate myocardial dysfunction through their direct depressive effect on contractile function and by mediating coronary constriction, respectively\(^{12(13)}\). There is experimental evidence of a direct toxic effect of the venom on the inotropic properties of the heart, although this alone does not explain the reduced systolic performance\(^{32}\).

The cardiac involvement observed manifests clinically mainly as a reversible acute left ventricle (LV) dysfunction of different degrees of severity, with altered global or regional mobility occurring soon after the sting, and possible progression to APE. It is accompanied by increased serum levels of cardiac markers, as well as by changes in the electrocardiogram (ECG) and echocardiogram (ECHO) readouts\(^{3(13)(15)(36)(37)(38)(39)(40)(41)}\). Another characteristic of the cardiac dysfunction mediated by catecholamine concerns the ECHO, whose findings do not follow the anatomic distribution of the coronary arteries.

The first description of myocardial perfusion after scorpion envenoming was published by Gueron et al.\(^{42}\), who reported regional perfusion defects in resting myocardial scintigraphy (\(^{20}\)Thallium) in 14-year-old patients with serious scorpion envenoming, APE, and a 33% LV ejection fraction (LVEF), 2h after the sting. These changes regressed after 72h. Bahloul et al.\(^{43}\) later described perfusion changes compatible with LV dysfunction in 6 patients (3 children and 3 adults) 12-74h after _Androctonus australis_ envenoming; these changes also correlated with ECHO findings. Exams repeated after 6 and 15 days in two patients showed partial regression of these findings.

In Brazil, changes in myocardial perfusion scintigraphy (\(^{99}\)Technetium) in 12 patients aged 1 to 12 years with serious _T. serrulatus_ envenoming were observed during the first 72h after the sting. The topography and intensity of these changes also correlated with those detected by ECHO, and were not consistent with the territory of coronary artery distribution\(^{44(45)}\). The intensity of cardiac dysfunction was correlated with the severity of envenoming, since 6 of the 7 patients with LVEF < 35% (severe dysfunction) had APE, as opposed to only 1 patient with LVEF ≥ 35%, corroborating the cardiogenic etiology of APE. Control exams performed on all patients were practically normal. These reported changes of perfusion are compatible with the occurrence of spasm of the coronary microcirculation, supporting the role of adrenergic hyperstimulation.

Several other clinical situations in addition to scorpion envenoming are associated with excessive concentrations of catecholamines released through an endogenous pathway, as is the case for pheochromocytoma\(^{46}\), subarachnoid hemorrhage\(^{47}\), and stress-induced cardiomyopathy\(^{48}\), or by an exogenous pathway as is the case for accidental administration of high epinephrine doses\(^{49}\). In all of these conditions, the cardiopulmonary manifestations are similar to those observed in scorpion envenoming.

We recently reported cardiac magnetic resonance (CMR) findings for a 7-year-old patient with serious _T. serrulatus_ envenoming associated with APE\(^{50}\). Apical LV ballooning was observed in association with 29% LVEF; this was accompanied by global edema of the middle and apical myocardium. Full recovery of apical region mobility and of LVEF (60%), just like of the global edema occurred and was observed in CMR repeated 7 months later. These findings are similar to those observed in _takotsubo cardiomyopathy_\(^{51}\), suggesting that excess catecholamine release may be the common mechanism underlying the physiopathology of cardiac dysfunction in these two situations.

Regarding APE, available evidence strongly indicates a cardiogenic etiology\(^{40(41)(43)(44)(45)(50)(52)}\) as described above, although it cannot be ruled out that non-cardiogenic factors may also contribute to this complication\(^{8(9)(10)(11)(53)}\). In general, APE develops within the first hours after envenoming, possibly occurring during the first 24h.

**COMPLEMENTARY EXAMS**

Complementary exams are performed only in patients with moderate and serious envenomings, and in most cases are reversible within the first week, depending on the severity\(^{15(27)(33)(36)(42)}\). The biochemical exams normalize as early as during the first hours after scorpion antivenom (SAV).

**Blood**

Hyperglycemia, leukocytosis, and hypopotassemia occur early, and an increase in blood amylase level is observed in a large percentage of cases. When cardiac involvement occurs, there is an increase in the enzymes phosphocreatine kinase CK-MB, glutamic oxaloacetic transaminase (GOT), lactic dehydrogenase (LDH), troponin I, and aminoterminal pro-brain natriuretic peptide (NT-proBNP) in serial determination, similar to the profile detected in myocardial infarction. A disorder of acid-base equilibrium of the mixed type is usually observed; initially, this presents as metabolic acidosis and respiratory alkalosis, and may progress to respiratory acidosis.

The presence of hyperglycemia is a useful early finding when there is no history or certainty about the episode of envenoming (in the case of children, they may commonly wake up crying and with vomiting of no apparent cause). This exam can be performed rapidly at practically all health stations with the use of glucose meters.

**Urine**

Glycosuria and at times, ketonuria, are observed in moderate and serious cases.

**Electrocardiogram**

This is very useful for initial evaluation and for patient follow-up. The changes most frequently detected are tachycardia or sinus
bradycardia, ventricular extrasystoles, arrhythmias, and disorders of ventricular repolarization such as T wave inversion, presence of prominent U waves, changes similar to those observed in acute myocardial infarction (presence of Q waves and a positive or negative deflection of the ST segment, a changing pacemaker, and corrected QT prolongation).

**Chest X-ray**

May reveal an enlarged cardiac area and signs of APE, eventually unilateral.

**Echocardiography**

Systolic LV dysfunction may occur with reduced EF of different degrees and with changes in regional or global mobility, dilatation of the cardiac chambers, and mitral valve regurgitation. Involvement of the right ventricle (RV) has been reported in up to 50% of patients with serious envenoming (40) (41) (54) (55), although in Brazil the reports mainly concern the LV. A study conducted in India on victims of serious scorpion envenoming showed a correlation between the seriousness of systolic dysfunction and TnI and NT-proBNP levels. The exams were performed within the first 6h after patient admission, but there was no mention of the time of the sting, and 75% of the patients had EF<50% (39).

It should be emphasized that, in serious cases, ECHO changes may be present as early as the first few hours after the sting, with ECHO being an important tool for patient diagnosis and prognosis. However, this exam is not yet available 24h/day in most hospitals.

**Computed brain tomography**

May be useful when a cerebrovascular accident or other neurological complications are suspected, a considerably rare eventuality in Brazil (23) (24).

**TREATMENT**

Since the 1980s, the treatment of serious scorpion envenoming in Brazil has been based on three approaches: symptomatic treatment, support of vital conditions, and specific treatment, i.e., SAV (36). However, even though the use of antivenom after snake or spider envenoming has never been questioned, its use after scorpion envenoming has been one of the topics most frequently discussed in the literature over the last decades. This is despite the fact that more than 85-90% of the scorpion envenoming cases are mild and do not require SAV (60). Although a consensus has still not been reached, advances have been made in this topic. Some authors consider the use of SAV to be fundamental, whereas others question its efficacy for the prevention of either death or cardiovascular manifestations in serious cases.

The use of SAV has the objective of neutralizing the circulating venom and the venom that is being absorbed at the sting site (since the scorpion does not inject its venom directly into the circulation) (36), thus reducing or stopping the release of mediators, before their effects on target organs. However, if this already has occurred, SAV treatment alone is ineffective; but the objective is to neutralize the venom that is still circulating or is still being absorbed, in order to prevent worsening of the clinical condition. At the same time, the objective is to deal with shock, cardiac failure and APE, as is commonly the case in situations other than scorpion envenoming.

Experimental studies of the pharmacokinetics of subcutaneous scorpion venom conducted in Brazil and abroad have demonstrated that venom absorption starts rapidly (reaching a peak at about 60 minutes), that distribution to the tissues is rapid and that, by 6 to 8h after inoculation, the venom is no longer detected in serum. The elimination half-life of SAV is more than 40h and administration of SAV 1h after venom inoculation considerably reduces the serum and tissue concentrations of the venom (57) (58).

Studies on the kinetics of venom clearance in humans have corroborated the experimental findings. Intravenous SAV treatment elicited plasma clearance 1h after application in patients with systemic manifestations of scorpion envenoming; this was true even for those who reached hospital up to 3h after the sting. After SAV, there was a marked improvement of general clinical manifestations such as diaphoresis, agitation, chills, vomiting, and changes in arterial pressure (56) (59) (60). This supports the idea that SAV can be used later in serious cases, since the venom persists in serum up to 6 to 8h. However, the patient should be monitored continuously during the first 24h since, as already cited, SAV only neutralizes circulating venom but does not attenuate the effect of mediators that may already be acting on target organs, the heart, particularly.

More recently, randomized studies conducted in India have demonstrated a beneficial action of SAV in combination with prazosin in patients stung by *M. tamulus*, even when SAV is used within 4h after the sting. This resulted in a more rapid clinical improvement, reduction of the quantity of prazosin and/or dobutamine in more serious patients, and even a reduction of cardiac dysfunction (61) (62) (63) (64) (65). Similarly, studies on children stung by *Centruroides* in Arizona have reported significant improvement in the neurological picture, as well as a reduction of circulating venom compared to placebo (21).

**SYMPTOMATIC TREATMENT AND SUPPORT OF VITAL CONDITIONS**

Treatment of pain of mild or moderate intensity may be initiated using oral analgesics and hot water compresses in the affected site. In the case of more severe pain, parenteral analgesics and/or local infiltration or blockade using anesthetic agents without a vasoconstrictor may also be utilized and repeated up to three times, with a 1-h interval.

A rigorous water balance should be induced to not only avoid large volume but also hypovolemia.

Hyponatremia, hyperglycemia and acid-base disorder normalize within the first hours after SAV, generally requiring no correction. The same occurs with arterial hypertension.

Antiemetics can be used for profuse vomiting that does not cease after SAV.

Patients stung by *T. obscurus* presenting myoclonus can be medicated with benzodiazepines.

Patients with systemic manifestations at admission may progress in two ways during the first hours after SAV: 1. Total
regression of clinical manifestations; 2. Improvement of general symptoms, with progression to tachycardia and tachypnea of different degrees, which may last 48-72h, indicating the probable occurrence of cardiac involvement (serious envenomings). These patients may progress well with no other complications and usually show enzyme and ECG changes, as well as ECHO changes (mild dysfunction), but others may develop APE and cardiogenic shock. For less serious patients, continuous monitoring, rigorous water balance and supplementary oxygen may be sufficient. For more severe patients, intensive care is indicated with vasoactive amines and, if necessary, mechanical ventilation.

### SPECIFIC TREATMENT

Scorpion antivenom is indicated in moderate cases, in children younger than 7 years, and in all patients with serious scorpion envenomation. Three ampoules of scorpion antivenom (when not available, spider antivenom can be used) are recommended for moderate cases and 6 for serious cases, administered intravenously over a period of 15 to 20 minutes with patient monitoring.

Among children older than 7 years and adults with moderate scorpion envenomation, the pain should first be treated and the patient evaluated. If systemic manifestations persist even after analgesia, SAV is indicated.

### PROGNOSIS

The prognosis is very good in cases of mild and moderate envenomation and in most of the severe cases if properly treated.

Some risk factors affect the prognosis, i.e., age of less than 10 years, scorpion size and species (T. serrulatus accounts for most serious cases of envenoming), and time between the sting and patient arrival at the hospital.

In serious cases, SAV should be instituted as rapidly as possible. The identification and treatment of clinical complications and early intubation, whenever necessary, considerably improve the prognosis of the patients, especially children. This underscores the importance of recognizing the severity of envenoming on the part of the professionals who provide first aid care, and who can count on the help of Toxicological Assistance Centers if doubts arise. It is also important that care be taken in the initial treatment with saline expansion (risk of precipitating APE) and with the use of any other medication, even antiemetics. Analgesia should be provided, oxygen saturation should be assessed, a venous access should be provided if necessary, and the patient should be referred as soon as possible to a hospital where SAV is available.

### CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

### REFERENCES

10. Fukuhara YDM, Reis ML, Dellaibera-Joviliano R, Cunha FQC, 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.


58. Ismail M. Review article: The scorpion envenoming syndrome. Toxicon 1995; 33:825-858.


