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REVIEW ARTICLE

Scorpion-related cardiomyopathy: Clinical characteristics, pathophysiology, and treatment

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Context. Scorpion envenomation is a threat to more than 2 billion people worldwide with an annual sting number exceeding one million. Acute heart failure presenting as cardiogenic shock or pulmonary edema, or both is the most severe presentation of scorpion envenomation accounting for 0.27% lethality rate. *Objective*. The purpose of this review is to characterize the scorpion-related cardiomyopathy, clarify its pathophysiological mechanisms, and describe potentially useful treatments in this particular context. *Methods*. We searched major databases on observational or interventional studies (whether clinical or experimental) on the cardiorespiratory consequences of scorpion envenomation and their treatment. No limit of age or language was imposed. A critical appraisal of the literature was conducted in order to provide a pathophysiological scheme that reconciles reported patterns of cardiovascular toxicity and hypotheses and assumptions made so far. *Results*. Early cardiovascular dysfunction is related to the so-called "vascular phase" of scorpion envenomation, which is related to a profound catecholamine-related vasoconstriction leading to a sharp increase in left ventricular (LV) afterload, thereby impeding LV emptying, and increasing LV filling pressure. Following this vascular phase, a myocardial phase occurs, characterized by a striking alteration in LV contractility (myocardial stunning), low cardiac output, and hypotensive state. The right ventricle involvement is symmetric to that of LV with a profound and reversible alteration in right ventricular performance. This phase is unique in that it is reversible spontaneously or under inotropic treatment. Scorpion myocardiopathy combines the features of takotsubo myocardiopathy (or stress myocardiopathy) which is linked to a massive release in catecholamines leading to myocardial ischemia through coronary vasomotor abnormalities (epicardial coronary spasm and/or increase in coronary microvascular resistance). Treatment of pulmonary edema due to scorpion envenomation follows the same principles as those applied for the treatment of cardiogenic pulmonary edema in general: this begins with oxygen supplementation targeting an oxygen saturation of 92% or more, by oxygen mask, continuous positive airway pressure, noninvasive ventilation, or conventional mechanical ventilation. Dobutamine effectively improves hemodynamic parameters and may reduce mortality in severe scorpion envenomation. *Conclusion*. Scorpion cardiomyopathy is characterized by a marked and reversible alteration in biventricular performance. Supportive treatment relying on ventilatory support and dobutamine infusion is a bridge toward recovery in the majority of patients.

Keywords Scorpion; Myocardiopathy; Heart failure; Pulmonary edema

Introduction

Scorpion envenomation is a threat to 2.3 billion at-risk inhabitants in intertropical areas.[1] The annual sting number exceeds 1.2 million with an overall lethality rate of 0.27% varying from 0.03% in Brazil to 0.52% in North Africa.[1] All potentially dangerous scorpion species to humans belong to the Buthidae family. However, the clinical manifestations of scorpion envenomation vary in type and severity according to scorpion species with more neuromuscular toxicity in Arizona and Mexico (where dominant species are *Centruroides*), whereas toxicity ensuing from Old World scorpions is primarily cardiovascular.[2] The latter scorpion species are found mainly in North Africa (*Androctonus* and *Buthus* species), the Middle East (*Leiurus quinquestriatus*), and India (*Mesobuthus tamulus*). One genus of the New World (*Tityus* present in Brazil), generates clinical symptoms dominated by cardiovascular events similar to that observed among the scorpions species of the Old World. In the rest of the manuscript, all clinical descriptions referred to as the "Old World" also apply to the genus *Tityus*. Acute heart failure presenting as either cardiogenic shock or pulmonary edema, or both is the most severe presentation of scorpion envenomation occurring in 1–3% of scorpion stings and around 10% patients exhibiting systemic signs of envenomation.[1,3–5] It is the main cause of mortality due to scorpion envenomation worldwide.[1,2] This review covers mainly the clinical manifestations of Old World scorpion envenomation dominated by cardiovascular toxicity.

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Materials and methods

Data sources and searches

We searched MEDLINE, EMBASE, and Cumulative Index to Nursing and Allied Health Literature or CINAHL, for articles published until 28 February, 2015 using the following MeSH and key word terms: ("scorpion venoms" OR "scorpions") AND ("cardiovascular system" OR "left ventricle" OR "right ventricle" OR "vessels"). We also searched supplementary data sources, including references of included studies and review articles. We did not impose language restrictions.

Study selection

We included all studies whether observational (cohort and case–control studies) or having a prospective and controlled design. These studies could be experimental or conducted in envenomated adults or children. Interventional studies, whether clinical or experimental could have evaluated any drug with potential effects on the cardiovascular or respiratory system. Studies conducted with the specific aim to evaluate scorpion antivenom were discarded unless they reported cardiovascular changes.

Results

Clinical features of scorpion envenomation

Many scales have been proposed in the literature, often as regionally specific guidelines, but according to the last consensus on the classification, more than 90% of scorpion stings only produce effects localized to the area of sting.[2,6,7] This corresponds to Grade-I envenomation evoked by a sting unaccompanied by venom injection, or a "dry" sting.[6] In 7–10% of cases there are systemic manifestations (tachycardia, sweating, fever, vomiting, etc.) without life-threatening manifestations (Grade-II envenomation). In less than 3% of cases there is an organ system failure (Grade-III envenomation), mainly of the circulatory or the respiratory system accounting for the mortality related to scorpion envenomation.[6]

Acute respiratory failure has been recognized as the most dreaded complication of scorpion envenomation.[8–10] Along with a putative action of scorpion venom on respiratory centers, acute respiratory failure is usually related to acute pulmonary edema.[11–13] Both hemodynamic and permeability mechanisms are advocated as underlying causes of pulmonary edema following scorpion envenomation.[5,14–17] The presence of circulating inflammatory and coagulation factors in ways similar to that of sepsis and septic shock suggest an alteration of the alveolar capillary barrier like in acute lung injury or acute respiratory distress syndrome (ARDS).[18–21] Accordingly, for a long time, patients were treated with anti-inflammatory drugs, anti-histaminics, fluid challenge, etc.[3,22–26] However, there was a compelling body of evidence suggesting an involvement of the left ventricle in severe envenomation.[27–29] Electrocardiogram (EKG) changes mimicking ischemia frequently occur.[30–34] Isotopic studies reported myocardial perfusion abnormalities.[27,35] Yarom and Braun reported histopathological changes resembling ischemic disease in the left ventricle in dogs injected with *L. quinquestriatus* venom.[36,37] Various reports describe increased serum concentrations of creatine phosphokinase (CPK),[38,39] troponin,[39–41] and natriuretic peptides[42] after scorpion envenomation. Studies that invasively measured LV filling pressure in envenomated patients suffering from pulmonary edema consistently recorded an increase in pulmonary artery occlusion pressure (PAOP).[4,43,44] In 1991, we reported the first cohort of envenomated patients admitted to the intensive care unit (ICU) for pulmonary edema and shock, in whom we measured PAOP following the insertion of a Swan–Ganz catheter.[4] In this very small cohort, PAOP was consistently increased, with a hemodynamic pattern suggestive of acute left heart failure: in addition to the increased PAOP, there was a sharp decrease in cardiac index and an increase in systemic vascular resistances. Of interest, all patients who were mechanically ventilated and received supportive inotropic drugs eventually recovered in a few days illustrating the efficacy of supportive therapy in this context. This observation also summarizes the real challenge in the management of severe scorpion envenomation: provided it is available, supportive treatment is an effective bridge to recovery. This supportive treatment is unfortunately not always available in under-resourced health systems in the affected areas.

Cardiac dysfunction hallmarks

The main clinical features of severe Old World scorpion envenomation include combined severe systolic dysfunction of the left and right ventricles (myocardial stunning), with recovery of both ventricles to normal function within a few days with appropriate supportive care.

Echocardiographic studies have recorded a marked decrease in indicators of LV contractility (fractional shortening or ejection fraction [EF]).[35,44–47] Kumar et al. reported the first series of envenomated children who had serial echocardiographic measurements during their hospitalization.[47] Out of 30 included patients, 12 (40%) had impaired LV contractility (LVEF $<$ 55%). Recovery was quite rapid with normalization in EF in 24–48 h in all but one child who took several weeks to recover. In patients admitted to the ICU for cardiogenic shock and pulmonary edema, Abroug et al. recorded a mean LV fractional shortening of 12% which returned toward normal range after recovery in few days (Fig. 1).[44] More recently, Sagarad et al. measured EF in 84 consecutive patients and reported that 71% had reduced EF ($<$ 50%), with severe LV dysfunction (EF $<$ 30%) observed in 33%.[48] Of interest, the authors reported simultaneous involvement of the right ventricle in half the patients who had LV dysfunction.[48] In a previous study conducted by our group and focusing on the right ventricular (RV) function with Swan–Ganz catheter equipped with a rapid responding thermistor, we have shown a sharp decrease in RVEF (24 ± 7%), with a decreased RV end-systolic pressure/volume ratio (0.56 ± 0.19 mmHg/mL/m2), suggesting an

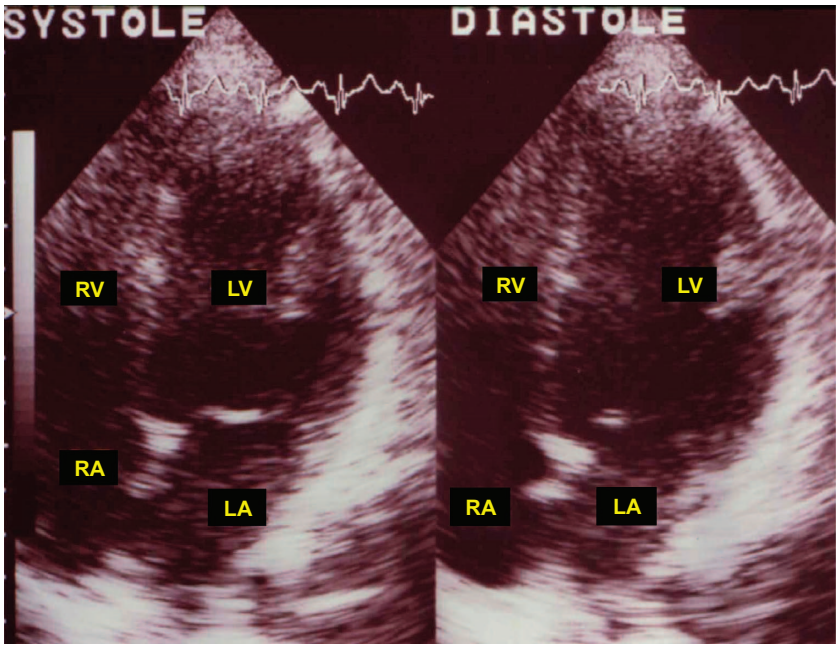

Fig. 1. Apical four-chamber-view echocardiography showing almost similar LV dimensions (myocardial stunning) between systole and diastole in a young patient stung by scorpion *A. australis.*

altered RV contractility.[49] In this study we also recorded a rapid improvement in overall hemodynamic disturbances and more specifically in indicators of RV function, with a trend toward full recovery in few days.[49]

Animal studies on scorpion envenomation

In a canine model of scorpion envenomation, animals were challenged with intravenous injection of the G50 toxic fraction of *Androctonus australis hector* (Aah) venom. The G50 toxic fraction is obtained through the gel filtration of the main scorpion toxic fraction on a Sephadex G-50 column.[50] In this experiment, the sublethal dose (125 µg/kg) resulted in doubling of the mean arterial pressure (MAP) within 5 min.[51] High levels of systemic pressure lasted for approximately 30 min and tended to decrease afterward to reach the baseline levels at 60 min, and continue to decrease to reach hypotensive levels by the second hour (Fig. 2).

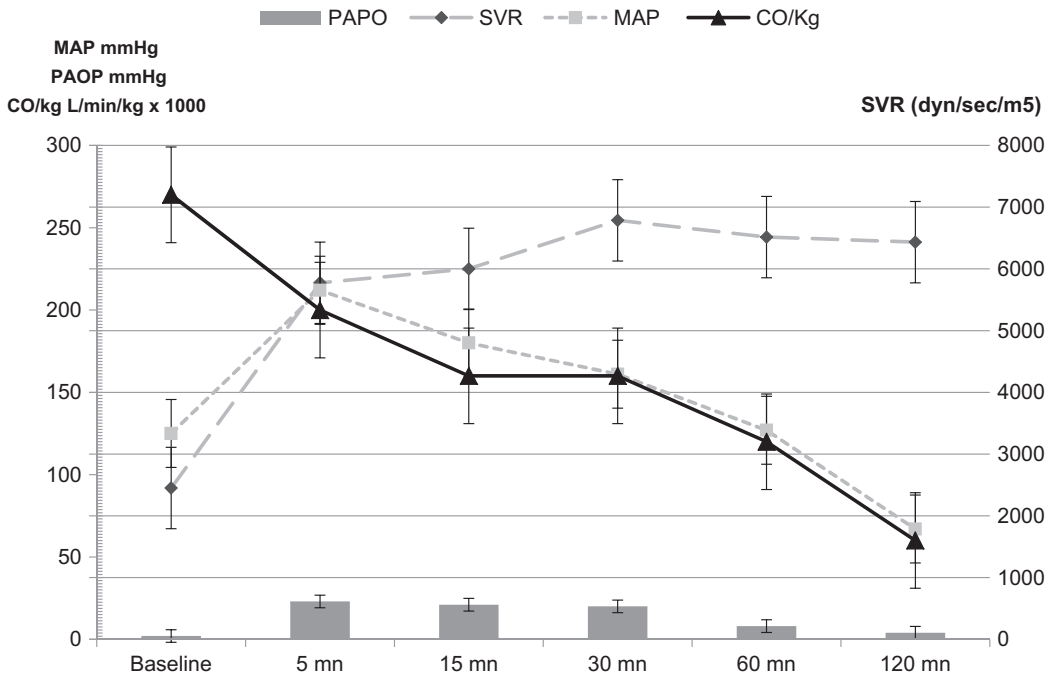

Fig. 2. Hemodynamic variation following experimental intravenous injection of the fraction G50 of the scorpion *A. australis* (canine study). MAP, mean arterial pressure (mmHg); SVR, systemic vascular resistance (dynes/cm2); PAOP, pulmonary artery occlusion pressure (mmHg).

In some other experiments in canine models, an early and transient increase in the cardiac output has been reported, but in the lack of continuous measurement of cardiac output, we were not able to capture this very early "hyperdynamic" phase.[52] In our canine model, cardiac output and stroke volume tended to decrease early following venom injection, to achieve the level of statistical significance by the 30th minute. This trend was sustained throughout the study period. In fact, the initial increase in MAP despite the decreased cardiac output, is related to a major vasoconstrictive effect of scorpion venom injection as reflected by a substantial rise in systemic vascular resistance, which doubled at the 5th minute and remained high throughout the experiment period, a fact that explains that systemic pressure remained almost normal for a long time despite decreased cardiac output. In this canine model, LV dysfunction occurred early as reflected by the rapid elevation in LV filling pressure (PAOP), which was well correlated with the increase in MAP and systemic vascular resistance.

Some authors attribute the early and profound vasoconstriction to neurotoxins which affect sodium, potassium, calcium, and chloride channels to trigger abrupt release of catecholamines ("catecholamine storm").[14,53–55] In another canine study, Nouira et al. observed rapid increases in plasma concentrations of norepinephrine (28-fold) and epinephrine (25-fold) after intravenous injection of AahG50.[56] Simultaneously, they observed release of two potent vasoconstrictive peptides, neuropeptide Y (NPY) and endothelin, in what the authors described as the peptidic pathway (Fig. 3).[56] MAP was closely correlated to circulating catecholamine concentrations.

In keeping with our data obtained from dogs, Zeghal et al. recorded a 30–40-fold increase in epinephrine and norepinephrine concentrations after intravenous injection of a sublethal dose of *Buthus occitanus tunetanus* venom in rats.[56,57] Studies investigating both normal and adrenalectomized rats demonstrated that scorpion venom (*Leiurus quinquestriatus*) produces massive discharge of catecholamines originating from both adrenal glands and postganglionic nerve endings into the blood.[55,58]

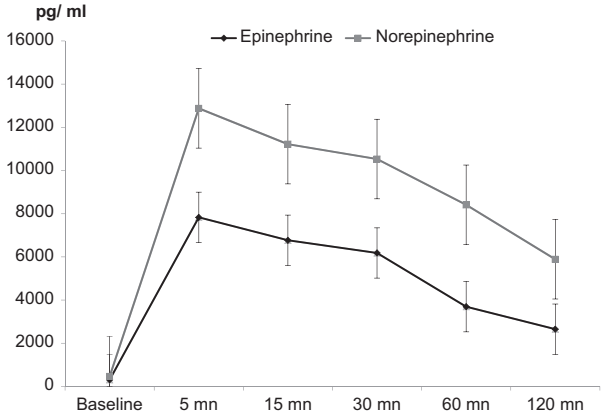

Fig. 3. Catecholamines change following experimental injection of the fraction G50 of the scorpion *A. australis* (canine study).

The final question regarding the pathophysiology of scorpion envenomation is whether cardiovascular effects are actually due to direct effects of scorpion venom or mediated by neurohormone release. Some authors assert that direct effects of the venom on target organs explain the clinical findings.[9,13,59] Hence, all the vascular, cardiac, pulmonary, and renal effects observed in scorpion envenomation have been related to a direct effect of scorpion venom on target organs in guinea pigs and rabbits, respectively.[13,60] Moreover, this theory supports the rationale for antivenom to neutralize circulating venom.[14,61,62] Other data contradict the theory of direct venom effect and instead support the catecholamine storm theory to explain the toxic cardiovascular effects.

To delineate the respective role of direct and mediated effect of scorpion venom, we conducted an experimental canine study to determine whether a second challenge with scorpion venom (G50 fraction of Aah venom) would elicit cardiovascular effects similar to the initial challenge administered 30 min earlier.[63] We hypothesized that if scorpion venom acts directly on its target cells, the presence of the same amount of circulating toxin 30 min after the first challenge would produce the same physiopathologic effects. However, if cardiovascular effects are actually mediated by catecholamine release, the second venom challenge would not produce the same type of effects provided that catecholamine stocks are exhausted following the first challenge. In the experiment, we observed that despite similar toxin levels achieved in blood by the first and the second challenge with scorpion venom, cardiovascular consequences of both venom challenges were not consistent given that only the first one evoked the increase in catecholamine levels. The characteristic hemodynamic changes usually associated with experimental scorpion envenomation were not observed following the second venom challenge. Our findings suggest that catecholamines rather than venom are directly responsible for the cardiovascular effects of envenomation.

Scorpion envenomation: Pathophysiologic pathway

In summary, early cardiac dysfunction is related to the so-called "vascular phase" of scorpion envenomation. This is characterized by profound catecholamine-related vasoconstriction leading to increased LV afterload, impaired LV emptying, increased LV filling pressure, and capillary critical pressure, resulting in pulmonary edema and increased RV afterload (Fig. 4). As a response, LV work and contractility (and oxygen consumption) are increased maintaining transiently cardiac output at acceptable levels. Following this vascular phase, occurs the so-called "myocardial phase" characterized by an altered contractility (myocardial stunning), low cardiac output, and hypotensive state (shock). Three putative mechanisms have been proposed so far: an ischemic myocardiopathy, a catecholaminergic myocardiopathy, or a specific scorpion myocardiopathy. Given its singular presentation characterized by a profound and reversible biventricular involvement, in a context of sudden and important increase in circulating catecholamines, scorpion-related myocardiopathy shares the characteristics of the takotsubo

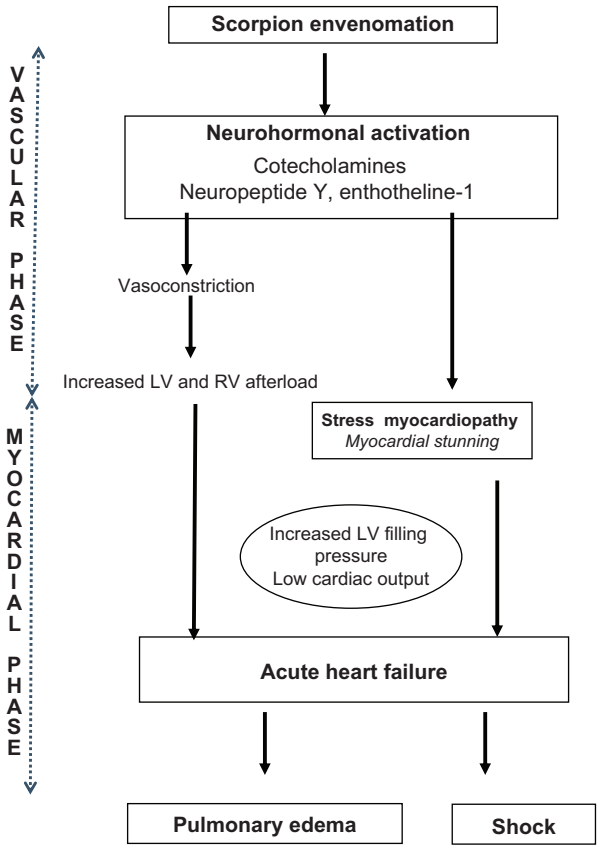

Fig. 4. Schematic description of physiopathologic consequences of scorpion envenomation.

myocardiopathy (or stress myocardiopathy) which is linked to the massive release in catecholamines inducing a severe alteration in LV contractility predominating in the apical or mid-segments of the LV, and sparing LV basis.[64–67] Miranda et al. have recently given strong scientific ground to this hypothesis by reporting the first case of a 7-year-old boy with a severe acute heart failure (EF of 29%) related to scorpion envenomation (*Tityus serrulatus*) in which an early cardiac magnetic resonance (CMR) showed an apical ballooning in the left ventricle associated with a global myocardial edema.[68] This was the first study providing typical takotsubo CMR pattern which was totally reversible in 7 months.[68] Such a mechanism could explain the frequent ischemic-like phenomena observed in severe scorpion envenomation.[30,31,33,34] These consisted in ischemic EKG changes, troponin and CPK release, and abnormalities in myocardial perfusion.[39–41,69] Myocardial ischemia is a pivotal component of stress myocardiopathy.[67] This is rather related to microvascular spasm and microvascular vasomotor dysfunction.[67] The lack of coronary vessel abnormalities in envenomated patients is consistent with ischemia due to microvascular dysfunction.[31]

Supportive treatment in scorpion myocardiopathy

Numerous supportive treatments have been proposed in scorpion envenomation with variable levels of evidence surrounding their effectiveness. Most clinical studies dealing with scorpion envenomation treatment lean markedly toward the explanatory end and suggest that more pragmatic approaches may be needed.[70] Indications of these supportive treatments depend on patient's severity. Symptomatic treatment of major organ system failure occurring after scorpion envenomation is now relatively well codified in the light of the recent advances in understanding scorpion envenomation pathophysiology.[71] The progress achieved in reducing the death toll of scorpion envenomation is largely due to the proposed symptomatic treatment. The most important clinical situations requiring adequate therapeutic management during severe scorpion envenomation are acute heart failure presenting as cardiogenic shock or acute pulmonary edema, or both. Hypertensive crisis which is more frequent in some areas should be either observed (since it disappears spontaneously in a short time), or treated under strict surveillance.

In severe scorpion envenomation, the standard intensive care treatment for acute pulmonary edema and cardiogenic shock appears to be appropriate and often includes oxygenation, ventilation, use of inotropes,[72] and specific vasodilators.[73,74]

Treatment of pulmonary edema due to scorpion envenomation follows the same principles as those for the treatment of cardiogenic pulmonary edema in general. The initial treatment goal for pulmonary edema caused by scorpion envenomation is to maintain oxygen saturation at or above 92%. This can be achieved through oxygen mask or CPAP.[71] In many cases, use of conventional mechanical ventilation is considered necessary. There are no clinical trials of noninvasive ventilation (NIV) in adult patients with scorpion-related pulmonary edema. However, Yildizdas et al. reported a cohort of three children with cardiogenic pulmonary edema due to scorpion envenomation (unknown species) in order to evaluate the feasibility of NIV through a helmet. The helmet was well tolerated by all children.[75] An improvement of oxygenation was observed within 2 h of treatment.[75] Intubation and mechanical ventilation with application of positive end expiratory pressure and pulmonary protective ventilation are indicated when acute respiratory failure is associated with neurologic impairment or cardiogenic shock. Intravenous nitrates and diuretics can also be considered if necessary.

Dobutamine is the drug of choice in the most severe forms of scorpion envenomation manifested by acute heart failure. Dobutamine effectively improves hemodynamic parameters and may reduce mortality in severe scorpion envenomation.[72,76] Despite the lack of a randomized clinical trial specifically designed to assess the effect of dobutamine infusion on mortality in scorpion envenomation with cardiorespiratory failure, the study by Elatrous et al. is strongly suggestive of this type of effect.[72] In a cohort of 19 patients who had severe scorpion envenomation (due to *A. australis*) with all patients exhibiting pulmonary edema, associated with cardiogenic shock in ten, Elatrous et al. examined the effect of a continuous infusion of dobutamine titrated to normalization of systemic blood pressure.[72] At a mean dose of 17 ± 7 µg/kg/min, dobutamine allowed a significant increase in cardiac output, stroke volume index, and tissue oxygenation parameters. Achievement of this hemodynamic goal was associated with a substantial

reduction in the LV preload and filling pressure. Dobutamine had also similar beneficial effects on RV function with a significant improvement in the RVEF.

The frequency of systemic hypertensive crisis is highly variable depending on scorpion species, consultation delays, and the victim age (children are more vulnerable than adults).[71] The lowest rate (almost 4%) was reported after envenomation with *A. australis*, and the highest rate (30%) is more frequent in case of *Mesobuthus* envenomation.[3,77,78] Hypertensive crisis is mostly transient and these patients are themselves potential candidates for delayed vascular collapse and cardiogenic shock. We recommend observing high blood pressure without using antihypertensive medication except in cases of hypertensive crises with acute pulmonary edema or in patients with preexisting chronic hypertension. When the decision to treat hypertension is taken, hydralazine,[79] clonidine,[15] nifedipine,[79,80] and prazosin,[73,81,82] have been tested in the management of severe scorpion envenomation. Of these, prazosin is most extensively studied. Bawaskar et al. recommend prazosin as specific treatment for severe scorpion envenomations caused by the Indian scorpion (*M. tamulus*).[73,83,84] They also observed that patients treated with prazosin plus antivenom recovered more quickly than those treated with prazosin alone.[73] Prazosin, an α-1 antagonist with a phosphodiesterase inhibitory effect, reduces preload and LV impedance without raising heart rate. Bawaskar et al. regard prazosin as part of the specific treatment of severe envenomations by the Indian scorpion (*M. tamulus*).[73] It still seems risky to administer such treatment at the stage of envenomation with hypotension. In their study validating prazosin as a treatment associated with serotherapy, Bawaskar et al. explicitly excluded patients with hypotension (grade-III envenomation).[73] Therefore, it would be hazardous to extrapolate the results of a positive study to hypotensive patients, which excluded such group of patients. In addition, on the remaining included subjects (grade-II envenomation), the chosen endpoint (time to recovery) was not a hard endpoint (such as mortality and the need for mechanical ventilation). Precise determination of the time lapse to recovery is indeed somewhat subjective especially in the lack of predetermined objective criteria in an open-label study.

From a mechanistic standpoint alpha-blockers, like beta-blockers, might be beneficial during the initial catecholamine surge early in the course of envenomation, but before the onset of overt heart failure.

Conclusion

Catecholamine storm appears to be the mechanism of cardiovascular toxicity of Old World scorpion envenomation. Over the last few decades, although the majority of scientific research focused on the antidotic approach (serotherapy), the most significant progress made in the care of envenomated patients has stemmed from a better understanding of the pathophysiology of the disease. Hence, future research should be directed at controlling the consequences of catecholamine discharge following envenomation. The ideal antagonist of scorpion venom could simply be that which limits the effects of catecholamines and their potentiators (endothelin and NPY). Treatment of scorpion-related cardiomyopathy should focus on providing optimal supportive care, which is generally associated with favorable outcomes.

Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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