Intensive Care Med
https://doi.org/10.1007/s00134-018-5226-5

WHAT'S NEW IN INTENSIVE CARE

Scorpion envenomation: from a neglected to a helpful disease?

Fekri Abroug*, Lamia Ouanes-Besbes and Slah Bouchoucha

Scorpion envenomation is a life-threatening accident encountered in tropical and subtropical areas. It remains an under-reported disease but around 1.2 million stings are yearly recorded around the world, ensuing in 3250 deaths as a consequence of acute heart and respiratory failure) [1]. The great majority (> 90%) of stings by the Old World scorpions (North Africa, India, and the Middle East) are so-called dry stings, resulting in localized discomfort. When systemic envenomation occurs, several systems may be affected, including the gastrointestinal, neurological, inflammatory systems, etc. [2]. Life-threatening presentations with acute heart failure features occur in less than 1% of cases. In what follows, we will strive to show how the little research dedicated to this neglected disease has led to significant scientific advances both through the derived experimental model of the widespread Takotsubo syndrome and by the proliferation of venom-derived drugs.

In 1995, we published a study in *Intensive Care Medecine* which included 9 consecutive young patients admitted to the ICU for pulmonary edema consecutive to severe scorpion envenomation [3]. Early upon ICU admission, all patients where equipped with a pulmonary artery catheter, and had serial echo-doppler examinations in order to assess left ventricular function in comparison to 14 matched controls. This report confirmed the findings of a previous study which was one of the first to unveil the hemodynamic nature of the scorpion envenomation-related pulmonary edema [4]. In addition, the study highlighted two of the peculiar features of scorpion-induced LV dysfunction: the marked and reversible (in days) depression in LV systolic function. The next study has brought together arguments in favor of the third characteristic of the scorpion-related cardiomyopathy: the right ventricle may also be involved and to the same extent as the LV making unlikely the ischemic hypothesis of scorpion-related cardiomyopathy, especially since the majority of victims are young with healthy coronary circulation [5]. Subsequent studies have tried to unravel the mechanisms involved in scorpion-related cardiomyopathy where a scorpion-specific, ischemic, or catecholaminergic cardiomyopathy were also advocated [6].

Scorpion envenomation as a model of Takotsubo syndrome

The combination of irrefutable arguments linking this cardiomyopathy to the massive discharge of catecholamines reported after severe envenomation eventually led to the argument in favor of a catecholaminergic cardiomyopathy [7]. The Takotsubo syndrome, which typically occurs in stressful or traumatic situations as a consequence of catecholamines discharge, made it possible to reconcile all the observations accumulated around severe envenomation: the severely altered ventricular contractility, most often involving both ventricles, and its rapidly reversible character [8, 9]. Echocardiographic and scintigraphic findings, and ECG abnormalities mimicking ischemia, troponin and BNP release in proportions dissimilar to what is generally measured in acute coronary syndromes, can thus be explained by the Takotsubo syndrome [3, 10–12]. Several studies have recently reported typical Takotsubo syndrome features in severe scorpion envenomation, with reversible circumferential ventricular dysfunction made peculiar by the fact that regional wall motion abnormalities are not limited to

*Correspondence: f.abroug@rns.tn
Intensive Care Unit and Research Laboratory LR12SP15, CHU Fatouma Bourguiba. University of Monastir, 5000 Monastir, Tunisia

Springer

the distribution of a coronary artery [13–15]. It has been hypothesized that scorpion envenomation can even be considered a model of Takotsubo syndrome [16]. This pathohysiological breakthrough opens new horizons for the management of severe scorpion envenomation where dobutamine, the cornerstone of scorpion-related cardiomyopathy treatment, should probably be considered cautiously in this particular setting. Administration of beta blockers for the secondary prevention after scorpion sting, the overall prognosis, could also be approached differently in the light of these new insights. Figure 1 details the algorithm of current recommendations on the treatment of scorpion envenomation.

Scorpion venom as a valuable source of new therapeutic agents

Despite its confinement to low–middle income countries, scorpion envenomation (and especially scorpion venom and contained toxin peptides) has succeeded in attracting research laboratories with high potential in basic research. They were first interested by the decryption of the mechanisms of activation/inhibition of cellular channels (principally Na+ and K+) in order to explain the pathophysiological consequences of human envenomation. It was rapidly obvious that scorpion peptides are potent selective probes of the ion channels with a potential to modulate biological mechanisms involved in the immunological response, the response to infection, and neoplastic diseases, and with a potential for therapeutic applications in human and veterinary medicine [17, 18]. The majority of the pharmaceutical applications of venom peptides originate from snake venoms which are biochemically simple, and target either the neuromuscular or the cardiovascular systems. Venom-based drug discovery began in the 1970s with the development of the antihypertensive drug captopril from an inhibitor of the

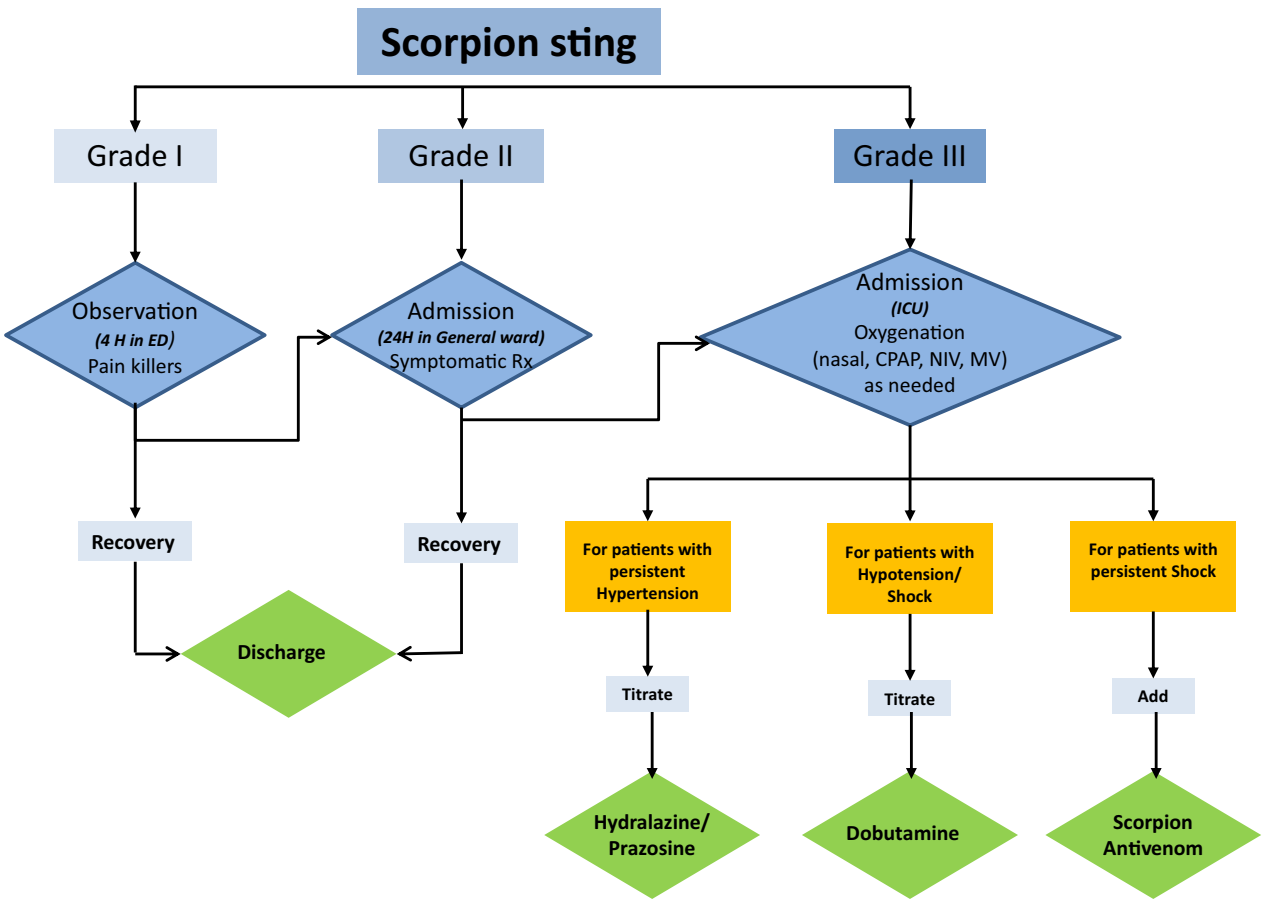

Fig. 1 Treatment algorithm currently recommended for scorpion stung patients. *Grade I* corresponds to patients with only localized pain (usually a dry sting), *Grade II* to patients with signs of systemic envenomation but with no life-threatening symptoms (vomiting, hyperthermia, sudoresis etc.), and *Grade III* to an envenomation resulting in acute heart failure manifestations (cardiogenic shock or pulmonary edema), A change of clinical grade is possible with delayed worsening in the clinical presentation (*arrows*). *Blue diamonds* indicate Class I recommendations while *green diamonds* indicate Class II recommendations

angiotensin-converting enzyme isolated from the *Bothrops jararaca* viper [19]. Several venom-derived peptides have proved effective for the treatment of hypertension, diabetes, pain, etc. [20]. Six drugs derived from venom peptides have so far been FDA-approved [18]. In contrast, scorpion venom is more complex, and contains several hundred components with ~ 100,000 bioactive peptides [17]. Table 1 (supplementary material) provides a short inventory of scorpion peptide toxins with potential application as drug substances in various diseases.

In conclusion: in the last 20 years, scorpion envenomation has evolved from an accident confined to underdeveloped countries with no tradition in research to an experimental and reproducible model of the Takotsubo syndrome, a disease encountered in many stressful and often dramatic circumstances. This disease has yet to fully reveal its physiopathology, for which preventive and curative therapeutic strategies are lacking, and whose potential for recovery is still under investigation. In the same time interval, molecular sequencing techniques, usually resulting in the understanding of the structure/function relationships, have also been used to analyze the many peptides of scorpion venom. The discovery of new pharmacodynamic properties should lead to new drug discoveries whose entry into the international pharmacopoeia could provide new solutions to well-known diseases.

Electronic supplementary material
The online version of this article (https://doi.org/10.1007/s00134-018-5226-5) contains supplementary material, which is available to authorized users.

Received: 23 April 2018 Accepted: 10 May 2018
Published online: 30 May 2018

References

1. Chippaux JP, Goyffon M (2008) Epidemiology of scorpionism: a global appraisal. Acta Trop 107(2):71–79. https://doi.org/10.1016/j.actatropica.2008.05.021
2. Bahloul M, Chaari A, Khlaf-Bouaziz N et al (2005) Gastrointestinal manifestations in severe scorpion envenomation. Gastroenterol Clin Biol 29(10):1001–1005
3. Abroug F, Ayari M, Nouira S et al (1995) Assessment of left ventricular function in severe scorpion envenomation: combined hemodynamic and echo-Doppler study. Intensive Care Med 21(8):629–635
4. Abroug F, Boujdaria R, Belghith M et al (1991) Cardiac dysfunction and pulmonary edema following scorpion envenomation. Chest 100(4):1057–1059
5. Nouira S, Abroug F, Haguiga H et al (1995) Right ventricular dysfunction following severe scorpion envenomation. Chest 108(3):682–687
6. Abroug F, Souheil E, Ouanes I et al (2015) Scorpion-related cardiomyopathy: clinical characteristics, pathophysiology, and treatment. Clin Toxicol 53(6):511–518. https://doi.org/10.3109/15563650.2015.1030676
7. Abroug F, Nouira S, El Atrous S et al (2003) A canine study of immunotherapy in scorpion envenomation. Intensive Care Med 29(12):2266–2276. https://doi.org/10.1007/s00134-003-1947-0
8. Lyon AR, Bossone E, Schneider B et al (2016) Current state of knowledge on Takotsubo syndrome: a Position Statement from the Taskforce on Takotsubo Syndrome of the Heart Failure Association of the European Society of Cardiology. Eur J Heart Fail 18(1):8–27. https://doi.org/10.1002/ejhf.424
9. Kato K, Lyon AR, Ghadri JR et al (2017) Takotsubo syndrome: aetiology, presentation and treatment. Heart 103(18):1461–1469. https://doi.org/10.1136/heartjnl-2016-309783
10. Bahloul M, Ben Hamida C, Chtourou K et al (2004) Evidence of myocardial ischaemia in severe scorpion envenomation. Myocardial perfusion scintigraphy study. Intensive Care Med 30(3):461–467. https://doi.org/10.1007/s00134-003-2082-7
11. Sagarad SV, Thakur BS, Reddy SS et al (2013) NT-proBNP in myocarditis after a Scorpion sting envenomation. J Clin Diagn Res 7(1):118–121. https://doi.org/10.7860/jcdr/2012/4858.2684
12. Kumar CM, Prasad SV (2015) Echocardiologic evaluation and follow-up of cardiovascular complications in children with scorpion sting in coastal South India. Indian J Crit Care Med 19(1):42–46. https://doi.org/10.4103/0972-5229.148645
13. Abroug F, Ouanes I, Maatouk M et al (2018) Inverted Takotsubo syndrome in Androctonus australis scorpion envenomation. Clin Toxicol 56(5):381–383. https://doi.org/10.1080/15563650.2017.1377221
14. Miranda CH, Braggion-Santos MF, Schmidt A et al (2015) 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 33(6):862 e5–862 e7. https://doi.org/10.1016/j.ajem.2014.12.044
15. Miranda CH, Braggion-Santos MF, Schmidt A et al (2015) Evolution of the electrocardiogram QRS complexes voltage in scorpion envenomation-induced Takotsubo syndrome. Am J Emerg Med 33(6):837–838. https://doi.org/10.1016/j.ajem.2015.02.039
16. Madias JE (2015) Scorpion envenomation cardiomyopathy: a promising model for takotsubo syndrome. Clin Toxicol 53(7):787. https://doi.org/10.3109/15563650.2015.1052500
17. Hmed B, Serria HT, Mounir ZK (2013) Scorpion peptides: potential use for new drug development. J Toxicol 2013:958797. https://doi.org/10.1155/2013/958797
18. King GF (2011) Venoms as a platform for human drugs: translating toxins into therapeutics. Exp Opin Biol Ther 11(11):1469–1484. https://doi.org/10.1517/14712598.2011.621940
19. Cushman DW, Ondetti MA (1991) History of the design of captopril and related inhibitors of angiotensin converting enzyme. Hypertension 17(4):589–592
20. Schmidtko A, Lotsch J, Freynhagen R et al (2010) Ziconotide for treatment of severe chronic pain. Lancet 375(9725):1569–1577. https://doi.org/10.1016/s0140-6736(10)60354-6