Insulin-Glucose infusion Reverses Metabolic, Cardiovascular, ECG changes, Pulmonary oedema and all clinical manifestations due to Massive Release of Counter-regulatory Hormones in Scorpion Envenoming Syndrome caused by Scorpion (Buthidae family) Stings

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K. Radha Krishna Murthy receive Thomas Addison Award-2014 in Endocrinology and Metabolism by Photon Foundation.

Article history:
Received: 25 June, 2014
Accepted: 29 June, 2014
Available online: 09 October, 2014

Keywords:
Autonomic storm, Angiotensin II, Hypertension, hypotension, Glycogenolysis, hyperglycemia, counter-regulatory hormones, suppressed insulin secretion, insulin resistance, Free Fatty Acids, ARDS, MSOF, Insulin-glucose infusion, glycogenesis, Lipogenesis

Abbreviations:
FFA Free Fatty Acids
Na+ - K+ ATPase Sodium Potassium stimulated ATPase activities
Mg++ ATPase Magnesium stimulated ATPase activities Ca2+ ATPase activities Calcium stimulated ATPase activities
CNS Central Nervous System
DIC Disseminated Intravascular Coagulation
ARDS Adult Respiratory Distress Syndrome
MCP Mean Circulatory Pressure
C O Cardiac Output
PVR Pulmonary Vascular Resistance
PeArit Arterial Critical Closing Pressure
SIRS Systemic Inflammatory Response Syndrome
MBT venom Mesobuthus taniulus scorpion venom
S.C. Sub cutaneous route
i.m. Intra muscular route
i.v. Intravenous route po
PDG Phenylbiguanide

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Abstract
Death caused by scorpion (Buthidae family) stings is a common event in many developing countries all over the world. Scorpion envenoming syndrome results in an autonomic storm with a massive release of catecholamines, angiotensin II, glucagon, glucocorticoids and either suppressed insulin levels or hyperinsulinemia. Catecholamines and angiotensin II result in hypertension, hypotension and shock. Catecholamines and counter-regulatory hormones cause hyperglycemia and sudden increase in FFA levels. FFA increase the oxygen consumption, susceptibility of the ventricles to the disorganized electrical behavior, aggravates the ischemic injury to myocardium predisposing to arrhythmias, heart failure, DIC, ARDS; many other clinical manifestations, cause MSOF and death. Scorpion envenoming is a syndrome of fuel–energy deficits and an inability to use the existing metabolic substrates by vital organs causing MSOF and death. In our hands, insulin–glucose infusion is highly effective, life saving reversed cardiovascular, ECG changes, ARDS, hormonal, metabolic disturbances in the experimental animals and in scorpion sting victims. Continuous infusion of regular crystalline insulin should be given at the rate of 0.3 U/g glucose and glucose at the rate of 0.1 g/kg body weight/hour, for 48-72 hours, with supplementation of potassium as needed and maintenance of fluid, electrolytes and acid-base balance. Producing an effective and species specific anti-scorpion venom serum (in the developing countries) against hundreds of species of scorpions of Buthidae family is difficult and expensive. Insulin has many life saving actions as demonstrated in our scorpion sting victims to reverse ECG changes, hypertension, hypotension, acute myocarditis, acute pancreatitis, DIC, ARDS, MSOF and many other clinical manifestations.

Citation:

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Photon Ignitor: ISJN57438481D723909102014
1. Introduction

1.1 Death due to poisonous scorpion stings is common event in all the developing countries

Death due to scorpion envenoming syndrome is a common event all over the world and especially in tropical and sub-tropical countries. Several hundreds of thousands of scorpion sting victims (Body weight between 3 kg to 100 kg or more) (infants, children, pregnant and non-pregnant women, adult males) die annually throughout the world. Scorpion envenomation is a major concern only in less developed countries where scientific research has not been a priority, which might account for lack of data. The estimated number of annual human envenomations in Mexico is 100, 000 to 200,000, with mortalities of 500 to 1000. In Algeria, Tunisia, and Saudi Arabia, envenomation range between 24,000 and 45,000 per country per year and in In Brazil the incidence of scorpion bite is 38,144 cases per year in 2007 according to the DATA SUS (Souza 2013). Scorpion stings are also common in China, India, Iraq, Iran, Saudi Arabia, Middle East, and Central and South Africa, although the exact number of victims is unknown (Radha Krishna Murthy 2014 a; b; c; 2013; 2002; 1982; Radha Krishna Murthy et al 2003; 2002; 2001; 1999; 1998; 1994; 1992; 1991; 1990; 1989; 1988 a; b; c; 1986 a; b; c; d; e; f; Abdel-Haleem et al 2006; Abdoon et al 2006; Alamir 1992; Ismail 1995, 1993; 1992; Gueron et al 1993; 1992; 1990; 1987; Moss et al 1973; Bahloul et al 2005; Duddin et al 1991; Gadwalkar et al 2006; Sarkar et al 2008; Dittrich et al 1995; Souza et al 2013; Udaykumar et al 2006; Kankanakorg et al 1992; Naut et al 2006; Mahadevan 2000; Yugandhar et al 1999; Bhaskara Reddy & Suvarna Kumari 1972; Bichile et al 1984; Bisarya et al 1977; Boyer et al 2009; Chadha & Leviav 1979; Reddy et al 1972; Rezende et al 1998; 1995; Rimsza et al 1980; Shah et al 1972; Shivraj et al 1981; Singh et al 1991; 1971; Sofer et al 1998; 1997; 1996; 1995; 1992 a; b; 1991; Tarasiuk et al 1999; 1997; 1994; Tiwari et al 1988; Cordeiro et al 2006; De Matos et al 1997; Abdoon et al 2006; Bucareicha et al 1005; Margulis et al 1994; Benvenuti et al 2002; Devi et al 1970; Amaral et al 1994, 1993; Hering et al 1993; Deshpande ; Freire –Maia et al 1994; 1993; Mathur et al 1983; Rahav et al 1980).

1.2 Cause of death in scorpion envenoming syndrome

Scorpion envenoming syndrome results in a severe autonomic storm with a massive release of epinephrine, norepinephrine, increased levels of angiotensin II, counter-regulatory hormones - glucagon, glucocorticoids, thyroid hormones and changes in insulin secretions (suppressed insulin levels or hyperinsulinemia), hyperglycemia and increased circulating free fatty acid levels. Free fatty acids increase the oxygen consumption, aggravate the ischemic injury to myocardium predisposing to arrhythmias, heart failure, increase the susceptibility of the ventricles to the disorganized electrical behavior, inhibit cardiac sarcolemmal and erythrocyte Na⁺ - K⁺ ATPase activity, increase the tendency to intravascular thrombus-Disseminated Intravascular Coagulation (DIC) and many other abnormalities. These hormonal and metabolic changes could be responsible for the pathogenesis of a variety of clinical manifestations in scorpion envenoming syndrome. Under these conditions, scorpion envenoming syndrome with acute myocarditis, myocardial damage, disseminated intravascular coagulation (DIC), cardiovascular disturbances, peripheral circulatory failure, cardiac pulmonary oedema, Adult Respiratory Distress Syndrome (ARDS), and many other clinical manifestations may cause Multi-System-Organ-Failure (MSOF) and death. Under these altered conditions in the hormonal milieu due to autonomic storm and massive release of catecholamines, scorpion envenoming essentially results in a syndrome of fuel – energy deficits and an inability to use the existing metabolic substrates by vital organs causing MSOF and death (1).

1.3 Justification of the present review article and associated research

Scorpion stings result in hundreds of thousands of deaths annually in many of the tropical and sub-tropical regions and comprises the majority of underdeveloped and developing countries throughout the world. There is not even a “guess-estimate” regarding the incidences due to poisonous scorpion stings in health statistics of many of these countries.

1.3.1 There is no agreement whatsoever on the proper treatment of these patients.

There is no agreement whatsoever on the proper treatment of these patients. An attempt and effort is made to explain the pathophysiology of the scorpion envenoming syndrome; explain the physiological and pharmacological basis of administration of Insulin-Glucose infusion to reverses the metabolic, cardiovascular, ECG changes, pulmonary oedema and all clinical manifestations due to massive release of counter-regulatory hormones in scorpion envenoming syndrome caused by scorpion (Buthidae family) stings.

1.3.2 Limitations of species specific anti-scorpion venom serum

Effective and species specific anti-scorpion venom serum is the best treatment. There are more than
600 species of poisonous “killer scorpions” of Buthidae family. Many countries harbor more than 5 to 10 species of poisonous scorpions of Buthidae family.

Producing an effective and species specific anti-scorpion venom serum (in the developing countries) against hundreds of species of scorpions of Buthidae family is highly difficult and expensive.

1.4 Highly toxic venomous scorpions of the world belong to Buthidae family
The highly toxic venomous scorpions of the world belong to Androctonus, Bathus, Centruroides, Leiurus Quinquestriatus, and Tityus genera come under Buthidae family. Riyadh harbors the killer scorpions that belong to Androctonus crassicauda, Apis obstusus pterygocercus, Bathus yotvatanis nigroaculeatus, Bathus leptocheles, Compsobuthus arabicus, Leiurus quinquestriatus and Orthochirus innesi, Bathos jayokari, Bathos epaceus, Bathos schach, Campobuthus matthiesseni, Campobuthus regulosus, Kraepelinita kalpator, Liobuthus kessleri, Bathus saadyi, Hemiscorpius lepturus, Mesobuthus epaceus, Odontobuthus doriae, Odontobuthus odonturus, Olivierus causcius, Othochirus scrobiculosus, Razianus zarudnyi, Sasanidiotus zardinyl, Simonoida farzanpaya and Scorpion mauros are few species of scorpions under Buthidae family in Iran.

1.5 Poisonous, killer scorpions that belong to the Buthidae family from India (Bastawade and Jadhav, 2009).
Androctonus finitimus (Pocock), Baloorthochirus becvari Kovarik, Bathus agarwali Zambre & Lourenco, Buthoscoporus politus (Pocock), Bathoscoporus rayalenis, Bathoscoporus sarasinorum (Karsch), Charmus brignolii Lourenco, Charmus indicus Hirst, Charmus sinhagadensis Tikader and Bastawade, Compsobuthus Vachon andresi Lourenco, Compsobuthus Vachon atrostriatus (Pocock), Compsobuthus Vachon rugosulus (Pocock), Hemibuthus crassimanus (Pocock), Hottentotta jabalpurenensis Kovarik, Hottentotta pachyurus (Pocock), Hottentotta penjabensis Kovarik, Hottentotta rugiscitus (Pocock), Hottentotta stockweli Kovarik, Hottentotta tamulus (Fabricius), Himalayobuthus abdulreda Lourenco, Himalayobuthus martensi Lourenco, Isometrus acahanurus Pocock, Isometrus assamensis Oates, Isometrus brachycentrus Pocock, Isometrus corbeti Tikader and Bastawade, Isometrus isadensis Tikader and Bastawade, Isometrus khamnamensis Kovarik, Isometrus maculates, Isometrus problematicus Kovarik, Isometrus rigidulus Pocock, Isometrus thurstoni Pocock., Isometrus vittatus Pocock, Lychas aareyensis Mirza & Sanap, Lychas alhimanus Henderson, Lychas bhiranensis Tikader & Bastawade, Lychas gravelyi Henderson, Lychas hendersoni (Pocock), Lychas hillyardi Kovarik, Lychas kamshetensis Tikader & Bastawade, Lychas kharpladi Bastawade, Lychas laevifrons Pocock, Lychas macronatus Fabricius, Lychas nigristerinis (Pocock), Lychas rackae Kovarik, Lychas rugosus (Pocock), Lychas scaber (Pocock), Lychas tricarinatus (Simon), Odontobuthus odonturus (Pocock), Orthochirus bastawadei Zambre, Orthochirus bicolor (Pocock), Orthochiris flavescens (Pocock), Orthochirus fascipes (Pocock), Orthochirus krishnai Tikader & Bastawade, 1 Orthochirus pallidus (Pocock), Thaicharmus lowei Kovarik, Soleglad & Fet, Vachonus rajasthanicus Tikader & Bastawade.

1.6 Problem of scorpion envenoming syndrome has been ignored/ neglected by the international scientific community
The consequences of scorpion envenoming syndrome have been underestimated in health statistic of these developing countries due to inadequate detection and / or data entry of the cases. There is not even a “guesstimate” regarding the number of deaths due to these “nocturnal visitors” (Radha Krishna Murthy 2014 a; b; c: 2013; 2000; Ismail 1995; 1993; Gueron and Osvycher 1987).

1.7 Textbooks of Medicine, Cardiology or Endocrinology ignored scorpion envenoming
Most of the standard textbooks of Physiology (Ganong 1987; Keel and Neil 2004), Pharmacology (Westfall and Westfall 2006; Jackson 2006), Medicine (Cecil 1976, Davidson 2010, Kumar and Clark 2005; Oxford Textbook of Medicine 2003; Textbook of Medicine - Kumar & Clark; Current Medical Diagnosis & treatment 2012, Rosen’s Emergency Medicine 2006, Braunwald’s Heart Disease 2011), dismiss the scorpion envenoming syndrome in few lines! Most of these standard Textbooks completely ignore scorpion envenoming syndrome! Very little or “no clinical information” useful to the physician to manage and treat a victim of severe scorpion envenoming syndrome is provided in these textbooks of physiology (Ganong 1987; Keel and Neil 2004), Pharmacology (Westfall and Westfall 2006; Jackson 2006), Medicine (Cecil 1976, Davidson 2010, Kumar and Clark 2005; Oxford Textbook of Medicine 2003; Textbook of Medicine - Kumar & Clark; Current Medical Diagnosis & treatment 2012, Rosen’s Emergency Medicine 2006, Braunwald’s Heart Disease 2011)!
1.8 High incidence of mortality among scorpion sting victims


1.9 Treatment of scorpion envenoming syndrome is a difficult problem

The treatment of scorpion envenoming syndrome is a difficult problem. It requires extensive knowledge of the clinical manifestations and an understanding of the mechanisms behind the clinical symptomatology.

The Concepts of the mechanisms underlying the action of the scorpion venom as can be explained by the results of different research workers and the results obtained by our investigators are presented to emphasize the physiological basis of medical practice of “insulin-glucose infusion to reverses metabolic, cardiovascular, ECG changes, pulmonary oedema and all clinical manifestations due to massive release of counter-regulatory hormones in scorpion envenoming syndrome”.

1.10 Prohibitive cost and difficulties in producing species specific anti-scorpion venom serum

* Death due to poisonous scorpion stings is a common event mainly in more than 50-100 developing countries throughout the world.

* Scorpion envenoming syndrome is a rural emergency.

* Administration of species specific anti-scorpion venom serum in scorpion envenoming syndrome is the best treatment provided the species specific anti-scorpion venom serum is available to the scorpion sting victims.

* More than 600 species of killer scorpions that belong to Buthidae family arresponsible for death of hundreds and thousands of scorpion sting victims every year.

* Under these conditions, catching and identification of the killer scorpions that belong to Buthidae family is a difficult problem.

* Milking of the venom from different species of “killer scorpions” and processing the scorpion venom for species specific anti-scorpion venom serum, is equally difficult.

* Very few countries in the world succeeded in Producing an effective species specific anti-scorpion venom serum.

1.11 Necessity to have physiological antidote to treat scorpion sting victims

Therefore, it is necessary to have

* An effective, cheap (less expensive), fast acting and life saving physiological and pharmacological antidote in the form of Insulin to treat

* The acute myocarditis,

* Cardiovascular, hemodynamic changes,

* Initial transient hypertension,

* Hypotension,

* Arrhythmias, conduction defects, ischemia, Infarction like patterns,

* Disseminated intravascular coagulation,

* Acute pancreatitis,

* Pulmonary edema,

* Adult respiratory distress syndrome and many other clinical manifestations.

1.12 The clinical presentation of scorpion sting victims throughout the world, is similar

The clinical presentation of local pain (pain at the site of sting), nausea / vomiting, sialorrhea, lacrimation, profuse sweating, abdominal pain, tachydispnoea, precordial pain, arrhythmias, hypertension, agitation, tremors, hyperglycemia, restlessness, prostration, tachyynnea, pulmonary oedema and many manifestations in scorpion sting

1.13 Experimental basis of various patho-physiological mechanisms & their reversal with administration of insulin

The experimental basis of the physiological basis of various patho-physiological mechanisms involved in the genesis of scorpion envenoming syndrome and its reversal in the experimental animals and scorpion sting victims by administration of insulin are reviewed. The results obtained in our experimental animals and in scorpion sting victims after administration of insulin as a therapeutic agent, are also reviewed.

1.14 Challenges in the treatment of scorpion envenoming syndrome

In the Electrocardiographic studies, *L. quinquestriatus* venom caused, irrespective of the route of administration, an initial moderate and a terminal severe bradycardia. This was accompanied by nodal and conducting defects comprising first degree heart block, ectopic foci high or low in the atrium and left bundle branch block. The most significant changes induced by the scorpion venom appeared to be due to myocardial ischemia and either inferior or anterior wall infarction. Myocardial infarction was confirmed by postmortem examination.

Although anti-scorpion venom, given before injection of scorpion toxin, almost totally prevents the cardiac effects injection after the toxin does not abolish them. Myocardial ischemia and either inferior or anterior wall infarction occurred rapidly following either the i.v., s.c. or i.m. injection of the venom. Ismail and his co-workers argued that it was logical to assume that the absorption and myocardial effects of the venom occur rapidly and that the myocardial damage is irreversible by its nature, then the treatment by the antivenom after insult is not expected to correct these changes until the measures to improve the effectiveness of antivenom are achieved (Ismail et al., 1992).

1.15 A conspicuous increase in the arterial blood adrenaline content and a marked rise in the arterial blood pressure

A marked rise in angiotensin II and initial transient hypertension in dogs and rabbits upon injection of Indian red scorpion (*Mesobuthus tamulus concanesis*, Pocock) venom (Radha Krishna Murthy & Vakil 1988), conspicuous increase in the arterial blood epinephrine (adrenaline) content and a marked rise in the arterial blood pressure were observed upon injection of Middle East scorpion (*Leiurus quinquestriatus*) venom in dogs (Ismail et al 1995; 1993; 1992; Gueron et al 1993; 1992; 1990; 1987; Radha Krishna Murthy & Vakil 1988; Moss et al 1973; La Grange 1977).

1.16 Catecholamine metabolites excretion

Sofer and Gueron reported the catecholamine metabolites excretion in 12 scorpion sting victims. Abnormal serum level and increased catecholamine metabolite urine excretion was also reported from scorpion sting patients (Gueron et al 1993; 1992; 1990; 1987; 1980).

1.17 Elevated circulating levels of catecholamines and rennin angiotensin Elevated circulating levels of catecholamines and rennin angiotensin had been observed in clinical and experimental envenomation (Gueron et al 1993; 1992; 1990; 1987; 1980; Radha Krishna Murthy et al 1988). Plasma nor-epinephrine levels were elevated on admission (1279 pg/ml) in children stung by *Tityus zulianus* from Venezuela (Carmen et al 2002).

Thus there is autonomic storm, massive release of epinephrine and norepinephrine (catecholamines) in scorpion envenoming syndrome. This review article reviews the signs, symptoms and clinical manifestations (due to scorpion envenoming syndrome) as reflected by major actions of Catecholamines and their reversal by administration of insulin, under the following headings:

2. A peripheral excitatory action on certain types of smooth muscle, such as those in blood vessels supplying skin, kidney, and mucus membranes, and on gland cells, such as those in salivary and sweat glands.
3. A peripheral inhibitory action on certain other types of smooth muscle, such as those on the wall of the gut, in the bronchial tree, and in blood vessels supplying skeletal muscle;

4. A cardiac excitatory action that increases heart rate and force of contraction;

5. Endocrine actions, such as modulation (increasing or decreasing) of the secretion of insulin, Renin, glucagon, glucocorticoids and thyroid hormones;

6. Metabolic actions, such as an increase in the rate of glycogenolysis in liver, cardiac muscle and liberation of free fatty acids from adipose tissue;

7. Actions in the central nervous system (CNS) such as respiratory stimulation, an increase in wakefulness and psychomotor activity and, Prejunctional action that either inhibit or facilitate the release of neurotransmitters, the inhibitory action being physiologically more important.

2. A peripheral excitatory action on certain types of smooth muscle, such as those in blood vessels supplying skin, kidney, and mucus membranes, and on gland cells, such as those in salivary and sweat glands

2.1 Hypertension in scorpion sting victims with elevated cardiac enzymes


Hypertension in scorpion sting in children (age 1 year to 2.8 years)

Sofer and Gueron reported hypertension (ranging between 172/125 mm Hg to 150/120 mm Hg) in scorpion sting children (age 1 year to 2.8 years) with myocardial infarction like pattern, interstitial pulmonary oedema, elevated creatine phosphokinase (CPK) levels (range 277 to 3000 U/liter), Serum Glutamate Oxaloacetic Transaminase levels (SGOT) (range 64 – 240 U/liter) and elevation of creatine phosphokinase isoenzyme (CPK-MB) fraction elevated to 110 U/liter (Sofer et al 1992; Gueron et al 1993; 1992; 1990; 1987; Bahoul et al 2005). Myocarditis, convulsions, brain oedema, shock and respiratory distress were encountered in scorpion sting children from Jerusalem (Duddin et al 1991).

Hypertension in scorpion sting in children (age 0.5 year to 14 years)

Gueron et al from Israel reported severe hypertension (ranging between 180/120 mm Hg to 150/103 mm Hg), elevated SGOT levels (range 40 -57 Units), increased CPK levels (range 238 – 524 U/liter), MB-PK ratio (%) (Range 6.8 – 20%) in children (age 0.5 year to 14 years). Abnormal echocardiograms were observed. Poorly contracting wall motion (global) with decreased systolic left ventricular performance was seen in these scorpion sting children (Gueron et al 1990).

Arterial hypertension, tremors, hyperglycemia, hypothermia and hypotension was observed due to severe scorpion envenomation in children caused by *Tityus bahiensis* and *Tityus serrulatus* from Brazil (Souza et al 2013).

Tachycardia and hypertension are common in children following scorpion envenomation. In children with heart failure and pulmonary oedema, the clinical picture resembles myocardial infarction including typical electrocardiographic (ECG) changes and elevated serum enzyme levels (glutamine oxaloacetic transaminase (SGOT) and creatine phosphokinase (CPK). Elevated SGOT levels on admission were observed in 25 out of 27 victims. Elevated CPK levels on arrival were observed in 15 of the 27 victims. Elevated CK-MB levels were observed in all the scorpion sting children (Sofer et al 1997; 1996; 1995; 1992; 1988; Tarasiuk et al 1999; 1997; 1994).

Sofer and his co-workers observed hypertension in 21 out of 27 in children with myocardial injury due to *Leiurus quinquestriatus* envenoming from Israel. Many of these children had enzymatic myocardial involvement characterized by high total CPK level, elevated CK-MB level, CK-MB/CPK ratio exceeding 6% and ECG changes consistent with myocardial damage (Sofer et al 1995).

Lung oedema evoked by *Tityus serrulatus* scorpion venom in the rat is due, at least in part, to release of vascular permeability factors such as platelet activating factors, leukotriens, and prostaglandins. As the scorpion venom also induces acute arterial hypertension, it seems likely that hypertension may also have an effect on the oedema formation evoked by scorpion venom (De Matos et al 1997).

2.2 Initial transient hypertension followed by hypotension

Kymographic recording of arterial blood pressure after administration of scorpion venom is shown in the Fig. 1. Initial transient hypertension followed by hypotension is observed in our experimental animals. This could be due to massive discharge of
catecholamines and angiotensin II (Radha Krishna Murthy et al 1988) (Fig. 2).

2.3 Elevation of blood pressure and plasma Renin levels
Stimulation of the sympathetic nervous system can increase the Renin output. La Grange demonstrated elevation of blood pressure and plasma Renin levels by *Centruroides sculpturatus* and *Leiurus quinquestriatus* venoms and proposed that the Renin - angiotensin system participates in the hypertensive response to scorpion venom along with the increased catecholamines (La Grange 1977). Other workers using *B. minax* and *B. tamulus* venoms were able to block the hypertensive action using alpha blocking agent phenoxybenzamine. However, in the hands of La Grange (1977) alpha blocking did not prevent the hypertensive effect of the venom.

2.4 Inotropic state due to increase in the level of circulatory catecholamines
Tarasiuk et al observed in their experimental dogs an inotropic state immediately following intravenous injection of 0.05 mg kg\(^{-1}\) venom from scorpion *Leiurus quinquestriatus*. The inotropic state has been ascribed to the increase in the level of circulatory catecholamines and produced the following changes (Tarasiuk et al 1997).

2.4 (a) Blood Pressure
Baseline Blood pressure was 98 mm Hg. Blood pressure increased to 177 mm Hg at 15 min, 168 mm Hg at 30 min after venom injection. The Blood pressure dropped to 88 mm Hg at 90 min and 65 mm Hg at 120 min (decreased to 63% below baseline value) following envenomation.

(b) Mean Circulatory Pressure (MCP)
MCP provides the best estimate of the upstream pressure driving blood to the heart, because it is relatively independent of cardiac output. At baseline, MCP was 6-8 torr. Five minutes following venom injection, MCP increased by 300% and remained elevated for 60 min. At 120 min, MCP returned to baseline values.

© Cardiac output (C O)
Baseline Cardiac output (L min\(^{-1}\)) was 2.9. Fifteen minutes following venom injection, C O increased to 250% following envenomation. C O dropped to 40% and 35% below baseline at 90 and 120 min following venom injection.

(d) Systemic Vascular Resistance (SVR)
SVR increased by 35% by 90 min after venom injection.

(e) Pulmonary Vascular Resistance (PVR)
PVR increased to a maximal value of 53% above baseline at 120 min following venom injection.

(f) Arterial Critical Closing Pressure (Pcrit)
It is the minimal pressure required to keep the blood vessel open. P_{crit} was 32 mm Hg before venom injection. It increased to 102 mm Hg at 15 min, 107 mm Hg at 30 min, and became 38 mm Hg at 90 min and 28 mm Hg at 120 min following envenomation.

(g) Redistribution of blood flow
The increase in MCP immediately following venom injection is probably due to Sympathoadrenal response known to occur following scorpion envenoming. This effect is mediated either by vasoconstriction of peripheral venous reservoirs or by shift of blood from unstressed to stressed vascular compartments. An increase in circulating catecholamines can induce reduction of vascular capacitance, leading to redistribution of blood flow to organs, and can induce an increase in Right Atrial Pressure (RAP). According to Frank-Starling mechanism, elevation of RAP will contribute to an increase in cardiac output.

2.5 Other underlying mechanism/s that explain the haemodynamic changes
Another underlying mechanism that explains the haemodynamic changes may involve activation and release of cytokines and other pro-inflammatory substances, causing pathophysiological cascades similar to those seen in endotoxic shock.

(a) Systemic Inflammatory Response Syndrome (SIRS)
Elevated serum interleukin-6 is reported in patients admitted with “Systemic Inflammatory Response Syndrome” (SIRS) following scorpion sting (Sofer et al 1996; Abdel-Haleem 2006).

(b) Scorpion venom – neuropeptides - effect of endothelin release
Scorpion venom is composed primarily of neuropeptides, which target ion channels. Since the movement of sodium ions (Na\(^+\)), Potassium ions (K\(^+\)), chloride ions (Cl\(^-\)) and Calcium ions (Ca\(^{2+}\)) in and out of the cells through ion channels is absolutely essential in neural and muscular function, these channels act as primary targets for the offending scorpion venom. Neurotoxins present in the scorpion venom affect the gating mechanisms of excitable membrane. Long toxins (60-70 amino acids) interfere with sodium channels, causing cell destruction by the influx of Na\(^+\) and Ca\(^{2+}\) ions into the cell. Short toxins (31 -37 amino acids) modify the potassium channel’s function and may specially block Ca\(^{2+}\) activated L\(^{\*}\) channels. These effects on vascular endothelial
cells may exert different reactions on different organs. All these responses may resemble the effect of endothelin release. Cumulative actions of scorpion neurotoxins may be traced to activation of sodium channels of neuronal terminals may lead to depolarization of membranes and release of several neurotransmitters, which eventually affect various systems including gastrointestinal tract, and the respiratory, cardiovascular and nervous systems. In addition to neurotransmitters, other mediators such as those affecting inflammatory processes may be released after scorpion envenoming. These include kinins, eicosanoids, cytokines, platelet activating factor, permeability increasing factor, and nitric oxide. This release of cytokines and other mediators account for several of the inflammatory manifestations observed such as acute respiratory distress (ARDS). The ARDS, a syndrome that is related to the uncontrolled production and release of cytokines and products of activated macrophages, lymphocytes and tissue resident cells, has been reported in scorpion sting children and may encompass the venom elicited non-cardiogenic pulmonary oedema. Clinical signs and symptoms of SIRS, a condition with massive release of cytokines and may be involved in the pathogenesis of shock, cardiac dysfunction and pulmonary oedema, has been documented in severely envenomed victims (Amaral et al 1994; 1993).

© Other probable mechanisms that could explain “Hypertension”

It is possible that the scorpion venom, through delaying the inactivation of the fast Na⁺ channels and blocking the Ca²⁺ activated K⁺ channels, would enhance the rate of afferent discharge along the sensory nerves causing increased neurotransmitter release within the central nervous system and augmented reflex autonomic and probably also somatic effects. The nerve terminals are likely the primary site of venom action. The excitatory pre-synaptic action of scorpion venom is due to an action at the relatively exposed regions of the nerves at their endings closer to the synaptic regions.

A selective action of scorpion venom on the sympathetic and parasympathetic centers of the medulla would explain most of the effects of the venom. Stimulation of the hypothalamus by scorpion venom could explain more adequately the pathophysiology of scorpion envenomation.

The disturbance in the integrative function of the hypothalamic centers can explain such symptoms as shivering, piloerection, increased body temperature, hyperirritability, and leucocytosis. Tityus toxin caused nearly eight fold increase in transmitter release after the preparation was incubated. The enhancement of transmitter release is likely due to the toxin-induced potentiation of the duration of the action potential. The nerve fiber apparently remains sensitized for a long period of time; the response to a second stimulus after a previous exposure to scorpion venom is probably amplified several fold (Ismail 1995; 1993).

(d) Scorpion Venom prolongs repolarization and refractory time of the compound action potential

Indian red scorpion (Mesobuthus tamulus Concannes, Pocock; (MBT) venom prolonged the repolarization and refractory time of the compound action potential by involving calcium-dependent mechanism through both Ca²⁺ sensitive and Ca²⁺ - insensitive mechanisms. The Ca²⁺ influx occurred via L-type of calcium channels (Deshpande 1998).

(f) Significant prolongation of the repolarization time

Significant prolongation of the repolarization time was seen with 0.6 ug/ml of MBT venom. The maximal prolongation of the repolarization time, nearly 100 times the duration of the control was seen with 6 ug/ml of the venom.

Significant increases in refractory period

MBT venom (0.6 ug/ml) increased the refractory period by 2.5 times the control response. The maximal prolongation of the refractory period (225 times the duration of the control) was seen with 6 ug/ml of the venom.

Autonomic storms after scorpion envenoming due to neuronal changes

The repolarization of the compound action potential is due to the inactivation of Na⁺ permeability (channels) and activation of K⁺ permeability. These events occur within 2-3 msec and restore the membrane potential to its original state under normal conditions. The refractoriness depends upon the restoration of the membrane potential by inactivation of Na⁺ system. The toxins from other poisonous species of scorpions (Leiurus quinquestriatius and Tityus serrulatus) prolonged the duration of action potential by slowing the Na⁺ inactivation process. MBT venom increases the neuronal excitability. The autonomic storm may be due to such neuronal changes.

(e) Renin - angiotensin system participates significantly in the pathophysiology of hypertension, congestive heart failure and myocardial infarction which are common clinical manifestations in acute myocarditis due to scorpion envenoming.

2.6 The beta-adrenergic receptor pathway controlling Renin secretion

The major determinant of the rate of angiotensin II production is the amount of Renin released by the
kidney. Renin is synthesized, stored, and secreted into the arterial circulation by the juxtaglomerular cells.

The secretion of Renin from juxtaglomerular cells is controlled by three pathways: two acting locally within the kidney and the third acting through the central nervous system (CNS) and mediated by the release of norepinephrine from postganglionic sympathetic nerves; activation of beta receptors on juxtaglomerular cells enhances Renin secretion.

Increased Renin secretion enhances the formation of angiotensin II. Angiotensin II increases arterial blood pressure (Radha Krishna Murthy et al 1988; Westfall & Westfall 2006).

2.7 Elevated plasma angiotensin levels in the experimental animals
Following the injection of *Mesobuthus tamulus Concanesis*, Pocock venom, plasma angiotensin levels were elevated in dogs as well as rabbits (Radha Krishna Murthy et al 1988).

(a) Functions and effects of Renin-Angiotensin system
The Renin-Angiotensin system plays a major role in short term regulation of arterial blood pressure. Modest increases in plasma concentrations of angiotensin II acutely raise blood pressure; on a molar basis, angiotensin II is approximately 40 times more potent than norepinephrine. This rapid pressor response to angiotensin II is due to a swift increase in total peripheral resistance – a response that helps to maintain arterial blood pressure. Angiotensin II stimulates the release of catecholamines from the adrenal medulla by depolarizing chromaffin cells.

(b) Insulin administration reduced Plasma angiotensin levels
Administration of insulin reduced these levels in dogs. Administration of Insulin, Tolazoline (alpha blocker) and sodium bicarbonate reduced the plasma angiotensin levels, drastically (Radha Krishna Murthy et al 1988).

2.8 Low concentrations of scorpion venom produce sustained hypertensive response and an increase in plasma Renin activity
Relatively low concentrations of scorpion venom (*L.quinquestiatus*) are capable of producing sustained hypertensive response and an increase in plasma Renin activity. Venom from scorpion, *Centruroides sculpturatus* and *L. quinquestiatus* elevated plasma Renin activity (La Grange 1977).

2.9 Highly abnormal Renin and aldosterone levels in scorpion sting child
Renin and aldosterone levels evaluated in a 2-year old patient showed highly abnormal values: Renin – 35 nano/ml/hour (normal 0.2 – 2.8) and aldosterone 1000 pg/ml (normal 15 – 150 pg/ml) (Gueron et al 1992; Ismail 1995; La Grange 1977).

2.10 Hypertension
All the poisonous scorpions under Family Buthidae produce severe pronounced initial transient hypertension in the experimental animals and scorpion sting victims

2.11 Indirect evidence of an increased sympathetic activity
Hypertension, tachycardia, diaphoresis, restlessness, cardiac arrhythmias, cardiac failure, pulmonary oedema, hyperglycemia, leucocytosis, hypokalemia are few of the indirect evidences of an increased sympathetic activity (Bucaretchi 1995).

(a) Myocardial damage
Myocardial damage after scorpion envenomation accompanied by heart failure or pulmonary oedema is a frequent observation. Experimental evidence with the *Tityus serrulatus* venom in a Landgerdorff preparation has shown a reduction of the coronary flow during the initial tachycardia and the increased contractile force. Perfusion defects and left ventricular dilation was observed in one group of dogs and right ventricular dilation in other dogs immediately after scorpion envenoming.

(b) Perfusion defects
Margulis and his coworkers observed patchy perfusion abnormalities recorded 2 hours after the scorpion sting in a patient with low ejection fraction and severe wall motion abnormalities. Perfusion defects during the initial stages of envenoming were observed (Margulis et al 1994).

(1) Sympathetic effects of the venom dominate severe tachycardia while rhythm abnormalities reduce the cardiac output and coronary blood flow.

(2) Impaired ventricular relaxation due to catecholamine – induced metabolic intra myocardial cell changes (calcium overload) and the acute increase in coronary blood flow during diastole.

(3) Hormonal influences such as catecholamines and Renin angiotensin with their effects on the coronary circulation.

The abnormal thallium scans and the I.V. dilation observed are additional indicators of the myocardial damage and are related to the overall
changes induced by the over stimulated sympathetic nervous system.

The venom of *L. quinquestriatus* produces severe and complex haemodynamic effects. The cardiovascular effects occur in two phases, an initial inotropic phase characterized by hypertension, tachycardia, and increased myocardial contractility, followed by a hypokinetic phase with hypotension and impairment of left ventricular (LV) systolic function (Tarasiuk 1997; 1994).

The increases in blood pressure, left ventricular pressure, and contractility following scorpion sting may be extreme and have been related to release of catecholamines by the sympathetic nervous system and adrenal glands.

Gueron et al concluded that heart failure and pulmonary oedema induced by i. v. injection of *Leiurus quinquenstriatius* venom in dogs is related to catecholamine-induced reduction in left ventricular compliance inducing severe impairment of diastolic filling and left ventricular emptying (Gueron et al 1990).

(c) Abnormal coronary perfusion - severe left ventricular dysfunction.

Several mechanisms are involved in the pathogenesis of myocardial damage and pulmonary oedema in human or experimental envenomation. Echocardiographic or radio nuclear evidence of moderate to severe left ventricular dysfunction, ventricular hypokinesia and reduced ejection fraction had been documented in clinical envenomation in addition to the haemodynamic abnormalities (97). Scintigraphy has the potential for distinguishing viable myocardium. The uptake of Thallium by myocardial cells is an active process, dependent on regional flow. Early images correspond to the initial distribution of the tracer which is mainly flow dependent. Myocardial damage after scorpion envenomation accompanied by heart failure or pulmonary oedema is a frequent observation.

5. The abnormal thallium scans and the Left Ventricular (LV) dilation observed in the experimental scorpion envenoming are additional indicators of myocardial damage and are related to the overall changes induced by the over-stimulated sympathetic nervous system (Margulis et al 1994).

2. 12 Electrocardiographic changes

(a) Electrocardiographic studies using *A. amoreuxi* venom. *A. amoreuxi* venom in doses lower than 0.5 mg/kg did not cause any significant ECG changes, while 1 mg/kg i.v. and higher doses caused definite changes within 30-120 minutes. The first effect noticed was a short-lasting bradycardia which changed to slight tachycardia after 2-3 min. Some arrhythmias were observed in some animals. The tachycardia was over within 5-15 min and was followed by bradycardia which persisted until death of the animal. The ST Segment was elevated in I, aVL and V5, but depressed in II, III and V1, 3 min after venom injection. Ten minutes after venom injection, the T wave was inverted in I, II, III and aVL, and inverted or biphasic in V1. Some extra systoles were seen in I, II, III, and aVL. Thirty minutes after venom injection the T wave was inverted in I, aVL. The ST segment was depressed in I and V5. The inversion of the T wave in I, aVL and V1 was more prominent 60 min after venom injection. Ninety minutes after venom injection there was very marked bradycardia with prolonged P-R intervals. There was no sinus rhythm and 2:1, 3:1 and several rhythms were seen.
The ST Segment was elevated in I and V5. This was accompanied in most cases by respiratory arrest leading to death of the animal (Ismail 1995; Ismail et al 1993; 1992).

When the venom was injected s.c. (rabbits) or i.m. (rabbits), the onset of the electrocardiographic effects and death were delayed although the course of the change was the same as the i.v. route. The bradycardia occurred 40-60 min following the s.c. injection of the venom and somewhat longer following the i.m. route.

The rabbits showed miosis with excessive salivation, lachrymation and defecation 20 – 30 min following venom injection. Auscultation revealed humid rattle and crepitations at times of pronounced electrocardiographic changes. Postmortem examination of the animals showed large infarcted areas either in the antero-septal or inferior aspects of the heart.

The most striking ECG changes caused by the venom seemed to be myocardial ischemia and anterior wall infarction. The myocardial ischemia was evidenced from depression of the ST segment in II, III and V1. The anterior wall infarction was revealed from elevation of the ST segment in I, aVL and V5 and the inversion of the T wave in I, aVL and V1. These changes occurred 30 – 60 minutes following venom injection (Ismail 1995; Ismail et al 1993; 1992).

(b) ECG studies using L. quinquestriatus venom
The i.v. injection of L. quinquestriatus venom (1 mg/kg) into rabbits caused an initial moderate bradycardia and immediate inversion of the T wave in I. This was either accompanied or followed by inversion of T wave in III, aVL, aVF, V1 and V5. In most animals, the ST segment was depressed in I, II, aVL and V5. A notched R wave in I or an RSr’ pattern in II was seen at the same time.

The bradycardia progressed with time and became very severe near the time of death, which generally occurred 10-50 min following venom injection.

Other electrocardiographic abnormalities included a prominent “Q” wave in I, aVR, V1 and V5. Some dropped beats and occasional coupled beats. Bigemini was very prominent during the phases of marked bradycardia.

Tall peaked and slender T wave, S wave > R wave, prolonged ST interval and wide QRS complexes were frequently observed. When the venom was injected into animals maintained under artificial ventilation, neither the electrocardiographic changes nor the death time were altered (Ismail 1995; Ismail et al 1993; 1992).

c) ECG studies using Indian red scorpion Mesobuthus tamulus concanesis, Pocock (earlier called Buthus tamalus)
Scorpion sting myocardial toxicity is more common than neurotoxicity and often is the cause of death. Acute myocarditis is frequently unrecognized because of the severity of the associated condition. In myocarditis, the ECG may show atrial and ventricular extra systoles, arrhythmias, conduction disturbances and ST-T wave abnormalities (Radha Krishna Murthy 2014 a; b; c; 2013; 2002; 1982; Radha Krishna Murthy et al 2003; 2002; 2001; 1999, 1998; 1994; 1992; 1991; 1990; 1989; 1988 a; b; c; 1986 a; b; c; d; e; f).

The scorpion venom is a powerful arrhythmogenic agent by virtue of stimulating autonomic sympathetic system and adrenal glands. The common immediate arrhythmias are sinus arrest or sinus bradycardia with different escape rhythms (for example: Junctional rhythm), premature ventricular tachycardia. Each one of these ECG changes has been recorded by us. Further, the arrhythmias were present before the full haemodynamic venom induced effects. Many abnormal ECG changes were observed after envenoming. These include early myocardial infarction like pattern with ST segment elevation, ST segment depression, Presence of Q waves. These abnormalities were observed within a fraction of a minute after administration of the scorpion venom. In addition to these changes, there were: Rhythm disturbances such as AV disassociation, SA Block, Atrial tachycardia and Ventricular tachycardia, Bundle branch block and Pericarditis like patterns.

(d) ECG changes in our experimental animals
We observed several abnormalities in the electrocardiographic tracings pertaining to changes in the configuration of complexes, conduction defects at various levels and arrhythmias of several types in the experimental animals. The abnormalities included sinus bradycardia, sinus tachycardia, prolonged PR interval, Short PR interval, and abnormal “Q” wave, narrow QRS, broad QRS of intra-ventricular conduction defect type, Bundle Branch Block pattern, flat T wave, inverted T wave, ST segment elevation and ST segment depression, myocardial infarction like pattern. ECG tracings also showed change of axis, electrical alternans, First degree heart block, Junctional rhythm, atrial and ventricular fibrillation. We have recorded myocardial infarction like pattern, Junctional rhythm and electrical alternans hitherto unreported in experimental myocarditis due to Mesobuthus tamulus Concenesis, Pocock but reported in human victims in 1986 (Radha Krishna Murthy and Yeolekar 1986)! Change of axis in the ECG
tracings noticed by us has not been reported either in the experimental studies or in patients affected by scorpion stings. We claim to have recorded almost all ECG changes (in the experimental studies) noticed in humans affected by scorpion stings (Radha Krishna Murthy 2014 a; b; c; 2013; 2002; 1982; Radha Krishna Murthy et al 2003; 2002; 2001; 1999; 1998; 1994; 1992; 1991; 1990; 1989; 1988 a; b; c; 1986 a; b; c; d; e; f).

(e) Hyperacute injury pattern
We have observed the following ECG changes in the rabbits after scorpion envenoming. Hyperacute injury pattern with ST elevation, Ventricular tachycardia, Sinus tachycardia with ST-T changes, Acute infarction, Sinus arrest, Infarction like pattern, Runs of ventricular premature beats, Multi-focal ventricular premature beats (Hyperacute injury pattern).

(f) “Acute myocarditis”
We have recorded the following ECG abnormalities in our experimental animals with “acute myocarditis” a) Sinus tachycardia, b) Sinus bradycardia, c) T inversion, d) ST elevation, e) ST depression, f) AV conduction defects with sinus arrest, g) Ventricular premature contraction, h) T wave configuration changes, i) Prolonged PR, j) Short PR, j) ST depression, k) Narrow QRS, l) Wide QRS and l) Extra systoles (Radha Krishna Murthy 2014 a; b; c; 2013; 2002; 1982; Radha Krishna Murthy et al 2003; 2002; 2001; 1999; 1998; 1994; 1992; 1991; 1990; 1989; 1988 a; b; c; 1986 a; b; c; d; e; f).

(g) ECG Changes in our experimental animals
We have also reported myocardial infarction like pattern with ST elevation, Ventricular tachycardia, Sinus tachycardia with ST-T changes, acute infarction, Sinus arrest, Infarction like pattern, Runs of ventricular premature beats, Multi-focal ventricular premature beats.

(h) ECG changes observed in our experimental dogs
i. Myocardial infarction like pattern
ii. Escape Beats & Escape Rhythms: Junction rhythm, Junction escape, ventricular escape.

iii. Premature Systoles & Para systoles: APC, Bigeminy, Junctional extra systoles, VPC
iv.Paroxysmal & Non-paroxysmal Tachycardia:
   Nodal tachycardia, Ventricular tachycardia
v. Fibrillation & Flutter: Ventricular fibrillation
vi. Conduction Block: S – A block, AV dissociation, Bundle branch block, Wide QRS

vii. Other disturbances in ECG: Sinus tachycardia, Sinus bradycardia, Absent P wave, Axis change, Voltage changes, Electrical alternans, ST depression, ST elevation, Infarction like pattern, T flat / T inversion (Radha Krishna Murthy et al 1988 a, b, c, d; 1986 a, b, c, d, e).

(i) After insulin administration: ECG changes and arrhythmias were not noticed after insulin administration in 68% of the animals whereas in the remaining 32% of the animals it took 20 minutes after insulin administration for the arrhythmias like nodal premature contractions, first degree heart block, nodal rhythms and other changes like wide QRS, T inversion and low voltage to revert towards normal (Radha Krishna Murthy et al 1988).

2. 13 Electrolyte changes and ECG
The ECG effects of the scorpion venom are markedly influenced by electrolyte disturbances; the effects are aggravated by hyperkalemia and hypocalcemia (36). The cardiac effects in the experimental animals were comparable to the changes observed in humans accidentally stung by scorpion.

We have reported hyperkalemia (Radha Krishna Murthy 1988), hyperglycemia (35 – 52) and hypocalcemia (Radha Krishna Murthy et al 1986) in the experimental animals with scorpion envenoming.

(a) Hypocalcemia
The prolonged ST segment or QT<sub>C</sub> interval in addition to the S wave > R wave is characteristic of Hypocalcemia. The tall and peaked T waves and the prolonged QT<sub>C</sub> interval were also recorded in all the victims of yellow scorpion stings.

The effects of autonomic stimulation usually mask those of electrolyte changes. It seems likely that vagal stimulation potentiates, while sympathetic stimulation masks the effect of electrolyte changes in the ECG recordings, since the changes were more rapid in onset and much more pronounced when the sympathetic actions of the venom were blocked.

(b) Hyperkalemia in scorpion envenoming
Altered cardiac sarcolemmal & erythrocyte Na<sup>+</sup> - K<sup>+</sup> ATPase activities Hyperkalemia could be seen by the tall, peaked, and slender T waves, and the wide QRS complex characteristic of Hyperkalemia. There was an increase in serum potassium levels in dogs after venom injection (Radha Krishna Murthy et al 1986). There is enough evidence to show that these animals also had cardiac sarcolemmal defects indicated by altered Na<sup>+</sup> - K<sup>+</sup> ATPase, Mg<sup>2+</sup> ATPase and Ca<sup>2+</sup> ATPase activities and a reduction in Na<sup>+</sup> - K<sup>+</sup> ATPase activity of erythrocytes.
((Radha Krishna Murthy et al 1982). These results indicate that the cell membrane is leaking, and this could be the reason for hyperkalemia.

**Hyperkalemia and arrhythmias**

Hyperkalemia is known to produce atrio-ventricular abnormalities and AV block, Junctional or ventricular rhythms and terminally ventricular fibrillation. Few of the venom treated animals had these types of ECG abnormalities. *Amoreuxi venom* caused a significant fall in serum potassium level 15 min after venom injection, returned to the pre-injection level 5 hr after injection and Hyperkalemia 7 hr after injection.

**Fig. 1**

**SCORPION ENVENOMING**

Autonomic storm

<table>
<thead>
<tr>
<th>Catecholamines</th>
<th>Angiotensin II</th>
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<tr>
<td>Glucagon, Cortisol</td>
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↓

Insulin Secretion

Insulin Resistance

↓

INCREASE IN SERUM FREE FATTY ACIDS

↓

Myocardial O₂ Consumption               Na⁺ - K⁺ ATPase activity

Arrhythmias, Conduction defects,        Disseminated Intravascular Coagulation

Myocardial Ischemia & Infarction        Gluconeogenesis, Glycogenolysis- Hyperglycemia

↓

DEATH

**Figure 2:** Probable mechanisms leading to death in scorpion envenoming syndrome

**Fig. 2**

**SCORPION ENVENOMING**

+

Autonomic storm

↓

Massive release of Catecholamines

↓

**INITIAL TRANSIENT HYPERTENSION**

↓

HYPOTENSION

↓

Sinus bradycardia - sinus arrest

Arrhythmias – Conduction defects

Ischemia, infarction like patterns

↓

Administration of insulin

Reversal of

ECG, Cardio-vascular, Metabolic changes

Pulmonary oedema relieved

Normal blood pressure,

Sinus Rhythm
3. Actions of epinephrine and norepinephrine in the CNS

Actions of epinephrine and norepinephrine (Catecholamines) in the CNS are: respiratory stimulation, an increase in wakefulness and psychomotor activity and, Prejunctional action that either inhibit or facilitate the release of neurotransmitters, the inhibitory action being physiologically more important.

3.1 Clinical manifestations reflect massive epinephrine and norepinephrine liberation
The clinical manifestations reflect a massive catecholamine liberation (epinephrine and nor epinephrine). Scorpion envenomation can produce neurological manifestations, which are an indicator of the severity of the scorpion sting. Thermoregulatory disturbance is often present after scorpion envenomation. Hypothermia transforms into hyperthermia.

3.2 Massive liberation of cytokines
These thermoregulatory abnormalities can be explained by a direct action of scorpion venom on the central nervous system or by a massive liberation of cytokines (IL-1-alpha, IL-6, IL-10, TNF-alpha, IL-1 beta). In severe cases, the clinical manifestations become more pronounced and reflect a massive catecholamine liberation (epinephrine and nor epinephrine) secondary to a neurovegetative system disorder leading to a cellular hypermetabolism, and can be manifested by hyper-sweating, myoclonia, agitation, and priapism (Bahloul et al 2005; Abdel-Haleem et al 2006).

3.3 Neurological manifestations
In very severe cases, neurological manifestations are more pronounced. Generalized or localized convulsions, brain edema, shock, with or without coma, can be observed. Other neurological manifestations, such as, miosis, mydriasis, nystagmus, squint, and erratic eye movements indicate severe forms of scorpion envenomation (Duddin et al 1991).

3.4 Hypertensive encephalopathy
Scorpion envenomation leads to a high arterial blood pressure by a massive Catecholamine discharge. When arterial blood pressure is excessive (exceeding sometimes the cerebral antiregulatory plateau), it leads to cerebral damage (edema and ischemia). This hypothesis explains anatomical abnormalities in the central nervous system secondary to severe scorpion envenomation, such as hemorrhagic, ischemic, and cerebral infarction (Bahloul et al 2005; Gadwalkar et al 2006; Souza et al 2013; Yugandhar et al 1999; Mahadevan 2000; Bhaskara Reddy & Suvarna Kumari 1972; Bisarya et al 1977; Rezende et al 1998; 1995; Rimsza et al 1980; Shah et al 1981; Shivraj et al 1981; Singh et al 1979; Sofer et al 1997; 1996; 1995; 1992).

3.5 Cerebro-vascular accidents
(a) An acute rise in the blood pressure (arterial hypertension) during the autonomic storm may rupture unprotected, especially the perforating arteries resulting in hemorrhagic stroke. Intraventricular hemorrhage and hemorrhage in putamen with an acute rise in blood pressure (260/130 mm Hg) due to autonomic storm were reported (Sarkar et al 2008; Dittrich et al 1995; Daniel et al 2013).
(b) Toxic myocarditis may precipitate arrhythmias that may give rise to embolic stroke. Changes in the blood coagulation profile may play a contributory role.

c) Stroke can occur due to Disseminated Intravascular Coagulation (DIC). We have demonstrated Disseminated Intravascular Coagulation in our experimental animals (Radha Krishna Murthy et al 1988; Devi et al 1970). This has been confirmed by the demonstration of fibrin deposits in the affected vessels in autopsy studies of victims of scorpion sting. The venom is known to increase platelet aggregation. Thrombotic stroke with the involvement of the middle cerebral artery territory – due to DIC had been reported (Dittrich et al 1995).

d) The venom is vasculotoxic with the ability to damage endothelial cells and cause vasculitis. This can initiate thrombosis.

e) Catecholamine excess, with firing of alpha receptors, enhances endothelin secretion leading to severe vasoconstriction of the cerebral vessels. This can result low flow infarcts (Gadawalkar et al 2006; Udaykumar et al 2006).

3.6 Brain ischemia due to a defect in oxygen transport secondary to pulmonary oedema and cardiogenic shock

Brain ischemia can result from a defect in oxygen transport secondary to pulmonary oedema and cardiogenic shock in scorpion envenomation. The effects of scorpion venom on the central nervous system are due to its peripheral action and the observed neurological manifestations are the consequence of other associated peripheral disturbances (Ismail et al 1993; 1992; Bichile et al 1984; Bisarya et al 1977; Boyer et al 2009; Amaral et al 1994; 1993; 1991.

3.7 Direct action of venom on central nervous system

Scorpion venom can cross the hemato-encephalic barrier in immature children, analogous to the passage of the venom in immature mammals. This central nervous system lesion can result from excitatory amino acid neurotransmitter liberation and an accumulation of intracellular calcium secondary to the direct action of the venom. Besides the clinical manifestations, central nervous system lesions are proved by electroencephalographic studies. Consciousness impairments and coma are common among the children stung by scorpions. Coma is associated with poor outcome.

A statistically significant correlation is found between Coma and young age (p<0.001), respiratory failure (p<0.001), convulsion (p<0.001), hyperthermia (p<0.05), pulmonary oedema (p<0.001), heart failure (p<0.01), and liver failure (p<0.01) (Bahloul et al 2005).

3.8 Multiple cerebral infarcts

Multiple cerebral infarcts, bilateral optic neuropathy with limb ischemia was observed in a 17 year old subject due to Mesobuthus tamulus sting. Multiple bilateral triangular watershed cerebral infarcts involving the frontoparietal regions anteriorly and temporo-occipital regions posteriorly in the distribution of the middle cerebral artery especially on the right side were seen. The patient showed improvement slowly over next 2 weeks but deterioration of vision in both eyes. Fundus examination showed bilateral disc pallor with perimacular hemorrhage and pigmentary retinal degeneration on the left. By the tenth week, he was able to walk with residual left hemiparesis. The arterial pulsations in the right arm and the carotids were palpable but blindness of the left eye persisted (Thacker and Misra 2002).

4. A peripheral excitatory action on certain types of smooth muscle, such as those in blood vessels supplying skin, kidney, and mucus membranes, and on gland cells, such as those in salivary and sweat glands

4.1 Behavioral changes

The following behavioral changes were observed in our experimental animals treated with scorpion (Mesobuthus tamulus Concanesis, Pocock) venom procured from Haffkine Institute, Mumbai, India. There was intense lacrimation and profuse thick (ropy) (which can not be wiped out) salivary secretions dribbling from the mouth, distension of the abdomen, defecation and frequent micturition. The stools were, sometimes, stained with bile and blood. In some animals, ejaculation occurred. Ejaculation is frequently observed in the experimental animals. The animals had immediate cessation of breathing (laryngeal spasm), apnoea, muscular fasciculations, clonus and tetany like contractions in the skeletal muscles of the body. At the end, the pupils were widely dilated and there was protrusion of the eye balls which looked glossy (Radha Krishna Murthy 2014 a; b; c; 2013; 2002; 1982; Radha Krishna Murthy et al 2003; 2002; 2001; 1999; 1998; 1994; 1992; 1991; 1990; 1989; 1988 a; b; c; 1986 a; b; c; d; e; f).

4.2 General neurotoxicity

General neurotoxicity of an excitatory nature, including the autonomic (parasympathetic and sympathetic) as well as the skeletal neuromuscular system was indicated following envenoming by scorpions of Buthidae family (Radha Krishna Murthy 2014 a; b; c; 2013; 2002; 1982; Radha
Although either the CNS or the cardiovascular manifestations could occur first in the early phases of the scorpion envenoming syndrome, CNS manifestations always preceded the terminal hypotension and cardiac arrest. This strongly suggests the possible involvement of a central cardiac and/or vasomotor depression in fatal cases of human scorpionism (Ismail et al 1995; 1992).

A variety of CNS symptoms were reported in human scorpionism, including hyperirritability, focal and generalized seizures, hemiplegia, hyperthermia and hypothermia, unconsciousness and coma. Few investigators reported anatomical changes in the CNS in fatal cases of scorpion sting including cerebral congestion, diffuse punctate hemorrhages, cerebral infarction and cerebrovascular thrombosis (Benvenuti et al 2002; Bhaskara Reddy & Suvarnakumari 1972; Bichile et al 1984; Bisarya et al 1977; Böyer et al 2009; Chadha & Leviav 1979; Reddy et al 1972).

4.8 Autonomic storm

4.9 Effect of catecholamines on insulin secretion
Catecholamines have a dual effect on insulin secretion; they inhibit insulin secretion via alpha-2 adrenergic receptors and stimulate insulin secretion via beta adrenergic receptors. The net effect of epinephrine and nor-epinephrine is usually inhibition of insulin secretion. However, if catecholamines are infused after administration of alpha – adrenergic blocking drugs, the inhibition is converted to stimulation of insulin secretion (Ganong 1987; Keele & Neil 2004).

4.10 Role of adrenergic blockers in the scorpion envenoming syndrome
The autonomic innervation of the pancreas is involved in the overall regulation of insulin secretion. Stimulation of the sympathetic nerves to the endocrine pancreas inhibits insulin secretion. The inhibition is produced by released nor-epinephrine acting on alpha-2 adrenergic receptors. However, if alpha - adrenergic receptors are blocked, stimulation of the sympathetic system is blocked and it causes increased insulin secretion.
mediated by beta_{2} adrenergic receptors (Ganong 1987; Keele & Neil 2004).

Therefore, an attempt is made in this review article to explain the pathophysiology due to scorpion envenoming syndrome and its reversal by administration of insulin in the experimental animals and in the scorpion sting victims. The review article will highlight the role of insulin and glucose infusion as a therapy in the severe scorpion envenoming syndrome.

4.11 Chemical myocarditis
The scorpion venom may act directly on heart cells causing “Chemical myocarditis” and destruction of myofibrils. Catecholamines may increase heart rate, blood pressure and cardiac oxygen consumption (Ganong 1987; Keele & Neil 2004).

4.12 Symptoms of systemic intoxication
Symptoms of systemic intoxication may start within minutes after the sting. They may be caused by the venom itself or by neurotransmitters (catecholamines) released by the venom. Symptoms may reflect stimulation or depression of the CNS and stimulation of the autonomic - Sympathetic and/ or Para-sympathetic nervous system.

CNS symptoms may include: irritability, tremor, muscle rigidity, nystagmus, hyperthermia or hypothermia and decreased level of consciousness as well as coma and convulsions.

Symptoms related to stimulation of the sympathetic nervous system may include: hypertension, tachycardia mydriasis, excessive sweating and urinary retention.

Symptoms related to stimulation of the para-sympathetic nervous system may include: excessive secretions, bradycardia, hypotension, priapism in males and miosis (Sofer 1995).

4.13 Severity of clinical envenoming
Local pain, vomiting, sweating, agitation, tachypnea, tachycardia, hypertension, pulmonary oedema, hyperglycemia, leucocytosis and hyperamilasemia are observed in patients stung by T. serrulatus. The scorpion sting victims by T. serrulatus scorpions admitted with systemic manifestations of envenoming had higher plasma venom concentration (ELISA) than those with local pain at the site of sting. The severity of clinical envenoming is related to plasma venom concentration (Cordeiro et al 2006).

4.14 Scorpion venom leads to gastrointestinal ischemia: signs and symptoms
Gastrointestinal signs and symptoms including gastric dilation, vomiting and diarrhea, and pancreatitis are reported in scorpion sting victims. Changes in mucosal function and mucosal ulcers are reported following injection of venom in rats. A case of Gram-negative sepsis following scorpion sting which may be related to translocation of intestinal flora across the bowel wall, possibly an effect of regional bowel ischemia is reported (Sofer et al 1996).

4.15 Continued presence of increased serum lactate
There was an increase in the gastric mucosal Pco_{2} and an increase in the gradient between mucosal Pco_{2} and Paco_{2} and decrease in mucosal pH. These findings indicate gut mucosal ischemia. Continued presence of increased serum lactate suggests that additional organs remained ischemic (Sofer et al 1996).

4.16 Shunting of blood from metabolically active areas
Despite increased peripheral oxygen delivery, scorpion envenomation is associated with evidence of ischemia of the gastrointestinal tract. This association could be due to shunting of blood from metabolically active areas, possibly associated with massive catecholamine release, or a direct toxic effect of the venom on regional oxygen transport at the cellular level (Sofer et al 1996).

4.17 Peripheral ischemia: Increased lactate formation, Decreased HCO_{3}^{-} and persistent metabolic acidosis
Catecholamine infusion can lead to increased lactate formation because of increased conversion of glucose to lactate and Pyruvate. The presence of decreased HCO_{3}^{-} and persistent metabolic acidosis suggests that increased lactate was due to peripheral ischemia (Sofer et al 1997).

4.18 Diverting blood flow and circulation from unimportant areas to vital organs
Massive Sympathoadrenal output would result in diverting blood flow and circulation from unimportant (unstressed) areas like skin, subcutaneous tissue, gastro-intestinal tract and spleen to (stressed) vital organs (Tarasiuk 1999; 1997; 1994).

4.19 Reduction of vascular capacitance
An increase in circulating catecholamines can induce reduction of vascular capacitance, and can induce an increase in Right Atrial Pressure (RAP). According to Frank - Starling mechanism, elevation of Right Atrial Pressure will contribute to the increase in Cardiac output (Keele & Neil 2004;
4.20 Respiratory failure
Respiratory failure in scorpion envenoming syndrome has been attributed to
* cardiogenic pulmonary oedema,
* Upper airway obstruction and
* Bradycardia or apneic episodes.
Above changes could be due to
* Direct central nervous system depression,
* Stimulation of the carotid bodies,
* An afferent vagal fibers and to
* Hypertensive encephalopathy

The respiratory effects are not related with any cardiovascular effects. The respiratory effects are due to central respiratory depressant effects of one or more components of the venom (Sofer et al 1997; 1996; Sofer & Gueron 1992).

4.21 Respiratory failure-Hemodynamic and Neurological aspects
The toxicity is dose-dependent and the pediatric age group is more vulnerable (Tiwari and Deshpande 1993; Mahadevan 2000). The venom stimulates the autonomic nervous system and induces severe cardiovascular abnormalities. Some of the clinical reports described respiratory failure.

4.22 Variety of neurological abnormalities
The breathing disturbances have been observed in children with or without pulmonary oedema and myocardial damage. The central nervous system is also involved in scorpion envenomation. Convulsions, coma, hemiplegia, hypothermia, hyperthermia, tremors, restlessness, myoclonic twitchings and hyper-irritability are few of the neurological abnormalities observed in human or experimental envenomation.

Respiratory arrest or respiratory failures without cardiac abnormalities have been reported following Centruroides sculpturatus sting. Abnormal breathing patterns with gasping and apneic episodes, stridor with expiratory wheezing, were observed (Sofer & Gueron 1988).

4.23 Microscopic findings
The microscopic findings in different degrees of pulmonary oedema with diffuse parenchymal hemorrhages are: Intra alveolar hemorrhages, Perivascular edema, Perivascular and Interstitial cell infiltration and edema fluid in the air spaces. These changes are progressive and were most prominent 3 hr following envenomation (Sofer & Gueron 1988).

4.24 Different respiratory patterns
Hyperpnoea, tachypnea, gasping respiratory movements and periodic respiration have been observed in the animal experiments with Tityus toxin or L. quinquestriatus scorpion venom. These abnormal respiratory movements have been attributed to the venom effect on the parasympathetic (Vagal) nervous system, being therefore considered as reflex in nature (Sofer & Gueron 1988).

4.25 Systemic Inflammatory Response like Syndrome (SIRS)
Systemic Inflammatory Response like Syndrome is triggered during envenomation caused by scorpion species Tityus serrulatus. Increased levels of Interleukin-6, IL-1A and IFN-gamma were seen in all the patients. Studies from Egypt indicate that levels of IL-6, IL-1 beta, nitric oxide and alpha1-antitrypsir declined after initial rise in children who survived. Endothelial nitric oxide (e NOS) is constitutively expressed by endothelium and other cell types but inducible nitric oxide (1 NOS) is expressed in response to stimuli such as pro-inflammatory cytokines (Sofer et al 1996).

4.26 Adrenaline apnea
It is known that epinephrine, in very large doses in man, may cause brief periods of apnea (adrenaline apnea) and even death by interference with gaseous exchange due to the development of pulmonary edema (Ganong 1987; Keele & Neil 2004).

4.27 Respiratory apnoea
The typical manifestations of envenomation such as lacrimation, salivation, alteration in cardiorespiratory parameters, convulsions etc were seen before the death of the experimental animals poisoned with Mesobuthus tamulus concanesis Pocock venom. There was blood stained viscous discharge from eyes and exhibited increased autonomic activity. The typical envenomation syndrome is characterized in the following order

1) Immediate local pain at the site of injection of the venom
2) hyper-excitability and restlessness,
3) Salivation and lacrimation,
4) Convulsions and muscle twitchings,
5) Spastic paralysis of limbs etc.

Respiratory arrest was observed at short latency (<5 sec.). Despite respiratory arrest, the cardiac function still remained at a reasonable level indicating the non-involvement of circulatory system. But, after 10 Sec. the circulatory system and other systems were also affected. Thus, it is very difficult to attribute the cause of death due to venom to a single mechanism (Radha Krishna Murthy 2014 a, b; 2013; 2002; 2000).
4.28 Scorpion venom contains variety of toxins
There is instantaneous apnoea following venom administration. It could be due to the suppression of respiratory centers by neurally mediated mechanism. It can be further presumed that the initial arrest of respiration is because of direct suppression/ inhibition of respiratory centers, possibly involving vagus mediated mechanism. Scorpion venom contains variety of toxins (Iberotoxin, tamapine, lipidotrine etc.), amines (Histamine, 5-HT, Bradykinin etc.) and peptides. Administration of venom (i.v.) results in injection of the above agents and stimulates vagal afferents including pulmonary C-fibers. The activation of pulmonary C-fiber by capsaicin/ PDG results in apnea. The venom also contained a pulmonary edema producing toxin (poTx) which sensitizes the afferent terminals. Venom also releases a number of inflammatory agents (kinins, prostaglandins, leukotriens etc) (Radha Krishna Murthy 2014 a; b; 2013; 2002; 2000), which sensitize the pulmonary C-fiber afferents and may cause suppression of respiration (Bagchi and Deshpande 2001; 1999; 1998).

4.29 Pulmonary edema producing toxin (poTx)
The scorpion venom excites the nerve terminals/ neurons by virtue of having a pulmonary edema producing toxin (poTx) and having the ability to release a number of inflammatory agents (kinins, prostaglandins, leukotriens etc). The venom prolonged the action potential and also prolonged the refractory period to several hundred folds. As a result, initial stimulation of either excitatory or inhibitory group of neurons in the entire nervous system remains in a refractory state, thus, making them non-responsive to either normal or reflex excitation of neurons. This could be the cause of respiratory arrest because of non-responsiveness of medullary neurons (Bagchi and Deshpande 2001; 1999; 1998; Prem Kumar Choudhary 2006).

4.30 Relation between apnoea and fall of mean arterial blood pressure
Deshpande and his group of workers reported apnoea and fall of mean arterial blood pressure in their experimental animals. The fall in mean arterial blood pressure is due to stimulation of vagal efferent fibers. The Vagal efferent fibers supply several visceral organs. Heart is the first organ to be affected by such vagal efferent stimulation, presents as hypotension, and bradycardia (Bagchi and Deshpande 2001; 1999; 1998; Prem Kumar Choudhary 2006).

4.31 Impaired ventilation
Vagal efferents stimulate bronchiolar smooth muscle as well as the glands. The bronchoconstriction results in impaired ventilation. The increased trachea-bronchiolar secretion is a common observation in the envenomed experimental animals. The increased trachea-bronchiolar secretion also blocks the respiratory passages further aggravating the decreased ventilation (Bagchi and Deshpande 2001; 1999; 1998; Prem Kumar Choudhary 2006).

4.32 Pathogenesis of respiratory failure is multifactorial
The haemodynamic and metabolic gas exchange data indicates that the pathogenesis of respiratory failure is multifactorial. Some of the scorpion sting victims may be stuporous with respiratory failure. It is possible that CNS dysfunction is the result and not the cause of respiratory failure. This view is strengthened because some of the scorpion sting victims are in coma with seizures without respiratory abnormalities.

Some of these victims have no clinical, electrocardiographic or enzymatic evidence of myocardial damage. All these patients were severely stuporous with alternating episodes of lethargy or irritability. Majority of these patients developed hypertension. There was no clinical evidence of pulmonary oedema while respiratory failure was severe.

4.33 Effects of Epinephrine
Epinephrine may cause restlessness, apprehension and tremor in many persons and in animals; large doses cause stupor, spasticity and even convulsions. The contribution of abnormal gas exchange should also be considered.

4.34 Progressive respiratory and metabolic acidosis
Scorpion envenoming causes progressive respiratory and metabolic acidosis. The hypercapnia in the presence of constant minute ventilation is probably due to pulmonary vascular effects of the venom, which could include altered dead space and non-cardiogenic pulmonary oedema. Acidosis is lactic acidosis. Lactate might be released not because of poor overall peripheral perfusion but because of abnormalities of either regional perfusion or O2 use or extraction, because acidosis began when cardiac output was elevated. Acid-base abnormalities would act additively to other factors in depressing cardio-circulatory function with administration of scorpion venom (Sofer et al 1997).

4.35 Pulmonary Oedema and respiratory arrhythmias
Clinical reports on scorpion sting victims described different types of abnormal respiratory movements that may lead to death. Thus, * Tachypnoea,
Stimulation of pulmonary C-fibers, and J receptors, mediators like kinins, prostaglandins etc.

Extra-alveolar mechanisms include pulmonary hypertension, generation of inflammatory mediators like kinins, prostaglandins etc. Stimulation of pulmonary C-fibers, and J receptors, cardiacogenic factors also aggravate the extra-alveolar causes to produce pulmonary edema (Bagchi and Deshpande 2001; 1999; 1998; Prem Kumar Choudhary 2006; Deshpande and Aparna 1998).

4.36 Pulmonary oedema: Alveolar and extra-alveolar mechanisms

Alveolar and extra-alveolar mechanisms may be implicated in the production of pulmonary oedema. Alveolar mechanisms include alveolar epithelial damage or decrease in surfactant.

Extra-alveolar mechanisms include pulmonary hypertension, generation of inflammatory mediators like kinins, prostaglandins etc. Stimulation of pulmonary C-fibers, and J receptors, cardiacogenic factors also aggravate the extra-alveolar causes to produce pulmonary edema (Bagchi and Deshpande 2001; 1999; 1998; Prem Kumar Choudhary 2006; Deshpande and Aparna 2012; Aparna and Deshpande 2013).

Decreased pulmonary circulation as a result of circulatory failure, obstruction to bronchial secretion depresses surfactant production from type-II pneumocytes leading to the development of pulmonary oedema. The synthesis of surfactant requires insulin (Radha Krishna Murthy 2014 a, b; 2013; 2002; 2000). In the absence of insulin drive, the pneumocytes – II function, is greatly impaired and escalates pulmonary oedema.

4.37 Non-cardiogenic mechanisms for pulmonary edema

It has been shown that scorpion venom produces acute inflammatory responses in various organs and leads to multi-system-organ-failure and death (Radha Krishna Murthy 2014 a, b; 2013; 2002; 2000, Radha Krishna Murthy et al 1992; 1991; 1988 a, b, c, d). The involvement of kinins in venom induced pulmonary edema had been demonstrated (Deshpande 1998; Deshpande and Aparna 2012; Aparna and Deshpande 2013). Deshpande and his group of workers demonstrated the involvement of kinin mediated NO-guanylate cyclase-cGMP pathway, activating chloride channels to increase the interstitial fluid volume. In addition to kinins, involvement of prostaglandins, PAF and histamine has also been reported. Further, a pulmonary edema inducing toxin (PoTx) has been purified from MBT venom. All these results suggest the involvement of inflammatory mediators in addition to the hemodynamic mechanisms for the venom – induced pulmonary edema (Bagchi and Deshpande 2001; 1999; 1998; Prem Kumar Choudhary 2006; Deshpande 1998; Deshpande and Aparna 2012; Aparna and Deshpande 2013).

4.38 Acute myocarditis and pulmonary oedema

Scorpion venom produces acute myocarditis either in the experimental animals or in scorpion sting victims. Acute myocarditis leads to congestive heart failure and decrease blood flow to the vital organs leading to multi-system-organ-failure (MSOF) including circulatory failure. Kinins aggravate this condition by their effect of vasodilatation and pooling of blood at the periphery causing peripheral circulatory failure. These conditions can result in irreversible cardiogenic shock and shock syndrome. Decreased nutrient supply/ blood supply to the vital organs such as brain, liver, kidney, lung etc causes multi-system-organ-failure (MSOF). Acute myocarditis by decreasing the pumping activity of heart causes pulmonary hypertension and can worsen the existing pulmonary oedema (Deshpande 1998; Deshpande and Aparna 2012; Aparna and Deshpande 2013).

4.39 Unilateral lung oedema

Freire-Maia et al studied a total of 3866 patients stung by Tityus serrulatus scorpion, over a 16 – year period. Lung oedema was unilateral in several cases, with the presence of air bronchograms and a peripheral distribution suggesting that a non-cardiogenic factor is also involved in the genesis of lung oedema (Amaral et al 1994; 1993; 1991).

4.40 Effect of venom on lungs - increased alveo-capillary membrane permeability

Some species of scorpions Tityus discrepans, Mesobuthus tamulus Concanensis, Pocock cause abundant micro-thrombi in the experimental animals like rabbits and dogs. It is suggested that these clotting alterations are fundamental to produce acute lung injury and increase alveo-capillary membrane permeability (Comellias et al 2010; Amaral et al 1994; 1993; 1991).

4.41 Phospholipase A2 pathway for the venom-induced augmentation of cardio-pulmonary reflexes

MBT venom induced responses (augmentation of phenyldiguanide [PDG] reflex response and increased pulmonary water content) involve PLA(2) – prostaglandin pathway that is triggered by br(2) kinin receptors to sensitize the receptors located on the Vagal C-fibers (Radha Krishna Murthy 2014 a, b; 2013; 2002; 2000; Rezende et al 1998; 1995; Rimsza et al 1980; Rinaldo 1994;

4.42 Predominantly unilateral pulmonary oedema
Many factors may be implicated in its genesis of acute pulmonary oedema. Cardiogenic and non-cardiogenic factors are involved in the pathogenesis of pulmonary oedema following scorpion sting. Amaral et al reported predominantly unilateral pulmonary oedema. Unilateral pulmonary oedema secondary to left-sided heart failure seldom occurs in the absence of previous lung injury. This may be explained by a simultaneous and localized increase in pulmonary vascular permeability induced by scorpion venom. The patchy and peripheral distribution of lung oedema indicates increased vascular permeability. Amaral et al reported an increase in the ratio of trachea-bronchial aspirate to plasma protein concentration; light microscopic features of the lung compatible with Adult Respiratory Distress Syndrome (ARDS); electron microscopic findings compatible with acute lung injury; and increased alvelo-capillary membrane permeability in a 16-year old boy, who died with acute pulmonary oedema after *Tityus serrulatus* sting (Amaral et al 1994; 1993; 1991).

4.43 Adult Respiratory Distress Syndrome
ARDS is pulmonary manifestation of pan-systemic injury and Multi-System –Organ-Failure (MSOF). The chemical composition and the functional activity of surfactant are altered in ARDS (Rinaldo 1994; Amaral et al 1994; 1993; 1991; Petty 1990). Investigations from India and Saudi Arabia reported the effectiveness of aprotinin, the kallikrein-kinin inhibitor, in preventing the development of pulmonary oedema and decreasing the mortality rate of rats and rabbits injected with lethal doses of *L. quinquestratus* venom. Freire-Maia and Mats, showed the effectiveness of heparin or BN 52021, a PAF antagonist, in preventing acute pulmonary oedema by *Tityus serrulatus* venom in rats (Freire-Maia et al 1994; 1993). However, heparin, which decreased pulmonary vascular permeability and prevented pulmonary oedema, failed to prevent pulmonary oedema formation following envenoming by Mesobuthus tamulus concanesis (Freire-Maia et al 1994; 1993; Bagchi et al 2001; 1999; 1998; Ismail 1995; 1993).

4.44 Pulmonary Oedema in scorpion envenoming Syndrome
Cardiogenic and non-cardiogenic factors are involved in the pathogenesis of acute pulmonary oedema following scorpion stings. Mathur et al have demonstrated non-cardiogenic pulmonary oedema without left ventricular dysfunction as shown by clinical, radiological, and Echocardiographic findings. Rahav and Weiss using Scintigraphy described a scorpion sting victim with pulmonary oedema with a normal wedge pressure, indicating the possibility of capillary leak syndrome with ARDS. The clinical presentation of ARDS is essentially a constellation of symptoms and findings that would be expected to result from hypoxemia and pulmonary oedema initially. ARDS is a pulmonary manifestation of pan systemic injury and MSOF (Mathur et al 1993; Rahav 1980; Petty 1990).

The presence of MSOF can be inferred by the appearance of concurrent and other wise unexplained pulmonary, CNS, renal, hepatic, and hematological functional abnormalities in a clinical setting either infectious or non-infectious inflammation or tissue injury. ARDS is commonly diagnosed first because of edematous lung injury has immediate life-threatening clinical manifestations. In contrast, other organs may maintain functional integrity despite extravasations of edematous fluid. Some of the subtle manifestations of extra pulmonary dysfunction include altered mental condition, hyperglycemia, ongoing volume requirements to maintain blood pressure, diminished urine output, thrombocytopenia, prolongation of Prothrombin time, Heme positive stools. These problems may be so overshadowed by respiratory failure as to attract little attention.

Freire-Maia and De Matos showed the efficacy of heparin or BN 52021, a PAF antagonist in the prevention of acute pulmonary oedema by *Tityus serrulatus* venom in rats (Freire-Maia et al 1994; 1993). However, heparin, which decreased pulmonary vascular permeability and prevented pulmonary oedema, failed to prevent pulmonary oedema formation following envenoming by Mesobuthus tamulus concanesis (Freire-Maia et al 1994; 1993; Bagchi et al 2001; 1999; 1998).

The chemical composition and the functional activity of the surfactant are altered in ARDS. Surfactant deficiency could be the final common pathway in the pathogenesis of ARDS. The loss or insufficient quantity of surfactant may explain the pulmonary oedema associated with scorpion envenoming, since surfactant is preferably formed from glucose and glycogen rather than from glycerol, and insulin is required for the formation of surfactant. 40% of our patients had pulmonary oedema. All the patients had circulatory failure, myocardial damage, and many other clinical manifestations. All these scorpion sting victims, recovered after the administration of insulin-glucose infusion. None of the victims received ventilator support (Radha Krishna Murthy et al 1992). Radha Krishna Murthy 2000; 2014 a, b; 2002; Radha Krishna Murthy et al 1992; Natu et al 2006).
Insulin-glucose infusion and conventional therapy were given to patients with both ARDS and MSOF following septic shock syndrome. Blood gases improved between 2 and 8 hours after insulin-glucose infusion resulting in normal biochemical profile, radiological clearance of the lungs, and clinical improvement. If surfactant damage or insufficiency is truly the final common pathway, and thus, a key step in the development of pulmonary oedema in scorpion envenoming and ARDS, therapeutic opportunities of surfactant replacement by insulin-glucose administration offer exciting, cheap, and effective possibilities for early intervention (Radha Krishna Murthy et al 1992).

4.45 Surfactant is preferentially formed from glucose and glycogen and insulin is required for the formation of surfactant
Insulin increases alveolar fluid reabsorption and Na⁺ - K⁺ ATPase activity by increasing its translocation to the plasma membrane in alveolar epithelial cells (Comellas et al 2010). Surfactant deficiency could be the final common pathway in ARDS pathogenesis. The loss or insufficient quantity of surfactant may explain the pulmonary oedema associated with scorpion envenoming, since surfactant is preferentially formed from glucose and glycogen rather than from glycerol, and insulin is required for the formation of surfactant (Radha Krishna Murthy et al 1992; Aparna A., Deshpande S.B. 2013; Deshpande S.B., Aparna A. 2012; Radha Krishna Murthy 2013; 2000).

5. Endocrine actions of epinephrine such as modulation (increasing or decreasing) of the secretion of insulin, renin, glucagon, glucocorticoids and thyroid hormones manifested in scorpion envenoming syndrome
Scorpion envenoming syndrome results in a severe autonomic storm with a massive release of epinephrine, nor-epinephrine, increased levels of angiotensin II, counter-regulatory hormones - glucagon, glucocorticoids, thyroid hormones and changes in insulin secretions (suppressed insulin levels or hyperinsulinemia, hyperglycemia and increased circulating free fatty acid levels.

5.1 Severe Scorpion Envenoming causes Hyperglycemia (Fig. 3, 4)
Severe scorpion envenoming causes an increase in the circulating levels of blood sugar, insulin, glucagon, and Cortisol. Subcutaneous (s.c.) injection or i.v. injection of scorpion venom (Mesobuthus tamulus Concaneis, Pocock) in the dogs caused hypo-insulin secretion 30 min after venom injection, and elevated insulin levels 60 min after venom injection. Insulin and blood glucose were higher after 60 and 120 min of venom injection (Radha Krishna Murthy and Anita 1986; Radha Krishna Murthy 1986 a, b, c, d; Radha Krishna Murthy and Abbas Zare 2001; 2002; 1999; 1998; Radha Krishna Murthy et al 2003; 1992; 1988 a, b, c, d).

5.2 Nor-epinephrine released from the adrenergic nerve terminals of the pancreas may be a more effective stimulus to glucagon secretion
Leiurus quinquestriatus scorpion venom in the rat pancreatic islets inhibited insulin secretion and stimulation of glucagon secretion. Nor-epinephrine released from the adrenergic nerve terminals of the pancreas may be a more effective stimulus to glucagon secretion than nor-epinephrine reaching the pancreas through the general circulation (Johnson et al 1976; Johnson and Ensinck 1976).

5.3 Release of increased glucocorticoids secretion
Increased glucocorticoid levels were observed after scorpion venom injection in our experimental animals (Radha Krishna Murthy and Haghnazari 1999; Radha Krishna Murthy et al 2003). Glucocorticoids could also be released following stress or injury. The Sympatho-adrenal axis primarily serves to maintain the pressure necessary for organ perfusion. Thus, during the “ebb phase”, the insulin levels are reduced and with the onset of hyper-metabolism, characteristic of the “flow phase”, the hormonal environment is changed and the insulin levels are increased (Douglas 1986).

5.4 The effects of the hormonal actions are synergistic in the presence of increased circulating levels of all the catabolic counter-regulatory hormones
In the presence of increased circulating levels of all these catabolic counter-regulatory hormones, the effects of these hormonal actions are synergistic and sustained hepatic glucose production is observed (Susan 1996). The simultaneous elaboration of the counter-regulatory hormones is partly responsible for the pathogenesis of a variety of clinical and biochemical manifestations following scorpion envenoming. This could be the reason for glycogenolysis in the atria, ventricles, and liver; and skeletal muscles (Balasubramaniam and Radha Krishna Murthy 1984; 1981; Radha Krishna Murthy and Haghnazari 1999; Radha Krishna Murthy et al 2003). Glucocorticoids could also be released following stress or injury. The Sympatho-adrenal axis primarily serves to maintain the pressure necessary for organ perfusion. Thus, during the “ebb phase”, the insulin levels are reduced and with the onset of hyper-metabolism, characteristic of the “flow phase”, the hormonal environment is changed and the insulin levels are increased (Douglas 1986).

5.5 Hyperinsulinemia - insulin resistance
Hyperinsulinemia observed in our studies could be equated with insulin resistance. Insulin resistance could be caused by a change in the receptor membrane, a change in hormone-receptor binding characteristics, or a change in the post receptor events (Izzo 1984).

5.6 Severe scorpion envenoming is a syndrome of fuel-energy deficits & Result in Multi-System-Organ-Failure (MSOF)
Severe scorpion envenoming is thus a syndrome of fuel-energy deficits and an inability of the vital organs to utilize the existing metabolic substrates. This ultimately may result in Multi-System-Organ-Failure (MSOF) and death. These changes are brought about by a massive release of catecholamines, angiotensin II, glucagon, glucocorticoids, and either insulin deficiency or insulin resistance.

5.7 Mechanisms of production of Hyperglycemia
(Fig. 3, 4)
Epinephrine elevates blood glucose and lactate concentration by a series of enzyme activities. In addition, insulin secretion is predominantly inhibited via alpha receptors (Keele and Neil 2004; Ganong 1987; Edwin 2006; Westfall & Westfall 2006).

Epinephrine also can cause glycogenolysis in muscle (Balasubramaniam and Radha Krishna Murthy 1981; 1984; Radha Krishna Murthy and Hase 1994; Radha Krishna Murthy et al 1988 a, b, c; 1990; 1992; 1999; 2003; Radha Krishna Murthy 2000; 2002; 2013; 2014 a, b) thus providing substrate in the form of lactate for hepatic gluconeogenesis. In addition to circulating catecholamines, Nor-epinephrine released from nerve endings in the liver might influence glucose production. The liver is richly innervated by Sympathetic and Para - sympathetic nerves; Stimulation of Sympathetic system can lead to increased glucose production, an effect mediated mostly through activation of alpha adrenergic receptors. This indicates a possible role of Nor-epinephrine released by the nerve terminals in the glucose production (Bondy & Rosenberg 1980; Naomkarau-Freidman 1984).

5.8 Physiological Basis of the Glycogenolysis -- Hyperglycemia in scorpion envenoming

5.8 Role of Glucagon

Glucagon acts mostly on the liver and adipose tissue where it antagonizes the action of insulin. Glucagon raises blood glucose concentration by enhancing the breakdown of liver glycogen to glucose (glycogenolysis) and by promoting gluconeogenesis from lactate, Pyruvate, glycerol and amino acids. Glycogenolysis produces a rapid rise in blood glucose within a few minutes; gluconeogenesis produces a slower, more sustained rise in blood glucose lasting for hours or days.

Glycogenolysis is mediated by activation of adenyl cyclase in the hepatic cell membrane and subsequent increase in intracellular c AMP and activation of protein kinases which in turn activate the Phosphorylase responsible for converting glycogen to glucose-6-phosphate, and inactivates glycogen synthetase. Phosphatase in the liver then acts on glucose -6- phosphate to release glucose into the hepatic venous blood (Keele & Neil 2004, Ganong 1987).

Glucagon is potent as a stimulant of glucose output from the liver
Glucagon as a stimulant of glucose output from the liver is, on a molar basis, more potent than insulin as a promoter of glucose retention (Keele & Neil 2004, Ganong 1987).

5.9 Role of catecholamines
Catecholamines (Adrenaline and Nor-adrenaline) act similarly (like glucagon) to enhance glycogenolysis but on molar basis, Adrenaline and Nor-adrenaline, are weaker than glucagon; however, Nor-adrenaline released locally at sympathetic nerve terminals might have powerful effects.

Catecholamines (Adrenaline and Nor-adrenaline) antagonize insulin by increasing c AMP formation in the liver, fat and muscle; in the liver this activates Phosphorylase, promotes glycogenolysis, and leads to hyperglycemia (Keele & Neil 2004, Ganong 1987).

Catecholamines promote glycogenolysis, in muscle and enhance lactate formation.

5.10 Adrenalin inhibits glucose-induced secretion of insulin

The acute hyperglycemia seen in acute myocarditis induced by injection of scorpion venom (Buthus tamulus) could be because of suppression of insulin release from beta cells of the pancreas as well as
the capacity for adrenal catecholamines to provoke glycogen breakdown and peripheral inhibition of glucose uptake (Johnson et al 1976; Johnson and Ensink 1976; Bondy & Rosenberg 1980; Naomikarau-Friedman 1984).

5.11 Reduction in glycogen content
Epinephrine stimulates inhibition of insulin secretion which in turn stimulates glycogenolysis in the muscle, thus providing a substrate in the form of lactate for hepatic gluconeogenesis. This might explain the reduction in glycogen content of atria, ventricle, and liver and skeletal muscle in rabbits after venom injection and hyperglycemia in the dogs 30 min after venom injection (Radha Krishna Murthy 2014 a, b; 2013; 2002; 2000; Balasubramaniam and Radha Krishna Murthy 1981; 1984; Radha Krishna Murthy et al 1988 a, b, c, 1990; 2003; Radha Krishna Murthy and Abbas Zare 1998; 2002; 1992).

5.12 Effects of acute ischemia on myocardial metabolism
The immediate metabolic changes in the myocardium during acute ischemia are largely determined by the rates of Glycolysis and glycogenolysis and to a lesser extent, of fatty acid availability in relation to the demand for phosphorylation (Bondy & Rosenberg 1980; Radha Krishna Murthy 1994).

Glycolysis increases with mild hypoxia, and in areas of profound hypoxia, decreased glycogenolysis occurs. Hydrolysis of stored triglycerides results from the activation of myocardial lipase with increases in FFA. Greater glycogenolysis was observed in atria and ventricular tissue in response to a smaller dose of scorpion venom compared to lower rate of glycogenolysis with a higher dose of scorpion venom Balasubramaniam and Radha Krishna Murthy 1981; 1984). Important early systemic changes have been recorded in man in the first few hours of the onset of acute myocardial ischemia. These changes probably result from the anxiety and pain associated with ischemia, including a sustained rise in plasma catecholamines, a marked increase in plasma FFA(Radha Krishna Murthy and Medhi1986; Radha Krishna Murthy et al 1998 a, b, c; 1990; 1992; Radha Krishna Murthy 2014 a, b; 2013, 2002; 2000; Kankonkar et al 1992) and plasma Cortisol concentrations (Radha Krishna Murthy and Abbas Zare; Radha Krishna Murthy et al 2003) a transient elevation in blood glucose (Radha Krishna Murthy and Abbas Zare; Radha Krishna Murthy et al 2003; 2004; 1986 a, b, c, d; 1988 a, b, c; 1990; 1992; Kankonkar et al 1992) and decreased plasma insulin levels (Radha Krishna Murthy and Anita 1986; 1988 a, b, c; Radha Krishna Murthy and Abbas Zare; Radha Krishna Murthy et al 2003).

Plasma FFA is absorbed by tissues in an exponential relationship to their molar binding with plasma albumin, while glucose uptake depends on adequate concentrations of plasma insulin, which is reduced in acute myocardial infarction. In many patients, the increase in plasma FFA concentrations is such that the two main binding sites of albumin are saturated, and the ischemic myocardium extracts proportionately more FFA than at lower plasma concentrations. The ischemic myocardium is presented, therefore, with a considerable excess of FFA relative to glucose and, in a severely ischemic zone, the available oxygen may be insufficient for oxidation (Oliver 1975; Muller et al 1978).

5.13 Renin -angiotensin system
Increased sympathetic activity causes elevated Renin release by direct stimulation of juxtaglomerular cells. A subsequent increase in angiotensin II secretion enhances the ongoing sympathetic nerve output by a direct action on the brainstem and by a blunting of Baroreceptor mechanisms. Thus, the Renin-angiotensin system is an important facilitator of ongoing Sympathoadrenal traffic (Edwin 2006).

5.14 Hyperglycemia in scorpion envenoming
Hyperglycemia was found after envenoming. This could be due to a massive release of catecholamines, increased glucagon, Cortisol (Radha Krishna Murthy and Abbas Zare; Radha Krishna Murthy et al 2003; 2004; 1986 a, b, c, d; 1988 a, b, c; 1990; 1992; Kankonkar et al 1992) and changes in insulin secretion (decreased plasma insulin levels/ increased insulin levels) (Radha Krishna Murthy and Anita 1986; 1988 a, b, c; Radha Krishna Murthy and Abbas Zare; Radha Krishna Murthy et al 2003).

5.15 Effects of an acute increase in epinephrine and Cortisol on carbohydrate metabolism during insulin deficiency
Elevations in plasma epinephrine and Cortisol levels are associated with scorpion envenoming (Radha Krishna Murthy and Abbas Zare; Radha Krishna Murthy et al 2003; 2004; 1986 a, b, c, d; 1988 a, b, c; 1990; 1992; Kankonkar et al 1992; Radha Krishna Murthy and Anita 1986; 1988 a, b, c; Radha Krishna Murthy and Abbas Zare; Radha Krishna Murthy et al 2003). In diabetic patients, plasma epinephrine and Cortisol levels increase during diabetic keto-acidosis. Goldstein et al. demonstrated an acute physiological rise in the plasma epinephrine level was associated with a transient increase in hepatic glucose production and a sustained fall in glucose clearance, which caused
persistent hyperglycemia. The initial increase in glucose production was primarily due to an increase in hepatic glucogenesis, whereas the later elevation in glucose production was due to a stimulation of gluconeogenesis (Bondy 1980; Oliver 1975; Izzo 1991; Naomikarau-Freidman 1984; Muller et al 1978; Hannele 1992; Susan 1996; Goldstein et al 1995).

5.16 Cortisol may be synergistic with other stress hormones
Cortisol may be synergistic with other stress hormones. Glucose production was reported to be synergistically enhanced by a combined epinephrine, glucagon, and Cortisol infusion, while glucose production was increased in an additive manner by epinephrine and glucagon infusions. Glucagon and Cortisol modify lactate gluconeogenesis in an additive rather than a synergistic manner.

5.17 Small increases in the plasma epinephrine level during insulin deficiency can significantly worsen the resulting hyperglycemia.
Small increases in the plasma epinephrine level during insulin deficiency can significantly worsen the resulting hyperglycemia. This occurs as a result of what is probably an additive effect on hepatic glucose production, without any additional change in glucose clearance. The small increase in epinephrine significantly increases the importance of gluconeogenesis, as the period of insulin deficiency becomes prolonged (Bondy 1980; Oliver 1975; Izzo 1991; Naomikarau-Freidman 1984; Muller et al 1978; Hannele 1992; Susan 1996; Goldstein et al 1995).

5.18 Glucose toxicity
In virtually all tissues except the brain, glucose, at a fixed insulin concentration, promotes its own utilization in a concentration-dependent manner. The superiority of insulin in stimulating glucose oxidation seems to be explained by its anti-lipolytic effect. Even a small increment in serum insulin concentration promptly suppresses lipolysis, and consequently, the use of FFA for energy production, which in turn, enhances glucose oxidation. In contrast, glucose per se is unable to suppress lipolysis in man. Glucose per se (i.e. hyperglycemia) is a cellular toxin. Hyperglycemia may cause a generalized desensitization of all cells in the body through the down-regulation of the glucose receptors in the glucose transport system (Hannele 1992).

5.19 Defect in insulin action - impairment in insulin secretion
In muscles and adipocytes, this would be reflected by a defect in insulin action, whereas at the level of beta cells of the islets of Langerhans, this would be manifested by impairment in insulin secretion (Defronzo 1988).

5.20 Haemodynamic abnormalities in short-term insulin deficiency
Magnified lipolysis and beta oxidation of FFA: Hepatic overproduction and peripheral underutilization of ketone bodies

5.16 Insulin levels in scorpion envenoming
Insulin levels, as measured by radioimmunoassay, were significantly either suppressed or elevated after venom injection (Radha Krishna Murthy and Anita 1986; Radha Krishna Murthy and Vakil 1988; Radha Krishna Murthy and Hahnzari 1999; Radha Krishna Murthy et al 2003; 1988 a, b, c, 1990; Kankonkar et al 1992; Radha Krishna Murthy and Abbas Zare 1998-1999-2002.

5.17 Insulin / glucagon (I/G) ratio
Catabolic state with low Insulin / glucagon (I/G) ratio
The insulin/glucagon ratio (I/G ratio) may be more important than the levels of individual hormones. A high I/G ratio produces an anabolic state with more nutrient incorporation into peripheral tissues. A high ratio is associated with low levels of c AMP and a respiratory quotient close to 1, indicating that carbohydrates are the predominant energy source (Radha Krishna Murthy and Hahnzari 1999; Susan 1996).

When I/G ratio are low, a catabolic state is produced in which nutrients are mobilized. Scorpion envenoming causes a low I/G ratio (Radha Krishna Murthy and Hahnzari 1999; Radha Krishna Murthy et al 2003; Susan 1996).
5.18 "Hyperinsulinemia"

Hyperinsulinemia is said to exist when plasma insulin levels are inappropriate for the blood glucose estimated simultaneously.

**Insulin resistance**

When insulin levels are elevated with a normal glucose level, "true hyperinsulinemia" is the most appropriate term, while high insulin levels with elevated blood glucose levels may be referred to as "insulin resistance". Elevated insulin levels were observed 30 min following venom injection (Radha Krishna Murthy and Haghnazari 1999; Radha Krishna Murthy et al 2003; 1990, 1992; Kankonkar et al 1992; Radha Krishna Murthy and Abbas Zare 2001).

5.19 **Mechanisms that can produce Hyper-insulinemia and hyperglycemia in scorpion envenoming syndrome**

We have observed hyperglycemia along with suppressed/reduced insulin secretion (hypo-insulin secretion) and hyperglycemia along with hyper-insulinemia in all our experimental animals (Radha Krishna Murthy and Haghnazari 1999; Radha Krishna Murthy et al 2003; 1990, 1992; Kankonkar et al 1992; Radha Krishna Murthy and Abbas Zare 2001). This was confirmed by Deshpande and his co-workers in their experimental animals (Premkumar Choudhary 2006).

5.20 **Insulin receptor and the signaling pathways not defective**

Exogenous insulin administration reversed haemodynamic, cardiovascular, metabolic, electrocardio graphic (ECG) changes, pulmonary oedema and many other clinical manifestations in the experimental animals and in the scorpion sting victims suggesting that the insulin receptor and the signaling pathways are not defective (1, 47, 50, 124).

5.21 **Counter-regulatory hormones and hyperglycemia**

Hyper-insulinemia and hyperglycemia are observed in scorpion envenoming syndrome. The increased circulating insulin levels and failure to counter the hyperglycemia may indicate the action of counter-regulatory hormones (14). We have reported an elevation of glucagon and Cortisol in experimental animals along with changes in insulin secretion. Various investigators have reported increased Renin-angiotensin II levels in the experimental animals and scorpion sting victims (8). Epinephrine and nor-epinephrine levels were also elevated in scorpion envenoming syndrome (118).

5.22 **Hyperglycemia and hyper – insulinemia - insulin resistance**

Hyperglycemia and hyper-insulinemia - insulin resistance is observed in all our experimental animals (37, 39, 46, 47, 50) and in the studies reported by Prem Kumar Choudhary (118). Thus, development of insulin resistance is a possibility in scorpion envenoming syndrome.

5.23 **Insulin resistant state**

The relationship between insulin resistance, plasma insulin level, and glucose intolerance is mediated to a significant degree by changes in ambient plasma FFA concentration (Serrano et al 1992; Defronzo 1988). Plasma FFA levels can be suppressed by relatively small increments in insulin concentration. Consequently, an elevation of circulating FFA concentration can be prevented if large amounts of insulin are secreted. If hyperinsulinemia can not be maintained, plasma FFA concentration will not be suppressed normally, and the increase in plasma FFA concentration will result in increased hepatic glucose production and insulin resistance. Short-term hyperglycemia can induce insulin resistance (Hannele 1992).

5.24 **Causes of insulin resistance**

In any insulin-resistant state, the cause of insulin resistance can be due to an abnormal beta cell secretory product, circulating insulin antagonists, or target tissue defect in insulin action (Johnson and Ensinck 1976; Johnson et al 1976; Oliver 1975; Serrano et al 1992; Defronzo 1988).

Insulin resistance could be caused by a change in the receptor number, hormone-receptor binding characteristics, or post-receptor events. Insulin receptors are probably down-regulated by high concentrations of agonist hormone/s (Izzo 1991).

5.25 **Insulin resistance - pre-receptor, receptor, and post-receptor abnormalities**

Insulin resistance may occur because of pre-receptor, receptor, and post-receptor abnormalities (Serrano et al 1992).

Insulin resistance as a result of pre-receptor abnormalities involves metabolic (elevated counter-regulatory hormonal and non-hormonal) factors. Circulating insulin antagonists as a cause of insulin resistance have been clearly demonstrated in a variety of clinical syndromes. Excess endogenous or exogenous glucocorticoids are often associated with carbohydrate intolerance. Availability of substrates and plasma levels of glucagon, glucocorticoids stimulate hepatic glucose production through increased activity of hepatic gluconeogenic enzymes (Serrano et al 1992).

5.26 **Post-receptor resistance - Hormonal antagonists**
Hormonal antagonists consist of all counter-regulatory hormones

Post-receptor resistance can be caused by other hormones (Serrano et al 1992; Muller et al 1978; Hannele 1992; Bondy and Rosenberg 1980). Hormonal antagonists consist of all counter-regulatory hormones, such as growth hormone, Cortisol, glucagon, and epinephrine. Increases in circulating levels of glucagon, Cortisol and catecholamines have been demonstrated in scorpion envenoming (Radha Krishna Murthy and Haghnazari 1999; Radha Krishna Murthy et al 2003).

5.27 Corticosteroids decrease peripheral glucose utilization

In addition, a rise in corticosteroids decreases peripheral glucose utilization by diminishing the activity of glucose transporters and inhibiting insulin-mediated translocation of these facilitative transporters. Additionally, glucocorticoids affect insulin receptor affinity and number, decreasing insulin binding to its receptor (Keele and Neil 2004; Ganong 1987; Serrano et al 1992).

5.28 Catecholaminergic hyperactivity antagonize insulin effects

States of Catecholaminergic hyperactivity antagonize insulin effects through several mechanisms. Catecholamines stimulate hepatic glucose production by direct stimulation of glycogenolysis and gluconeogenesis and indirectly by increasing glucagon secretion. Additionally, catecholamines decrease peripheral glucose disposal both in vitro and in vivo Catecholaminergic hyperactivity (Serrano et al 1992).

5.29 Effect of acidic pH to accelerate insulin dissociation from the receptor

The accelerated receptor degradation has been found to be responsible for a decreased number of receptors. The effect of acidic pH to accelerate insulin dissociation from the receptor is markedly reduced, leading to an inhibition of receptor recycling and acceleration of receptor degradation (Serrano et al 1992). An increase in pH (acidosis) has been demonstrated in the experimental scorpion envenoming (Radha Krishna Murthy et al 1988 a, b, c).

In addition to animal studies, several in vitro models of insulin resistance suggest defects in the receptor Kinase activity. Catecholamines induce a 90% inhibition of the tyrosine Kinase activity (Serrano et al 1992).

5.30 Tissue insensitivity to insulin

Tissue insensitivity to insulin is an important pathogenic disturbance that contributes to glucose intolerance (Vik Harald 1981; Oliver 1975; Bondy and Rosenberg 1980).

5.31 Tissue insensitivity to insulin in the basal state

In the basal state, the liver represents a major state of insulin resistance. This is reflected by an overproduction of glucose despite the presence of fasting hyperglycemia and hyperinsulinemia (Defronzo 1988).

5.32 Tissue insensitivity to insulin in the insulin-resistance state

In the insulin-resistance state, muscle is the primary tissue responsible for insulin resistance (Defronzo 1988).

5.33 Severe scorpion envenoming syndrome is a syndrome of fuel-energy deficits, Multi-System-Organ-Failure (MSOF) resulting in death

Severe scorpion envenoming syndrome is thus a syndrome of fuel-energy deficits and an inability of the vital organs to utilize the existing metabolic substrates. This ultimately may result in Multi-System-Organ-Failure (MSOF) and death. These changes are bought about by a massive release of catecholamines, Angiotensin II, glucagon, Glucagon, Glucocorticoids, and either insulin deficiency, suppressed insulin secretion, or insulin resistance.

6. Metabolic actions - sudden increase in Free Fatty Acids (Fig. 3)

6.1 Scorpion envenoming causes sudden increase in Free Fatty Acids

Massive release of catecholamines, release of Angiotensin II, increased glucagon, increased Cortisol and/or hypo-insulin secretion or insulin resistance thus produced can cause hyperglycemia and activate the hormone sensitive lipase, promote free fatty acid mobilization and produce a sudden increase in free fatty acid levels after venom injection. We have demonstrated release of Angiotensin II, increased glucagon, increased Cortisol and/or hypo-insulin secretion, hyperglycemia and a sudden increase in free fatty acid levels after venom injection (Radha Krishna Murthy 2014 a, b; 2013; 2002; 2000; Radha Krishna Murthy and Vakil 1986; Radha Krishna Murthy and Anita 1986; Radha Krishna Murthy 1988 a, b, c; Radha Krishna Murthy et al 1990; Radha Krishna Murthy et al 1992; Radha Krishna Murthy and Haghnazari 1999; Radha Krishna Murthy et al 2003; Radha Krishna Murthy and Hossein 1986 a, b; Radha Krishna Murthy and Medh 1986).

6.2 Significance of sudden increase in serum Free Fatty Acids
The catecholamines make available for active tissues more oxidizable substrates and at the same time depress the oxidation of glucose. Thus, there may be an excess of free fatty acids in the ischemic myocardium especially at the time when sudden death from arrhythmias are known to be common (Johnson and Ensinck 1976; Johnson et al 1976; Vik Harald 1981). Thus the excess of un-oxidizable free fatty acids could be toxic.

6.3 Physiological Basis of the increased Free Fatty Acid levels in scorpion envenoming
Role of Glucagon
Glucagon is a powerful lipolytic agent, acting via cAMP to phosphorylate a lipase in adipose tissue which releases FFA and glycerol in to circulation (Keele & Neil 2004; Ganong 1987; Radha Krishna Murthy and Haghnavazari 1999; Radha Krishna Murthy 2003; Johnson and Ensinck 1976; Vik Harald 1981).

6.4 Role of Adrenalin and Nor-adrenalin
Adrenalin and noradrenalin activate specific lipase in adipose tissue and muscle which breaks down triglycerides to FFA and glycerol. This lipolysis might be mediated by cyclic AMP. This action is antagonized by insulin (Keele & Neil 2004; Ganong 1987).

6.5 Lipolytic action of adrenaline and the action of noradrenaline
The catecholamines make available for active tissue more oxidizable structures, such as FFA, glycerol, and ketone bodies, and at the same time depress the oxidation of glucose. The lipolytic action of adrenalin is brief and the action of noradrenaline is prolonged. The catecholamines promote lipolysis in adipose tissue and proteolysis in muscle (Keele & Neil 2004; Ganong 1987).

6.6 Effect of increased Free Fatty Acids on the Heart
Increased oxygen consumption in the heart
The use of increased amounts of Free Fatty Acids results in increased oxygen consumption. This could aggravate the ischemic injury to myocardium, predisposing to arrhythmias and heart failure (Bondy 1980; Cecil 1976; Braunwald 2011; Oxford Textbook of Medicine 2003; Kumar and Clark clinical Medicine 2005; Current Medical Diagnosis & Treatment 2012; Rosen’ emergency Medicine 2006).

6.7 Increase the susceptibility of the ventricles to the disorganized electrical behavior
The elevated free fatty acids also increase the susceptibility of the ventricles to the disorganized electrical behavior and produce ectopic beats in the vulnerable period of cardiac cycle (Vik Harald and Ole 1981).

6.8 Depressed left ventricular systolic function
Scorpion stings can be accompanied by enzymatic and electrocardiographic evidence of myocardial damage. Examination of myocardial ultra structure following scorpion sting reveals various types of cellular damage. Echocardiographic and radionuclide studies in human victims have shown depressed L.V. systolic function in patients tested within a few hours of scorpion sting (Tarasiuk et al 1999; 1997; 1994; Bondy and Rosenberg 1980; Oliver 1975; Muller et al 1978).

6.9 O2 demand/ supply ratio - ischemia
Myocardial ischemia immediately following administration of scorpion venom is related to increased myocardial oxygen consumption associated with catecholamine release coupled with a decrease in oxygen supply due to transient reduction of coronary blood flow. Thus, immediately post-envenomation, the myocardial O2 demand/ supply ratio would be adversely affected, resulting in ischemia (Ismail 1995; 1993; Ismail et al 1992; Gueron et al 1992; 1990; 1987; 1980; Tarasiuk et al 1999; 1997; 1994; Goldstein et al 1995; Oliver 1975; Fyge et al 1971).

6.10 Increase the tendency to intravascular thrombus
The increased Free Fatty Acids, by altering the functions of platelets, may increase the tendency to intravascular thrombus and result in disseminated intravascular coagulation (Radha Krishna Murthy 2014 a, b; 2013; 2002; 2000; Radha Krishna Murthy et al 1988 a, b, c; Devi et al 1970).

6.11 Metabolism of normal myocardium and role of insulin
Under normal conditions, the myocardium derives its energy from the aerobic metabolism of substrates extracted from the plasma. The most important fuels are Free Fatty Acids (FFA),...
glucose, triglycerides, amino acids, Pyruvate and lactate. At rest, the myocardial extraction of many of these substrates is generally related to their arterial concentrations, but the relative uptake of each compound may be modified by hormones and utilization of other substrates. Thus, glucose transport into the myocardial cell depends on insulin, and increases of plasma insulin concentration enhance the extraction of glucose by the heart (Ismail 1995; 1993; Ismail et al 1992; Gueron et al 1992; 1990; 1987; 1980; Tarasiuk et al 1999; 1997; 1994; Goldstein et al 1995; Oliver 1975; Frye et al 1971).

6.12 Metabolism of injured myocardium and role of insulin
Myocardial glucose utilization is negatively correlated with plasma FFA levels, which means that high plasma FFA concentrations inhibit glucose uptake by the heart. In the human heart, a 10% increase of plasma FFA decreases the myocardial extraction of glucose by 17%, while a 10% increase of plasma insulin enhances glucose utilization by an average of 24%. We have consistently demonstrated a sudden increase in FFA levels (200 to 300%) in the experimental scorpion envenoming (Radha Krishna Murthy and Medh 1986; Radha Krishna Murthy et al 1988 a, b, c; 1990; 1991; 1992; 2003Radha Krishna Murthy and Hase 1994; Radha Krishna Murthy and Haghnazari 1999; Kankonkar et al 1992; Radha Krishna Murthy and Abbas Zare 1998; 2001; 2002).

6.13 Metabolism of injured myocardium
High plasma FFA concentration increases myocardial oxygen consumption without augmenting mechanical performance. In the anoxic myocardium, the synthesis of ATP from FFA is suppressed, and the only way to maintain the energy supply for contraction is by anaerobic metabolism of glucose. However, if utilization is inhibited by FFA, an increase in plasma FFA levels may be disadvantageous to the ischemic myocardium. High plasma FFA levels in patients with myocardial infarction are associated with increased incidence of arrhythmias, decrease heart contractility, and increase the extent of myocardial damage (Radha Krishna Murthy and Medh 1986; Radha Krishna Murthy et al 1988 a, b, c; 1990; 1991; 1992; 2003Radha Krishna Murthy and Hase 1994; Radha Krishna Murthy and Haghnazari 1999; Kankonkar et al 1992; Radha Krishna Murthy and Abbas Zare 1998; 2001; 2002; Oliver 1975).

6.14 Effects of acute ischemia on myocardial metabolism
The immediate metabolic changes in the myocardium during acute ischemia are largely determined by the rates of Glycolysis and glycogenolysis. Glycolysis increases with mild hypoxia, and in areas of profound hypoxia, decreased glycogenolysis occurs. Hydrolysis of stored triglycerides results from the activation of myocardial lipase with increases in FFA. Greater glycogenolysis was observed in atria and ventricular tissue in response to a smaller dose of scorpion venom compared to lower rate of glycogenolysis with a higher dose of scorpion venom (60, 61). Important early systemic changes have been recorded in man in the first few hours of the onset of acute myocardial ischemia. These changes include a sustained rise in plasma catecholamines, a marked increase in plasma FFA and plasma Cortisol concentrations, a transient elevation in blood glucose, and decreased plasma insulin levels (Scheuer and Stetzosi 1969; Sofer et al 1997; Tarasiuk et al 1999; 1997; 1994; Vik Harald 1981; Oliver 1975).

Plasma FFA is absorbed by tissues in an exponential relationship to their molar binding with plasma albumin, while glucose uptake depends on adequate concentrations of plasma insulin, which is reduced in acute myocardial infarction. The ischemic myocardium extracts proportionately more FFA than at lower plasma concentrations. The ischemic myocardium is presented, therefore, with a considerable excess of FFA relative to glucose and, in a severely ischemic zone, the available oxygen may be insufficient for oxidation (Vik Harald 1981; Oliver 1975; Bondy and Rosenberg 1980).

6.15 Myocardia vulnerability
While myocardial vulnerability may finally be determined by critical extra and intra cellular gradients in the availability of Ca++, Mg++ and K+, the intracellular concentrations of these ions, are in turn, dependent on factors which influence their transference across the cell and mitochondrial membranes. A decreased availability of Ca++ can interfere with Actin-Myosin coupling so that contractility is impaired. An excess of K+ could alter the action potential so that self perpetuating re-entry currents are established (Oliver 1975). We have demonstrated hyperkalemia (Radha Krishna Murthy et al 1986 b).

Low concentrations of myocardial Mg++ are associated with arrhythmias and sudden death (Vik Harald and Ole 1981; Oliver 1975; Skou 1992). We have demonstrated alterations in cardiac sarcolemmal Mg dependent Na+ - K+ ATPase and Mg++ ATPase activities (Radha Krishna Murthy 1982).
6.16 Accumulation of excess intra cellular FFA: Detergent effect on cell membranes
Accumulation of excess intra cellular FFA could have a detergent effect on cell membranes. This accumulation could result from decreased oxidation in the myocardium and catecholamine-induced hydrolysis of stored triglycerides in addition to increased uptake resulting from higher concentrations in arterial blood. Elevated concentrations of plasma FFA have been associated with an increased prevalence of serious ventricular arrhythmias and death in man and in dogs. Elevated FFA levels have also been shown to increase myocardial oxygen consumption and, when there is an under-perfusion of the left ventricle, to decrease myocardial contractility. High plasma FFA levels increased ST elevation in the ECG and plasma CK enzyme levels, suggesting that they may lead to more extensive damage (Pande and Mead 1968; Vik Harald 1981; Oliver 1975).

6.17 Excess un-oxidized FFA probably become toxic to the myocardium
Excess un-oxidized FFA probably becomes toxic to the myocardium only when there is acute ischemia. It is difficult to dissociate the toxic effects of increased local FFA concentrations from those of catecholamines, although it is possible to experimentally show that elevations of plasma concentrations of FFA can lead to adverse effects on myocardial function in the absence of changes in the catecholamine levels (Radha Krishna Murthy 2014 a, b, 2013; 2002; 2000).

6.18 Interfere with tropomyosin-troponin activation of Actin-Myosin coupling
The biochemical consequences which result from the intra cellular accumulation of excess un-oxidized FFA for Ca++ will occur simultaneously with protein binding, possibly making less ionic calcium available for passage into the sarcotubular reticulum. This might interfere with tropomyosin-troponin activation of Actin-Myosin coupling (Oliver 1975).

6.19 Intra cellular depletion of Mg++ would be exaggerated
Magnesium – fatty acid complexes could result and any intra cellular depletion of Mg++ would be exaggerated. This might lead to uncoupling of oxidative phosphorylation, possibly by interfering with a Magnesium-dependent ATPase system (Mg++ ATPase). Cardiac sarcolemmal Na' - K' ATPase is also a Magnesium-dependent ATPase system (Oliver 1975; Radha Krishna Murthy 1982; Skou 1992).

6.20 Excess un-oxidized fatty acids or metabolites could alter stabilization of lysosomal membranes
Fatty acids may be transported intra-cellularly in the un-esterified form and have specific affinities for certain subcellular structures. Esterification of certain phospholipids of the mitochondrial and cell membranes may be altered when there is excess un-oxidized FFA. Different cell membranes have lipoprotein layers with variable permeability for ions, and this could also be changed if the intra cellular accumulation of FFA were to have a detergent action leading to cat-ion loss. Excess un-oxidized fatty acids or metabolites could alter the stabilization of lysosomal membranes and mitochondrial integrity, and together they can have a synergistic effect (Oliver 1975; Radha Krishna Murthy 1982; 2014 a, b, 2013; 2002; 2000; Skou 1992; Oliver 1975).

6.21 Elevated FFA levels-incidence of different types of arrhythmias, conduction defects, ischemia, and infarction-like patterns
Elevated FFA levels with incidence of different types of arrhythmias, conduction defects, ischemia, and infarction – like patterns in ECG have been shown in our experimental animals with scorpion envenoming and in scorpion sting victims (Radha Krishna Murthy 2014 a; b; c; 2013; 2002; 1982; Radha Krishna Murthy et al 2003; 2002; 2001; 1999; 1998; 1994; 1992; 1991; 1990; 1989; 1988 a; b; c; 1986 a; b; c; d; e; f).

6.22 Hemodynamic abnormalities in short-term insulin deficiency
Magnified lipolysis and beta oxidation of FFA; Hepatic overproduction and peripheral underutilization of ketone bodies
In diabetic keto-acidosis, the simultaneous relative insulin deficiency and excessive secretion of counter-regulatory hormones lead to magnified lipolysis and beta oxidation of FFA with a parallel hepatic overproduction and peripheral underutilization of ketone bodies. The clinical characteristics of patients are drowsiness and over-breathing. In addition, signs of circulatory collapse, such as tachycardia, weak pulse, and low blood pressure are normally present. Many of these clinical manifestations are commonly observed in scorpion envenoming syndrome (Defronzo 1988).

6.23 Increased FFA oxidation can inhibit glycogen synthatase activity
Increased FFA oxidation can inhibit glycogen synthatase activity directly by causing a dissociation of its sub-units (Defronzo 1988).

6.24 Elevated rate of FFA oxidation can reproduce all major intracellular abnormalities
An elevated rate of FFA oxidation can reproduce all major intracellular abnormalities (decreased glucose transport, decreased glycogen synthatase, decreased Pyruvate Dehydrogenase and could account for the defects in glucose oxidation and
storage. Physiological elevations in plasma FFA concentrations cause a stimulation of FFA oxidation, which in turn, inhibits glucose oxidation and storage (Defronzo 1988).

6.25 FFA stimulates gluconeogenesis
An elevated rate of FFA oxidation also has important effects on the hepatic glucose metabolism. In vitro studies have demonstrated that FFA stimulates gluconeogenesis (Defronzo 1988; Pande and Mead 1968). The following sequence might explain the relationship between plasma FFA concentrations, lipid oxidation, and glucose metabolism at the level of the liver:

1. Increased plasma FFA, by mass action, enhance their cellular uptake, which leads to an increase in lipid oxidation that provides the stimulus for activation of the key enzymes involved in the regulation of gluconeogenesis;

2. At the same time, the augmented rate of lipid oxidation provides a continued source of energy (ATP) and substrate to drive gluconeogenesis;

3. In addition, the uptake of circulating gluconeogenic precursors by the liver is elevated. The inhibitory influence of insulin on gluconeogenesis is much more resistant than its restraining action on glycolysis.

With the disturbed carbohydrate metabolism, dissimilation of fat is incomplete, since ‘fats burn in the flame of carbohydrates’ leading to ketosis and this is aggravated by low glycogen content in the liver (Keele and Neil 2004).

6.26 Respiratory Acidosis & Metabolic Acidosis
In addition to respiratory acidosis, metabolic acidosis could also be the basis of acidosis resulting in cardiovascular deficiency and death in envenoming (40). Both experimental dogs and pigs due to scorpion envenoming developed a marked metabolic acidosis. This phenomenon is also a common feature of envenomed human victims that may be present with no apparent organ failure. This finding strongly suggests a decrease in peripheral organ oxygen utilization relative to demand (Ismail 1995; 1993; Ismail et al 1992; Gueron et al 1993; 1992; 1990; 1987; Sofer 1995; Sofer et al 1992; 1996; 1997; Tarasiuk et al 1999; 1997; 1994).

We have demonstrated metabolic acidosis in our experimental animals (Radha Krishna Murthy et al 1988 a).

6. 27 Lactate and peripheral ischemia
Although measurement of Lactate to Pyruvate ratio would have been necessary to be certain of peripheral ischemia as opposed to increased glucose utilization, the presence of decreased HCO₃ and persistent metabolic acidosis in our envenomed animals (Radha Krishna Murthy et al 1988 a) strongly suggests that increased lactate was at least in part due to peripheral ischemia (Ismail 1995; 1993; Ismail et al 1992; Gueron et al 1993; 1992; 1990; 1987; Sofer 1995; Sofer et al 1992; 1996; 1997; Tarasiuk et al 1999; 1997; 1994).

6. 28 Lactate – catecholamine- Respiratory failure- Hypoxia

Production of ketone bodies in scorpion envenoming could be mediated by suppression of endogenous insulin secretion (Radha Krishna Murthy et al 1988 a) due to massive release of catecholamines.


6.29 Insulin administration-reduced FFA levels, disappearance of arrhythmias, conduction defects, ischemia, and infarction – like patterns - normal sinus rhythm
We have reported a reduction in FFA levels, disappearance of different arrhythmias, conduction defects, ischemia, and infarction – like ECG patterns with normal sinus rhythm after insulin administration in experimental envenoming (Radha Krishna Murthy et al 1988 a; 1990) and in scorpion sting victims (Radha Krishna Murthy et al 1991; Yugandhar and Radha Krishna Murthy 1999).

6.30 Insulin counteracts all the deleterious effects of FFA by
(a) Inhibiting the catecholamine-induced lipolysis in the adipose tissue, thus reducing the plasma FFA level,

(b) Facilitating the glucose transport to the myocardium and glucose metabolism through different pathways; an
Insulin administration reversed metabolic changes and other abnormalities due to envenoming. Insulin stimulates activation of glycogen synthetase system. This could be the reason for an increase in glycogen content of cardiac, skeletal muscles and liver of the insulin, alpha blocker + sodium bicarbonate treated animals after envenomation (Keele and Neil 2004; Ganong 1987). Moreover, glycogen availability may be an important independent determinant of cardiac function. Elevated glycogen in heart partially protects against mechanical deterioration in anoxia (Scheuer and Stezoski 1969).

Insulin stimulates glycogen synthesis (Keele and Neil 2004; Ganong 1987). Thus insulin counteracts the effects of catecholamines favoring glucose uptake and inhibition of glucose release from liver. This could be the reason for an increased glycogen content of atria, ventricle, liver and skeletal muscle after insulin administration.

Insulin administration suppresses the release of FFA from adipose tissue and this effect is immediate and even faster than the effect on plasma glucose levels (Keele and Neil 2004; Ganong 1987; Edwin 2006).

Insulin stimulates lipogenesis (Keele and Neil 2004; Ganong 1987). This could be the reason for the sudden reduction of free fatty acid levels and increased triglyceride levels in the venom poisoned animals after administration of insulin. Moreover, infusion of glucose in these animals along with insulin, will suppress fat mobilization by favoring re-esterification.

In our hands, administration of insulin (Radha Krishna Murthy 1988 a) or insulin + alpha blocker (Tolazodine) + Sodium bicarbonate (Radha Krishna Murthy 1990) successfully reversed the metabolic as well as ECG changes.

Insulin + alpha blocker (Tolazodine) + Sodium bicarbonate (Radha Krishna Murthy 1990) produced little more glycogenesis and lipogenesis than insulin. However, alpha blockers are known to stimulate the gastric acid secretion and this in turn could aggravate the existing sub-clinical pancreatitis into fully blown up fulminating acute pancreatitis in scorpion sting victims.

Insulin assists in the recovery of myocardial contractility after ischemic arrest and increases cardiac output. Insulin also assists glucose transport and can accelerate ATP production in ischemic areas. Insulin stimulates cardiac sarcolemmal Na⁺-K⁺ ATPase activity, inhibits Ca²⁺⁺ ATPase activity, and stabilizes lysosomal membranes.

The Na⁺ - K⁺ pump has a key function in the exchange of substances between the cells and its surroundings, in trans-epithelial transport, and in transmission of information. Three isoforms of Na⁺-K⁺ ATPase alpha sub-unit have been identified. The functional implications of having three isoforms of the Na⁺-K⁺ ATPase enzyme are still unknown. The only observation that points towards a special function is that the affinity of the alpha 2 isoforms for Na⁺ from muscles and adipocytes is increased by insulin (Skou 1992).

The activity of Na⁺ - K⁺ pump in the intact membrane is determined by a combined effect of the cyto-plasmic and extra cellular Na⁺ to K⁺ concentration ratios and other factors. Insulin, epinephrine, and nor-epinephrine have a stimulating effect on the pump. The alterations in the cardiac sarcolemmal and red blood cell Na⁺-K⁺ ATPase activities and reduction in insulin secretion are shown in scorpion envenoming.

We concur with Gueron et al that the management of human severe scorpion envenomation should be directed toward neutralizing the over stimulated autonomic nervous system (Gueron et al 1992; 1990; 1987; 1980). All patients with systemic manifestations, such as severe hypertension, Hypovolemia, pulmonary oedema or patients in shock should be admitted to a critical care unit under close electrocardiographic, Echocardiographic and invasive haemodynamic monitoring. These facilities are not available in many of the developing countries where scorpion envenoming is a rural emergency. We feel that the administration of insulin-glucose infusion is directed toward neutralizing the over stimulated autonomic nervous system. The administration of insulin-glucose infusion will also regulate severe hypertension, Hypovolemia, pulmonary oedema or patients in shock.

Recently, both in vivo and in vitro studies have shown that resolution of oedema from the air spaces of the lungs depended on an active sodium transport pump that removed oedema fluid, even in the face of a rising alveolar oedema protein concentration in excess of plasma protein concentrations (Comellas et al 2010).

**Conclusion**

The initial transient hypertension followed by hypotension, cardiovascular manifestations, metabolic disturbances, electrocardiographic changes, and adult respiratory distress syndrome
and many other clinical manifestations produced by scorpion venom toxicity could be due to:

1. Action of catecholamines causing increased myocardial oxygen consumption due to positive and chronotropic effects, coronary vasoconstriction, peripheral vasoconstriction and increased after load, Lipolysis resulting in increased FFA;

2. Action of angiotensin II resulting in coronary and peripheral vasoconstriction, potentiation of catecholamine mediated effects,

3. Insulin deficiency

4. Increased FFA resulting increased myocardial oxygen consumption; and

5. Arrhythmogenic effect of catecholamines, angiotensin II and free fatty acids.

Insulin administration resulted in glycogenesis, lipogenesis, stopped arrhythmias and reversed the ECG changes to sinus rhythm.

7. Administration of insulin

Administration of insulin under these circumstances should counter-act the metabolic effects of catecholamines, stimulate lipogenesis, glycogenesis, reverse the metabolic and electrocardiographic changes in acute myocarditis induced by Indian red scorpion (Buthus tamulus) venom in the experimental dogs.

7.1 The dose of insulin in scorpion sting victims

The dose of insulin is 0.3 Units of regular insulin per gram of glucose, and glucose 0.1 g Kg⁻¹ per hour. Blood glucose, serum electrolytes, electrocardiogram, and arterial blood gases should be investigated on admission. In addition to regular clinical observations, estimations of blood glucose should be carried out two hourly and of serum electrolytes 12-hourly. Glucose levels should be maintained between 130 and 180 mg dl⁻¹ of blood (Radha Krishna Murthy et al 1991; 1988 a; 1990; Yugandhar and Radha Krishna Murthy 1999).

Insulin administration produced a reduction in FFA, an increase in triglyceride levels and increased tissue glycogen content in cardiac and skeletal muscle and that of liver (Radha Krishna Murthy et al 1991; 1988 a; 1990; 2004; Radha Krishna Murthy and Haghnavazari 1999; Radha Krishna Murthy and Abbas Zare 1999; 2001; 2002).

7.2 Effect of insulin administration on “hypertension”


7.3 Effect of insulin administration on “hypotension”


7.4 The following drugs are either not useful or contra-indicated in scorpion envenoming syndrome

(a) Cardiac glycosides;
(b) Atropine;
(c) Diuretics;
(d) Corticosteroids;
(e) Beta-blockers;
(f) Emetine hydrochloride (with local xylocaine injection);
(g) Adrenaline (with local xylocaine injection);
(h) Angiotensin Converting Enzyme (ACE) inhibitors.

7.5 (a) Cardiac glycosides

The Cardiac glycosides are not effective in pulmonary oedema in the presence of sinus Tachycardia and normal cardiac size. The Cardiac glycosides are known to act by inhibiting Na⁺ - K⁺ ATPase activity. The scorpion venom produces cardiac sarcolemmal defects displayed as inhibition of Na⁺ - K⁺ ATPase activity.

(b) Atropine

Atropine should not be given routinely. This has been the common practice because of heavy perspiration and increased salivation.

Atropine may intensify the tachycardia and sympathetic effects due to the venom after blocking the cholinergic effects.

Atropine potentiates hypertensive effect.

Moreover, atropine is a Parasympatholytic drug and inhibits insulin secretion from endocrine pancreas. Increase in duration as well as severity of clinical signs, including myocardial injury were observed in scorpion sting victims treated with atropine compared to scorpion sting victims who did not receive atropine.

Atropine increases the severity of pulmonary oedema induced by scorpion toxin.
7.7 © Diuretics
Diuretics are contraindicated, owing to their dehydrating effect, alteration in blood viscosity and stimulation of rennin-angiotensin secretion.

7.7 (d) Corticosteroids
Glucocorticoids are contraindicated because they are catabolic hormones and anti – insulin in action. They stimulate the rennin-angiotensin system. Moreover, glucocorticoids act like, “asbestos suit against fire but they themselves do not extinguish the fire”, and in the absence of specific drugs, glucocorticoids are likely to spread the inflammation. Besides, glucocorticoids are contraindicated in non-cardiogenic pulmonary oedema.

(e) Angiotensin Converting Enzyme (ACE) inhibitors
Captopril is an angiotensin – converting enzyme inhibitor that inhibits the conversion of the relatively inactive angiotensin I to the active angiotensin II. It also inhibits the degradation of bradykinin and potentiates its hypotensive action. It is used in the management of hypertension, congestive heart failure and hypertensive emergencies. Captopril and other angiotensin-converting enzyme inhibitors are inferior to other vasodilators in the treatment of heart failure. Ismail, however, cautioned against the use of Captopril since the drug inhibits kininase enzyme and thus would lead to the accumulation of bradykinin, the neuro humoral agent, incriminated experimentally for the pulmonary oedema of the scorpion envenoming syndrome (11, 17, 18).

(f) Adrenaline (with local xylocaine injection)
Scorpion venom is known to an autonomic storm releasing massive quantities of catecholamine hence adrenaline (with local xylocaine injection) is contraindicated.

Summary: Scorpion envenoming syndrome is due to autonomic storm releasing massive quantities of catecholamines, angiotensin II, glucagon, Cortisol and either suppressed insulin secretion, or hyper-insulinemia/ insulin resistance (failure of the actions of internally secreted insulin). The metabolic actions of all these hormones cause suppressed insulin secretion, or hyper-insulinemia/ insulin resistance resulting in hyperglycemia and sudden increase in Free Fatty Acids. Severe scorpion envenoming syndrome is a syndrome of fuel – energy deficits and an inability of the vital organs to utilize the existing metabolic substrates. This ultimately may result in Multi-System-Organ Failure (MSOF) and death. Sudden increase in Free Fatty Acids cause sarcolemmal defects reflected in alterations in cardiac sarcolemmal ATPase activities of Na\(^+\)-K\(^+\) ATPase, Mg\(^{++}\) ATPase and Ca\(^{++}\) ATPase activities. These sarcolemmal defects may be responsible for the subsequent pathological conditions.

Insulin-glucose infusion resulted in glycogenesis, lipogenesis, stopped arrhythmias and reversed the ECG changes to sinus rhythm in the scorpion envenomed animals and in the scorpion sting victims. Insulin administration following scorpion envenoming reversed the ECG and metabolic changes in the experimental animals as well as in scorpion sting victims.

The administration of insulin-glucose infusion should be recommended as the first choice therapy given as soon as possible, immediately after hospitalization in intensive care units to envenomed scorpion sting victims whose clinical picture is dominated by pulmonary oedema, cardiovascular, and many other clinical manifestations. 

Research Highlight
Death due to poisonous scorpion stings is a common event in all the developing countries including India. All the poisonous scorpions causing death belong to Buthidae family. The signs and symptoms in the scorpion sting victims due to scorpion envenoming syndrome are common all over the world. Scorpion envenoming syndrome results in acute myocarditis, arrhythmias, conduction defects, ischemia, infarction like patterns, acute pancreatitis, disseminated intravascular coagulation, cardiogenic and non-cardiogenic pulmonary edema (Adult Respiratory Distress Syndrome), many other clinical manifestations and death. Scorpion envenoming syndrome causes massive release of counter-regulatory hormones (Adrenaline, Nor-Adrenaline, Glucagon, glucocorticoids, thyroid hormones)-suppressed insulin secretion/ hyperinsulinemia causing hyperglycemia, ipolysis–massive production of free fatty acid levels.

Sudden increase in FFA is toxic and could be responsible for the above mentioned patho-physiological conditions. Administration of Insulin-glucose infusion reversed all the above mentioned patho-physiological conditions and brought back all the clinical manifestation to the normal in all our experimental animals and in scorpion sting victims. Exogenously administered Insulin acts against the metabolic actions of all the counter-regulatory hormones. Insulin is cheap, available in all parts of the world including all the developing countries.
Administration of insulin infusion is easy and it can be easily switched “on” or “off”. Insulin is a “new life saving agent” in many of the emergency clinical conditions.

It is concluded that the venom from the scorpions of Family Buthidae produce autonomic storm, massive release of epinephrine, nor-epinephrine (catecholamines), an elevation in angiotensin levels, an increase in counter-regulatory hormones and suppressed insulin secretion or insulin resistance, cause metabolic and cardio-respiratory changes-The metabolic, cardio-respiratory changes, ECG changes, pulmonary edema, ARDS and many other clinical manifestations are reversed by administration of insulin.

Recommendations

The administration of insulin-glucose infusion should be recommended as the first choice therapy given as soon as possible, immediately after hospitalization in intensive care units to envenomed scorpion sting victims whose clinical picture is dominated by pulmonary oedema, cardiovascular, and many other clinical manifestations.

Author’s Contribution and Competing Interests

The author declares that he has no conflict of interests. The author declares that he complies with the Principles of Ethical Publishing in The Journal for Endocrinology and Metabolism

Acknowledgement

The author thanks Dr. M. Santhiramudu and Dr. M. Madhavi Latha for their encouragement.

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