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ECG ABNORMALITIES INDUCED BY SCORPION VENOM ADMINISTRATION: THE EFFECT AND THE MECHANISM

By

MOHAMMED A. A. OMRAN* Z. I. NABIL* and H. A. IBRAHIM**
* Zoology Department, Faculty of Science, Suez Canal University, Ismailia, Egypt
** Zoology Department, Faculty of Science, Mansoura University, Mansoura, Egypt

شذوذ رسم القلب الكهربي الناشئ عن سم العقرب
التأثير والآلية

محمد علاء عبد الله عمران و زهور إبراهيم نبيل
حمدي عبد الحميد إبراهيم

أسفر الحقن بالسم المنقي للعقرب ليوريس كونيكوستريياتس (١٠٠ ، ٢٠٠ ، ٤٠٠ ميكروجرام/كجم) في العضلة الخلفية لأرجل الفئران عن تغييرات شديدة في النشاط الكهربي لعضلة القلب . هذا وقد سجلت معظم هذه الحالات الشاذة بعد الحقن بالجرعتين الأعلى (٢٠٠ ، ٤٠٠ ميكروجرام/كجم) خلال وقت التجربة وهو ٤ ساعات . وجدير بالذكر أن هذه الحالات التي لوحظت في أثناء الدراسة كانت إما عدم إتساق أو تغيير في التوصيل .

وقد تمثلت الحالة الأولى في عدم إتساقات جيبية ونشوء بؤرات وكان التأثير السام - في الحالة الثانية - على الجهاز الموصل في القلب قد سجل على هيئة درجات مختلفة من السده القلبية .

هذا وقد تم حقن عقار البروبرانولول (عقار ضد عدم الاتساق) في مجموعة أخرى من الحيوانات (١ مجم/كجم في التجويف البريتوني) قبل ٢٠ دقيقة من حقن السم بأكبر جرعة وذلك لتوضيح دور الكاتيكولامينات في إحداث مثل هذه الحالات الشاذة . ولمزيد من دراسة ميكانيكية التأثير السام على القلب فقد تمت دراسة التأثيرات الهستوباثولوجية للسم على عضلة القلب .

وقد كشفت نتائج هذا البحث عن أن السم له تأثيرات شديدة على النشاط الفسيولوجي الكهربي لعضلة القلب بسبب التعرض المتزايد للكاتيكولامينات وفي نفس الوقت فإن السم ومكوناته - لهم تأثير هستوباثولوجي مباشر بالإضافة إلى التأثير المشابه للتأثير السمبثاوي . من ناحية أخرى فإن معالجة القلب بالبروبرانولول قد أنهى حالات الشذوذ إلى حد كبير . هذا وقد بدا واضحاً أن التأثيرات الهستوباثولوجية المباشرة لهذا السم قد تتناول الجهاز الموصل للقلب مما يؤدي إلى حدوث حالات السده القلبية المميتة - والتي تم تسجيلها في هذه الدراسة .

Key Words: Scorpion venom; ECG; Anti arrhythmic drug; Histopathology.

ABSTRACT

Intramuscular administration of scorpion *(Leiurus quinquestriatus)* lyophilized venom (100, 200 and 400 mg/kg) into rats produced drastic changes in the electrical activity of the cardiac muscle. These abnormalities were most significant after the injection of higher doses (200 and 400 mg/kg). Most of the ECG changes recorded in this study were in rhythmicity and conductivity. The

changes in rhythmicity were in the form of sinus abnormalities and ectopic beats, while the toxic effects on the conduction system were recorded as varying degrees of heart block. Propranolol (an antiarrhythmic drug) was injected into another group of animals (1 mg/kg, i.p.) 20 min. prior to venom administration (400 mg/kg) to get a clear evidence about the role of catecholamines in producing such abnormalities.

To study further the mechanism of the cardiotoxic effect of the venom, another technique was performed to examine the histopathological effects of the venom on the cardiac muscle. The results of this study revealed that the venom had a drastic effect on the electrophysiological responses of the cardiac muscle due to their exposure to an excessive venom-dependent released catecholamines. At the same time, the venom and its components have a direct histopathological effect on the heart in addition to their sympathomimetic action. On the other hand, propranolol pretreatment abolishes these abnormalities to a great extent. It is important to emphasize also, that the direct histopathological effect of this poison may affect the specialized fibers forming the conduction system of the heart and thereby induce the fatal recorded heart blocks.

INTRODUCTION

Although envenomation by poisonous animals, including scorpions, has been a scourge of humanity since antiquity, only recently have we learned about the chemical nature and physiological effects of the toxins present in the venoms. In fact, interest in scorpion venoms has stemmed largely from their importance as health hazards to humans, especially in tropical and subtropical countries. The neurotoxins in scorpion venoms are proteins and represent some of the most powerful poisons known [1]. Cardiotoxins are one of the active substances identified in the scorpion venom components [2].

Scorpion venom evokes potent cardiovascular responses in humans and in experimental animals. The similarity of these responses "clinical and pathological" to catecholamine overdosage implies that the clinical sympatomatology is related to direct adrenergic and sympathetic nervous system stimulation by the venom [3]. The same authors found that blood epinephrine levels increased in dogs during the first 30 min. after injection with venom. Moreover, elevated blood epinephrine in patients following scorpion stings has been reported. The maximal increase occurred within a few hours after the sting and persisted for 6 hours, followed by a gradual decline.

On the basis of extensive experimental evidence, it is well established that venoms from *Leiurus quinquestriatus* and other North Africa scorpions lead to a release of catecholamines from the sympathetic nervous system and stimulate the cardiac adrenergic endings [4-6].

Detailed information about the alterations of the electrophysiological activities of the cardiac muscles due to envenomation by most of scorpion species have not previously been reported exclusively. Some authors, however, have reported that the injection of small doses of a purified scorpion *(Tityus serrulatus)* toxin into anesthetized rats evoked sinus tachycardia, whereas larger doses produced sinus bradycardia, sinoatrial and atrioventricular block, ventricular ectopic beats and idioventricular rhythm [4, 7]. Ismail *et al.* [8] demonstrated that injection of *Buthus minax* venom into rabbits caused either bradycardia or tachycardia. Among the many factors that can precipitate or exacerbate arrhythmias are excessive catecholamine exposure, autonomic influences, drug toxicity and overstretching of the cardiac fibers [9].

Since electrophysiological alterations are a principle manifestation of cardiotoxicity, electrocardiographic monitoring is mandate in preclinical drug testing. This permits early detection of the electrophysiologic precursors of cardiotoxicity and monitoring their continued course [10].

The present study was undertaken, therefore, to get detailed information about the possible ECG abnormalities evoked as a result of scorpion venom administration and the mechanism of such cardiotoxic effect by using pharmacological and histopathological tools.

MATERIALS AND METHODS

Scorpions were collected from South Sinai peninsula, Egypt, during the summer season. They were kept separately in containers containing sand, with controlled temperature and humidity. They were fed on cockroaches and water was given once every ten days. The crude venom was obtained by electrical stimulation of the distal intersegmental membrane of the metasoma of the scorpion. The venom was suspended in distilled water, centrifuged and the supernatant was lyophilized and was kept in a dessicator over calcium chloride. The lyophilized venom was reconstituted in saline solution to the needed concentrations just before use.

Male Sprague-Dawley rats (350-400 gm) were used in this study. Rats were randomly assigned to five groups (5 animals/group). The first group was treated with saline and used as a control group. Animals of the 2nd, 3rd and 4th groups were injected intramuscularly with the venom at the dose levels of 100, 200 and 400 mg/kg respectively to study the cardiotoxic effect of the venom. Rats of the 5th group were treated intraperitoneally with propranolol (1 mg/kg) 20 min. before venom administration (400 mg/kg). Rats of all ages were killed by an overdose of ether four hours following venom treatment. Samples of heart tissues were taken for gross necroscopy studies. Tissues were prepared by routine histological procedures and stained with hematoxyline and eosin. Microscopic examinations were made for control and treated rats.

For electrocardiographic recordings, rats were anesthetized with urethane (1.25 g/kg). Animals were given a single intramuscular injections of the lyophilized venom at dose levels of 100, 200 or 400 mg/kg prior to the recordings. The ECG was recorded according to the method described by Buchman *et al.* [11] using bipolar electrodes "lead II". Electrodes were connected to an ECG coupler (Beckman Type 9855) for recording ECG parameters. This coupler was attached to a Beckman R511A four-channel recorder

(Beckman Instruments NJ, USA). After insertion of the electrodes, the animals were left for a while before recordings were made. ECG was recorded for 10 min. to serve as a control prior to treatment. Data were collected for 4 hours following venom administration.

RESULTS

Observations on the ECG recordings obtained from the control group showed no kind of abnormality during the entire time course. This shows that the stress and the experimental conditions had no adverse effect on the animals. In contrast, several cases of ECG disorder were recorded as a result of the intramuscular injection of the scorpion venom, especially after the administration of the two highest doses (200 & 400 mg/kg). Most of these abnormalities were in rhythmicity (sinus arhythmias and ectopic beats; Plate I). and conductivity (several degrees of heart block; Plate II).

- Sinus arrhythmias (Plate I A, B & C)

The most common disorders observed as a result of injection of scorpion venom were sinus arrhythmias. Three types of sinus arhythmias were recorded during the course of 4 hours experiment.

Sinus tachycardia was recorded in the two treated groups (5 cases each). At 200 mg/kg dose tachycardia was noted all over the time course starting 15 min. after venom injection. On the other hand, administration of 400 mg/kg dose evoked sinus tachycardia during the first hour and at the end of the experiment. As demonstrated in Plate I A, the tachycardia recorded in the ECG traces was accompanied by normal waves and sequences, but the rate was faster than in normal controls.

The second disorder was *sinus bradycardia.* This was observed more often after the injection of the highest dose (3 cases) starting after 1 hour to 2 hours following venom treatment. It was also recorded in one case 30 min. after the injection of the 200 mg/kg dose. The bradycardia recorded in the ECG traces was accompanied by normal waves and sequences, but the rate was slower than the control rate (Plate I B).

The last type of arrhythmias, *wandering pacemaker* was developed in 2 and 4 cases after the application of 200 and 400 mg/kg doses respectively. It is shown in Plate I C and characterized by alternating "normal and inverted" deflections of the P-waves. This implies alterations of the direction of the excitation waves from the normal pacemaker to other foci in the conductive system.

- Ectopic rhythm (Plate 1 D)

Ectopic beats (premature contractions or extrasystoles) are types of disorder that are accompanied by the generation of a cardiac impulse from an ectopic focus in the heart. Abnormal impulses were discharged at irregular intervals during the cardiac rhythm. In this investigation *atrial fibrillation* was recorded in 3 instances in each treatment group. Very rapid irregular fine or coarse, chaotic contractions of the musculature of the atria were observed (Plate I D) and the P-waves were replaced by "f" or fibrillatory waves at a very high rate.

It is important to mention that the pretreatment of the envenomated rats with the antiarrhythmic drug propranolol (1 mg/kg) almost prevented the appearance of most of the cardiac disorders described above.

Conductivity changes (Heart block, H.B.)

Atrioventricular block of first, second and third degrees was observed in this investigation. *First degree heart block* was recorded in one case 2 hours after injection of the 200 mg/kg dose and in 3 cases 90 minutes following the administration of the highest dose of scorpion venom. In this type of heart block conductivity was delayed along the atrioventricular node, or bundle of His as illustrated in Plate II A, and the Wenckbach phenomenon can be observed.

A *second degree heart block* is shown in Plate II B & C. This abnormality was observed only following treatment with a 400 mg/kg dose (2 cases) where the first degree H.B. developed to a second degree H.B. after 3 hours. In this condition one atrial impulse is conducted through AVN to the ventricles and the following one is missing.

The last type of conduction problem was a *third degree heart block* or *complete heart block* (Plate II D). This disorder was induced only by the administration of the highest venom dose (3 cases). The atrial and ventricular contractions were independent from each other, where no impulse was conducted from atria to ventricles due to complete block of AVN Thus P-waves occurred regularly according to the normal SAN and QRS complexes were also regular but at a slower rate according to the idioventricular rhythm initiated by the ventricles.

It is worth noting that H.B. almost occurred among animals exhibiting bradycardia. Moreover, both second and third degree H.B. were preceded by first degree H.B. in all cases. Incidences of complete heart block were followed by the death of some of the experimental animals.

Histopathological investigations

Examination of different heart samples obtained from the control group showed no pathological changes in the tissues under investigation. On the other hand, significant findings were observed in the cardiac muscles of the venom-administered rats, especially those injected with the highest dose (400 mg/kg).

As shown in Plate III A, the heart muscle of the control rats is composed of a group of cardiac muscle fibers running parallel to each other and interpersed with connective tissues strands. These fibers are connected together, forming a network-like structure. Each muscle fiber possesses a number of ovoid nuclei lying in a central position. Striation is another common feature of these cardiac muscle fibers.

The most prominent changes in the cardiac muscle fibers of venom-injected rats consisted of degenerative changes, focal necrosis, interstitial edema and cellularity, with maximum involvement of the papillary muscles as well as the subendocardial areas. In addition, more circumscribed areas of myocardial hemorrhage appeared as lakes of extravasted erythrocytes between the muscle fibers. In some parts of the

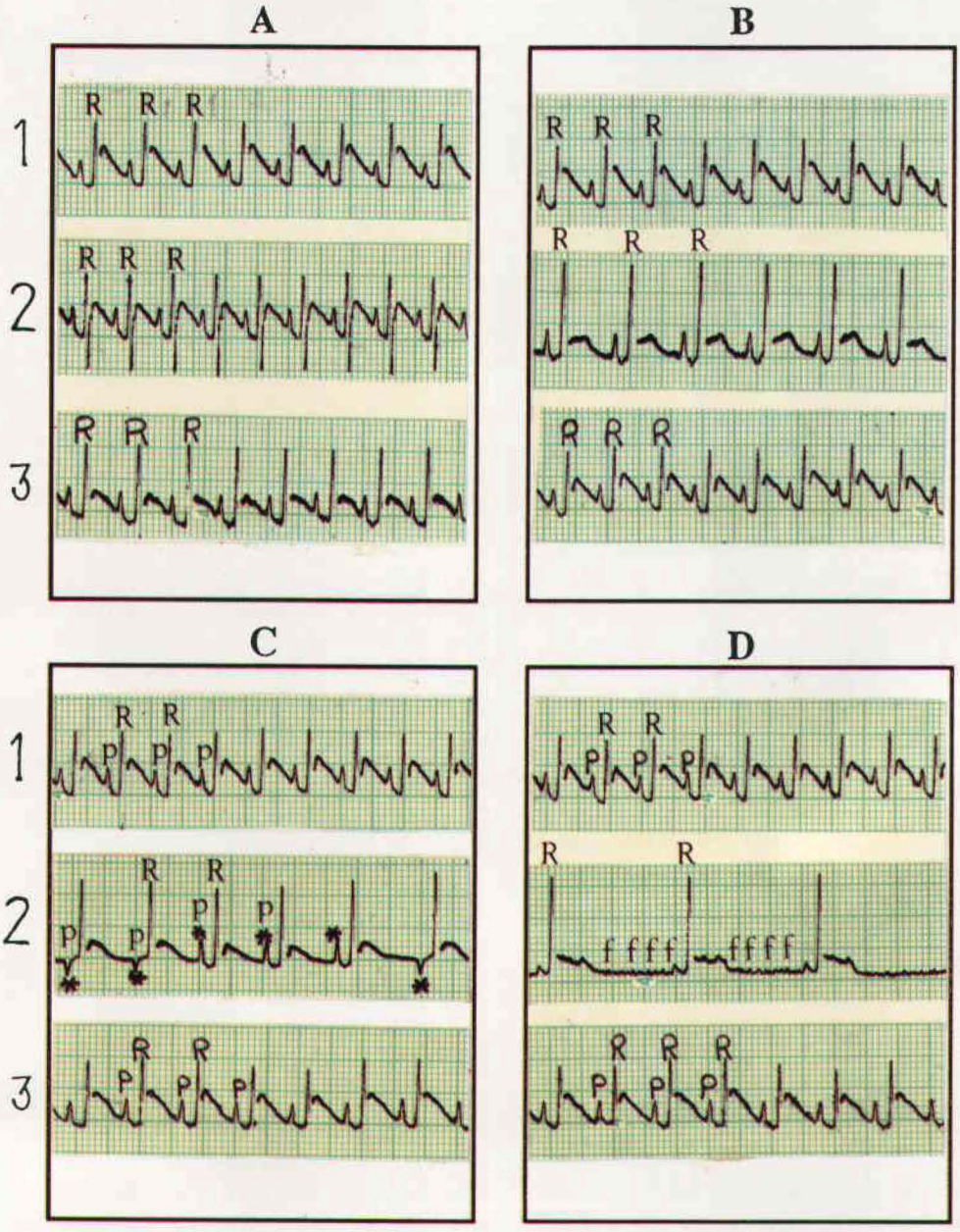

Plate (I)

Cardiac arrhythmias and ectopic rhythm recorded as a result of intramuscular injection of scorpion venom (200 and 400 µg/kg).

A = Sinus tachycardia, B = Sinus bradycardia, C = Wandering pace maker (stars) and D = Atrial fibrillation (f waves). Paper speed = 50 mm/sec.

1- Control tracing.

2- Abnormality tracing.

3- Recovery tracing.

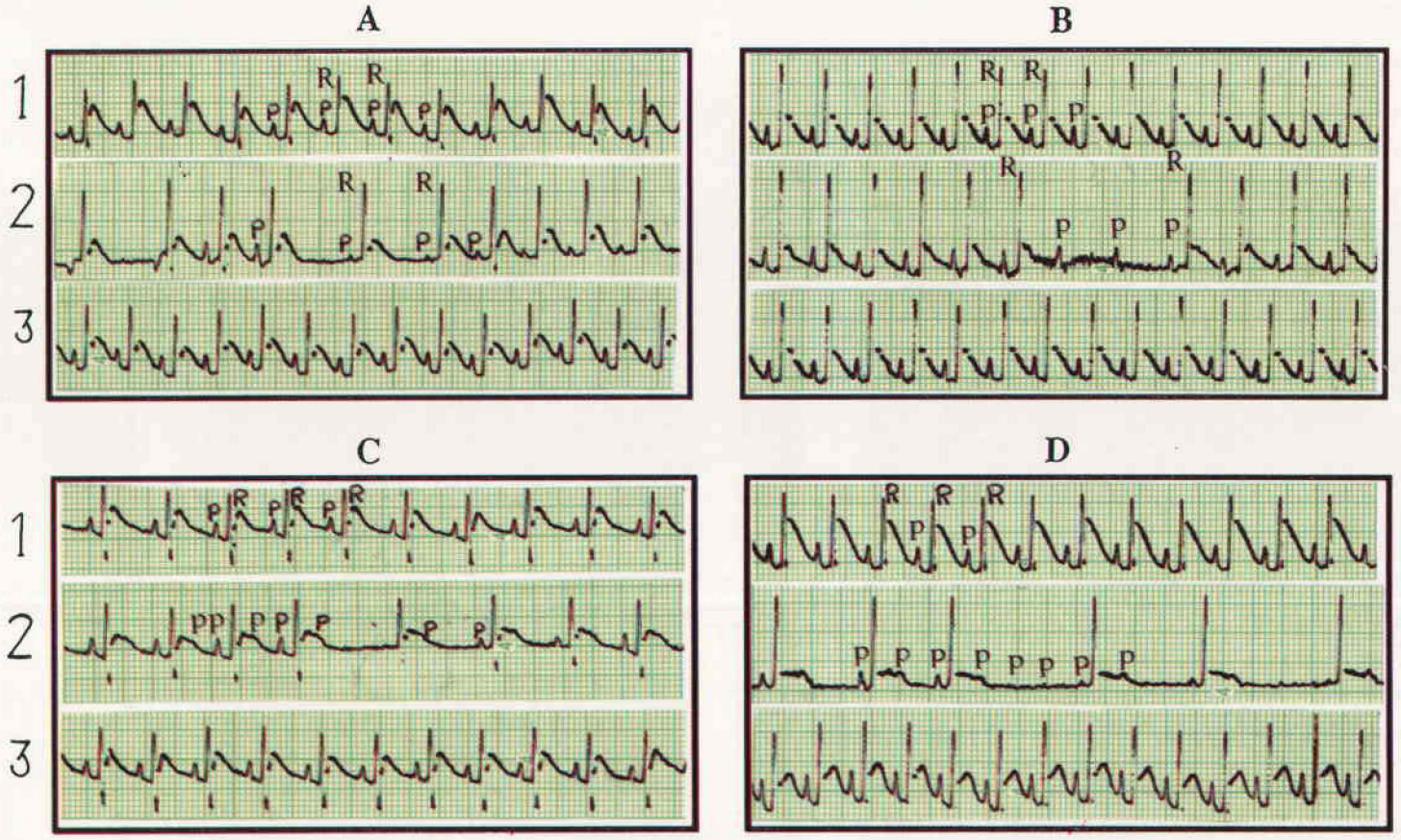

Plate (II)

Different degrees of atrioventricular block recorded as a result of intramuscular injection of scorpion venom (200 and 400 µg/kg).

A = First degree heart block (Wenckbach phenomenon), B and C = Second degree heart block and D = Third degree heart block (complete heart block). Paper speed = 50 mm/sec.

1- Control tracing.

2- Abnormality tracing.

3- Recovery tracing.

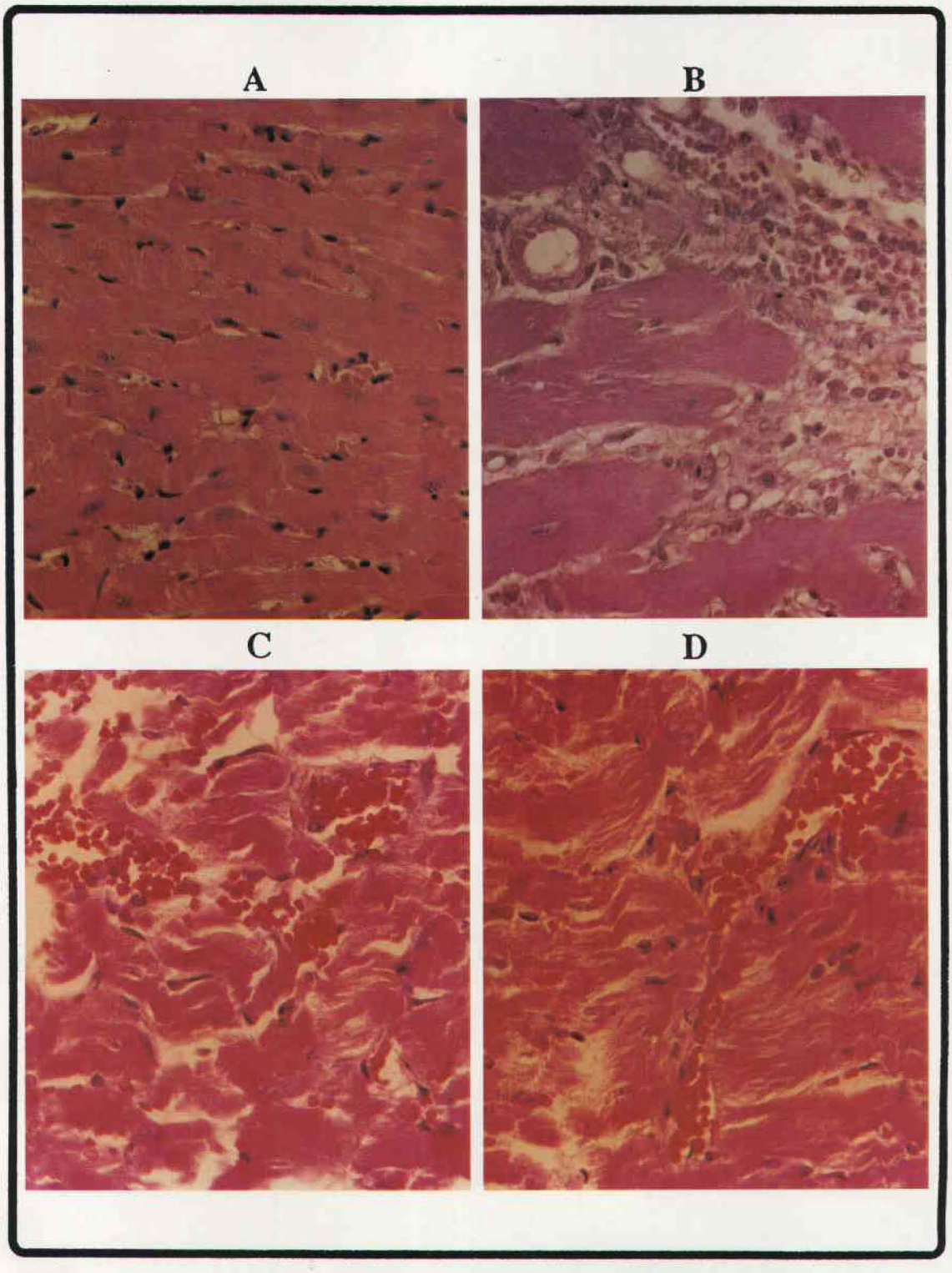

Plate (III)

A photomicrograph showing histopathological changes as a result of intramuscular injection of scorpion venom (400 μg/kg).

A = Normal cardiac muscle fibers of control rats (H. & E., X 400).

B, C and D = Cardiac muscle fibers of envenomated rats. (H. & E., X 400).

myocardium, the myofibrils lost their normal organization and showed areas of severe myolytic necrosis. Instead of being oval or elliptical and having a finely granulated chromatin, the nuclei of the necrotic muscle fibers became pyknotic and appeared spindle or fusiform in shape, darkly stained and structureless. Antichkow-type cells were also seen (Plate III B, C & D). 50% of the animals pretreated with propranolol before venom administration showed no significant histopathological changes in their cardiac muscles.

DISCUSSION

In some areas of the world such as the Middle East, North and South Africa as well as India, scorpion stings produce severe morbidity and occasionally mortality [12]. Although the stings of scorpions occur frequently in such areas, there are relatively few investigations in the medical literature dealing with the clinical aspects of these stings [13]. On the other hand, in the last decade some authors have described the pathophysiology of scorpion poisoning, as well as the clinical findings and the treatment. They concluded that scorpion venom acts on the peripheral nervous system, with the release of chemical mediators (e.g. acytelcholine and catecholamines), and that part of the effect is reflex in nature and secondary to stimulation of vagal afferent fibers [6, 14, 15]. Moreover it was reported that the toxicity of venoms from scorpions of different species shows great variations [16].

Chemicals and poisons can selectively affect the heart or the vasculature. The effect may last only during the exposure period, and its magnitude is usually dose related [17]. The detection of cardiovascular toxicity requires complete ECG monitoring which is an indicator of cardiac function [18].

In this study the most important manifestations of cardiac effects arose from the alterations of electrical or contractile properties of the heart. Scorpion venom may influence the cardiac muscles by affecting their chronotropic, dromotropic, bathmotropic and/or inotropic properties.

Acute administration of scorpion *(Leiurus quinquestriatus)* venom (200 & 400 mg/kg) evoked several cases of arrhythmias and conductivity abnormalities. The effects were dose-dependent regarding to the severity and frequency. It is well known that an arrhythmia can be caused by an alteration in the cardiac impulse rate, in the site of origin of the cadiac impulse, or in the velocity of cardiac impulse conduction.

Injection of the tested venom at the dose level of 200 mg/kg dose produced sinus tachycardia in all treated animals, whereas administration of the 400 mg/kg dose evoked tachycardia followed by bradycardia then tachycardia at the end of the experiment. Freire-Maia and Diniz [4] reported that injection of small doses of purified scorpion *(Tityus serrulatus)* toxin into anesthetized rats induced sinus tachycadia, while larger doses produced sinus bradycardia. They concluded that the positive chronotropic effect was caused by activation of β-adrenergic receptors in the heart, by catecholamines released by the toxin; and that the negative chronotropic effect was due to the release of acetylcholine by the action of the toxins on vagal ganglia and postganglionic nerve endings in the heart. This assumption concerning sinus tachycardia is in agreement with our own findings since injection of propranolol prevented the appearance of this effect. We believe that this stimulatory action of the venom is the predominant effect, and the bradycardia recorded after the administration of the high dose is due to a reflex action increasing the vagal tone to overcome and control the hypertension and the positive chronotropic and inotropic effect observed at that time [6, 19]. This postulation is supported by the appearance of sinus tachycardia accompanied with hypertension following bradycardia in the case of high dose treatment.

Another type of arrhythmia, wandering pacemaker, developed after administration of both doses of venom. In this case, there was an alteration of the direction of the excitation waves from the normal pacemaker and another focus in the conductive system. This might also be due to the excitatory effect of the venom components and/or the effect of the increased circulating catecholamines on the cardiac fibers. This is because propranolol pretreatment prevented the appearance of some of these effects but not all of them. It is important to emphasize that this type of arrhythmia has not been recorded before as a result of scorpion envenomation.

Atrial fibrillation has been recorded by some investigators [20, 21] after scorpion venom application. They concluded that the different types of recorded arrhythmia, leading to fibrillation, were due to the involvement of intracardiac receptors, particularly β-adrenergic receptors. This was confirmed by our results, in which the administration of the β - blocking agent prevented this kind of abnormality.

Atrioventricular block with varying degrees, was observed in the ECG recordings obtained in this work. In their work on scorpion *(Leiurus quinquestriatus* and *Tityus serrulatus)* venoms, Freire-Maia *et al.* [7] and Braun *et al.* [22], noticed the appearance of AV-block. Cantor *et al.* [23] concluded that the presence of bradyarrhythmia, with varying degrees of AV-block in some envenomated victims was consistent with the parasympathomimetric action of the yellow scorpion venom. They added that the immediate and complete response to atropine, followed by a normal ECG, supports this assumption. We believe that another explanation of these manifestations might be the toxic damage and the histopathological effects occurred to the cardiac conduction system, as mentioned before. Moreover, although administration of atropine prevented the appearance of bradycardia in some cases (unpublished data), it did not abolish the recorded AV-block in all cases.

The object of the examination of the histological configuration of the heart of the envenomated rats, was to assess whether the pathophysiological responses are associated with the morphological changes of this organ, or whether adrenergic blocking agents influence these changes. Most of the myocardiac lesions observed in this study resembled those reported as a rsult of catecholamines overdosage [24, 25]. They consisted of degenerative muscle fiber changes, focal necrosis, interstitial edema, hemorrhage and cellularity with maximal involvement of the papillary muscles and subendocardial areas. Similar anatomical changes have been induced experimentally in different animals injected with different scorpion venoms [26 - 28]. The presumption of sympathomimetic over-stimulation as the primary cause of

myocardiac injury was supported by its diminution following the use of adrenergic blocking agents [26, 29].

In conclusion, it can be postulated that the histopathological effects of scorpion *(Leiurus quinquestriatus).* venom on rat cardiac muscle are probably related to the release of huge amounts of catecholamines following venom injection. Moreover, a possible direct effect of the venom components on the cardiac fibers, and especially on the conduction system, is very evident.

The histological changes reported in this study were correlated with the ECG data, indicating a typical myocardial infarct pattern. Furthermore, the impression gained from the results of these experiments was that, by using beta blocking agents, prevention of myocardial damage may be achieved in some cases.

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