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Original paper

THE USE OF SEROTHERAPHY TO REVERSE ECG and CARDIAC ENZYME CHANGES CAUSED BY SCORPION *Mesobuthus tamulus concanesis*, Pocock ENVENOMING

K. RADHA KRISHNA MURTHY[1] ✉ , M. ABBAS ZARE[1] , L. HAGHNAZARI[1]

1 Department of Physiology, Seth G.S. Medical College & K.E.M. Hospital, Parel, Mumbai 400 012, India.

ABSTRACT: Acute myocardiopathy in experimental dogs and rabbits was induced by subcutaneous (SQ) injection of 3.5 mg/kg of scorpion venom from *Mesobuthus tamulus concanesis*, Pocock. An increase in circulating lactic dehydrogenase (LDH), serum glutamic oxalacetic transaminase (SGOT), creatine kinase-MB isoenzyme (CK-MB), serum glutamine pyrovate transaminase (SGPT) and alpha hydroxy butyrate dehydrogenase (HBDH) enzyme levels was observed in dogs 60 min after venom injection, and a further rise was observed 120 min after venom injection. The administration of the species-specific scorpion antivenom (SAV) at different time intervals after venom injection resulted in reversal of electrocardiographic changes and a reduction in cardiac enzyme levels. The administration of SAV to scorpion envenomed alloxan-pretreated animals did not cause clinical or biochemical improvement. On the other hand, administering insulin to envenomed only animals or envenomed alloxan-pretreated animals resulted in a biochemical and clinical improvement, as well as in a reduction of the cardiac enzyme levels. Insulin administration in scorpion envenoming syndrome is essentially a metabolic support to control the adverse effects triggered by catecholamines and other counter-regulatory hormones.

☑ **KEY WORDS:** *Mesobuthus tamulus concanesis,* electrocardiography, glutamicoxalacetate transaminase, glutamine pyruvate transaminase, lactate dehydrogenase, creatine kinase - MB, alpha hydroxy butyrate dehydrogenase.

INTRODUCTION

Scorpion stings are responsible for a number of deaths in infants, children, and adults in developing countries all over the world **(8,11,14,15,31,39,40)**. Non-specific electrocardiographic (ECG) changes are characteristic of scorpion myocardiopathy **(7,22,25,26,28-30)**. Myocardial damage was indicated by elevated enzymatic levels of succinate dehydrogenase, serum glutamic oxalacetic transaminase (SGPT)**,** creatine phosphokinase (CPK), MB isoenzyme (CK-MB) creatine phosphokinase (CPK) and CK-MB/CPK ratio **(38)**, lactic dehydrogenases (LH), LDH1 specific for heart disease, and the ratio of LDH1 to LDH **(24),** electrocardiographic, echocardiographic, radionuclide, and ventriculography studies **(1,10,15,16,20,34,37,38,41).**

Scorpion envenoming causes an autonomic storm resulting in a massive release of catecholamines **(11,38)**, counter-regulatory hormones (glucagon and cortisol) **(33)**, angiotensin II **(27)**, and a reduced insulin secretion **(23,25,27-29)**. The administration of insulin reversed the electrocardiographic and metabolic changes induced by scorpion envenoming **(28,30)**, as well as the haemodynamic changes and pulmonary oedema in children and adults stung by venomous scorpion (Family Buthidae) **(30,40,41,43)**. Additionally, insulin administration to the patients with adult respiratory distress syndrome (ARDS) following septic shock resulted in a normal biochemical profile, radiological clearance of the lungs, and clinical improvement **(31)**.

Serotherapy for scorpion envenoming syndrome is irrationally convicted without trial **(8,14,15)**. The efficacy of species specific SAV in preventing, neutralizing, and reversing the toxicity caused by scorpion envenoming **(18,25)** in experimental animals and in scorpion sting victims **(2,14,15)** has been reported. We have suggested

that SAV is essentially acting through the release of insulin **(25)**.

If SAV is essentially acting through the release of insulin, then it is logical to expect that it may not be effective in reversing the scorpion venom-induced toxicity in alloxan-pretreated animals, since alloxan is known to specifically destroy the beta cells of pancreas secreting insulin. Therefore, an attempt is made to study the myocardial damage indicated by elevated cardiac enzyme levels due to envenoming following alloxan pretreatment and the effect of administering SAV or insulin.

MATERIALS AND METHODS

Lyophilized, crude scorpion venom from *Mesobuthus tamulus concanesis,* Pocock (earlier called *Buthus tamulus*) was purchased from the Haffkine Institute, Mumbai (Bombay), India. The species-specific scorpion antivenom (SAV) was produced at the Haffkine Biopharmaceutical Corporation Ltd., Mumbai, India. The whole contents of each SAV vial was reconstituted by the addition of 10 ml of water for injection to neutralize 12-18 mg of crude scorpion venom. All of the reconstituted SAV was given intravenously (IV) to the experimental dogs from Groups 3, 4, and 5.

Forty-two mongrel dogs (weight 8 ± 2 kg) and 45 rabbits (weight 1.5 to 2.0 kg) were used in this study. After an overnight fast of 12-14 hours, the dogs were anaesthetized with IV thiopentone sodium (35 mg/kg).

The experimental dogs and rabbits were randomly divided into eleven groups as described below.

	Alloxan	Venom	SAV	Insulin
Dogs				
Group 1 (n = 12)	-	+	-	-
Group 2 (n = 6)	+	+	-	-
Group 3 (n = 9)	-	+	+	-
Group 4 (n = 7)	-	+	+	-
Group 5 (n = 7)	-	+	+	-
Rabbits				
Group 6 (n = 6)	-	-	-	-
Group 7 (n = 6)	+	-	-	-
Group 8 (n = 6)	+	+	-	-
Group 9 (n = 8)	+	+	+	-
Group 10 (n = 6)	+	+	-	+
Group 11 (n = 13)	-	+	-	+

+ = given; - = not given and **n** = number of animals

Scorpion venom (3.5 mg/kg) was given SC to all the animals. The dogs in Group 2 received 40 mg/kg and rabbits in Groups 7, 8, 9, 10 received 125 mg/kg of alloxan intravenously. These experimental animals received scorpion venom 72 h after the alloxan treatment.

The dogs in Groups 3, 4, and 5 were given reconstituted SAV 0, 30, and 60 min respectively, following envenoming.

Rabbits in Group 9 were given 2.5 ml of reconstituted SAV 1 hour following envenoming, and rabbits in Group 10 were given 4 units of insulin IV 90 min following envenoming.

BLOOD COLLECTION

Group 1	Before venom injection, 60, and 120 min following envenoming.
Group 2	Before administration of alloxan, 72 h after alloxan pretreatment, and 60 min after venom injection.
Group 3	These animals were simultaneously injected with venom SC and SAV IV. Blood was collected before injection and at 30-minute intervals for the 2 hours following envenoming.
Group 4	Blood was collected before and 30 min after envenoming and then at 30-minute intervals for the 2 hours following SAV administration.
Group 5	Blood was collected before, 30, and 60 min following envenoming. SAV was then administered at 30-minute intervals for the 2 hours following SAV.
Group 6	These rabbits were the control group. These animals did not receive alloxan, venom, SAV, or insulin.
Group 7	Blood collected was used to assess the effect of alloxan treatment.
Group 8	Blood was collected 1 hour following envenoming.
Group 9 and Group 10	Blood was collected 1 hour after the administration of either SAV (Group 9) or insulin (Group 10).
Group 11	Blood was collected before and 90 min after venom injection. Then, these animals received 4 units of insulin IV. Blood was collected 20 h after insulin therapy. All the blood samples

collected from this group of rabbits were analysed for blood sugar **(2)**, lactic dehydrogenase activity, and free fatty acids.

All the blood samples were processed for LDH, SGOT, SGPT, alpha HBDH levels using diagnostic reagent kits (Miles India Ltd.). All the results were statistically analysed using either the Student "t" test or the paired "t" test.

Limb Lead II ECG was recorded continuously in the animals of Group 5 before and after envenoming, and after administration of the SAV.

RESULTS

Many abnormal ECG changes following scorpion envenoming were observed in Group 5. These ECG changes were reversed after the administration of SAV (**Figure 1** and **Figure 2**). Many arrhythmias, conduction defects, ischemia, and infarction-like patterns were also observed after scorpion envenoming. All these abnormalities, including the pathological Q wave, disappeared after administration of SAV.

FIGURE 1. ECG changes after scorpion envenoming and after administration of scorpion antivenom (SAV). All the ECG tracing from Limb Lead II, paper speed 50 mm/sec. in Group 5.
12-00 V : changing R-R (30 min after venom)
12-42 V : changing R-R (42 min after venom)
12-52 V : Nodal extrasystoles (no P wave) (52 min after venom)
12-54 V : Nodal rhythm (No P wave) (54 min after venom)
12-57 V : Nodal rhythm (No P wave) (57 min after venom)

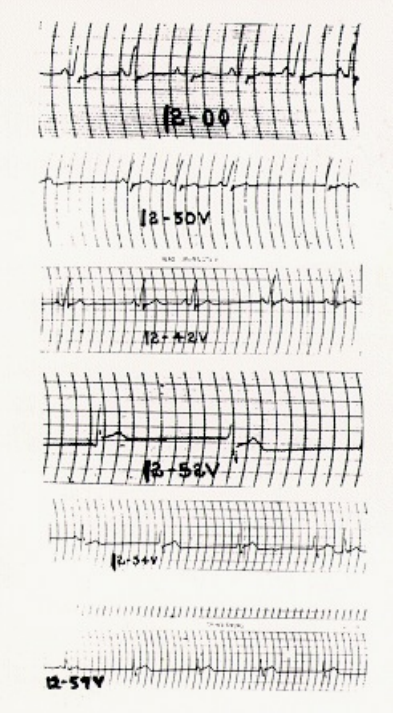

FIGURE 2. ECG changes after scorpion envenoming and after administration of scorpion antivenom (SAV). All the ECG tracing from Limb Lead II, paper speed 50 mm/sec. in Group 5.
12-05 AV : 5 minutes (after SAV and 65 min after venom) Few normal sinus beats.
12-15 AV : Sinus beats (15 min after SAV and 75 min after venom)
12-25 AV : Normal sinus beats (25 min after SAV and 85 min after venom)
12-45 AV : Normal sinus beats (45 min after SAV and 105 min after venom)
12-65 AV : Normal sinus beats (65 min after SAV and 125 min after venom)
12-90 AV : Normal sinus beats (90 min after SAV and 150 min after venom)

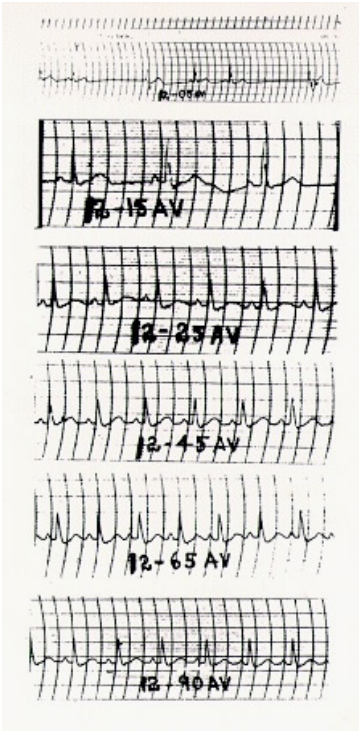

Table 1 shows the changes in the cardiac levels of LDH, SGOT, SGPT, CK-MB and HBDH before, 60, and 120 min following scorpion envenoming in Group 1, highlighting a significant increase in all the enzyme levels following scorpion envenoming.

TABLE 1. The effect of the venom from the scorpion *Mesobuthus tamulus concanesis,* Pocock (3.5 mg/kg) SC on cardiac enzyme levels in dogs (Group 1) (Mean ± S. E. D.)

Cardiac Enzyme (IU/L)	Before Venom	After Venom	
		60 min	120 min
Glutamine Oxalacetate Transaminase	12.60	17.60*** ± 1.1	26.60**** ± 1.7
Glutamine Pyruvate Transaminase	13.80	18.10**** ± 0.7	23.90**** ± 1.5
Lactate Dehydrogenase	41.20	57.30**** ± 1.4	94.30**** ± 6.4
Creatine Kinase - MB	11.30	24.30**** ± 1.5	13.90 ± 1.7
Alpha Hydroxy Butyrate Dehydrogenase	93.40	177.00**** ± 5.3	226.10**** ± 13.5

Alloxan administration did not result in any significant changes in these enzyme levels (**Table 2**). However, scorpion envenoming in Group 2 also caused a significant increase in all the enzyme levels (**Table 2**).

TABLE 2. The effect of alloxan and scorpion venom on cardiac enzyme levels in dogs (Group 2) (Mean ± S. E. D.).

Cardiac Enzyme (IU/L)	Before Alloxan	After Alloxan	After Alloxan + Venom
Glutamine Oxalacetate Transaminase	12.40	22.10 ± 2.4	32.10** ± 6.8
Glutamine Pyruvate Transaminase	18.60	15.20 ± 0.9	23.10** ± 1.1
Lactate Dehydrogenase	27.50	19.10 ± 1.7	49.80**** ± 2.1
Creatine Kinase - MB	11.70	23.30 ± 2.6	25.40*** ± 2.3
Alpha Hydroxy Butyrate Dehydrogenase	82.60	71.50 ± 5.2	165.10*** ± 11.0

Table 3 shows that the intravenous administration of SAV to Group 3 along with the SQ injection of venom resulted in a significant elevation of SGOT levels 30, 60, 90, and 120 min after venom injection. However, a statistically significant rise in LDH levels was observed only 30 and 60 min following venom injection.

TABLE 3. The effect of scorpion venom and SAV on cardiac enzyme levels in dogs (Group 3) (Mean ± S. E. D.).

Cardiac Enzyme (IU/L)	Before venom and SAV	After venom and SAV			
	0 min	30 min	60 min	90 min	120 min
Lactate Dehydrogenase	75.14	99.30** ± 14.22	89.12* ± 19.23	100.00 ± 42.65	80.00 ± 32.00
Glutamine Oxalacetate Transaminase	30.11	35.00*** ± 1.5	42.00*** ± 3.0	47.00**** ± 4.0	38.33** ± 4.0

SAV was given to Group 4 30 min following envenoming. The levels of SGOT were found to be elevated 30 and 60 min following envenoming. Thereafter, there was no further significant elevation of SGOT levels. The levels of LDH were found to be increased immediately after envenoming. A significant increase in LDH with a tendency for these levels to subsequently fall was observed. (**Table 4**).

TABLE 4. The effect of scorpion venom and SAV on cardiac enzyme levels in dogs (Group 4) (Mean ± S. E. D.).

Cardiac Enzyme (IU/L)	Before venom and SAV	After venom and SAV				
	0 min	30 min	30 min	60 min	90 min	120 min
Lactate Dehydrogenase	69.37	113.91***±10.0	128.45*±14.0	85.31**±7.32	89.20**±8.5	75.00***±7.44
Glutamine Oxalacetate Transaminase	42.00	50.83**±2.5	51.33**±6.0	64.33 ±32.00	92.83 ±26.0	94.00 ±27.0

Table 5 shows that Group 5 received SAV 60 min after venom injection. The levels of SGOT and SGPT were seen to increase 60 min following envenoming, with no further significant change in these cardiac enzyme activities 90 and 120 min after envenoming.

TABLE 5. The effect of scorpion venom and SAV on cardiac enzyme levels in dogs (Group 5) (Mean ± S. E. D.).

Cardiac Enzyme (IU/L)	Before venom and SAV			After venom and SAV			
	0 min	30 min	60 min	30 min	60 min	90 min	120 min
Glutamine Oxalacetate Transaminase	21.62	24.37*±1.0	30.00*±5.1	30.00*±6.8	30.37*±4.8	32.37 ±9.1	36.85 ±9.8
Glutamine Pyruvate Transaminase	5.00	5.60 ±0.2	8.00 ±0.6	13.60 ±6.3	14.12 ±5.3	15.20 ±5.7	13.40 ±5.2

Alloxan pretreatment did not cause any change in LDH, SGOT, and SGPT levels in Group 7 (**Table 6**). Scorpion envenoming in Group 8 caused a significant rise in SGOT and SGPT levels. Administration of SAV to Group 9 resulted in a rise in SGPT levels. Administration of insulin to Group 10 resulted in much less, but still significant rises in SGPT levels (**Table 6**).

TABLE 6. The effect of administering either SAV or insulin on cardiac enzyme levels in rabbits envenomed (3.5 mg/kg) by the scorpion *Mesobuthus tamulus concanesis*, Pocock (Groups 6, 7, 8, 9 and 10) (Mean ± S. E. D.).

Cardiac enzyme (IU/L)	Group 6 (n = 6)	Group 7 (n = 6)	Group 8 (n = 6)	Group 9 (n = 8)	Group 10 (n = 6)
Lactate Dehydrogenase	54.00 ±5.6	30.90 ±4.0	35.30 ±9.2	47.10 ±10.2	48.40 ±5.8
Glutamine Oxalacetate Transaminase	38.20 ±4.5	44.40**±14.8	99.80**±6.9	55.70 ±9.8	52.10 ±7.0
Glutamine Pyruvate Transaminase	22.90 ±4.6	47.10 ±20.2	62.60*±16.9	63.20***±7.8	49.80****±3.4

Table 7 shows that Group 11 were treated with insulin following venom injection. There was a rise in blood sugar, free fatty acid levels, and LDH activities 90 min following venom injection. Insulin treatment resulted in a fall in blood sugar and free fatty acid levels.

TABLE 7. The effect of administering insulin on cardiac enzyme levels in scorpion envenomed rabbits (Group 11) (Mean ± S. E. D.).

	Before venom (n = 13)	90 minutes After venom (n = 13)	20 hours After Insulin (n = 13)
Blood sugar (mg/dl)	120.66	326.80****± 38.5	117.00****±23.62
Lactate Dehydrogenase (IU/L)	28.00	45.00**±3.7	48.00 ±9.3
Free fatty acids (U mol/L)	330.25	729.80****±4.2	269.50****±35.00

DISCUSSION

Scorpion myocardiopathy is often missed because of the severity of the associated clinical manifestations **(1,4,11,34,36,39)**. Many times, the ECG tracings of these victims were normal on admission **(7)** but bizarre, broad, notched, biphasic T waves with ST segment changes (elevation or depression), Q waves and myocardial infarction-like patterns, junctional rhythm, and electrical alternans recorded in experimental envenoming **(23)** were also observed in scorpion sting victims **(9,21)**.

An increase in succinate dehydrogenase and CPK activities was observed following *Leiurus quinquestriatus* envenoming **(42)**. Envenoming by *Androctonus amoreuxi* resulted in an apparent, but not significant increase in SGOT, LDH, and G-6-P dehydrogenase levels **(16)**, whereas SGOT, SGPT, LDH, and CPK activities were normal in

patients stung by the scorpion *Hemiscorpius lepturus* **(35)**. A rise in SGPT **(6)** and SGOT levels was reported with the results from the scorpion *Buthus tamulus* **(17)**. Sofer and Gueron **(38)** reported high levels of SGOT, CPK, and CK-MB and suggested that myocardial lesions were too small to cause heart failure, but these might account for the cardiovascular changes. The electrocardiographic, echocardiographic, radionuclide, and ventriculography studies also showed an elevation of SGOT, CPK, and CK-MB ratio in scorpion sting victims **(1,3,10,13,20,34).**

The cardiac enzymes are retained within the cells surrounded by metabolically active plasma membrane. A reduction in the oxygenated blood supply will promote deterioration of the membrane and leakage of the enzymes from damaged or dying cells into circulation. The leaked enzymes remain in the circulation until they are metabolically degraded. This could be the reason for an apparent and significant rise in the enzyme levels in envenoming, and for an apparent but insignificant rise following the different administration of SAV to the envenomed animals.

The transient elevation of SGOT levels sometimes raises practical difficulties in the diagnosis of myocardial damage, and normal levels do not exclude this diagnosis. The elevation of LDH levels, though also transient persists much longer, but elevated LDH levels are not always seen after myocardial damage. The measurement of the activity of CK-MB is now widely used to detect and monitor myocardial damage. When ECG and necropsy studies are performed they can confirm or exclude myocardial damage **(12)**. A second component may be regarded as alpha hydroxy butyric dehydrogenase (alpha HBDH) and is found to be above normal due to myocardial damage **(19)**.

Total LDH, SGOT, SGPT, CK-MB, and alpha HBDH levels were increased following envenoming (**Table 1**). SGOT and LDH activities were elevated in dogs (**Table 3**,**Table 4**, **Table 5**) and blood glucose, free fatty acids, and LDH were elevated in rabbits following envenoming (**Table 7**). Alloxan treatment did not cause any increase in LDH, SGOT, SGPT, CK-MB, and alpha-HBDH levels in dogs (**Table 2**) or rabbits (**Table 6**).

The administration of SAV prevented the toxic effects of venom in Group 3. The antivenom neutralised the toxic effects when it was given to Groups 4 and 5 30 and 60 minutes after venom injection. Antivenom arrested a further rise in blood sugar levels and caused euglycemia and lipogenesis in Group 11. If the antivenom did not inhibit the excess catecholamines and other hormonal secretions as well as mediated venom toxicity causing suppressed release of insulin secretion, then, we would have observed only the arrest of a further increase in the products of glycogenolysis and lipolysis. The level of euglycemia and lipogenesis seen after SAV indicated that the antivenom effectively neutralised the circulating venom, and probably the scorpion venom that was bound to the tissues **(35)**, and while doing so, it inhibited the action of the catecholamines **(3,13,33)** on insulin secretion.

An apparent but non-significant increase in SGOT (Groups 4 and 5) and SGPT (Group 5) was observed after SAV. However, the reversal of ECG abnormalities after SAV indicated reversible cardiomyopathy **(13)**.

If SAV is essentially acting by releasing of insulin and reversing the metabolic, haematological, cardiovascular, and ECG changes **(18,32)**, it is then logical to expect that SAV may not be effective in envenoming following alloxan-induced diabetes (Group 9). Alloxan destroys the beta cells in the islets of Langerhans of pancreas secreting insulin. Group 9 did not show any clinical improvement and died following SAV. On the other hand, insulin administration produced clinical improvement (Group 10), marked glycogenesis in liver, atria, ventricle, rectus abdominus, gastrocnamius muscles, and euglycemia.

Insulin therapy reduced the levels of blood glucose, free fatty acids, and LDH to normal (**Table 7**). These animals were observed for another 3 weeks after insulin**,** and all of them survived.

Continuous infusion of regular crystalline insulin (0.3 u/g of insulin and glucose 0.1 g/kg/h) with supplementary potassium as needed and the maintenance of fluids, electrolytes, and acid-base balance **(25,30)** resulted in complete recovery of 125 out of 130 scorpion sting victims of cardiomyopathy, peripheral circulatory failure, and pulmonary oedema **(41,43).**

Scorpion envenoming is a syndrome of fuel-energy deficits and the inability to utilize the existing metabolic substrates by vital organs, which ultimately may result in multisystem organ failure (MSOF) and death. This is caused by a massive release of catecholamines, angiotensin II, an increase in glucagon and cortisol, and a reduction in insulin levels **(3,5,7,9,11,23) (27-29,33,38)**. The rise in glucagon, cortisol, and catecholamine levels oppose the metabolic functions of insulin. Circulating insulin antagonists (catecholamines, glucagon, cortisol, and growth hormone) cause insulin resistance by different mechanisms **(25)**. As a consequence of these changes in the hormonal environment, glycogenolysis, lipolysis, and other catabolic activities take place. Insulin is the only physiological antagonist against the actions of the catecholamines **(25)**.

Scorpion antivenom therapy not only neutralises the circulating venom and tissue-bound venom **(35)**, but also blocks the release of catecholamines, and the consequent release of insulin. Serotherapy, on the other hand, is able to reverse the metabolic, hormonal, cardiovascular, haemodynamic, and ECG disturbances by changes in the hormonal Milieu **(18,25)**. SAV is found to be effective in the prevention or elimination of the various clinical manifestations in human scorpionism **(13,14,15,35)**.

It can be concluded that scorpion envenoming syndrome results in a significant elevation of LDH, SGOT, CK-MB and alpha HBDH enzyme levels associated with changes in the ECG. Scorpion envenoming is a rural medical emergency occurring mainly in developing countries, where the facilities to monitor and treat scorpion sting victims in intensive care units are scarce **(14,15)**. The monitoring of either LDH or SGOT enzyme levels supported by ECG recording under such circumstances may prove to be helpful. Experimental protocols are required to check the value of either SAV in appropriate doses, insulin-glucose infusion **(25,41,43),** or any other drug/s maintaining the acid-base-fluid-electrolyte balance to reduce the morbidity and mortality caused by scorpion stings.

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✉ **CORRESPONDENCE TO:**
K. RADHA KRISHNA MURTHY - Professor of Physiology, Seth G.S. Medical College & K. E. M. Hospital, Parel, Mumbai 400 012, India.

Caixa Postal 577
18618-000 Botucatu SP Brazil
Tel. / Fax: +55 14 3814-5555 | 3814-5446 | 3811-7241
e-Mail
jvat@cevap.org.br