Cardiovascular Response

The present study was undertaken to describe the early sequential hemodynamic changes in an animal model in which doses of snake venoms were administered, intravenously or by direct bite, in anesthetized dogs on assisted ventilation.

MATERIALS AND METHODS

1. Experimental Protocol

Fourteen venoms were administered to twenty-eight anesthetized (sodium pentobarbital) mongrel dogs weighing between 10-12 Kgs. All experiments were conducted acutely. Endotracheal intubation and assisted ventilation with a model 607 Harvard pump was initiated. Through a left fourth or fifth interspace thoracotomy, the pericardium was opened and large bore polyethylene catheters (Clay-Adams PE 205) were inserted into the main pulmonary artery and right and left atria. A calibrated Biotronex Laboratory flow probe was placed around the main pulmonary artery. Another catheter was introduced into the right femoral artery. The electrocardiogram was recorded via bilateral subcutaneous chest needle electrodes.

2. Methods of Hemodynamic Measurement

Pulmonary arterial flow was measured with a Biotronex Laboratory 310 sine wave electromagnetic flow meter. The right and left atrial catheters were connected to 268B Sanborn pressure transducers and the pulmonary and femoral arterial catheters were connected to 267AC Sanborn pressure transducers.

Electrocardiogram, heart rate, pulmonary arterial flow, pulmonary arterial pressure, right and left atrial pressures and femoral arterial pressure were simultaneously measured and recorded on an eight channel direct writing Hewlett-Packard recorder.

Pulmonary vascular resistance (PVR) and systemic vascular resistance (SVR) were derived using the following formulae:

$$PVR = \frac{mPAP - LAP}{CO} \times 7{,}992$$

$$SVR = \frac{mAP - RAP}{CO} \times 7{,}992$$

Where mPAP is mean pulmonary arterial pressure, LAP is left atrial pressure; mAP is mean arterial pressure, RAP is right atrial pressure; both arterial and atrial pressures are expressed in mm Hg. Left (LVSW) and right ventricular stroke work (RVSW) were calculated according to the formulae:

$$LVSW = \frac{SV \times mAP \times 13.5}{1{,}000}$$

$$RVSW = \frac{SV \times mPAP \times 13.5}{1{,}000}$$

Average stroke volume (SV) was determined by dividing cardiac output by the heart rate. Cardiac output was calculated from the pulmonary arterial flow curve. All calculations were solved by an Olivetti-Underwood 101 electronic computer programmed for this purpose.

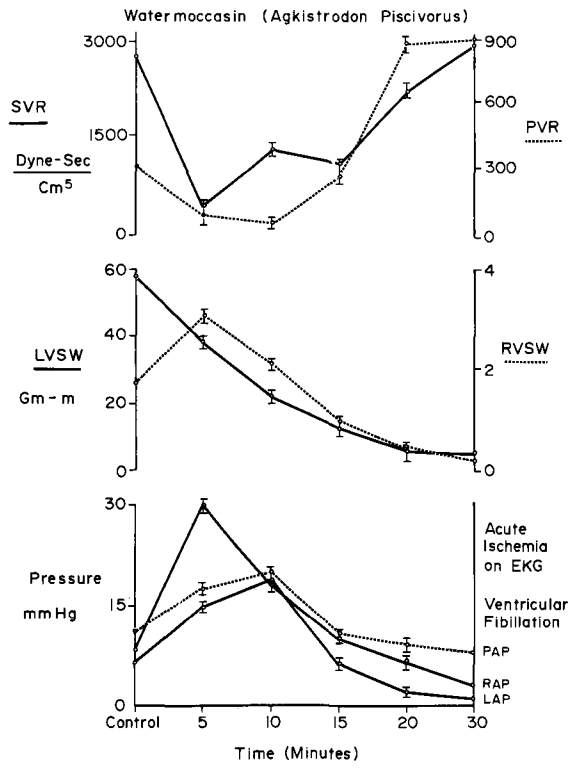

Figure 1

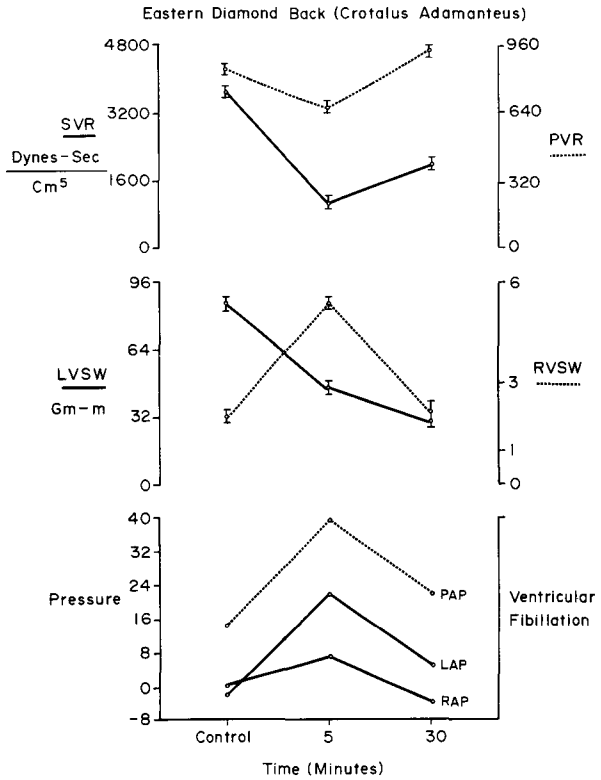

Figure 2

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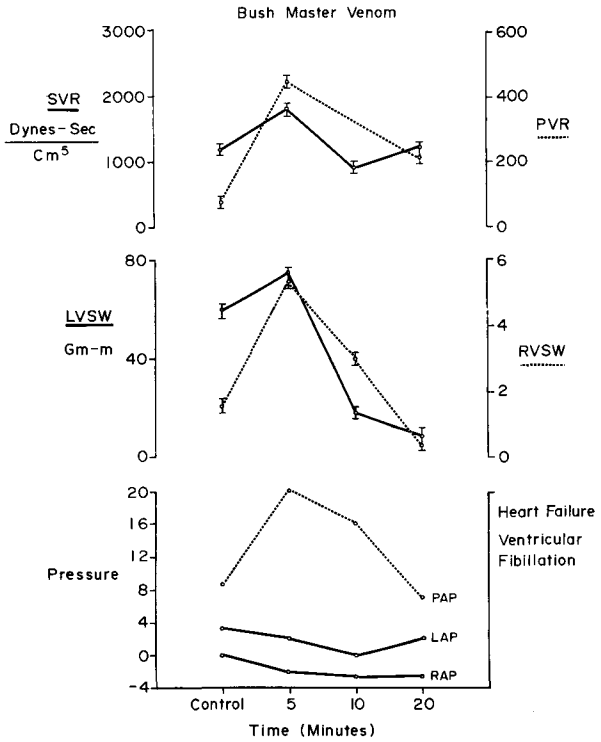


Figure 3

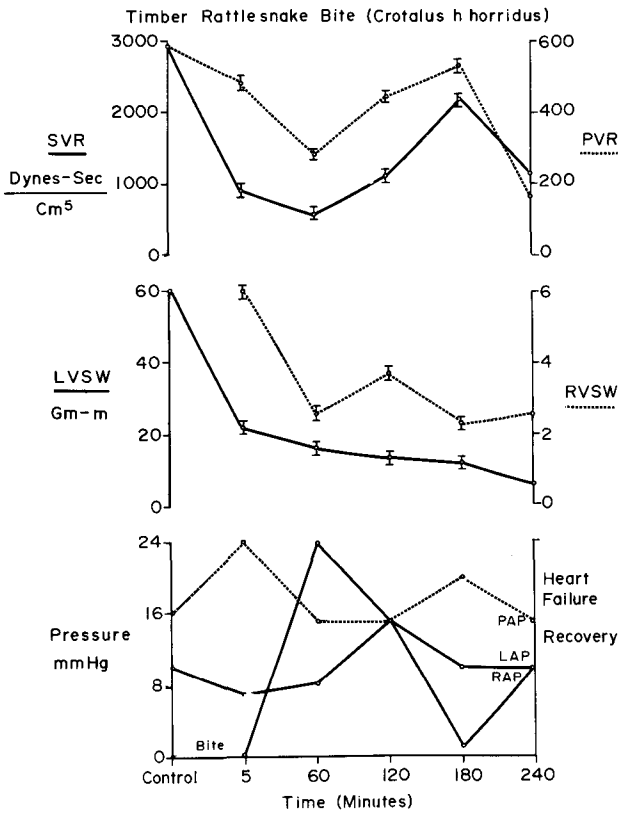


Figure 4

3. Experimental Protocol

Lypholized doses of snake venom were injected intravenously in the experimental model. Snake venoms representative of Elapidae, Crotalidae, Viperidae and Hydrophidae families were used.

Table I lists the venoms and doses used.

Continuous recordings of all measured parameters and assisted ventilation were used throughout all experiments.

Duplicate experiments were performed for each venom studied.

In conducting the research described in this report, the investigators adhered to the "Guide for Laboratory Animal Facilities and Care," as promulgated by the Committee on Revision of the Guide for Laboratory Animal Facilities and Care of the Institute of Laboratory Animal Resources, National Academy of Sciences—National Research Council.

TABLE I

Venom	**Dose**
Snake Venoms	
Crotalidae	
Crotalus H. horridus	Bite (approx, 3 mgm/Kg)
Agkistrodon piscivorus	10.0 mgm/Kg
Lachesis Mutus	1.0 mgm/Kg
Crotalus Adamanteus	10.0 mgm/Kg
Viperidae	
Bitis Gabonica	6 mgm/Kg
Vipera Aspis	1.8 mgm/Kg
Elapidae	
Ophiophagus hannah	Bite (approx. 1.5 mgm/Kg)
Naja Naje	1.5 mgm/Kg
Dendroaspis Augusticeps	1.5 mgm/Kg
Hydrophadia	
Laticauda Semifasciata	1.0 mgm/Kg

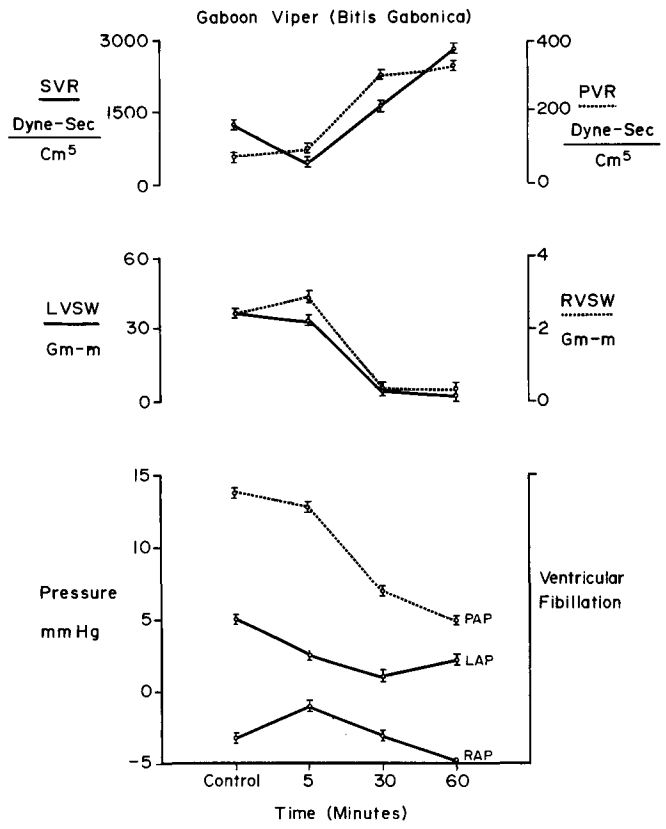


Figure 5

RESULTS AND DISCUSSION

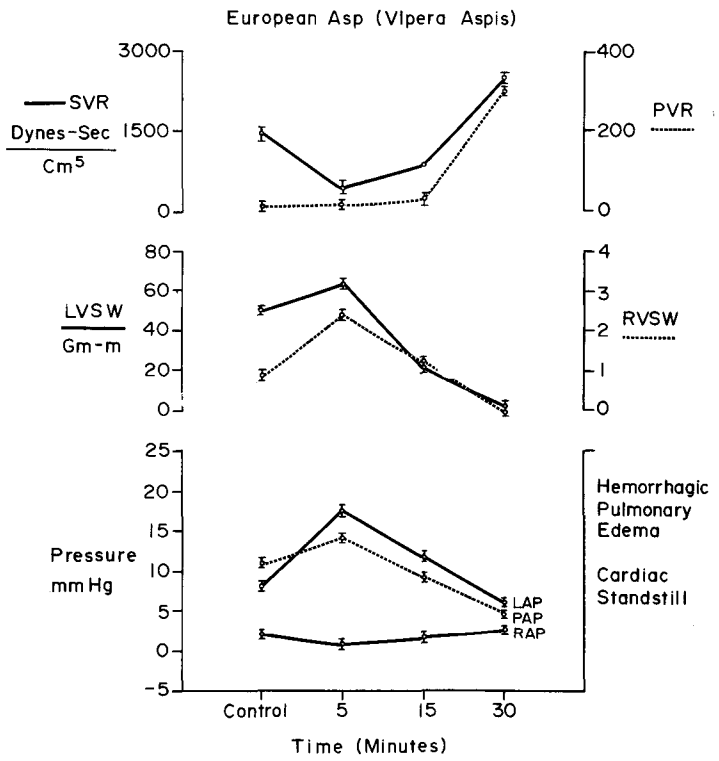
Snake Venoms

Figures 1 through 4 summarize the effects of the venoms of the family Crotalidae, Watermoccasin (Agkistrodon Piscivorus), Figure 1; Eastern Diamond Back (Crotalus Adamanteus), Figure 2; Bushmaster (Lachesis Muta), Figure 3; and Timber Rattlesnake (Cortalus h. horridus), Figure 4; venoms caused similar hemodynamic responses. Decreases in ventricular stroke work, elevation of the systemic and pulmonary vascular resistances, and biventricular cardiac failure occurred in all. Ventricular fibrillation occurred within 30 minutes with all but the Timber Rattlesnake. In this latter case, envenomation occurred by direct bite and the dose of venom was unknown. This study indicates that the primary toxicity of Crotalus venom is myocardial rather than pulmonary (1, 2, 3).

Venoms of the Gaboon Viper (Bitis Gabonica) Figure 5, and the European Asp (Vipera Aspis Figure 6, of the Viperidae family caused death within 60 minutes. Both venoms caused elevations of the systemic and pulmonary vascular resistances with concomitant falling cardiac stroke work. Envenomation by the European Asp caused hemorrhagic pulmonary edema and cardiac standstill; whereas Gaboon viper venom caused no gross pulmonary manifestations but created ventricular fibrillation at 60 minutes.

Venoms representative of the families Elapidae (Figures 7 through 9) caused initial cardiac failure as manifested by varying degrees of reduction in ventricular stroke work. Hemodynamic recovery occurred in all. These venoms have been shown to be primarily neurotoxic (4, 7).

Sea Snake venom (Laticauda Semifasciata), Figure 10, from the family Hydrophidia caused essentially no immediate hemodynamic changes other than an initial blood pressure fall. It has been shown that this venom acts primarily on the post-synaptic membrane and death is due to respiratory paralysis (8).



• Figure 6

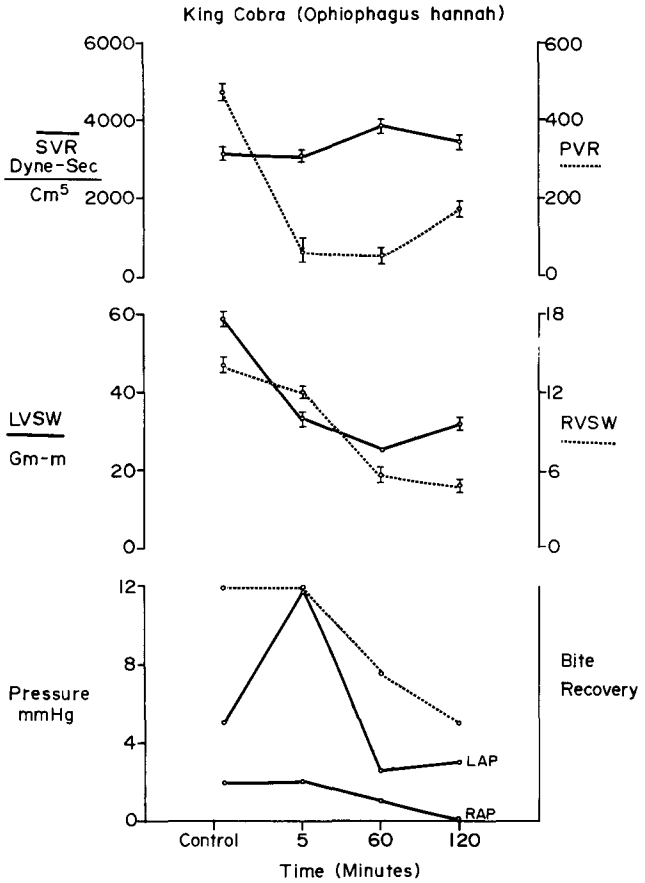


Figure 7

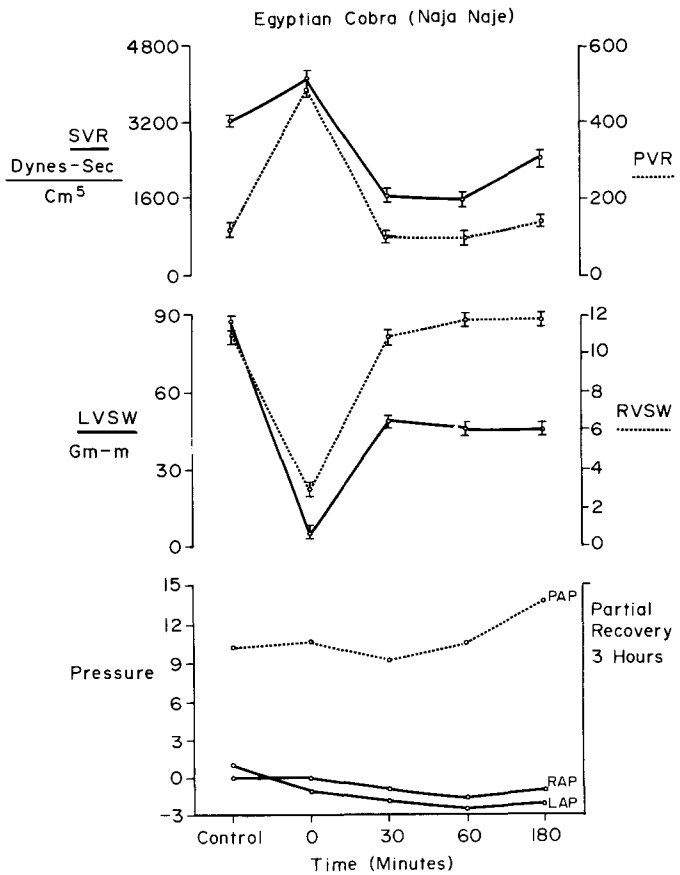


Figure 8

Venoms are complex mixtures, some containing as many as 15 or 20 specific biologically active components (3). Besides the individual components of venoms, the envenomated organism can produce and release autopharmacological substances which may not only complicate the poisoning but which may in themselves sometimes produce more serious consequences than the venom.

Though venoms have been studied extensively (9), their chemical composition and most of the specific physiopharmacological effects of these poisons and their fractions have not yet been determined.

The inadequate but widely accepted classification of venoms into "neurotoxins", "hemotoxins", and "cardiotoxins", led the author to design his study to eliminate as much as possible the "neurotoxic" and "hemotoxic" effects of venoms. Assisted ventilation was utilized to eliminate the secondary effects of anoxia (due to respiratory paralysis) on cardiovascular function. Acute, rather than chronic, studies were performed to eliminate the delayed "hemotoxic" and autopharmacoligical effects of these venoms.

Table II summarizes the cardiovascular and pulmonary effects of all venoms studied.

TABLE II

Summary of the Immediate Effects of Venoms on Cardiac and Pulmonary Function

	Cardiac	Pulmonary	Time to Death (Min.)
Snake Venoms			
Crotalidae	Profound*	Moderate	30 (recovery from Timber Rattlesnake bite)
Viperidae	Profound	Profound (Asp)*	60
Elapidae	Mild*	None	Recovery
Hydrophidia	None	None	Recovery

*Denotes primary effect

SUMMARY

The cardiovascular effects of intravenous doses of snake venoms were studied in open chest ventilated mongrel dogs.

Representative venoms of the families Crotalidae and Elapidae had direct myocardial toxic effects while those of the Viperidae had their primary effects on both the pulmonary vascular bed and myocardium.

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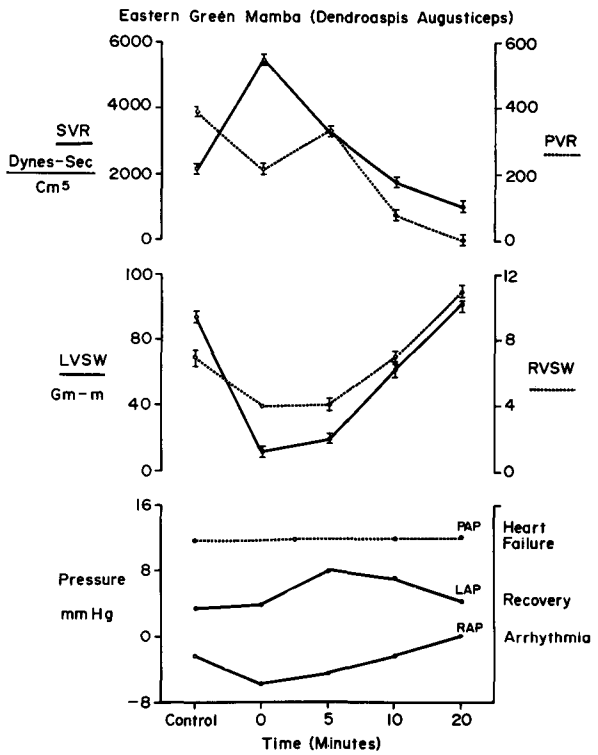

Figure 9

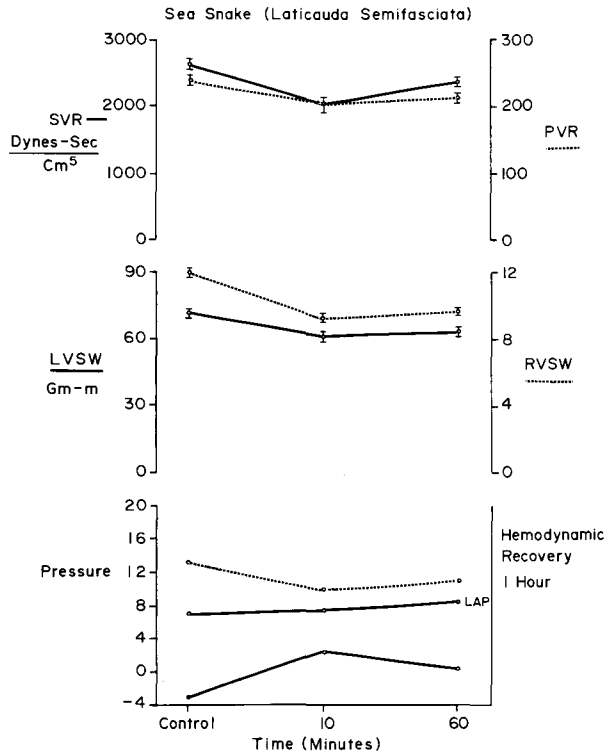

Figure 10