

# Hemodynamic study of effect of the cobra venom on the circulation in the dog by the dye dilution method.

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## Abstract

Studies were made hemodynamic changes following infusion of 60 r/kg, 120 r/kg, 0.1mg/kg, 0.5mg/kg..of crude venom into dogs. Intravenous venom injection produced a precipitous fall in arterial pressure concurrently with a marked reduction in cardiac output and in left ventricular work. The onset of the pressure changes occurred within 30 sec after infusion and reached a low value which average 45% of the control by 5 min following which the pressure and cardiac output increased toward control values. The initial drop of arterial pressure was caused by a remarkable decrease of left ventricular work and that almost no change in central venous pressure and central blood volume and a slight change in peripheral resistance were caused by cobra venom. An increase of the dose of cobra venom would lead to a remarkable decrease of both left ventricular work and total peripheral resistance. The drop of blood pressure was essentially caused by the decrease of left ventricular work and vasodilatation. The effects of cobra venom on the circulation were similar before and after vagotomy, cutting of glossopharyngeal nerve, administration of atropine, bilateral common carotid artery occlusion. Hypotension is still occurred. Cobra venom would not affect central nervous system. Hypotension was caused by cobra venom is essentially peripheral effect upon the heart and vascular system.

## Introduction

In a research report W. Feldberg (1) showed in 1937 that a pronounced cardiovascular change produced by the intravenous injection of cobra venom will result immediately in a fall of systemic arterial pressure and venous pressure. If a large dose of venom is used, the injection will cause a rise in venous pressure and final fall in systemic pressure. The most conspicuous and consistent cardiovascular change produced by cobra venom is a immediate fall in systemic arterial pressure, if the venom is administered intravenously. The experiment carried out in dogs with crossed cephalic circulation also underlined the absence of a central effect (8). By means of heart lung preparation (2), cobra venom can cause rapid loss of total peripheral resistance and fall in arterial pressure. The preliminary mechanism of death is respiratory failure (3) (Vick 1965). If respiration is supported, survival time increases, but all animal subsequently expire revealing signs of cardiovascular failure. The purpose of this hemodynamic study is to investigate, by the dye-dilution method, the effect of the cobra venom on the circulation in the dog.

## Materials and Methods

The dogs ( $7.7 \pm 3.4$  kg) after fasting overnight, were anesthetized with 30 mg/kg sodium pentobarbital besides, heparine sodium was used as anticoagulant at dosage of 3 mg/kg intravenously. The crude venom (*Naja naja atra*) was reconstituted to the desired concentration with Tyrode solution, was injected into the right atrium or superior vena cava. Hemodynamic data were recorded with NIHON KOHDEN multipurpose polygraph. The pressure transducer was used for recording arterial blood pressure, mean blood pressure and central venous pressure, EKG was recorded with the polygraph by using the standard limb lead, heart rate was calculated from the curve of arterial blood pressure or EKG (a lead II electrocardiogram). cardiac output was determined by the indicator dilution method (5)(6)(10) using indocyanine green dye, a Gilford instrument company model no. 1031R curvette desitometer and a single syringe infusion withdrawal pump. The method for calculating mean transit time or mean circulation time, central blood volume, total peripheral resistance and left ventricular work has been described previously (5)(6)(10). The experiment were divided into the following group. Group I. Thirteen animals with spontaneous respiration were used to study the hemodynamic effects of cobra venom. Group II. Five animals were used to study the hemodynamic effects of cobra venom on artificially ventilated respiration. Group III. One animal was used to study how injection of atropin, bilateral vagotomy cutting of the glossopharyngeal nerve and occlusion of common carotid artery brought about the hemodynamic effect of cobra venom on spontaneous respiration.

## Results

Hemodynamic effect of cobra venom on spontaneous respiration. Intravenous injection of 60 r/kg of cobra venom from extrajugular vein into the vena cava or atrium produced significant changes in all hemodynamic parameters which were measured (Fig 1 and Table 1). Arterial mean blood pressure, cardiac output, stroke volume heart rate and left ventricular work decreased precipitously and were significantly below control by 5 min postenvenomation ( $p < 0.01$ ). The onset of the fall in arterial pressure occurred within 40 sec after venom injection and reached a low value which averaged 45% of control by 5 min. 30-50 min after envenomation arterial blood pressure tended to reach the control level again. If a second similar dose of venom was injected there was not significant change in the cardiovascular system. After recovery had taken place, an injection of a double dose of venom resulted in a smaller change in the cardiovascular system than the previous injection (Fig 1). When the dose increased to 480 r/kg, arterial mean blood pressure, left ventricular work, stroke volume and cardiac output decreased. Mean circulation time prolonged (Fig 1). 30-60 min after envenomation, the respiration stopped and then a sharp increase of the arterial systolic blood pressure and pulse pressure which followed a sharp decrease down to 0. After cessation of spontaneous respiration, the animal placed

on the positive pressure respirator survived for additional 4-6 hours at this time however the animal developed arrhythmias and hypotension which ultimately led to death.

Hemodynamic effects of cobra venom on artificially ventilated respiration. The effects of an intravenous injection of 0.1 mg/kg of cobra venom are shown in Fig 1 and Table 2. Left ventricular work, arterial mean blood pressure, cardiac output and total peripheral resistance fell precipitantly which were significant ( $0.05 > P$ ). Mean circulation time increased to 140% of control, it was not significant ( $p > 0.05$ ). Central venous blood pressure increased to 116% of control, it was not significant too. The hemodynamic change tends to recover the control level 30-60 min after envenomation. After the recovery took place, a second injection with a dose of 0.5 mg/kg of venom did not bring about any further action on the circulation because of tachyphylaxis phenomenon. An injection of a larger dose of venom (2 mg/kg) also produced no further action on the circulation. When no more injection of venom was given, then the animal survived for 2-3 hours after administration of 2 mg/kg of venom. Before death the blood pressure dropped suddenly and would not rise again.

The effects of cobra venom (60 r/kg) on circulation were similar before (Table 1) and after (Table 3) bilateral vagotomy, injection of atropine sulfate cryst (2 mg), cutting of the glossopharyngeal nerve and occlusion of bilateral common carotid artery. Cardiac output decreased to 76% of control. Left ventricular work decreased to 18% of control. Mean circulation time increased to 141% of control. Total peripheral resistance and central blood volume almost no changed. Hypotension is still occurred.

## Discussion

A complex pattern of hemodynamic changes results from infusion of cobra venom into anesthetized dogs. An immediate and profound drop in cardiac output, arterial blood pressure and left ventricular work concurrently with a marked prolongation of mean circulation time. It was considered that the initial drop of blood pressure was not caused by heart failure, but by vasodilatation which followed constriction of splanchnic area. It was also believed that the drop of blood pressure was either caused by constriction of hepatic vein and injury of liver cell (7) (2) or by a decrease of total peripheral resistance (2)(8)(10). The investigation of the effects of cobra venom on cardiovascular system by the dye-dilution method has let to the findings that the initial drop of blood pressure was caused by a remarkable decrease of left ventricular work and that almost no change in central venous pressure and central blood volume and a slight change in peripheral resistance were caused by cobra venom. It was also found that an increase of the dose of cobra venom would lead to a remarkable decrease of both left ventricular work and total peripheral resistance. The drop of blood pressure was essentially caused by the decrease of left ventricular work and vasodilatation. The effects of cobra venom on circulation were similar before and after vagotomy, cutting of glossopharyngeal nerve, administration of

atropine and occlusion of common carotid artery just like that Bhangana (2) and others have found in the previous experiment cobra venom would not affect central nervous system. Hypotension was caused by cobra venom is essentially peripheral effect upon the heart and vascular system.

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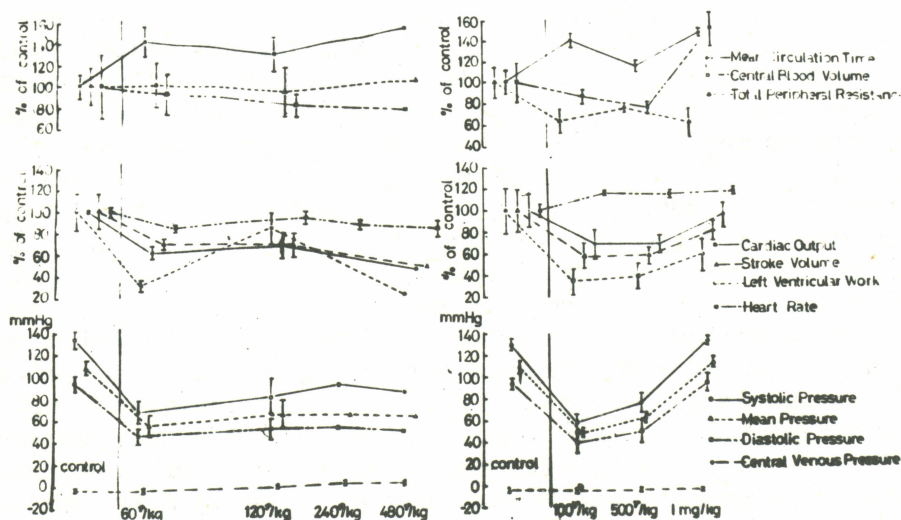


Fig 1 Variation of hemodynamic factors after injection of cobra venom with spontaneous respiration(left) and with ventilated respiration(right). Values are means  $\pm$  SEM.

Table 1 Mean values SEM significant t and p values for body weight hemodynamic factors from comparison between the control and the measurements after injection of cobra venom into jugular vein

|                                   | Control |       | After injection of 60 r/kg cobra venom |       |       |                   |
|-----------------------------------|---------|-------|----------------------------------------|-------|-------|-------------------|
|                                   | Mean    | SEM   | Mean                                   | SEM   | t     | p                 |
| Body weight (kg)                  | 7.71    | 1.34  |                                        |       |       |                   |
| Cardiac output (l/min)            | 0.98    | 0.01  | 0.61                                   | 0.06  | 3.63  | 0.01 > P > 0.005  |
| Heart rate (beats/min)            | 188.46  | 10.68 | 160.32                                 | 6.99  | 4.03  | 0.005 > P > 0.001 |
| Stroke volume (ml/beat)           | 5.64    | 0.94  | 3.98                                   | 0.31  | 5.59  | 0.001 > P         |
| Left ventricular work (kg-m/min)  | 1.65    | 0.29  | 0.53                                   | 0.09  | 12.54 | 0.001 > P         |
| Systolic pressure (mm Hg)         | 135     | 8.01  | 68.86                                  | 11.29 | 5.84  | 0.001 > P         |
| Mean pressure (mm Hg)             | 109.54  | 6.62  | 67.03                                  | 9.08  | 3.63  | 0.005 > P > 0.001 |
| Diastolic pressure (mm Hg)        | 94      | 7.12  | 47.94                                  | 8.00  | 4.28  | 0.005 > P > 0.001 |
| Central blood pressure (mm Hg)    | -2.80   | 1.68  | -3.65                                  | 2.30  | 0.13  | P > 0.5           |
| Mean circulation time (sec)       | 9.76    | 1.09  | 13.84                                  | 1.38  | 2.90  | 0.02 > P > 0.01   |
| Total peripheral resistance (PRU) | 8.27    | 1.40  | 8.50                                   | 1.80  | 1.29  | 0.4 > P > 0.2     |
| Central blood volume (ml/mm)      | 214.7   | 64.1  | 196.23                                 | 38.17 | 0.43  | P > 0.5           |

Table 2 Mean values SEM significant t and p values for body weight hemodynamic factors from comparison between the control and the measurements after injection of cobra venoms into jugular vein in the ventilated dog

|                                   | Control |       | After injection of 0.1 mg/kg cobra cobra vernom |      |      |                   |
|-----------------------------------|---------|-------|-------------------------------------------------|------|------|-------------------|
|                                   | Mean    | SEM   | Mean                                            | SEM  | t    | p                 |
| Body weight (kg)                  | 6.7     | 0.72  |                                                 |      |      |                   |
| Cardiac output (l/min)            | 0.68    | 0.12  | 0.47                                            | 0.09 | 4.27 | 0.05 > P > 0.02   |
| Heart rate (beats/min)            | 186.6   | 11.58 | 222.05                                          | 3.4  | 7.43 | 0.01 > P > 0.005  |
| Left ventricular work (kg-m/min)  | 1.39    | 0.33  | 0.48                                            | 0.17 | 7.0  | 0.01 > P > 0.005  |
| Systolic pressure (mm Hg)         | 132     | 5.4   | 60.9                                            | 9.8  | 5.76 | 0.02 > P > 0.01   |
| Diastolic pressure (mm Hg)        | 96.5    | 3.4   | 41.3                                            | 8.5  | 6.23 | 0.01 > P > 0.005  |
| Mean pressure (mm Hg)             | 114.7   | 6.6   | 58.5                                            | 11.4 | 6.05 | 0.01 > P > 0.005  |
| Central blood pressure (mm Hg)    | 2.4     | 0.1   | 1.8                                             | 0.05 | 1.5  | P > 0.5           |
| Mean circulation time (sec)       | 11.5    | 1.3   | 16.1                                            | 2.07 | 2.26 | 0.2 > P > 0.1     |
| Total peripheral resistance (PRU) | 12.9    | 1.9   | 8.3                                             | 1.4  | 4.06 | 0.05 > P > 0.025  |
| Central blood volume (ml/min)     | 125.7   | 34    | 110.4                                           | 9.5  | 3.08 | 0.1 > P > 0.05    |
| Stroke volume (ml/beat)           | 3.7     | 0.7   | 2.2                                             | 0.4  | 6.16 | 0.001 > P > 0.005 |

Table 3 After vagotomy, cutting of the glossopharangeal nerve, administration of atropine and occlusion of bilateral common carotid artery brought about the hemodynamic effect of cobra venom, on spontaneous respiration.

|                                        | Control | 60 r/kg |
|----------------------------------------|---------|---------|
| Cardiac output<br>(l/min)              | 0.911   | 0.603   |
| Mean circulation time<br>(sec)         | 9.36    | 13.21   |
| Heart rate<br>(beats/min)              | 171     | 150     |
| Systolic pressure<br>(mm Hg)           | 140     | 25      |
| Diastolic pressure<br>(mm Hg)          | 80      | 15      |
| Mean blood pressure<br>(mm Hg)         | 100     | 19.6    |
| Left ventricular work<br>(kg-m/min)    | 0.96    | 0.18    |
| Total peripheral resistance<br>(P R U) | 6.6     | 6.56    |
| Stroke volume<br>(ml/beat)             | 5.3     | 4.6     |
| Central blood volume<br>(ml/min)       | 187.6   | 169.3   |

## 中 文 摘 要

### 用色素稀釋的方法研究蛇毒對狗體循環的影響

不同濃度的蛇毒分別爲 60 r/kg, 120 r/kg, 0.1 mg/kg, 0.5 mg/kg……等由靜脈注入狗體內，研究其血流力學之變化。蛇毒由靜脈注入後立刻產生明顯的血壓下降，同時伴隨着顯著心排出量和左心室作功機能的減少。在注入後30秒內血壓開始改變，五分鐘時降至最低點，爲原來對照時的45%之後血壓，心排出量漸次恢復到正常的狀態。蛇毒引起初期動脈血壓的下降是由於心臟左心室作功顯著的減少，而中心靜脈血壓中心血量幾乎沒有改變，周圍末梢總阻力則微微的變化，但不明顯。蛇毒大量時引起周圍末梢總阻力和左心室作功顯著的減少。此時血壓的下降主要受左心室作功減少和血管擴張的影響。蛇毒對於切斷迷走神經，舌咽神經和注入阿託品及結紮頸動脈前後所引起循環系統的影響相似。低血壓現象依然存在，其影響不是中樞性的，蛇毒引起低血壓主要爲末梢性，其作用方式爲直接作用心臟和血管系統。