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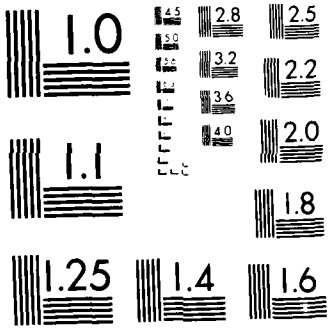

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Role of Afferent Nervous Stimulation in Hemorrhagic Shock

John D. O'Benar, Ph.D.

DIVISION OF MILITARY TRAUMA RESEARCH

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

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Pigs (25±5 kg) anesthetized with chloralose and urethane were used to determine the effects of sciatic nerve stimulation (square-wave, 70V, 0.3mA, 10 Hz bursts) on the physiologic responses to rapid hemorrhage (28 ml/kg over 15 min). Compared to sham-operated controls (n=10), a majority (n=17) of the stimulated animals showed significant elevations in blood pressure and cardiac output. There were no effects of stimulation on right atrial, pulmonary artery or pulmonary capillary wedge pressure. Although plasma epinephrine and norepinephrine levels were greatly elevated by hemorrhage, there was too much variability to ascertain responses to stimulation. Sectioning the nerve proximal (but not distal) to the stimulating electrodes abolished all hemodynamic effects. A minority of animals (n=5) showed hypotensive responses to sciatic stimulation. These responses may have been due to a selective activation of a subpopulation of afferents. We conclude that hemorrhage accompanied by afferent, stimulation results in a hemodynamic status different than exists following blood loss alone.

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ABSTRACT

Pigs (25±5 kg) anesthetized with chloralose and urethane were used to determine the effects of sciatic nerve stimulation (square-wave, 70V, 0.3mA, 10 Hz bursts) on the physiologic responses to rapid hemorrhage (28 ml/kg over 15 min). Compared to sham-operated controls (n=10), a majority (n=17) of the stimulated animals showed significant elevations in blood pressure and cardiac output. There were no effects of stimulation on right atrial, pulmonary artery or pulmonary capillary wedge pressure. Although plasma epinephrine and norepinephrine levels were greatly elevated by hemorrhage, there was too much variability to ascertain responses to stimulation. Sectioning the nerve proximal (but not distal) to the stimulating electrodes abolished all hemodynamic effects. A minority of animals (n=5) showed hypotensive responses to sciatic stimulation. These responses may have been due to a selective activation of a subpopulation of afferents. We conclude that hemorrhage accompanied by afferent stimulation results in a hemodynamic status different than that which exists following blood loss alone.

INTRODUCTION

One of the problems in shock research is the development of an animal model which imitates the responses of humans during hemorrhage induced by trauma. In the Division of Military Trauma Research, a fixed-volume withdrawal model (and its variations) was developed to supplant the fixed-pressure or "Wiggers" model because of its greater similarity to the actual situation encountered in a patient undergoing blood loss (1). The rationale has been that a wounded soldier does not exsanguinate to some fixed level of hypotension and maintain that level until transfusion; instead he suffers a blood loss dependent on the location and severity of his wound and with blood pressure constantly adjusted and readjusted according to whatever impaired homeostatic mechanisms can provide.

Hemorrhage to find volume without continuous volume adjustment to maintain pressure is thus more likely to replicate the situation in the combat casualty, but it still lacks one essential verisimilitude--the trauma itself. It would be of value, therefore, if--even under conditions imposed by anesthesia--some of the traumatic aspects of casualty could be added to the fixed-volume hemorrhage model under controlled laboratory conditions. In this regard, the aspect of trauma to be addressed in this protocol is that of the afferent input which invariably accompanies injury.

Shock researchers were aware of the confounding effect of afferent input as long as forty years ago. Many noted that the symptoms and severity of shock due to hemorrhage differed from those encountered after trauma (2, 3). An attempt to study these differences was made by Gregersen (4, 5) who found that CNS depression was more pronounced in traumatic shock than in hemorrhagic shock. In those instances where both types of shock produced the same degree of hypovolemia, blood pressure was maintained at higher levels after limb trauma than after hemorrhage (4). This difference could be abolished if the trauma experiments were done following elimination of afferent input by spinal cord transection (5).

In studying shock induced by traumatizing hind limb muscle, Eversole and coworkers (6) found that spinal

anesthesia prevented some symptoms of otherwise fatal shock and that local anesthesia of the traumatized region with a 4 percent procaine solution prevented fatal shock in 7 of the 10 animals tested. They concluded that afferent nociceptive input associated with the trauma was an important contributing factor to the overall shock syndrome.

Shock with trauma often proves to be more fatal than shock produced by hemorrhage alone (7, 8). This is illustrated by the fact that the blood volume reduction to produce 50% mortality was significantly greater following hemorrhage than with accompanying trauma. This suggested that stimulation of afferent nerves decreased the resistance to blood loss. To verify this, Overman and Wang (9, 10) subjected dogs to sublethal hemorrhage, after which the central ends of the sciatic nerves were stimulated electrically. In these studies 50% mortality occurred at considerably lower blood volumes caused by hemorrhage plus stimulation than at those caused by hemorrhage alone. Furthermore, the alterations of heart rate, blood pressure and clinical appearance approximated those seen in clinical shock. To further finalize the role of afferent stimulation, they performed a study with the afferent nerves sectioned at the lumbosacral level and this caused the LD_{50} to occur after significantly higher blood volume had been lost (11). In addition to all of the foregoing evidence that trauma adds an afferent effect to hemorrhage which worsens the syndrome, there is also evidence that the basic pharmacologic response of the animal can differ qualitatively. Powers et al (12) produced traumatic and hemorrhagic hypotension of equal severity in dogs and then administered morphine. The narcotic had a pressor effect in the hemorrhaged animals but worsened the hypotension in the traumatized ones. It is tempting to speculate on the different status of these groups in view of modern developments surrounding endogenous opiates.

The purpose of the present study is to assess the effects of hemorrhage, with and without sciatic nerve stimulation, on hemodynamic status and catecholamine secretion. Catecholamines in plasma have been shown to increase both after hemorrhage (13) and after traumatic stimulation (14), but it is uncertain how these two responses will interact under conditions of combined hemorrhage and nociceptive stimulation.

MATERIALS AND METHODS

Yorkshire pigs (n=34, body weight 24.5 ± 3.8 kg) were premedicated with ketamine (2.2 mg/kg), xylazine (2.2 mg/kg) and atropine (0.08 mg/kg) given as an intramuscular injection. Then the animals were anesthetized with halothane, intubated, and maintained with halothane and nitrous oxide during instrumentation. An arterial line was placed via the femoral artery and advanced in the abdominal aorta to approximately the level of the diaphragm for recording arterial pressure. A catheter was also placed in the contralateral femoral artery and connected to a variable speed Masterflex pump for blood withdrawal. Via the femoral vein, a Swan Ganz catheter was placed into the pulmonary artery using the pressure tracing and the occurrence of wedge pressure as a guide. This catheter was used to record pulmonary artery pressure and central venous pressure as well as cardiac output by the thermodilution technique. Rectal temperature was recorded and maintained within normal limits using one or two thermal blankets.

After instrumentation, the ventilator was disconnected and the animal was weaned from halothane anesthesia after intravenous injection of a chloralose (15 mg/kg) and urethane (50 mg/kg) mixture to minimize the hypotensive effect of halothane and to restore a more active baroreflex. Arterial and venous pressures as well as cardiac output were monitored continuously over this transition period. A twenty-minute stabilization period was then allowed, over which heart rate and arterial pressure remained reasonably constant (within ± 10%). At this point baseline readings and samples were obtained.

After control readings, the arterial hemorrhage was begun at a fixed rate. The rate was determined by the goal of a 40% blood loss (28 ml/kg) over 15 minutes. The blood was removed at as constant a rate as possible. The Masterflex pump was adjusted slightly during hemorrhage so as to meet this target value. Another set of data was taken immediately after blood removal.

At this point, in experimental animals (n=17), two 10-minute periods of sciatic nerve stimulation (70V,

0.3mA, isolated square wave, 10 Hz trains, 2 trains/sec) were administered via a Grass 588 stimulator, separated by a twenty-minute rest period. Control animals (n=10) were treated identically, including isolation of the nerve and placement of the electrodes but the current was not applied. Data points were taken as follows: before hemorrhage, after hemorrhage, 5 minutes after stimulus was turned on, at the termination of 10 min of stimulation, 5 minutes before the application of the second stimulus, 5 minutes after stimulation, at the end of 10 minutes of stimulation and 20 minutes after the stimulus was terminated. Arterial blood samples were also obtained at these data points for catecholamine analysis by high-performance liquid chromatography with electrochemical detection.

In two additional animals the same data were obtained in nerve section experiments. In one the nerve was cut distal and in one proximal to the stimulating electrodes to ascertain whether any response obtained was purely the result of afferent impulses generated by the stimulus.

Data collected after hemorrhage were subjected to two-way analysis of variance followed by a Newman-Keuls test to identify significant differences at the $p<0.05$ level. The data collected before hemorrhage were not included in the statistical analysis to minimize the effects of pre-hemorrhage differences. In 5 animals the stimulus was hypotensive and these animals were removed from analysis.

RESULTS AND DISCUSSION

The mean arterial pressure fell dramatically in both stimulated and unstimulated groups after a 40% blood loss from a control value of 98 mmHg to a post-hemorrhage value of 27 to 35 mmHg (Fig. 1) with no significant difference between groups. After initiation of the stimulus, the arterial pressure rose (with a latency of 12 to 25 seconds) to 62 mmHg while the controls remained below 35 mmHg, a difference that was statistically significant. Arterial pressure continued to increase in both groups with that of the stimulated group remaining statistically higher than that of the control. Special notice was taken of the

sharp pressure increase occurring after the onset of the second stimulation period. After termination of the stimulation the pressure dropped from this elevated value so that 20 minutes after cessation of stimulation there again was no difference between the stimulated group and controls.

Cardiac output data (Fig. 2) showed time courses and intergroup differences similar to those for arterial pressures. Again, increases in cardiac outputs were noted after the onset of electrical stimulation for both periods of afferent activation, but after the second period of stimulation the output in the experimental group rapidly declined until there was no significant difference between the two groups.

In contrast to cardiac output and arterial pressure, there were no consistent differences between the groups in central venous, pulmonary artery or pulmonary capillary wedge pressures.

Data for heart rates are shown in Fig. 3. Although hemorrhage produced a major increase in heart rate for both groups, sciatic stimulation did not cause any significant change in heart rate at any time. The derived hemodynamic parameters of stroke volume and total peripheral resistance are shown in Figures 4 and 5. In the case of total peripheral resistance, it is clear that hemorrhage caused an increase in this variable which continued during the entire course of the experiment. No differences between control and experimental groups were evident, implying that resistance changes were not responsible for the increased arterial pressure during stimulation. Stroke volume, by contrast, was higher in the stimulated group, albeit the difference was not statistically significant. The trend is obvious, however, including the small increment that occurs after the onset of the second period of stimulation. After this period, stroke volume rapidly declined to the same low level as that of the unstimulated control group. Given that cardiac output but not the heart rate increased during stimulation, it is reasonable to conclude that stroke volume did indeed rise, possibly due to a reflexly mediated increase in the inotropic state. Alternatively, venous return could have increased via a decrease in vascular capacitance somehow elicited by stimulation.

The plasma catecholamine levels during the experiment are shown in Figure 6 and 7. The concentrations of both epinephrine and norepinephrine were increased by hemorrhage. Although norepinephrine levels tended to be higher in the stimulated group, there was no significant group effect for this parameter. Thus the cardiostimulatory effect of sciatic stimulation could not be attributed to a circulatory catecholaminergic effect.

In the nerve sectioning experiments it was determined that cutting the nerve proximal (but not distal) to the stimulating electrodes abolished all hemodynamic effects. This is taken to mean that these effects were mediated wholly by afferent input, possibly nociceptive, to the central nervous system and not the result of any afferent effect such as the release of metabolites by the distally contracting muscle

In addition to the animals reported above, a small proportion of animals (n=5) showed hypotensive responses to sciatic stimulation. These responses were transitory and of low amplitude and were generally noticed in a deeper anesthetic state or after more severe responses to hemorrhage. There were no statistically significant differences between the unstimulated group and these depressed responses, possibly because of the small sample size and great variability involved. It is possible that such anomalous responses may have been due to a selective subpopulation of afferent fibers. Alternatively, such responses may have been the result of a qualitatively different state of the neural substrate in central regions of the system.

In summary, of the 34 animals utilized, 17 showed definitive hypertensive and positive inotropic responses to stimulation, 10 were sham-stimulated controls, 2 were used in sectioning experiments and 5 showed inconsistent hypotensive responses that were not statistically different from controls. The significance of these findings for the combat surgeon may be that a blood pressure reading might be higher in a casualty who is suffering pain than would be consistent with the volume of blood loss observed or suspected.

Also, in patients given pain medication, an increase in blood pressure or cardiac output may not represent real "clinical improvement" but could merely be the manifestation of the mechanism described in this paper becoming evident as the medication becomes less effective.

Conclusions

Electrical stimulation of the sciatic nerve after hemorrhage typically resulted in an elevation of blood pressure and cardiac output. These effects of sciatic nerve stimulation resulted entirely from the activation of afferent fibers.

Plasma epinephrine and norepinephrine concentrations rose after hemorrhage, but the hormone levels did not differ between the stimulated group and the sham-stimulated controls.

The increase in cardiac output following nerve stimulation is very likely due to an increase in stroke volume rather than heart rate.

The hemodynamic status following hemorrhage in an animal subjected to stimulation differs substantially from that induced by blood loss alone.

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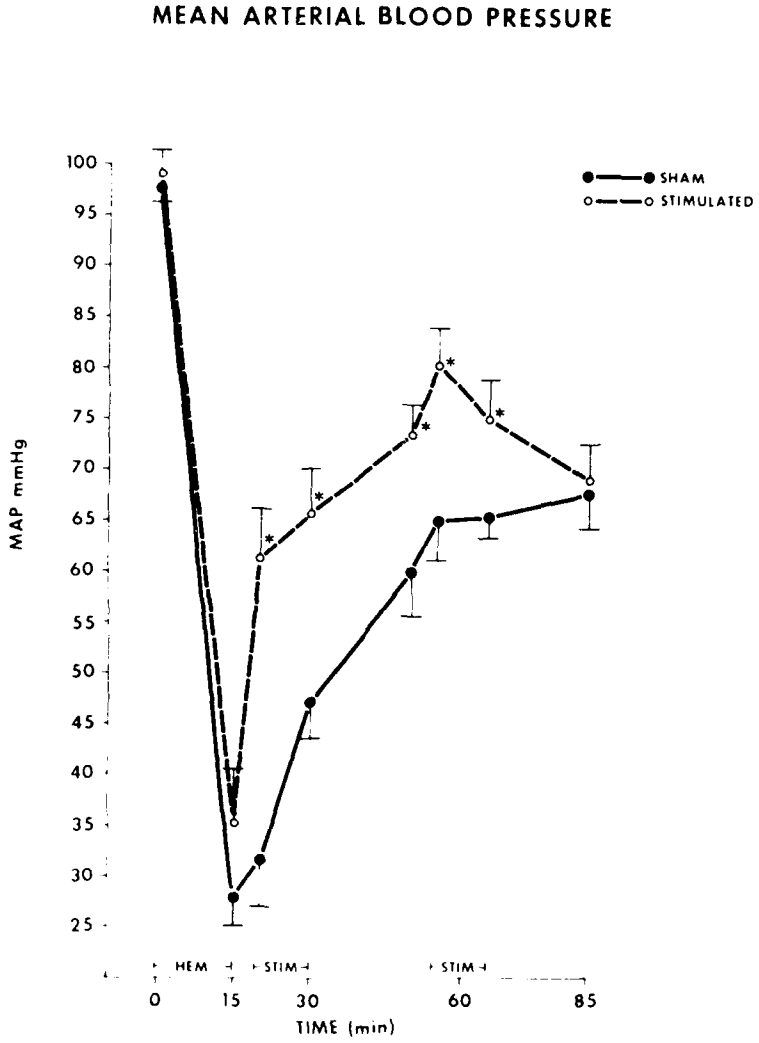

Figure 1. Mean arterial blood pressure versus time for experimental (n=17) and control (n=10) groups. Difference after termination of hemorrhage significant at the $p<0.05$ level indicated by * in this and subsequent figures.

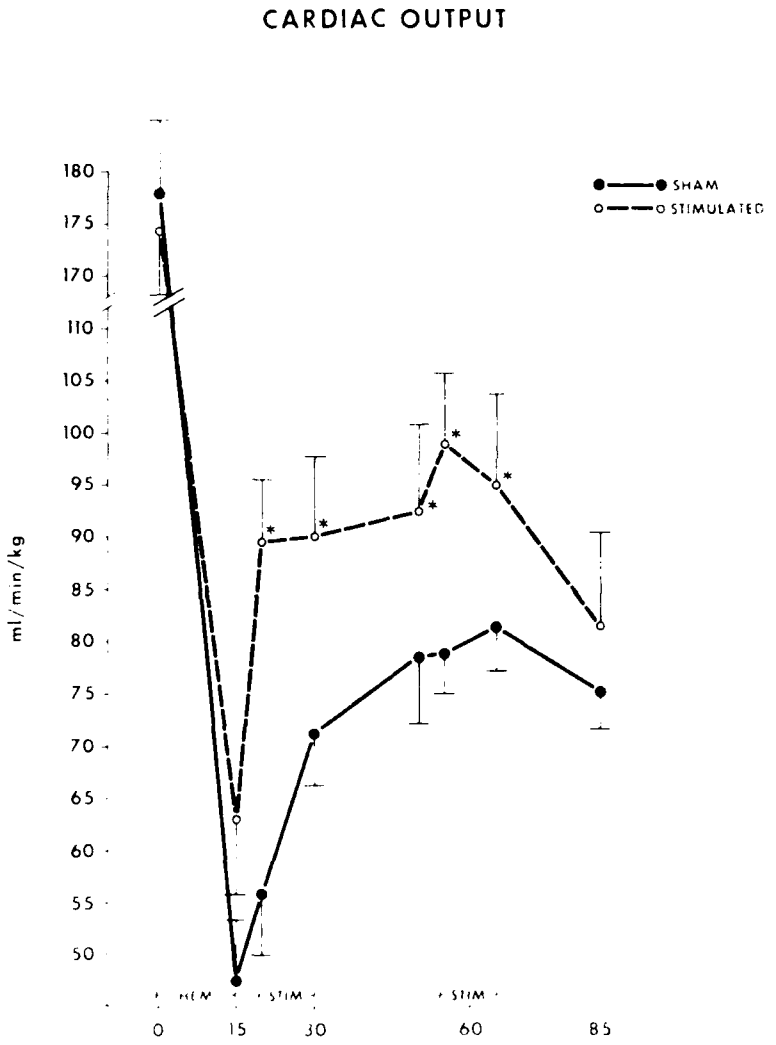

Figure 2. Cardiac output versus time for both groups.

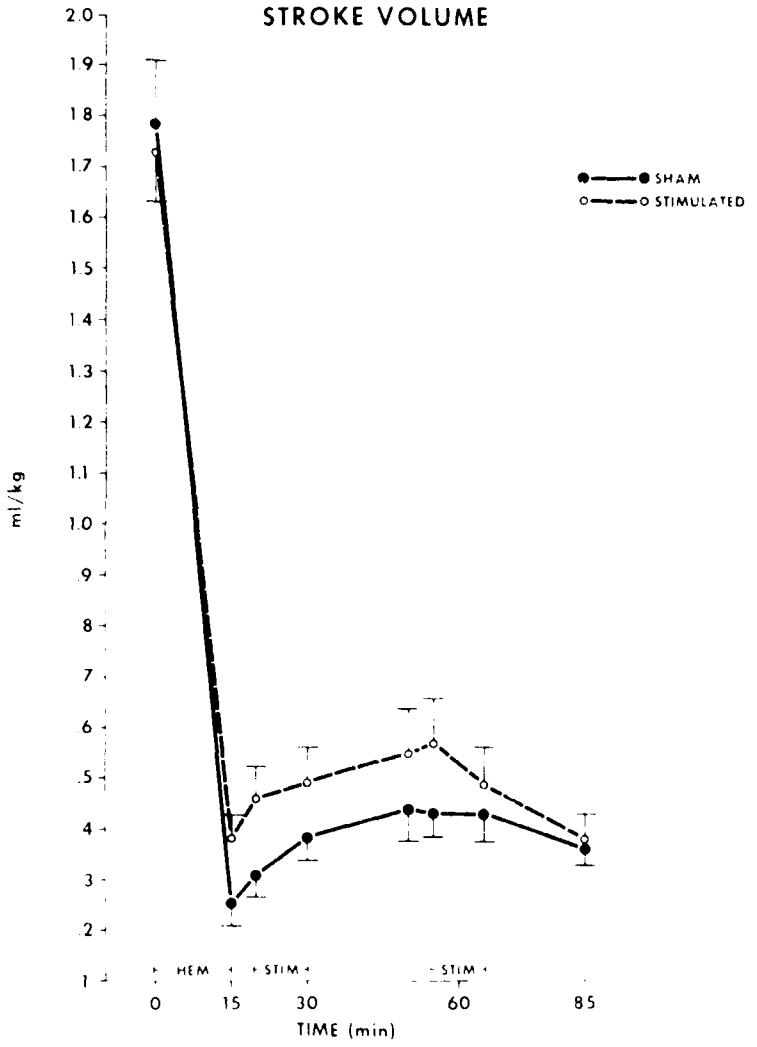

Figure 4. Stroke volume versus time for both groups.

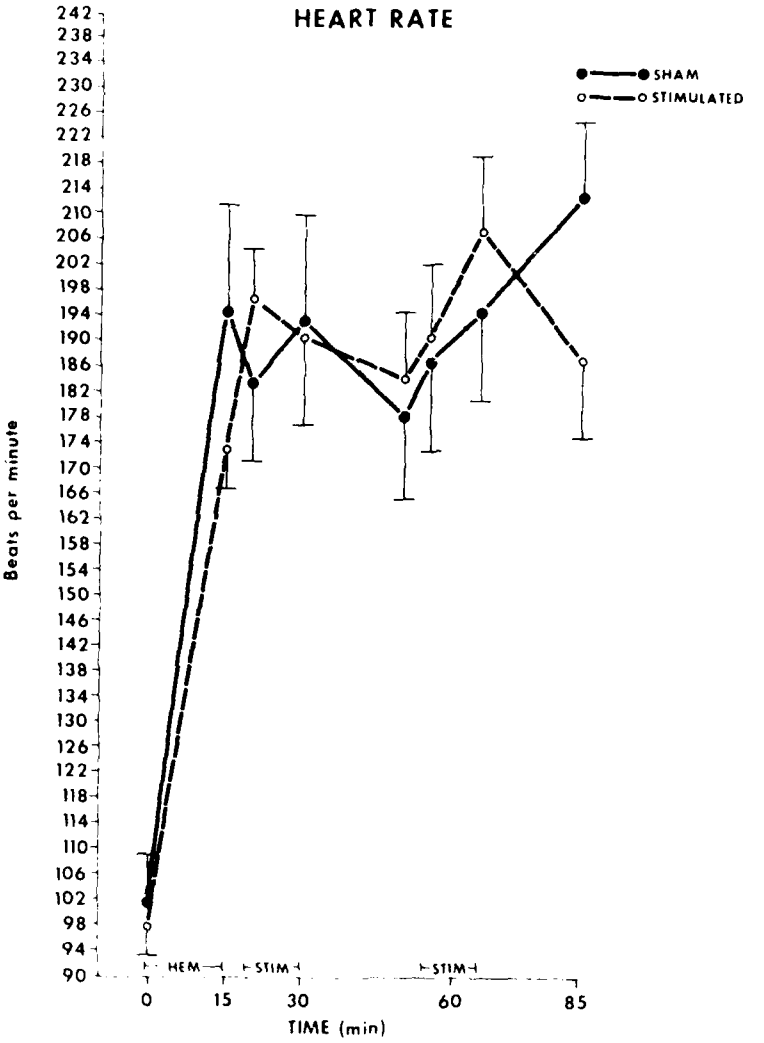

Figure 3. Heart rate versus time for both groups.

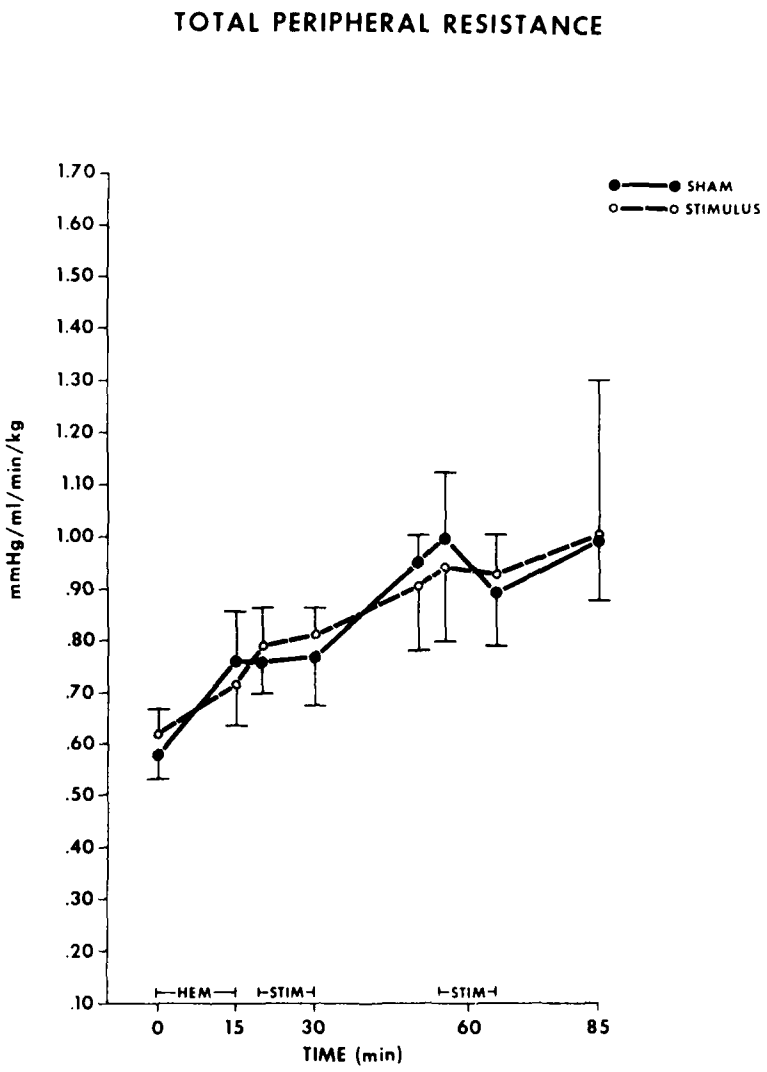

Figure 5. Total peripheral resistance versus time for both groups.

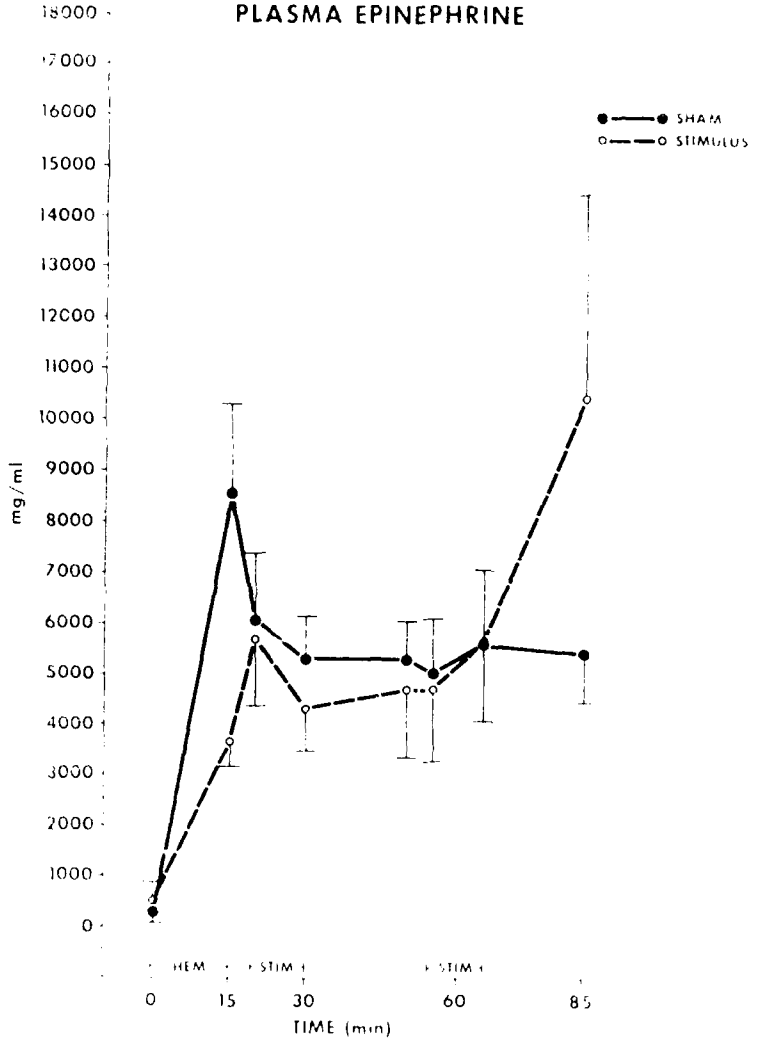

Figure 6. Plasma epinephrine versus time for both groups.

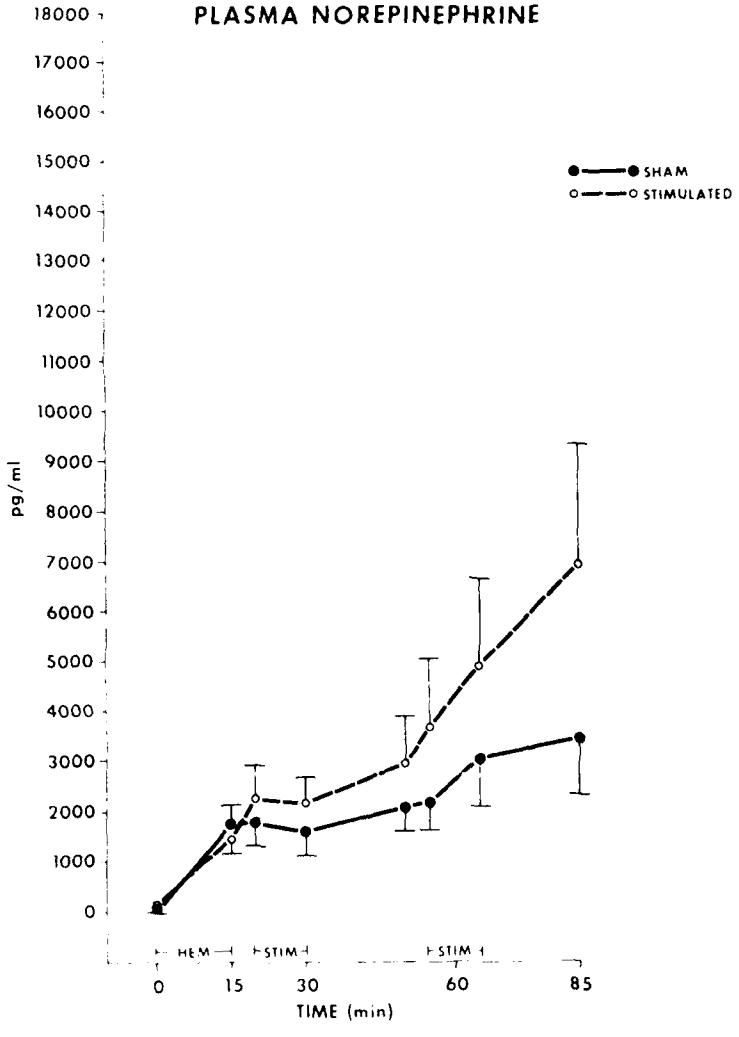

Figure 7. Plasma norepinephrine versus time for both groups.

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