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Special Aspects of Aviation Occupational Medicine

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by

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CARDIOVASCULAR AND NERVOUS SYSTEM EFFECTS OF BROMOTRIFLUOROMETHANE

by

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CARDIOVASCULAR AND NERVOUS SYSTEM EFFECTS OF BROMOTRIFLUOROMETHANE

K.C.Back and E.W.Van Stee

In aviation there is intense interest in the development and up-dating of chemical fire extinguishing agents and systems. Designs range from fully automated fire protection systems to hand held portable fire extinguishers and uses extend from aircraft and ballistic systems to everyday applications for working and storage areas. The chemical agents which appear to be most effective for many fire fighting applications are haloalkanes. Of these, three fluorocarbons have been determined to be of special interest. The compounds are designated as F1301 or $CBrF_3$, F1211 or CF_2BrCl and F2402 or F_2BrCl-$CBrF_2$. F1301 has been given the most attention as a candidate all-purpose extinguishing agent and, for that reason, it has also been afforded the most effort to understand its biological (toxicological) properties. This paper will review pertinent experiments performed to assess the toxic hazards associated with the use of F1301 ($CBrF_3$) and to come to some understanding of the mechanisms of its pharmacodynamic properties. The ultimate goals of this effort are to help establish human exposure limits considering both operator performance and reversibility of effects for use in accidental exposure situations, and for governing occupational exposures to personnel whose jobs require routine handling of such chemicals.

In the first experiments, we studied the effects of breathing mixtures of 10 to 80% $CBrF_3$ mixed with oxygen on dogs, monkeys and baboons[1].

Twelve beagle dogs (five males, seven females) 18-30 months of age which weighed 7.8-12.4 kg, four young adult female monkeys (Macaca mulatta) which weighed 4.6-6.1 kg, and two female baboons (Papio sp.) which weighed 10.0 and 12.5 kg were exposed to 10, 20, 30, 40, 50, 60, 70 or 80% bromotrifluoromethane ($CBrF_3$) in oxygen.

Conscious monkeys were restrained in a chair device. Dogs were restrained in a ventilated box of our own design in the normal ventrum-down posture of a reclining dog.

Five of the twelve and all four monkeys were exposed to $CBrF_3$ while conscious. All the animals used were exposed to $CBrF_3$ while anesthetized. A majority of the exposures were to concentrations greater than 40% $CBrF_3$. At least two exposures at each concentration from 10 to 80% were performed on at least five dogs and three monkeys in both the conscious and anesthetized states. The baboons were exposed only to 50-80% $CBrF_3$.

Two dogs under pentobarbital anesthesia were exposed to an 80% mixture of $CBrF_3$ in O_2 for 35 and 40 minutes, respectively. The intravenous injection of 10 μg/kg of epinephrine resulted in ventricular fibrillation and cardiac arrest in both animals (Fig.1).

The general response of the dog to nonlethal exposures of $CBrF_3$ consisted of a cardiovascular effect and a central nervous system effect. All the central nervous manifestations of $CBrF_3$ toxicity which were observed in the conscious dog were eliminated by the induction of Stage III Plane I pentobarbital anesthesia. At least some alteration of cardiovascular function was seen in all dogs in all experiments, whether conscious or anesthetized, when the dogs were exposed to 20-30% or greater $CBrF_3$ levels.

The heart rate was irregularly increased by 10-15% from resting rates of 67-100 beats/min during the first several seconds of breathing 20-30% $CBrF_3$. The increase in heart rate was definite and regularly reproducible when the dogs were exposed to 40% or higher $CBrF_3$ concentrations. When arrhythmias appeared, which usually began 15-120 seconds after starting the exposure to $CBrF_3$, a simple tachycardia became impossible to distinguish.

An increase in heart rate accompanied by some degree of hypotension was studied most extensively while the dogs were breathing the 50% or 80% mixture. The blood pressure fall varied from 20 to 60 mmHg. The pulse pressure was decreased by 0-30 mmHg from an average normal of 40-55 mmHg.

The changes in heart rate, blood pressure, and pulse pressure reversed when an animal exposed to $CBrF_3$ was switched to room air. Recovery required approximately twice as long as development.

Figure 2 illustrates the results of a typical experiment in which an anesthetized dog was allowed to respire spontaneously a 50% mixture of $CBrF_3$. The most striking response to the $CBrF_3$ was the rapidly changing blood pressure. The heart rate changed irregularly with cardiac output generally varying directly with heart rate. Peripheral

vascular resistance was lowered during exposure to $CBrF_3$. Determinations of cardiac output and calculation of total peripheral vascular resistance during the $CBrF_3$ exposures were performed after 2-3 minutes of exposure and at the end of 5-minute exposures. Exposure to 50% $CBrF_3$ did not affect pulse pressure during the relatively short periods of these experiments. Longer exposures produced a gradual decrease in pulse pressure over a period of 25-30 minutes. Pulse pressure decreased more rapidly when the gas mixture contained 80% $CBrF_3$.

Four of the nine conscious dogs exposed to $CBrF_3$ had epileptiform convulsions of 10-30 second duration. The convulsions were characterized by generalized rigidity, apnea, and cyanosis of the tongue. The only apparent residual effects were an elevation in body temperature and fatigue which was associated with the muscular effort of the convulsion. Convulsions were precipitated with 2-5 successive exposures within a period of an hour. When exposed to 80% $CBrF_3$, the onset of the convulsions took place within 3-4 minutes. The length of exposure which was required to precipitate the convulsions was greater at lower concentrations of $CBrF_3$. Convulsions appeared after 12 minutes exposure to 50% $CBrF_3$, the lowest concentration which caused convulsions after any length of exposure under 40 minutes. The dogs that did not develop convulsions showed the same general signs of those that convulsed. Dogs exposed to 20% or greater concentrations of $CBrF_3$ became visibly agitated within 1-2 minutes. The severity of the agitation increased with the concentrations of $CBrF_3$. The dogs looked about the room apprehensively. Within 1-3 minutes generalized muscular tremors (shivering) could be distinguished. Episodes of shivering lasted a few seconds and recurred every 5-20 seconds. General anesthesia induced by pentobarbital or thiamylal blocked all central nervous system signs.

The responses of the monkeys and baboons to $CBrF_3$ were very similar.

Two monkeys and both baboons were exposed to 80% $CBrF_3$ under pentobarbital anesthesia for 10 minutes or more. The intravenous injection of 10 μg/kg of epinephrine produced little significant alteration of the ECG. Although brief episodes of ventricular fibrillation were observed, no deaths occurred.

The general responses of the primates to $CBrF_3$ bore many similarities to those of the dog. The cardiovascular response was similar to that of the dog except that cardiac arrest could not be induced with large doses of epinephrine during exposure to the compound. The central nervous response was markedly different from that of the dog.

All four monkeys which were exposed to $CBrF_3$ while conscious exhibited signs of cortical depression in contradistinction to the agitation exhibited by dogs. Shivering was observed in monkeys exposed to $CBrF_3$. This was accompanied by tranquilization of the normally aggressive behavior of macaques. Their eyelids remained half-closed and they refused to bare the teeth or bite. They remained conscious, however, and showed enough interest in orange juice to swallow a few drops when offered.

The next group of experiments was designed to examine the characteristics of the cardiac arrhythmias which often appeared spontaneously during exposure of animals to $CBrF_3$ (Ref.2).

Eight monkeys (Macaca mulatta) from 2 to 4 years old and weighing 2.5 to 5.0 kg were used. A single group of five of the monkeys was used for three different experiments. Animals were anesthetized with intravenous 4 percent pentobarbital sodium. An initial dose of 30 mg/kg was given and subsequent small injections were given to maintain Stage III, Plane I anesthesia. Femoral arterial and venous catheters were inserted. Endotracheal catheters were inserted and connected to a Harvard respiration pump and the monkeys were ventilated at 9 to 16 cpm. Arterial blood samples were obtained throughout the experiments at approximately 30-minute intervals and pH, P_{CO_2} determined.

During the first experiment (control) arterial blood pH was regulated between 7.35 and 7.45 with 100 percent O_2 at 10 respiratory cycles per minute by adjusting tidal volume. During the second experiment (acidosis) the arterial blood pH was regulated between 7.10 and 7.30 with oxygen to which was added 0 to 5 percent CO_2. The animals were ventilated at nine respiratory cycles per minute and a tidal volume of not less than 25 ml/kg. During the third experiment (alkalosis) the arterial blood pH was regulated between 7.50 and 7.80 with 100 percent O_2. The animals were ventilated at 12 to 16 respiratory cycles per minute and a tidal volume of about 35 ml/kg.

The animals were observed for 30 to 60 minutes in the control, acidotic, or alkalotic state and then exposed to 10, 20, 30, 40, 50, 60, 70 and 80 percent $CBrF_3$ in O_2 (or O_2 and CO_2) for 10-minute periods in succession. Electrocardiogram Lead II was monitored on a Grass direct-writing electrocardiograph. Arrhythmias resulting from ventricular ectopic pacemaker formation appeared spontaneously during the first 5 minutes of exposure to 30 percent or greater concentrations of $CBrF_3$. When the arrhythmias appeared the arterial blood pressure, monitored using a Statham pressure transducer, was lowered by bleeding from a vein. The blood pressure was lowered until the arrhythmias were abolished; then the blood was reinfused which returned the blood pressure to normal and caused the reappearance of the arrhythmias (Figure 3, lower tracing). Exsanguination and reinfusion were performed at each concentration of $CBrF_3$ from 30 to 80 percent. The successive exposures were performed twice on each animal during each experiment, providing 4 arterial blood pressure values at which arrhythmias were abolished or reappeared for each animal, at each concentration, and in each acid-base state. Arterial blood pressure in most cases was not high enough to trigger arrhythmias spontaneously at $CBrF_3$ concentrations of 10 and 20 percent. During these exposures epinephrine was infused to raise the blood pressure to levels high enough to trigger arrhythmias (Figure 4, upper tracing).

The data, in brief, on the acid-base balance experiments show that acidosis decreased the threshold for arrhythmias and alkalosis increased the threshold at concentrations of 10 to 20% $CBrF_3$ but were without effect at concentrations greater than 30%.

The upper tracing of Figure 4 illustrates how the arrhythmias were induced by the expansion of the plasma volume with 6% dextran to raise blood pressure. The lower tracing of Figure 4 shows the development of arrhythmias by aortic constriction to raise blood pressure. The arrhythmias were abolished following release of the aortic constriction.

In another group of experiments using anesthetized dogs, it was found that exposure to 70% $CBrF_3$ produced a fall in total arterial blood pressure without a significant decrease in cardiac output which indicated a fall in peripheral resistance[3]. Experiments with open-chested animals indicated that $CBrF_3$ reduced myocardial contractility as evidenced by a rise in left ventricular end diastolic pressure (see Figure 5).

The next set of experiments were designed to determine the cause or causes of blood pressure changes during exposure to $CBrF_3$.

The purpose of the first group of experiments described hereafter was to determine if (i) the blood pressure decrease was the result of a peripheral vascular resistance change. If so, (ii) was the peripheral vascular resistance change the result of a direct vascular smooth muscle effect, a neurogenic vasomotor effect, or a combination of the two? And the purpose of the second set of experiments (iii) was to determine if exposure to $CBrF_3$ significantly impaired ganglionic transmission[4].

Thirty-seven male beagles weighing from 7.7 to 13.6 kg were selected. They were free from obvious diseases, defects and parasites. They were housed in individual cages and maintained on a standard laboratory diet and water *ad libitum*. Food was withheld for 24 hours prior to the experiment.

Blood was cross-matched for each pair of the 32 dogs selected for the 16 cross-circulation experiments.

The dogs used in the cross-circulation experiments were anesthetized with a single intravenous dose of thiamylal sodium (18 mg/kg in 4% solution). Endotracheal and venous catheters were inserted. Immobilization was maintained by the continuous intravenous infusion of 10% alpha-chloralose in polyethylene glycol (PEG-200) at a nominal rate of 20 mg/kg/hr. Cutdown sites were infiltrated subcutaneously with 0.5% lidocaine hydrochloride prior to surgery.

The dogs were ventilated mechanically at a tidal volume of 125 ml and rate of 14-18 cycles per minute. Respiratory rate was regulated manually throughout the experiments in order to maintain arterial blood pH between 7.35 and 7.45 and P_{CO_2} between 35 and 45 torr. Blood gas and pH determinations were made with a blood gas analyzer.

Polyethylene catheters were inserted into a brachial artery of each dog. The catheters were attached to pressure transducers and recordings made on a direct-writing recorder.

A polyethylene catheter was advanced to the level of the abdominal aorta through a femoral artery of one of the dogs (donor). The catheter was attached to a length of vinyl tubing that passed through the finger mechanism of a constant-flow perfusion pump. The outflow end of the pump tubing contained a bubble trap and a "T" for attachment to a pressure transducer. The end of the tubing was connected to a polyethylene catheter that was inserted in a peripheral direction 2 cm into a femoral artery of the other dog (recipient). The venous effluent was returned to the donor by gravitation through polyethylene catheters leading from the femoral vein of the perfused hind limb (HL) of the recipient to the post cava of the donor via a femoral vein of the donor. the extracorporeal circuit was filled with cross-matched blood from a third donor. A tight nylon ligature was placed around the perfused hind limb as high on the leg as possible to minimize the mixing of the circulations. The perfusion rate was regulated between 8.0 and 15.5 ml/min to establish a control pressure that approximated the arterial blood pressure of the recipient.

Twenty to thirty mg of sodium heparin was given to the donor intravenously.

The perfused leg temperature was maintained with hot water bottles and thermal insulation.

The donor was ventilated with 100% O_2 at all times except when it was being exposed to a fluorocarbon mixture. The recipient was ventilated with air between exposures.

Mixtures of about 70% (67-70%) bromotrifluoromethane (99.7% purity) in O_2 were made by flowing the respective gases into a mixing bag volumetrically. Exposure of the dogs was performed by attaching a hose from the mixing bag to the appropriate respiration pump inlet.

Electrocardiograms (Lead II) were recorded from each dog throughout the experiments (see Figure 6).

The dogs used in the ganglionic transmission experiments were given subcutaneous injections of 1.5 ml of a mixture of 0.4 mg/ml fentanyl and 20 mg/ml droperiodol. Thirty minutes later an intravenous injection of 10 mg/kg of pentobarbital sodium was given followed by fractional doses of pentobarbital sufficient to maintain light surgical anesthesia (Plane I, Stage III). Arterial blood pressure was monitored as described for the previous set of experiments. Nictitating membrane tension was determined using a force displacement transducer attached to the membrane with a silk thread.

Following anesthetization the right vagosympathetic trunk was transected and silver wire electrodes from a constant voltage stimulator were attached to the central and peripheral cut ends of the trunk. Ten-second trains of 5 v, 100 Hz, 1 msec, biphasic pulses were delivered to the central cut end and 5-second, 5-10 v, 100 Hz, 1 msec, biphasic pulses were delivered to the peripheral cut end at the appropriate times during the experiment.

The experiment was designed with a pre-exposure control period, an exposure period, and a postexposure period. The animals were exposed to 80% $CBrF_3$ in O_2 for 40-78 minutes during the exposure period and to air at other times. During the consecutive periods the following determinations were performed.

At intervals of 3 to 5 minutes 3 trains of electrical stimuli were applied first to the central and then to the peripheral cut ends of the vagosympathetic trunk. Nictitating membrane tension was recorded during electrical stimulation of the central cut end of the vagosympathetic trunk and blood pressure was recorded during the other procedure. Recordings were obtained prior to exposure, during exposure (beginning not before 10 minutes of exposure to the $CBrF_3$) and postexposure (beginning not before 30 minutes postexposure).

The results of the cross-circulation experiments are as follows. Exposure of the donor (Fig.7) to $CBrF_3$ was accompanied by an average decrease in mean arterial blood pressure of 31 torr. Four of the 16 donor dogs were pretreated with reserpine which greatly attenuated their hypotensive response to $CBrF_3$ and observations made on these animals were not included in these calculations. The mean perfusion pressure of the recipient HL was unchanged by the exposure of the donor to $CBrF_3$.

Exposure of the recipient (Fig.8), on the other hand, resulted in not only an average decrease of 25 torr in the recipient mean arterial blood pressure, but also an average decrease of 22 torr in the HL mean perfusion pressure.

The decrease in the HL perfusion pressure during $CBrF_3$ exposure of the recipient was largely abolished by the pretreatment of the HL with phenoxybenzamine (Figs.10, 11), a treatment that was without a significant effect on the recipient systemic arterial blood pressure decrease during the exposure. Pretreatment of the recipient with hexamethonium completely abolished the pressure change responses in both the recipient mean arterial and HL mean perfusion pressures (Fig.9).

Results of the ganglionic transmission experiments are as follows. Figure 12 illustrates the effect of exposure to 80% $CBrF_3$ on nictitating membrane (membrana nictitans) tension (M.N. Tension) during constant electrical stimulation of the central cut end of the vagosympathetic trunk (sympathetic innervation of the nictitating membrane via the superior cervical ganglion). Tension is given in arbitrary units. Tension was reduced by 40 percent or more during the exposure. The tension returned to pre-exposure values after 30 minutes postexposure.

Figure 13 illustrates the effect of exposure to $CBrF_3$ on vagal inhibition of the heart. Prior to exposure the stimulus was adjusted to just produce a brief cardiac arrest followed by excape from the vagal inhibition. The identical stimulus was subsequently applied during exposure and postexposure. Vagal inhibition was shown to be significantly reduced during the period of $CBrF_3$ exposure and to return to control values postexposure.

A few words concerning the effects of $CBrF_3$ on the central nervous systems other than outward signs of intoxication, as shown by convulsions in dogs or loss of aggressiveness in conscious monkeys, are in order. In dogs and monkeys immobilized with tubocurarine and exposed to 70-80% $CBrF_3$, the most significant findings were dominance of the EEG's by 6-9 Hz waves beginning 2-3 minutes after exposure, and a nearly normal susceptibility of the EEG to activation by auditory and photic stimuli. This is different than during anesthetic exposure to halothane[5].

In another group of experiments, Chikos et al. presented data to support the hypothesis that $CBrF_3$ produces cortical depression with relative sparing of the reticular activating system, permitting alterations in performance without loss of consciousness in the monkey[6].

Carter et al. reported on the effects of $CBrF_3$ on performance in trained monkeys. Seven monkeys trained on continuous and discrete avoidance performance tasks were exposed to concentrations of $CBrF_3$ ranging from 10.5 to 42.0%. Significant performance decrements were observed in all subjects during exposures of 20-25% $CBrF_3$. Higher concentrations resulted in impaired performance to the point of complete disruption of operant behavior in some subjects. No visible signs of central nervous system depression or analgesia accompanied this loss of ability to perform on conditioned performance tasks. These results suggest that the mechanism by which $CBrF_3$ causes impaired performance differs from the central nervous system depression and analgesia produced by halogenated anesthetics[7].

We have performed some experiments on two other compounds; namely, F2402 and F1211 for comparative purposes. Preliminary sereening of F1211 ($CBrClF_2$) for cardiovascular effects has been completed in 2 sets of experiments with repeated observations within each experimental setup. Although this sample size is not large enough for a definitive statement of the cardiovascular consequences of F1211 exposure, the technics involved have been in use in our laboratory for a considerable length of time and are known to be highly reliable. The additional experiments that will complete this study are not expected to alter the conclusions significantly from those expressed here.

Donor and recipient dogs, respectively, were exposed to 15% F1211 for 5 minutes in cross-circulation experiments as described earlier for experiments with F1301. Exposure of the donor resulted in a decrease in the donor mean arterial blood pressure with no change in the cross circulated hind limb perfusion pressure (constant perfusion flow rate). Exposure of the recipient, on the other hand, resulted in a decrease of both the recipient mean arterial blood pressure and hind limb perfusion pressure. These responses to F1211 exposure were unaltered by the pretreatment of both dogs with 0.3 mg/kg atropine sulfate and pretreatment of the donor (and, hence, the recipient perfused hind limb) with 2 mg/kg of propranolol intravenously. Ten mg/kg of hexamethonium given intravenously to the recipient dog prevented the change in hind limb perfusion pressure during exposure of the recipient to F1211.

These experiments suggest that exposure to F1211 resulted in a decrease in peripheral vascular resistance by causing a decrease in vasoconstrictor tone. F1211 was shown not to have a direct peripheral vascular smooth muscle effect or cause the indirect release of vasoactive humoral agents or local accumulation of vasoactive metabolites. The decreased peripheral vascular resistance was shown not to be the result of the activation of vasodilatory beta-adrenergic or cholinergic receptors peripherally or of active vasodilatation mediated centrally.

A complementary set of experiments has been performed using single, open-chested, 10 kg dogs. Dogs were exposed to 15% F1211 for 5 minutes, and responses monitored continuously from a period pre-exposure to 20-25 minutes postexposure. The exposure to F1211 resulted in a reversible decrease in mean arterial pressure. The fall in blood pressure was attributed to a decrease in vasoconstrictor tone and a negative inotropic effect on the heart. The decrease in peripheral vascular resistance was of sufficient magnitude that cardiac output rose during the exposure[8].

In summary, F1301, F1211 and F2402 possess pharmacodynamic actions of the same qualitative kind. The difference between the compounds tend to be related to the dose of each necessary to produce the effects noted on blood pressure, cardiac rhythmicity and the nervous system. Work remains, though, to quantitate the effects of each compound so that they can be placed in a relative order of biological potency. These data can then be used to assess a relative hazard index and hence, enable engineers and medical authorities to select jointly the best fire-fighting agent for a specific application while keeping the toxicological hazard at a minimum. Preliminary data indicate that F1301 at 80% has the same relative biologic potency on dog blood pressure as 15% F1211 and 1% F2402. These and other data show that F1301 is safe to use at levels below 6% in air for 6 minutes without protection as is F1211 at 5% or below for the same time period. Exposure to F2402 should be kept at a minimum and respiratory protection should be used until more data can be obtained. The important thing to recognize is that any of these agents can and should be used for fighting fires if the proper precautions are taken. Much too often, an agent becomes deleted from use because of fears of toxic effects. It is out contention that if the agent is the best available for the specific use intended one should recognize the toxic hazards and, one should engineer around these hazards in order to get the job done. An aircraft fire is of greater consequence, in most instances, than any toxicity which might accrue from the agent used to put it out.

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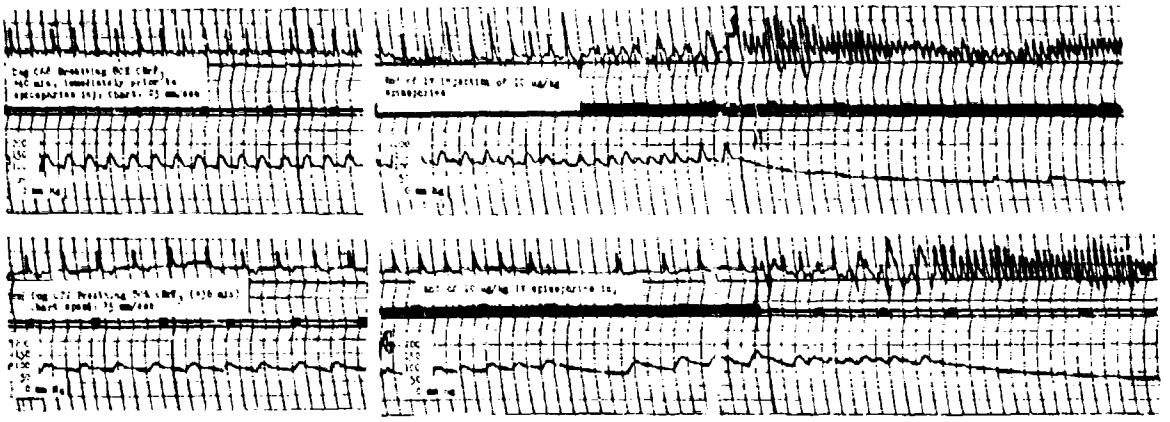

Fig.1 Electrocardiogram (lead II) and central arterial blood pressure recordings from 2 dogs exposed to bromotrifluoromethane immediately before and during the intravenous injection of 10 μg/kg of epinephrine which show the onset of ventricular fibrillation and subsequent cardiac arrest

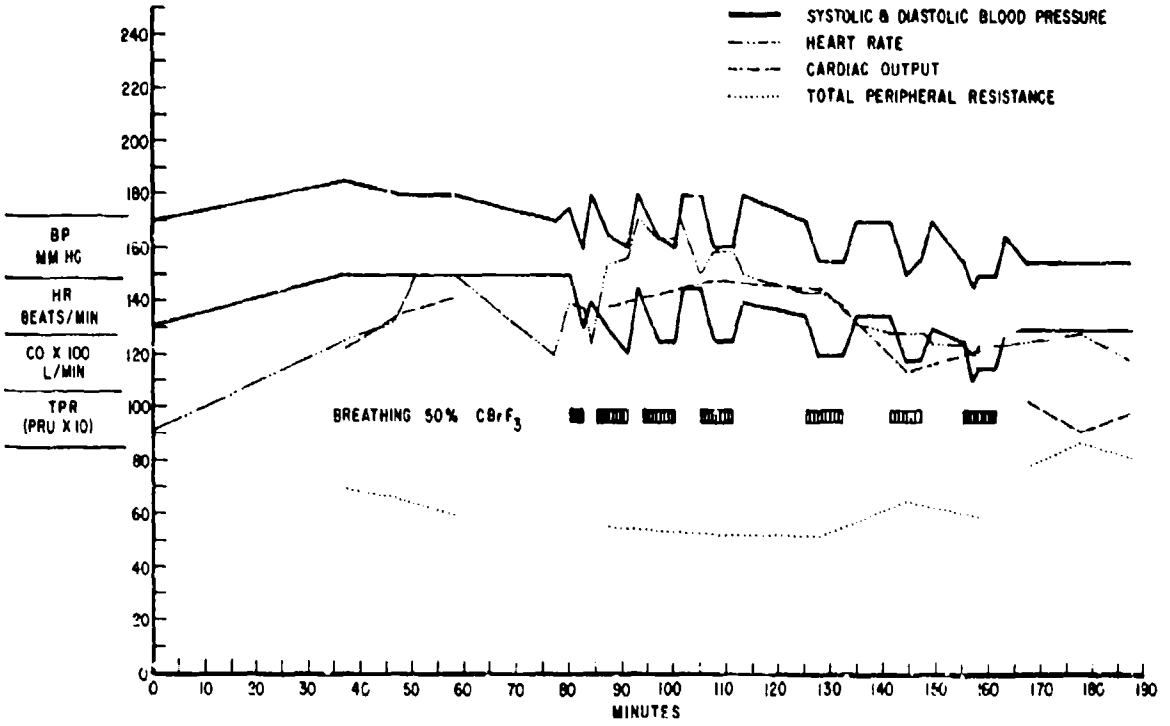

Fig.2 Results of an experiment in which a dog under pentobarbital anesthesia was exposed to 50% bromotrifluoromethane intermittently. During these periods a significant hypotension was seen which was reversed immediately upon removal of the $CBrF_3$

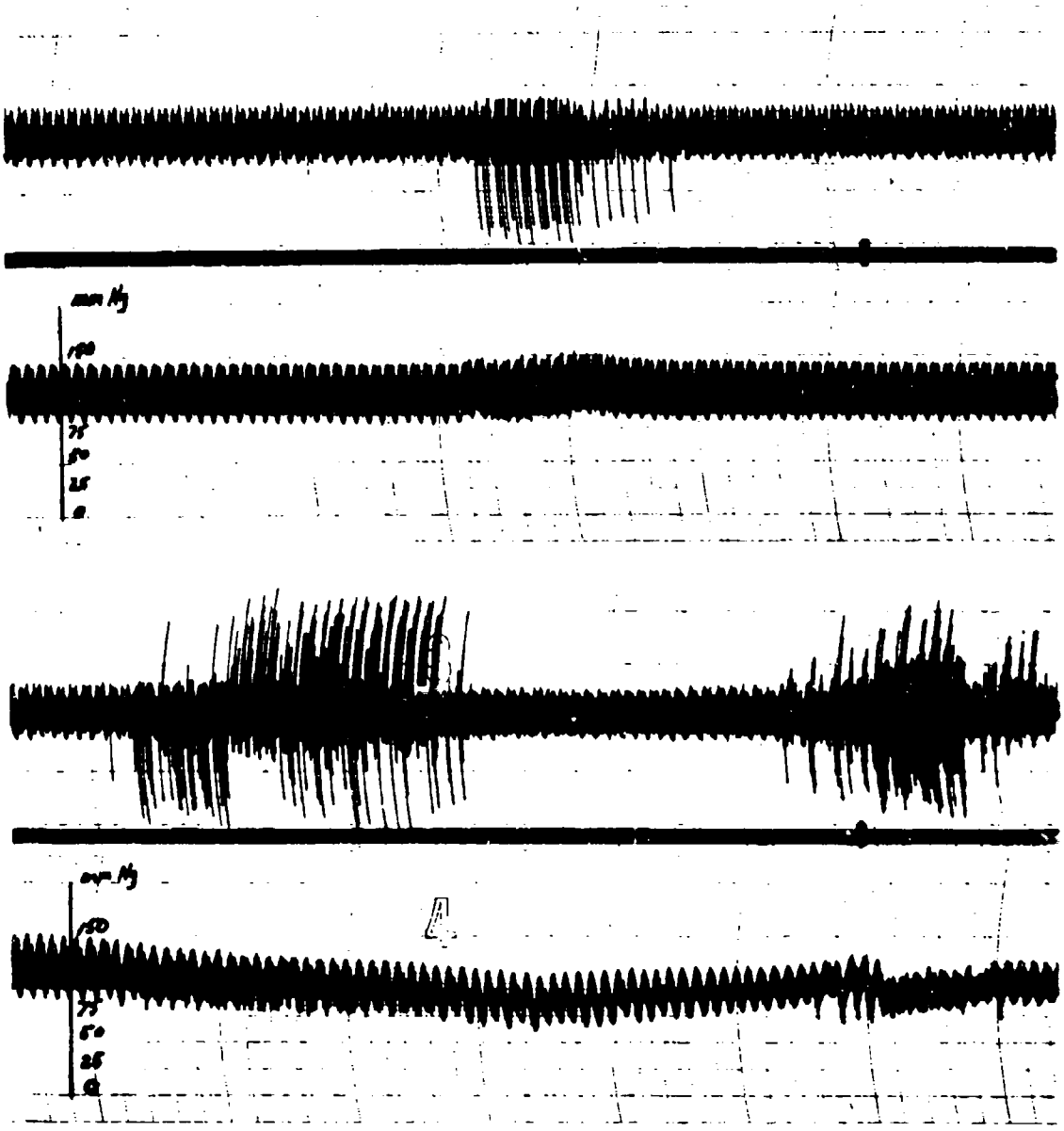

Fig.3 The occurrence of cardiac arrhythmias depended on the maintenance of a minimal blood pressure. Arrhythmias were triggered by raising the blood pressure by the intravenous infusion of epinephrine (upper tracing). Arrhythmias also were abolished and restored by the alteration of blood pressure by exsanguination and reinfusion (lower tracing).

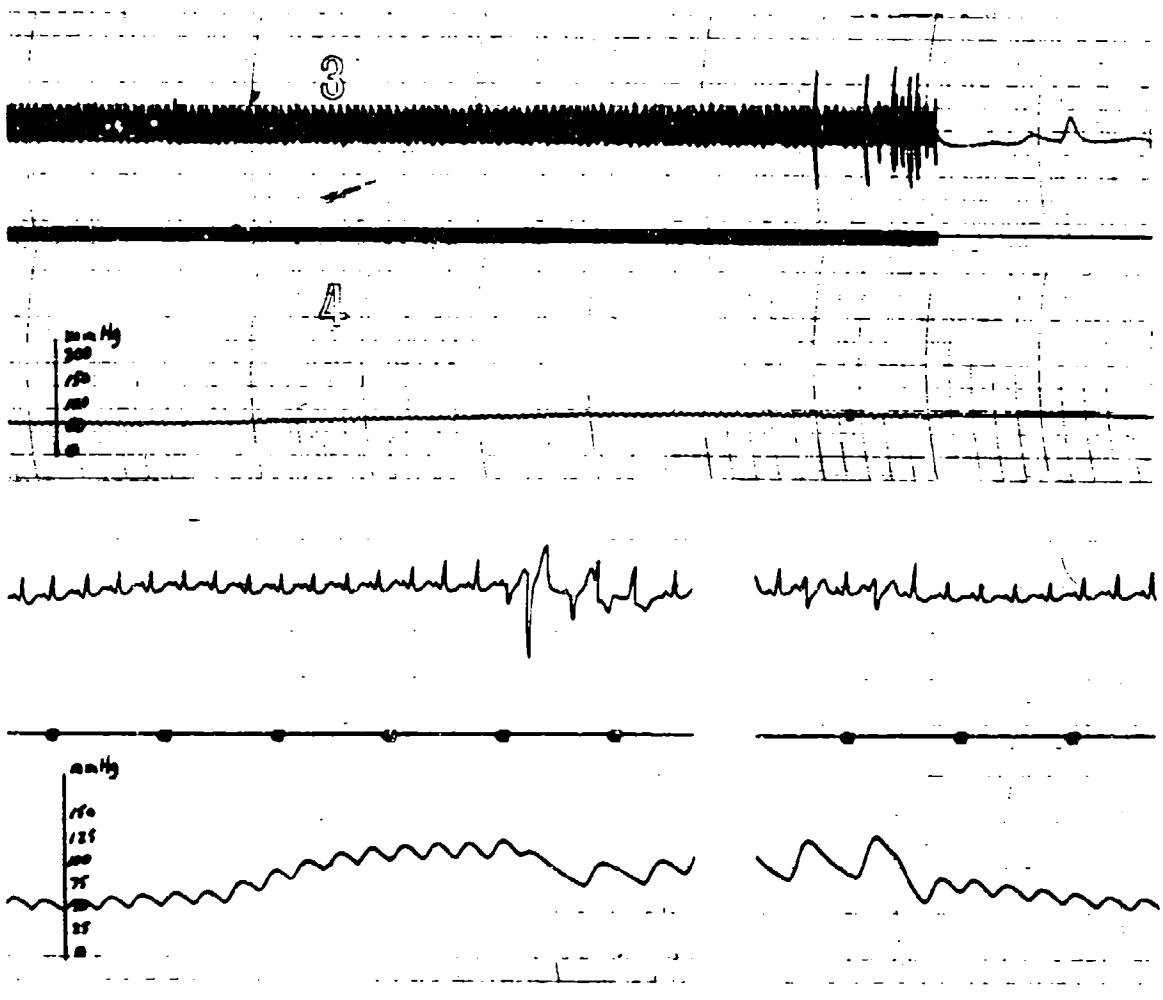

Fig.4 The upper tracing illustrates the triggering of arrhythmias in a monkey exposed to 70% $CBrF_3$ by the expansion of plasma volume with 6% dextran. The lower tracing illustrates the triggering and abolition of arrhythmias during exposure to 70% $CBrF_3$ by constriction and release, respectively, of the thoracic aorta

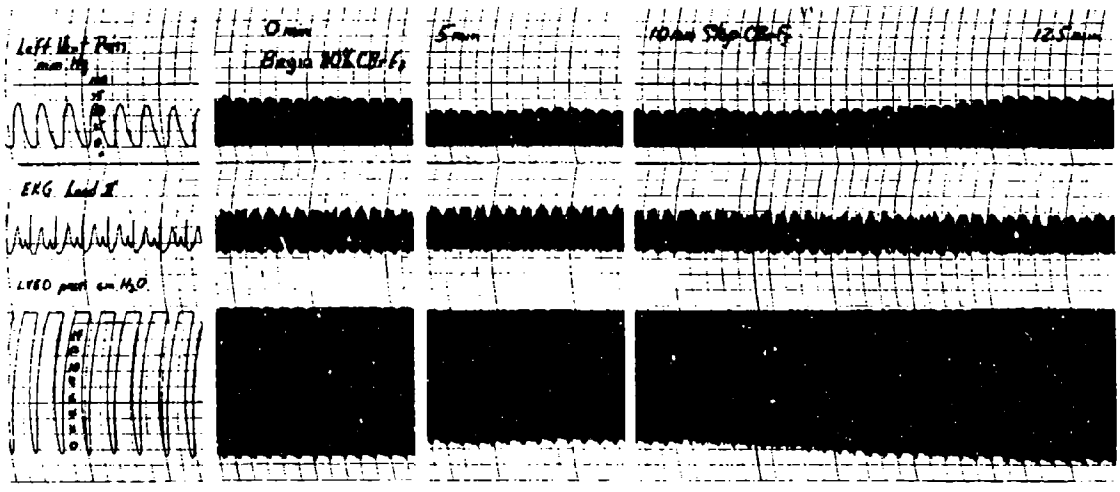

Fig.5 Effect of $CBrF_3$ exposure on left ventricular blood pressure in the open-chested monkey. The top tracing shows the fall in systolic blood pressure during $CBrF_3$ exposure. The bottom tracing shows the same ventricular pressure curve amplified to show the rise in left ventricular end diastolic (LVED) pressure (systolic pressure is not shown in the bottom tracing)

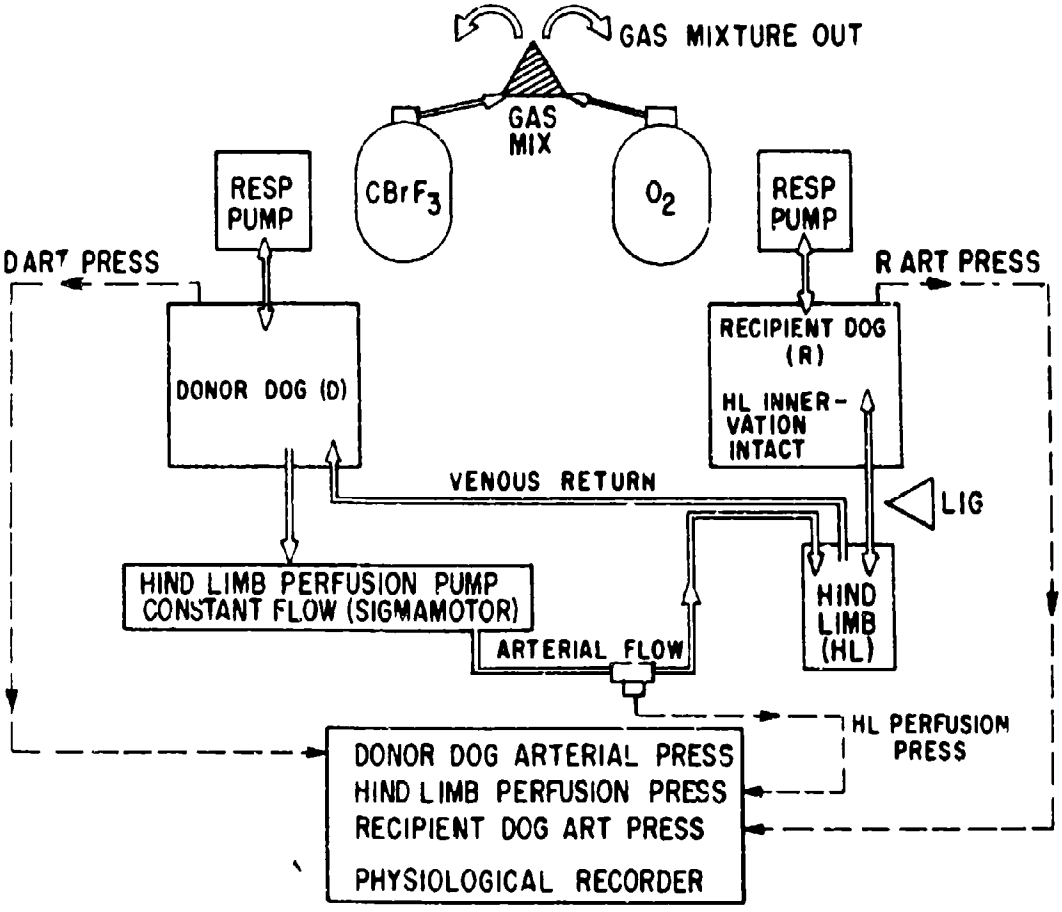

Fig.6 Schematic diagram of cross-circulation experiments. Arterial blood from the donor was pumped at constant flow through the hind limb of the recipient. The normal innervation of the HL remained intact. $CBrF_3$ and O_2 were mixed (7.3 v/v) and administered to the respective dogs by way of the respiration pump inlets

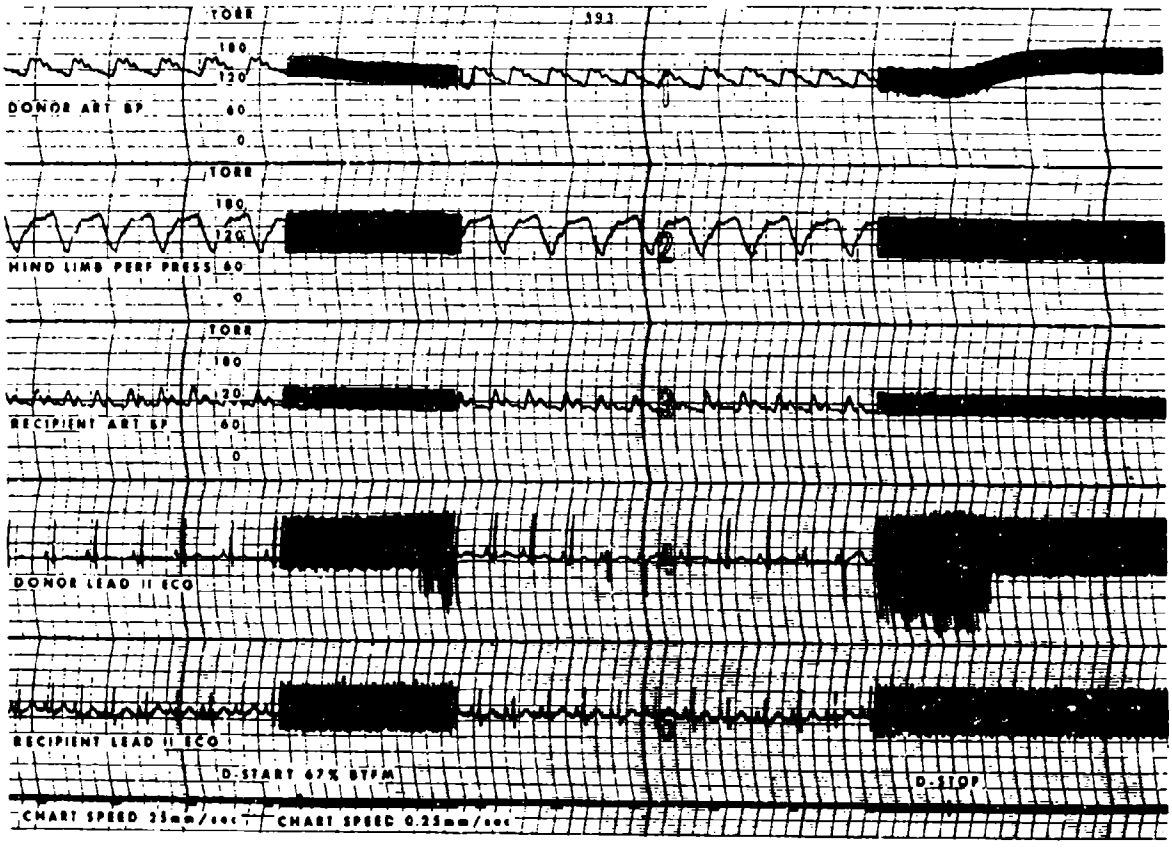

Fig.7 Donor arterial, hind limb perfusion, and recipient arterial blood pressures were recorded during the exposure of the donor to 67% $CBrF_3$ (BTFM). The beginning and end of the exposure are represented by the first 2 vertical marks on the bottom line. Donor arterial blood pressure decreased during exposure to $CBrF_3$. Hind limb perfusion pressure remained unchanged. These results suggest that $CBrF_3$ had no direct effect on vascular smooth muscle and no other effect that would result in the liberation of significant amounts vasodilatory humoral agents locally in the peripheral vascular bed or remotely into the general circulation. Evidence for PVCs that occurred during the exposure may be seen in donor lead II ECG (Van Stee and Back, 1969)

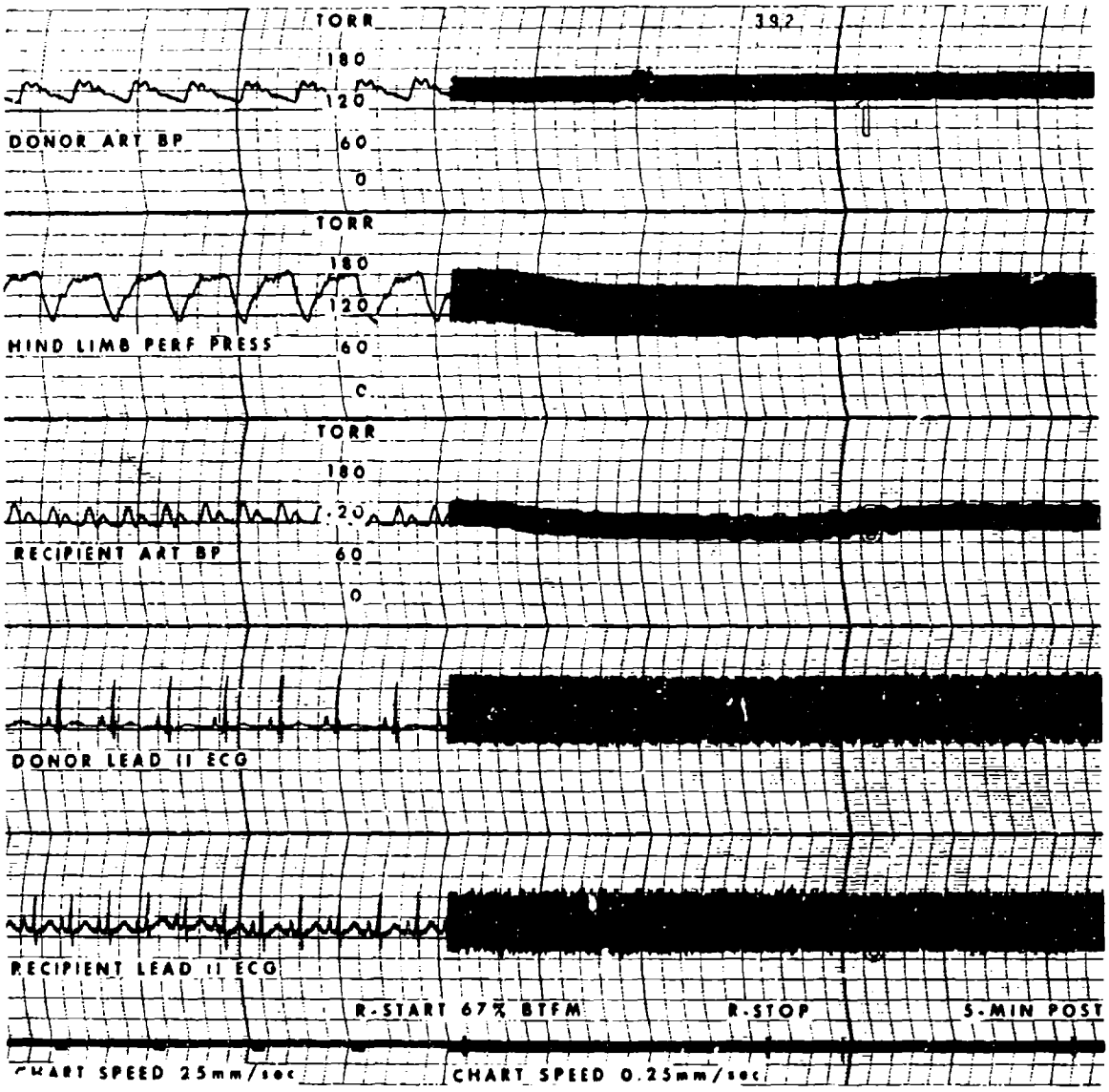

Fig.8 Donor arterial, hind limb perfusion, and recipient arterial blood pressures were recorded during the exposure of the recipient to 67% $CBrF_3$ (BTFM). The beginning and end of the exposure are represented by the first 2 vertical marks on the bottom line. Donor arterial blood pressure remained unchanged during the exposure. HL perfusion and recipient arterial pressures decreased simultaneously during the exposure. These results suggest that $CBrF_3$ caused a decrease in vasoconstrictor tone

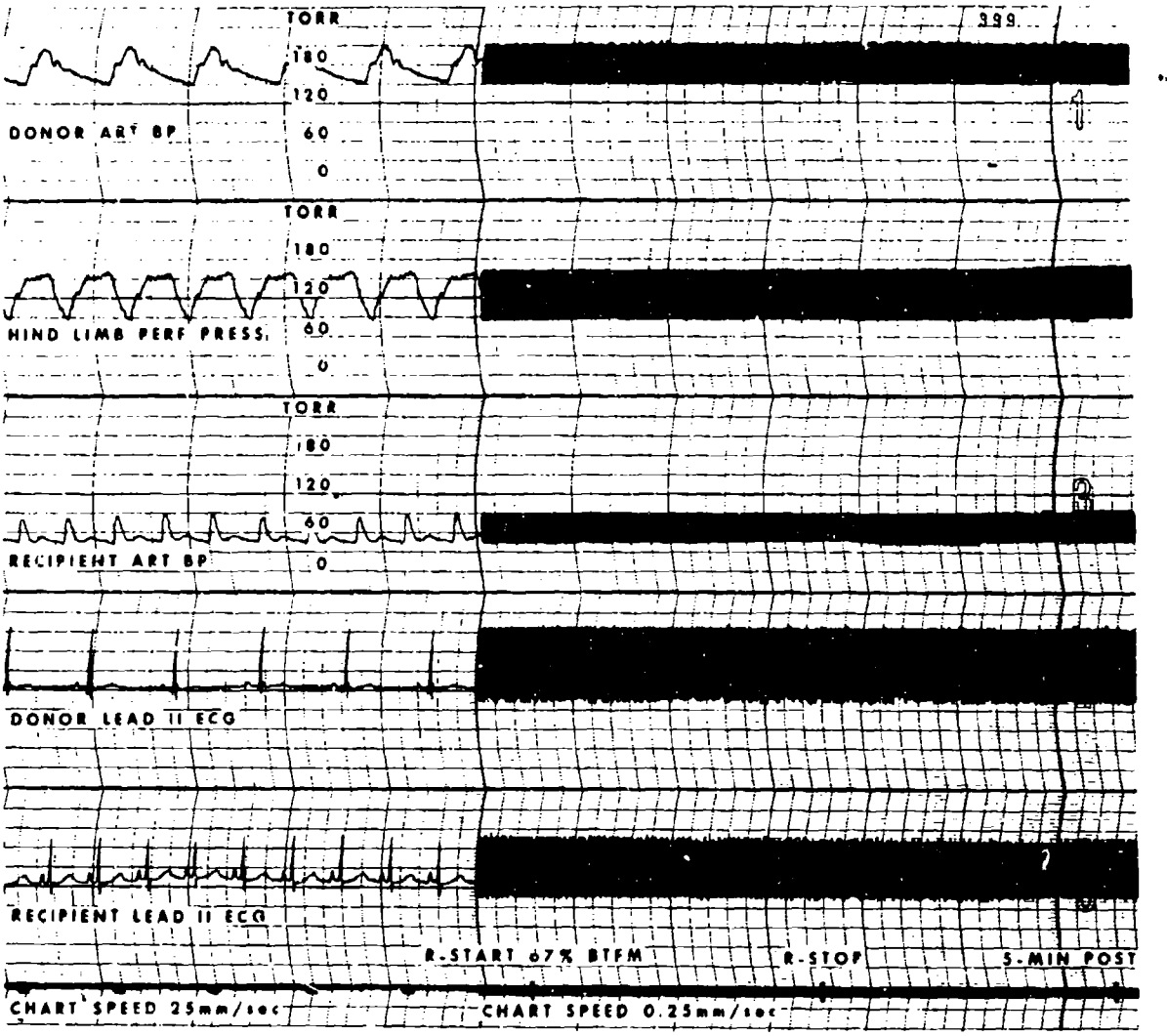

Fig.9 Donor arterial, hind limb perfusion, and recipient arterial blood pressures were recorded during exposure of the recipient to 67% $CBrF_3$ (BTFM) following treatment of the recipient with 10 μg/kg of hexamethonium. The beginning and end of the exposure are represented by the first 2 vertical marks on the bottom line. All 3 pressures remained unchanged during the exposure. These results suggest that in the absence of vasoconstrictor tone no further decrease in peripheral vascular resistance occurs during exposure to $CBrF_3$

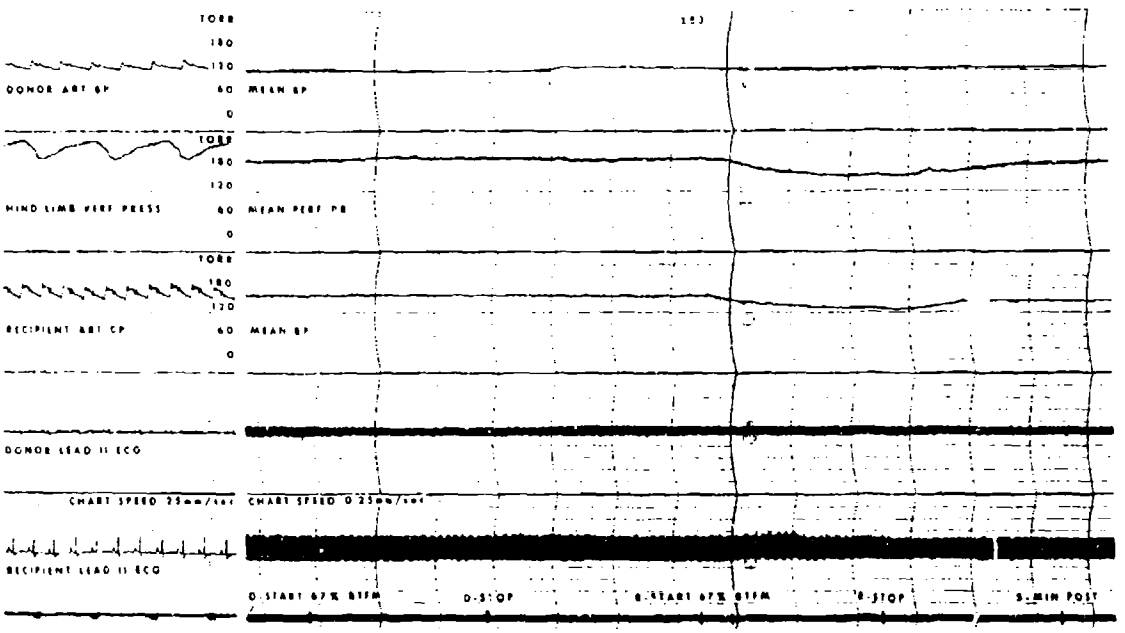

Fig.10 Donor arterial, hind limb perfusion, and recipient arterial blood pressures were recorded during exposure of first the donor, and then the recipient, to 67% $CBrF_3$ (BTFM). The periods of exposure are represented by the vertical marks on the bottom line. Donor mean arterial blood pressure decreased during exposure of the donor and hind limb perfusion and recipient arterial mean pressures decreased during exposure of the recipient

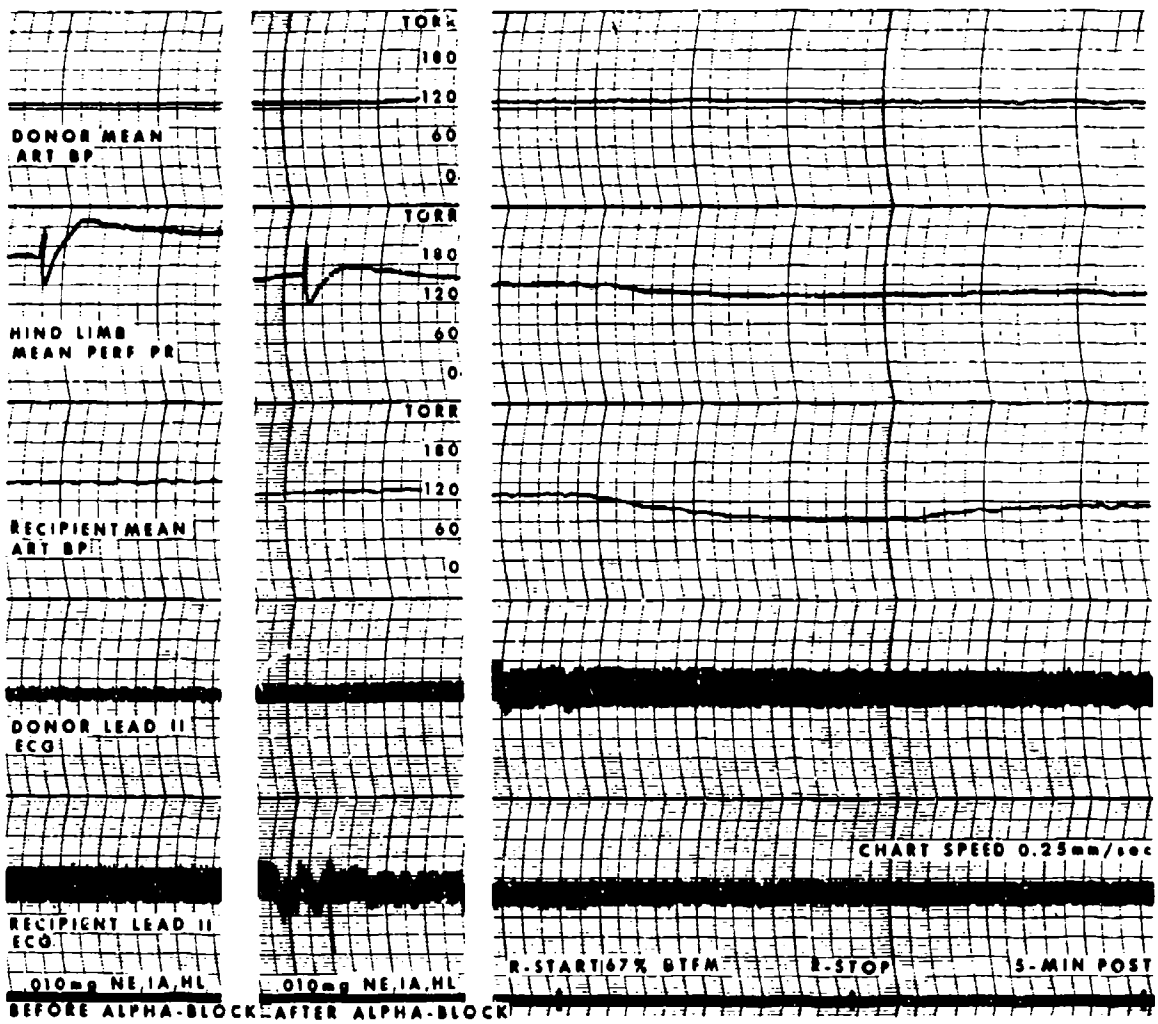

Fig. 11 This is a continuation of Figure 10. The hind limb mean pressure responses to the hind limb intraarterial injection of 10 μg of norepinephrine shown in the first 2 panels before and after treatment of the hind limb with phenoxybenzamine. The third panel shows that the hind limb perfusion pressure decrease was markedly attentuated during exposure of the recipient to 67% $CBrF_3$ (BTFM) as compared to a similar exposure represented in Figure 10

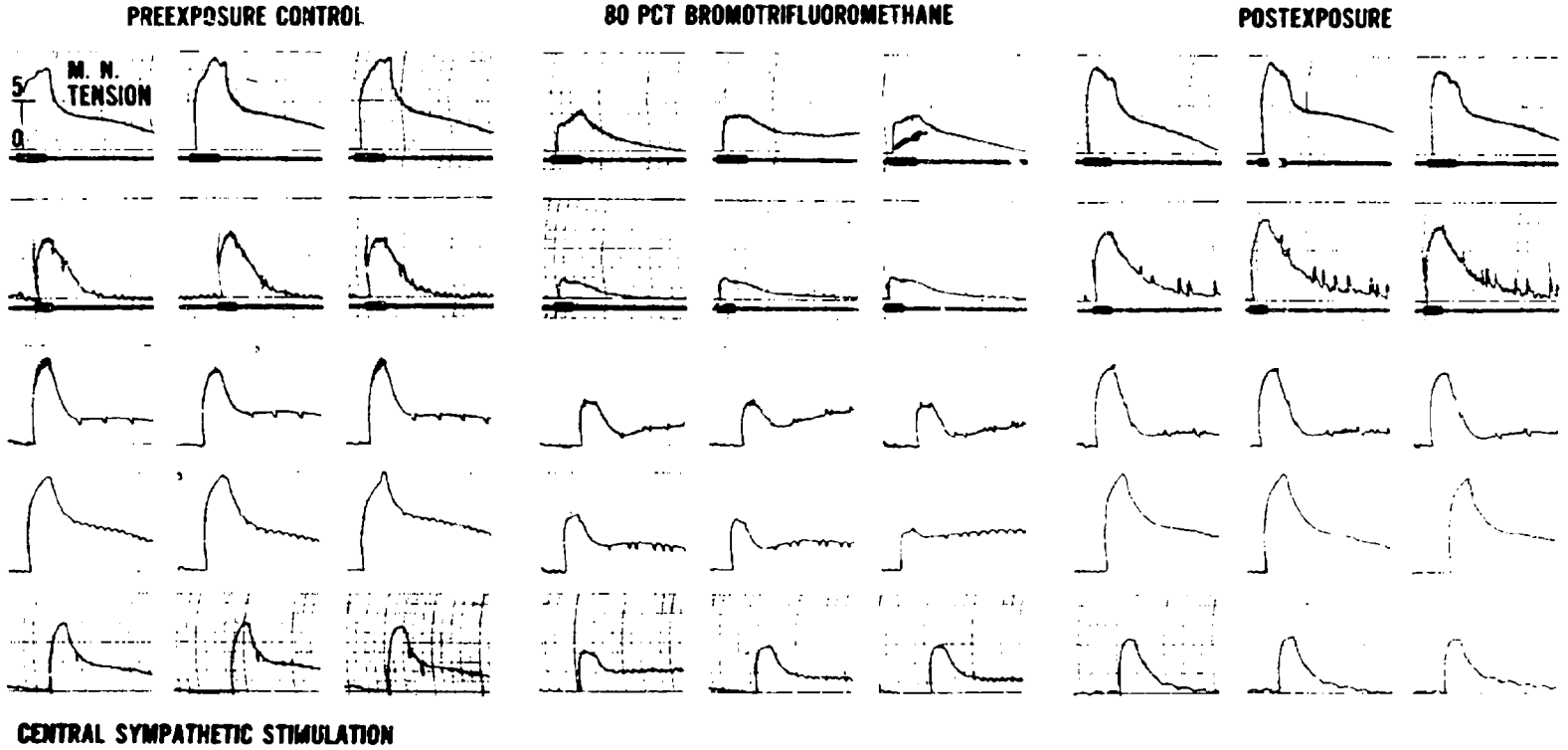

Fig. 12 Electrical stimuli were applied to the central cut end of the vagosympathetic trunks of 5 dogs before, during, and after exposure to 80% $CBrF_3$. Maximal tension (arbitrary units) developed in the nictitating membrane (M.N.) was significantly lower during $CBrF_3$ exposure

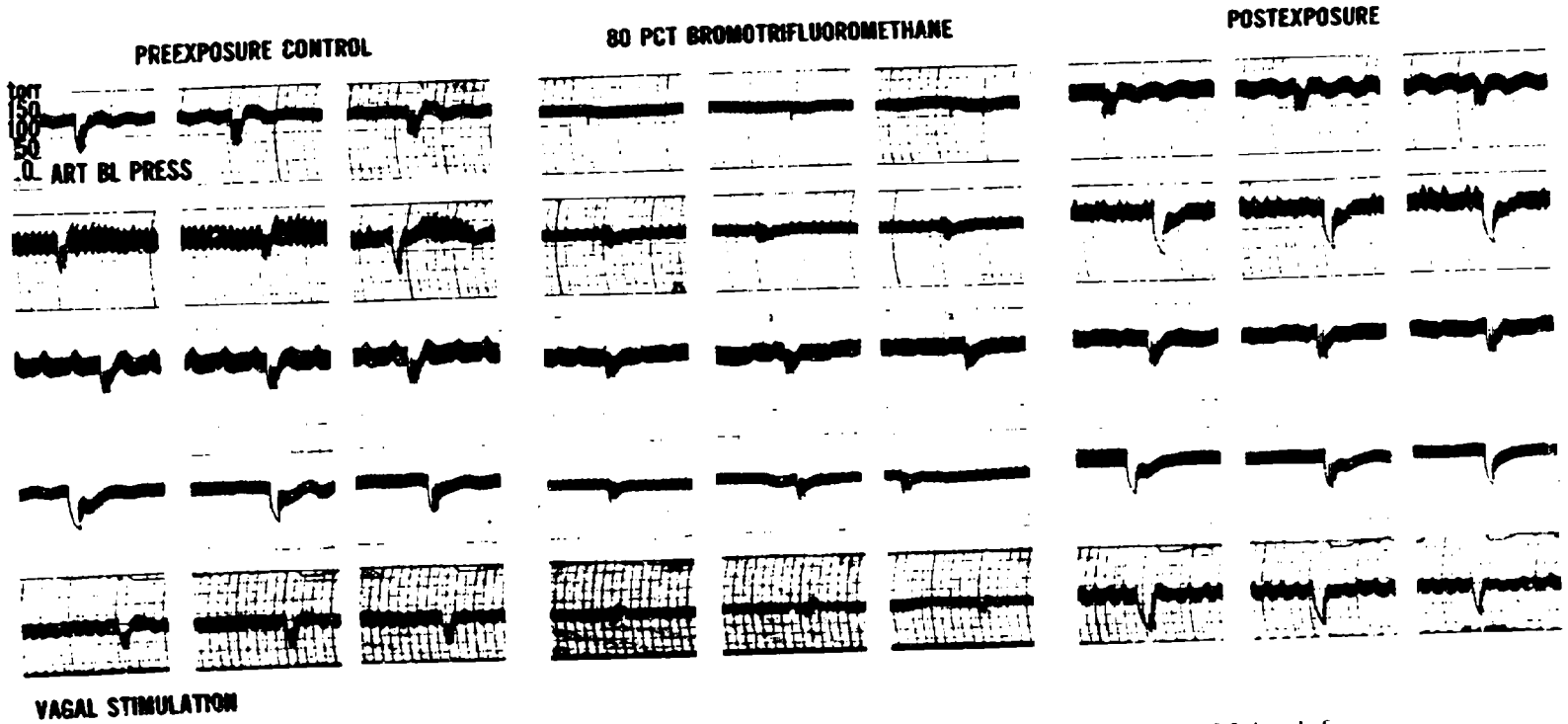

Fig.13 Electrical stimuli were applied to the peripheral cut ends of the vagosympathetic trunks of 5 dogs before, during, and after exposure to 80% $CBrF_3$. The degree of vagal inhibition was decreased during the $CBrF_3$ exposure

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