AMRL-TR-68-182

HYPOTENSION DURING BROMOTRIFLUOROMETHANE EXPOSURE

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AUGUST 1971

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The experiments reported herein were conducted according to the "Guide for Laboratory Animal Facilities and Care," 1965 prepared by the Committee on the Guide for Laboratory Animal Resources, National Academy of Sciences – National Research Council.

AIR FORCE: 22-10-71/100

Security Classification

DOCUMENT CONTROL DATA - R & D

(Security classification of title, body of abstract and indexing annotation must be entered when the overall report is classified)

1. ORIGINATING ACTIVITY (Corporate author)	2a. REPORT SECURITY CLASSIFICATION
Aerospace Medical Research Laboratory Aerospace Medical Division, Air Force Systems Command, Wright-Patterson Air Force Base, Ohio 45433	UNCLASSIFIED
	2b. GROUP N/A

3. REPORT TITLE

HYPOTENSION DURING BROMOTRIFLUOROMETHANE EXPOSURE

4. DESCRIPTIVE NOTES (Type of report and inclusive dates)

Final Report

5. AUTHOR(S) (First name, middle initial, last name)

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6. REPORT DATE	7a. TOTAL NO. OF PAGES	7b. NO. OF REFS
August 1971	20	6

8a. CONTRACT OR GRANT NO.	9a. ORIGINATOR'S REPORT NUMBER(S)
b. PROJECT NO. 6302	AMRL-TR-68-182
c. Task No. 630202	9b. OTHER REPORT NO(S) (Any other numbers that may be assigned this report)
d.	

10. DISTRIBUTION STATEMENT

Approved for public release; distribution unlimited

11. SUPPLEMENTARY NOTES	12. SPONSORING MILITARY ACTIVITY
	Aerospace Medical Research Laboratory Aerospace Medical Div, Air Force Systems Command, Wright-Patterson AFB, OH 45433

13. ABSTRACT

Cardiac output and mean arterial blood pressure measurements were performed on anesthetized dogs during exposure to bromotrifluoromethane. Left ventricular end diastolic pressure was recorded from anesthetized open-chested dogs and monkeys during exposure to $CBrF_3$. A significant decrease in total peripheral resistance and myocardial contractility were shown to combine to produce a reversible hypotension during exposure to $CBrF_3$.

DD FORM 1 NOV 65 1473

Security Classification

FOREWORD

The research reported in this paper was performed in the Aerospace Medical Research Laboratory, Aerospace Medical Division, Air Force Systems Command, Wright-Patterson Air Force Base, Ohio.

The authors wish to thank Sgt Doyle Manion for his assistance in performing these experiments.

This technical report has been reviewed and is approved.

CLINTON L. HOLT, Colonel, USAF, MC
Commander
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SECTION I

INTRODUCTION

Bromotrifluoromethane ($CBrF_3$, Freon 1301) is of interest to the United States Air Force, the National Aeronautics and Space Administration, and the private aircraft industry for potential use in fire-extinguishing systems to be used in closed environments (Botteri & Manheim, 1969). $CBrF_3$ is a fully halogenated hydrocarbon of relatively low toxicity. Exposure of dogs and monkeys to atmospheres containing from 10% to 80% $CBrF_3$ in oxygen was shown to cause a fall in mean arterial blood pressure, spontaneous cardiac arrhythmias, and lethargy (Van Stee & Back, 1969).

These experiments were designed to elucidate the mechanism of the initial fall in mean arterial blood pressure which was seen prior to the onset of cardiac arrhythmias.

SECTION II

METHOD

Eight beagle dogs of both sexes from 18 to 30 months of age weighing from 7.8 to 12.3 kg were used. The dogs were anesthetized by a single intravenous injection of 30 mg/kg of sodium pentobarbital. Endotracheal catheters were inserted and femoral venous and arterial cutdowns performed. Stage III, plane 1 anesthesia was maintained by the slow intravenous drip of a mixture of sodium pentobarbital (2500 mg/L) and tubocurarine hydrochloride (60mg/L). The animals were ventilated mechanically at a rate of 150 ml/min/kg. The respiratory dead space of the mechanical system was 30 ml which was added to the required tidal volume.

Electrocardiograms were obtained from which heart rate was calculated. Arterial blood pressure was determined with the use of a pressure transducer (Statham). Cardiac output was determined by the indicator-dilution technic using indocyanine green.

Total peripheral resistance (TPR) was calculated by dividing the mean blood pressure drop (ΔP) across the peripheral vascular bed by the cardiac output in ml/sec (Burton, 1965). Mean blood pressure was estimated from the central arterial blood pressure recordings according to the formula:

$$\frac{(\text{Systolic pressure} + 2 \times \text{diastolic pressure})}{3}$$

Venous pressure was assumed to be 5 mm Hg and thus ΔP was estimated to be equal to the mean arterial pressure minus 5 mm Hg. Since the calculation of TPR varies inversely with cardiac output, values for TPR were multiplied by body weight to provide values for TPR-kg which afforded a basis for comparisons among different subjects.

Figure 1 illustrates the design of the experiment. The 8 dogs were divided into groups of 5 and 3, respectively. Five determinations of cardiac output were performed at 10 minute intervals during each period. The treatments of the series of treated dogs differed from the series of untreated dogs only during the second period during exposure to 70% $CBrF_3$.

Comparisons of the mean values for mean arterial blood pressure, cardiac output, total peripheral resistance, heart rate, and stroke volume between the treated and untreated groups were made using a 2-way analysis of variance with interaction (Freund et al, 1960).

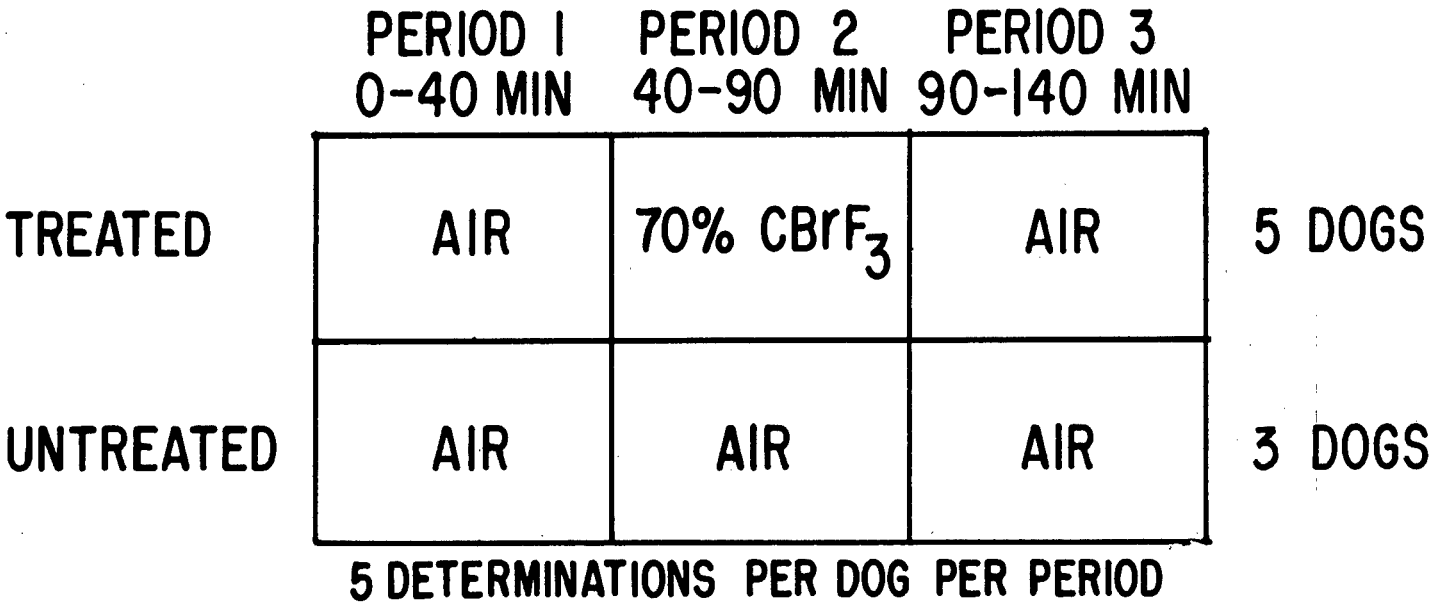

Figure 1. Design of Experiment to Determine if Exposure to $CBrF_3$ Alters Peripheral Vascular Resistance

Five determinations of cardiac output were performed on each dog at 10-minute intervals during 3 consecutive exposure periods and the means for each period reported.

Seven dogs from 6.5 - 9.0 kg and five monkeys from 2.0 to 5.5 kg were prepared for the measurement of left intraventricular pressure. They were anesthetized with sodium pentobarbital, intubated, and placed on a mechanical respirator. The heart was exposed by making a left parasternal incision through the costal cartilages from T2 to the xiphoid process. The pericardium was incised and a plastic catheter placed in the left ventricle through the left ventricular myocardium. The catheter was connected to a pressure transducer and the recordings of left ventricular pressure and end diastolic (LVED) pressure made on a direct writing oscillograph.

The gaseous mixtures for the exposures were prepared by flowing the appropriate volumes of $CBrF_3$ and oxygen from their respective high-pressure cylinders through flow meters (rotameters) into a mixing bag. From the mixing bag the mixture was delivered to the intake of the respiration pump which ventilated the animals without rebreathing.

RESULTS

The effect of exposure to 70% $CBrF_3$ on mean arterial blood pressure is illustrated in figure 2. The increase with time was significant at the 5% level. The decrease attributable to the $CBrF_3$ exposure was significant at the 1% level (table 1).

The effect of exposure to 70% $CBrF_3$ on cardiac output is illustrated in figure 3. Cardiac output decreased significantly (5% level) with time. Exposure to $CBrF_3$ had no significant effect on cardiac output (table 2).

The effect of exposure to 70% $CBrF_3$ on peripheral resistance is illustrated in figure 4. The increase attributable to the passage of time and the decrease attributable to exposure to $CBrF_3$ were significant at the 1% level. The difference attributable to interaction was significant at the 5% level (table 3).

The effect of exposure to 70% $CBrF_3$ on heart rate is illustrated in figure 5. The decrease attributable to $CBrF_3$ was significant at the 5% level. No significant difference in heart rate was observed with the passage of time (table 4).

The effect of exposure to 70% $CBrF_3$ on stroke volume is illustrated in figure 6. The stroke volume decreased significantly with time (1% level). A difference attributable to interaction was significant at the 1% level. The increase in stroke volume attributable to the $CBrF_3$ exposure was significant at the 5% level (table 5).

The alterations in the hemodynamic variables which were observed in the untreated dogs and illustrated in figures 2 - 6 are consistent with those which

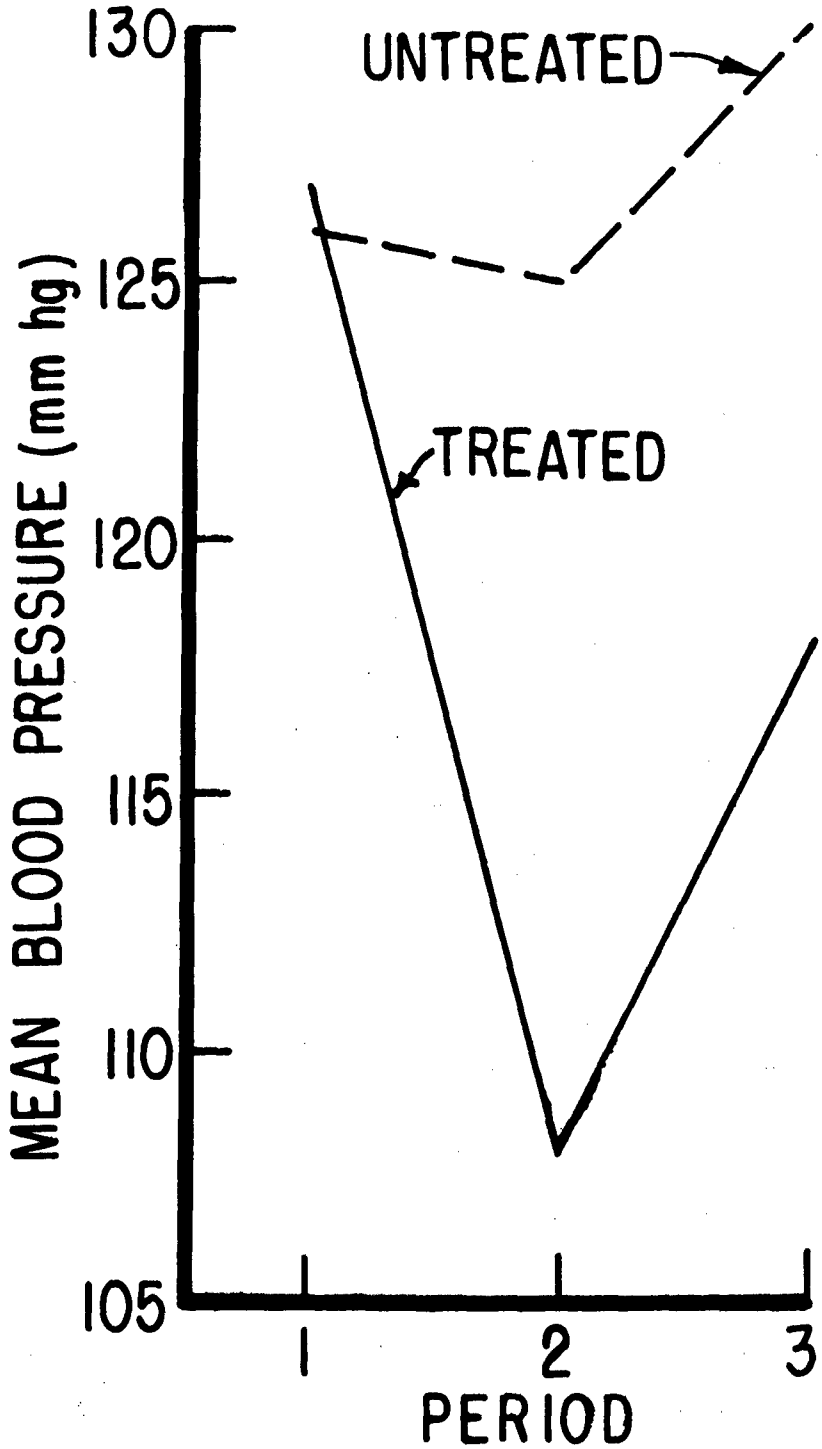

Figure 2. The Effect of Exposure to 70% $CBrF_3$ on Mean Arterial Blood Pressure

A difference attributable to period was significant at the 5% level.
A difference attributable to treatment was significant at the 1% level.

TABLE I

ANALYSIS OF VARIANCE OF THE EFFECT OF BREATHING 70% $CBrF_3$ ON MEAN BLOOD PRESSURE

Source of Variation	Degrees of Freedom	Sum of Squares	Mean Square	F	Significance
Total	120	1,820,860			
Mean	1	1,774,873.63			
Period	2	3,242.82	1,621.41	4.794	5%
Treatment	1	2,577.62	2,577.62	7.622	1%
Interaction	2	1,611.34	805.67	2.382	NS
Error	114	38,554.59	338.19		

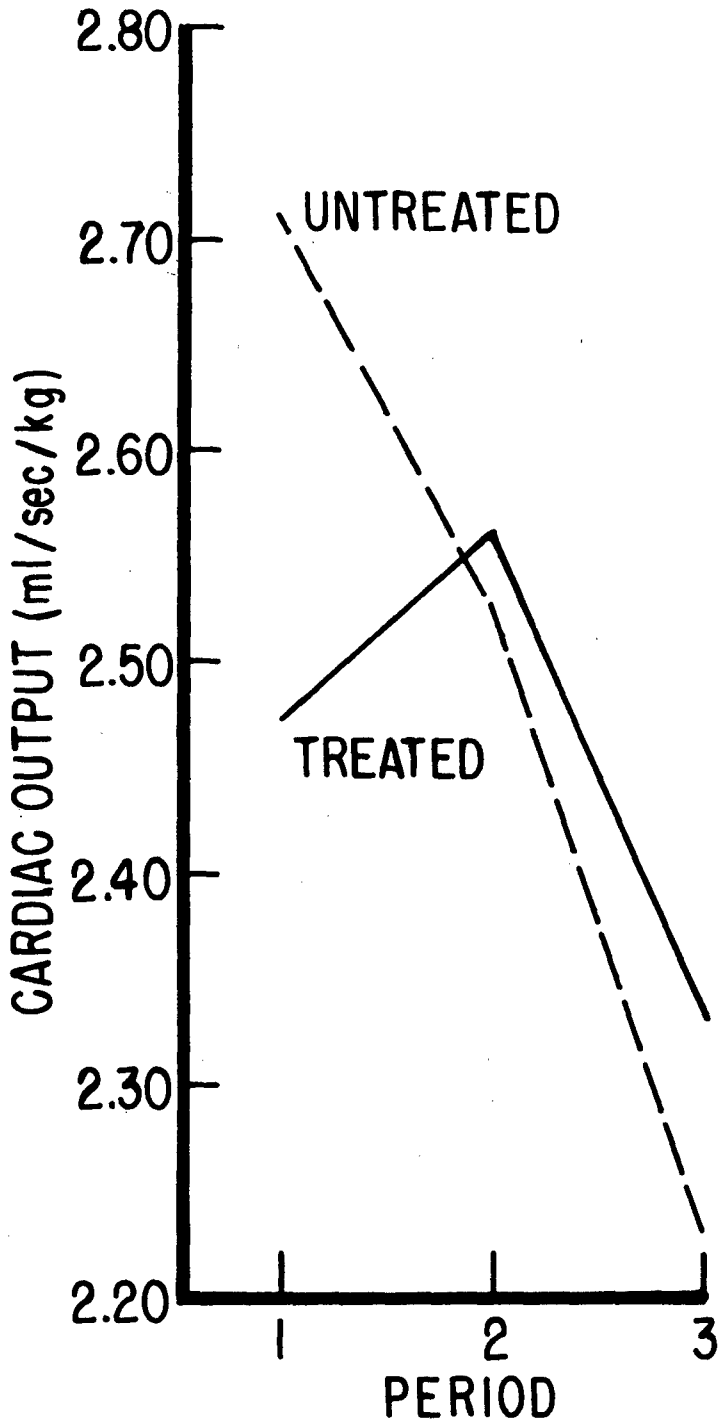

Figure 3. The Effect of Exposure to 70% $CBrF_3$ on Cardiac Output. A difference attributable to period was significant at the 5% level

TABLE II

ANALYSIS OF VARIANCE OF THE EFFECT OF BREATHING 70% $CBrF_3$ ON CARDIAC OUTPUT

Source of Variation	Degrees of Freedom	Sum of Squares	Mean Square	F	Significance
Total	120	766.7919			
Mean	1	737.105900			
Period	2	1.633382	0.81669100	3.401	5%
Treatment	1	0.024568	0.02456800	0.102	NS
Interaction	2	0.652698	0.32634900	1.359	NS
Error	114	27.375352	0.24013466		

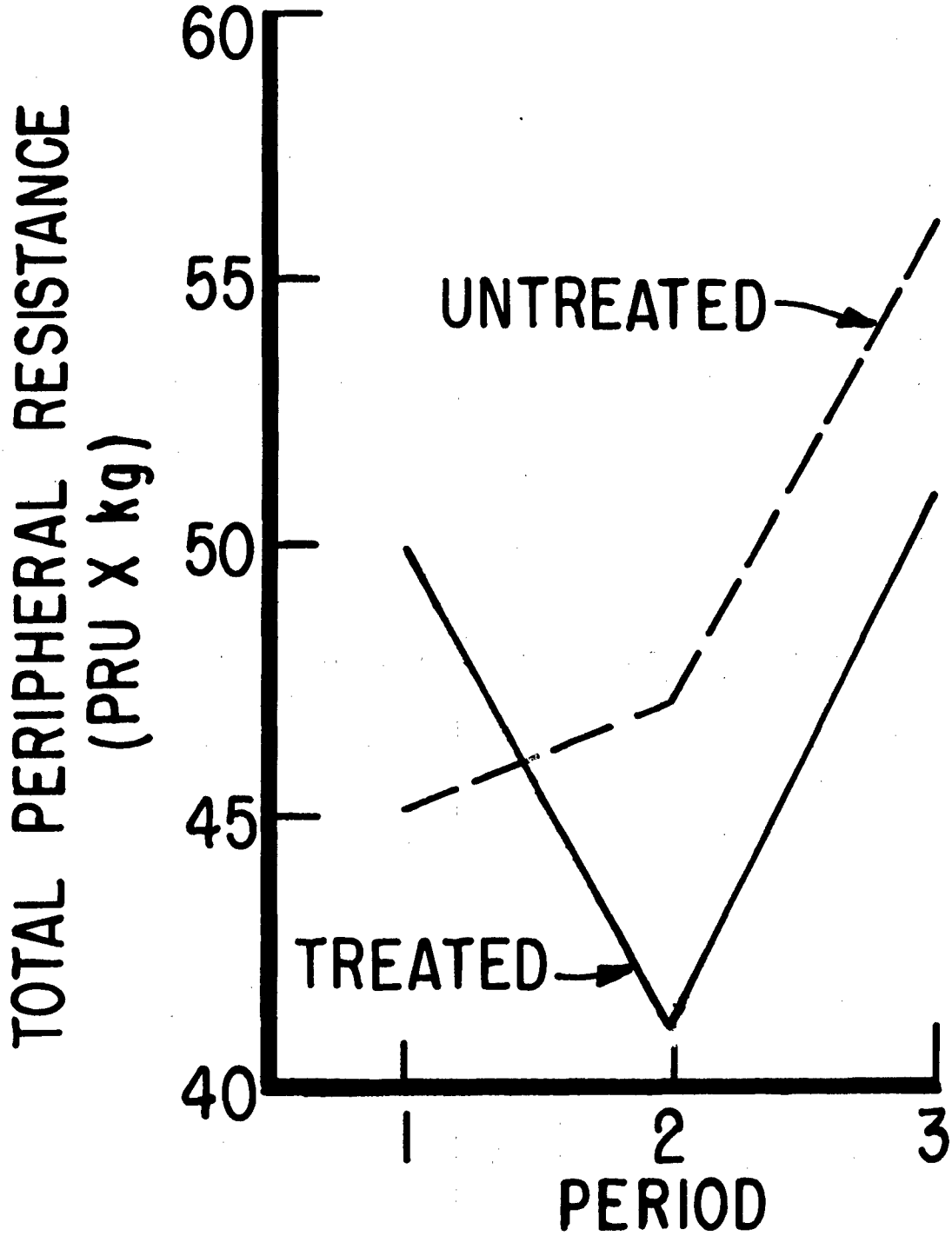

Figure 4. The Effect of Exposure to 70% $CBrF_3$ on Peripheral Resistance

Differences attributable to period and treatment were significant at the 1% level. A difference attributable to interaction was significant at the 5% level. The interaction effect was not interpreted as having biological significance since it was a mathematical result of the crossing of the respective curves.

TABLE III

ANALYSIS OF VARIANCE OF THE EFFECT OF BREATHING 70% $CBrF_3$
ON TOTAL PERIPHERAL RESISTANCE

Source of Variation	Degrees of Freedom	Sum of Squares	Mean Square	F	Significance
Total	120	296,870			
Mean	1	283,240			
Period	2	1,787.15	893.5750	10.180	1%
Treatment	1	1,035.55	1,035.55	11.797	1%
Interaction	2	800.535	400.2675	4.560	5%
Error	114	10,006.765	87.7786		

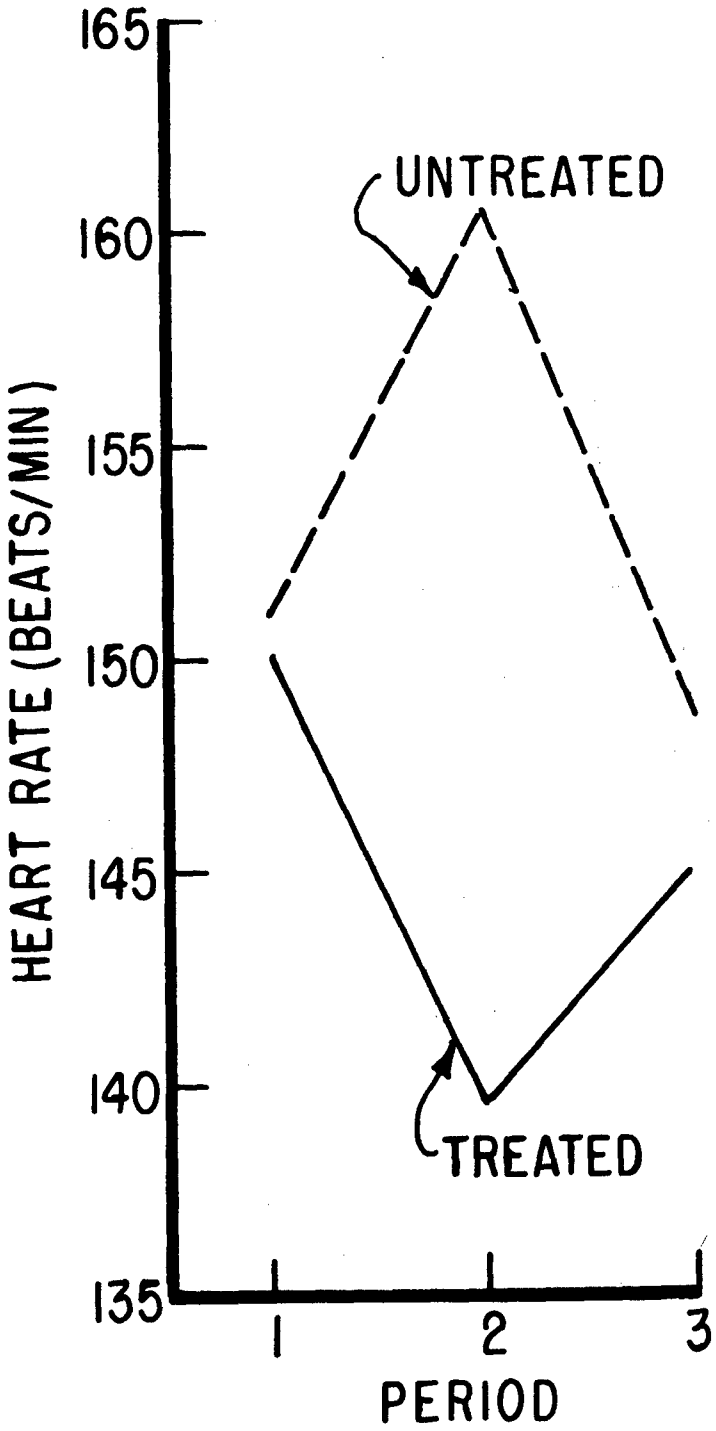

Figure 5. The Effect of Exposure to 70% $CBrF_3$ on Heart Rate

A difference attributable to treatment was significant at the 5% level.

TABLE IV

ANALYSIS OF VARIANCE OF THE EFFECT OF BREATHING 70% $CBrF_3$ ON HEART RATE

Source of Variation	Degrees of Freedom	Sum of Squares	Mean Square	F	Significance
Total	120	2,692,440			
Mean	1	2,642,113.63			
Period	2	511.12	255.56	0.642	NS
Treatment	1	2,077.97	2,077.97	5.216	5%
Interaction	2	2,325.09	1.162.5450	2.918	NS
Error	114	45,412.17	398.3523		

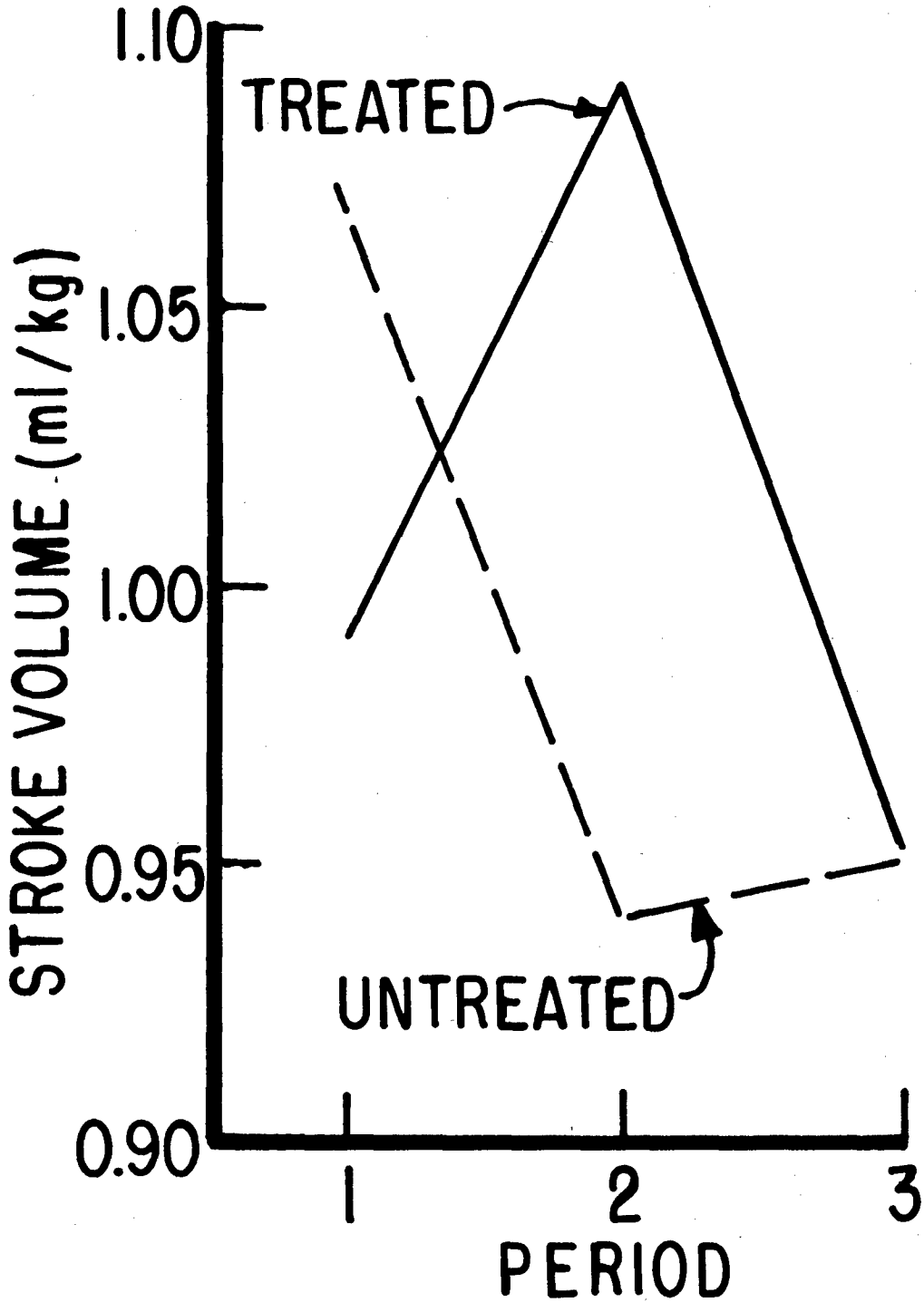

Figure 6. The Effect of Exposure to 70% $CBrF_3$ on Stroke Volume

The differences attributable to period and interaction were significant at the 1% level. The difference attributable to treatment was significant at the 5% level. The interaction effect was not interpreted as having biological significance since it was a mathematical result of the crossing of the respective curves.

TABLE V

ANALYSIS OF VARIANCE OF THE EFFECT OF BREATHING 70% $CBrF_3$ ON STROKE VOLUME

Source of Variation	Degrees of Freedom	Sum of Squares	Mean Square	F	Significance
Total	120	125.0794			
Mean	1	121.323630			
Period	2	0.176435	0.08821750	30.430	1%
Treatment	1	0.014450	0.014450	4.984	5%
Interaction	2	0.260029	0.13001450	44.848	1%
Error	114	3.304856	0.002898996		

have been documented for dogs under pentobarbital anesthesia (Priano et al, 1969). The fact that the pentobarbital-induced state represents a distinctly abnormal physiologic situation necessitated the experimental design (figure 1) which included untreated controls.

Figure 7 illustrates one example of the progressive rise in left ventricular end diastolic pressure (bottom series of recordings) during exposure to 80% $CBrF_3$. This example is entirely representative of the observations made on all similar preparations. The end diastolic pressure returned to pre-exposure values postexposure. As the end diastolic pressure rose the left ventricular systolic pressure (top series of recordings) fell markedly during exposure to $CBrF_3$.

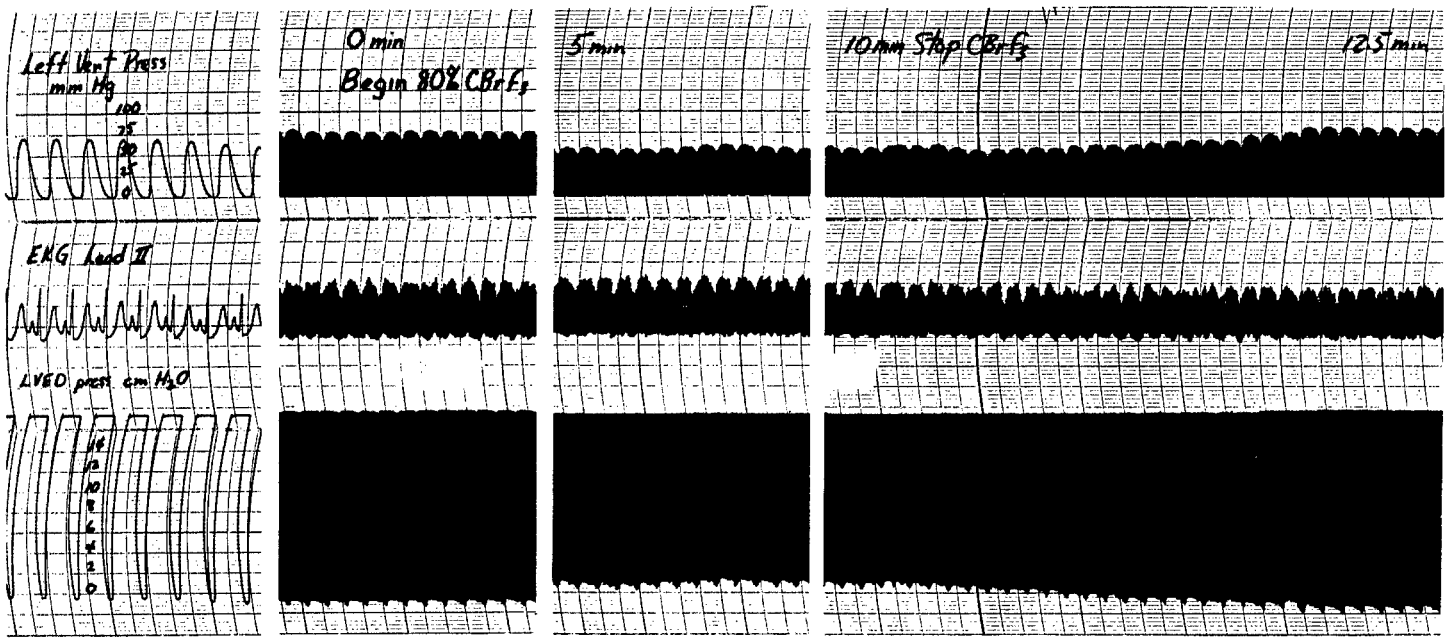

Figure 7. Effect of $CBrF_3$ Exposure on Left Ventricular Blood Pressure in the Open-Chested Monkey

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 and diastolic (LVED) pressure (systolic pressure is not shown in the bottom tracing).

SECTION III

DISCUSSION

Blood pressure fell during exposure to $CBrF_3$. Cardiac output did not vary significantly between the treated and untreated groups. A decrease in blood pressure without a change in cardiac output indicated a fall in peripheral resistance. Cardiac output is the product of heart rate and stroke volume. Since cardiac output did not change significantly during exposure to $CBrF_3$ and HR fell significantly, stroke volume apparently increased. The decrease in resistance to the outflow of blood from the left ventricle was sufficient, even in the presence of a decreased heart rate, to allow the stroke volume to rise significantly to maintain cardiac output during $CBrF_3$ exposure. If the blood pressure fall had been the result solely of impaired cardiac function without a concurrent relaxation of the resistance vessels the TPR would have been expected to rise sharply since the force tending to distend the arterioles would have been reduced which would have resulted in a decrease of diameter. This in turn would sharply raise resistance to the flow of blood (law of LaPlace, Burton, 1965).

The experiments with open-chested animals indicated that exposure to $CBrF_3$ reduced the myocardial contractility and possibly the intrinsic sinus rate also. When blood pressure falls activation of the baroreceptor reflexes normally results in reduced vagal tone which has the effect of increasing both the heart rate and force of contraction. However, heart rate decreased significantly during the exposure of the intact dogs in the first experiment (figure 5).

The rise in the LVED pressure associated with exposure to $CBrF_3$ was apparently the result of a combination of two factors: (1) decreased resistance vessel tone and (2) decreased myocardial contractility. The initial effect of $CBrF_3$ appeared to be a relaxation of the resistance vessels, which caused the TPR to fall. The capacitance vessels distended in response to the flow of high pressure arterial blood into the venous system and this shift of blood caused the pressure fall in the arterial system. Because of the greater compliance of the venous system the venous pressure rises approximately 1 mm Hg for each fall of 24 mm Hg in the arterial side (Guyton, 1966). As the right arterial pressure rose in response to the filling of the venous system the heterometric auto-regulatory response of the normal heart would increase the cardiac output. The exposure of the heart to CBrF3 results in a reduced myocardial contractility which interfered with its ability to compensate entirely for the increased venous return and blood was pooled in the venous system resulting in an elevated LVED pressure. A balance between the two factors

of decreased TPR and myocardial contractility was established. The increased venous return was not entirely accommodated by the weakened heart which continued to pump against a reduced resistance with the result that the cardiac output remained the same and the LVED pressure rose (Guyton, 1966).

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☆U.S.Government Printing Office: 1971 — 759-078/145