Response of the Cardiovascular System to Vibration and Combined Stresses

FINAL REPORT
1979–1982
Air Force Office of Scientific Research
Grant No. 80-0039

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November, 1982

UNCLASSIFIED

SECURITY CLASSIFICATION OF THIS PAGE (When Data Entered)

REPORT DOCUMENTATION PAGE	READ INSTRUCTIONS BEFORE COMPLETING FORM
1. REPORT NUMBER: AFOSR-TR- 83-0008	2. GOVT ACCESSION NO.: A125225
	3. RECIPIENT'S CATALOG NUMBER:
4. TITLE (and Subtitle): Response of the Cardiovascular System to Vibration and Combined Stresses	5. TYPE OF REPORT & PERIOD COVERED: [redacted] Report Final 10/1/79 - 9/30/82
	6. PERFORMING ORG. REPORT NUMBER:
7. AUTHOR(s): C. F. Knapp, Ph.D., J. M. Evans, M.S. and D. C. Randall, Ph.D.	8. CONTRACT OR GRANT NUMBER(s): AFOSR 80-0039
9. PERFORMING ORGANIZATION NAME AND ADDRESS: Wenner-Gren Research Laboratory, University of Kentucky, Rose Street, Lexington, KY 40506	10. PROGRAM ELEMENT, PROJECT, TASK AREA & WORK UNIT NUMBERS: 61102F, 2312/A1
11. CONTROLLING OFFICE NAME AND ADDRESS: AFOSR/NL, Bolling AFB, DC 20332	12. REPORT DATE: November, 1982
	13. NUMBER OF PAGES: 75
14.	15. SECURITY CLASS. (of this report): Unclassified
	15a. DECLASSIFICATION/DOWNGRADING SCHEDULE:

16. DISTRIBUTION STATEMENT (of this Report)

Approved for public release; distribution unlimited.

17. DISTRIBUTION STATEMENT (of the abstract entered in Block 20, if different from Report)

18. SUPPLEMENTARY NOTES

19. KEY WORDS (Continue on reverse side if necessary and identify by block number)

sinusoidal acceleration, cardiovascular regulation, chronic instrumentation, cardiac denervation, total autonomic blockade, ganglionic blockade, left ventricular volume, arginine vasopressin, plasma volume, renin, epinephrine, norepinephrine, cardiac output, stroke volume, heart rate, peripheral resistance, microprocessor controlled heart rate, atrioventricular sequential pacing

20. ABSTRACT (Continue on reverse side if necessary and identify by block number)

During the three year grant period, efforts were focused on the relative contribution of cardiac (in addition to peripheral vascular) mechanisms to the frequency response characteristics of integrated cardiovascular regulation during time-dependent acceleration stress. To this end, our chronically instrumented animal preparation was enhanced to include cardiac denervation. In these animals, ultrasonic dimension crystals were also added for measuring left ventricular major and minor axis, wall thickness and calculated volume. This is in addition to instrumentation for measuring aortic flow, left and right

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ventricular and aortic arch pressures, cardiac output, peripheral resistance, stroke volume, max dp/dt and heart rate. The animal preparation was further refined to include A/V nodal ablation to permit manipulation of heart rate (30 to 300 b/min) via a microprocessor controlled, opened or closed loop system. Closed loop control can be achieved between heart rate and a measured variable or combinations of variables such as arterial pressure, acceleration etc.

A separate study was also conducted to investigate the differences between cardiovascular responses to + and - G_y acceleration vectors as well as combinations of G_y and G_z loadings. This study was initiated because of a lack of information concerning cardiovascular responses to G_y loadings and various G blends anticipated from the ACM's of AFTI type aircraft.

A summary of major results is presented below:

1. Forty four dogs (21 normal and 23 cardiac denervated) were used to investigate the role of heart volume in the inadequate maintenance of stroke volume during the $+G_z$ portion of ± 2 G_z sinusoidal acceleration (0.001 to 0.25 Hz). A significant decrease (24%) in heart volume occurred during $+G_z$ in unblocked normal and denervated dogs at frequencies below 0.032 Hz returning toward control volume at higher frequencies. This frequency dependent change in volume was of autonomic origin in normal dogs since it disappeared after autonomic blockade; in denervated dogs the dependence could not be attributed to neural activity.

2. Three minutes each of sustained acceleration were used to study steady state cardiovascular responses to +2 G_y and -2 G_y stress. In 6 normally innervated and 4 cardiac denervated dogs, in both unblocked and blocked tests, left ventricular end diastolic volume was significantly lower during 3 min of +2 G_y than during preacceleration control or 3 min of -2 G_y acceleration. There were corresponding, (n.s.) changes in right ventricular diastolic pressure that accompanied these changes in volume. The significantly smaller heart volumes measured during 3 min of sustained +2 G_y acceleration appeared to be due to the combined effects of acceleration and anatomical differences with the net result being a decreased filling volume of the heart during this acceleration vector.

3. Comparison of + to -2 G_y responses during sinusoidal acceleration (+2 G_z to -2 G_y to -2 G_z to +2 G_y), indicated frequency dependence in several variables:

a) Between 0.001 and 0.052 Hz, -2 G_y aortic pressures were greater than +2 G_y pressures due to elevated -2 G_y peripheral resistance values which peaked between 0.021 and 0.032 Hz. The resistance response appeared to be stimulated by the +2 G_z vector which had preceded it and simply reflected a phase lag in resistance which has been reported earlier (previous progress reports).

b) Between 0.052 and 0.110 Hz, differences in -2 G_y and +2 G_y responses were found in terms of the variables contributing to maintenance of cardiac output; -2 G_y heart rates were significantly elevated over those at +2 G_y while -2 G_y end diastolic and stroke volumes were significantly lower than those at +2 G_y.

c) Between 0.110 and 0.250 Hz, -2 G_y aortic pressure was elevated above +2 G_y pressure due to elevated heart rate and recovery of venous return as reflected in recovery of end diastolic volume and stroke volume.

Results are also presented from studies related to neurohumoral components of an acceleration-induced pressor response; to differences between autonomic effector and ganglionic blockade; and to preliminary experiments using our microprocessor controlled, heart rate / animal preparation.

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The studies contained in this report were conducted in accordance with DHEW No. (NIH) 78-23.

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I. PROGRAM SUMMARY 1979-82

SUMMARY 1979-80

The research effort of this year was concerned with blood pressure regulation in dogs undergoing ± 2 G_z step and sinusoidal, low frequency, acceleration (0.001 to 0.25 Hz) produced by our specially modified centrifuge (described in previous reports). This effort is summarized below under two main topics.

1. <u>Comparison of the response of normal animals to that of animals lacking cardiac innervation</u>. Studies of the previous year (1978-1979) indicated an inability of cardiac denervated dogs to maintain stroke volume during the $+G_z$ portion of sinusoidal $\pm$ 2 G_z acceleration stress across the frequency range of 0.001 to 0.25 Hz. To investigate the inadequacy of stroke volume maintenance in these chronically instrumented animals, three cardiac dimensions were added to provide heart volume information in addition to our standard instrumentation for measuring aortic flow, left and right ventricular and aortic arch pressures, cardiac output, peripheral resistance, stroke volume, max dp/dt and heart rate. Ultrasonic dimension crystals were implanted to record heart size in 27 animals (16 normal and 11 cardiac denervated) whose body weights ranged from 17 to 26 kg. In the normal dogs, at surgery, major axis averaged 70.1 $\pm$ 1.6 mm (S.E.M.), minor axis averaged 53.4 $\pm$ 1.1 mm, wall thickness averaged 12.6 $\pm$ 0.9 and calculated volumes averaged 25.0 $\pm$ 3.5 cc. For cardiac denervated dogs, following denervation surgery, major axis averaged 67.2 $\pm$ 1.6 mm, minor axis averaged 55.5 $\pm$ 2.3 mm, wall thickness averaged

12.3 ± 0.7 mm and calculated volumes averaged 31.0 ± 6.7 cc. Verifications of actual heart volumes by silastic casts in 10 animals at autopsy indicated a mean volume of 29.1 ± 1.5 cc as compared to average calculated autopsy volumes from ultrasonic dimension data of 25.6 ± 4.8 cc. During experiments performed on these 10 animals, volumes in the control state averaged 29 ± 5 cc, generally increased with beta blockade (21 ± 7%), decreased slightly with the addition of cholinergic blockade and were slightly enlarged with the addition of alpha blockade, resulting in the largest control volume seen for the series. In the 11 cardiac denervated dogs, heart size was measured before and immediately after the denervation surgery (a 1 1/2 hour procedure). Heart size was found to generally increase with denervation from 27 ± 7 to 32 ± 7 cc.

Seven normal and 5 cardiac denervated animals were also studied on the centrifuge. As with our past studies, the protocol consisted of sinusoidal ± 2 G_z acceleration from 0.001 to 0.25 Hz (total time of about 40 min.) followed by a series of 3 min. ±2 G_z and ±2 G_y steps in the 1) normal or cardiac denervated animal, 2) beta blocked animal, 3) beta and cholinergically blocked animal and finally, 4) the totally blocked animal (beta, alpha and cholinergically blocked states). An analysis of left ventricular volume changes and corresponding changes in pressure, stroke volume, heart rate and peripheral resistance in response to the acceleration stress and pharmacologic interventions was begun before the year ended.

2. Neurohumoral components of an acceleration induced pressor response. In the second phase of our research effort, acceleration induced changes in circulating levels of arginine vasopressin (ADH), plasma osmolality, plasma renin activity, plasma volume and circulating epinephrine and norepinephrine were measured. This investigation was initiated because in previous studies we observed an acceleration-induced increase in aortic pressure which was evident within the first few minutes of the onset of centrifugation, persisted throughout the sinusoidal acceleration test period, appeared to be fairly independent of the frequency of acceleration, and remained for several (5 to 10) minutes following the end of the test period. In addition, it appeared to be independent of both cardiac innervation, particularly right heart afferent information and of autonomic effector activity, since it was present to a greater extent in the same dogs following pharamcological blockade of sympathetic alpha, beta and cholinergic activity. The magnitude of the increase in aortic pressure was approximately 15 mm Hg in reflexive dogs, whether normal or cardiac denervated, and more than double that amount in the same dogs in the nonreflexive state.

Analysis of the neurohumoral agents, combined with the dissection of the pressor response in to its cardiac output and peripheral resistance components, implicated cardiac output, via neurally-mediated heart rate increases, as responsible for the unblocked pressure increases. In the autonomically blocked animals, the response was due completely to increased peripheral resistance, which correlated with

increased plasma levels of arginine vasopressin, but not with increased osmolality, plasma volume, renin activity, epinephrine or norepinephrine. Finally it was determined that the neurally mediated increase in heart rate in the unblocked state was accompanied by an active vasodilation which buffered the vasoactive pressor substance. This neural activity was of beta adrenergic origin with no contribution from alpha adrenergic, muscarinic or nicotinic effector activity. Conclusions from this study were that acceleration induced the release of a nonadrenergic vasoconstrictor (vasopressin or some unmeasured substance) whose vascular effect was buffered by active beta adrenergic vasodilation accompanied by an increase in heart rate in unblocked animals.

SUMMARY 1980-81

The effort for this year was a completion of the investigation of acceleration-induced heart volume changes begun in 1979-80 and of two studies begun several years ago: one, to explore the differences between autonomic effector and ganglionic blockades on our standard animal preparation and the second one to enhance our understanding of the effects of autonomic effector blockade on our cardiac denervated animal preparation. Each of these three phases added to our systematic investigation of the frequency response characteristics of cardiovascular regulation. The frequency response characteristics were obtained from the analysis of pressure, flow and heart volume responses to low frequency, sinusoidal acceleration (0.001 to 0.25 Hz $\pm$ 2 G_z).

1. <u>Heart volume measurements in unblocked and autonomically blocked, normal and cardiac denervated dogs undergoing low frequency +/-2 Gz sinusoidal acceleration</u>. To investigate the inadequacy of stroke volume maintenance during $+G_z$ as described in the 1979-80 Summary, three pairs of cardiac dimension crystals were implanted in 44 dogs (21 normal and 23 cardiac denervated). Comparisons of calculated mean volumes with autopsy silastic casts indicated that 8 normal dogs had calculated volumes of 30.6 ± 5.2 cc and cast volumes of 29.7 ± 2.6 cc while 8 cardiac denervated dogs had calculated volumes of 26.2 ± 4.7 cc and cast volumes of 32.8 ± 2.6 cc. Blockades of autonomic effector activity elevated end diastolic volumes (n.s.) from 39.4 ± 3.6 cc to 47.4 ± 4.9 cc and end systolic volume (sig.) from 18.5 ± 2.1 cc to 28.4 ± 3.6 cc in 7 normal dogs. In 4 cardiac denervated dogs, end diastolic volumes increased (n.s.) from 48.8 ± 8.9 to 54.7 ± 11.6 cc with blockade and end systolic volumes increased (sig.) from 25.9 ± 7.3 to 38.5 ± 11.6 cc. There was a significant decrease (24%) in mean volume of the heart during $+ G_z$ in unblocked normal and cardiac denervated dogs at frequencies below 0.032 Hz with a return toward control volume at higher frequencies. This frequency dependent change in volume was of autonomic origin in normal dogs since it disappeared after autonomic blockade; in cardiac denervated dogs the dependence could not be attributed to neural activity. In normal, unblocked dogs, volumes were significantly greater during $-2\ G_z$ than during $+2\ G_z$; a difference which was not evident in unblocked cardiac denervated dogs.

2. Comparison of autonomic effector blockade with ganglionic blockade. In an effort to determine the best hydraulic "nonreflexive" cardiovascular system for study, 6 animals underwent our centrifuge protocol after blockade of alpha, beta and muscarinic effector sites and again after addition of ganglionic blockade to the effector blockade. Results of this study indicated that 1) The ganglionic blockade lowered heart rate and increased stroke volume when added to the autonomic blockade but had no effect on cardiac output, peripheral resistance or aortic pressure. 2) The post-acceleration increase in peripheral resistance, but not aortic pressure, was greater with ganglionic as opposed to effector blockade. 3) In general, the ganglionic blockade was thought to more closely approximate the hydraulic "nonreflexive" aspect of the circulatory system than does autonomic effector blockade.

3. The effect of cardiac denervation on cardiovascular function before and after autonomic effector blockade. After several years of using cardiac denervated animals in our acceleration studies we have summarized the effects of cardiac denervation per se. In unblocked "reflexive" dogs cardiac denervation resulted in decreased plasma renin activity (sig.), norepinephrine (sig.), epinephrine (n.s.) and plasma volume (n.s.). In this state there was no difference in aortic pressure, right ventricular diastolic pressure, cardiac output, heart rate, stroke volume, peripheral resistance, plasma osmolality or vasopressin. After autonomic effector blockade, cardiac denervated animals were found to have lower "intrinsic" heart rates (sig.) and higher stroke volumes

(sig.) and maintained lower levels of plasma volume, renin, norepinephrine and epinephrine but these differences were no longer significant.

SUMMARY (1981-82)

During this year our research effort was divided into two areas: 1) The completion of an examination of differences between cardiovascular responses to + and -2 G_y sinusoidal and step acceleration profiles, and 2) the development of an enhanced animal preparation, capable of computer controlled heart rate changes for examining in detail, and in an interactive way, the positive and potentially negative role of heart rate in cardiovascular regulation during acceleration stress.

Both studies are summarized below.

1. <u>Comparison of cardiovascular responses to +/-2 Gy sinusoidal and step acceleration profiles</u>

   a. Comparison of 3 min each of +2 G_y to -2 G_y steps in acceleration led to the following conclusions:

      1) In 13 normally innervated dogs, there were no significant differences in the responses to 3 min of +2 G_y as compared to -2 G_y step acceleration in aortic pressure, heart rate, cardiac output, stroke volume peripheral vascular resistance or diastolic right ventricular pressure. This was true for unblocked animals and for the same animals after autonomic blockade.

2) In 6 normally innervated and 4 cardiac denervated dogs, in both the unblocked and blocked tests, left ventricular end diastolic volume was significantly lower during 3 min of +2 G_y than during preacceleration control or 3 min of -2 G_y acceleration. There were corresponding, but not significant changes in right ventricular diastolic pressure that accompanied the changes in volume.

3) The significantly smaller heart volumes measured during 3 min of sustained +2 G_y acceleration appeared to be due to the combined effects of acceleration and anatomical differences with the net results being a decreased filling volume of the heart during this acceleration vector.

b. Comparison of +2 G_y to -2 G_y responses during sinusoidal acceleration (+2 G_z to -2 G_y to -2 G_z to +2 G_y) indicated a strong frequency dependence in several variables:

1) Between 0.001 and 0.052 Hz, -2 G_y aortic pressures were greater than +2 G_y aortic pressures due to elevated -2 G_y peripheral resistance values which peaked between 0.021 and 0.032 Hz. The resistance response appeared to be stimulated by the +2 G_z vector which had preceded it and simply reflected a phase lag in resistance which has been reported earlier (previous progress reports). There appears to be a hydraulic component to this response since -2 G_y blocked aortic pressures were significantly higher than +2 G_y pressures for

frequencies up to 0.021 Hz.

2) Between 0.052 and 0.110 Hz, -2 G_y aortic pressure was slightly higher than +2 G_y pressure due to elevated resistance. However large differences in -2 G_y and +2 G_y responses were found in terms of the variables contributing to the maintenance of cardiac output; -2 G_y heart rates were significantly elevated over +2 G_y while -2 G_y end diastolic volumes and stroke volumes were significantly lowered with respect to +2 G_y. Although the elevated heart rates strongly contributed to the lowering of end diastolic volume, some of the effect was thought to be due to loss of venous return. Loss of venous return can be attributed to the hydraulic effect of the actual time required for blood shifts to occur, in this case causing the effect of the preceding +2 G_z blood pooling to persist into the -2 G_y phase of the acceleration cycle. The effect of the diminishing (but large) amplitudes of oscillations of peripheral resistance, which were becoming increasingly out of phase with the +2 G_z portion of the acceleration cycle, may also have contributed to the loss of venous return during -2 G_y acceleration, but this observation can only be inferred from the data of this study.

3) Between 0.110 and 0.250 Hz, -2 G_y aortic pressure was elevated above +2 G_y pressure due to elevated heart rate and recovery of venous return as reflected in recovery of end diastolic volume and stroke volume.

2. Is the neural feedback control of heart rate operating to produce optimal cardiovascular regulation during time-dependent acceleration stress?

The rationale of this study is based on results from previous years which suggests that some heart rate changes during time-dependent acceleration loadings may be counterproductive to the optimal maintenance of arterial blood pressure and flow. During this year a set of preliminary experiments were conducted to explore the basic characteristics of our enhanced chronically instrumented animal preparation which is now capable of A/V sequential pacing and a complete arterial pressure/heart rate, micropressor controlled, feedback loop. In the first experiment, instantaneous increases in heart rate were examined under no acceleration; then the effects of different levels of constant paced heart rate on stroke volume and cardiac output during +1 G_x (supine) and +1 G_z (head up) loadings were examined; following this, different levels of constant heart rates were controlled on board the centrifuge during our ±2 G_z sinusoidal acceleration protocol; and lastly, heart rate was sinusoidally varied by computer during the ±2 G_z sinusoidal acceleration loadings. A summary of each experiment follows.

a. The effects of step changes in pacing rate on the ability of the heart to make such changes and the response of other regulatory mechanisms to these changes.

From the results of this experimental it was concluded that:

1) The ventricle could increase and decrease its rate of contraction as rapidly (within 1 beat) as it was electrically activated (ranged from 30 to 270 b/min) in

contrast to the responses seen when the heart was under its own neural control. Under neural control it always took at least several seconds to reach the maximum heart rate. The disparity between the organ response time and the control system-organ response time may lie in the processing of neural signals, the deactivation time of the neurotransmitters responsible for heart rate control in the intact regulatory system, or some combination of both.

2) A three fold step increase in heart rate immediately increased cardiac output by almost the same amount and resulted in a 20 mm Hg increase in pressure. An oscillatory peripheral vascular resistance response to this increased pressure may have resulted from conflicting atrial and arterial stretch receptors to increase and decrease vasomotor tone.
3) A five fold step decrease in heart rate doubled stroke volume but resulted in decreased cardiac output and therefore pressure. The response to return pressure toward normal was another doubling of stroke volume, and therefore cardiac output, that took 3 min to develop and only increased pressure by 15 mm Hg.
4) Step changes in heart rate and therefore cardiac output resulted in immediate (within one second) and sustained changes in calculated vascular resistance, apparantly due to the mechanical effects of changes in arterial volume rather than neural mediation of vascular tone.

b. The effects of different levels of paced heart rate on stroke volume and cardiac output during +1 G_x (supine) and +1 G_z (head up) loadings.

Results of 3 min each of 7, randomly applied, constant heart rates (A/V sequential paced) in animals during +1 G_x and +1 G_z loadings led to the following conclusion.

1) Both cardiac output and stroke volume were lowered during +1 G_z at all heart rates. Cardiac output was decreased by 17% at very low heart rates (< 60 b/min) and by 30% at heart rates above 90 b/min. Stroke volume was decreased by 29% at all heart rates. It was assumed that the decreases in both cardic output and stroke volume were due to loss of venous return.

2) As a result of increased heart rate, there was an increase in cardiac output up to 150 b/min during +1 G_x and up to 120 b/min during +1 G_z.

3) Heart rates over 120 b/min cannot be expected to increase cardiac output and thereby maintain aortic pressure in animals who are undergoing + Gz acceleration of 1 G or greater.

c) The effects of mean heart rate on the amplitude of pressure oscillations induced by ±2 Gz sinusoidal acceleration.

Conclusions from this portion of the study were:

1) Mean heart rate level was a major determinant of acceleration-induced oscillations in aortic and central venous pressure.

2) The magnitude of aortic pressure oscillations increased with increasing heart rate while the magnitude of

central venous pressure oscillations decreased with increasing heart rate.

3) The increase in heart rate resulted in an increase in cardiac output which appeared to be responsible for the increase in mean aortic pressure and the increase in magnitude of aortic pressure oscillations.

4) The increase in mean and oscillatory aortic pressures and the decrease in mean and oscillatory central venous pressures with increasing rate was compatible with a shifting of blood from the venous to the arterial systems.

5) The acceleration frequency dependence of aortic pressure oscillations was amplified at increased heart rates.

d. The effects of heart rate oscillations desynchronized from right heart filling pressure oscillations in regulation of blood pressure during ±2 G_z sinusoidal acceleration.

In this experiment, heart rate was sinusoidally oscillated (100 ± 40 b/min) at 0.038 Hz while the animal received ±2 G_z sinusoidal acceleration at a slightly different (0.035 Hz) frequency. In this study it was observed that:

1) A "beating" phenomenon developed in all hemodynamic variables, and was especially pronounced in the aortic pressure response where amplitudes of pressure oscillations were as small as 25 mm Hg when peak heart rate coincided with +2 G_z and as large as 120 mm Hg when peak heart rate coincided with -2 G_z.

2) The desynchronization of heart rate and acceleration revealed the relatively greater importance of heart rate

over cardiac filling pressure in the reflexive canine at ± 2 G_z. While filling pressure (diastolic right ventricular pressure) varied only with the acceleration vector, all other measured variables were determined by both heart rate and filling pressure oscillations. Indeed, diastolic left ventricular pressure oscillations seemed determined solely by heart rate, since they followed heart rate undiminished through all phases of acceleration.

II. PROGRESS REPORT
1981-82

(Current Efforts)

II. PROGRESS REPORT 1981-82 (CURRENT EFFORTS)

A. COMPARISON OF CARDIOVASCULAR RESPONSES TO ±2 G_Y OSCILLATORY AND STEP INPUT ACCELERATION PROFILES

INTRODUCTION

The blending of G_y and G_z acceleration profiles in advanced aircraft manuevers prompted an investigation of the cardiovascular response to the G_y component of our alternating $\pm G_y$ and $\pm G_z$ stress. Our previous research efforts focused on time dependent G_z spinal axis acceleration stress and were used to identify the frequency response characteristics of the cardiovascular system to this particular acceleration vector. While overall cardiovascular responses to sustained G_z loadings are considerably larger when compared to G_y forces, the complicated anatomial arrangement of the heart and pulmonary system relative to the G_y direction and the decoupling influence of the lungs on the right and left side of the heart suggested the need for further investigation. In this section we now focus our attention on the steady state and oscillatory responses of the cardiovascular system to lateral G_y acceleration stress and compare them to the G_z responses previously reported.

For this series of studies, 22 normally innervated and four cardiac denervated, chronically instrumented canines were subjected to a series of step and oscillatory acceleration profiles in which an acceleration sequence of $+2G_y$, $+2\ G_z$, $-2\ G_y$ and $-2\ G_z$ was held 3 min for each step and was sinusoidally varied through the sequence at different frequencies, for the oscillatory tests, each of which also lasted 3 to 4 min. The

oscillatory tests simulate an aircraft "roll" during a 2 G maneuver while the step input accelerations produce a sudden shift in the acceleration vector which simulates projected AFTI maneuvers.

METHODS

Surgical procedures:

Each animal was anesthetized with sodium thiopental, intubated, positive pressure respirated, and an L4 thorocotomy performed under sterile conditions. In 6 normal and 4 cardiac denervated dogs left ventricular chamber volumes using the technique of Rankin (1) were measured in addition to our standard cardiovascular variables. In these animals, a pair of 5 mm diameter ultrasonic dimension transducers were positioned to record the maxmimum anterior to posterior epicardial left venricular chamber diameter. Another 5 mm pair was positioned to give epicardial major axis diameter (one crystal was placed in the groove between the left atrium and the pulmonary artery and the other was located near the apical dimple). Wall thickness of the left ventricle was measured by a 1 mm diameter crystal tunneled to the endocardial surface of the anterior wall and a 3 mm diameter crystal positioned directly over it. Each pair of crystals was aligned at surgery to give the best received signal possible, and futher monitoring was done following placement of the remaining instrumentation (left ventricular pressure gauge, aortic flow probe, right atrial cannula) to ensure continued signal quality. Placement of the other transducers has been detailed in past progress reports. The chest wall was closed,

the leads placed in a subcutaneous dacron pouch and the animal was allowed at least three weeks of postoperative recovery.

Digital data acquisition and analysis:

Calculations of heart volume were made on an off-line basis using a PDP 11/34 computer. All analog signals including the three heart dimension measurements were recorded on a 14 channel Ampex tape recorder during each experiment. The recorded physiological data were sampled at two millisecond intervals and smoothed with a digital filter. The geometry of the left ventricle was represented as a three-dimensional, prolate ellipsoidal shell. The following assumptions about the ellipsoial shell were made: 1) the measured minor and major axis diameters were assumed to represent the external diameter of the shell, 2) the measured anterior wall thickness was used as the dynamic shell thickness at the minor axis cicumference, 3) the shell thickness at the base and apex was assumed to be 55% of the equatorial value (based on measurements of postmortem hearts). The dynamic internal volume of the shell was computed using the formula for a prolate ellipsoid:

$$V = \pi/6\ (b-2h)^2\ (a-1.1h)$$

where b is the external minor axis diameter, h is the equatorial wall thickness, and a is the external major axis diameter. Stroke volume was computed as the change in internal shell volume during ejection. Stroke volume was also calculated by integration of the aortic flow curve assuming zero flow at end-diastole. The stroke volume measured with the flowmeter can also be compared to

the data calculated from the dimension measurements.

Procedures for normalization of volume data by acceleration-induced shape changes:

After postmortem comparison of cast heart volumes to calculated heart volumes, retrograde adjustments were made for each dimension reading at each stage of the experiment. To date, dimension measurements have been made on 21 normal and 23 cardiac denervated dogs undergoing our centrifuge protocol (1980-1981 Progress Report). Two slightly different analyses of heart volume changes during acceleration have been tried, both on and off-line basis. The first, a continuous calculation of volume, using either analog or digital techniques, gave a record of volume throughout the total experiment. This analysis indicated slight changes in volume in the sacrificed animal that could be interpreted as actual volume changes due to acceleration-induced pressure difference across the valves of the heart. An alternative explanation could be the coupling of surgical implant adhesions with acceleration to produce changes in the shape of the ventricle which would also be present in the beating heart. Since there was no indication of flow from the aortic flow probe, the shape change was felt to be more likely and therefore the changes seen in the animal after sacrifice were used to normalize the changes seen in the live animal.

Volume data for two frequencies before and after the above normalizations are shown in Figure A1. The normalization procedure consisted of several steps, the first of which was analyzing left ventricular chamber wall thickness (h), and both major (a) and minor (b) axes for frequency dependent variations

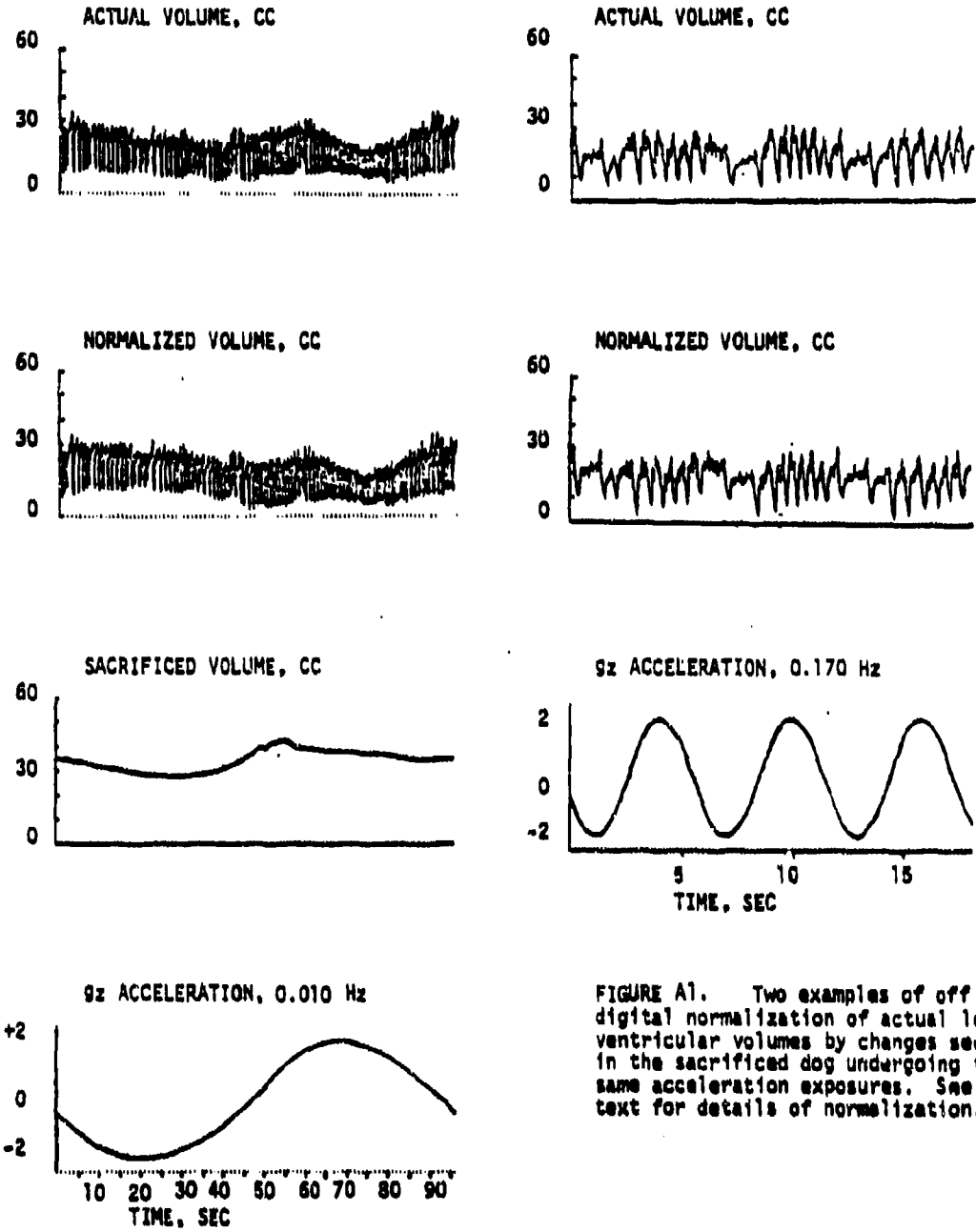

FIGURE A1. Two examples of off line, digital normalization of actual left ventricular volumes by changes seen in the sacrificed dog undergoing the same acceleration exposures. See text for details of normalization.

during acceleration of the dead dog. The dead dog data was not found to be frequency dependent. Two cycles of acceleration, and corresponding wall thickness, and major and minor axes were sampled from the dead dog data a at 3.1 msec. rate. This data was then used for the normalization of data from the live dog data. The live dog was sampled at 6.2 msec. for both a high and low acceleration frequency. The following formula was used to calculate left ventricular chamber volumes for the dead dog and the live dog accelerations: $v = \pi/6(b-2h)^2 (a-1.1h)$. The dead dog volume used to normalize the low frequency live dog volume was placed in phase with the live dog data. Linear interpolation was used to expand the dead dog data to the same number of points per cycle as the live dog data. Dead dog and live dog data were of the same frequency for the high frequency test. The normalization data for the high frequency test was created by using every other point from the dead dog volume data and repeating the data three times. The following formula was used to normalize the volumes from the live dog for each acceleration frequency : $v_n = v_l - (v_d - \bar{v}_d)(v_l / \bar{v}_d)$, where v_n = normalized volume, v_d = dead dog volume, and v_l = live dog volume.

For a continuous playback analysis of the data, considerable amount of time for off-line signal processing would be required.e An alternative analysis has proven to be accurate and much less time consuming. At four points in the acceleration cycle (2 g_z, -2 G_z, +2 G_y, and -2 G_y) data was taken from each of the three dimension channels and a volume was calculated. The same procedure was done in the animal postmortem and changes from the

mean at each of these points were then either added to or subtracted from the mean value for live dog at the same points depending on whether or not the values were above or below the mean. It should be emphasized that these changes are normally quite small when compared to the total acceleration-induced changes seen in the live animal.

EXPERIMENTAL PROTOCOL

On the day of the experiment, the animal was tranquilized with an intramuscular injection of Innovar Vet at 0.075 cc/kg. Piezoelectric manometer-tipped catheters (Millar PC 350, 5 French) were placed, under local anesthetic, in the right and left ventricles via small branches of a main femoral vein and artery, respectively. The arterial Millar gauge was used to calibrate the implanted Konigsberg gauge and then retracted into the aorta, just outside the aortic valve, to measure arterial pressure. The animal was maintained in a lightly tranquilized state for the duration of the experiment with serial injections of Innovar (0.5 cc/hr) administered through the right atrial cannula.

The measured physiologial variables included aortic pressure and flow, left and right ventricular pressure and heart rate. In addition, measurements of left ventricular, major and minor axis dimensions and wall thickness were added as described above. On-line digitally calculated variables included beat-by-beat stroke volume, cardiac output, peripheral vascular resistance, maximum dp/dt, and the pressure difference from the aorta to the right atrium. Left ventricular volume was either calculated digitally

off-line or on-line by an analog computer circuit.

Procedures To Produce Autonomic Effector Blockade:

In order to delineate the neural and nonneural components of the measured cardiovascular responses to acceleration, a pharmacologically-induced total autonomic blockade was used to inhibit adrenergic and cholinergic activity at the effector site, thus removing normal reflex barostatic action.

The total autonomic blockade consisted of the alpha adrenergic blocker phenoxybenzamine (Dibenzyline) at 20 to 30 mg/kg administered over an hour, beta blockade with propranolol (Inderal) at 1 to 2 mg/kg over approximately ten minutes, and muscarinic blockade with atropine (Atropine Sulfate) at 0.1 to 0.2 mg/kg over approximately five minutes. The efficacy of the blockade was tested and verified by a comparison of systemic responses to specific agonists given prior to blockade, following blockade and then again at the conclusion of the blocked acceleration sequence. These consisted of a 50 ug/kg bolus of phenylephrine (Neosynephrine) to test the alpha blockade and 0.5 ug/kg bolus of isoproterenol (Isuprel) to test the beta blockade. If heart rate showed evidence of reflexive parasympathetic activity (i.e., a decrease following phenylephrine) the atropine dosage was supplemented.

Test Sequence:

The test sequence and experimental conditions were the same as in the previous years to allow for correlation of the experimenal results. The sequence consisted of ±2 G sinusoidal acceleration where + G_y preceded +2 G_z followed by -2 G_y and -2

G_z starting at the low frequency and moving to the next higher frequency at 3 to 4 minute intervals witout stopping the centrifuge. Previous years' studies indicated that this protocol allowed steady state conditons to develop more rapidly than did a protocol which stopped the centrifuge between frequencies. The sinusoidal series of tests was followed by a step input series consisting of 3 minutes each for +2 G_z to -2 G_y to -2 G_z to +2 G_y to 2 G_z to -2 G_z to +2 G_z and back to -2 G_y. The first 4 inputs were produced by 90 degree rotation of the platform while the centrifuge was producing 2 G radial acceleration. The last 2 inputs were produced by a 180 degree rotation each.

RESULTS AND CONCLUSIONS

1. Comparison of 3 Min Cardiovascular Responses to Sustained +2 Gy and -2 Gy Acceleration

Results reported in this section are for 13 normally innervated dogs. The data were averaged over 3 min each of control and +2 G_y and -2 G_y acceleration before and after autonomic effector (alpha, beta and muscarinic) blockades. For each variable, the data (Figure A2) were examined for an acceleration effect, a blockade effect and a combined acceleration and blockade effect using a treatments-by-treatments-by subjects analysis of variance. Post hoc testing to compare individual means (differences between +2 G_y and -2 G_y and/or control, etc.) was done with a Duncan multiple range test.

There were significant acceleration effects and blockade effects but in only one variable were significant differences found between +2 G_y and -2 G_y acceleration responses.

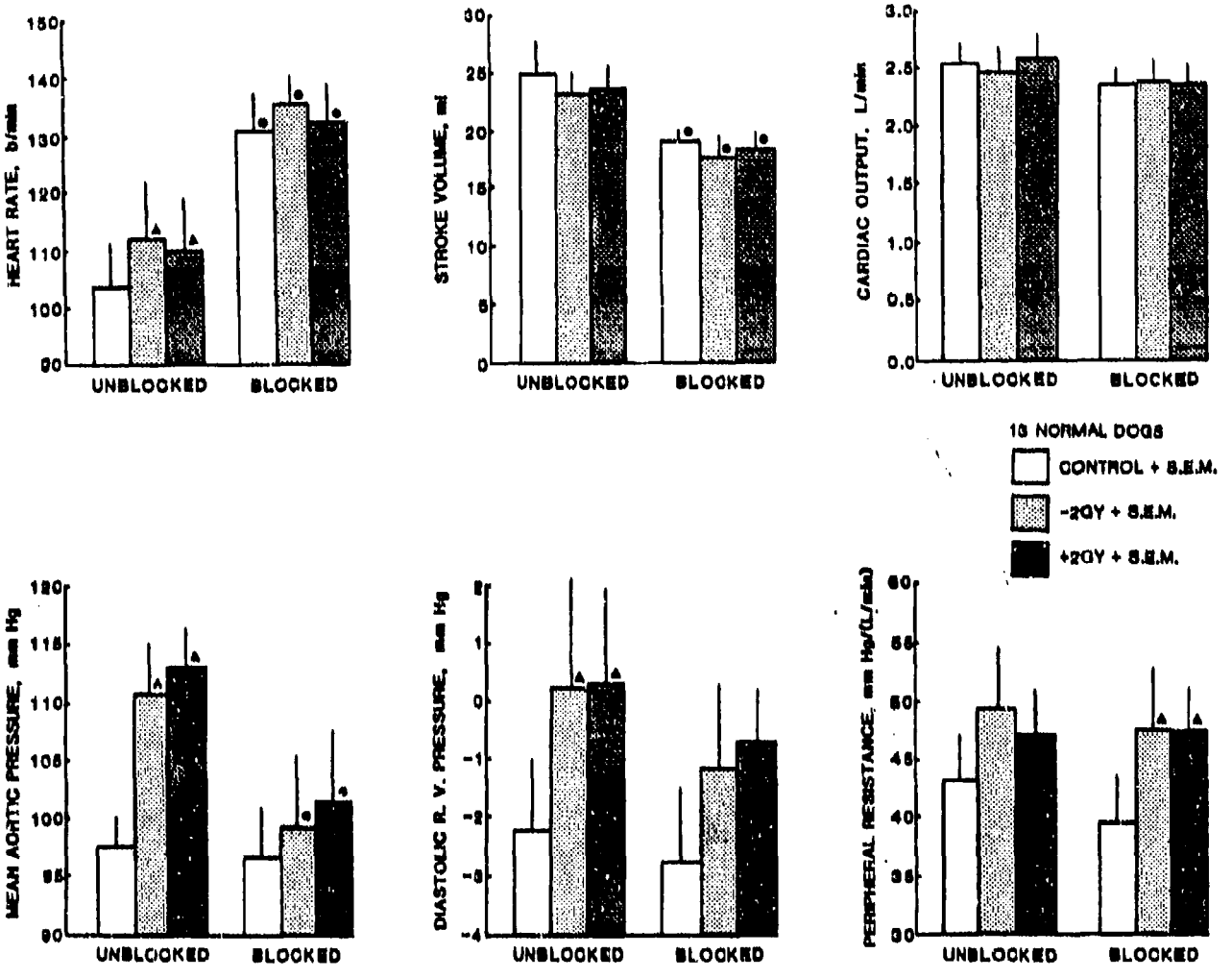

Figure A2. Comparison of control, and 3 minutes each of +2Gy and -2Gy acceleration in 13 normal innervated dogs in the unblocked and autonomically blocked states. Significant changes from control due to acceleration are indicated by▲ and significant changes due to blockade are indicated by● . There were no significant differences in any of these variables between +2Gy and -2Gy.

Heart rate was elevated significantly from a preacceleration control of 104 to 112 b/min with -2 G_y and 110 b/min with +2 G_y and blockade significantly elevated heart rate in all cases. There was no acceleration effect on either stroke volume or cardiac output, however blockade did significantly lower stroke volume. Aortic pressure was significantly elevated from 98 to 111 mm Hg by -2 G_y acceleration and to 113 mm Hg by +2 G_y acceleration. This pressure response to sustained acceleration was significantly attenuated by the autonomic blockade. Right ventricular diastolic pressure (a measure of central venous pressure) was significantly elevated by acceleration in the unblocked state and this response was also attenuated by the blockade. Unblocked right ventricular systolic pressure (a measure of pulmonary artery pressure, data not shown) increased from 24.7 to 31.3 mm Hg with -2 G_y and to 28.4 mm Hg with +2 G_y; none of these was significantly different from the other. The increase in right ventricular systolic pressure with either acceleration was attenuated in the blocked state. There was an increase in peripheral vascular resistance with acceleration that was only significant after autonomic blockade. In none of these variables was there a significant difference between +2 G_y and -2 G_y after 3 min of either stress.

A comparison of the response of average heart volumes to the 3 min each of +2 G_y and -2 G_y acceleration in 6 normal dogs is shown in Figure A3 . In this variable, and only this variable, was there a significant difference between the + 2 G_y and -2 G_y response in that -2 G_y heart volumes were significantly greater

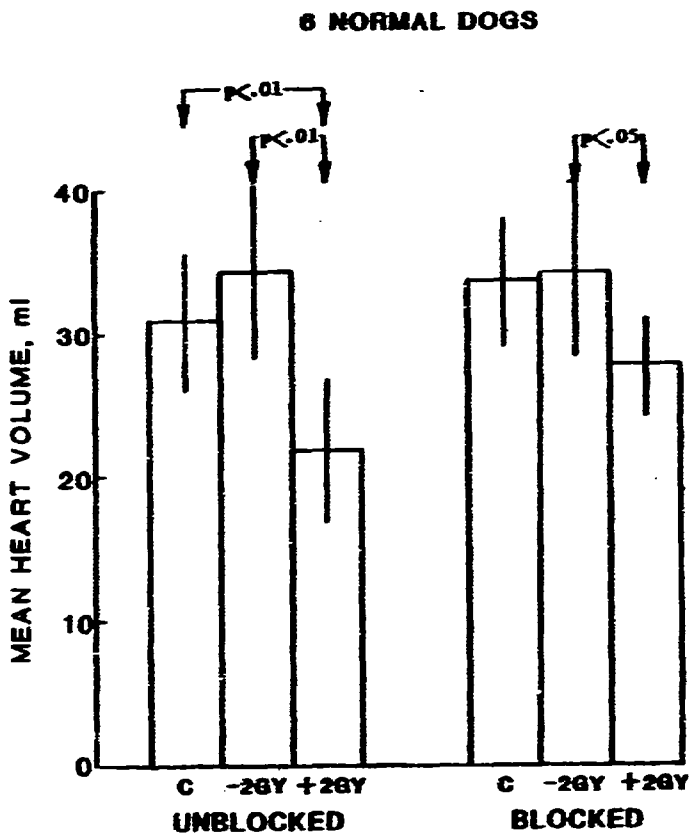

Figure A3. Average heart volume of 6 normally innervated tranquilized dogs during 3 min each of preacceleration control, -2 G_y and +2 G_y acceleration in the unblocked (reflexive) state and later in the autonomically blocked (areflexive) state.

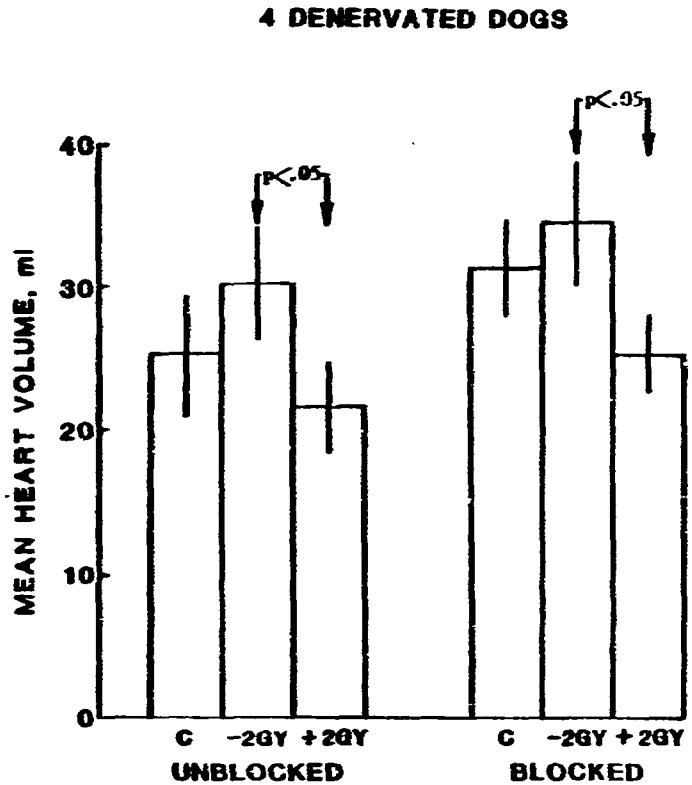

Figure A4. Average heart volume of 4 cardiac denervated, tranquilized dogs during 3 min each of preacceleration control, -2 G_y and +2 G_y acceleration in the unblocked and autonomically blocked states.

than +2 G_y volumes in both the unblocked and blocked state. Furthermore this effect was significant in 4 cardiac denervated animals (shown in Figure A4) in both the unblocked and the blocked state. The persistance of the effect in both normal and cardiac denervated dogs in both the unblocked and blocked states prompted us to look at these animals in detail for other variables which would indicate a response to this difference. However, as in the larger group shown previously, there was not much else to indicate this effect. Unblocked heart rates were elevated by both -2 G_y and + 2 G_y acceleration but there was no difference between them. Unblocked and blocked aortic pressures were elevated by both -2 G_y and +2 G_y acceleration but again no difference was seen between the two. Cardiac outputs were not really affected by acceleration at all; peripheral resistance did increase with acceleration, particularly in the blocked state but again there was no difference between +2 G_y and -2 G_y. Diastolic right ventricular pressure (Figure A5), however, did indicate an elevated, but not significant, pressure during -2 G_y acceleration as compared to +2 G_y acceleration in both the unblocked and blocked states. Since an elevation in diastolic right ventricular pressure would indicate an increase in ventricular filling, we went back and looked at the large data set again in greater detail. In 22 normal, unblocked animals, diastolic right ventricular pressure was greater during -2 G_y acceleration than during +2 G_y acceleration in 14 animals, less in 6 and no difference in two. Analysis of variance had not indicated significant differences between the -2 G_y and +2 G_y groups,

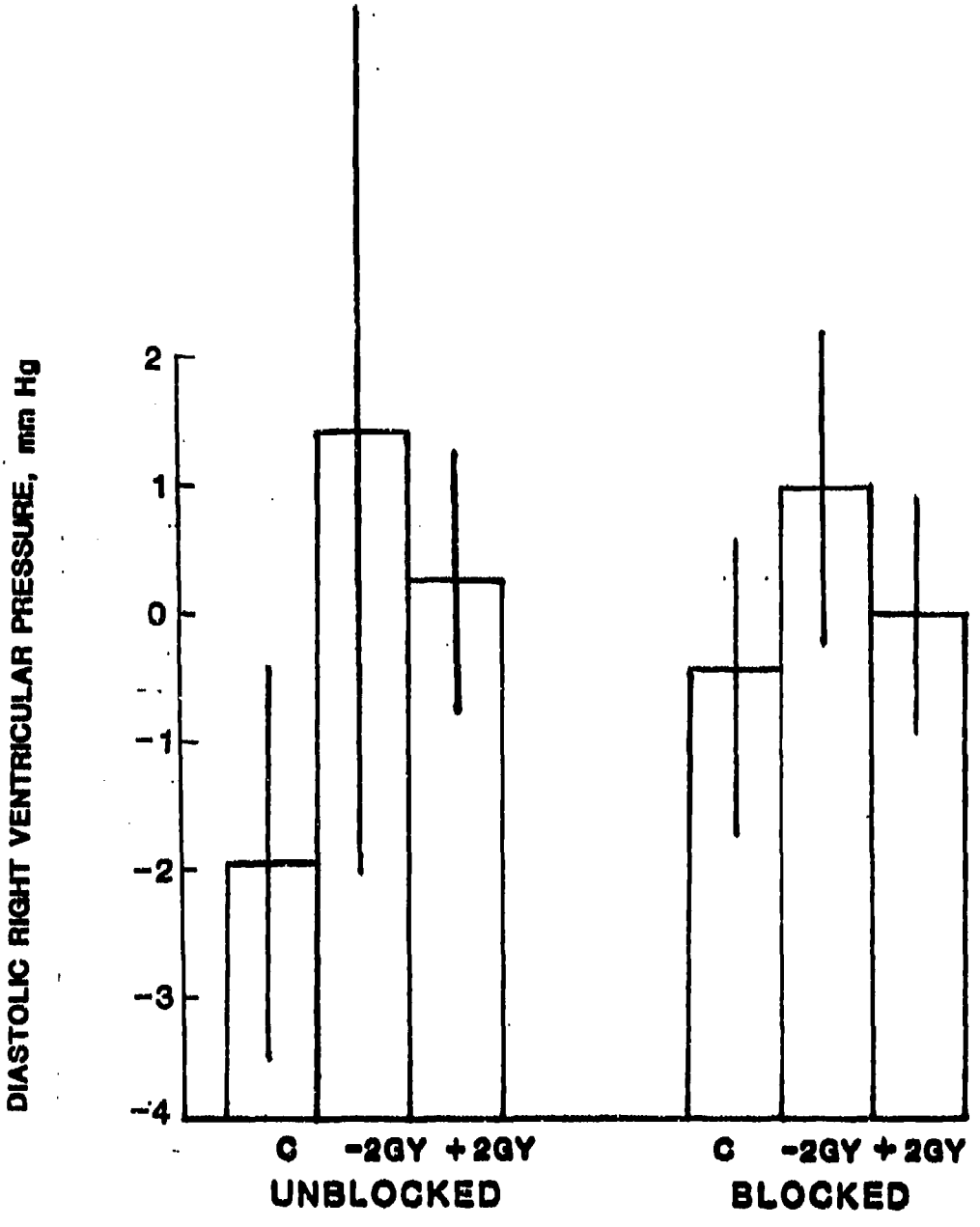

Figure A5. Average diastolic right ventricular pressure (central venous pressure) in 6 normally innervated, tranquilized dogs during preacceleration control, -2 Gy and +2 Gy acceleration in the unblocked and autonomically blocked states.

however a nonparametric (Wilcoxon Sign) test did ($p < .05$). In 15 autonomically blocked animals, diastolic right ventricular pressure was greater during -2 G_y than during +2 G_y in 11 animals and was less in four. Testing of the blocked data did not indicate a significant effect using either analysis of variance or the nonparametric test. Finally a linear correlation (Figure A6) of diastolic right ventricular pressure as a function of average heart volume in preacceleration control, +2 G_y and -2 G_y states for the animals (6 normal and 4 cardiac denervated, unblocked and blocked) yielded a Pearson product moment correlation coefficient of 0.32 ($t = 2.58$ which was significant at the 0.02 level for $df = 58$). The slope of this line was 0.13 mm Hg/ml with an intercept at -9.7 mm Hg.

The difference in average heart volume during -2 G_y and +2 G_y acceleration was a real (non-artifactual) effect that probably resulted from changes in filling volume of the ventricle (since stroke volume was not different). This statement is based on the following, rather inconclusive, results: 1) Two-thirds of the animals had elevated diastolic right ventricular pressures during -2 G_y as opposed to +2 G_y in both the unblocked and blocked states, 2) Diastolic right ventricular pressure was significantly elevated during -2 G_y as opposed to +2 G_y acceleration in the unblocked state using the nonparametric test. 3) A significant but very low correlation coefficient between average heart volume and diastolic right ventricular pressure was found in both unblocked and blocked animals.

Differences in -2 G_y and +2 G_y filling volumes could be due

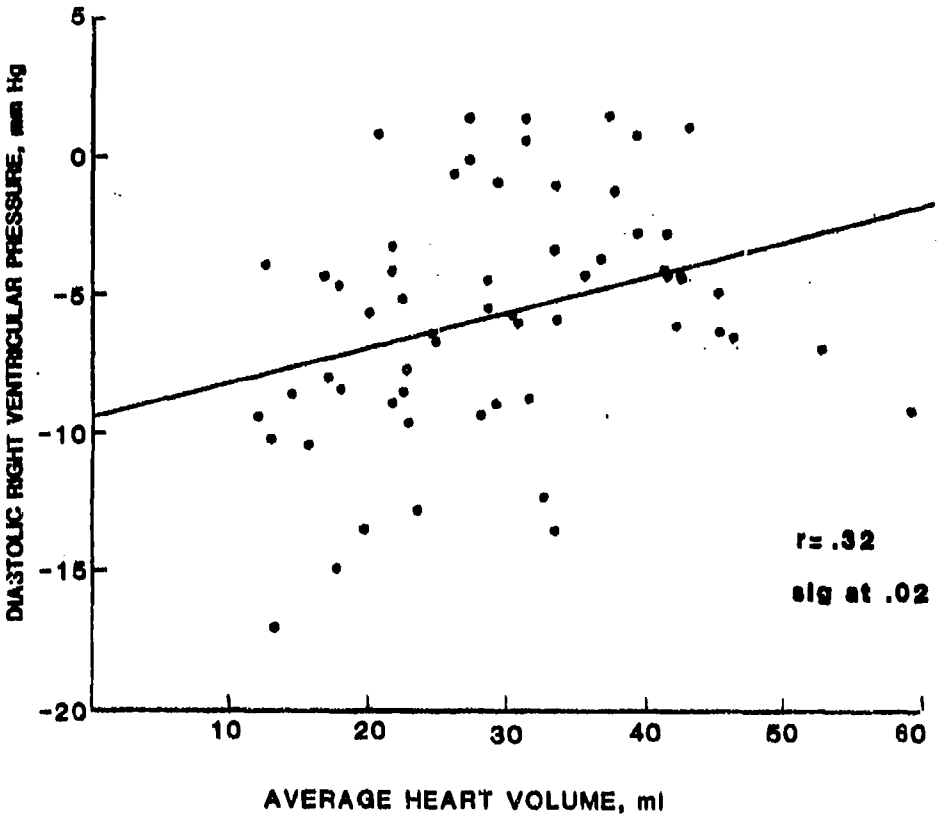

Figure A6. Correlation of unblocked and blocked right ventricular diastolic pressures with average left ventricular volumes for 6 normal and 4 cardiac denervated dogs during preacceleration control, -2 G_y and +2 G_y acceleration. The correlation coefficient was significant at $p < .02$ using a Pearson product moment correlation.

to combined effects of acceleration and anatomical differences or could reflect a carry-over effect due to hormonal responses to the more stressful $+G_z$ and $-G_z$ acceleration states preceding the $+G_y$ and $-G_y$ acceleration states. In our protocol, +2 G_y is preceded by 3 min of -2 G_z and -2 G_y is preceded by 3 min of +2 G_z. However since the results were each averaged over 3 min of -2 G_y or +2 G_y acceleration, and since not all animals received the acceleration sequence in the same order, it appeared that the difference was probably due to the combined effcts of acceleration with anatomical differences that resulted in diminished left ventricular filling volume during +2 G_y acceleration as compared to either -2 G_y acceleration or unaccelerated control.

2. Comparison of Cardiovascular Responses to +/-2 Gy and +/-2 Gz Sinusoidally Oscillating Acceleration

RESULTS

Results reported in this section are from 6 normally innervated dogs undergoing our standard acceleration profile in which they were rotated in a 2 G field with +2 G_y preceding +2 G_z followed by -2 G_y and -2G_z for ≃ 3 min each at 10 acceleration frequencies ranging from 0.001 to 0.25 Hz. In this section we will concentrate on differences between the +2 G_y and -2 G_y states and, when appropriate, we will compare these responses with both +2 G_z and -2 G_z states. The 6 dogs in this section are the same 6 as in the preceding section which dealt with responses to 3 min of sustained acceleration at the 4 different G vectors. These animals had heart volume measurements taken in addition to the flow and pressure measurements reported earlier (previous progress reports). The data for this section were taken at four points of the acceleration trace (+2 G_y, +2 G_z, -2 G_y and -2 G_z) and represent an average over 4 to 5 heart beats per reading per animal at each of these acceleration vectors. Significant differences between mean values were tested using the same analysis of variance reported in the results and conclusions section of A1.

Unblocked +2 G_y and -2 G_y aortic pressure responses to frequencies from 0.001 to 0.25 Hz are shown in the top half of Figure A7, and the responses of the same animals after autonomic blockade are shown in the lower half of the same figure. A peak in unblocked aortic pressure was evident in the fourth frequency bin for both +2 G_y and -2 G_y with -2 G_y significantly ($p < .05$)

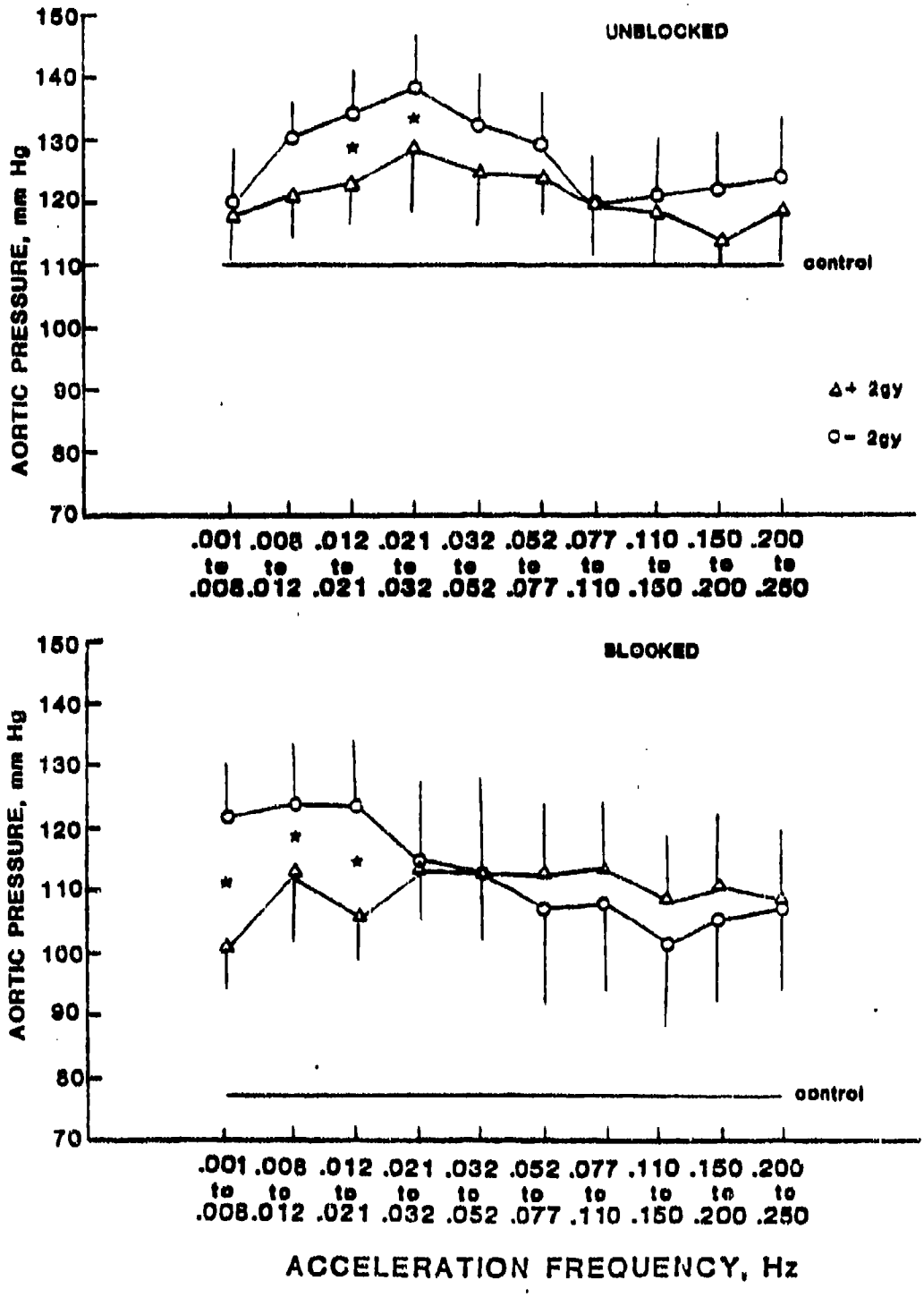

Figure A7. Comparison of +2 Gy and -2 Gy values of mean aortic pressure in 6 normally innervated animals in the unblocked (top half) and autonomically blocked states (bottom half). Values shown are mean over 6 animals ± SEM. Significant differences between the acceleration vectors ($p < .05$) at any frequency is indicated by *.

higher than +2 G_y in bins 3 and 4. In the blocked state -2 G_y pressures were significantly greater than +2 G_y pressures in the first 3 frequency bins.

Simultaneous peripheral vascular resistance responses are shown in Figure A8, again the unblocked responses to + and -2 G_y are shown in the top half and blocked responses in the bottom half of the figure. Unblocked resistance during -2 G_y was significantly greater than during +2 G_y for frequencies up to 0.052 Hz with a pronounced peak in -2 G_y resistance in the fourth frequency bin. Blocked resistance was significantly greater during -2 G_y than +2 G_y in bins 1 and 4. A comparison of -2 G_y unblocked to blocked resistance indicated unblocked -2 G_y responses to be significantly greater than blocked -2 G_y responses in bins 3, 4 and 5 (significance not shown on figure) implying an active regulatory component in the unblocked response.

Simultaneous cardiac outputs (digital integration of the electromagnetic flow signal) are shown in Figure A9, with the same format as the preceding two figures. In this case, there was very little difference between +2 G_y and -2 G_y acceleration effects; cardiac outputs tended to increase for both acceleration vectors at the higher frequencies in both the unblocked and the blocked states, and unblocked cardiac output was slightly, but not significantly, lower during -2 G_y in bins 2, 3 and 4. In the blocked state -2 G_y cardiac output was significantly lower than that for +2 G_y in bins 7 and 9.

Heart rate responses to the same acceleration stress, again

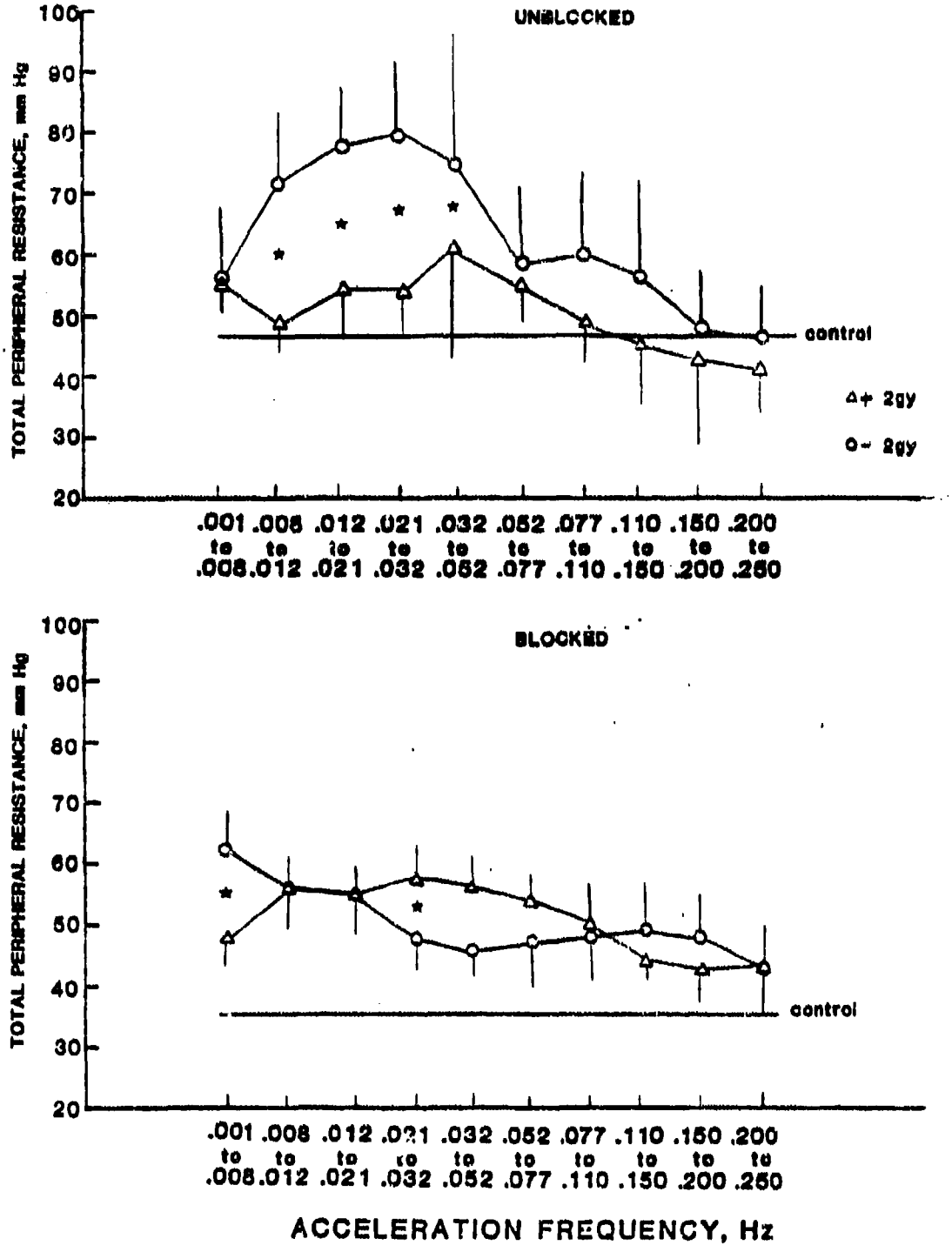

Figure A8. Comparison of +2 G_y and -2 G_y values of total peripheral resistance in 6 normally innervated animals in the unblocked (top half) and autonomically blocked states (bottom half). Values shown are mean over 6 animals ± SEM. Significant differences between the acceleration vectors ($p < .05$) at any frequency is indicated by *.

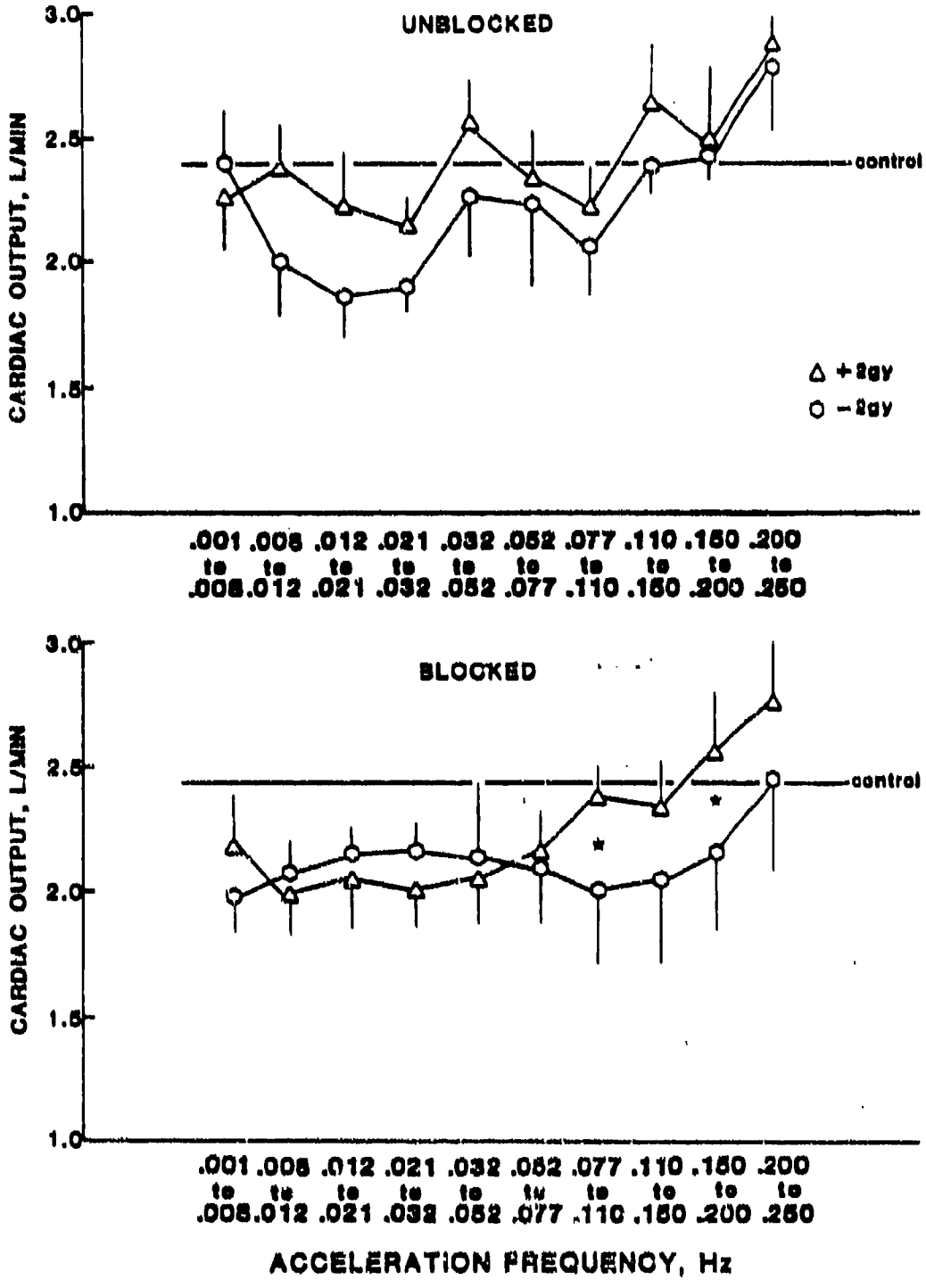

Figure A9. Comparison of +2 G_y and -2 G_y values of cardiac output in 6 normally innervated animals in the unblocked (top half) and autonomically blocked states (bottom half). Values shown are mean over 6 animals ± SEM. Significant differences between the acceleration vectors ($p < .05$) at any frequency is indicated by *.

simultaneous with the above data and with the same format, are shown in Figure A10 . The unblocked +2 G_y response and the blocked ±2 G_y responses were quite constant across the frequency range while the unblocked -2 G_y response was biphasic, dipping below the +2 G_y response in bins 2, 3 (sig.) and 4 and rising above it in bins 5 thru 10 (significant for bins 6 thru 10).

Stroke volumes (simultaneous with the above data, same format) for these animals are shown in Figure A11. In this variable there was a large difference between +2 G_y and -2 G_y response in the unblocked but not in the blocked state. Up to 0.032 Hz in the unblocked state, the animals maintained stroke volume during both +2 G_y and -2 G_y at about control level; from 0.032 Hz to 0.11 Hz stroke volume dropped precipitously during -2 G_y (significant for bins 6 thru 9) and then between 0.11 Hz and 0.25 Hz, -2 G_y stroke volumes returned toward control levels. Unblocked stroke volume during +2 G_y did not differ from control across the frequency range.

Left ventricular, end diastolic volume measurements for these animals are shown in Figure A12. These data were obtained by calculating average heart volume from the dimension crystal measurements and adding to that one half the stroke volume taken from the electromagnetic flow tracings. In this variable, as in stroke volume there was a large difference between unblocked +2 G_y and -2 G_y values across the frequency range. In the blocked case, +2 G_y and -2 G_y end diastolic volumes decreased with increasing frequency across the range studied with no significant difference between the two. However

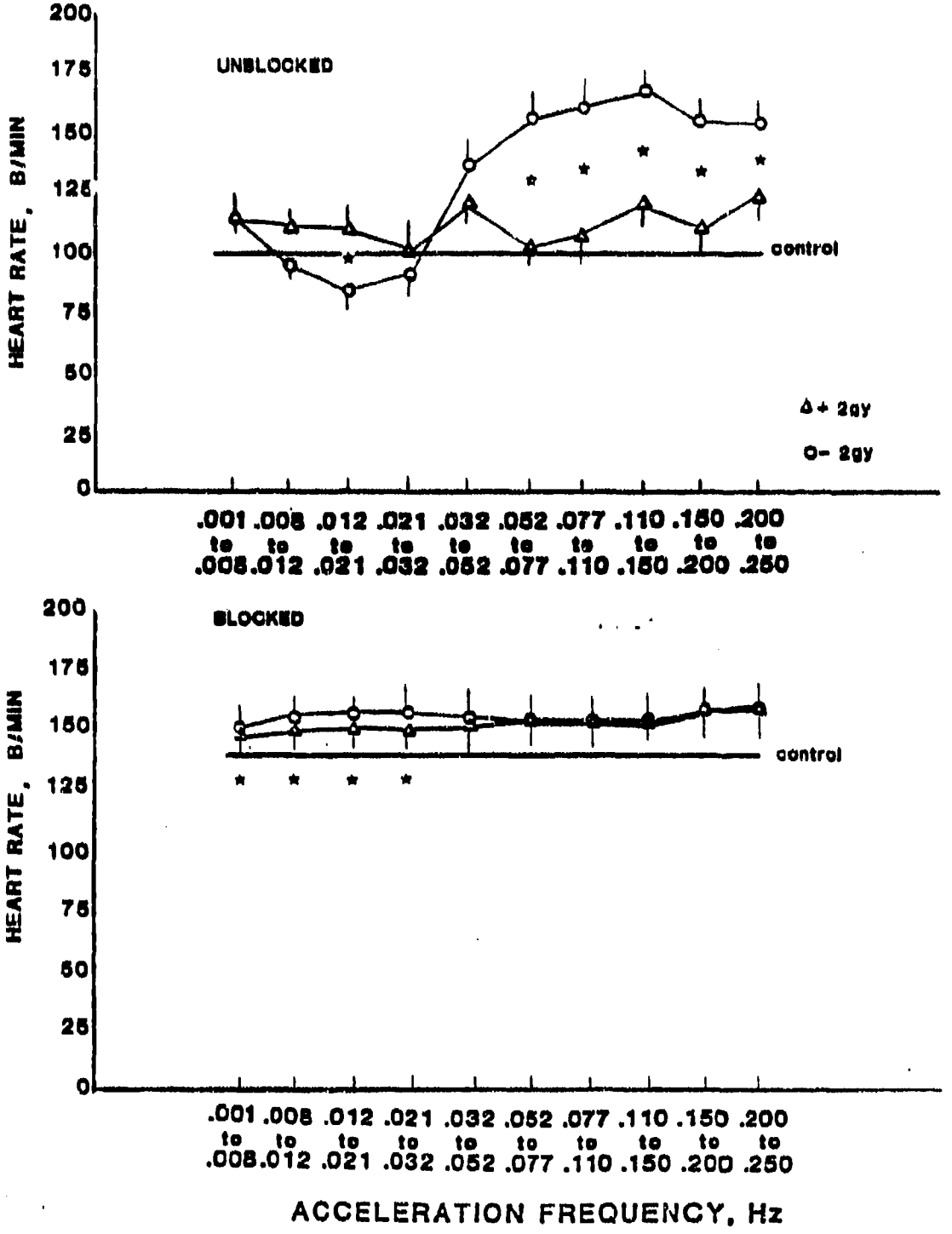

Figure A10. Comparison of +2 G_y and -2 G_y values of heart rate in 6 normally innervated animals in the unblocked (top half) and autonomically blocked states (bottom half). Values shown are mean over 6 animals ± SEM. Significant differences between the acceleration vectors ($p < .05$) at any frequency is indicated by *.

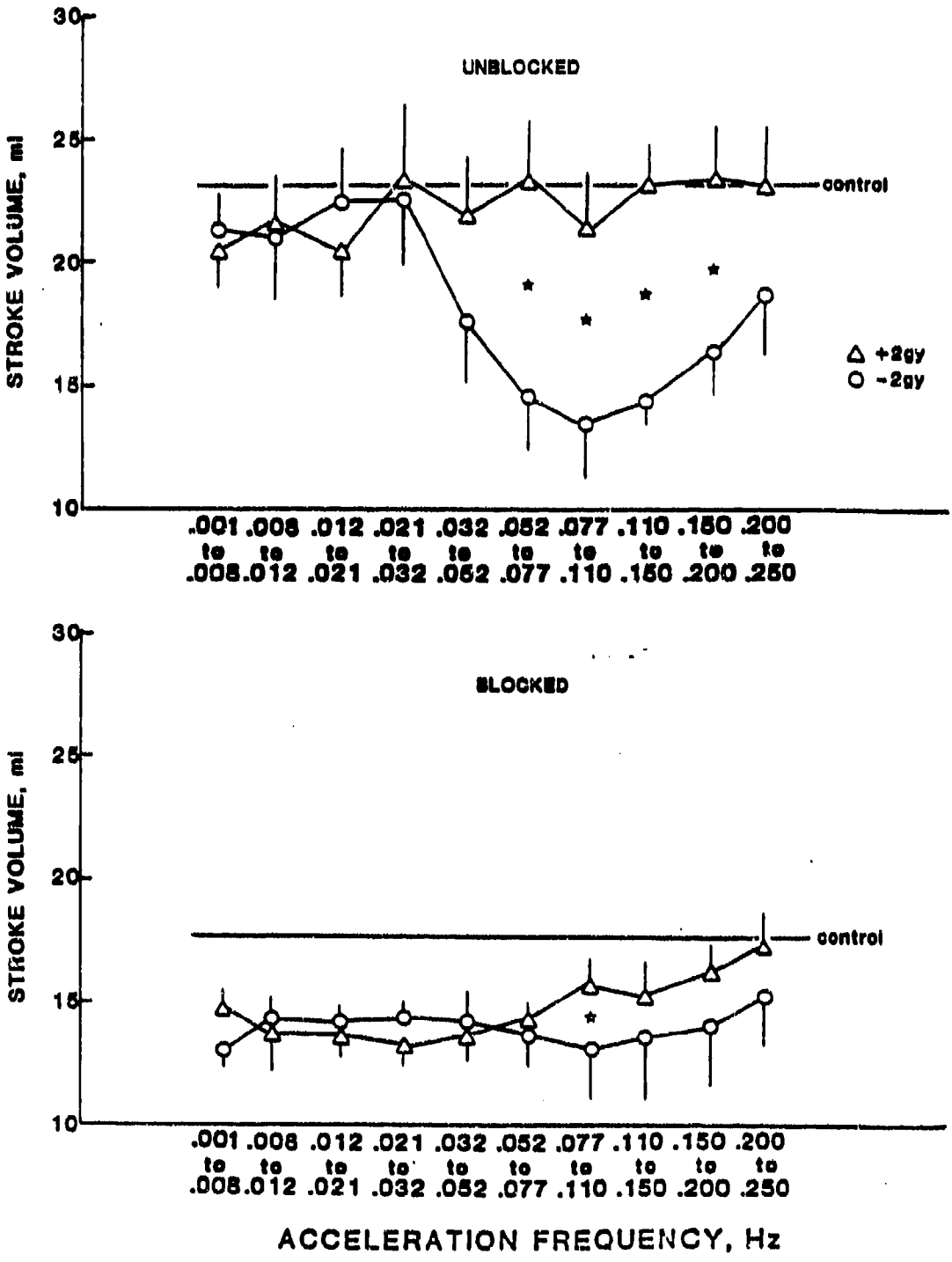

Figure All. Comparison of +2 G_y and -2 G_y values of stroke volume in 6 normally innervated animals in the unblocked (top half) and autonomically blocked states (bottom half). Values shown are mean over 6 animals $\pm$ SEM. Significant differences between the acceleration vectors ($p < .05$) at any frequency is indicated by *.

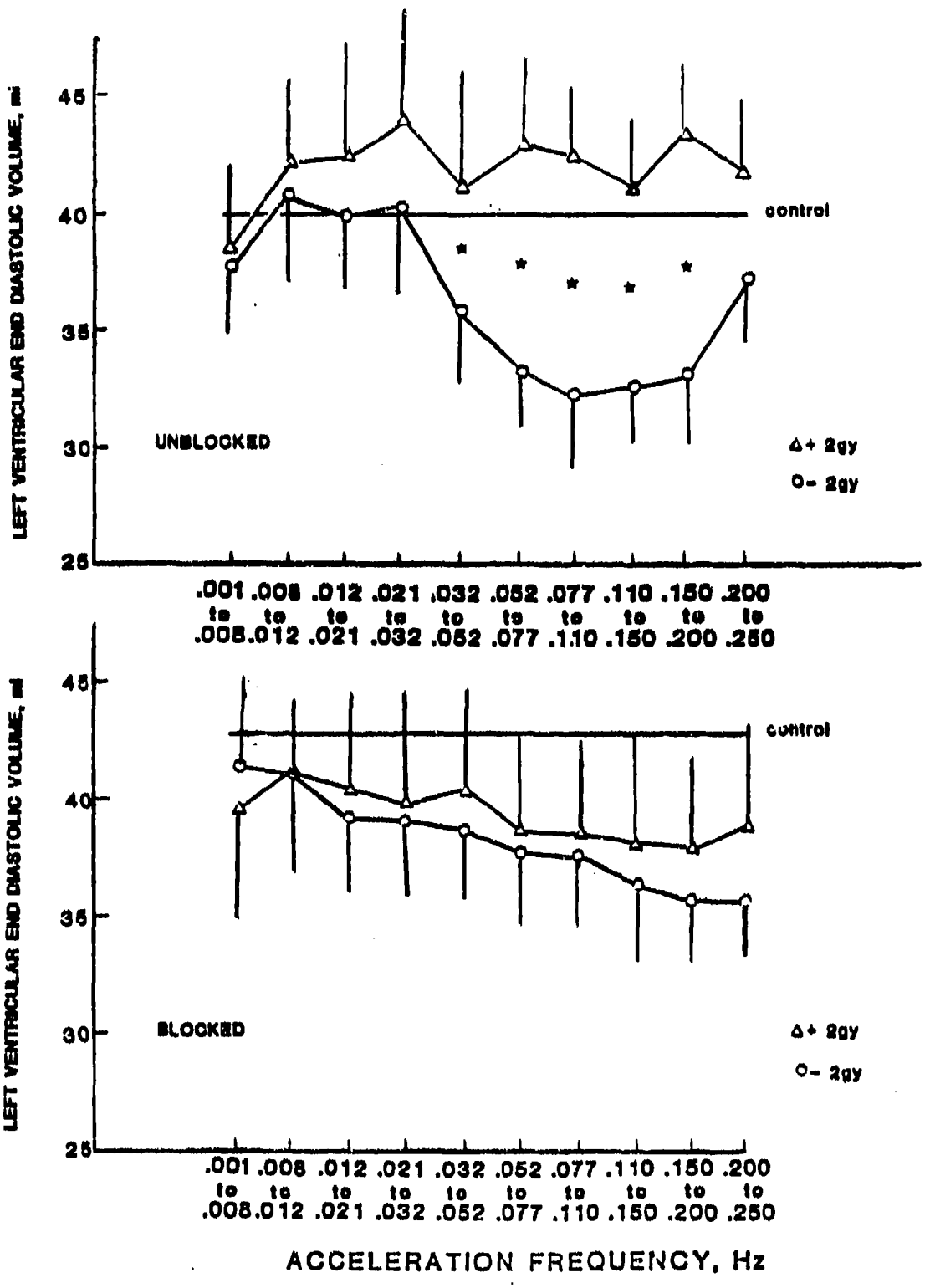

Figure A12. Comparison of +2 G_y and -2 Gy values of left ventricular end diastolic volume in 6 normally innervated animals in the unblocked (top half) and autonomically blocked states (bottom half). Values shown are mean over 6 animals ± SEM. Significant differences between the acceleration vectors ($p < .05$) at any frequency is indicated by *.

the blockade itself as reported earlier (1980-81 Progress Report) resulted in larger end diastolic volumes and dramatically reduced stroke volumes. In the unblocked case, end diastolic volumes were about the same for +2 G_y and -2 G_y up to 0.032 Hz; end diastolic volume then fell significantly during -2 G_y for frequencies between 0.032 Hz and 0.11 Hz and then returned toward control (and +2 G_y) values for frequencies between 0.11 Hz and 0.25 Hz.

Diastolic right ventricular pressure for these animals is shown in Figure A13. In the unblocked case, both +2 G_y and -2 G_y diastolic pressures increased above control as frequency increased with -2 G_y slightly higher than +2 G_y across the frequency range, but significantly higher only in bin 9. In the blocked case, both +2 G_y and -2 G_y diastolic pressures increased with increasing frequency for frequencies above 0.012 Hz. Minus 2 G_y was significantly greater than +2 G_y in bins 7 and 8.

CONCLUSIONS

a) If all of these results are viewed at with respect to maintenance of aortic pressure across the acceleration frequency range, several conclusions can be made. Unblocked aortic pressure was elevated above control across the frequency range due to: a) elevated peripheral vascular resistance between 0.001 and 0.052 Hz, b) elevated heart rate and peripheral reistance between 0.052 and 0.110 Hz and c) elevated heart rate and venous return between 0.110 and 0.250 Hz.

b) The resistance response during -2 G_y appeared to be a

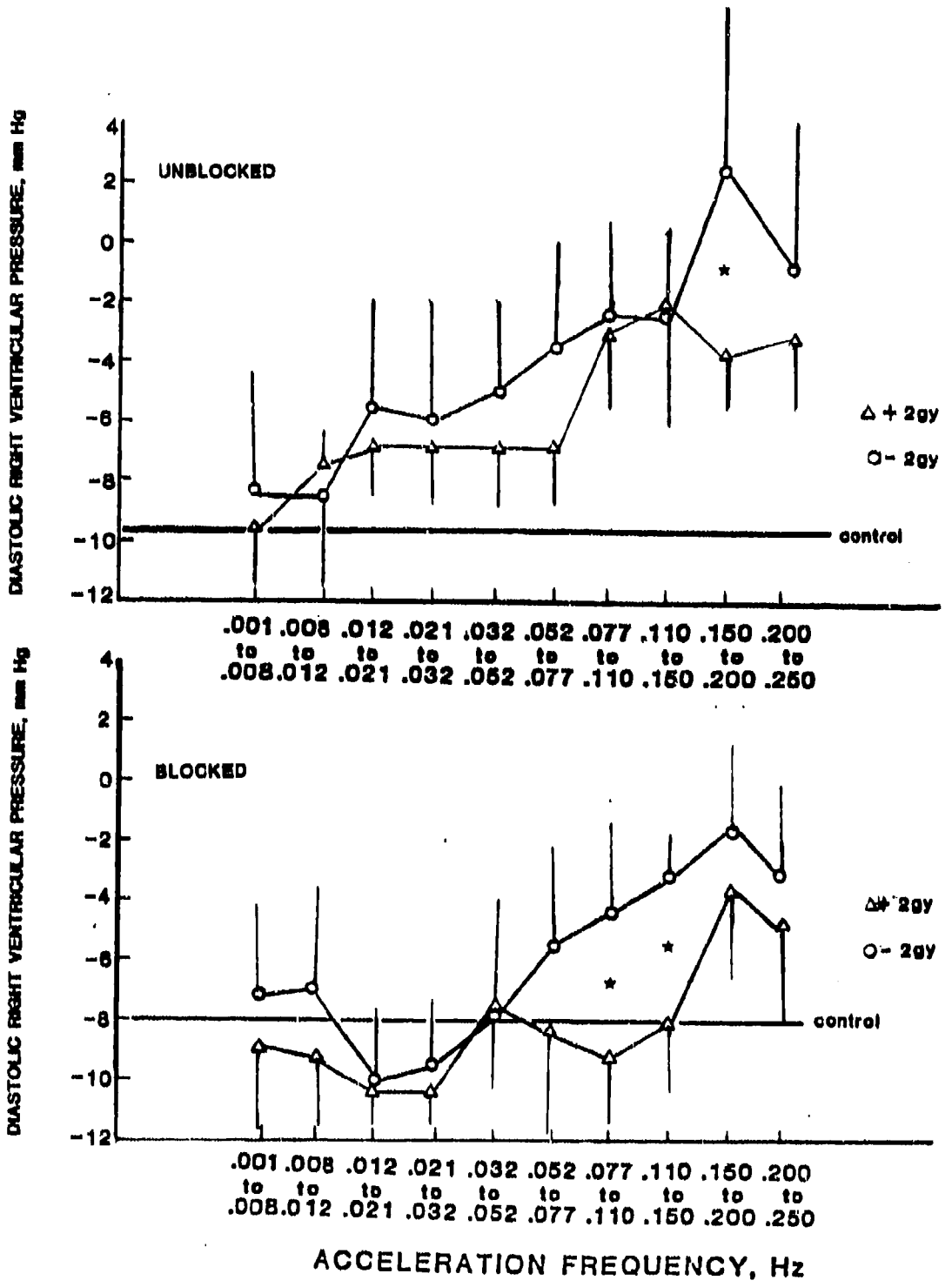

Figure A13. Comparison of +2 Gy and -2 Gy values of right ventricular diastolic pressure in 6 normally innervated animals in the unblocked (top half) and autonomically blocked states (bottom half). Values shown are mean over 6 animals ± SEM. Significant differences between the acceleration vectors ($p < .05$) at any frequency is indicated by *.

result of the resistance response to the +2 G_z acceleration vector which preceded it. Below 0.010 Hz this response was maximal and in time with +2 G_z (previous progress reports). As the frequency increased, the resistance peak diminished but moved in phase with the -2 G_y acceleration vector.

c) During -2 G_y acceleration at the lower (<0.032 Hz) frequencies, cardiac output was lower than control or +2 G_y due to lower heart rates. Between 0.032 and 0.11 Hz, -2 G_y cardiac outputs were only slightly lower than control or +2 G_y. This occurred even though stroke volume had dropped to 1/2 its control or +2 G_y value, because heart rate increased and compensated for the loss of stroke volume. For frequencies between 0.220 and 0.250 Hz cardiac output was elevated above control, for both + and -2 G_y due to elevated heart rate and stroke volume.

d) The stroke volume response itself appeared to be a mixture of changes in end diastolic volume with changes in heart rate. Minus 2 G_y end diastolic volume, heart rate and stroke volume all remained close to +2 G_y and control values for frequencies up to 0.032 Hz. However between 0.032 Hz and 0.110 Hz, end diastolic volume fell by 21% and heart rate rose 77% resulting in a fall in stroke volume of 40% (actually elevating cardiac output by 8%). Between 0.110 Hz and 0.250 Hz, stroke volume rose due to a rise in end diastolic volume.

e) The large frequency effect on unblocked, end diastolic -2 G_y volumes (22% decrease between 0.032 and 0.11 Hz)

appeared to be a combination of several effects: a) Increasing the frequency of acceleraton oscillation limited the actual time for blood shifts to occur, causing the effect of the +2 G_z blood pooling to persist into the -2 G_y state immediately following it. This effect was not large however, judging by the much slower convergence of the blocked +2 G_z volumes (Figure A14, bottom half) with the -2 G_y volumes as compared to the convergence of these traces (upper half, Figure A14) in the unblocked state. b) The large increase in -2 G_y heart rates between 0.032 and 0.110 Hz appeared to be the variable that was principally responsible for the decrease in -2 G_y end diastolic volume. The stimulus for the increased rate appeared to be the preceding +2 G_z acceleration vector which has previously been shown to elicit increasingly lagging, and decreasing (but still large) amplitudes of oscillations in heart rate for frequencies above 0.05 Hz (2). c) The effect of diminishing (but still large) amplitudes of oscillations of peripheral resistance (with increasing acceleration frequency) which also were becoming increasingly out of phase with acceleration (2) was seen in these data [Figure A8]. However, its effect on unblocked end diastolic volumes with increasing acceleration frequency can only be suggested by data from the present study. d) Since the effect of our autonomic blockade was to greatly increase end diastolic volume and decrease stroke volume, caution is advised in comparing the unblocked to blocked data with

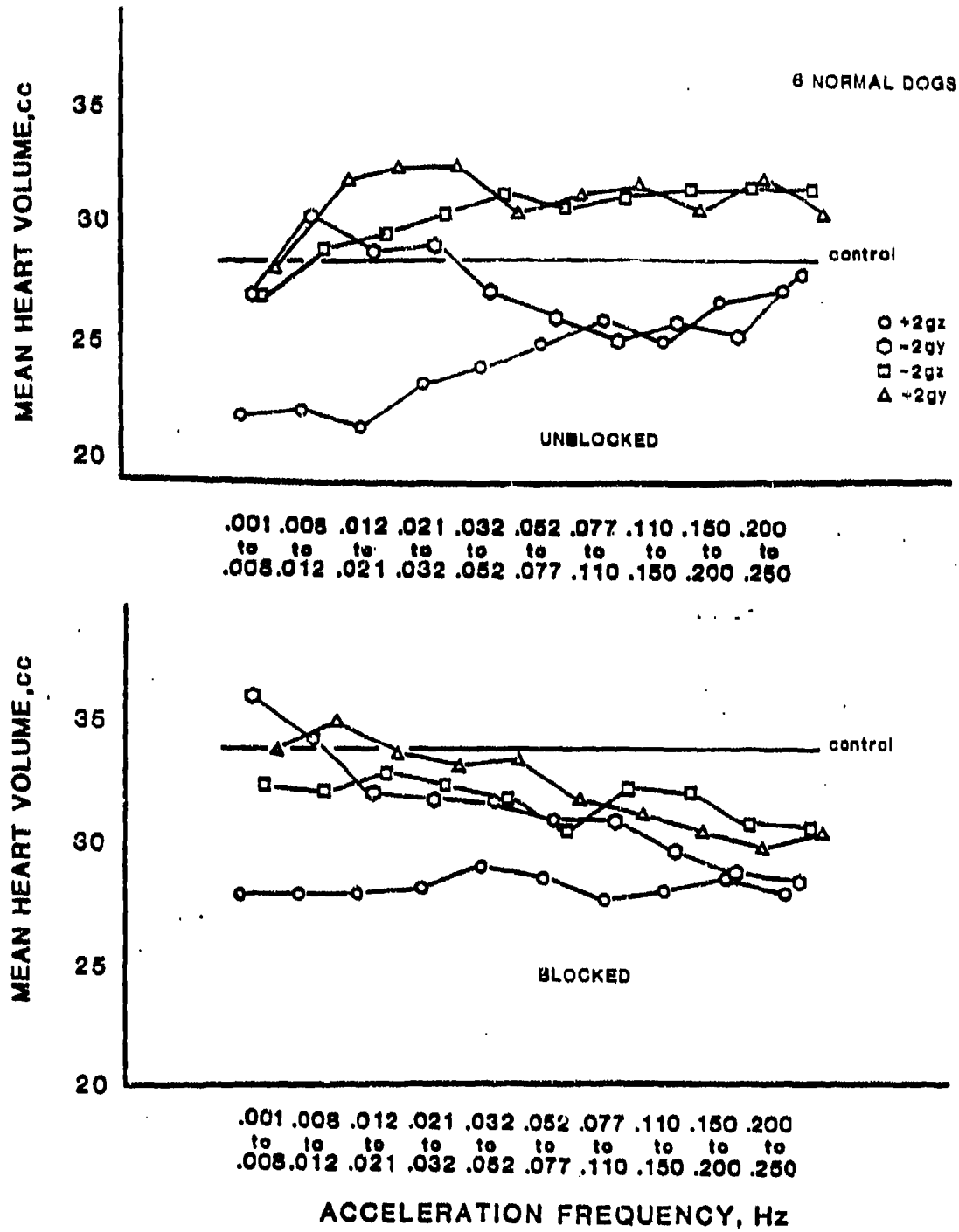

Figure A14. Average heart volumes for 6 normally innervated, unblocked and blocked dogs across the frequency range 0.001 to 0.25 Hz were measured at +2Gz, -2Gy, -2Gz, and +2Gy. Unblocked data is shown in the upper half of the figure and blocked data is shown in the lower half.

respect to assuming heart function to be the same in both states, but again this comparison is beyond the scope of this study.

3. Neural effects of heart volume regulation during acceleration stress

An attempt has been made to identify the role of neural regulation of heart volumes during acceleration by comparing unblocked to blocked heart volumes during ±2 G_z and ±2 G_y sinusoidal acceleration across the frequency range of 0.001 to 0.25 Hz. The data reported here are from the normal dogs of the previous section. Figure A15 indicates the average heart volumes ± SEM of 6 dogs at each frequency. These numbers were obtained by averaging the +2 G_y, -2 G_y, +2 G_z and -2 G_z values for each dog for each frequency and represents the average during the heart beat over each acceleration cycle over 6 animals. In the upper half of the figure the trends reported in the previous section are quite clear: 1) Unblocked volumes dropped below control at the lowest frequency, and rose as frequency increased to above control at the highest frequency with an elevated recovery value. A significant difference between unblocked and blocked values at each frequency is indicated by a †. 2) Blockade of autonomic effector activity increased heart volume above the unblocked control value and volume returned toward unblocked control values as frequency increased; in this case the recovery value was about the same as the blocked control value. In the lower portion of this figure the average ratio of unblocked to blocked heart volume is shown as a function of frequency and a significant departure of any value from unity is

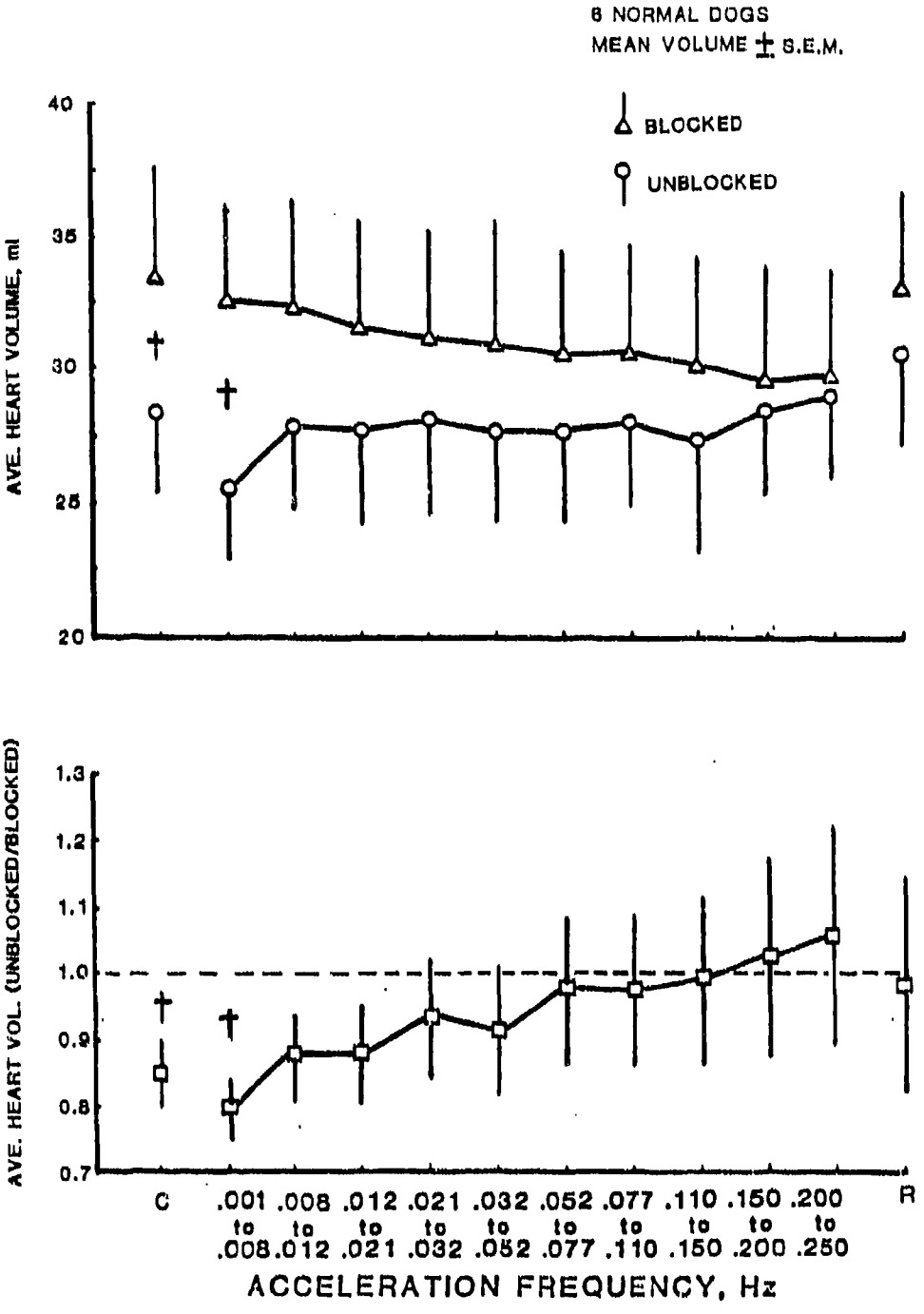

Figure A15. Upper Half. Averaged (over the acceleration cycle) heart volume for 6 unblocked and blocked normal dogs in response to +/-2Gz acceleration across the frequency range 0.001 to 0.250 Hz. Significant differences as a result of autonomic blockade are indicated by †.

Lower Half. Neurally mediated attenuation of heart volume as a function of acceleration in the same 6 dogs. Significant attenuation of heart volume is indicated by †.

indicated by a †. The interpretation of the significant difference between unblocked and blocked control and lowest frequency values implied a neural role in attenuaton of actual volume in each of those states. In the control state this implied that the normal resting volume was at less than maximum dilation and would indicate a potential role for Starling effects in volume regulation. At the lowest frequency, where we expect the +2 G_z value (which reflects lack of venous return) to dominate the average, a neural attenuation of volume is less easily explained. In order to look more closely at the response, each component of average heart volume was examined separately, Figure A16, using the same technique with an added 3 point smoothing. Because of the amount of averaging, these data were not examined statistically and is presented only as an indicator of trends. What is apparent from these data is that the low frequency attenuation of heart volume due to neural inputs is not restricted to the +2 G_z portion of the cycle, each of the other components is attenuated also. As frequency increased, the neural attenuation diminshed such that the net effect is the opposite at the highest frequency. One explanation for the low frequency attenuation of volume may be the adverse effect of higher heart rates on stroke volume seen at the lowest frequencies. In this situation where oscillations in heart rate are not large but heart rate remains at an elevated level, we have reason to suspect that this alone compromises filling which could be further substantiated by this attenuation data.

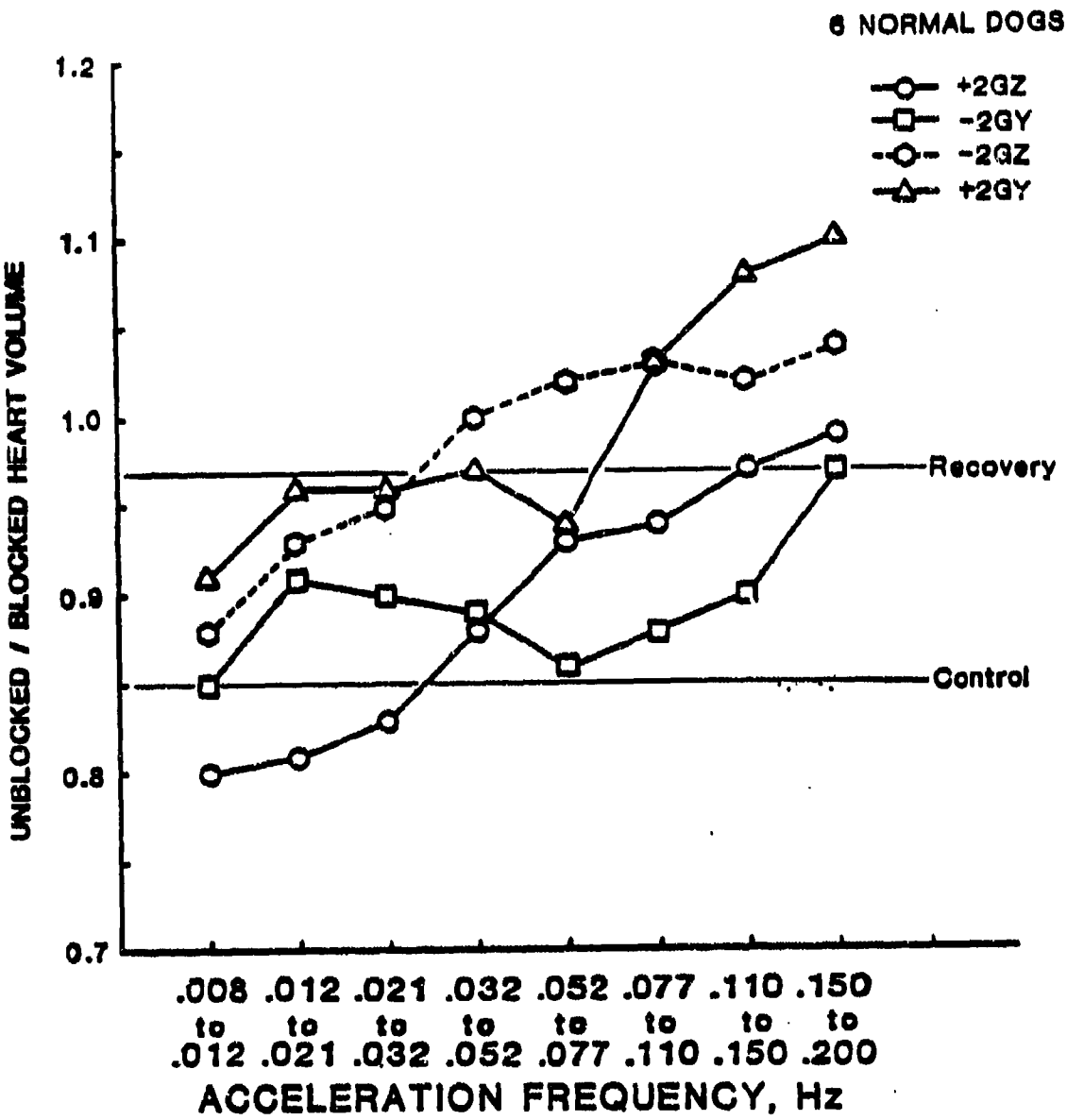

Figure A16. Neural attenuation of heart volume at +2Gz, -2Gy, -2Gz and +2Gy as a function of acceleration frequency.

B. IS THE NEURAL FEEDBACK CONTROL OF HEART RATE OPERATING TO PRODUCE OPTIMAL CARDIOVASCULAR REGULATION DURING TIME-DEPENDENT ACCELERATION STRESS?

INTRODUCTION

The rationale for our overall program is based on the premise that the design of effective countermeasures to rapid onset rates of acceleration stress depends upon understanding of the mechanisms responsible for cardiovascular regulation and their frequency response characteristics. This understanding becomes especially important when combined with the possiblity of pre-planned computer controlled flights at low altitude and high speeds. The need now exists more than ever before for a very deliberate and organized approach to system identification of physiological mechanisms as to their frequency response characteristics and as to the upper limit of a particular subsystem to function in extreme acceleration environments. For example, from our previous studies, it is not clear that the decreased effectiveness of cardiovascular regulation in the acceleration frequency range of 0.012 to 0.052 Hz is a true limitation of <u>individual</u> organs (cardiac or vascular). The possibility exists, for example, that the decreased effectiveness of regulation during an unfamiliar acceleration stress may be a result of a less than optimal carotid sinus-heart rate feedback pathway; one that has adapted to the relatively low level, pressure disturbances resulting from normal daily gravitational stimuli and one that has not "seen" relatively high frequency (0.012 - 0.052 Hz) content in pressure disturbances because of the hydraulic filtering provided by the passive circulatory

system (previous progress reports). To be more specific, we have observed that the stroke volume response to +2 G_z acceleration in unblocked dogs dropped to the same values as blocked responses. One explanation of this phenomenon could be that heart rate in the unblocked state climbed to such high values that ventricular filling was substantially compromised during a time when venous return was reduced. Preliminary results from our studies indicate that with the administration of a beta blocker, which reduced peak heart rates during +2 G_z, the diminished stroke volume during +2 G_z was not as pronounced as that occurring in the unblocked state. Beta blockade has also been shown to improve orthostatic tolerance to +3 G_z acceleration stress in humans (3). Observations of this kind suggest that the full capability of cardiovascular regulation, to name just one physiological system, is not known. Understanding and quantification of the upper limits of the regulatory system through basic research with animals can provide the background data base to aid in the design of new countermeasures to acceleration stress. Therefore, in order to determine the potential limits of cardiovascular regulation under G stress, we have begun a preliminary study that will be the basis for a systematic investigation of suspected weaknesses in the acceleration-induced regulatory process.

METHODS

Animal Model:

The animal model was one in which the artrio-ventricular node was destroyed using the technique of Steiner and Kovalik (4) at the time of instrumentation implant surgery. Bipolar atrial

and ventricular pacing leads were then added to our standard instruments for measuring aortic flow and right and left ventricular and aortic pressure. This model allows investigator control of heart rate over the range of 30 to 300 b/min. In these animals a ventricular pacemaker (Medtronics) with a screw-in epicardial lead on the apex of the right ventricle was also implanted to pace their hearts at 90 b/min during the three week post operative recovery period.

Pacing Procedures:

At the time of study this lead was disconnected from the pulse generator and used as one half of a bipolar ventricular lead (the other was a Davis and Geck cardiac conduction wire that had been placed at implant surgery less than <1 cm away on the right ventricular epicardial surface. In addition, atrial bipolar leads had been implanted so that at the time of the experiment, atrio ventricular pacing with any desired delay could be delivered. A microprocessor (Z - 80 based with 4 D/A and 4 A/D converters) delivered the pacing signal(s) and processed the electromagnetic flow signal to remove the pacing artifacts, integrate the flow over the beat, and report a 2 msec delayed, digital-to-analog, artifact-free, flow signal and a one-beat-delayed value of cardiac output. On initiation of either atrial or ventricular pacing signals (each of 8 msec pulse duration), the flow signal was not read for 22 msec. Atrial ventricular delay was adjustable from 24 msec up to, but not including, the shortest interbeat interval. Both atrial and ventricular pacing signals had independent adjustable gains for voltages between 0

and 8 volts. Paced heart rate as a function of time can be set for any desired waveform (sinusoidal, step, ramp, etc. or programmed to match the rate response of the intact dog)providing that it does not exceed 4000 beats before repeating.

RESULTS AND CONCLUSIONS

In the first experiment, instantaneous increases in heart rate were examined under no acceleration; then, in the second experiment, the effects of different levels of constant paced heart rate on stroke volume and cardiac output during +1 G_x (supine) and +1 G_z (head up) loadings were examined; following this, different levels of constant heart rates were controlled on board the centrifuge during our ± 2 G_z sinusoidal acceleration protocol; and lastly, heart rates were sinusoidally varied by computer during the ± 2 G_z sinusoidal acceleration loadings. The results and conclusions of each experiment follow.

1. <u>The effect of step changes in heart rate on the ability of the heart to make such changes and the response of other regulatory mechanisms to these changes.</u>

In this series the transient response of the heart in terms of rate, stroke volume, cardiac output, arterial and venous pressure and vascular resistance were examined during step changes in heart rate. In the following examples the atria were paced 60 msec ahead of the ventricle. The transient cardiovascular response to an increase in heart rate from 66 b/min to 190 b/min is shown in Figure B1. At the low heart rate (expanded chart speed), the electrical dissociation of the chambers due to the earlier atrioventricular blockade is evident by the reflection of atrial contractions that are not followed by ventricular

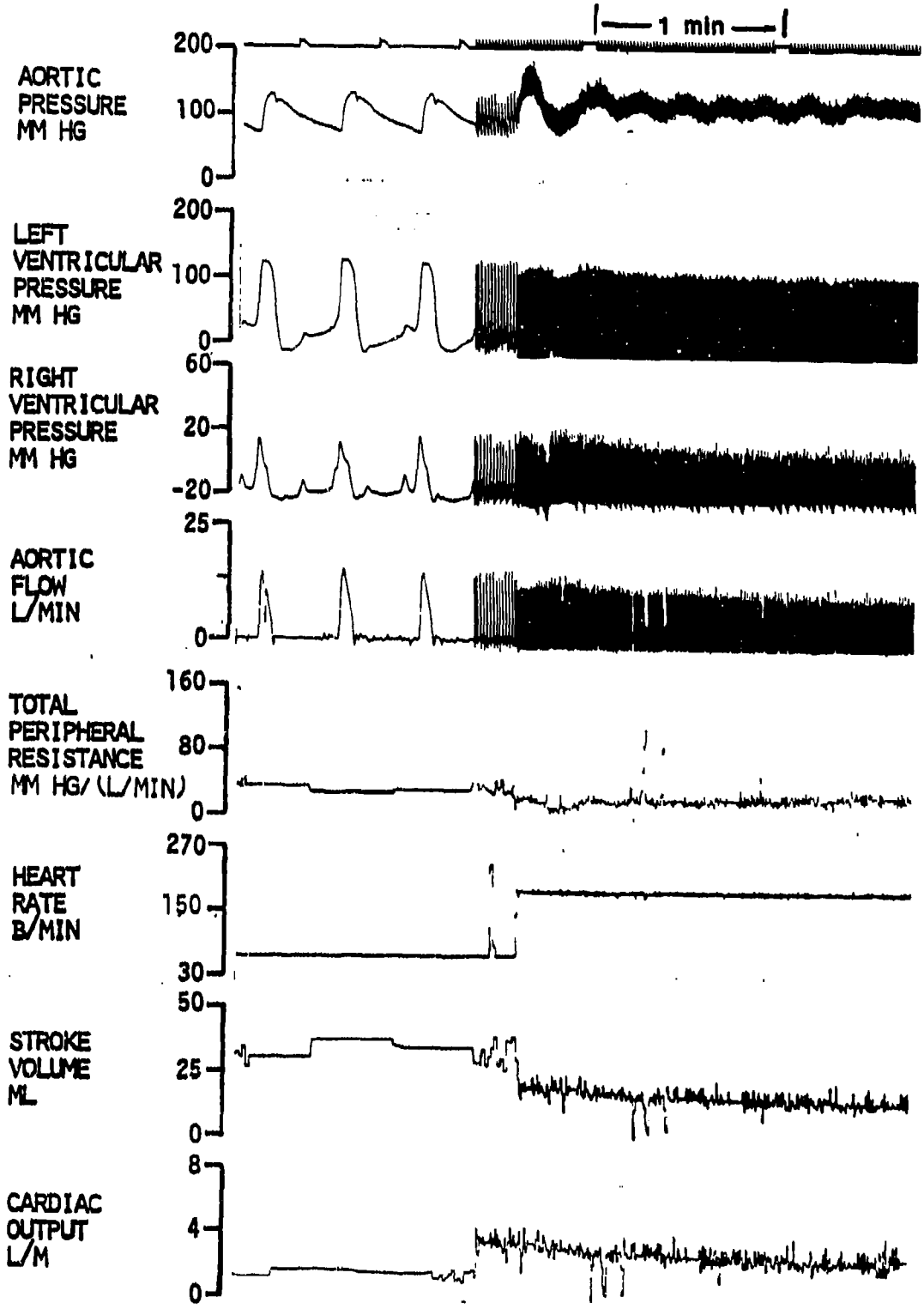

Figure B1. Response of a supine, tranquilized dog to a step increase in heart rate from 60 b/min to 180 b/min. There was a 60 msec delay between atrial and ventricular pacing in this animal.

contractions in both the right ventricular and left ventricular pressure traces. The ability of the pacing program (See Methods) to remove pacing spikes from the electromagnetic aortic flow trace is also evident in this figure. The 3 fold step increase in heart rate in this example produced a transient response in aortic pressure in which pressure oscillated around a new pressure that was ≃ 20 mm Hg higher than the old pressure. The effect of the increased rate was to: 1) almost triple the cardiac output in this dog within two heart beats 2) decrease stroke volume and 3) reduce peripheral vascular resistance by one fourth, also within the time of two heart beats. The elevation in mean pressure due to the increased output appeared then to be modulated by changes in calculated vascular resistance. There was an associated reduction in left atrial pressure by 10 mm Hg and, less rapidly, a reduction in right atrial pressure by 5 mm Hg. Over the next two minutes, cardiac output (via reduced stroke volume) peripheral resistance and aortic pressure slowly returned to steady state conditions that were characterized by slightly elevated pressure and cardiac output and slightly lowered peripheral resistance and stroke volume. This response has been reported earlier by Erlich (5) in standing, awake dogs with intact conduction who were subjected to doubled cardiac rates due to atrial stimulation. The resulting pressure adjustments were attributed to a combination of mechanical effects due to increased arterial volume and conflicting reflex effects from atrial stretch receptors to increase sympathetic tone and arterial stretch receptors to decrease sympathetic tone.

The response to a stepwise decrease in heart rate from 200 to 40 b/min is shown in Figure B2. There was no measurable oscillatory adjustment to this change, pressure was reduced from 105 mm Hg to 60 mm Hg via reduced cardiac output from 2.4 to 0.5 L/min and an immediate peripheral vascular resistance increase from 25 to 50 mm Hg/(L/min). Over the next 3 min, cardiac output, via increased stroke volume, increased to 1.6 L/min, peripheral resistance returned to 25 mm Hg/(L/min) and aortic pressure returned to 70 mm Hg, reflecting the reduced cardiac output. The immediate response of resistance to both the step increase and step decrease in heart rate, and therefore cardiac output, points toward a mechanical rather than neural effect of changes in vascular volume on resistance.

Conclusions from this phase of the study are that:

a) The ventricle can increase and decrease its rate of contraction as rapidly as it can be electrically activated this is in contrast to the responses seen when the heart is under its own neural control when several seconds are required to reach maximum heart rate. The disparity between the organ response time and the control system - organ response time may lie in the processing of neural signals, the deactivation time of the neurotransmitters responsible for heart rate control in the intact regulatory system, or some combination of both.

b) A three fold step increase in heart rate immediately increased cardiac output by almost the same amount and resulted in a 20 mmg increase in pressure. The

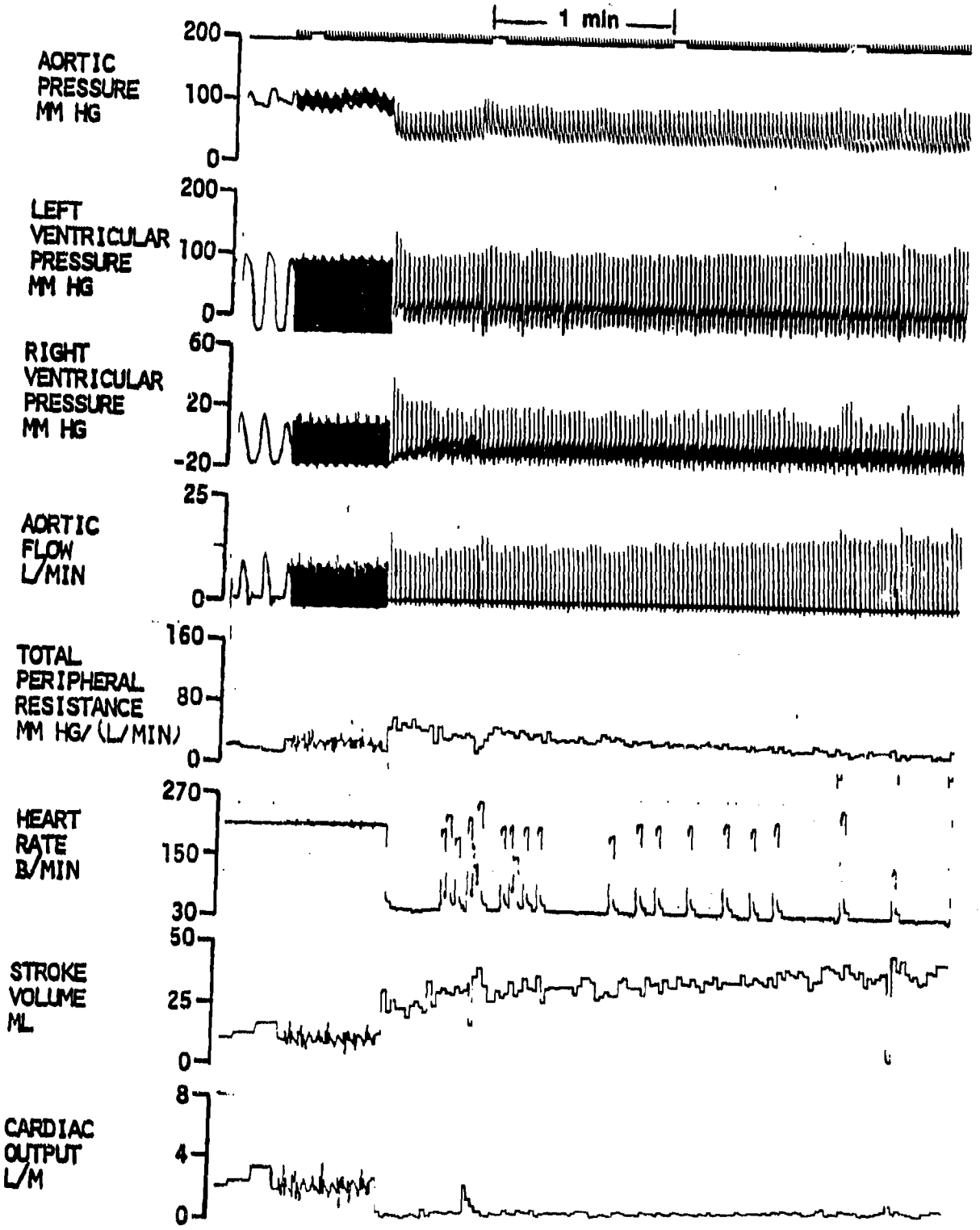

Figure B2. Response of a supine, tranquilized dog to a step decrease in heart rate from 200 b/min to 40 b/min.

oscillatory peripheral vascular resistance response to the increased pressure may have resulted from conflicting atrial and arterial stretch receptors to increase and decrease vasomotor tone.

c) A five fold step decrease in heart rate doubled stroke volume but resulted in decreased cardiac output and therefore pressure. The response to return pressure toward normal was another doubling of stroke volume, and therefore cardiac output, that took 3 min to develop and only increased pressure by 15 mm Hg.

d) Step changes in heart rate and therefore cardiac output resulted in immediate (within 1 beat) changes in calculated vascular resistance that were felt to be due to the mechanical effects of changes in arterial volume rather than neural mediation of vascular tone.

2. <u>The effects of different levels of paced heart rate on stroke volume and cardiac output during ±1 Gx (supine) and ±1 Gz (head up) loadings</u>.

The results of 3 min each of 7, randomly applied constant heart rates on steady state cardiac output are shown in Figure B3 for animals during +1 G_x (supine) and the +1 G_z (head up) loadings. For both +1 G_x and +1 G_z states there was a linear (though of different slope) increase in cardiac output as heart rate was increased from 30 to 120 b/min. From 120 to 150 b/min the +1 G_x animals increased cardiac output slightly with no further increase in cardiac output as heart rate was increased from 150 to 210 b/min. The increase in cardiac output as a function of

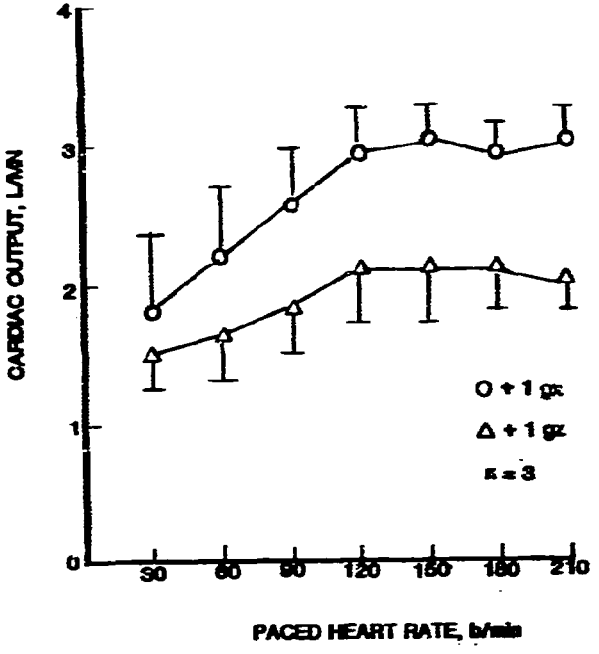

Figure B3. Cardiac output responses to increased heart rate in 3 A/V sequential paced dogs in the supine (+1 G_x) and head up (+1 G_z) position.

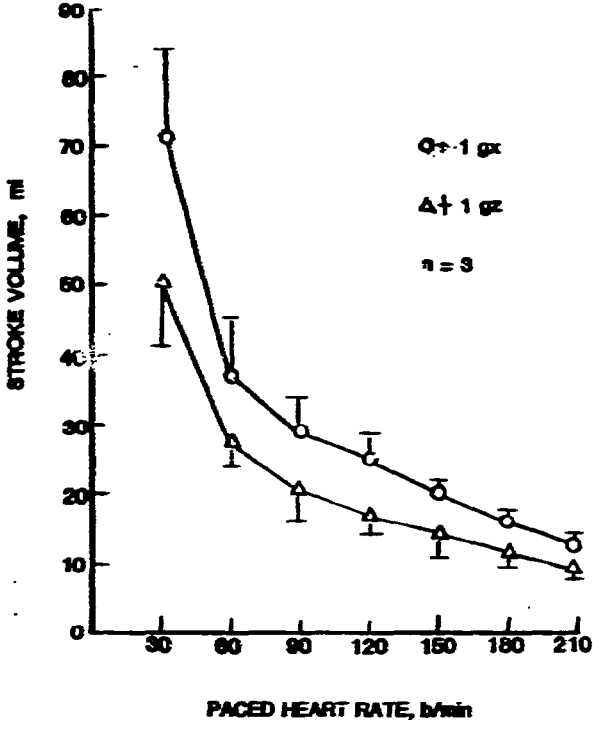

Figure B4. Stroke volume responses to increased heart rate in 3 A/V sequential paced dogs in the supine (+1 G_x) and head up (+1 G_z) position.

increasing rate for these same animals in the +1 G_z state stopped at 120 b/min. The <u>percentage decrease</u> in cardiac output as a function of +1 G_z [obtained by comparing the +1 G_z to 1 G_x values (data not shown)] and its associated loss of venous return ranged from 17% at heart rates of 30 b/min, to 25% at 60 b/min, to 30% for heart rates between 90 and 210 b/min. Simultaneous stroke volumes as a function of increasing heart rate are shown for the same animals in Figure B4. For both +1 G_x and + 1 G_z animals, stroke volume dropped dramatically (46% and 49%) as heart rate increased from 30 to 60 b/min, and 41% and 25% as heart rate increased from 60 to 90 b/min. Thereafter stroke volume decreased linearly with increasing rate for both cases. The effect of + 1 Gz was a 29 ± 1% decrease in stroke volume at <u>all</u> heart rates.

Our conclusions from this segment of the study are:

a) Both cardiac output and stroke volume were lowered by + 1 G_z at all heart rates. Cardiac output was decreased by 17% at very low heart rates and by 30% at heart rates above 90 b/min. Stroke volume was decreased by 29% at all heart rates. It is assumed that the decrease in both cardiac output and stroke volume was due to loss of venous return.

b) As a result of increased heart rate, there was an increase in cardiac output up to 150 b/min in +1 G_x animals and up to 120 b/min in +1 G_z animals.

c) Heart rates over 120 b/min cannot be expected to increase

cardiac output and thereby maintain aortic pressure in animals who are undergoing + G_z acceleration of 1 G or greater.

3. <u>The effect of mean heart rate on the amplitude of pressure oscillations induced by ±2 Gz sinusoidal acceleration.</u>

To examine the effect of mean heart rate on the ability of barostatic mechanisms to control oscillations in arterial blood pressure, unblocked animals were run at each frequency at low (60 b/min) medium (120 b/min) and high (180 b/min) heart rates. An example of the response of one animal to three cycles each of 0.035 Hz acceleration at each heart rate is shown in Figure B5. At a heart rate of 60 b/min (first three cycles), there was a barely distinguishable (15 mm Hg) oscillation in diastolic aortic pressure that corresponded to the acceleration frequency. At 120 b/min the amplitude of diastolic aortic pressure oscillations had increased, to 40 mm Hg, and at 180 b/min the amplitude was 60 mm Hg. At each higher heart rate, mean pressure was also slightly increased, 95 to 105 to 115 mm Hg due to increased levels of cardiac output (1.9 to 2.4 to 2.6 L/min) even though mean levels of peripheral resistance decreased [60 to 50 to 40 mm Hg/(L/min)]. The amplitude of oscillations of peripheral resistance around these diminishing mean values were fairly constant at each heart rate while the amplitude of oscillations of cardiac output around the increasing mean were increased. Maximum values of aortic pressure always occurred during -2 G_z and, at the higher heart rates, resulted from elevated (but not maximum) values of both cardiac output (stroke

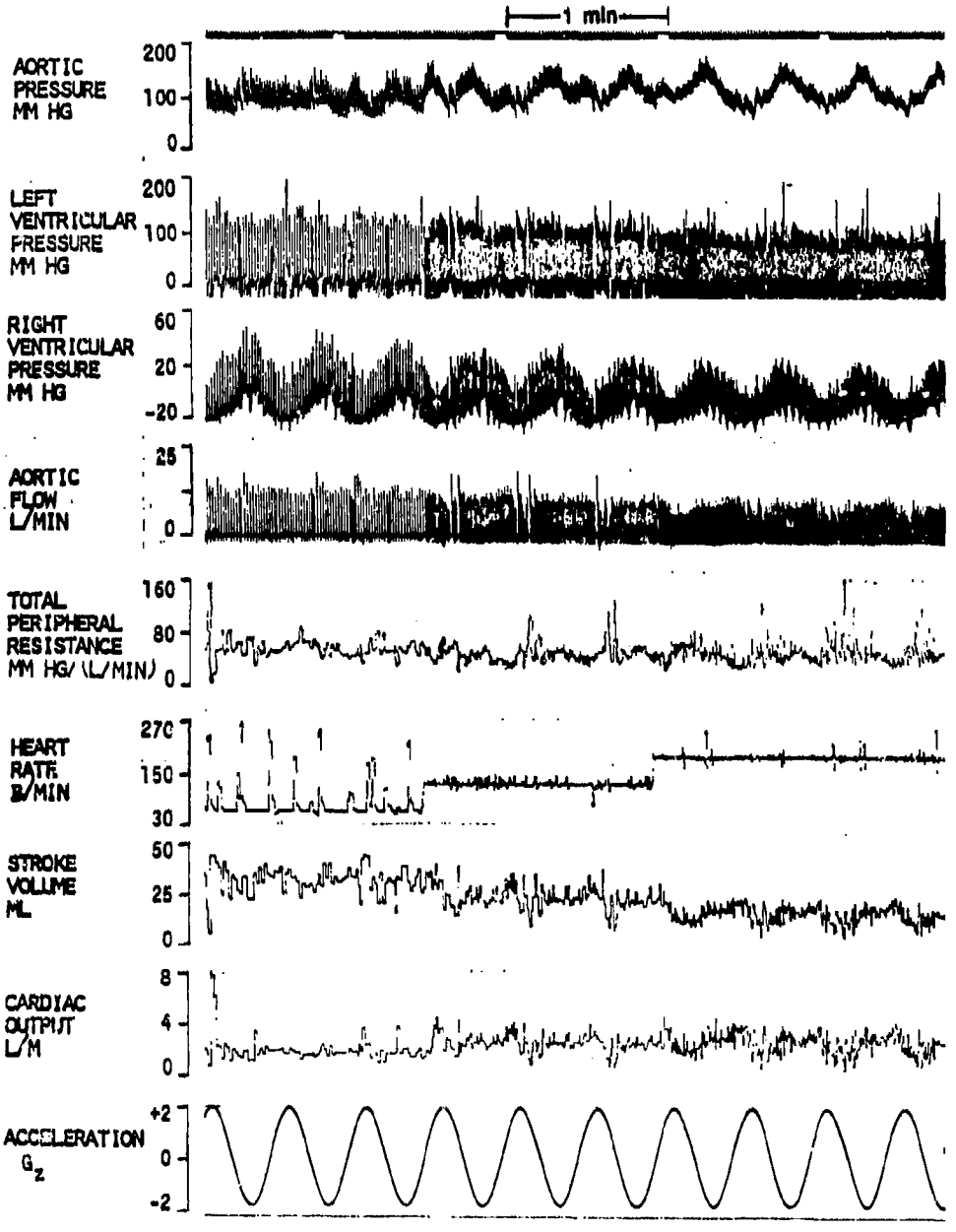

Figure B5. Response of a tranquilized dog to +2 G_z whole body, .035 Hz acceleration at 3 different mean heart rates. During the first 3 cycles of acceleration, the animals' heart rate was kept at 40 b/min, during the next 3 cycles of acceleration the heart rate was 120 b/min and during the last 3, the heart rate was at 180 b/min.

volume) and peripheral resistance. Minimum values of aortic pressures occurred during + $2G_z$ and resulted from reduced (but not minimum) values of resistance and cardiac output (stroke volume). Oscillations in central venous pressure (the diastolic portion of right ventricular pressure) occurred in time with acceleration (with maximum at $-2G_z$ and minimum at $+2G_z$); furthermore the amplitudes of these oscillations changed with mean heart rate: 20 mm Hg at 60 b/min, 16 mm Hg at 120 b/min and 12 mm Hg at 180 b/min. An examination of the effects of mean heart rate on aortic pressure oscillations across the frequency range of interest (0.008 to 0.23 Hz) is shown in Figure B6. At each acceleration frequency, the animal was held for several acceleration cycles at 60, 120 and 180 b/min (as in Figure B5). The amplitude of mean aortic pr · ure oscillations for each heart rate is plotted here for each acceleration frequency. At 60 b/min there was a fairly constant amplitude of ≃ 30 mm Hg across the frequency range, however at 120 b/min the amplitude of oscillations increased to a maximum of 50 mm Hg at 0.055 Hz and at 180 b/min the amplitude at 0.055 Hz was 75 mm Hg.

Conclusions from this portion of the study are:

a) Mean heart rate level was a major determinant of acceleration induced oscillations in aortic and central venous pressure.

b) The magnitude of aortic pressure oscillations increased with increasing heart rate while the magnitude of central venous pressure oscillations decreased with increasing heart rate.

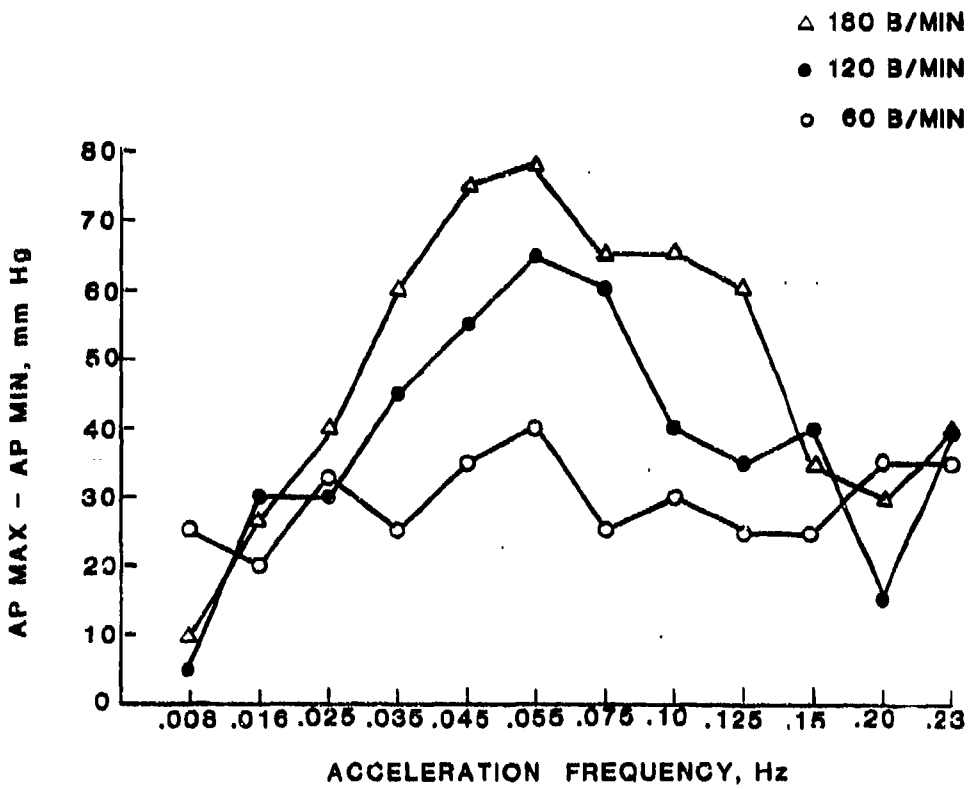

Figure B6. Amplitudes of oscillations in aortic pressure as a function of ± 2 G_z acceleration frequency for one animal at a low heart rate (60 b/min), medium heart rate (120 b/min) and high heart rate (180 b/min).

c) The increase in rate resulted in an increase in cardiac output which appeared to be responsible for the increase in mean aortic pressure and the increase in magnitude of aortic pressure oscillations.

d) The increase in mean and oscillatory aortic pressures and the decrease in mean and oscillatory central venous pressures with increasing rate was compatible with a shifting of blood from the venous to the arterial systems.

e) The acceleration frequency dependence of aortic pressure oscillations was amplified at increased heart rates.

4. <u>The effect of heart rate oscillations desynchronized from right heart filling pressure oscillations in regulation of blood pressure during ± 2 Gz sinusoidal acceleration.</u>

The computer-driven pacing signal permitted varying heart rate in a predetermined manner as well as maintaining constant levels. To investigate the importance of the phase relationship between pumping rate (heart rate) and cardiac filling (diastolic right ventricular pressure), due to acceleration, a sinusoidal variation was selected. Heart rate oscillated between 60 and 140 bpm at 0.038 Hz (26.3 sec per cycle), while acceleration varied between ± $2G_z$ at 0.035 Hz (28.6 sec per cycle). This difference in frequencies resulted in a "beating" phenomenon in the hemodynamic variables with a frequency of 0.003 Hz (333.3 sec/beat). Thus, as heart rate "walked forward" through acceleration, any particular phase relationship was repeated after 5.5 min.

A portion of the results is presented in Figure B7. At the beginning of the record, heart rate was in phase with

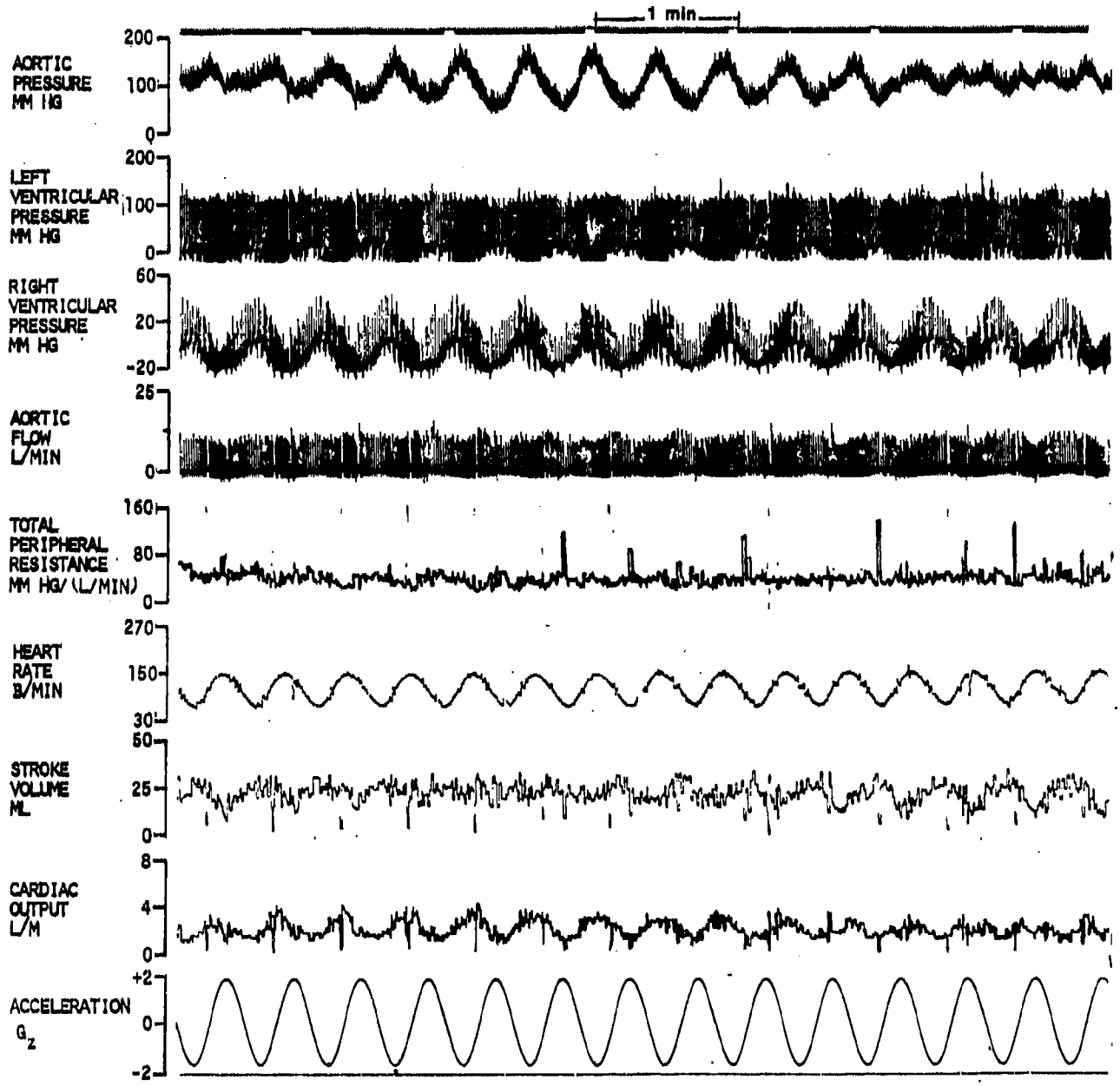

Figure 87. Cardiovascular response to desynchronization of heart rate oscillation frequency (.035 Hz) and acceleration frequency (.038 Hz).

acceleration. After 7 heart rate cycles, it preceded acceleration by half a cycle. The original phase relationship was restored in another 7 cycles. Amplitudes of oscillations in left and right ventricular pressures were not influenced by the phase difference between heart rate and acceleration. The oscillations in cardiac output, stroke volume and total peripheral resistance were modulated by heart rate-acceleration phase. Stroke volume oscillations were largest when heart rate was in phase with acceleration, and were minimal when it was out of phase. Stroke volume was at its minimum when high heart rate coincided with high G_z acceleration: reduced filling time was combined with the smallest cardiac filling pressure (i.e., diastolic right ventricular pressure). Conversely, maximum stroke volume resulted when heart rate was low and $-G_z$ acceleration provided maximum filling pressure. At intermediate phase relationships, filling time and filling pressure did not reinforce each other, and stroke volume remained roughly constant over each cycle. Cardiac output oscillated in phase with heart rate throughout the record. When heart rate and acceleration were nearly in phase, heart rate increased faster than stroke volume declined, giving a large cardiac output. As heart rate and acceleration drifted apart, high heart rate coincided with a roughly constant stroke volume to produce cardiac output oscillations which followed heart rate closely. Arterial pressure exhibited the most striking beat manifestation. Pressure oscillations were minimal when heart rate and acceleration were in phase, and increased as peak heart rate

moved away from peak acceleration. These oscillations increased primarily through a reduction in arterial pressure minimum , with little change in maximum pressure. Calculated total peripheral resistance oscillated only slightly, again in phase with heart rate.

The desynchronization of heart rate and acceleration revealed the relatively equal importance of heart rate and cardiac filling pressure in the reflexive canine at ± 2 G_z. While filling pressure (diastolic right ventricular pressure) varied only with the acceleration vector, all other measured variables were determined by both heart rate and filling pressure oscillations. Indeed, diastolic left ventricular pressure seemed determined solely by heart rate, since it followed heart rate undiminished through all phases of acceleration.

In Summary:

a) Right ventricular diastolic pressure oscillations reflected variations in venous return due to the direction of the acceleration vector.

b) Left ventricular diastolic pressure varied directly with heart rate, due to the influence of filling time on left ventricular blood volume.

c) Stroke volume was a function of both cardiac filling time (heart rate) and filling pressure (diastolic right ventricular pressure).

d) Cardiac output varied with both pumping rate (heart rate) and output volume (stroke volume).

e) Peripheral resistance varied only slightly as a function of

both heart rate and diastolic right ventricular pressure.

f) Arterial pressure oscillated roughly in phase with heart rate, the amplitude of the oscillations being determined by the relative phase of heart rate and acceleration.

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III. RESEARCH TEAM

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The formation of this research team is based on a general plan which integrates the advanced analytical techniques and instrumentation development capabilities of an interdisciplinary team, consisting of physiologists and biomedical engineers, in an effort to resolve problems associated with acceleration stress.

Measurements from the invasive instrumentation of the chronically implanted animal preparation of this study are essential for identifiying the most meaningful variables for assessing acceleration-induced cardiovascular responses when less invasive measurements are eventually to be made on man. It is our belief that this basic research effort will provide the background for the design and implementation of human investigations, investigations which will lead to improved protective equipment and operational procedures for military personnel exposed to acceleration environments resulting from the optimal utilization of advanced aerospace systems.

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