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CORONARY FLOW AND MYOCARDIAL BIOCHEMICAL RESPONSES TO HIGH SUST--ETC(U)
1976 H L STONE , L A SORDHAL, R T DOWELL AF-AFOSR-2622-74
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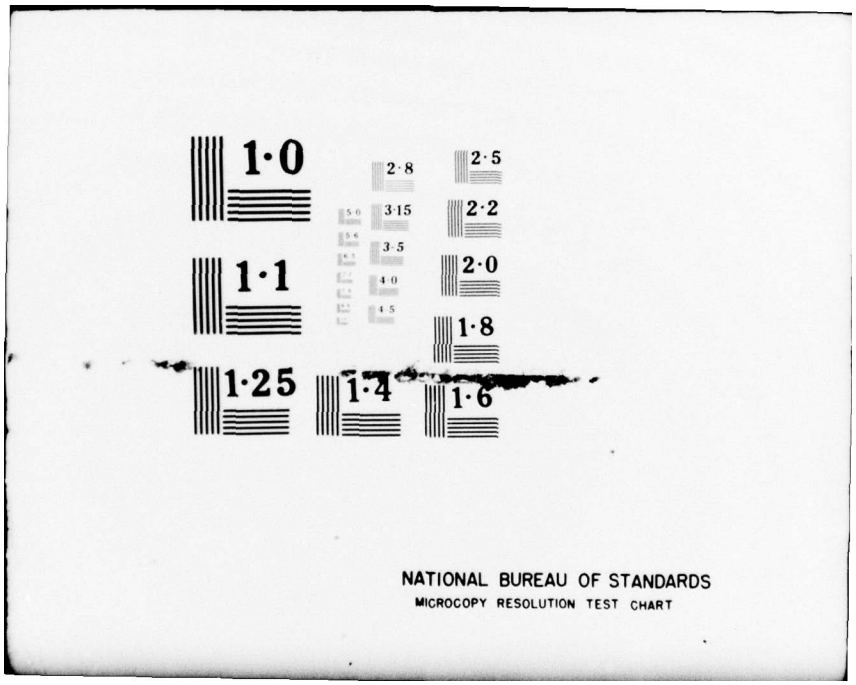
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The Pathophysiology of High Sustained $+G_z$ Acceleration, Limitation to Air Combat Manoeuvering and the Use of Centrifuges in Performance Training

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In order to determine directly the myocardial response to $+G_z$ acceleration, miniature swine were used as the experimental subjects. Some of the animals underwent surgical implantation of flow probes around the left circumflex coronary artery and a solid-state pressure transducer in the left ventricular cavity. All of the unanesthetized instrumented subjects were exposed to multiple $+G_z$ acceleration levels for 60-120 seconds (3, 5, 7, 9, 11 $+G_z$) on the

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USAF School of Aerospace Medicine human centrifuge. Other subjects were exposed to a single acceleration level (9 $+G_z$) for 120 seconds and the hearts removed for biochemical analyses 1-2 hours later. Mitochondria and a lysosomal fraction were isolated from the left ventricle of all animals. Mitochondrial analysis of ADP:O ratio, respiratory control index (RCI), oxygen uptake (QO_2) and calcium uptake were made. Free and bound acid phosphatase measurements were made in the lysosomal fraction. Left circumflex coronary artery flow (LCCF), heart rate (HR), left ventricular pressure (LVP), and the rate of rise of LVP ($\dot{P}$) were measured in the instrumental animals. LVP and HR increased at all levels of acceleration studied while $\dot{P}$ increased initially but would decline later. LCCF decreased at all levels of acceleration stress. The mitochondrial ADP:O ratio and the RCI were unchanged but the QO_2 and calcium uptake were increased at 9 $+G_z$. Free acid phosphatase increased at the same level of acceleration.

QO2 (Oxygen Uptake)

+G(Z)

RCI (Respiratory Control Index)

CORONARY FLOW AND MYOCARDIAL BIOCHEMICAL RESPONSES TO HIGH SUSTAINED $+G_z$ ACCELERATION

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SUMMARY

In order to determine directly the myocardial response to $+G_z$ acceleration, miniature swine were used as the experimental subjects. Some of the animals underwent surgical implantation of flow probes around the left circumflex coronary artery and a solid-state pressure transducer in the left ventricular cavity. All of the unanesthetized instrumented subjects were exposed to multiple $+G_z$ acceleration levels for 60-120 seconds (3, 5, 7, 9, 11 $+G_z$) on the USAF School of Aerospace Medicine human centrifuge. Other subjects were exposed to a single acceleration level (9 $+G_z$) for 120 seconds and the hearts removed for biochemical analysis 1-2 hours later. Mitochondria and a lysosomal fraction were isolated from the left ventricle of all animals. Mitochondrial analysis of ADP:O ratio, respiratory control index (RCI), oxygen uptake (QO_2) and calcium uptake were made. Free and bound acid phosphatase measurements were made in the lysosomal fraction. Left circumflex coronary artery flow (LCCF), heart rate (HR), left ventricular pressure (LVP), and the rate of rise of LVP ($\dot{P}$) were measured in the instrumental animals. LVP and HR increased at all levels of acceleration studied while $\dot{P}$ increased initially but would decline later. LCCF decreased at all levels of acceleration stress. The mitochondrial ADP:O ratio and the RCI were unchanged but the QO_2 and calcium uptake were increased at 9 $+G_z$. Free acid phosphatase increased at the same level of acceleration.

INTRODUCTION

The increased capability of high performance aircraft has necessitated a new investigation into the cardiovascular response to high sustained $+G_z$ acceleration levels. In man during $+G_z$ acceleration exposure, abnormalities in the electrocardiogram and some arrhythmias have been noted (1, 2, 3, 4). The changes in the electrocardiogram have been associated with the S-T segment and are felt to suggest myocardial ischemia. For many reasons other measurements in man have not been made at high $+G_z$ levels, thus the use of an animal model is appropriate. Miniature swine have been used in this regard (5, 6) and found to show similar changes to that observed in man. The coronary vasculature in the swine is much more analogous to man than most other animals. High levels of $+G_z$ acceleration in swine have been found to be associated with subendocardial hemorrhage and pathological changes in the myocardial cell (7). Evidence indicates that, in both man and swine, myocardial ischemia must be considered as a consequence of high sustained $+G_z$ acceleration.

Myocardial ischemia is the result of a dramatic reduction or cessation of coronary flow to all or discrete portions of the myocardium (8). When coronary flow becomes the limiting factor in the delivery of oxygen to the myocardial cells, the contractile mechanism begins to fail following apparent changes in the cell membrane that allow the inward leakage of sodium ions and other cations and the outward leakage of protein molecules. At a certain step in the process of cell leakage, the enzymes that are contained in lysosomes are released and begin to destroy other proteins through their hydrolytic actions. The energy producing organelles are also affected by this process. Mitochondria increase their respiratory activity in response to the reduction in oxygen in an attempt to increase the amount of energy available for cellular processes. Thus, the key mechanisms in cellular dysfunction and arrhythmia production (9, 10) with high sustained $+G_z$ acceleration may be a reduction in coronary flow. In the conscious miniature swine, it should be possible to detect changes in the coronary flow with $+G_z$ acceleration and at the same time determine if myocardial ischemia may be occurring either through a reduction in total coronary flow or a divergence of flow away from the endocardium (8). These results could be correlated with biochemical changes associated with ischemia such as lysosomal and mitochondrial function.

MATERIALS & METHODS

The present study was made up of two groups of miniature swine. Group 1 animals were used to determine the effects of acceleration on left ventricular pressure and coronary flow, while Group 2 animals were used to study the relationship of acceleration to the changes in lysosomal and mitochondrial function.

Group 1

This group of animals was anesthetized with sodium pentothal and surgical anesthesia was maintained with a mixture of oxygen, nitrous oxide, and halothane. The heart was exposed through the left 5th intercostal space. The left circumflex coronary artery was exposed for a length of 3 cm along the atrioventricular groove. An electromagnetic flow probe was placed around the vessel, as was a balloon occluder distal to the flow probe. A solid-state pressure transducer was positioned in the left ventricle through a stab incision in the apex of the heart. A silastic catheter was placed in the left atrium via the left atrial appendage. The wires from the two transducers and the two silastic catheters were passed out of the chest through the 6th intercostal space and left in a subcutaneous pouch. The chest incision was carefully closed to prevent adhesions between the lungs and chest wall. The animals were allowed to recover for 30 days before being used for any experimental procedure. At the end of this period, the lead wires were exposed under local anesthesia and taped to the animals' backs.

The conscious animals were placed in a fiberglass couch and positioned on the animal arm of the USAF School of Aerospace Medicine centrifuge. The animals were minimally restrained during the experimental

period. The wires from the two transducers were connected to appropriate electronics. The electrocardiogram was measured from limb leads or from the pressure transducer. The case of the miniature solid-state pressure transducer plus an additional ground lead can be used for this purpose. Left circumflex coronary artery flow (LCCF), left ventricular pressure (LVP), heart rate (HR), the rate of rise of left ventricular pressure ($\dot{P}$), mean left circumflex coronary flow (MLCCF), and the level of acceleration ($+G_z$) were recorded on both a direct-writing oscillograph and magnetic tape. The animals were exposed randomly to levels of 3, 5, 7, and 9 $+G_z$ acceleration with a rapid onset rate of 1 G/sec. Peak levels of acceleration were maintained for either 120 seconds at the lower levels or 60 seconds at the higher levels. The animals were allowed a minimum of 20 minutes for recovery between runs. Before each acceleration profile, the LCCA was briefly occluded to establish zero flow. The resulting hyperemic response was allowed to disappear before beginning the profile. At the termination of the experiment, the wires were taped to the sides of the animals for future use.

The left ventricular pressure transducer and the electromagnetic flow transducer were calibrated prior to implantation. The zero reference for both transducers was established at the beginning and at the termination of each experiment. The sensitivity of both transducers has not been found to vary over the course of the time involved with these experiments.

Group 2

The animals in this group were exposed to a single $+G_z$ profile. The animals were placed in the couch and loosely strapped in place. Limb leads were connected for the measurement of the electrocardiogram. The animals were exposed to 9 $+G_z$ for 120 seconds following a rapid onset rate of 1 G/sec. One to two hours following this acceleration profile, the animals were anesthetized with sodium pentothal and the hearts rapidly excised. Samples were taken from the left ventricular free wall for biochemical analyses.

Mitochondria were isolated from the samples of left ventricular free wall and their respiratory activity and oxidative phosphorylation capabilities were measured polargraphically (11). Respiratory substrate-supported mitochondrial calcium uptake was measured by dual-beam spectroscopy. Acid phosphatase was utilized as a heart lysosomal marker enzyme. Left ventricular free wall tissue homogenates were prepared in 0.25M sucrose using a blade homogenizer. Enzyme activity was partitioned into sequestered (lysosomal) and free (soluble) fractions using modifications of a differential centrifugation procedure and assay (12). The ratio of acid phosphatase specific activity present in these fractions (soluble/lysosomal) provided an estimation of lysosomal membrane integrity. The results of this portion of the study were compared to results obtained from unoperated-control and operated-control animals.

RESULTS

Physiological Responses

The miniature swine seemed to tolerate the exposure to the various levels of acceleration used in this study. The peak levels of acceleration were randomized for each animal so as to minimize the effect of the first exposure level on the subsequent results. At 9 $+G_z$, all of the animals appeared to remain conscious. The criterion for this was the kicking and grunting behavior of the animal. Closed circuit television allowed the observer to watch and hear the animal during the various profiles. Two types of responses were observed in this study. The first can be seen in Figure 1. In this animal, the heart rate increased and remained elevated during the entire profile. In the second response, seen in Figure 2, heart rate increased with acceleration but then very abruptly decreased into a bradycardia. At most of the high acceleration levels (+7 and +9), some degree of bradycardia was noted. The severity of this bradycardia varied greatly between animals. All of the measured parameters were allowed to return to control values prior to any succeeding runs.

After the animal had been placed on the centrifuge and before each level of acceleration, control values were taken for heart rate, left ventricular systolic and diastolic pressure, left circumflex coronary flow, and the maximum rate of rise of left ventricular pressure. The maximum rate of rise of the left ventricular pressure was used as an index of the contractile state of the myocardium. The average values with one standard error of the mean were found to be: HR, 97 $\pm$ 3 bpm; LV systolic pressure, 156 $\pm$ 8 mm Hg; LV diastolic pressure, 4 $\pm$ 1 mm Hg; LCCF, 58 $\pm$ 5 cc/min; and, $\dot{P}$, 2472 $\pm$ 164 mm Hg/sec.

The results of exposure to 3, 5, 7, and 9 $+G_z$ acceleration for various periods of time can be seen in Table 1. The average heart rate increased with acceleration, but the magnitude of increase became less with successive increases in the level of $+G_z$ acceleration. At the point of measurement, the left ventricular systolic pressure increased, but it must be noticed that this was not a transmural pressure. Coronary flow decreased at all levels of acceleration studied. There did seem to be a tendency for coronary flow to increase during individual acceleration profiles but in most of the studies remained below control values. The contractile index of the left ventricle increased with acceleration. The increase seemed to be less with higher levels of acceleration. At times, there appeared to be waves in the coronary flow that coincided with changes in heart rate.

Biochemical Responses

Biochemical measurements from miniature swine hearts were established in unoperated and operated-control animals. In control heart mitochondria, three parameters were measured: ADP:O ratio, respiratory control index (RCI), and the rate of mitochondrial oxygen uptake during State 3 respiration (QO_2). The ADP:O ratio is a measure of the efficiency of ADP phosphorylation and was found to be 3.2 with glutamate-malate as the substrate and the average RCI was 6.1. The State 3 respiration (QO_2) is the active rate of respiration for phosphorylation and is indicative of the amount of active enzymatic protein present in the inner mitochondrial membrane. In the control heart preparations, a value of 185 natoms/min/mg mitochondria protein was found. These values fall within acceptable normal limits. It is important to note that there were no differences between the unoperated and operated-control animals.

In the animals exposed to 9 $+G_z$, a marked increase in active respiratory rate in the presence of ADP (State 3) was found in the mitochondria. The average value was 285 natoms/min/mg mitochondria protein. The oxidative phosporylation (ADP:O) and RCI were unchanged in these animals.

Calcium transport by the mitochondrial inner membrane is an energy linked process. This measure of mitochondrial function may be another way of assessing the functional integrity of mitochondria. The concentration of calcium necessary to produce the maximum velocity of calcium uptake was 150 μ mol while the actual rate of calcium uptake was approximately 200-250 nmoles/min/mg mitochondrial protein. Instrumentation of the animals was found to have no effect on these parameters. Significant increases in active rates of calcium transport were observed in the mitochondria from animals exposed to 9 $+G_z$ accleration. The average calcium uptake in mitochondria isolated from these hearts was 280 nmoles/min/mg mitochondrial protein.

The lysosomal fraction of the heart was analyzed for the specific activity of alkaline phosphatase and compared to the alkaline phosphatase activity of the soluble fraction. Lysosomal fraction activity averaged 11.2 $\pm$ 0.9 (standard error of the mean) while the soluble fraction averaged 12.1 $\pm$ 1.0 (SEM) nmoles/min/mg protein. Instrumented and uninstrumented animals were not significantly different with respect to lysosomal enzyme activity. The soluble fraction/lysosomal fraction ratio in control animals was 1.08. 9 $+G_z$ acceleration drastically reduced the specific activity of the lysosomal fraction and elevated the activity in the soluble fraction. Lysosomal fraction activity was 9.7 $\pm$ 0.4 (SEM) while the soluble fraction was 32.4 $\pm$ 1.3. These enzyme responses resulted in approximately a 2-fold increase in the soluble fraction/lysosomal fraction specific activity ratio. The loss of enzyme activity from the membrane-bound lysosomal fraction and the increased soluble fraction activity suggests that the integrity of the lysosomal membrane had been disrupted by acceleration. The loss of lysosomal membrane integrity was apparently a generalized phenomenon throughout the left ventricle since nearly identical results were observed in epicardial and endocardial samples.

DISCUSSION

The major area of concern in the current study was the relationship between coronary blood flow, myocardial intracellular function, and acceleration stress. Previous reports (7) indicate the presence of subendocardial hemorrhage in miniature swine subjected to various levels of $+G_z$ acceleration. It also had been pointed out that some type of myocardial necrosis was found in other areas of the myocardium. The question thus arose does the myocardial cell become hypoxic and/or ischemic during exposure to high sustained $+G_z$ acceleration or if the mechanical forces were severe enough to cause the microscopic damage.

Coronary flow studies in unanesthetized and anesthetized dogs (13, 14) have found a decrease in the coronary blood flow with exposure to low levels of $+G_z$ acceleration. In the unanesthetized miniature swine, coronary flow was found to be reduced at all levels of acceleration, as measured in the left circumflex coronary artery. Coronary flow should have increased due to the increase in the contractile state of the myocardium and the increase in heart rate. Both heart rate and contractility are major determinants of myocardial oxygen consumption (15, 16) and would normally contribute to an increase in coronary flow. The real question then becomes the lack of increase in coronary flow during $+G_z$ acceleration. Perfusion pressure of the coronary vessels will influence flow; however, during acceleration, aortic root pressure is likely to be elevated due to 1) the hydrostatic column effect and 2) compensatory mechanisms which maintain head level arterial pressure. The increased heart rate reduces the diastolic period thus tending to reduce coronary flow. In conscious miniature swine, Denn (17) has found a linear increase in coronary flow with increasing heart rate up to 240 bpm. Therefore, heart rate does not seem to contribute to the decrease in coronary flow during $+G_z$ acceleration stress. The tension within the myocardial wall of the left ventricle will cause changes in the coronary flow patterns. With the beginning of isovolumic systole, tension increases and the coronary arterial transmural pressure decreases. The decrease in transmural pressure will cause a decrease in coronary flow during each cardiac systole. During $+G_z$ acceleration, the left ventricular wall tension may be increased as the result of 1) increased aortic root pressure, 2) increased pleural pressure, and 3) deformation of the heart by a caudal movement from the accelerative forces. All of these factors would tend to decrease coronary flow. The caudal movement of the heart toward the diaphragm has been seen by Sandler (personal communication) while studying anesthetized dogs via cineangiography. Since the arch of the aorta is tethered by the branches arising from it, the ascending aorta may be stretched. A possible constriction of the coronary artery ostia may increase the blood inflow resistance during high levels of acceleration. The increased resistance would reduce coronary flow. The coronary vascular bed has an abundance of alpha-adrenergic receptors (18). Alpha-adrenergic receptors will cause vasoconstriction when activated by either circulating catecholamines or the sympathetic nervous system. The neurogenic component of a constrictor mechanism may be activated by heart displacement or by other receptors located in the cardiopulmonary region.

Myocardial oxygen consumption would be expected to increase with increases in heart rate, contractility, and myocardial wall tension. Since coronary flow was found to be reduced below control values at all levels of acceleration studied, the increased demand for oxygen can only be met by an increase in extraction of oxygen from the coronary blood. Myocardial oxygen consumption measurements have not been made to date but usually myocardial oxygen extraction does not change a great deal under a wide variety of conditions (15). Myocardial ischemia and/or hypoxia would seem to be existent under these conditions. This conclusion agrees with the data from some human studies (1) in which changes in the S-T segment of the electrocardiogram have been felt to be synonymous with myocardial ischemia.

Hypoxia and/or ischemia exert marked effects on intracellular systems of cardiac muscle. Lysosomal enzyme activation is elevated in infarcted heart tissue following coronary artery ligation (19). Acute anoxia also increases the proportion of lysosomal enzymes present in the free form within the heart (20). In the current study, a tremendous increase in free lysosomal activity was found at 9 $+G_z$ which suggests some type of myocardial ischemic insult. This would agree with the reduction in coronary flow found during the studies conducted in the instrumented animals. Depressed mitochondrial function would be expected in hearts subjected to hypoxic and/or ischemic insult (21, 22). In the present study, mitochondrial function was elevated which would mitigate against hypoxia and/or ischemia in the acceleration

stressed heart. An increase in intracellular calcium concentration (23) may contribute to the increased mitochondrial activity seen in 9 $+G_z$ stressed animals. This may occur through an increased release of catecholamines in the heart or an increase in the level of circulating catecholamines (24, 25). Other subcellular systems may be affected by brief transient ischemia such as that seen with $+G_z$ acceleration. These systems may contribute to the increased mitochondrial function and cannot be ignored.

In summary, high sustained $+G_z$ acceleration in miniature swine results in a decrease in coronary blood flow and an increase in the average heart rate and contractility while at 9 $+G_z$. An increase in free lysosomal enzymes and an increase in mitochondrial function were found also. These changes may be associated with some type of ischemic damage to the myocardium resulting from the reduction in coronary flow. The reduction in coronary flow may not be the sole factor responsible for the ischemic damage, and other factors such as catecholamines and mechanical forces must be considered. However, a transient ischemic condition may represent the underlying basis for the myocardial cell death reported by Burton (7). Recovery from this insult requires more than 1-2 hours since a portion of the present study was accomplished in this time period. The current study emphasizes the need for more definition of the transient ischemic period under these conditions, and major efforts are being made to accomplish this goal.

This work was supported in part by U.S.A.F. AFOSR 74 - 2622.

DISCUSSION

SEM-JACOBSEN (Norway): The bradycardia is similar to what I found in pilots who black out. It would be interesting to measure the EEG at this time to see if the animals actually went unconscious.

STONE: We have not done this yet, but it should be done.

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TABLE 1

The average values for heart rate (HR), left ventricular pressure (LVP), the maximum derivative of left ventricular pressure ($\dot{P}$), and the mean left circumflex coronary flow (LCCF) expressed as the percent of the absolute control values in response to $+G_z$ acceleration. The values were taken at the indicated times after reaching peak acceleration levels. The numbers in parentheses are ± one standard error of the mean.

G	T (sec)	H.R.	LVP		LCCF	$\dot{P}$
			Systolic	Diastolic		
3	60	202 (22)	138 (23)	64 (15)	77 (27)	172 (20)
	120	219 (25)	146 (33)	53 (21)	53 (14)	126 (4)
5	30	217 (21)	151 (27)	50 (20)	58 (18)	170 (22)
	60	169 (25)	151 (23)	62 (20)	60 (18)	140 (12)
7	30	148 (22)	173 (22)	127 (9)	80 (22)	144 (13)
	60	167 (29)	152 (20)	101 (14)	54 (9)	112 (16)
9	30	145 (21)	146 (45)	77 (19)	78 (26)	116 (11)
	60	93 (24)	145 (70)	136 (36)	85 (27)	120 (26)

Pig 77 +7G_z

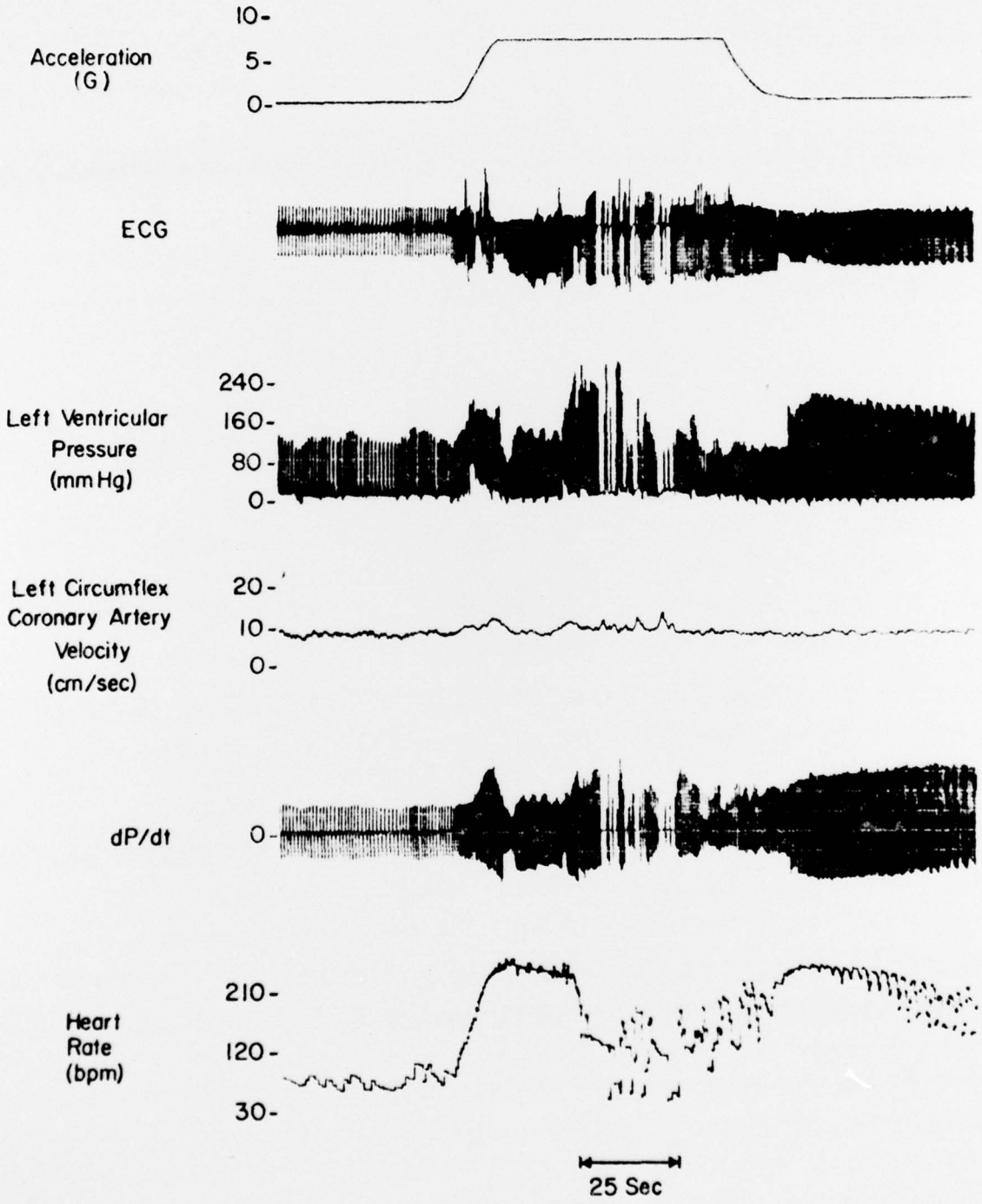

FIGURE 1. A typical response pattern to +7G_z in an unanesthetized miniature swine. Note the heart rate response to the acceleration profile.

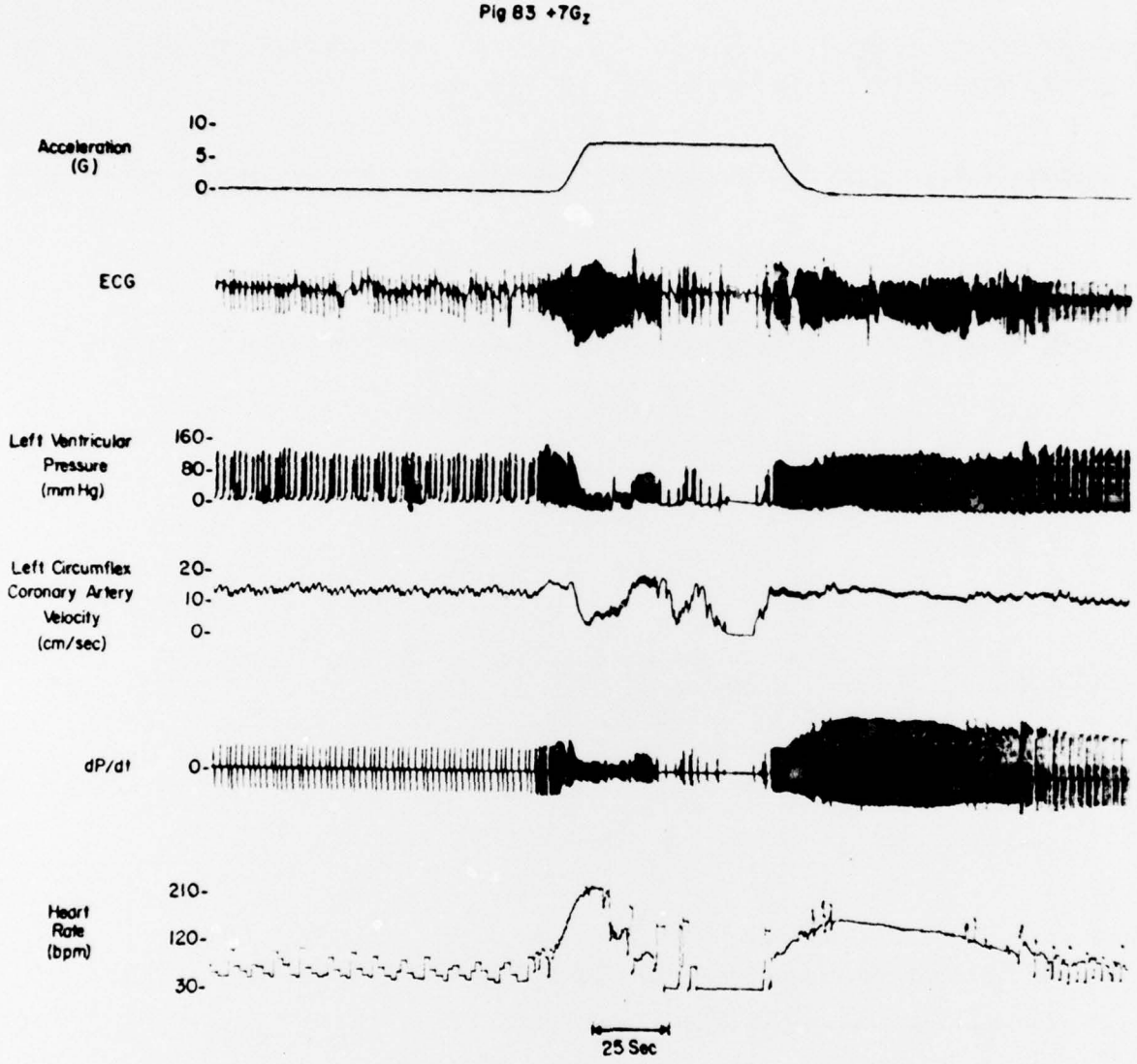

FIGURE 2. A second typical response pattern to $+7G_z$ in an unanesthetized miniature swine. Compare the heart rate response of this animal to that seen in Figure 1.