ECG Analysis of Golden Hamsters Exposed to Long Term $-G_z$ Conditions: Ordinary and Pathological Findings

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Abstract Changes of ECG due to long and intense $-G_z$ acceleration was investigated in anesthetized Syrian golden hamsters. The R-R interval decreased (heart rate increased) slightly at the very initial phase of steady $-G_z$ load. However, the R-R interval increased during the rest of the whole steady $-G_z$ period. The P-R interval increased with a smaller $-G_z$ load (-4 and $-6 G_z$), but it decreased with a larger $-G_z$ (-8 and $-10 G_z$). The size of the QRS complex was measured as R amplitude. It decreased in all $-G_z$ conditions. Effects were a little different for smaller and larger $-G_z$, as was observed in the case of P-R changes. Pathological ECGs were frequently observed. They were: (1) Arrhythmia of heart rate with or without atrio-ventricular blocks. (2) Abnormal P wave; e.g., splitting, flattening, or abolition of P wave. (3) Alteration of the QRS complex in amplitude or contour. (4) Changes in ST-T components. In spite of all these changes, however, it should be noted that several Syrian golden hamsters could tolerate up to $-10 G_z$ for as long as 1,000 s.

Key words: hypergravity, acceleration, $-G_z$, ECG, temporal changes, pathological ECG.

Hypergravitational acceleration along the long axis of the body ($+G_z$ or $-G_z$), particularly $+G_z$, was reported to cause severe functional changes in the cardiovascular system when man or animals were exposed to it. Many studies have been conducted along this line (LINDBERG and WOOD, 1963; HOWARD, 1965a, b; PARKHURST *et al.*, 1972; SHUBROOKS, 1972; LEVERETT and WHINNERY, 1985; SATAKE *et al.*, 1985), but $-G_z$ experiments are few in number (RYAN *et al.*, 1950; DUANE *et al.*, 1952; BECKMAN *et al.*, 1953; SATAKE *et al.*, 1985), probably from

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practical reasons of more dangerous conditions to subjects. Moreover, most of these experiments were conducted with short term of Gz exposure, mostly ranging from 5 to 30 seconds, because Gz acceleration causes serious effects on cardiopulmonary functions. Animals could be exposed to longer periods, but it is still dangerous, and therefore, experiments for more than 1,000s were quite few. In addition, the compensatory mechanisms of cardiovascular function to long and large Gz exposure are interesting from the perspective of gravitational as well as heart physiology. Recent advancement of computer technology could make it possible to quantitatively analyze a large amount of ECG data for longer periods. In the present study, we analyzed ECG parameters of the Syrian golden hamster exposed under hyper $-G_z$ acceleration for 1,000s, which was considerably longer than in previous experiments. In addition, we applied $-G_z$ acceleration instead of $+G_z$, because $+G_z$ was more deadly than $-G_z$. Actually most golden hamsters died very early when $+G_z$ was provisionally applied in pilot experiments. We will also provide detailed descriptions of pathological changes in the ECG of this animal.

MATERIALS AND METHODS

A total of twenty-four Syrian golden hamsters (body weight, 100–190 g) were used. With larger $-G_z$, the number of animals which could tolerate the whole course of $-G_z$ exposure decreased. Respective numbers for each group will be given in the RESULTS (cf. Table 1). The animal was anesthetized with sodium isopentylbarbiturate (Amobarbital, 100 mg/kg body weight; i.p.). Additional doses were administered, if necessary, to stabilize anesthetic conditions. Because the

Table 1. Summary of pathological ECG findings for 24 hamsters.

Animal		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24
ECG	P			SP		SP									+										
	R																								
	T						SP	↑	↑	↑							SP	SP							
	Arr		++											++		++									
-6G	P				SP	SP	SP																		
	R														SP		SP	SP	SP						
	T						↑																	↑	
	Arr									+				++											
-8G	P														SP										
	R														-		SP	SP	SP	+	-				
	T														↑		↑							↑	
	Arr																								
-10G	P																								
	R														-		SP	SP		SP	IV	SP	-		
	T																↑								
	Arr															++								++	

P, P wave; R, R wave; T, T component; Arr, Arrhythmia; SP, Split; IV, invert; ↑, elevation; +, ++, appearance mode; —, abolish. Vertical bar, animal could not complete 15 min G-exposure.

Fig. 1. Generation of $-G_z$ acceleration using the disorientator equipped with a swing bucket type gondola. A composed vector (V) of rotatory acceleration (a) and the earth gravity ($1G$) acts always along the long axis of the body (G_z) when an animal was fixed on the z-wall. $+G_z$ (nose up) or $-G_z$ (nose down) could be selected. Similarly $-G_x$ (prone position) or $+G_x$ (supine position) could be applied if the animal was fixed on the x-wall, as illustrated in dotted line. The gondola sways at the pivot.

Syrian golden hamster is very resistant to sodium pentobarbital (SATAKE *et al.*, 1985, 1986, 1987; KAWASHIMA *et al.*, 1988), we preferred to use the longer acting drug Amobarbital. Nevertheless, additional doses were required. However, we were very careful to keep the heart rate in the range of 250 to 300 beat/min. The heart rate in a conscious state was a little higher, in a range between 280–320. When anesthesia was light or the animal was reviving, the heart rate increased toward 300 beat/min or more and the animal began struggling to escape from the constraints, and large EMGs recruited and overshadowed the ECGs. Therefore, in order to avoid muscle movements we were very concerned about the anesthetic conditions of the animal. The animal was fastened with cotton strings (1.5 mm diameter) onto a metal plate (30×30 cm) in a prone position, with all extremities extended. In order to give $-G_z$ acceleration to an animal, the metal plate was then perpendicularly fixed to the inner wall of a gondola with the head of the animal down. The gondola (a swing bucket type) was hung at one end of a horizontal arm (1.5 m) of a disorientator (Shimadzu Co.), so that the gondola was swung out from the perpendicular vertical position upwards toward a horizontal plane when the gondola was rotated in a horizontal circle with a 1.5 m radius. The actual acceleration applied to the animal was the composed vector (V in Fig. 1) of an applied rotational acceleration (a in Fig. 1) and the earth's gravity ($1G$). The composed vector always acts along the long axis of the body, when the animal was

positioned onto the z-wall, with nose down ($-G_z$) or nose up ($+G_z$). Similarly, the composed vector acts across the long axis of the body, if the animal was fixed to the x-wall in the prone position ($+G_x$), the supine position ($-G_x$), or in the side position (G_y). Thus the apparatus could generate a hyper-acceleration as large as 15 G along any selected body axis by changing the posture of the animal relative to the bucket wall (Fig. 1). Speed of rotation, duration and rate of rise and fall of acceleration were all controlled with a microcomputer (M232 Mark III, Sord Computer System).

ECG was recorded in a standard lead (lead I and II), together with an impedance plethysmograph on the chest, before, during and after the exposure of the animal to a hyper $-G_z$ acceleration. These biological signals were transmitted through a telemeter to a monitoring system (Polygraph, NEC-San'ei Co.). The signals were simultaneously recorded on paper and tape for later off-line analysis with a minicomputer.

The animal was exposed to negative hyper-gravitational fields of -2 , -4 , -6 , -8 Gz, and, sometimes -10 Gz. The entire exposure period for every level of $-G_z$ lasted 1,000 s, including rising and steady acceleration and deceleration periods. The rate of increase for every $-G_z$ was 0.025 G/s for the first 40 s (e.g. up to -2 Gz) and thereafter 0.05 G/s. The deceleration rate was 0.05 G/s. Therefore, the actual duration of the steady state $-G_z$ period was a little different for each $-G_z$ level. The duration of the steady state $-G_z$ period was 940 s for -2 Gz, 900 s for -4 Gz, 860 s for -6 Gz, 820 s for -8 Gz, and 780 s for -10 Gz.

Data analysis. The stored ECG signals were analyzed with a minicomputer (7T17, NEC-San'ei Co.). Sampling points of ECG parameters for each $-G_z$ acceleration are illustrated in Fig. 2A. Soon after the acquisition of control data (-1 Gz), experimental data were first sampled during the rising phase of $-G_z$ acceleration every 1 min at 2–3 points (depending on the duration of rising phase). The number of sampling points increased for a larger $-G_z$. Then in the steady phase of hyper $-G_z$ conditions, data were sampled at points 1, 3, 5, 7, 9, 11, and 13 min from the onset of steady $-G_z$ conditions (Figs. 2A and 3). The number of sampling points was more for a smaller $-G_z$ exposure, because the duration of the steady $-G_z$ period was longer. Data after withdrawal of the $-G_z$ load were sampled at 1, 6, and sometimes 9 min after the complete cessation of $-G_z$ acceleration. All these data were digitized and stored on floppy disks.

Digitized data for each sampling point was processed with a minicomputer. The ECG signal was triggered at a level of 95% of the peak of the R wave in order to derive a sum and average for 30 heart beats (Fig. 2B) at each sampling point. The P wave was not appropriate as a regular triggering signal for automatic data processing with the computer because it was small and sometimes disappeared in animals subjected to a larger $-G_z$ load. However, the P wave was used as a triggering signal when the P-R interval had to be precisely determined. The upper illustration of Fig. 2B shows superposed raw data and the lower illustration displays the averaged data from the same sources.

A

B ANALYZING METHOD

Fig. 2. Procedures for data sampling. A: A profile of temporal development of an applied $-G_z$ is illustrated as a trapezoidal trace (in this case, $-6G_z$), and sampling points of ECG data are indicated as vertical bars in the middle. The black bars indicate the sampling points during the rising phase of acceleration. White bars, sampling points of the control (far left), during the steady phase of acceleration (time in min) and after the cessation of acceleration (time in min). The time scale from the start to the end of the acceleration is given at the bottom (time in s). B: Definition of the P-R interval, R amplitude. Superposed (upper) and averaged (lower) traces are illustrated.

Using the averaged data, the P-R interval, the R-R interval, and the P and R amplitudes were first calculated with the computer. The changes in P-R and R-R intervals were expressed as percent or change relative to control values. The P-R interval (the Q wave was lacking in many instances, so we used the P-R interval instead of the P-Q interval) was defined as the time from the onset (30% level) of the P wave to the onset (10% value) of the QRS complex (rising slope to R peak).

Each percent level was determined to avoid a false triggering by noises or fluctuation of the base line.

When an averaged P wave was observed to change its shape (e.g., split or flattened), we always consulted the original raw data with care to ascertain whether these configuration changes (splitting or flattening) were real. When further recalculation was found to be required, then every P wave was checked retrogressively from the peak of the R wave with the aid of the computer. The peak of the P wave thus discovered was used as the new triggering signal for the averaged data. When the P wave split into two small peaks, the first one was used as a triggering signal.

The significance of changes of the experimental data from the control values was tested using a W test (two tails) for heart rate, P-R interval and R amplitude. Significances of 1% and 5% were noted in the illustrations by single or double asterisks respectively (Figs. 4 and 5).

RESULTS

1. Ordinary change

Figure 3 shows a typical example of temporal change of the ECG during the course of -4 Gz application. In this example, -4 Gz was applied. Figure 3A and B were the same data with different time scales. In Fig. 3A, averaged data at each sampling point are illustrated, aligned at the peak of the R wave. It shows the change of one beat cycle of the ECG. The R-R interval decreased in the first 1-3 min after the onset of steady -4 Gz exposure, but thereafter it increased with time. It was longer than the pre-exposure value at 5 min and continued increasing during the rest of the period of -4 Gz exposure. When the -4 Gz acceleration was halted, the R-R interval decreased. In the -4 Gz case, it returned almost to the control value 6 min after the cessation of -4 Gz acceleration.

Figure 3B shows the expanded P-QRS components. As is shown in the figure, the P-R interval was slightly prolonged during -4 Gz exposure. This elongated P-R interval did not return to the pre-exposure value even 6 min after the cessation of -4 Gz acceleration. The shape of the P wave also changed. The P wave in the control period had a single peak and was rather flat. However, it split into two peaks during -4 Gz application. Six minutes after the cessation of -4 Gz application, the two peaks fused into one, even though the two peaks were still observable 1 min after the cessation of -4 Gz acceleration. The QRS complex also showed a significant change in its shape. A notch or shoulder appeared on the slope that rose to the R peak, and the R amplitude decreased. After the cessation of -4 Gz exposure, the QRS complex almost completely regained its pre-exposure shape.

Figure 4 shows the temporal changes of R-R and P-R intervals and R amplitude in -4 and -6 Gz conditions ($n=9$ and 8, respectively). In -4 Gz conditions, the R-R interval slightly decreased at the very initial phase of -4 Gz exposure. This decrease may coincide with the transient tachycardia observed

Fig. 3. A specimen of temporal change of ECG during -Gz load (A) and its expanded figure at P-QRS components (B). The number at the left of each trace is the time of the sample.

Fig. 4. Temporal change of ECG parameters during and after -4Gz (upper frame) and -6Gz (lower frame) loads. Trapezoids on the abscissa indicate respective temporal profiles of applied $-Gz$ (cf. Fig. 2). Significant differences are indicated by single ($p < 0.01$) and double ($p < 0.05$) asterisks. Vertical bars are S.E. Ordinate, values relative to the control. Abscissa, time.

during the rising phase of $-Gz$ acceleration (KAWASHIMA *et al.*, 1989). The R-R interval then continued to increase during the rest of the steady -4Gz period and it remained at the increased level for more than 9 min after $-Gz$ cessation. The P-R interval similarly increased during -4Gz application with more increase in the later period. It stayed at the increased level after the cessation of $-Gz$ acceleration. The R amplitude decreased during steady -4Gz acceleration, but it soon returned to the pre-exposure value after the cessation of -4Gz acceleration.

The lower part of Fig. 4 shows similar ECG change in -6Gz conditions. The R-R interval was prolonged more than in -4Gz conditions, and the increased level remained after the cessation of $-Gz$ acceleration. The change of P-R interval was less than that in -4Gz conditions. It increased after the cessation of the steady -6Gz . The change of R amplitude was similar to that in -4Gz .

Figure 5 shows similar ECG changes in -8 and -10Gz conditions ($n=6$ and 4, respectively). In -8Gz conditions, the R-R interval increased rapidly to reach a steady value, but it was not significant due to the large S.E. The increased level did not return to the control level for more than 6 min after the cessation of -8Gz . The P-R interval seemed to decrease slightly, but it returned to the pre-exposure level in the later period of the steady -8Gz application. After the -8Gz load was ended, the P-R values showed values similar to the pre-exposure level. The R amplitude decreased for the steady -8Gz acceleration, but it soon returned to the pre-exposure level after -8Gz cessation. In -10Gz conditions, the effects of $-Gz$ acceleration were so large that arrhythmia or omissions of beat often

Fig. 5. Temporal change of ECG parameters during and after -8Gz (upper frame) and -10Gz (lower frame) loads. Trapezoids on the abscissa indicate respective temporal profiles of applied $-Gz$ (cf. Fig. 2). Significant differences are indicated with single ($p < 0.05$) and double ($p < 0.01$) asterisks. Vertical bars are S.E. Ordinate, relative values to the control. Abscissa, time.

appeared. Therefore, it is meaningless to give a mean heart rate, and accordingly, a figure of the R-R interval in the -10Gz condition was not presented. The P-R interval seems to decrease. The amplitude of the QRS complex decreased, but without significance, due to the large S.E.

Figure 6 is a composite figure of the results for the P-R interval and the R amplitude illustrated in Figs. 3 and 4. It is obvious from this figure that the effects of $-Gz$ acceleration on the ECG of the golden hamster seem to be different in smaller Gz (-4 and -6Gz) and larger Gz (-8 and -10Gz). In smaller $-Gz$ conditions, the P-R interval had a tendency to increase, while it decreased in larger $-Gz$ conditions. At the same time, $-Gz$ acceleration caused a decrease in R amplitude under all $-Gz$ conditions.

2. Pathological findings

Several pathological signs were observed in the ECG when golden hamsters were exposed to long term negative hyper $-Gz$ ($-Gz$) conditions. A general summary of the tabulated protocol of the experiments is given in Table 1. All 24 hamsters used in the present experiments could tolerate -4Gz conditions, but a split in the P wave appeared in 3 animals. Another 3 animals showed a split in the R wave. Abnormal T was observed in 2 animals. Under 22 of the 24 hamsters could tolerate -6Gz conditions, but the remaining 2 animals gave incomplete data. The incomplete data was not used for analysis. Of the 22 animals that could tolerate -6Gz exposure, 4 animals showed a split in the P wave. A split of the R

Fig. 6. Comparison of the differential effects of a smaller (-4 and -6 Gz) larger (-8 and -10 Gz) G-load on P-Q interval and R amplitude. Ordinate, values relative to the controls. Abscissa, sample time.

wave was observed in 4 animals. T components, mostly the elevation of ST-T, changed in 2 animals. Arrhythmia occurred in 2 animals. Twelve hamsters could tolerate -8 Gz hyperacceleration. Of these 12 animals, the P wave split in one hamster and disappeared (jiggling) in another 2 hamsters. The R wave split in 4 animals and disappeared in one. Changes of the T components occurred in 3 animals. Nine hamsters tolerated -10 Gz conditions. Of these 9 animals, a split of the P wave was observed in one animal. The P wave disappeared in 2 animals and inverted in one animal. Three hamsters showed a split of the R wave. Pathological T was observed in one animal. Arrhythmia occurred in 2 animals. Hereafter, a description will be made of some of these pathological changes.

3. A-V block

Atrio-ventricular (A-V) block of the first degree is a mildly abnormal ECG,

Fig. 7. An example of elongation of P-R interval during -Gz exposure. In this case -6 Gz was applied. Time from the onset of -Gz exposure is given at the left of each trace (min). Each trace was an average of 30 traces triggered at the peak of R waves.

which is defined as ECG accompanied by P-Q elongation without abortion of the QRS complex (GOLDMAN, 1970). In the present study, 6 animals showed that type of A-V block.

Figure 7 demonstrates an example of the elongation of the P-R interval (cf. METHODS) with time during -Gz exposure. The initial P-R interval was 57 ms in this case.

It became longer at 1 min after the onset of -6 Gz exposure. Thereafter the P-R interval maintained an almost constant value during the time from 1 to 5 min. Then it began increasing up to 103 ms (at 11 min) and finally the P wave disappeared at 13 min after the onset of -6 Gz exposure (Fig. 7). However, the P wave actually existed at this moment, but it could not be detected by the averaged data (Fig. 7), because the P-R interval at this period fluctuated so much that individual P waves disappeared below the noise level in the averaged data, when the signals were triggered by the peak of the R wave.

When -6 Gz application was ceased, P waves soon appeared again at 1 min after the -Gz cessation, but the shape was remarkably flat. This means that the P-R intervals still fluctuated. The P-R interval would not return to the pre-exposure value even 6 min after -6 Gz cessation.

The P-R interval at 1 min after -6 Gz cessation was almost the same as that

at 11 min of -6 Gz exposure, suggesting the presence of after-effects of -6 Gz exposure. The P-R interval remained in an increased state even 6 min after -6 Gz cessation.

In addition to the change in the P-R interval, the QRS complex and the S-T component changed in this animal. The QRS complex of this hamster was broad and had a notch on the rising slope to the R peak in the pre-exposure period. When -6 Gz was applied, the notch disappeared after 3 min exposure. The R amplitude also began increasing, and its width narrowed, forming a sharp QRS wave. In keeping with the growth of the R amplitude, the downward inflection of the S component deepened. ST elevation also appeared. These changes were more remarkable in the later period of -6 Gz exposure, e.g., from 11 to 13 min. Even when -6 Gz acceleration was halted, QRS and ST components did not return to the pre-exposure state for several minutes. They maintained features observed in the terminal period of steady -6 Gz exposure.

Another type of A-V block is the 2nd- or 3rd-type block, which is characterized by a periodic failure of the QRS complex to the P wave with fixed ratio of 2:1 or 3:1 (the second degree), or dissociation of the QRS rhythm from the P wave (the third degree; GOLDMAN, 1970). In our experiments, a failure with a two to one ratio could be observed ($n=5$).

As is shown in Fig. 8 (uppermost frame), the heart beat of this animal was regular (205 beats/min) in the pre-exposure period. When the animal was exposed to -4 Gz hypergravitation, the regular rhythm changed into arrhythmia at first with the 2nd type block (the 2nd left upper frame). After 14 successive cycles of this type of heart beat (only 8 cycles are illustrated in the figure), the rhythm changed into the 3rd type block, as is illustrated (the 2nd left lower frame). In addition to the rhythmic changes, the QRS-T segment seems to change. This is clearly demonstrated in the averaged data for the 3rd type block (the 2nd right frame). The amplitude of the QRS complex increased and S-T was deformed; e.g., the R amplitude increased, the S wave deepened, and S-T elevated slightly and elongated. When -4 Gz hypergravitation was removed, the heart beat was restored to a relatively regular rhythm, but some P waves still lacked QRS waves (the left bottom frame). The shape of the QRS complex and S-T did not completely resume to the pre-exposure features even 6 min after the cessation of -4 Gz acceleration (the right bottom frame).

4. Shortening of the PR interval

As was described above, the P-R interval increased in smaller $-Gz$ (-4 and -6 Gz), while it shortened in large $-Gz$ conditions (-8 and -10 Gz). Because this shortening may have some pathological meaning, it will be described in more detail. In this instance, the case of 20% shortening is taken as a typical example ($n=2$).

When the animal was exposed to -10 Gz acceleration, the P wave disappeared in the averaged ECG after 1 min of the exposure (Fig. 9A). However, when the

Fig. 8. An example of the 2nd and 3rd type of A-V block. First frame: ECG of pre-exposure to -4Gz . Left, continuous recording of ECG. Right, 30 traces are superposed (upper frame) and averaged (lower frame). Second frame: Left upper frame, recording to show 2nd type A-V block. Left lower frame, continuous recording to show 3rd type of A-V block. Right, superposed (upper) and averaged (lower) traces. P waves did not appeared at the fixed point. R amplitude increased and the T wave elevated and elongated. For further explanation, see text. Bottom frame. ECG of the post-exposure period, 6 min from the cessation of -4Gz . Most P waves are followed by the QRS complex, but the heart rate is still irregular. Right, superposed (upper) and averaged (lower) traces. Also note that the P wave still fluctuated when triggered at the peak of the R wave. The QRS complex and S-T did not return to their pre-exposure condition.

Fig. 9. An example of P-R shortening. A: Change of the P-R interval with time during -10 Gz exposure. B: Original data at 1 min from the onset of -10 Gz exposure. Heart rate is irregular and the P wave sometimes aborts. C: Superposed (upper) and averaged (lower) traces triggered at the peak of the R wave. Samples were marked with a star in B that had no P wave. D: Superposed and averaged traces for samples marked with asterisk. R-R interval fluctuated.

raw data was inspected, the P wave was found to exist in most individual beats (Fig. 9B), and only some beats lacked a P wave (e.g., two beats in the first row, the 3rd beat in the second row, and the first beat in the third row). Abolition of the P-wave could be clearly demonstrated (Fig. 4C) when several beats were summed and averaged, triggered by each preceding QRS wave marked with a star in Fig. 9B. However, the P wave remained in other beats marked with asterisk in Fig. 9B. Figure 9D shows superposed and averaged data for the latter case.

5. Change of P and QRS wave forms

It is often observed that P waves became flat or split into two peaks. In the present experiments, 7 animals showed splitting of the P wave, disappearance of the P wave was documented for 4 animals and one animal showed an inverted P wave. Also, a split of the QRS wave was observed in 6 animals (Table 1). Disappearance of the QRS complex occurred only in the animals' terminal stage.

Fig. 10. An example of change in the form of the QRS complex. Upper frame: superposed and averaged ECG of pre-exposure period. Middle frame: QRS waves at 11 min after $-6G_z$ exposure. The QRS wave has a shoulder on the slope rising to the peak of the R wave. Also splitting of the P wave is more distinct than in the control. Lower frame: post-exposure period ECG.

In the case of Fig. 10, the R wave split into two peaks and its amplitude decreased at 11 min after the onset of $-6G_z$ exposure. The P wave also had two peaks. These changes returned almost to their pre-exposure form after the cessation of $-G_z$ exposure. The ST segment showed little change in this instance. But changes of the ST-T segment were observed in the other 6 animals (cf. Table 1).

DISCUSSION

Changes in heart rate. Changes in heart rate during the steady phase of $-G_z$ acceleration were along the same lines as those of previous $-G_z$ experiments; it decreased (RYAN *et al.*, 1950; DUANE *et al.*, 1952; HOWARD, 1965b). However, the exposure period of steady $-G_z$ in the present study was longer (1,000 s) than any other previous experiments. It should be stressed that the Syrian golden hamster could tolerate up to $-10 G_z$ for that long a time. When human subjects were exposed to $-G_z$ of, for example, -4 or $-5 G_z$, care has been taken to apply acceleration for only several seconds; otherwise the subjects fall into a dangerous state of "red-out" (RYAN *et al.*, 1950; HOWARD, 1965b). Animal experiments allowed a longer exposure, but it still remained in the range of several seconds for miniature swine, dogs, or monkeys (CHIMOSKY, 1970; PETERSON *et al.*, 1975, 1989; BURNS *et al.*, 1986; SATAKE *et al.*, 1989, 1991).

The amount of increase in the R-R interval (decrease in the heart rate) during a steady $-G_z$ load seems to be larger for a larger $-G_z$. A gradual increase in the R-R interval with time was also observed during the exposure period of the sustained $-G_z$, although this gradually increasing trend diminished in the case of $-8 G_z$ exposure. Under G_z acceleration as used in the present experiments, the causes that produce such changes in the heart rate must be complex. Humoral, metabolic, as well as neuronal influences must be taken into account. Hereafter we will consider several possible reasons.

A slight decrease of the R-R interval (increase in the heart rate) could be detected at the very initial stage of $-G_z$ exposure, although it was not significant. We have reported a transient increase in heart rate during the rising phase of $-G_z$ acceleration, and it sometimes crept into the very early stage of the steady $-G_z$ acceleration (KAWASHIMA *et al.*, 1989). The present findings of a decrease in the R-R interval under $-G_z$ exposure could be explained by the residual effects of the tachycardia originally produced in the rising period of $-G_z$ acceleration.

The R-R interval increased (heart rate decreased) during the steady period of $-G_z$ acceleration that followed. The simplest explanation is that the increase in the R-R interval is produced as an expression of the baroreflex that counteracts increased blood flow toward the head, which is caused by the $-G_z$ load. Cardiac output was not calculated in the present experiments. However, our previous study demonstrated a decrease in cardiac output with a minor change in stroke volume during $-G_z$ load (SATAKE *et al.*, 1985). Therefore, it may be concluded that the blood supply was actually decreased in order to suppress the blood supply to the upper regions of the body, especially the head.

The amount of increase in the R-R interval was larger for the later stage of $-G_z$ exposure. This progressive increase in the R-R interval with time could not be explained solely by baroreflex. Many other factors may contribute the progressive R-R increase: O_2 deficiency due to coronary insufficiency, gradual fluid

shift from the capillary vessel into the tissues, changes of autonomic nerve balance accompanied by the change of transmitter release from the terminals and hormonal changes to regulate water balance (cf. BLOMQUIST and STONE, 1983). However, O₂ deficiency would be the most important factor (WHINNERY *et al.*, 1979; LAUGHLIN *et al.*, 1980; WHINNERY and LAUGHLIN, 1982; LAUGHLIN, 1986). It could also be a common causative factor underlying changes in the P-R time, as well as the P and QRS waves. We will refer to the O₂ deficiency problem in more detail in the following sections.

Changes in P-R interval. The P-R interval (which was considered to be equivalent to P-Q interval; cf. METHODS) increased in smaller -Gz conditions, while it decreased with larger -Gz conditions. It seems to be reasonable at first glance that the P-R interval in a smaller -Gz conditions increased with the increase in the R-R interval. However, it seems peculiar that the P-R interval shortened while the R-R interval remained elongated in the larger -Gz exposure. It should be remembered that the P-R interval mostly represents the conduction time for the atrio-ventricular (AV) node and that it is relatively stable while the R-R interval varies with respiration (IRISAWA, 1982). Therefore, the present findings of a dissociational change in the P-R and R-R intervals suggests some differential changes in the excitability of the AV node independent of the SA nodal region. Several reasons must be taken into account to explain the present findings of the change in P-R interval during -Gz application.

The P-Q interval shortened in human subjects after adrenaline was administered, as well as during exercise (IRISAWA and SEYAMA, 1966). Therefore, it is possible that under the stressful conditions of larger -Gz (e.g., -8 and -10 Gz), more noradrenaline was released from the sympathetic nerve terminal (CORR *et al.*, 1986), as well as adrenaline from the adrenal medulla into blood flow, causing a decrease in the P-R interval. An increase of secretory vesicles in the adrenal medulla was observed at the electron microscopic level in rats exposed to the same conditions as in the present experiments (Shoumura *et al.*, personal communication). However, the R-R interval remained in an elongated state, although it decreased slightly, in the later period of the steady -8 Gz load. If the amount of adrenaline/noradrenaline release increased during a steady -Gz stress load, then the R-R interval can be expected to decrease. Therefore, the assumption of a simple increase in adrenaline/noradrenaline in proportion to the applied -Gz load fails to explain the simultaneous increase in the R-R interval and the decrease in the P-R interval that was observed during larger -Gz accelerations. However, the differential P-R and R-R changes could partly be explained by the different innervation pattern of sympathetic and parasympathetic autonomic nerves to the SA and AV nodal regions (CORR *et al.*, 1986). The different patterns of autonomic innervation could provoke a different temporal development of effects on the SA and AV nodes when the animals were exposed to a longer -Gz load; speculatively speaking, parasympathetic effects were dominant relative to sympathetic effects in the SA node and subordinate in the AV node for one period, and vice versa for another

period.

Because the effects of catecholamines on the electrophysiological properties of pacemaker tissues (e.g., AV node) are significant (HOFFMAN and CRANFIELD, 1960), a consideration of the AV node conductivity in relation to catecholamine actions seems to be particularly important for interpretation of P-Q time, and it will be discussed briefly. Stimulation for 100 ms of the left or right stellate ganglion in dogs with their heart rate fixed by pacing resulted in acceleration of AV conduction (SPEAR and MOORE, 1973). In this respect, it is interesting that AV time in the pacing experiments in the dog increased when the R-R interval decreased (IRISAWA *et al.*, 1971). The increase in the AV time in the latter experiments was attributed to the effects of a refractory period produced in the shorter R-R time (higher frequency stimulation).

In keeping with the catecholamine function, it is also important that acetylcholine (ACh) from the vagal nerve terminal would modify the AV node conduction time, as was demonstrated by the elongation of the "nodal hump" after vagal nerve stimulation (PRUITT and ESSEX, 1960). Actually ACh could abolish action potential in the AV node (MATSUDA *et al.*, 1958; CRANFIELD *et al.*, 1959). These findings may provide the electrophysiological basis of AV conduction delay as well as AV block, whose most likely site is the atrionodal junction in the AV node (PRUITT and ESSEX, 1960).

The PQ time could be varied in hypoxia by changes of electrical excitability in the AV nodal regions. It has been repeatedly reported that a strong Gz load produced coronary insufficiency (LAUGHLIN, 1982, 1986) or a decrease in arterial oxygen partial pressure (BURTON, 1973; BURTON *et al.*, 1974). The initial effect of acute ischemia reported so far is that it renders the myocardium slightly more excitable with a decrease in the threshold current or stimulus duration (BROOKS *et al.*, 1960; ELHARRAR *et al.*, 1977; GETTES, 1986), probably due to the early change in extracellular potassium (SPEAR and MOORE, 1974). In parallel with these excitability changes, conduction through the AV node changed. Within the first 2–3 min of coronary ligation, conduction became faster and then slowed progressively (ELHARRAR *et al.*, 1977; HOLLAND and BROOKS, 1976; HILL and GETTES, 1980). This is frequently followed by the spontaneous restoration of conduction, after which conduction again slows progressively (DOWNAR *et al.*, 1977; HILL and GETTES, 1980). In the present experiments, effects of $-G_z$ load on P-R time were different in smaller $-G_z$ and larger $-G_z$, and this difference could partly be explained by the complex expression of ischemic effects as seen in the waxing and waning manner of excitability changes.

Change of P wave. The following changes in the contour of the P wave were observed in the present experiments, as they were in previous investigations (HOWARD, 1965a): splitting, flattening, or even disappearance of the P wave. The same factors used to explain the change in the P-R time could be applicable to the genesis of these P wave changes. However, before going into a physiological consideration of the changes in the P wave, the possibility that flattening of the P

wave in the present experiments was only the result of the averaging technique should be excluded. As already described in METHODS, we were very careful to avoid this possibility. First, we always referred to the original raw data. Second, averaging was repeated using the P waves instead of the peak of the R waves as the triggering signal (cf. METHODS).

At least two main factors may possibly provide an explanation for the P wave changes: the presence of a detour and the change in conduction velocity. The genesis of a detour in the atrium, probably due to O₂ deficiency, could provide the most simple explanation for the splitting of the P wave. In terms of morphology, the atria are not homogeneous structures, and they can provide at least three paths for P wave conduction from the SA to AV node. There are many experiments for or against the supposition (cf. SCHER and SPACH, 1979), but the presence of heterogeneity in electrical conduction in the atrium is widely accepted (ALLESSIE *et al.*, 1976). It is further possible that the difference of the P wave conductivity in the different paths could become significant enough to produce splitting of the P wave when the atrial muscles were exposed to O₂ deficient conditions.

The P wave is not a simple form with a single peak; it has two or more peaks even in normal human subjects, due to dys-synchronous excitation of the left and right atria (IRISAWA and SEYAMA, 1966). It has been further suggested that the electrical excitation does not radiate in the atrium uniformly with an isochronous front, but rather it spreads heterogeneously. This suggestion was later confirmed by ALLESSIE *et al.* (1976), using a multiple recording electrode. The multiple peaks in the normal P wave could fuse into one with an increase in amplitude when the two atria excited in time after the administration of adrenaline or mild exercise (IRISAWA and SEYAMA, 1966). In the meanwhile, the golden hamster in the present study did not show distinct notches in the normal P waves, probably because this animal is so small that the excitation time difference between the two atria was negligible compared to human subjects. However, when the golden hamster was exposed to hyper-acceleration that could produce an O₂ deficiency, then the P wave of the golden hamster would become flat or split, or even disappeared (jiggled). Therefore, we assumed that the flattening or splitting of the P wave in the golden hamster exposed to the present hyper-acceleration experiments reflected some pathological state.

Regional change in the conduction velocity was another possible source of the configuration change of the P wave. Even in the AV node, a regional difference in excitability could be expected due to an increase in extracellular K⁺ or a decrease in pH. Unequal amounts of extracellular potassium were recorded even with electrodes placed at the same myocardial depth (HILL and GETTES, 1980). Also temporal development of extracellular K⁺ and pH after occlusion was different in the ischemic center and the ischemic side of the lateral margin (JANSE *et al.*, 1979). Differences in lactate, creatinephosphate, and ATP have also been found in these different regions of the ischemic myocardium (JANSE *et al.*, 1979).

Change of QRS complex. The QRS complex deformed and its (R) amplitude

decreased. The QRS complex largely represents electrical excitability in the bundle of His to the ventricular muscles. Therefore, an abnormal configuration of the QRS wave indicates some defect in this system, which is notably represented as bundle branch block (SCHAEFER and HAAS, 1962; GOLDMAN, 1970; BURTON, 1973). The underlying mechanisms for the deformation of QRS complex observed in hyper-acceleration, so far as it was pathological, would be mostly the same as those in the abnormal genesis of the P wave: changes in electrical excitability due to changes in extracellular K^+ , pH, and other metabolites. Therefore, we will not further explain this problem from these perspectives.

However, increase or decrease in the QRS amplitude has often been observed when Gz acceleration was applied. Usually rather than considering this amplitude change a pathological sign, it has been viewed as a result of change in electroaxis due to a mere shift of the heart due to accelerative force (HOWARD, 1965a), because it soon returned to its pre-exposure form. Actually the heart was observed roentgenographically to be deformed (WOOD *et al.*, 1977). However, some QRS changes in the present experiments were not soon restored to their pre-exposure form. Rather, they endured for several minutes after cessation of $-G_z$ acceleration. In those instances, therefore, it is more likely that the effects of some electro-chemical disturbances continued due to the oxygen insufficiency in the myocardium after hyper-acceleration.

REFERENCES

- ALLESIE, M. A., BONKE, F. I. M., and SCHOPMAN, F. J. G. (1976) Observations on circus movement tachycardia in the isolated rabbit atrium. *In: The Conduction System of the Heart*, ed. by WELLENS, L. and JANSE, S. K., Leiden, pp. 249–260.
- BECKMAN, E. L., ZIEGLER, J. E., DUANE, T. D., and HUNTER, H. N. (1953) Some observations on human tolerance to accelerative stress. Phase II. Preliminary studies on primates subjected to maximum simple accelerative loads. *J. Aviat. Med.*, **24**: 377–392.
- BLOMQUIST, C. G. and STONE, H. L. (1983) Cardiovascular adjustments to gravitational stress. *In: Handbook of Physiology. The Cardiovascular System*, ed. by SHEPARD, J. T. and ABOUD, J. T., Am. Physiol. Soc., Bethesda, Washington, D.C., pp. 1025–1063.
- BROOKS, C. M., GILBERT, J. L., GREENSPAN, M. E., LANGE, G., and MAZZELLA, H. M. (1960) Excitability and electrical response of ischemic heart muscle. *Am. J. Physiol.*, **198**: 1143–1147.
- BURNS, J. W., PARNELL, M. J., BURTON, R. R. (1986) Hemodynamics of miniature swine during $+G_z$ with and without anti G support. *J. Appl. Physiol.*, **60**: 1628–1637.
- BURTON, R. R. (1973) Positive ($+G_z$) acceleration tolerance of the miniature swine: Application as a human analog. *Aerosp. Med.*, **44**: 294–298.
- BURTON, R. R., LEVERETT, S. D., Jr. and MICHAELSON, E. D. (1974) Man at high sustained $+G_z$ acceleration: A review *Aerosp. Med.*, **45**: 1115–1136.
- CHIMOSKY, J. E. (1970) Coronary blood flow and electro-cardiogram during headward acceleration in unanesthetized dogs. *Aerosp. Med.*, 1028–1030.
- CORR, B. H., YAMADA, K. A., and WITKOWSKI, F. X. (1986) Mechanisms controlling

- cardiac autonomic function and their relation to arrhythmogenesis. *In: The Heart and Cardiovascular System. II.*, ed. by FEZZARD, H. A., HARBER, E., JENNINGS, R. B., KATZ, A. M., and MORGAN, H. E., Raven Press, New York, pp. 1343-1430.
- CRANFIELD, P. F., HOFFMAN, B. F., and PAES DE CARVALHO, A. (1959) Effects of acetylcholine on single fibers of the atrioventricular node. *Circ. Res.*, 7: 19-23.
- DOWNER, E., JAMES, M. J., and DURRER, D. (1977) The effect of acute coronary artery occlusion on subepicardial transmembrane potentials in the intact porcine heart. *Circulation*, 56: 217-222.
- DUANE, T. D., WECHSLER, R. L., ZIEGLER, J. E., and BECKMAN, E. L. (1952) Studies on cerebral physiology of monkeys at 12 negative G. *J. Aviat. Med.*, 23: 479-489.
- ELHARRAR, V., FOSTER, P. R., JIRAK, T. L., GAUM, W. E., and ZIPES, D. P. (1977) Alterations in canine myocardial excitability during ischemia. *Circ. Res.*, 40: 98-105.
- GETTES, L. S. (1986) Effects of ischemia on cardiac electrophysiology. *In: The Heart and Cardiovascular System. II*, ed. by FOZZARD, H. A., HARBER, E., JENNINGS, R. B., KATZ, A. M., and MORGAN, H. E., Raven Press, New York, pp. 1317-1341.
- GOLDMAN, M. J. (1970) Principles of Clinical Electrocardiography, Lange Medical Publications, Maruzen, Tokyo.
- HILL, J. L. and GETTES, L. S. (1980) Effect of acute coronary artery occlusion on local myocardial extracellular K⁺ activity in swine. *Circulation*, 61: 768-777.
- HOFFMAN, B. F. and CRANFIELD, P. F. (1960) Electrophysiology of the Heart, McGraw-Hill, New York.
- HOLLAND, R. and BROOKS, H. (1976) The QRS complex during myocardial ischemia: An experimental analysis in the porcine heart. *J. Clin. Invest.*, 57: 541-550.
- HOWARD, P. (1965a) The physiology of positive acceleration. *In: A Textbook of Aviation Physiology*, ed. by GILLIS, J. A., Pergamon Press, London, pp. 551-687.
- HOWARD, P. (1965b) The physiology of negative acceleration. *In: A Textbook of Aviation Physiology*, ed. by GILLIS, J. A., Pergamon Press, London, pp. 688-716.
- IRISAWA, H. (1982) The Physiology of the Heart, Iwanami Publisher, Tokyo (in Japanese).
- IRISAWA, H., CALDEWELL, W. H., and WILSON, M. F. (1971) Neural regulation of atrioventricular conduction. *Jpn. J. Physiol.*, 21: 15-25.
- IRISAWA, H. and SEYAMA, I. (1966) The configuration of the P wave during mild exercise. *Am. Heart J.*, 71: 467-472.
- JANSE, M. J., CINCA, J., MORÉNA, H., FIOLET, J. W. T., KLÉBER, A. G., DEVRIES, G. P., BECKER, A. E., and DURRER, D. (1979) The "border" zone in myocardial ischemia: An electrophysiological, metabolic, and histochemical correlation in the pig heart. *Circ. Res.*, 44: 576-583.
- KAWASHIMA, T., SATAKE, H., and MATSUNAMI, K. (1989) Transient changes of heart rate during rising periods of hyper-G exposure. *In: Aerospace Science. 2nd Nihon Univ. Int. Symp. Aerosp. Sci.*, ed. by YAJIMA, K., Nihon Univ., Tokyo, pp. 395-399.
- KAWASHIMA, T., SATAKE, H., UEKI, S., and MATSUNAMI, K. (1988) Detail analysis of ECG of the hamster in hyper -G condition. *In: Aerospace Science. 1st Nihon Univ. Int. Symp. Aerosp. Sci.*, ed. by YAJIMA, K., Nihon Univ., Tokyo, pp. 177-179.
- LAUGHLIN, M. H. (1982) An analysis of the risk of human cardiac damage during +Gz stress: A review. *Aviat. Space Environ. Med.*, 53: 423-431.
- LAUGHLIN, M. H. (1986) The effects of +Gz on the coronary circulation: A review. *Aviat. Space Environ. Med.*, 57: 5-16.

- LAUGHLIN, M. H., YOUNG, J. T., WITT, W. M., and CRUMP, P. P. (1980) The importance of myocardial perfusion in the pathogenesis of the cardiac pathology associated with +Gz exposure in miniature swine. *Aviat. Space Environ. Med.*, **51**: 1197–1204.
- LEVERETT, S. D., Jr. and WHINNERY, J. E. (1985) Biodynamics: Sustained acceleration. In: *Fundamentals of Aerospace Medicine*, ed. by DEHART, R. L., Lea & Febiger Philadelphia, pp. 202–249.
- LINDBERG, E. F. and WOOD, E. H. (1963) Acceleration. In: *Physiology of Man in Space*, ed. by BROWN, J. H. U., Academic Press, London, pp. 61–111.
- MATSUDA, K., HOSHI, T., and KAMEYAMA, S. (1958) Action of acetylcholine and adrenaline upon the membrane potential of the atrio-ventricular node (Tawara). *Tohoku J. Exp. Med.*, **68**: 16.
- PARKHURST, M. J., LEVERETT, S. D., Jr., and SHUBROOKS, S. J., Jr. (1972) Human tolerance to high, sustained +Gz acceleration. *Aerosp. Med.*, **43**: 708–712.
- PETERSON, D. F., BISHOP, V. S., and ERICKSON, H. H. (1975) Cardiovascular changes during and following 1-min exposure to +Gz stress. *Aviat. Space Environ. Med.*, **46**: 775–779.
- PETERSON, D. F., BURNS, J. W., FANTON, J. W., and LAUGHLIN, M. H. (1989) Effects of dipyridamole on the cardiovascular response to +Gz stress in miniature swine. *Aviat. Space Environ. Med.*, 218–225.
- PRUITT, R. D. and ESSEX, H. E. (1960) Potential changes attending the excitation process in the atrioventricular conduction system of bovine and canine hearts. *Circ. Res.*, **8**: 149–174.
- RYAN, E. A., KERR, W. K., and FRANKS, W. R. (1950) Some physiological findings on normal men subjected to negative G. *J. Aviat. Med.*, **21**: 173–194.
- SATAKE, H. and MATSUNAMI, K. (1989) Cardiac responses of cats modulated by the vestibular system under the centrifugal acceleration. In: *Aerospace science, 2nd Nihon Univ. Int. Symp.*, ed. by YAJIMA, K., Nihon Univ., Tokyo, pp. 291–296.
- SATAKE, H., MATSUNAMI, K., and MIYATA, H. (1991) The vestibulo-autonomic function viewed from cardiac responses in centrifuged monkeys. *Acta Otolaryngol. (Stockh.) Suppl.*, **481**: 543–547.
- SATAKE, H., MIZUNO, Y., NAKASHIMA, M., and MATSUNAMI, K. (1987) Changes in the cardiac system of beta-1-blocked hamsters under hyper-gravity. In: *Biological Sciences in Space 1986*, ed. by WATANABE, S., MITARAI, G., and MORI, S., MYU Res., Tokyo, pp. 77–84.
- SATAKE, H., MIZUNO, Y., URANO, H., WATANABE, S., and MATSUNAMI, K. (1986) Difference in directional effects of centrifugal acceleration (+Gz, -Gz) upon cardiovascular system of hamster. In: *Proc. 15th Int. Symp. on Space Technol. and Sci.*, AGNE Publ., Tokyo, pp. 2073–2078.
- SATAKE, H., WATANABE, S., MIZUNO, Y., and URANO, H. (1985) Effects of -Gz centrifugal acceleration upon cardiac output of hamster. *J. J. Aerosp. Environ. Med.*, **22**: 53–64.
- SCHAEFER, H. and HAAS, H. G. (1962) Electrocardiography. In: *Handbook of Physiology. Section 2. Circulation, Vol. I.*, ed. by HAMILTON, W. F. and DOW, P., Am. Physiol. Soc., Bethesda, Washington, D.C., pp. 323–415.
- SCHER, AM. and SPACH, M. S. (1979) Cardiac depolarization and repolarization and the electrocardiogram. In: *Handbook of Physiology. Section 2: The Cardiovascular System*,

- Vol. I, ed. by BERNE, R. M., SPERELAKIS, N., and GEIGER, S. R., Am. Physiol. Soc., Bethesda, Washington, D.C., pp. 357-392.
- SHUBROOKS, S. J., Jr. (1972) Changes in cardiac rhythm during sustained high levels of positive (+Gz) acceleration. *Aerosp. Med.*, **43**: 1200-1206.
- SPEAR, J. F. and MOORE, E. N. (1973) Influence of brief vagal and stellate nerve stimulation on pacemaker activity and conduction within the atrioventricular conduction system of the dog. *Circ. Res.*, **32**: 27-41.
- SPEAR, J. F. and MOORE, E. N. (1974) Supernormal excitability and conduction in the His-Purkinje system of the dog. *Circ. Res.*, **35**: 782-792.
- WHINNERY, J. E., LAUGHLIN, M. H., and HICKMAN, J. R., Jr. (1979) Concurrent loss of consciousness and sino-atrial block during +Gz stress. *Aviat. Space Environ. Med.*, **50**: 635-638.
- WHINNERY, J. E. and LAUGHLIN, M. H. (1982) Right ventricular pressure response to +Gz acceleration stress. *J. Appl. Physiol.*, **53**: 908-913.
- WOOD, E. H., SASS, D. J., RITMAN, E. L., GREENLEAF, J. F., COULAM, C. M., NATHAN, D., and NOLAN, E. C. (1977) Some effects of acceleration in man and chimpanzees. In: *The Use of Nonhuman Primate in Space*, ed. by SIMMONDS, R. C. and BOURNE, G. H., NASA Conference Publication 005, Washington: NASA, pp. 103-164.