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ON PHYSICAL WORK CAPACITY
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EFFECTS OF SOME TRANQUILIZING, ANALEPTIC AND VASODILATING DRUGS ON PHYSICAL WORK CAPACITY AND ORTHOSTATIC TOLERANCE

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For ages, man has attempted to induce changes of psychosomatic behavior by utilizing plants or plant products with stimulating or sedating properties. Some of these products have become such normal ingredients of daily life that most people are no longer aware of their addiction to the specific biological effects of such chemicals as caffeine, nicotine or alcohol. During the most recent years, drugs which had been developed for controlling psychosomatic disturbances of various types and origins have become almost as popular as coffee, tobacco, or alcohol. There can be no doubt, however, that under certain conditions the individual's sensory and functional capacity might become affected by such pharmaca in a way interfering with, or being detrimental to, an important working task.

This investigation was predicated on the basis: (a) that drugs used for general therapeutic purposes, such as the tranquilizers of the meprobamate group, may affect the work capacity or efficiency of normal subjects; (b) that certain drugs, vaguely or specifically referred to as aids to heart function in persons evidencing cardiac insufficiency, may materially alter the maximal working capacity of normal healthy subjects; (c) that the biological effects of the drugs under investigation were of such a nature that their ingestion should be indicated or contra-indicated for persons in certain occupations

such as pilots, motor vehicle operators, or for individuals who might be subjected to extensive physical demands.

Methods and Procedure

Five healthy male subjects in the range from 29 to 54 years participated in one or the other phase of the experimental investigations. Two different testing procedures were employed for studying the effects of various drugs on hemodynamic adjustments to stress: (a) a tilt table test, for the assessment of orthostatic tolerance, and (b) a treadmill test for the determination of the aerobic work capacity and of the quality of the functional adjustments.

Tilt Table Test

The subject assumed a supine position on a horizontal tilt table, with the feet firmly planted against a footboard. Straps were pulled across the hips and across the forelegs, the head was slightly raised on a cushion. After a state of complete relaxation was attained, measurements of blood pressure and heart rate were made twice during each of 5 minutes in the supine position, likewise during a period of 10 minutes (unless syncope intervened) tilted footwards to a 60-degree angle, and during 3 minutes of supine recovery. The pulse rate count was obtained electronically, the blood pressure by the conventional auscultatory method.

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Treadmill Test

The treadmill test consisted of walking at a speed of 91.5 m/min (3.4 m.p.h.) at a grade of 1 per cent during the first minute, at 2, 3, 4, etc., per cent during each of the following minutes. The cardio-vascular response to the increasing metabolic demands was monitored regularly by measuring heart rate and blood pressure by the conventional Korotkoff method during the second half of each minute.⁽¹⁾

The subjects taking part in this study were accustomed to the walking on the treadmill and to all the laboratory procedures. They were in such a state of training condition that repeated but sufficiently spaced control tests elicited the same functional responses. In order to study the effects of a particular drug when taken routinely in several single doses during a 1 - 2 day period, the work capacity tests were terminated at submaximal efforts, at pulse rates of 160 beats per minute. In that way, two or three tests per day were possible without ill effects on the physiological responses due to fatigue.

After satisfactory control patterns had been established, the drug of particular interest was administered orally. The re-test then, was performed after elapse of the time necessary for the drug to become effective. The following drugs were studied: (1) Caffeine and Metrazol (Pentamethylenetretrasol) separately, and combined in a tablet containing .2g Caffeine and .4g Metrazol; (2) Recordil (flavon-7-ethyl oxyacetate), an Italian vasodilator substance,⁽²⁾ in a single dose of 200 mg; (3) Equanil (Meproamate), in the clinical dose of 5 x 400 mg/day, or in single dosages of varying amounts.

RESULTS

Caffeine-Metrazol: Preliminary experimentation with either one of the substances taken by a well-trained subject did not reveal any change in work capacity or in the cardiovascular response pattern to the test work. The combination of both drugs in a single tablet, when absorbed sublingually, had the effect as shown in Figure 1: for any given load during the gradually increasing test work the heart rate was 4 - 8

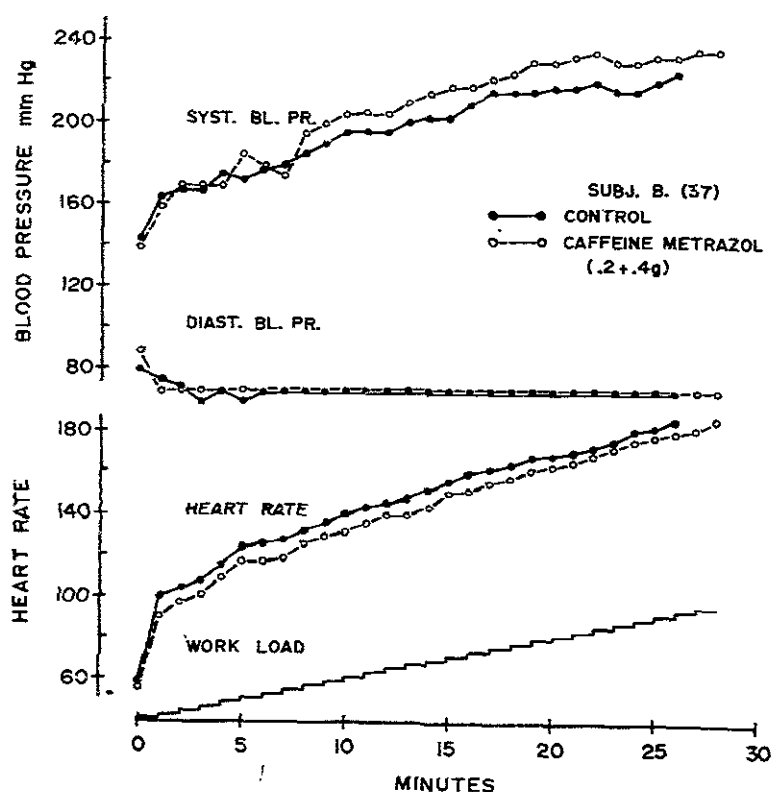


FIGURE 1: Effects of caffeine-metrazol on cardiovascular response to gradually increased energy expenditure.

beats per minute lower than in the control test, the systolic pressure about 6 - 10 mm Hg higher. Work capacity, under the effect of the drug, was improved: the oxygen intake at the crest load was 57.7 ml/kg/min against 54.4 ml/kg in the control test. In both cases the maximum pulse rate was 188 beats per minute, the maximum systolic pressure, however, was 235 mm Hg in the drug experiment compared to 225 mm Hg in the control test.

RECORDIL

Work Capacity Test: Four hours after ingestion of a single dose of 200 mg Recordil the

two participants in this study reached a higher peak load with an unusual subjective ease and with an uncommon lack of straining symptoms. Both subjects exceeded their maximum pulse rate of 162 beats per minute attained in the control tests, one reaching a final rate of 172, the other a rate of 174 beats per minute. In contrast to the previously reported experiment (caffeine-metrazol), in which pulse rate was lower and systolic pressure higher throughout the drug-test, in this series the heart rate was slightly higher most of the time, but both the systolic and diastolic pressure were substantially lower than in the control test (see Figure 2).

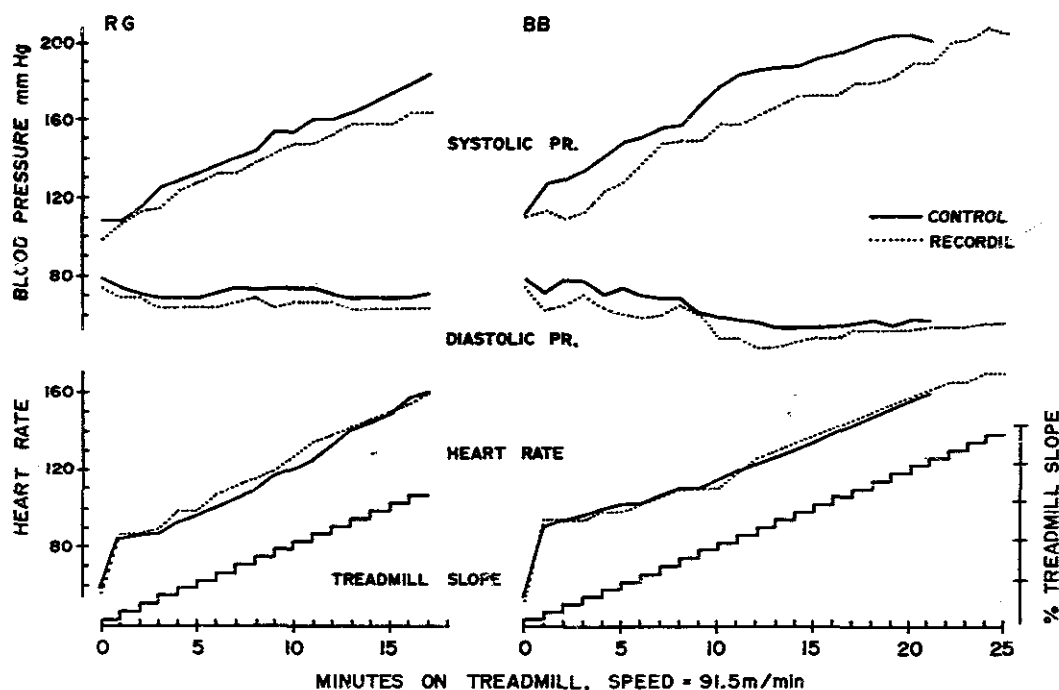


FIGURE 2: Effects of Recordil (flavon-7-ethyl-oxyacetate) on cardio-vascular response to the standard treadmill test.

Tilt Table Test: A general vasodilating effect of the drug was not only observed during the exercise but also in the supine as well as in the tilted position on the tilt table. In one of the subjects tilting caused syncope although the control tests before and 30 hours after drug administration had shown "normal" response pattern (see Figure 3).

Subjectively, the drug made the subjects feel "keyed up" for about 12 hours after ingestion. Approximately 24 hours later both individuals experienced faint anginal sensations of short duration.

EQUANIL

Work Capacity Test: The cardiovascular responses to the treadmill test work was practically unaffected by doses of up to 800 mg. The slight variations observed were similar to

those seen in repeatedly performed control tests. However, with dosages above 1200 mg, either in single or accumulated doses, a typical response pattern appeared to become evident in all subjects: at each given work load the systolic blood pressure was 10-20 mm Hg lower than in the controls while the diastolic blood pressure as well as the heart rate remained essentially unchanged. These responses are illustrated in Figure 4 which shows the relative changes of systolic pressure and heart rate from the control resting values (systolic Bl. Pr. = 112, Heart Rate = 42 beats/min.) for the course of the work capacity test. The product of these relative systolic pressure and pulse rate changes, serving as an indicator of relative changes in cardiac output during exercise (³), appears to disclose a depressing effect of the drug on the cardiac output. Equanil also caused a slight reduction of the systolic blood pressure during

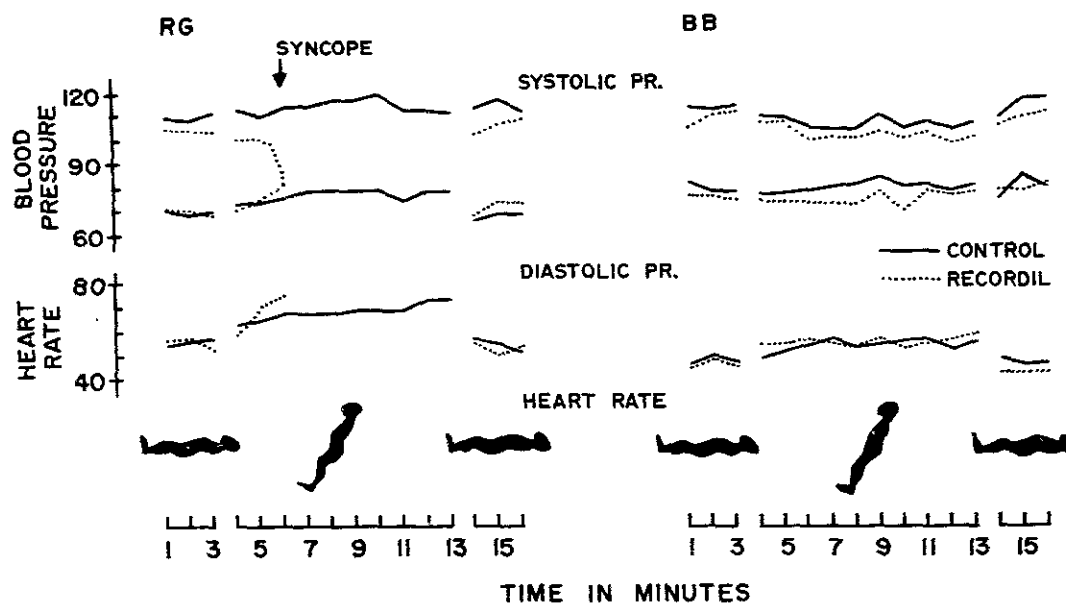


FIGURE 3: Effects of Recordil on cardiovascular response to passive changes of body position (tilting footwards to 60°).

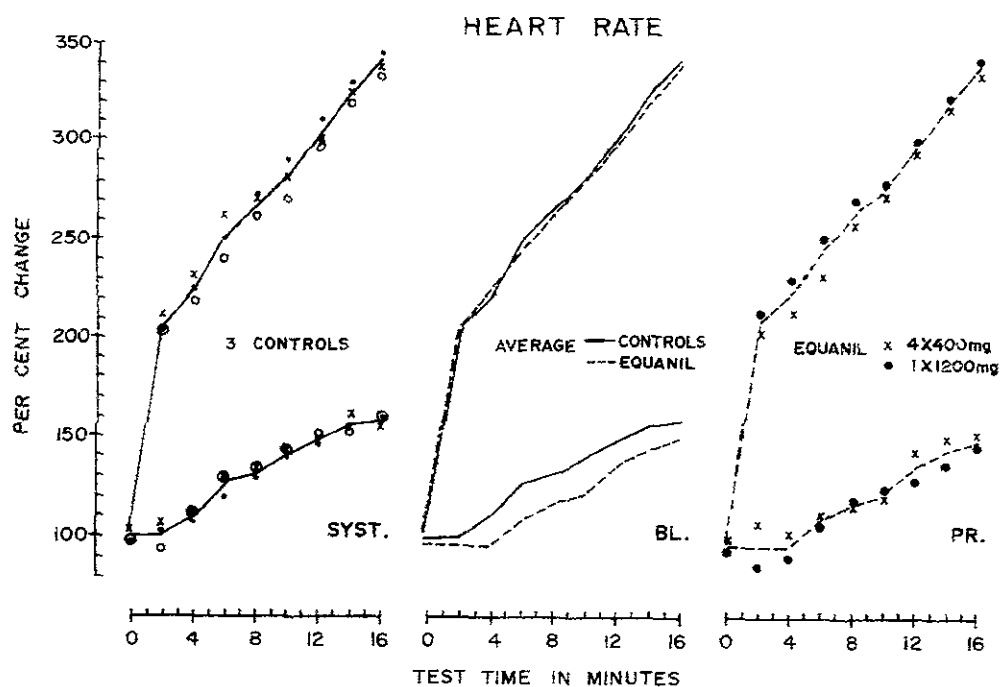


FIGURE 4: Relative changes of heart rate and systolic blood pressure as functional response to gradually increasing energy demands during three control tests and two work capacity tests affected by Equanil. Values are expressed as per cent changes from the resting pulse rate of 40 beats per minute and systolic blood pressure of 112 mm Hg.

relaxed resting conditions accompanied by a slight rise in heart rate while diastolic pressure, on the average, did not change (Table 1). The effect of tilting on blood pressure and heart rate was similar in both the control experiments and when different doses of the drug were ingested. As schematically indicated in Table 2,

tilting did not result in a uniform change of the systolic blood pressure, but in almost all cases a rise of the diastolic pressure and pulse rate did occur. Only after administration of a large single dose of 1200 mg the already lowered resting systolic pressure dropped furthermore upon tilting in the three subjects tested; no syncope was observed.

Subjects	Systolic Bl. Pr. mm Hg				Diastolic Bl. Pr. mm Hg				Heart Rate per minute			
	B	G	P	R	B	G	P	R	B	G	P	R
Control 1	122	110	120	135	74	77	75	71	56	54	48	62
Control 2	120	116	122	125	80	73	75	75	54	58	40	66
Average:	121	113	121	130	77	75	75	73	55	56	44	64
Equanil:												
2 x 400 mg	110	108	115	114	84	86	60	75	58	61	48	66
4-5 x 400 mg	110	107	115	124	72	72	72	80	57	60	40	60
1 x 1200 mg	—	111	102	121	—	75	70	80	—	60	48	62

TABLE 1: The effect of Equanil on blood pressure and heart rate in the supine resting state.

Subjects	Systolic Bl. Pr.				Diast. Bl. Pr.				Heart Rate			
	B	G	P	R	B	G	P	R	B	G	P	R
Control 1	—	=	=	—	=	+	+	+	+	+	+	+
Control 2	—	+	—	+	+	+	+	+	+	+	+	+
Equanil:												
2 x 400 mg	—	=	+	—	+	=	+	+	+	+	+	+
5 x 400 mg	—	=	=	+	=	+	+	+	+	+	+	—
1 x 1200 mg		—	—	—	+	+	+		+	+	+	

TABLE 2: Effects of Equanil on orthostatic tolerance. The direction of changes in blood pressure and heart rate from supine to the tilted position is indicated by — (drop), + (increase), = (no change).

DISCUSSION

Hartwich (⁴) reported beneficial effects from the ingestion of metrazol (cardiazol, pentamethylene tetrazol) on the work capacity of man during the German Himalayan Expedition (1931). According to Graf (⁵), this drug stimulates circulation in states of severe physical fatigue but has no effect on performance under normal conditions. In other experiments in which psychomotor performance was tested, improvement resulted in both cases when a combination of metrazol and caffeine (dose: .2g + .1g) was given. This combination of drugs also had the advantage of not producing the "sagging" after-effects frequently observed after administration of caffeine only.

The increase of aerobic work capacity in the experiment described in Figure 1 must have been the result of improved cardiac dynamics. Since oxygen intakes had remained the same at given work loads, cardiac output was assumed to have remained unchanged too. Therefore, the lowering in heart rate had to be compensated for by an increase in stroke volume. The increase in systolic blood pressure — relatively in the same order of magnitude as the decrease in heart rate — appeared to substantiate such postulation. The increase of the maximum oxygen intake capacity (about 6 per cent above the control test) was a consequence of the greater maximum cardiac output derived from a larger systolic blood volume at the maximum heart rate.

Atzler, Lehmann and Szakall(⁶) have reported on the role of caffeine in carbohydrate and protein metabolism. Undoubtedly, the caffeine-

metrazol combination assists in mobilizing energy from the body stores as was also observed in a field experiment simulating an emergency situation: one of the author's covered in 13 hours a distance of approximately 55 miles in the mountains with a vertical ascent totaling 10,000 feet. This performance required an energy expenditure of about 9,000 kilocalories, of which only 1,000 kcal were supplied by external food intake after 3 hours of work. Since in a well-trained athlete about 400 g of glycogen (~ 1,600 kcal) are available as energy source(⁷) 7,400 kcal of energy must have been supplied from mobilized fat and/or protein stores. Normally, even the trained organism is not capable of working at a very high rate of energy expenditure for a period much longer than 2-3 hours without brief "refueling." In this case, caffeine-metrazol (.2g + .2g) was administered sublingually whenever symptoms of approaching exhaustion called for a slowing down. Then, after awhile the pace picked up again and the improved work capacity lasted from 120 to 60 minutes, decreasing in duration with the accumulation of working time. In repeat dosages a total of 1.0 g caffeine and 1.0 g metrazol was consumed. Despite the deficit in caloric balances and general fatigue recovery was excellent and mountaineering was resumed after an eight-hour rest period.

Flavon-7-Ethyl-oxyacetate (Recordil), when used for the perfusion of the isolated rabbit heart by Setnikar and Zanolini (⁸), caused a marked dilatation of the coronary vessels without changes in amplitude or frequency of the beats. Tartara and Corbetta (⁹) were the first

to use this drug with cardiac patients and found an attenuation of symptoms in four out of five cases of recent myocardial infarct. Strausak, Cuttler and Schmid⁽¹⁰⁾ used Recordil in twenty anginal patients to determine their tolerance to walking on level ground and ascending steps. 60 to 90 mg were given daily for periods up to 16 months with considerable success. Starcich⁽¹¹⁾ prescribed Recordil for more than 25 cardiac patients and emphasized the lack of significant changes in blood pressure and pulse frequency. Epstein⁽¹²⁾ administered Recordil to medical students and faculty members for periods up to 30 days with dosages ranging from 30 - 660 mg daily. He noted slight lowering of hemoglobin levels with large dosages.

The results of this investigation, using a rather large dose of Recordil, indicates that the systolic and diastolic blood pressure were significantly altered during moderate to strenuous physical exercise. Ischemic pains, usually experienced during the later stages of the treadmill test, were less conspicuous in both subjects. The syncope of subject R.G. during tilting points to a marked peripheral vasodilation at rest as well as during work. Mild anginal pain was observed by both subjects about 24 hours after completion of the exercise test. One might speculate that the syndrome arose as an over-compensatory reaction of the coronary vessels after the drug effect had worn off.

The meprobamate drugs, whose general effects have been extensively discussed in the literature⁽¹³⁾, are known to be excellent muscle relaxants, create drowsiness, result in some ataxia, depress certain portions of the EEG records (particularly those nuclei associated with the thalamus). In very tense patients with marked muscle spasms, the drugs have proven quite useful.

The marked drop in the blood pressure after administration of Equanil may only have been the consequence of general muscular relaxation in the resting state, but the persistency of lower blood pressures during work of identical intensity on the treadmill suggests an involvement of the central nervous system. It is not improbable, in light of the generally observed effects of the meprobamate drugs, that the stimuli or lack of stimuli, which became evident in the blood pres-

sure disturbances, had a thalamic-medullary component of interest. The atypical cardiodynamic response was the result of some obscure effect on the vasomotor center. This could conceivably have arisen at some higher level in the central nervous system. There also seemed to be a lack of coordination in the response to sensory input stimuli arising in the muscles under identical working conditions. All subjects reported some motor instability during the early stages of the treadmill test and were, at the outset, disinclined to work. The extent of the vasomotor system depression is perhaps best emphasized by the fact that the "activity", even at the most strenuous level, did not alter the blood pressure response to work. Relatively low blood pressure during work was persistent.

Summary and Conclusions

Using standardized tests on the treadmill and on the tilt table the effects of the following analeptic and tranquilizing drugs on physical working capacity and on orthostatic tolerance were investigated: **Caffeine-Metrazol:** A combination of this drug (in combined dosages of .1g or .2g each) appeared to have potency as antifatiguing medication and ergogenic aid, accomplishing an improvement in cardiac economy by increasing the stroke volume at a lowered heart rate and augmenting maximum cardiac output as well as maximum oxygen intake. Further investigations of this drug are warranted.

Recordil: (Flavon-7-ethyl-oxyacetate): The physical working capacity of the subjects was materially benefited by a dose of 200 mg of this drug taken 4 hours before the exercise test. The absence of localized fatigue and leg pain supports the thesis that peripheral vasodilation is present and effective. The psychic-excitatory effect of Recordil could not be explained except on the basis of some conceivable increased cerebral blood flow mechanism for which there is no evidence at this time.

Equanil: One must not associate disinclination to exertion (a common effect of meprobamates) with potential working capacity of the individual. Although the latter was actually not altered even under massive doses of Equanil, disturbances of the vasomotor system became evident. A real hazard seemed to exist with the

tendency of blood pressures to be depressed, particularly with subjects who naturally possessed low blood pressure. These vasomotor disturbances suggested central nervous system depression, especially of thalamic origin.

The psychic energizing effects of benzedrine and amphetamine compounds are well known but the improvements in working capacity with these substances are more often the result of motivational factors than physiological improvement. Substances which enhance capacity without noticeable psychological side effects are of great value. One must be concerned, however, with the question of "real" improvements in efficacy since these artificial means of unlocking the individual's reserve energy stores may not be subject to the will.

One strongly questions the safety of people engaged in the operation of aircraft or motor vehicles when "sedated" by such drugs as the meprobamates. Blood pressure depressions, as observed, would be aggravated by sudden changes in posture and increased "g" forces during aircraft maneuvers. Serious incidents and fatal accidents may be precipitated by the emotional indifference to suddenly arising problems or as a consequence of delayed circulatory responses during flight maneuvers.

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