

Promethazine Affects Autonomic Cardiovascular Mechanisms Minimally¹

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ABSTRACT

Promethazine hydrochloride, Phenergan, is a phenothiazine derivative with antihistaminic (H₁), sedative, antiemetic, anticholinergic, and antimotion sickness properties. These properties have made promethazine a candidate for use in environments such as microgravity, which provoke emesis and motion sickness. Recently, we evaluated carotid baroreceptor-cardiac reflex responses during two Space Shuttle missions 18 to 20 hr after the 50 mg intramuscular administration of promethazine. Because the effects of promethazine on autonomic cardiovascular mechanisms in general and baroreflex function in particular were not known, we were unable to exclude a possible influence of promethazine on our results. Our purpose was to determine the ground-based effects of promethazine on autonomic cardiovascular control. Because of promethazine's an-

tihistaminic and anticholinergic properties, we expected that a 50-mg intramuscular injection of promethazine would affect sympathetically and vagally mediated cardiovascular mechanisms. Eight healthy young subjects, five men and three women, were studied at rest in recumbency. All reported drowsiness as a result of the promethazine injection; most also reported nervous excitation, dry mouth, and fatigue. Three subjects had significant reactions: two reported excessive anxiety and one reported dizziness. Measurements were performed immediately prior to injection and 3.1 ± 0.1 and 19.5 ± 0.4 hr postinjection. We found no significant effect of promethazine on resting mean R-R interval, arterial pressure, R-R interval power spectra, carotid baroreflex function, and venous plasma catecholamine levels.

Promethazine hydrochloride, Phenergan, is a phenothiazine derivative with antihistaminic (H₁), sedative, antiemetic, anticholinergic, and antimotion sickness properties. As an antihistamine, promethazine interferes with the binding of histamine to the H₁ receptor by competitive antagonism, thereby alleviating histaminic actions such as bronchoconstriction (O'Neill *et al.*, 1985) and intestinal contractions (Roytblat *et al.*, 1991) and enhancing immunosuppressive activity (Rychlik *et al.*, 1988). Promethazine has been used widely during labor (Zimmer *et al.*, 1990), for pediatric sedation (O'Brien *et al.*, 1991), and for premedication (Dodson and Eastley, 1978). One of promethazine's additional premedicant advantages is its antiemetic property, which has been linked to moderate anticholinergic activity (Peroutka and Snyder, 1982). Anticholinergic activity has long been a key feature of antimotion sickness agents (Wood and Graybiel, 1968).

The antiemetic and antimotion sickness properties of

promethazine have made it a candidate for use in environments, such as microgravity (Davis *et al.*, 1988), which provoke these symptoms. The incidence of space motion sickness during the first 44 flights of the Space Shuttle was 73% (Davis *et al.*, 1993). Although numerous medication, medication combinations, and routes of administration have been tested (Graybiel and Lackner, 1987; Wood *et al.*, 1987), intramuscular injection of promethazine is the current treatment of choice for space motion sickness (Wood *et al.*, 1992; Davis *et al.*, 1993) and has been administered on the Space Shuttle since 1989 (Bagian, 1991). Reasons for this choice include promethazine's ability to provide relief after the onset of nausea and vomiting (Graybiel and Lackner, 1987), its long duration of action (Wood *et al.*, 1992), and its apparent lack of significant adverse reactions under the operational conditions of spaceflight (Lackner and Graybiel, 1994).

Although a number of ground-based investigations has addressed the effects of promethazine on performance (Clarke and Nicholson, 1978; Kotzan *et al.*, 1986; Hyman *et al.*, 1988), few have addressed the effects of promethazine on autonomic cardiovascular mechanisms. Those that do exist use animal models (Goldberg *et al.*, 1969; Aronson and Hanno, 1979; Covert *et al.*, 1988) or use promethazine in combination with other medications (Sunahara *et al.*, 1987).

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ABBREVIATIONS: Baroreflex, carotid baroreceptor-cardiac reflex response; STS, Space Transportation System.

To our knowledge, no study has investigated the cardiovascular effects of promethazine alone in humans on the ground or during spaceflight; nonetheless, cardiovascular experiments are performed on the Space Shuttle relatively soon after the administration of intramuscular promethazine.

Recently, we evaluated carotid baroreceptor-cardiac reflex responses (baroreflexes) during two Space Shuttle missions, STS-40 and STS-55 (Space Transportation System), 18 to 20 hr after the 50 mg intramuscular administration of promethazine (Fritsch and Eckberg, 1992; Eckberg *et al.*, 1994). Because the effects of promethazine on autonomic cardiovascular mechanisms in general and baroreflex function in particular were not known, we were unable to exclude a possible influence of promethazine on our results. Our purpose was to determine the ground-based effects of promethazine on autonomic cardiovascular control. Because of promethazine's antihistaminic and anticholinergic properties, we expected that a 50-mg intramuscular injection of promethazine would alter sympathetically and vagally mediated autonomic cardiovascular mechanisms. All measurements were performed at rest in recumbency because this most closely approximated the circumstances during our microgravity measurements.

Methods

Subjects. Eight healthy subjects, five men and three women, whose average age and weight (\pm S.E.) were 25 ± 1 yr (range: 20-32) and 67 ± 4 kg (range: 52-86), were studied at rest in recumbency. Subjects abstained from alcohol, caffeine, and exercise at least 24 hr before and during their participation in this investigation. All three women used oral contraceptives; no other medications were used by any subject. None of the subjects were smokers. This investigation was approved by the human investigation committees of the Hunter Holmes McGuire Department of Veterans Affairs Medical Center and the Medical College of Virginia and was in accordance with the Declaration of Helsinki. All volunteers gave their informed written consent to participate.

Experimental protocol. An interrupted time series experimental design was used. Measurements were made immediately before 50-mg deep intramuscular injections of promethazine (Wyeth Laboratories, Philadelphia, PA) in the hip and 3.1 ± 0.1 and 19.5 ± 0.4 hr postinjection. These postinjection times were chosen for two reasons. First, peak plasma concentration occurs approximately 3 hr after a 50-mg intramuscular injection of promethazine (Schwinghammer *et al.*, 1984). Second, during two recent Space Shuttle flights, we assessed carotid baroreflex function 18 to 20 hr after a 50-mg intramuscular injection of promethazine (Fritsch and Eckberg, 1992; Eckberg *et al.*, 1994). Measurements for each of the three experimental conditions required approximately 45 min to complete and comprised a 10-min acclimation period, a 10-min measurement period during which subjects controlled respiration at a fixed rate and tidal volume, carotid baroreflex measurements, and blood sample collection. Experiments began in the early afternoon at least 2 hr after a meal and concluded the next morning.

During each of the three experimental conditions, we recorded the electrocardiogram with chest leads, integrated tidal volume (Transitime Ultrasonic Breath Analyzer, GHG Medizin-Elektronik, Zurich, Switzerland) with a face mask and three-way valve (Hans Rudolph, Kansas City, MO), abdominal respiratory movements with a bellows connected to a strain-gauge pressure transducer (Gould Inc., Cleveland, OH), manual (sphygmomanometer) and beat-to-beat (Finapres model 2300, Ohmeda, Englewood, CO) arterial pressure, and carotid distending pressure (E-2000 Neck Baro Reflex System, Engineering Development Laboratories, Inc., Newport News, VA) onto FM tape

and electrostatic paper. Control of respiratory rate and tidal volume has been shown to be very important for R-R interval spectral estimation (Brown *et al.*, 1993). Therefore, an auditory signal and a calibrated oscilloscope cued subjects to breathe at a rate of 15 breaths/min (0.25 Hz) at a comfortable, consistent, tidal volume.

Mean R-R interval and R-R interval periodicities. Electrocardiograms, integrated tidal volumes and abdominal respiratory movements were digitized at 1000 samples/sec, respectively (CODAS, Dataq Instruments, Akron, OH). R-R interval and respiratory periodicities were assessed with power spectral analysis techniques. Spectra were derived from R-R interval and respiratory time series with a custom program developed for use with a data analysis software package (DADiSP, DSP Development Co., Cambridge, MA). R-R interval power was measured from fixed respiratory (0.20-0.30 Hz), low (0.05-0.15 Hz), and very low (<0.05 Hz) frequency bandwidths³. Respiratory power was measured to verify that at least 95% of the total respiratory power fell within the fixed respiratory (0.20-0.30 Hz) bandwidth. This step was performed to ensure that respiratory frequency control was adequate. All data met this minimum criterion. In addition, use of fast-Fourier transform methods for power spectral analysis requires that signals be stationary. We did not formally test our data for stationarity but we did perform visual inspections to check for nonstationary trends in the R-R interval data. No data sets were eliminated for nonstationarity.

The technique we used for estimation of R-R interval and respiratory power was based on the Welch algorithm of averaging periodograms (Welch, 1967) implemented according to the method of Rabiner *et al.* (1979). The 588-sec time series of beat-to-beat R-R intervals and respiration were fitted to a cubic spline function, interpolated at 8 Hz to obtain equidistant time intervals, and divided into seven equal overlapping segments. Each segment was detrended, Hanning filtered, and fast-Fourier transformed to its frequency representation. The modified periodograms were averaged to produce the spectrum estimate. The method we used yields a frequency resolution of 0.0017 Hz and a flat response over the frequencies of interest.

Carotid baroreflex function. Vagally mediated carotid baroreceptor-cardiac reflex responses were elicited with pressure changes applied to a neck chamber during held expiration as described previously (Sprenkle *et al.*, 1986). Briefly, a stereotyped pressure sequence was delivered during held expiration as follows: pressure was raised initially to about 40 mmHg for 5 sec. Then, each successive electrocardiographic R-wave triggered a decrement of about 15 mmHg pressure until -65 mmHg was reached. Thus, after an initial compression, carotid sinuses were stretched by a series of neck pressure reductions superimposed on naturally occurring arterial pulses. Seven repetitions of this sequence were performed with each subject over about 15 min. Average R-R interval responses were plotted as functions of average carotid-distending pressures, calculated as systolic pressure minus neck chamber pressures. We did not correct for imperfect transmission of neck chamber pressures to the carotid sheath. An earlier study showed that pressure changes delivered by this equipment and the resultant R-R interval responses are highly reproducible (Eckberg *et al.*, 1992). Baroreflex stimulus-response relations were reduced to the following set of parameters for analysis: range of R-R intervals, maximum slope of the stimulus-response relation, and operational point. The maximum slope of the stimulus-response relation was identified by least squares linear regression analysis of each successive three pairs of data. The oper-

³ In this article, we use the terms "respiratory frequency" to signify R-R interval power between 0.20 and 0.30 Hz, "low frequency" to signify power between 0.05 and 0.15 Hz, and "very low frequency" to signify power below 0.05 Hz (0 Hz excluded). The 0.05 to 0.15 Hz range was chosen to encompass R-R interval frequencies that are considered to reflect baroreflex related vagal and sympathetic nerve traffic to the human heart (Koh *et al.*, 1994). Resting humans also have R-R interval spectral power at lower frequencies (below 0.05 Hz) which may be related to thermoregulation (Kitney, 1987) and fluctuations in peripheral vascular resistance (Akselrod *et al.*, 1985).

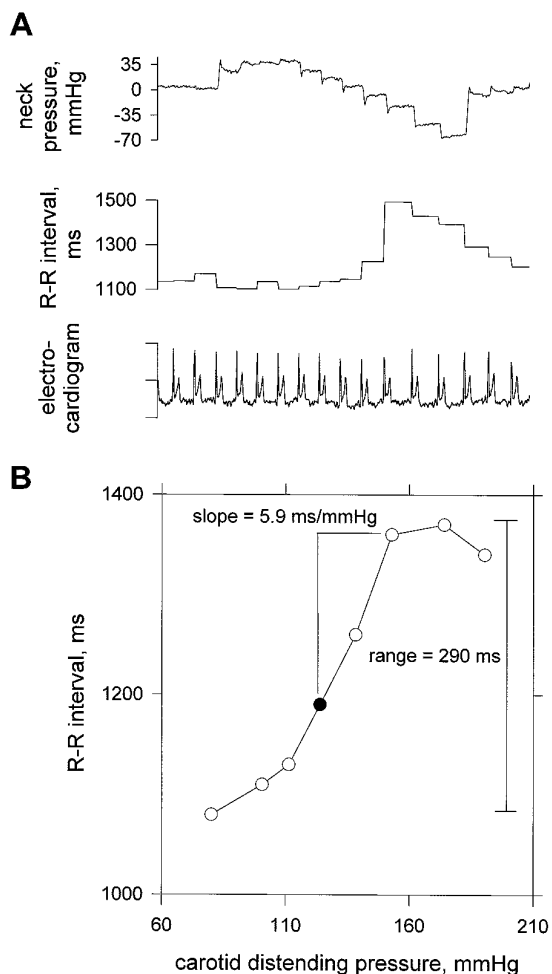


Fig. 1. Original record showing (A) neck pressure profile, electrocardiogram and R-R interval responses of one subject to one stimulus sequence and (B) the averaged response of the subject to seven stimulus sequences. The range, maximum slope, and operational point, ●, are displayed.

ational point is a measure of the amount of buffering capacity below and above baseline systolic pressure. Figure 1 shows (A) an original recording of the neck pressure sequence, a subject's response to this sequence, and (B) the averaged response of that subject to seven stimulus sequences.

Plasma catecholamines. Right antecubital vein blood samples were collected for plasma catecholamine analysis. Blood samples were collected immediately after insertion of butterfly catheters or multiple sample needles. All blood was placed in prechilled evacuated blood collection tubes that contained lithium heparin; collection tubes were then placed on ice. These tubes were centrifuged at 4°C at a rate of 2200 revolutions/min for 12 min. Plasma was then transferred to tubes and frozen at -70°C. Norepinephrine and epinephrine levels were measured with high-performance liquid chromatography as described previously (Eisenhofer *et al.*, 1986). The assays we used detected levels of norepinephrine and epinephrine as low as 6 and 10 pg/ml, respectively, with coefficients of variation of 2.3 and 7.5%.

Statistics. Mean R-R interval, systolic and diastolic pressure, R-R interval spectral power, carotid baroreflex responses, and plasma catecholamine levels were tested for normality with the Kolmogorov-Smirnov test (Lilliefors, 1967). Statistical comparisons on normally distributed data were performed with repeated measures analysis of variance to test for differences between the three experimental conditions. The Wilcoxon signed rank test was used in the few instances that assumptions for parametric tests were violated. Differences

were considered significant when $P \leq .05$; two-tailed tests were used. Sample size estimates for each variable were performed using the minimum difference between group means and standard deviations from the baseline, 3-hr and 18-hr treatment periods from the first seven subjects. For the estimates, alpha was set to 0.05 and power was set to 0.80.

Results

Adverse reactions to promethazine. Several side-effects were reported by the subjects. All reported drowsiness; most also reported nervous excitation, dry mouth, and fatigue. In all but one case, these symptoms disappeared by 19.5 hr postinjection. Three subjects had significant reactions. Two reported excessive anxiety 3.1 hr postinjection. One of these subjects panicked upon placement of the face mask and could not perform 10 min of controlled respiration. A third subject complained of dizziness during both postinjection experimental conditions.

Subject elimination. One subject did not permit postinjection blood samples to be drawn. This same subject had great difficulty with the fit of the mask during all controlled respiration periods. Subsequent analysis of these data revealed results so extreme that their validity were questioned. These aberrant data were tested and met the criteria of an outlier as defined by the maximum normal residual (Snedecor and Cochran, 1989). As a result, we excluded all of this subject's mean R-R interval, arterial pressure, R-R interval periodicity, and carotid baroreflex response data.

Mean R-R interval and arterial pressure. Mean R-R interval and arterial pressure (sphygmomanometer) levels for the three experimental conditions are given in Table 1. No significant differences were found among the three experimental conditions. β -Statistical error was not suspected because sample size estimates were more than 100 for mean R-R interval and diastolic pressure and 31 for systolic pressure.

TABLE 1

Autonomic cardiovascular effects of promethazine

	Preinjection	Postinjection	
		3.1 ± 0.1 hr	19.5 ± 0.4 hr
R-R interval (msec)	1071 ± 69	1065 ± 71	1046 ± 69
Arterial pressure (mmHg)			
Systolic	114 ± 5	109 ± 2	110 ± 2
Diastolic	65 ± 2	63 ± 1	64 ± 2
Spectral power (10 ⁻³ sec ² /mmHg)			
Respiratory frequencies (0.2–0.3 Hz)	4.5 ± 0.9	5.6 ± 1.6	2.6 ± 1.1
Low frequencies (0.05–0.15 Hz)	2.9 ± 0.6	3.6 ± 1.6	2.6 ± 0.6
Very low frequencies (<0.05 Hz)	4.3 ± 0.8	2.7 ± 0.8	6.1 ± 2.9
Carotid baroreflex			
Range (msec)	251 ± 36	246 ± 40	226 ± 28
Maximum slope (msec/mmHg)	5.2 ± 0.9	5.0 ± 1.0	4.9 ± 0.8
Operational point (%)	48 ± 9	50 ± 7	60 ± 10
Catecholamines (µg/ml)			
Norepinephrine	212 ± 26	226 ± 51	198 ± 37
Epinephrine	29 ± 10	14 ± 2	19 ± 6

R-R interval periodicities. R-R interval spectral power from the respiratory (0.20-0.30 Hz), low (0.05 to 0.15 Hz) and very low (<0.05 Hz) frequency bands are given in Table 1 for the preinjection and postinjection conditions. Averaged power spectra are shown in Figure 2. There were no significant differences among experimental conditions for any of the frequency bands. β -Statistical error was not suspected because sample size estimates were more than 100 for each frequency band.

Carotid baroreflex function. Baroreflex stimulus-response relations, shown in Figure 3, represent the average of seven subjects. Baroreflex range, maximum slope, and operational point for preinjection and postinjection conditions are given in Table 1. There were no significant differences among experimental conditions for range, maximum slope or operational point. β -Statistical error was not suspected because sample size estimates were more than 100 for range, maximum slope, and operational point. In addition, significance was not altered by including the results of the eliminated subject.

Plasma catecholamines. Plasma norepinephrine and epinephrine levels are given in Table 1. There were no significant differences among experimental conditions for plasma norepinephrine or plasma epinephrine. β -Statistical error was not suspected because sample size estimates were greater than 100 for plasma norepinephrine and 29 for plasma epinephrine.

Discussion

We studied the effects of promethazine on resting mean R-R interval, arterial pressure, R-R interval periodicities, carotid baroreflex function, and plasma catecholamine levels in humans. The major and surprising finding is that promethazine did not change any of the autonomic cardiovascular functions we measured. However, a number of adverse reactions were reported. Because of the antihistaminic and anticholinergic properties of promethazine, we had expected a significant influence during the peak plasma concentration 3 hr postinjection (Schwinghammer *et al.*, 1984) with minimal influence 18 to 20 hr post-injection. The half-life of a 50 mg intramuscular injection is 9.76 hr (Schwinghammer *et al.*, 1984).

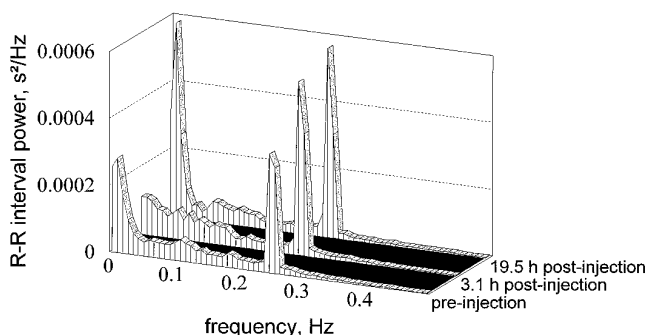


Fig. 2. Average R-R interval power spectral density from the preinjection and 3.1 and 19.5 hr postinjection experimental conditions. All analyses were performed between three defined frequency bands: respiratory (0.20-0.30 Hz); low (0.05-0.15 Hz), and very low (<0.05 Hz)³. Significant differences were not found between any experimental condition in any of the frequency bands.

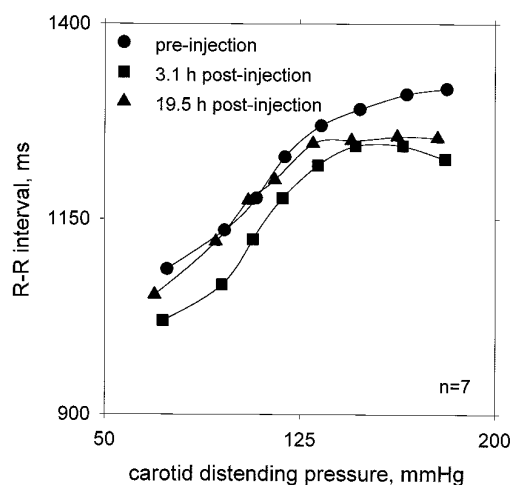


Fig. 3. Average carotid baroreflex stimulus-response relations from preinjection and 3.1 and 19.5 hr postinjection experimental conditions. No significant differences were found in the range, maximum slope, or operational point of the baroreflex.

Reactions to promethazine. All subjects reported drowsiness 3.1 hr postinjection followed by restful sleep that night. Most also reported nervous excitation, dry mouth, and fatigue. In all but one case, these symptoms disappeared by 19.5 hr postinjection. What prompted the greatest concern were the three of eight subjects who had significant reactions: two had excessive anxiety 3.1 hr postinjection and one had dizziness 3.1 and 19.5 hr postinjection. These symptoms were not surprising, such reactions are well established (Schroeder *et al.*, 1985; Wood *et al.*, 1985). However, the large percentage of adverse reactions was unexpected. This should be of concern when promethazine is used in situations where mental and physical performance must be at a high level, such as in the Space Shuttle, even though the reported incidence of sedation and adverse reactions during spaceflight appears to be much less than on earth (Bagian and Ward, 1994). This disparity is especially puzzling because the effective intramuscular dosage of 50 mg for space motion sickness (Graybiel and Lackner, 1987) is more than that recommended clinically for the control of nausea and vomiting (Wood *et al.*, 1992). Altered pharmacokinetics and pharmacodynamics during spaceflight may explain these differences (Derendorf, 1994; Tietze and Putcha, 1994).

Mean R-R interval and arterial pressure. Mean R-R interval and arterial pressure for the preinjection and postinjection conditions were not different, although there was a nonsignificant postinjection drop in systolic pressure (Table 1). In a study of awake resting dogs, promethazine decreased mean R-R interval and increased blood pressure (Goldberg *et al.*, 1969); we had expected similar results.

R-R interval periodicities. Fluctuations of R-R intervals are used widely as indexes of the level of autonomic traffic to the heart. This usage has its origin in a study published by Katona and Jih (1975) that showed that in anesthetized dogs with spontaneous breathing, respiration-related R-R interval periodicities are related linearly to absolute vagal firing rates. R-R interval periodicities are not only related to respiration, but are also related to the rhythmic fluctuations of systemic arterial blood pressure (Koepchen, 1984). There is substantial disagreement regarding mechanisms responsible for fluctuations centered around 0.10 Hz. Some argue that

they are mediated predominately by fluctuations of sympathetic neural traffic (Pagani *et al.*, 1986), although we and others have shown that vagal-cardiac motoneurons, probably mediated by a baroreflex mechanism, play an important role (Pomeranz *et al.*, 1985; Koh *et al.*, 1994; Sleight *et al.*, 1995). R-R interval periodicities of less than 0.05 Hz have been related to thermoregulation (Kitney and Rompelman, 1977) and to local fluctuations in peripheral vascular resistance associated with the regulation of blood flow through vascular beds (Akselrod *et al.*, 1985). The renin-angiotensin system also appears to play a significant role in the control of these local fluctuations (Akselrod *et al.*, 1981).

We expected the antihistaminic activity of promethazine to alter vascular resistance (Roytblat *et al.*, 1991) and the anticholinergic activity of promethazine to reduce vagally mediated baroreflex responses. The result would be altered R-R periodicities or spectral power. Contrary to expectations, the injection of promethazine did not significantly alter respiratory, low, or very low R-R interval spectral power (Table 1; Fig. 2). This lack of influence by promethazine on respiratory and low frequency periodicity indicates that the antihistaminic and anticholinergic activity associated with promethazine has minimal impact on efferent cardiovagal activity and carotid baroreceptor-cardiac reflex responsiveness.

Carotid baroreflex function. The key reason for this investigation was to determine the effects of a 50-mg intramuscular injection of promethazine on vagally mediated carotid baroreceptor-cardiac reflex responsiveness. We recently performed carotid baroreflex measurements during two Space Shuttle missions (STS-40 and STS-55) 18 to 20 hr after the administration of promethazine. To account for the potential influence of promethazine on those results, our study recreated the dosage and timing between administration of promethazine and measurement of the carotid baroreflex that occurred during our Space Shuttle investigations. In addition, we investigated the influence of promethazine on the baroreflex during its peak plasma concentration. Our results indicate that promethazine does not influence carotid baroreflex function. The range, maximum slope, and operational point were not significantly different at any time after the injection of promethazine (Table 1). Thus, it is likely that baroreflex changes measured during spaceflight were not influenced by promethazine.

Plasma catecholamine levels. We did not collect blood for plasma catecholamine analysis originally, but for other purposes. Because of this, blood was collected immediately after needle insertion. The decision to use the stored plasma for catecholamine analysis was supported by the results of Johnson *et al.* (1977) which showed that, after 30 min supine rest, plasma norepinephrine and epinephrine levels from blood collected immediately after venipuncture were not different from blood collected 30 min after venipuncture. In our study, plasma norepinephrine levels were not changed appreciably by promethazine. Although not significant, plasma epinephrine levels were lower 3.1 hr postinjection and had not returned to preinjection values after 19.5 hr (Table 1).

Potential limitations. Because this investigation was performed only at rest in recumbency, it was limited in scope and did not address the effects of promethazine on autonomic cardiovascular mechanisms during other conditions. Stimuli, such as motion sickness, which evoke strong autonomic re-

sponses, may elicit differences related to promethazine (Sunahara *et al.*, 1987).

The design of the investigation, without a control group, placebos, or cross-overs, did not account for the effects of time or circadian variability on the results. All subjects began the investigation in the early afternoon at least 2 hr after a meal. Therefore, the preinjection and 3 hr postinjection measurements were performed in the same afternoon. The 18 to 20 hr postinjection measurements were performed early the next morning. We know that carotid baroreflex responses are reproducible (Eckberg *et al.*, 1992) and do not exhibit circadian variability (Kasting *et al.*, 1987), but we acknowledge that the other measurements might have been influenced. Spectral analyses of R-R interval periodicities are also reproducible (Honziková *et al.*, 1990), especially under the conditions of controlled breathing (Óri *et al.*, 1992). However, R-R interval periodicities do exhibit circadian variability. Hayano *et al.* (1990) reported that in measurements performed during controlled breathing (15 breaths/min) in the supine position the respiratory frequency component was greater in the morning than in the late afternoon but the low frequency component did not change with the time of day. Our 18 hr respiratory frequency component, collected in the morning, was actually the smallest of the three treatment periods; therefore, the possibility exists that circadian variability masked a significant treatment effect.

After completion of our analyses, we addressed the possibility that a β -statistical error occurred and that we might have found statistically significant differences if we had studied more subjects. Sample size estimates for each parameter in Table 1 were performed using the minimum difference between group means and standard deviations from the baseline, 3-hr and 18-hr treatment periods from the first seven subjects. For the estimates, alpha was set to 0.05 and power was set to 0.80. The results of this analysis indicated that the minimum sample size for plasma epinephrine was 29 and for systolic pressure was 31; all others required more than 100 subjects. Thus, it seems highly unlikely that our negative results resulted from β -statistical errors.

In conclusion, we studied the effects of a large intramuscular dose of promethazine on autonomic cardiovascular mechanisms in a group of healthy young men and women. Because of promethazine's antihistaminic and anticholinergic properties, we expected that a 50-mg intramuscular dose would affect sympathetically and vagally mediated cardiovascular autonomic control substantially. We found no significant effect of promethazine on resting mean R-R interval, arterial pressure, R-R interval periodicities, carotid baroreflex function, or plasma catecholamine levels.

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