Effects of N_2O narcosis on breathing and effort sensations during exercise and inspiratory resistive loading

D. M. FOTHERGILL AND N. A. CARLSON
Naval Medical Research Institute, Bethesda, Maryland 20889-5607

Fothergill, D. M., and N. A. Carlson. Effects of N_2O narcosis on breathing and effort sensations during exercise and inspiratory resistive loading. *J. Appl. Physiol.* 81(4): 1562–1571, 1996.—The influence of nitrous oxide (N_2O) narcosis on the responses to exercise and inspiratory resistive loading was studied in thirteen male US Navy divers. Each diver performed an incremental bicycle exercise test at 1 ATA to volitional exhaustion while breathing a 23% N_2O gas mixture and a nonnarcotic gas of the same P_{O_2}, density, and viscosity. The same gas mixtures were used during four subsequent 30-min steady-state submaximal exercise trials in which the subjects breathed the mixtures both with and without an inspiratory resistance (5.5 vs. 1.1 $cmH_2O \cdot s \cdot l^{-1}$ at 1 l/s). Throughout each test, subjective ratings of respiratory effort (RE), leg exertion, and narcosis were obtained with a category-ratio scale. The level of narcosis was rated between slight and moderate for the N_2O mixture but showed great individual variation. Perceived leg exertion and the time to exhaustion were not significantly different with the two breathing mixtures. Heart rate was unaffected by the gas mixture and inspiratory resistance at rest and during steady-state exercise but was significantly lower with the N_2O mixture during incremental exercise ($P < 0.05$). Despite significant increases in inspiratory occlusion pressure (13%; $P < 0.05$), esophageal pressure (12%; $P < 0.001$), expired minute ventilation (4%; $P < 0.01$), and the work rate of breathing (15%; $P < 0.001$) when the subjects breathed the N_2O mixture, RE during both steady-state and incremental exercise was 25% lower with the narcotic gas than with the nonnarcotic mixture ($P < 0.05$). We conclude that the narcotic-mediated changes in ventilation, heart rate, and RE induced by 23% N_2O are not of sufficient magnitude to influence exercise tolerance at surface pressure. Furthermore, the load-compensating respiratory reflexes responsible for maintaining ventilation during resistive breathing are not depressed by N_2O narcosis.

nitrous oxide; respiratory sensation; perceived leg exertion; nitrous oxide narcosis; diving; exercise tolerance; breathing resistance

INERT GAS NARCOSIS is commonly encountered by divers and caisson workers when they breathe compressed air or nitrogen gas mixtures at depths > 30 m of sea water (msw). The signs and symptoms of narcosis include behavioral changes such as euphoria, lightheadedness, neuromuscular incoordination, and amnesia that become more severe as depth increases. Impaired performance at depth is a major safety concern for the working diver and has led to extensive research into the effects of narcosis on most aspects of human performance (4).

One area that has received little attention concerns the effects of narcosis on a diver's responses to exercise and resistive breathing. Such information is vital for understanding the impact of narcosis on work tolerance and diver safety in the hyperbaric environment. Unfortunately, the presence of multiple stressors in the undersea environment (i.e., cold, immersion, ambient pressure, gas density changes) and the change in partial pressures of the constituent gases in the breathing mixtures with dive depth make it difficult to isolate the effects of inert gas narcosis on exercise tolerance.

Although careful selection of diving depths and gas mixtures makes it possible to formulate an experimental design to control for most of these confounding variables (18), it is impossible to simultaneously control for both ambient pressure and gas density when comparing the effects of narcotic and nonnarcotic concentrations of N_2. Because gas density greatly influences the work of breathing and may, at high densities, introduce ventilatory limitations to exercise performance (16, 40), a clear interpretation of the effects of N_2 narcosis on exercise tolerance cannot be obtained with N_2 gas mixtures alone.

To isolate the effects of narcosis from other environmental and physical factors, we used a nitrous oxide (N_2O) gas mixture at surface pressure to simulate N_2 narcosis and an inspiratory resistance to simulate the additional external work of breathing at depth. In studies in which behavioral changes in humans have been compared under compressed air narcosis and N_2O narcosis, N_2O has been found to be ~19 times more narcotic than hyperbaric air (6, 10). Despite differences in narcotic potency, current evidence suggests that the narcotic signs and symptoms produced by N_2O and hyperbaric N_2 are similar (5, 6, 20). Because both hyperbaric N_2 and N_2O are believed to be biologically inert, the generic term commonly used to denote the effects produced by these gasses is inert gas narcosis (21).

The principal aim of the present study was to determine whether mild inert gas narcosis influences exercise tolerance independent of the ventilatory limitations on exercise performance that may exist at depth due to increases in gas density. A further objective was to see whether the ventilatory responses to resistive breathing were impaired by inert gas narcosis in healthy divers. The findings of this study may provide useful information to the diving community regarding the impact of mild inert gas narcosis on the ability of a diver to carry out physically demanding work and offer some insight into the mechanisms underlying respiratory sensation.

MATERIALS AND METHODS

Subjects

Thirteen male US Navy salvage and ship's husbandry divers volunteered for the study. Group mean (±SD) subject characteristics for age, body mass, stature, and vital capacity were 32.5 ± 2.8 yr, 80.9 ± 4.4 kg, 1.78 ± 0.07 m, and 5.94 ± 0.81 liters BTPS, respectively. All subjects gave their informed

consent after receiving a description of the procedures and potential risks involved. Six subjects were ex-smokers, and the remainder had never smoked. All divers had prior experience of N_2 narcosis during air dives to a depth of 50 msw. Ten subjects had experienced the effects of narcosis during simulated air dives to 87 msw. The subjects were instructed to abstain from caffeine, alcohol, nicotine products, and heavy exercise for at least 24 h before each test.

Breathing Mixtures

Two gas mixtures (Puritan Bennett, Linthicum, MD) certified to an accuracy of ±1% relative to the certified value for each component and of identical density (1.17 g/l at body temperature) and viscosity (190 μP at 25°C) were used. The narcotic mixture contained 23% N_2O, 44% O_2, 15% He, and the balance N_2 and was calculated to have a narcotic potency approximately equivalent to that at a compressed air depth of 46 msw (6, 10). The nonnarcotic gas mixture consisted of 44% O_2 with the balance N_2. A P_{O_2} of 0.44 ATA was selected for the breathing mixtures so that the inspired O_2 concentration would be comparable to related experiments performed during actual hyperbaric exposures (18). The breathing mixtures were supplied dry from high-pressure gas cylinders of identical shape and color. The gas cylinders were positioned out of the subjects' view during the trials to ensure that they remained blind to the exposure conditions.

Apparatus

The subjects breathed the experimental gas mixtures via a mouthpiece and low-resistance two-way valve (2700 series, Hans Rudolph, Kansas City, MO) connected to a demand regulator (US Divers Conshelf XIV, Collingswood, NJ) by 0.5 m of 3.5-cm-diam corrugated tubing. During the constant-load submaximal exercise trials, a mechanical iris was located in the inspired side of the breathing circuit to provide the external inspiratory resistance. Manual adjustment of the iris altered the diameter of the orifice through which gas could flow. For the inspiratory-loading trials (high-resistance condition), the orifice was set to 8 mm. This provided a curvilinear resistance (Fig. 1) of 5.5 $cmH_2O \cdot s \cdot l^{-1}$ at a flow rate of 1 l/s and 8.5 $cmH_2O \cdot s \cdot l^{-1}$ at 2 l/s. The inspiratory resistance of the breathing circuit during the unloaded conditions (low resistance), with the iris orifice fully open, was 1.1 $cmH_2O \cdot s \cdot l^{-1}$ at a flow rate of 1 l/s.

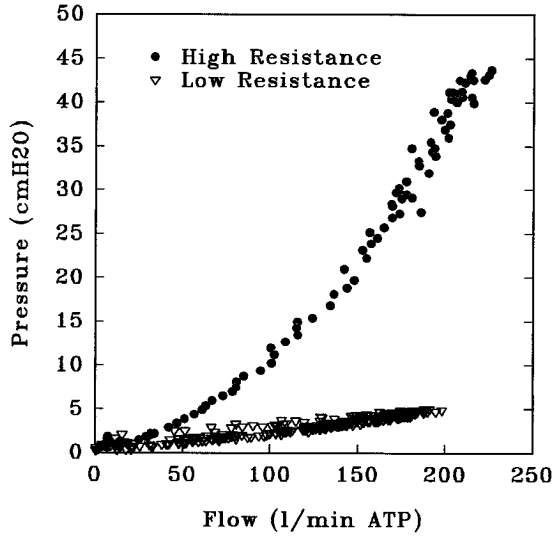

Fig. 1. Pressure-flow characteristics for low- and high-inspiratory resistances.

During the submaximal exercise trials, esophageal pressure (Pes) was measured with a balloon-tipped air-filled catheter attached to a ±50 cmH_2O differential pressure transducer (Validyne Engineering, Northridge, CA). The catheter consisted of 1.4-mm-ID polyethylene tubing, the distal end of which was pierced by small holes and covered with a 12 × 1.5 cm latex balloon filled with 2 ml of air. The balloon was inserted through the nostril and positioned in the lower esophagus ~30 cm from the nares and in a region free from cardiac artifact. Signals from both the Pes and mouth pressure (Pm) transducers were displayed on a two-channel strip-chart recorder (Gould, Cleveland, OH).

Brief inspiratory occlusions were performed at rest and at periodic intervals during the submaximal exercise trials with an inflatable balloon-type inspiratory occlusion pressure valve (series 9300, Hans Rudolph). A pneumatic hand-control switch supplied with He gas at 10 psi was used to inflate and deflate a small balloon on the inspired side of the breathing circuit. All occlusions were initiated during exhalation and released ~0.2 s after the onset of inspiration. During the period of occlusion, the strip-chart paper speed was set at 200 mm/s for the recording of occlusion pressure 100 ms after the onset of inspiration ($P_{0.1}$). During the trials, the subjects wore headphones into which music of their own choice was played. This minimized undue disturbances and ensured that the subjects had no prior warning of the occlusions.

A 386 IBM-clone microcomputer with an analog-to-digital converter (model DAS-16F, Keithley/Metrabyte, Taunton, MA) sampled and stored Pm, Pes, inspired flow, expired volume, and end-tidal P_{CO_2} ($P_{ET_{CO_2}}$) and O_2. Each channel was sampled at 60 Hz, stored on disk, and graphically displayed on-line with custom-designed software. Pm was monitored with a ±50 cmH_2O differential pressure transducer (Validyne Engineering) mounted on a tap proximal to the orifice of the mouthpiece. Gas samples were drawn from a separate tap on the mouthpiece and analyzed for $P_{ET_{CO_2}}$ and end-tidal O_2 with infrared (Beckman LB2, Schiller Park, IL) and paramagnetic (Beckman OM11) gas analyzers, respectively. Inspired flow was measured with a pneumotachometer (model 3813, Hans Rudolph) with a ±2 cmH_2O differential pressure transducer (Validyne Engineering). Expired volumes were measured with a S430A ventilation measuring system (K. L. Engineering; Northridge, CA). Heart rate (HR) was recorded with a three-lead electrocardiogram system (Spacelabs 400, Redmond, WA). The breath-by-breath data were analyzed off-line with in-house software that provides minute averages for peak inspired (P_I,m) and expired Pm (P_E,m), peak-to-peak Pes, $P_{ET_{CO_2}}$, expired minute ventilation ($\dot{V}_E$), tidal volume (V_T), breathing frequency (f), peak inspiratory flow, inspiratory time (T_I), total breath time (T_T), and inspiratory duty cycle (T_I/T_T).

The external work of breathing for inspiration (W_I) was estimated by integrating the inspired portion of the Pm signal with respect to time over a period of 1 min (i.e., $W_I = \int P \cdot dt = P_{I,m} \cdot T_I \cdot f$). In addition, the rate of mechanical work performed across the external inspiratory resistance ($\dot{W}_I$) was calculated from the product of $\int P \cdot dt$ and mean inspiratory flow. This latter quantity has been found to be linearly related to the O_2 cost of breathing (12).

Psychophysical Ratings

Psychophysical perceptions of respiratory effort (RE), leg exertion (LE), and narcosis (N) were rated with the Borg 10-point category-ratio scale (7). The subjects were allowed to

point between any two numbers on which a value halfway between numbers was assigned. For perceptual intensities that were considered "maximal," the subjects were instructed to choose a number > 10. Written instructions on rating each psychophysical variable were provided to the subjects before the investigation and reconfirmed at the start of each trial. For ratings of RE, subjects were instructed to "attend only to the specific sensations in your chest and not to concern yourself with any one factor, such as how fast or how deeply you are breathing, but to try and concentrate on your total feeling of respiratory effort." Perceived LE was defined as the intensity of effort, stress, or discomfort and/or fatigue that the subject felt in his legs while performing exercise at the current workload. To help in rating the perceived level of N, the subjects were instructed in the signs and symptoms of narcosis. However, all subjects had previously experienced compressed air narcosis and were aware of the feelings associated with breathing a narcotic gas. At the end of each exercise trial and after discontinuation of breathing the experimental gas mixture, the subjects were asked to relate their subjective impressions of the trial.

Experimental Design

The experimental protocol was reviewed and approved by the Institution's Committee for the Protection of Human Subjects. Exposures to the experimental breathing mixtures were conducted according to a single-blind design. Double-blind procedures were not implemented because of the need to closely monitor the subject's condition throughout the exercise trials and to provide an appropriate diagnosis in case of a medical emergency.

A total of six exercise tests were performed by each subject under dry conditions with an electromagnetically braked bicycle ergometer (Warren E. Collins, Braintree, MA). The first two tests were performed to maximal capacity while the subjects breathed the narcotic and nonnarcotic gas mixtures. Six subjects conducted the nonnarcotic trials first while the remaining subjects completed the narcotic trials first. Submaximal exercise trials were conducted during the 12-wk period after completion of the last maximal exercise trial. Each subject performed a total of four submaximal exercise trials in which the same narcotic and nonnarcotic gas mixtures were breathed both with and without an inspiratory resistive load (see *Apparatus*). Throughout both the maximal and submaximal exercise tests, the subjects rated their perceived levels of RE, LE, and N. Consecutive trials on an individual were separated by at least 1 wk, and the order of exposure to the experimental gas mixtures and inspiratory-loading conditions was randomly assigned.

Maximal exercise test. Before beginning to exercise, the subjects sat on the bicycle ergometer at rest breathing the test gas for 10 min. During the latter 5 min of the rest period, baseline physiological measurements and psychophysical ratings were taken. The exercise workload began at 50 W and was increased by 50 W every 3 min. When 200 W was reached, workload increments were reduced to 25 W. Pedal rate was maintained at ~70 rpm. Psychophysical ratings were taken during the last 30 s of each workload and at the termination of exercise. HR was recorded at the end of each minute. All other physiological variables were recorded continuously by the computer data-acquisition system. The exercise test was concluded when the subject stopped exercise of his own volition due to fatigue or when the subject was unable to maintain the pedal rate at 70 rpm. The maximal workload achieved was determined with the following formula: peak workload (W_{max}) = W_{com} + (t/180 × W_{inc}), where W_{com} is the last workload completed (in W), t/180 is the fraction of the final 3-min time period completed, and W_{inc} is the final workload increment (in W).

Submaximal exercise test. After 10 min of breathing the experimental gas mixture at rest, the subjects exercised for 10 min at 40% of W_{max}, followed immediately by 20 min at 75% of W_{max}. The subjects were not informed of the exact workloads but were instructed that the low workload would be below and the high workload above 50% of their maximal capacity. To avoid the temptation of subjects to simply repeat their psychophysical ratings of exertion from previous trials, they were informed that the exercise workloads may be different in subsequent trials. Pedal rate was maintained at 70 ± 5 rpm during all trials. Psychophysical ratings of RE, LE, and N were recorded at rest and at 3-min intervals throughout the exercise test. Resting and exercising HRs were obtained immediately after the psychophysical ratings. Occlusion pressure measurements were taken during the 2-min period after the psychophysical ratings. The precise timing of the occlusions was varied at random to avoid anticipatory reactions by the subjects. During the 8th and 25th minutes of exercise, the subjects were instructed to perform a maximal inspiration to determine their inspiratory capacity. Expiratory reserve volume (ERV) was calculated as the difference between vital capacity and inspiratory capacity, with the assumption that vital capacity and total lung capacity do not change significantly between light and moderately heavy exercise (43).

Statistical Analysis

Two-way repeated-measures analysis of variance was used to determine the significance of variability for the psychophysical ratings and physiological responses between the narcotic and nonnarcotic maximal exercise trials during rest and exercise. For the purpose of this analysis, exercise responses for an individual were averaged over the duration of exercise. Comparisons between the narcotic and nonnarcotic trials for exercise duration, psychophysical ratings, and peak HRs obtained during the last minute of exercise were performed with paired t-tests.

For each subject's submaximal exercise trial, mean values were calculated for each of the physiological variables for the rest and low- and high-workload periods. The multiple ratings given for RE, LE, and N during exercise at the low and high workloads were also averaged to provide a mean rating for these variables for each exercise level. Analysis of the psychophysical ratings and physiological responses was then performed with a 2 × 2 × 3 repeated-measures analysis of variance, with the independent variables being breathing mixture (narcotic vs. nonnarcotic), breathing resistance (low vs. high), and workload (rest, 40% W_{max}, and 75% W_{max}). When appropriate, means were compared for significance with Tukey's honestly significant difference post hoc test. A priori significance was set at the 0.05 level for all statistical tests. Data are presented as means ± SE.

Due to an injury sustained in an incident unrelated to the present study, one subject was unable to perform all four of the submaximal exercise tests. To retain a repeated-measures design, data from this latter subject was not used in the statistical analysis.

RESULTS

Maximal Exercise Test

Psychophysical ratings and exercise tolerance. The psychophysical and cardiorespiratory responses at rest and during exercise while the subjects breathed the

narcotic and nonnarcotic gas mixtures are shown in Table 1. Exercise duration (and hence W_{max} attained) was the same for the narcotic [duration 15.9 ± 1.02 (SE) min; workload 232 ± 8.88 W] and nonnarcotic trials (duration 16.0 ± 1.02 min; workload 233 ± 8.88 W; $P > 0.05$). The main reason reported for terminating exercise during both the narcotic and nonnarcotic exercise trials was leg fatigue. During the last minute of exercise, LE was rated as very severe during both maximal exercise trials [LE rating 6.7 ± 0.62 (narcotic) vs. 6.8 ± 0.61 (nonnarcotic); $P > 0.05$] and was unaffected by the gas mixture.

Figure 2 shows the differences in the group mean RE ratings between the narcotic and nonnarcotic exercise trials at each workload up to 225 W. Group mean data obtained for workloads above 225 W are not shown due to the decreasing number of subjects completing the workload. On average, perceived RE was 25% lower during exercise when the subjects breathed the narcotic gas ($P < 0.05$). However, analysis of the RE ratings taken at maximal exercise capacity revealed no significant difference between the narcotic and nonnarcotic trials ($P > 0.05$).

During the narcotic trials, there was no change in the perceived level of N between rest and exercise ($P > 0.05$). However, N ratings showed great individual variation ranging from zero (no narcosis at all) to eight (very severe narcosis). Only one subject reported a N rating > 0 during the nonnarcotic trials.

Ventilatory and HR responses. Average $\dot{V}_E$ at rest and during exercise was 16 and 2% greater, respectively, when the subjects breathed the N_2O gas mixture and resulted in a small but significant decrease in $P_{ET_{CO_2}}$ during the narcotic trials. The increase in $\dot{V}_E$ when the subjects breathed the narcotic gas mixture was predominantly a result of a significant increase in V_T. Post hoc analysis (Tukey's honestly significant difference test) of the significant interaction between gas mixture and workload for V_T ($F_{1,12} = 18.8$; $P < 0.001$) revealed that the increase in V_T under the narcotic conditions was more pronounced at rest than during exercise. $P_{I,m}$, $P_{E,m}$, and T_I/T_T values were not significantly different between the narcotic and nonnarcotic trials ($P > 0.05$).

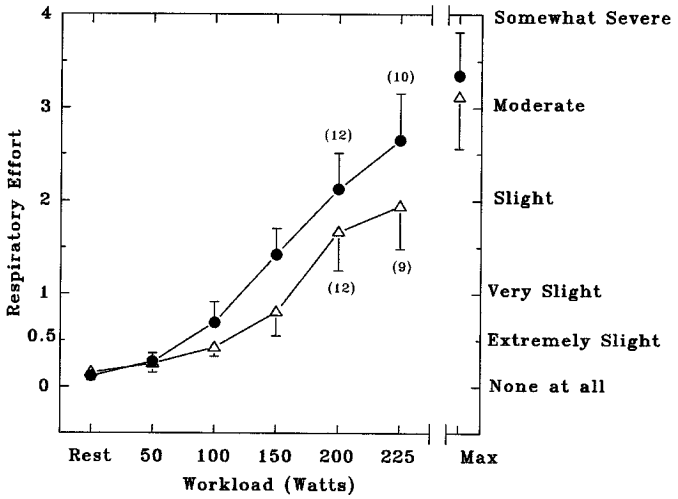

Fig. 2. Mean (±SE) ratings of respiratory effort during progressive incremental exercise test with subjects breathing narcotic (△) and nonnarcotic gas mixtures (●). n = 13 subjects except for no. of subjects in parentheses. Max, rating given for last minute of exercise.

Analysis of variance of the HR responses revealed a significant interaction between gas mixture and workload (i.e., rest vs. exercise; $F_{1,12} = 9.5$; $P < 0.01$). The average resting HR was 76 beats/min during both the narcotic and nonnarcotic trials. However, HR averaged across all exercise workloads was 8 beats/min lower when the subjects breathed the N_2O gas mixture ($P < 0.005$). Peak HRs during the final minute of exercise were also significantly lower when the subjects breathed the narcotic gas (nonnarcotic, 182 ± 2.1 beats/min; narcotic, 178 ± 2.5 beats/min; $P < 0.05$).

Submaximal Exercise Trials

Single-subject observations. Despite exercise workloads being set relative to each individual's maximal capacity, there was considerable intersubject variation in the perceived level of LE and work tolerance. Ratings of LE for the high workload ranged from "slight" to "very severe." Furthermore, one of the subjects was unable to complete the entire 20 min of exercise at the

Table 1. *Psychophysical perceptions of exertion and cardiorespiratory responses while breathing narcotic and nonnarcotic gas mixtures at rest and during maximal exercise test*

	Narcotic Gas Mixture		Nonnarcotic Gas Mixture		
	Rest	Exercise	Rest	Exercise	*P* Value
Respiratory effort	0.15 ± 0.09	1.34 ± 0.25	0.12 ± 0.06	1.79 ± 0.27	0.016*
Leg exertion	0.08 ± 0.05	3.06 ± 0.23	0.00 ± 0.00	3.23 ± 0.28	0.154
Narcosis	2.69 ± 0.33	2.24 ± 0.46	0.00 ± 0.00	0.00 ± 0.00	
$\dot{V}_E$, l/min BTPS	16.6 ± 1.49	55.3 ± 2.31	14.3 ± 1.37	54.3 ± 2.31	0.038*
V_T, liters BTPS	1.62 ± 0.10	2.34 ± 0.10	1.26 ± 0.07	2.36 ± 0.09	0.020*
f, breaths/min	10.5 ± 0.64	22.8 ± 0.93	11.5 ± 0.80	21.9 ± 0.97	0.891
$P_{ET_{CO_2}}$, Torr	34.4 ± 1.72	46.7 ± 0.77	37.2 ± 1.83	48.0 ± 0.93	0.013*
Heart rate, beats/min	75.4 ± 2.95	134.0 ± 3.29	76.5 ± 3.30	142.2 ± 3.06	0.045*
T_I/T_T	0.45 ± 0.02	0.48 ± 0.01	0.45 ± 0.02	0.48 ± 0.01	0.734
$P_{I,m}$, cmH_2O	2.9 ± 0.30	4.1 ± 0.34	2.5 ± 0.16	4.0 ± 0.14	0.564
$P_{E,m}$, cmH_2O	2.8 ± 0.44	6.0 ± 0.46	1.9 ± 0.13	5.7 ± 0.27	0.718

Values are means ± SE for 13 subjects. Values for exercise are means obtained from responses over total duration of exercise test. $\dot{V}_E$, expired minute ventilation; V_T, tidal volume; f, breathing frequency; $P_{ET_{CO_2}}$, end-tidal P_{CO_2}; T_I/T_T, duty cycle; $P_{I,m}$, inspired mouth pressure; $P_{E,m}$, expired mouth pressure. *Significant difference between narcotic and nonnarcotic trials after analysis of variance ($P < 0.05$).

high workload in all trials except for the nonnarcotic low-resistance condition. During the final minute of the aborted trials, this subject rated LE between "severe" and very severe (Borg score of 5–8), and his HR was within 3 beats/min of his peak HR recorded during his maximal exercise trials.

A second subject terminated exercise after completing 6 min of the heavy workload during the narcotic trial with the low-inspiratory resistance. At the termination of exercise, RE was rated as "moderate"; however, ratings for LE and perceived level of N were 10 (extremely severe) and 8, respectively. His HR on terminating exercise was 145 beats/min (82% of his peak HR recorded during the maximal exercise trials). During the posttrial debriefing, he reported having felt nauseous, dizzy, and sleepy and said he had a "hard time concentrating on keeping the rpm's up" while exercising. On a subsequent trial, in which the narcotic gas was breathed with the high-inspiratory resistance, he was able to complete the full exercise duration despite experiencing the same narcotic symptoms, although to a lesser degree (N rating 5.5).

Psychophysical ratings. Figure 3 shows the combined effects of gas mixture, breathing resistance, and workload level on the ratings of RE, LE, and N. Based on the group responses for LE shown in Fig. 3*B*, the low-exercise workload was considered as very slight (mean rating 0.9) and the high workload as between moderate and "somewhat severe" (mean rating 3.7). The mean rating for perceived level of N increased from 0.04 ("none at all") to 2.6 ("light" to moderate when the narcotic gas was substituted for the nonnarcotic gas mixture; $F_{1,11} = 22.18$; $P < 0.001$) and was not significantly affected by breathing resistance or workload. There was no difference in perceived LE between the narcotic and nonnarcotic trials; however, perceived RE ratings were, on average, 24% lower when the subjects breathed the narcotic gas ($F_{1,11} = 7.92$; $P < 0.05$; Fig. 3*A*). RE ratings were 31% greater during the inspiratory-loading trials compared with the unloaded trials ($F_{1,11} = 10.28$; $P < 0.01$). There were no significant two-way interactions between breathing mixture, breathing resistance, and workload for any of the psychophysical responses.

Respiratory responses to exercise and inspiratory resistive loading. Group means (±SE) for HR and respiratory responses at rest and at each workload when the subjects breathed the narcotic and nonnarcotic gas mixtures under the different inspiratory-loading conditions are shown in Table 2. The pattern of respiratory responses to inspiratory resistive loading was typical of those reported in other studies on normal subjects (2, 25, 26). Significant increases in Pes (39%; $P < 0.001$), $P_{0.1}$ (20%; $P < 0.005$), $P_{I,m}$ (209%; $P < 0.001$), T_I/T_T (14%; $P < 0.001$), and W_I (243%; $P < 0.001$) and a 20% decrease in peak inspiratory flow occurred when the subjects were exposed to the inspiratory resistive-loading conditions ($P < 0.001$).

Due to the nature of the inspiratory resistances used (Fig. 1), the low flow rates at rest resulted in minimal differences in inspiratory resistance between the loaded and unloaded conditions. However, because $\dot{V}_E$ and flow rate increased in response to the increase in workload, the difference in breathing resistance between the loaded and unloaded conditions became much more pronounced during exercise. This resulted in significant interactions

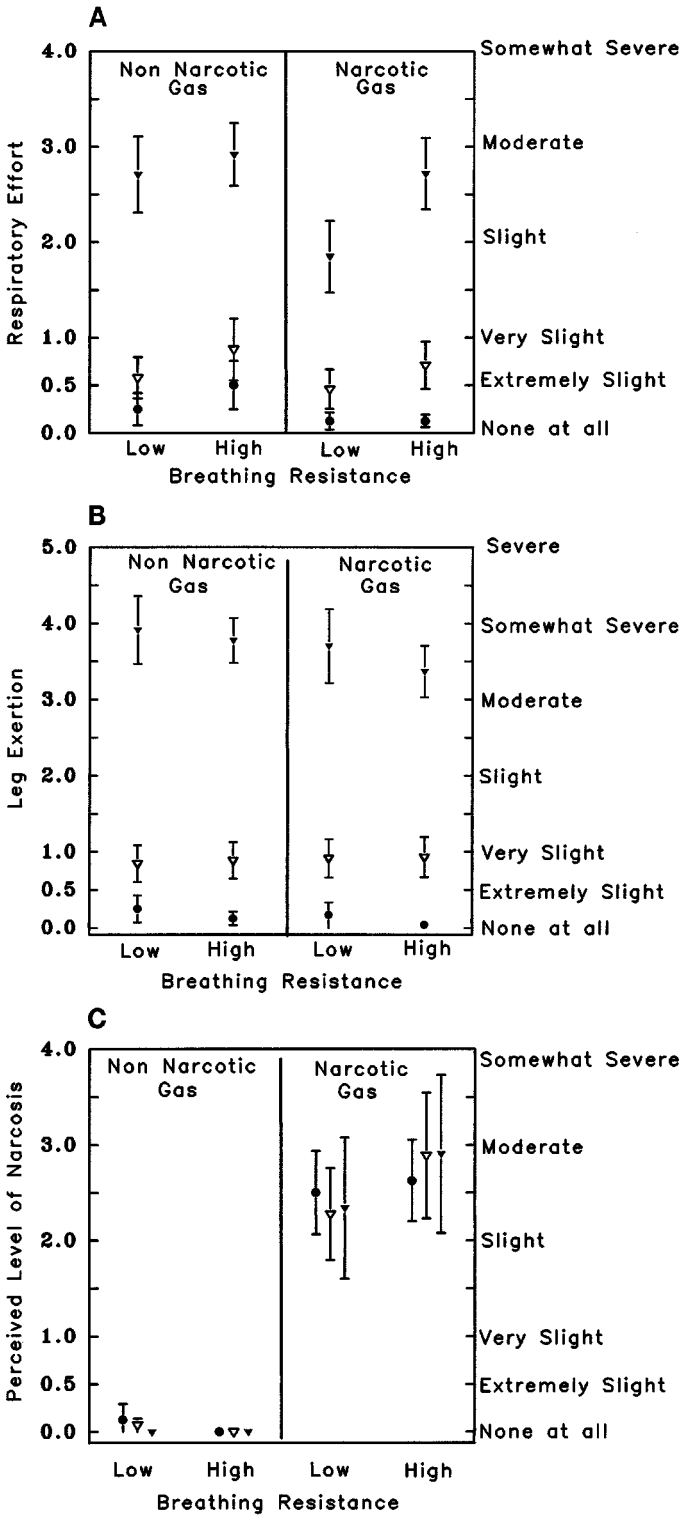

Fig. 3. Psychophysical perceptions of respiratory effort (*A*), leg exertion (*B*), and narcosis (*C*) at rest (●) and during constant-load cycle exercise at workloads of 40 (▽) and 75% maximal workload (▼) with subjects breathing narcotic and nonnarcotic gas mixtures under low and high inspiratory-loaded conditions. Values are means ± SE for 12 subjects.

Table 2. *Heart rate and respiratory responses at rest and during constant-load exercise while breathing narcotic and nonnarcotic gas mixtures both with and without an inspiratory load*

	Nonnarcotic Gas Mixture						Narcotic Gas Mixture					
	Breathing resistance						Breathing resistance					
	Low			High			Low			High		
	Rest	40% W_{max}	75% W_{max}	Rest	40% W_{max}	75% W_{max}	Rest	40% W_{max}	75% W_{max}	Rest	40% W_{max}	75% W_{max}
$\dot{V}_E$, l/min BTPS	11.7	34.4	65.6	11.1	32.2	62.7	13.4	36.3	69.0	12.1	32.8	62.6
	(0.84)	(1.13)	(2.54)	(0.66)	(1.39)	(3.16)	(0.90)	(1.31)	(2.79)	(0.98)	(1.77)	(2.40)
V_T, liters BTPS	0.95	1.89	2.68	0.98	1.91	2.81	1.16	1.89	2.60	1.21	1.94	2.66
	(0.054)	(0.060)	(0.089)	(0.047)	(0.075)	(0.132)	(0.075)	(0.083)	(0.111)	(0.097)	(0.118)	(0.117)
f, breaths/min	12.5	18.6	24.6	11.5	16.9	22.5	11.8	19.5	26.9	10.5	17.2	23.8
	(0.69)	(0.75)	(0.99)	(0.61)	(0.56)	(0.68)	(0.95)	(1.00)	(1.20)	(0.92)	(0.76)	(0.89)
$P_{ET_{CO_2}}$, Torr	38.8	47.2	47.4	38.9	49.0	49.5	36.7	46.3	46.5	38.4	47.3	49.1
	(1.05)	(0.88)	(1.08)	(1.27)	(0.83)	(1.20)	(1.41)	(0.83)	(1.20)	(1.66)	(0.83)	(1.07)
Heart rate, beats/min	75.9	109.6	154.0	70.9	106.4	153.0	73.1	110.9	155.3	73.8	107.6	153.0
	(4.1)	(3.2)	(2.3)	(1.9)	(3.7)	(3.4)	(2.8)	(2.9)	(4.1)	(4.1)	(4.0)	(4.7)
T_I/T_T	0.39	0.46	0.47	0.46	0.51	0.54	0.42	0.46	0.46	0.44	0.51	0.54
	(0.015)	(0.010)	(0.007)	(0.011)	(0.012)	(0.007)	(0.022)	(0.008)	(0.009)	(0.014)	(0.007)	(0.008)
W_I, J	0.51	0.99	1.55	1.03	3.09	6.63	0.64	1.12	1.70	1.23	3.25	7.16
	(0.050)	(0.064)	(0.789)	(0.069)	(0.170)	(0.265)	(0.046)	(0.046)	(0.097)	(0.107)	(0.189)	(0.315)
$\dot{W}_I$, J/min	1.68	7.93	22.34	2.84	20.55	76.28	2.35	9.22	25.92	3.80	22.74	86.79
	(0.24)	(0.56)	(1.75)	(0.34)	(1.80)	(5.54)	(0.20)	(0.53)	(2.28)	(0.54)	(2.11)	(5.95)
$P_{I,m}$, cmH_2O	−2.1	−3.2	−4.8	−4.2	−9.4	−18.4	−2.7	−3.6	−5.6	−5.1	−10.2	−20.3
	(0.15)	(0.16)	(0.24)	(0.36)	(0.51)	(0.75)	(0.18)	(0.14)	(0.23)	(0.43)	(0.60)	(0.84)
$P_{E,m}$, cmH_2O	1.8	3.5	6.6	1.8	3.5	6.9	2.3	3.8	7.4	2.0	3.8	7.6
	(0.11)	(0.14)	(0.30)	(0.11)	(0.18)	(0.34)	(0.22)	(0.17)	(0.35)	(0.19)	(0.21)	(0.41)
$P_{0.1}$, cmH_2O	−0.89	−4.26	−9.71	−0.95	−5.13	−13.32	−1.22	−5.11	−11.83	−1.12	−4.95	−14.38
	(0.176)	(0.400)	(0.563)	(0.226)	(0.624)	(1.126)	(0.262)	(0.54)	(0.964)	(0.208)	(0.489)	(1.496)
Pes, cmH_2O	7.7	14.6	25.2	9.8	19.0	36.2	10.2	15.3	27.0	11.4	21.6	41.0
	(0.44)	(0.42)	(0.95)	(0.49)	(0.75)	(0.94)	(0.76)	(0.64)	(1.31)	(0.86)	(1.02)	(1.63)
Peak inspired flow, l/min BTPS	62.5	122.9	196.3	54.4	102.0	158.5	77.6	131.0	214.4	61.1	104.5	165.5
	(3.73)	(4.32)	(6.65)	(3.78)	(4.29)	(4.27)	(5.75)	(4.86)	(6.88)	(4.36)	(4.11)	(3.56)

Values are means for 12 subjects; nos. in parentheses, SE. W_{max}, peak workload; W_I, external work of breathing for inspiration; $\dot{W}_I$, rate of mechanical work performed across external inspiratory resistance; $P_{0.1}$, occlusion pressure 0.1 s after onset of inspiration; Pes, esophageal pressure.

between breathing resistance and workload for the pressure-based measurements. When compared with the unloaded trials, the W_I during the loaded trials was twice as great at rest ($P < 0.005$), three times greater during light exercise ($P < 0.0005$), and four times greater during heavy exercise ($P < 0.0005$). A similar pattern of results was observed for $\dot{W}_I$. The inspiratory resistance resulted in increases of 66 ($P > 0.05$), 150 ($P < 0.0005$), and 238% ($P < 0.0005$) in W_I at rest and during the low and high workloads, respectively.

Under the inspiratory-loading conditions, $\dot{V}_E$ decreased by 7% ($P < 0.001$), resulting in a significant increase in $P_{ET_{CO_2}}$ (3.5%; $P < 0.05$). The decrease in $\dot{V}_E$ was predominantly a result of a decrease in f because there was no significant change in V_T. Peak $P_{E,m}$ and HR values were unaffected by changes in inspiratory resistance. HRs at the low and high workloads were 60 and 85%, respectively, of the peak HRs recorded during the final minute of the maximal exercise trials.

Effects of N_2O on HR and respiratory variables. Analysis of variance results for the main effect of gas mixture revealed a small but significant increase in $\dot{V}_E$ (4%; $P < 0.01$), with a concomitant decrease in $P_{ET_{CO_2}}$ (−2%; $P < 0.05$), during the narcotic trials. The increase in $\dot{V}_E$ was accompanied by significant increases in $P_{0.1}$ (12%; $P < 0.05$), Pes (12%; $P < 0.001$), $P_{I,m}$ (12%; $P < 0.005$), $P_{E,m}$ (11%; $P < 0.005$), peak inspired flow (8%; $P < 0.005$), W_I (9%; $P < 0.05$), and $\dot{W}_I$ (15%; $P < 0.005$). T_I/T_T, HR, and ERV were not significantly different between breathing mixtures.

Although the statistical analysis revealed a nonsignificant main effect of gas mixture on V_T and f, there were significant interactions between breathing mixture and workload for these variables. Post hoc analysis revealed that, at rest, V_T was significantly greater when the subjects breathed the narcotic mixture than when they breathed the nonnarcotic gas ($P < 0.005$). However, during constant-load exercise, V_T was not significantly different between the gas mixture conditions. In contrast, f was significantly greater during heavy exercise with the narcotic gas than with the nonnarcotic gas ($P < 0.001$) but was not significantly different between the gas mixtures at rest or during light exercise.

DISCUSSION

Influence of Inert Gas Narcosis on Exercise Tolerance and HR

This study showed that mild inert gas narcosis does not significantly influence work tolerance when exercise is limited by leg fatigue. Comparable times to exhaustion observed for the narcotic and nonnarcotic maximal exercise trials imply that the time of onset of muscle fatigue does not change significantly when the

subjects breathed N_2O. This is in agreement with the findings of Parkhouse et al. (35), who showed that the time of onset of fatigue in the forearm muscles (induced by ischemia) was unaffected by subjects breathing gas mixtures containing up to 40% N_2O. Despite having little effect on exercise tolerance, the N_2O gas mixture did exhibit small but consistent effects on ventilation and the perception of RE. Furthermore, HRs were lower with the N_2O gas mixture during the progressive incremental test but were unaffected by the gas mixture at rest and during steady-state submaximal exercise.

It is unclear what underlying mechanism was responsible for the attenuated HR response during the maximal exercise test with the N_2O gas mixture. One possibility is that the narcosis interfered with the central feedforward control of HR. From the behavioral literature, it is well known that inert gas narcosis slows central nervous system processing (20). It is therefore not unreasonable to expect that narcosis also slows central nervous system integration of neural information important in affecting cardiovascular control mechanisms and that this impairment results in a delayed HR response to step changes in work intensity. A second possibility is that inert gas narcosis may have affected reflex control of HR because it has been shown recently that 40% N_2O attenuates baroreflex-mediated tachycardia in humans subjected to pharmacological reductions in blood pressure (14).

One of the more consistent effects of the narcotic gas mixture was that it acted as a weak ventilatory stimulant while at the same time reducing the perception of RE during both loaded and unloaded breathing. Because the level of inspiratory resistive loading did not impact exercise tolerance at the workloads investigated, we cannot discount the possibility that inert gas narcosis may affect exercise tolerance under diving conditions where exercise is frequently limited by respiratory factors (16, 40). Indeed, several studies have suggested that mild N_2 narcosis may actually enhance exercise tolerance at depth (11, 18).

Possible Mechanisms for the Changes in Respiratory Sensation With Inert Gas Narcosis

Despite the many physiological correlates associated with psychophysical measures of breathlessness or dyspnea (1, 3, 15, 28, 30, 34, 38), the precise neurophysiological mechanism by which respiratory sensations are perceived remains uncertain. Currently, it is believed that afferent information from various respiratory receptors provides predominantly qualitative information for respiratory sensation, whereas conscious awareness of outgoing motor commands (i.e., the sum of all nervous traffic) to the muscles involved in the act of breathing provides us with quantitative information regarding the sense of respiratory effort (1, 15, 29).

The findings of the present study support the role of a significant behavioral component in respiratory sensation. The reduced perception of RE under the narcotic conditions is clearly in the opposite direction than would be expected from the observed changes in $\dot{V}_E$, Pes, $P_{0.1}$, and $\dot{W}_I$. The increase in these respiratory variables when the subjects breathed the narcotic gas implies that the intensity of the outgoing motor command to the respiratory muscles was greater than that during the nonnarcotic trials. Nonetheless, perceptions of RE were lower with the N_2O mixture. This suggests that inert gas narcosis may interfere with either central processing of the efferent copy of the outgoing motor command (i.e., central collateral discharge) or the perception of afferent information from the respiratory system.

To understand the nature of perception and information processing, behavioral models of central processing have been utilized by several authors. Rejeski (36) used the "parallel processing model of pain" described by Leventhal and Everhart (32) to demonstrate that the nature of perception is an active process rather than a passive one. The fundamental premise of this model is that the sensory cues associated with RE and perceived exertion can be manipulated before they reach the motor cortex. According to the model, the amount of sensory stimulation perceived may be modulated by the individuals "focal awareness" or proportion of potential stimuli to which the individual attends. Thus inert gas narcosis may have reduced the perception of RE by changing focal awareness (i.e., decreasing the amount of attention paid to the available sensory stimuli). However, because LE responses were not similarly affected, it seems likely that factors other than a change in focal awareness were responsible for the lower RE ratings under narcosis.

More recently, Fowler and co-workers (20, 21) introduced the slowed-processing model as a theoretical framework for the analysis of the effects of inert gas narcosis in humans. According to this model, inert gas narcosis may influence cognitive performance through disruption of structural (e.g., perceptual processing), functional (e.g., level of arousal or activation), or strategic variables (e.g., distribution of attention, decision criteria) either alone or in combination (20). With the use of this model, most of the performance decrements under narcosis have been attributed to a slowing of information processing due to decreases in arousal and alterations in strategic variables (20).

Within the design of the present study, it was not possible to determine whether the lower RE ratings under narcosis were due to decreases in cognitive arousal, changes in decision criteria, alterations in perception or attention, or some combination of these elements. However, some insight into the effects of N_2O narcosis on these factors has been provided by Chapman et al. (9). They used methodology based on a signal-detection theory to assess the analgesic effect of 33% N_2O. Their results demonstrated that N_2O reduces sensitivity to heat and painful stimuli and also induces a response bias, resulting in individuals less willing to report pain under the influence of narcosis than under control conditions.

Although the findings of Chapman et al. (9) suggest that response bias may be one possible explanation for the lower RE ratings with N_2O narcosis, they also point

to the possibility that there may have been narcotic-induced changes in perceptual sensitivity to respiratory stimuli in our subjects. If response bias was the sole cause of the lower RE ratings with N_2O narcosis, one would expect that similar effects would also show up in the LE response, which was not the case. This suggests that perceptual sensitivity to respiratory stimuli may have been reduced by N_2O narcosis. Alternatively, it could be that the sensory cues, or central processing of information associated with integrating information about the activity in the leg muscles/joints, are much less susceptible to the influence of N_2O narcosis than those sensory cues and neural systems involved in the perception of respiratory sensation.

Influence of Inert Gas Narcosis on Ventilation

The small but significant increase in $\dot{V}_E$ and concomitant reduction in $P_{ET_{CO_2}}$ under N_2O narcosis found in the present study has also been reported by others (8, 37, 39). In anesthetized cats, the increase in $\dot{V}_E$ has been attributed to stimulation of the pulmonary stretch receptors by N_2O (41). These authors suggested that this sensitization shortens inspiratory and expiratory half-times, thereby increasing f and decreasing V_T. The net result is a modest increase in ventilation (27).

In contrast to the findings of Witteridge and Bulbring (41), the present study found that the increase in resting ventilation when the subjects breathed N_2O was associated with increases in V_T rather than in respiratory rate. It was only during exercise at the high workload that significantly higher respiratory frequencies were encountered when the subjects breathed the N_2O gas mixture. These findings most likely reflect the complex interaction that occurs between the effects of exercise and N_2O on ventilatory control mechanisms and the possible influence of narcosis on the behavioral control of respiration.

The larger $P_{0.1}$ values with no change in ERV during the narcotic trials suggest that N_2O has a stimulating effect on central inspiratory activity (CIA). Similar changes in CIA have also been reported in subjects breathing hyperbaric air (33). Although it is difficult to isolate the changes in CIA associated with N_2 narcosis from the increase in CIA brought about by the elevated flow resistance at depth, there is some evidence that N_2 narcosis may increase respiratory activity independent of the ambient pressure and gas density (22). Although both N_2 and N_2O narcosis seem to increase respiratory activity, it is uncertain whether the same mechanism is responsible for these changes. In the present study, the stimulatory effect of inert gas narcosis on respiration is relatively weak and insufficient to return ventilation to control levels when faced with the additional work of resistive breathing. From a practical standpoint, this suggests a very limited benefit of breathing a narcotic gas mixture to offset the hypoventilation and subsequent CO_2 retention associated with breathing high-density gas mixtures at depth.

Our data also show that steady-state compensation to an added inspiratory resistance in healthy male divers is not decreased when they breathed 23% N_2O. This supports the findings of other investigators (39, 42) who have found that the load-compensating respiratory reflexes important in maintaining ventilation during inspiratory resistive loading are not impaired by breathing mixtures containing up to 50% N_2O. Moreover, in a recent study (13) in which the effects of 20% N_2O on the ventilatory responses to hypercapnia were studied in five subjects, it was concluded that this subanesthetic concentration of N_2O did not affect the peripheral chemoreflex loop.

Individual Susceptibility to Narcosis and the Effect of CO_2 Retention on Respiratory Sensation

Individual reactions to the level of narcosis induced by the 23% N_2O mixture demonstrated that there is considerable variation among subjects in their susceptibility to inert gas narcosis. In one case, the level of narcosis was sufficient to result in termination of one of the exercise tests. Although group analysis showed no effect of narcosis on exercise performance, there are clearly some individuals who are especially sensitive to inert gas narcosis and for whom physical performance capacity may be severely compromised by uncoordination or other narcotic-induced symptoms.

In the diving environment, the intensity of narcotic symptoms experienced by an individual may be augmented by raised levels of CO_2 (19, 23, 31). As shown in this study and by others (17, 24), most divers, when exposed to an increase in breathing resistance, tend to adopt a breathing pattern that reduces their respiratory pressures (and hence presumably RE) at the expense of a significant hypoventilation and subsequent CO_2 retention. Although in the present study the subjective ratings for narcosis did not change between conditions of high and low CO_2 retention (i.e., high and low breathing resistances), previous studies (19, 23) have shown that $P_{ET_{CO_2}}$ concentrations at levels similar to those observed during the inspiratory-loading trials can lead to significant decrements on sensitive tests of cognitive performance. These CO_2-induced impairments in performance are known to be additive on the cognitive impairments induced by inert gas narcosis (18, 23). It is therefore likely that with high levels of CO_2 retention, the perceptual processes involved in respiratory sensation may be further influenced by the effects of CO_2 narcosis.

Concluding Remarks

The role of subjective sensations in diver safety should not be underestimated. Extreme levels of respiratory effort resulting in dyspnea may serve as an important warning mechanism to "back off" before incapacitation or significant physiological embarrassment and possible damage occurs. Any factor that impairs the ability of a diver to perceive these sensations, whether it be an unfamiliarity with the significance of the sensations, an effect of inert gas narcosis on perception and cognitive processes, or a combination of these factors, puts the diver at an increased risk of a fatal occurrence. If inexperience is a predominating

factor, it raises the question of whether divers can be trained to monitor and improve awareness of their subjective sensations to prevent the development of life-threatening situations.

Ultimately, the main concern is that the diver should be able to perform underwater tasks without significantly compromising safety or performance. By isolating the effects of narcosis from other environmental factors, this study provides a better understanding of the influence of inert gas narcosis on a diver's perception of his or her physical status and ability to conduct physically demanding work. When applying this knowledge, it should be borne in mind that other factors such as the P_{O_2} of the breathing mixture, CO_2 retention, and individual susceptibility to narcosis can markedly influence narcotic intensity.

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Address for reprint requests: D. M. Fothergill, CODE 0534, Naval Medical Research Institute, 8901 Wisconsin Ave., Bethesda, MD 20889-5607 (Email: fothergill@piggy.nmri.nnmc.navy.mil).

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