Arterial baroreflex control during mild-to-moderate nitrous oxide narcosis

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Östlund A, Sundblad P, Demetriades AK, Linnarsson D. Arterial baroreflex control during mild-to-moderate nitrous oxide narcosis. Undersea Hyper Med 1999; 26(1):15–20.—We hypothesized that light-to-moderate inert gas narcosis might play a role in bradycardia in divers by altering sensitivity or response dynamics of arterial baroreflexes. Carotid-cardiac and carotid-mean arterial pressure (MAP) baroreflex response curves were generated by applying multiple levels of neck pressure and suction. Seven healthy volunteers were studied during air breathing (control) and during inhalation of 39% nitrous oxide (N_2O). Baseline (pre-stimulus) heart rate (HR) and MAP were not altered by N_2O. Range, threshold level, saturation level, and delay of responses did not differ between conditions. For hypertensive stimuli, sensitivity of responses did not differ between air control and N_2O inhalation, but for hypotensive stimuli, maximal response gain for HR tended to be reduced with N_2O inhalation ($P = 0.054$). Our results speak against inert gas narcosis as a primary mechanism for hyperbaric bradycardia, but it remains possible that an attenuation of tachycardic responses to hypotensive stimuli plays a role.

carotid baroreceptors, heart rate, blood pressure, neck suction, nitrous oxide

Bradycardia is commonly observed in a hyperbaric environment during both rest and exercise (1,2). With hyperbaric air the hyperoxia has been shown to cause part of the bradycardia (3,4), the remaining part being caused by some other factor of the hyperbaric environment. Experiments with normoxic gases have shown indirect evidence that the hydrostatic pressure also contributes to the bradycardia (5–7) whereas in addition to the hydrostatic pressure the combined presence of elevated gas density and mild-to-moderate inert gas narcosis seems to cause further bradycardia (6,7). The present research was conducted in an attempt to analyze whether mild-to-moderate inert gas narcosis in itself would cause bradycardia or influence cardiovascular control in such a way that bradycardia might result from other influences of the hyperbaric environment.

METHODS

Subjects: Seven healthy male volunteers were studied. Age, weight, and height ranged from 23 to 26 yr, 68–86 kg, and 176–189 cm. The experimental protocol used in the present study was approved by the Ethical Committee of Karolinska Institutet, and all subjects gave their informed consent after receiving a description of the procedure and potential risks involved. The subjects were instructed to have a light caffeine-free breakfast at least 2–3 h before the experiments. All experiments were performed in the morning, and the subjects had been familiarized with the experimental equipment and procedures in an earlier session.

Breathing mixtures and gas analysis: Two gas mixtures were used. The control consisted of 25% oxygen in 75% nitrogen, and the narcotic mixture comprised 25% O_2 + 39% nitrous oxide (N_2O) + 36% N_2. This N_2O level corresponds to 38% of 1 MAC (minimum alveolar concentration for surgical anesthesia). In terms of impairment of psychomotor performance, 39% N_2O is equivalent to the narcotic potency of compressed air at a water depth of 60–120 m (8,9). Subjects breathed the gas mixtures from a low-resistance demand regulator system. Inspired and end-expired N_2O and CO_2 fractional concentrations were monitored with an infrared gas analyzer (Multicap, Datex Instrumentarium Corp., Helsinki, Finland). Subjects breathed through a mouthpiece and wore a nose clip. A 5-min period of wash-in was allowed before measurements were initiated, enabling the subjects to reach a steady-state end-tidal N_2O level.

Procedures and experimental design: The subjects were seated comfortably in the semi-recumbent position. Carotid baroreceptor stimulation was performed with a neck suction/pressure (NS/NP) device described in detail by Sprenkle et al. (10). The subjects were instructed to breathe normally throughout the procedure. Graded levels of pressure and suction were generated by two vacuum

cleaners connected to tubes with two and five resistors in series, respectively. The system was calibrated to give pressure drops of 20 mmHg over each resistor. By means of a manifold with stopcocks, the neck chamber could be connected to one of the pressure levels: +40, +20, −20, −40, −60 and −80 mmHg. An R-wave-triggered, 3-way solenoid valve (type 323, Burkert, Germany) alternatively connected the neck-chamber to the pressure source or the atmosphere. Neck-collar pressure was measured continuously using a pressure transducer (Hewlett Packard 267b with amplifier 311a). Stimulations of the carotid sinus with NS or NP lasted 15 s and the neck-chamber pressure had reached the preset pressure 70 ms after the R-wave, this increase or decrease being coincidental with the pressure wave of the cardiac ventricular systole (11). The six levels of NS/NP were repeated 3 times during control and N_2O-breathing conditions. The order of pressure presentation was randomized between subjects but was always the same for a given subject. There was a 60-s resting time between successive NS/NP stimulations. Four of the subjects started with the control condition whereas the other three started with the N_2O-breathing condition. There was a 1-h resting period between air and N_2O experiments.

Cardiovascular measurements: Heart rate (HR) was calculated beat-by-beat using an analog HR meter (Gould ECG/Biotech amplifier, model 20-4615-65), while arterial pressure in a finger was continuously recorded with a photoplethysmographic device (Finapres, type 2300, Ohmeda, USA). The finger cuff was applied on the middle phalanx of the third digit. Mean arterial pressures measured with this method have been shown to closely agree with those obtained with invasive measurement techniques (12,13). Determination of the vertical distance between the carotid sinus and the cuff was done using a water level and ruler.

Data recording and analysis: Calibrated data were stored and subsequently analyzed in several steps using an Acqknowledge 3.2 Biopac digital data handling system (Goleta, CA, USA). The following variables were recorded at a sampling frequency of 100 Hz per channel: neck-chamber pressure, continuous arterial pressure, and beat-by-beat HR. The HR meter provided a signal level at each R–R interval proportional to the inverse of the duration of the preceding R–R interval. Initiation of data sampling occurred 15 s before each NS/NP stimulation and continued 10 s after the end of stimulation for a total of 40 s. The off-line analysis of each 40-s period comprised computation of carotid distending pressure (CDP) as being equal to the difference between neck chamber and arterial pressure at the onset of stimulation, after the hydrostatic pressure difference from finger cuff to carotid sinus was subtracted. Beat-by-beat mean arterial pressure (MAP) was computed as the time average between systolic peaks. MAP at heart level was computed by subtracting the hydrostatic pressure difference between heart level and finger cuff.

For each level and condition of NS/NP, individual and group ensemble mean curves were computed for MAP and HR; this was done using the instant of the onset of stimulation for time alignment. Individual ensemble mean curves were based on three NP/NS repetitions in each subject, level, and condition of NS/NP. Figure 1 shows how amplitude parameters were obtained from individual ensemble mean time courses of MAP and HR. Pre-stimulus grand mean levels of HR, MAP, and CDP were computed for all subjects and conditions. NS/NP-induced responses were added or subtracted from this grand mean to generate carotid baroreflex sensitivity curves, where HR and MAP were plotted as a function of CDP (Fig. 2). The individual ensemble mean response-curves were then used to obtain the maximal slope and the range of the baroreflex sensitivity curve in two ways. First, six-segment baroreflex response curves were constructed for each subject by linear interpolation. Maximum slope was computed from the segment showing the steepest slope. Second, continuous carotid baroreflex stimulus response curves were produced by fitting data to the 4-parameter logistic function described by Kent et al. (14) for each subject individually. This function incorporates the following equation:

$$\text{HR or MAP} = A1 \cdot [1+eE(A2(CDP-A3))]\ E-1+A4$$

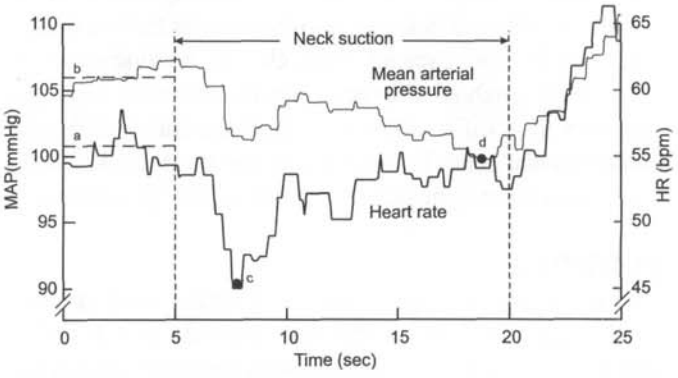

FIG. 1—Mean responses to −60 mmHg NS. Curves are ensemble mean time courses from three repetitions in one subject during N_2O inhalations. Onset of NS has been used for time alignment. Baseline values were taken as the mean in the 5 s before stimulation, *a* for HR, *b* for MAP. Maximal responses were taken as the minimum (in the case of NS) or the maximum (in the case of NP) during the period of stimulation (5–20 s); *c* represents the HR response and *d*, the MAP response. HR tracing lags by 1 beat because analog techometer displays a level during each R–R interval proportional to inverse of duration of preceding interval.

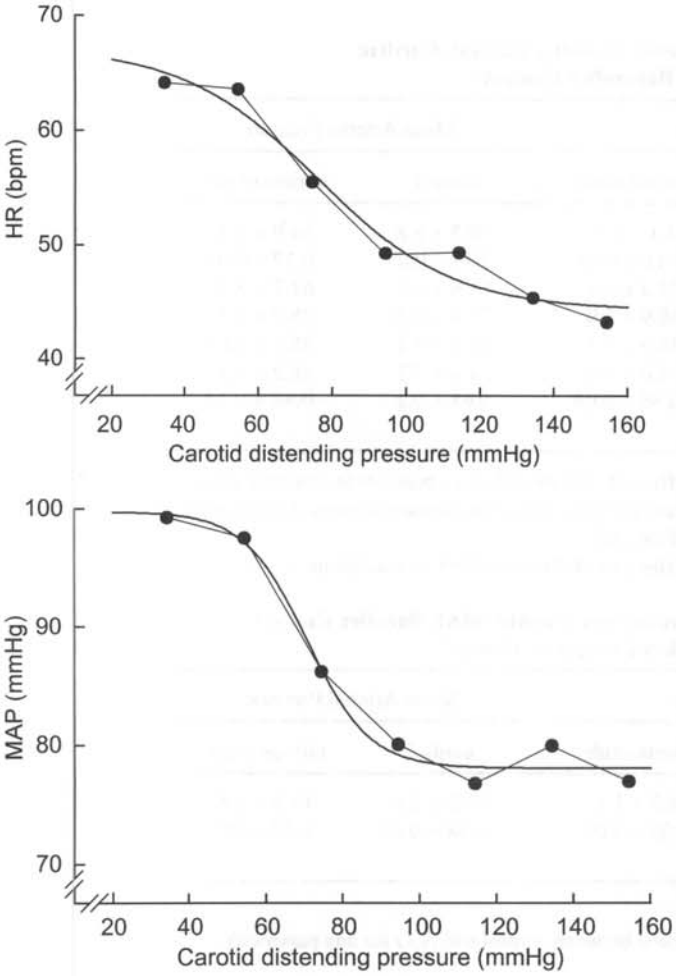

FIG. 2—Response of HR (*top*) and MAP (*bottom*) to NS/NP stimulations in one subject during N_2O inhalation. Data are shown as baroreflex response curves, i.e., HR and MAP responses are given as functions of carotid sinus distending pressure. *Points* represent means of the three actual recordings at each given pressure, and *heavy lines* represent their fitting into the logistic function described by Kent et al. (14). *Straight, thin lines* were interpolated between the points to assess baroreflex sensitivity in an alternative manner from the slope of the steepest segment.

where HR or MAP is the dependent variable, CDP the calculated carotid sinus pressure, A1 the range of response of HR or MAP (i.e., max-min), A2 the gain coefficient, A3 the CDP required to elicit equal pressor and depressor responses (optimum point) (15), and A4 the maximum response of HR or MAP. Data were fit to this model by an iterative, non-linear least-squares regression (Enzfitter, Elsevier-BIOSOFT, Cambridge, UK). The carotid sinus threshold and saturation were calculated as described by Chen and Chang (16). The sensitivity was also determined, defined as the maximum slope located at the optimum point of the carotid baroreflex response curve.

Statistical analysis: As described above, unique sets of curve parameters were obtained for each subject and condition, describing the slope range, etc., of baroreflex response curves for HR and MAP (Tables 1 and 2). For each parameter, paired comparisons were made between conditions. Differences between air control and N_2O inhalation were analyzed using Student's *t* test for dependent variables (Statistica, Statsoft, Tulsa, OK) with a 5% significance level.

RESULTS

Seven subjects completed the experiments. Pre-stimulus mean values ± SE for HR and MAP during air breathing were 58.0 ± 2.0 beats $\cdot\cdot min^{-1}$ and 80.1 ± 4.6 mmHg, respectively. The corresponding pre-stimulus mean values during N_2O inhalation were 56.3 ± 2.4 beats $\cdot$ min^{-1} and 81.9 ± 3.5 mmHg. There was no significant difference between air and N_2O condition. A typical individual mean response from three stimulations (Fig. 1) shows the response for both MAP and HR to NS stimulus. It can be seen that both HR and MAP started to fall immediately after initiation of the −60 mmHg NS stimulation. HR responded instantly to NS and reached its minimum after approximately 2.7 s, whereas the response in MAP had a biphasic pattern.

The first drop in MAP coincided with the bradycardic response, whereas the second drop, which is likely to be vasodilation-dependent, in this case took 13.5 s to develop. On removal of the stimulus at 20 s, both MAP and HR promptly increased to above the pre-stimulation levels. Typical response curves for HR and MAP obtained using the curve fitting program are superimposed in Fig. 2 onto the actual data points for the same person.

Tables 1 and 2 show parameters extracted from the complete baroreflex response curves. We found no significant differences between baroreflex response curves obtained during control and N_2O inhalation. This was true both for HR and MAP and for parameters obtained both with interpolation and with logistic-curve fitting. However, when the hypotensive and hypertensive parts of the baroreflex curve were analyzed separately, the sensitivity/max gain for HR responses to hypotension (NP) tended to be reduced from 0.32 ± 0.05 beats $\cdot\cdot min^{-1} \cdot\cdot mmHg^{-1}$ with air to 0.25 ± 0.05 beats $\cdot\cdot min^{-1} \cdot mmHg^{-1}$ with N_2O ($P = 0.054$). The HR response to hypertension (NS) did not show this tendency ($P > 0.8$), nor did the MAP response curves ($P > 0.7$). Interpolated baroreflex response curves based on group mean data are shown in Fig. 3.

Mean time delays for nadir/peak responses of HR to NS/NP stimulation were 5.52 ± 0.29 s during air breathing and 6.41 ± 0.98 s during N_2O inhalation. The corresponding times for MAP responses were 9.44 ± 0.14 s during air breathing and 9.05 ± 0.67 s during N_2O inhalation. The differences in response times between air and N_2O were not significant ($P > 0.3$). To further analyze the negative

Table 1: Logistic Model Parameters Defining Carotid–Cardiac and Carotid–MAP Baroreflex Control[a]

	Heart Rate		Mean Arterial Pressure	
	control	nitrous oxide	control	nitrous oxide
A1, bpm or mmHg	20.5 ± 4.7	14.1 ± 1.7	19.3 ± 5.8	14.9 ± 2.4
A2, $1 \cdot mmHg^{-1}$	0.16 ± 0.06	0.11 ± 0.02	0.21 ± 0.07	0.17 ± 0.06
A3, mmHg	62.8 ± 3.5	71.4 ± 4.1	54.8 ± 6.0	61.7 ± 5.2
A4, bpm or mmHg	49.2 ± 1.3	48.9 ± 1.9	73.8 ± 5.2	75.7 ± 3.7
CDPthr, mmHg	31.4 ± 12.0	48.9 ± 5.2	34.2 ± 9.2	35.1 ± 12.8
CDPsat, mmHg	94.3 ± 11.9	94.0 ± 6.6	74.4 ± 7.7	88.2 ± 5.5
Max gain, bpm · $mmHg^{-1}$ (or mmHg · $mmHg^{-1}$)	−0.52 ± 0.13	−0.35 ± 0.05	−0.68 ± 0.2	−0.48 ± 0.14

Key: A1, range (maximum–minimum); A2, gain coefficient; A3, carotid sinus pressure at optimum point; A4, minimum; CDPthr, threshold pressure at carotid sinus; CDPsat, saturation pressure at carotid sinus; max gain, maximum slope of logistic function as derived from A2.

[a]Values are mean ± SE; $n = 7$. No significant difference observed in the two conditions, $P > 0.05$.

Table 2: Parameters Defining Carotid–Cardiac and Carotid–MAP Baroflex Control Obtained From Interpolated Response Curves[a]

	Heart Rate		Mean Arterial Pressure	
	control	nitrous oxide	control	nitrous oxide
Range, bpm or mmHg	17.6 ± 2.5	14.2 ± 1.4	16.2 ± 2.0	13.8 ± 1.8
Max gain, bpm · $mmHg^{-1}$ or mmHg ·· $mmHg^{-1}$	−0.35 ± 0.04	−0.32 ± 0.02	−0.38 ± 0.03	−0.32 ± 0.05

Key: Max gain, slope of steepest segment.

[a]Values are mean ±SE; $n = 7$. No significant difference between control and N_2O for any parameter.

findings, with no significant differences between conditions, we performed an analysis of statistical power with regard to the most robust parameters of baroreflex sensitivity (Table 2). With the present number of observations and inter-individual variability, it can be stated with 99% likelihood that ranges did not differ by more than 10 beats ·· min^{-1} or mmHg between conditions. Also, it could be stated with 99 and 86% likelihood, respectively, that maximum gain for the whole baroreflex response curves did not differ more than 0.20 beats ·· min^{-1} ·· $mmHg^{-1}$ and 0.20 mmHg ·· $mmHg^{-1}$ between conditions for HR and MAP.

DISCUSSION

It is well established that inert gas narcosis impairs central nervous system processing and psychomotor performance (8,9). There is also an impairment of temperature control in man during mild-to-moderate inert gas narcosis, as shown by Mejkavić and Sundberg (17) in their study of thermogenic shivering responses in men during induced hypothermia and breathing 30% N_2O. One might thus expect a similar impairment in the integration of neural information processing involved in cardiovascular control mechanisms. Accordingly, Bristow et al. (18), while examining deep levels of surgical anesthesia, and Ebert (19) while examining mild-to-moderate N_2O narcosis, both concluded that there were significant changes in baroreflex sensitivity. In a comparison between present and previous results one needs to consider differences in a) anesthetic depth, b) anesthetic agent, and c) mode of baroreceptor stimulation:

a) Cardiopulmonary control functions, although severely impaired at deep levels of anesthesia (20), tend to maintain their functional integrity in light inert gas narcosis. Thus Fagraeus et al. (4) showed that cardiorespiratory responses to exercise were intact with light hyperbaric N_2 narcosis, apart from a relative bradycardia. Bristow et al. (18), on the other hand, reported a baroreflex slope decrease with thiopental, and both a baroreflex slope decrease and a resetting in 70% N_2O + 0.5–1% halothane. Neither of these studies are comparable with the present results in terms of the degree of narcosis. Studies of similar narcotic effects on cardiorespiratory control as in the present study have nonetheless been carried out by Ebert (19), who found a decrease in baroreflex-mediated tachycardia with N_2O. There are, however, other methodologic differences which will be addressed below.

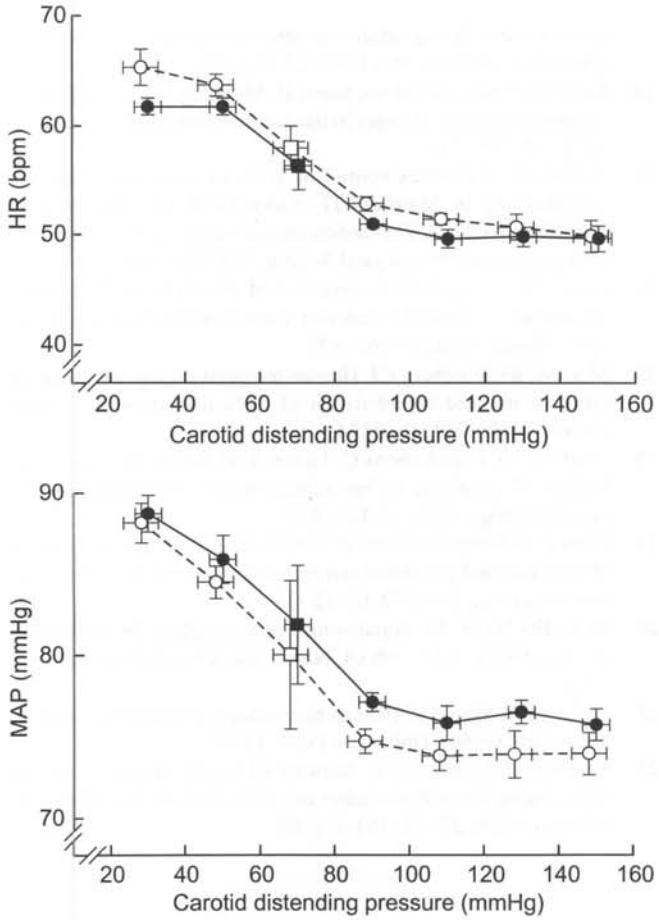

FIG. 3—Group mean ($n = 7$) responses for HR (*top*) and MAP (*bottom*) to NS/NP stimulation. *Solid circles* represent the narcotic (N_2O) situation and *open circles*, the control situation. *Vertical* and *horizontal bars* represent ±SE. For the pre-stimulus grand mean (*squares*), ±SE represents the distribution of baseline HR and MAP. For the remaining points (*circles*), ±SE represents the distribution of NS/NP-induced deviations from the individual pre-stimulus levels.

b) Several studies deal with clinically used anesthetic mixtures, such as halothane/N_2O or thiopental/N_2O (20), but only limited literature assesses N_2O alone. N_2O has an inherent sympathoexcitatory effect (19), in contrast to the aforementioned mixtures, which may have purely depressant effects. Hence the effects on cardiorespiratory control of one group of agents are not necessarily implicated in another. Also from this point of view then, the results of Bristow et al. (18) are less comparable with ours than are those of Ebert (19).

c) To be able to apply algebraic functions to compare slopes (i.e., sensitivity) in different conditions of baroreflex sensitivity function, the full range of the response curve is necessary (15,21). This will allow a complete perspective of the static open-loop carotid baroreflex behavior, from threshold to saturation. Such complete data seem to be absent in several previous studies where only one side of the curve has been examined, either the hypertensive alone (18) or the hypotensive (19). In the absence of this full picture (or near-full, as it is practically impossible to define the entire range in humans), it is extremely hard to determine the slope of the response curve. Comparison of slopes at the same point of the curve will provide information about that segment of the curve; however, comparison of gradients at two distinct points on the curve is very limited by the sigmoidal relationship and thus the expected slope shifts involved. Thus, studies using only one level of NS/NP cannot differentiate a true change in baroreflex sensitivity from a shift between positions with different slopes on an unchanged sigmoidal baroreflex curve.

Once the full response curves have been established, however, it is possible to compare hypotensive and hypertensive parts of the curves. The parameters defining the overall characteristics of the baroreflex response curves for HR and MAP did not differ between control and N_2O inhalation. Also, the latencies of HR and MAP responses to NS and NP stimuli were unaffected by N_2O and within the range found in previous work (22). These observations suggest that baroreflex control functions remain essentially intact at a level of inert gas narcosis, which at the same time produces clear impairments of psychomotor abilities (9) and temperature control in man (17). However, when the hypotensive and hypertensive parts of the baroreflex curve were studied separately in the present study, the sensitivity of the HR responses to hypotensive stimuli showed a tendency to be impaired by N_2O. This finding is in agreement with the findings of Ebert (19).

It might be speculated that a selective narcosis-induced reduction of carotid-cardiac baroreflex sensitivity to hypotensive stimuli may attenuate tachycardic responses to small cyclic blood pressure variations, whereas at the same time the corresponding bradycardic responses would be unaffected. The result for time-averaged HR would then be a slight bradycardia, which may become more evident in situations with enhanced intrathoracic pressure variations, such as when breathing a dense gas.

This study was supported by the Swedish Medical Research Council (grant no 5020).—*Manuscript received July 1998; accepted December 1998.*

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