SCIENTIFIC ARTICLES:

EFFECT OF AGE ON THE DIGIT BLOOD FLOW RESPONSE TO SEDATIVE CONCENTRATIONS OF NITROUS OXIDE

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SUMMARY

Twenty healthy male subjects [11 young, $\bar{x} = 25.4 \pm 0.8$ (SEM) years old; 9 elderly, $\bar{x} = 64.5 \pm 0.7$ years] volunteered for a study designed to investigate the effect of age on several cardiovascular parameters to inhaled N_2O-O_2. The protocol was designed to mimic the administration of N_2O-O_2 for sedation in the dental office, although no dental treatment was performed. Clinical criteria were used to judge the appropriate sedative level for each subject; no attempt was made to establish dose-response relationships. Digit blood flow was measured by strain-gauge plethysmography, and heart rate, arterial blood pressure, respiratory rate, and skin temperature were monitored and recorded. N_2O and CO_2 levels were monitored in end-tidal gas samples by gas chromatography; machine gauge readings were calibrated against known gas mixtures by the same technique.

Under the conditions of this experiment both healthy young and healthy elderly subjects experienced a marked (200-300%) increase in digit blood flow during N_2O inhalation, compared to that during air and 100% O_2 inhalation. There was no significant difference in the degree of flow increase between young and elderly subjects. Also, there were no significant differences in the response of these healthy young and healthy elderly subjects to sedative concentrations of N_2O with regard to heart rate, arterial blood pressure, respiratory rate, skin temperature, or mean end-tidal CO_2 levels. The data indicate that N_2O, in the concentrations routinely administered in the dental office for sedation, does not have a differential effect on the measured parameters in healthy elderly and healthy young males.

INTRODUCTION

Previous studies from this and other laboratories[1-6] indicated that nitrous oxide (N_2O), in concentrations employed in dental practice, affects the cardiovascular system. We have found,[1,2] for example, that inhalation of N_2O, in a concentration of 40% in oxygen (O_2), results in an apparent constriction of nailfold capillaries in the skin of humans. Although an alternative explanation of these findings has recently been offered,[7] it is clear from the accumulated evidence that nitrous oxide is not inert with respect to microvascular function. However, all of the studies dealing with the vascular effects of N_2O-O_2 in humans have concentrated on young subjects. We have been unable to find comparable studies dealing with the vascular effects of N_2O in the elderly.

Given the known anatomical and functional changes in the cardiovascular system of older individuals, and their decreased respiratory function, it is reasonable to expect age-related differences in the microcirculatory responses to inhaled N_2O.[8-10]

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Studies have indicated that the proportion of those 65 years of age or older in the United States will reach 20% of the total population by the year 2030.[11] It is expected that many of these older individuals will seek restorative and preventive dental care,[12] and many of these same individuals may be sedated with N_2O-O_2 gas mixtures. For these reasons, we undertook this study of the comparative effects of sedative doses of N_2O in healthy young and healthy elderly subjects.

METHODS

Twenty male subjects [eleven young, $\bar{x} = 25.4 \pm 0.8$ (SEM) yrs; range 22-30 yrs, and nine elderly, $\bar{x} = 64.5 \pm 0.7$ (SEM) yrs; range 63-69 yrs.] volunteered to participate in this study, and did so after giving informed consent. They were all classified as "healthy", based on self-report and medical history; none were taking medication and only two smoked. During a preliminary session each subject was familiarized with the experimental apparatus and inhaled N_2O-O_2 to become familar with its euphoric and sedative effects. During the experimental session the fasted subject (NPO for eight hours) was seated comfortably in a dental contour chair, with his arms positioned at heart level on the armrests. In sequence, the subject breathed air, 100% O_2 (5 min), N_2O-O_2 (30 min) and 100% O_2 (5 min) in a protocol mimicing that used in the dental office; O_2 and N_2O-O_2 were delivered from a dental inhalation sedation machine (Quantiflex M.D.M.) via a nasal mask and exhaled gases were vented from the system. The final concentration of N_2O for each subject was determined from the clinical subjective response, using the same technique employed in dental practice. No dental procedures were performed during the sessions. No attempt was made in this study to establish a dose-response relationship; therefore, no fixed doses of N_2O were administered. Mean levels of administered N_2O were checked with known gas mixtures by gas chromatography, which is more accurate than the machine readings. Alveolar N_2O and CO_2 levels were determined during the last 5 min. of the N_2O-O_2 period and during the recovery period of 100% O_2 and air by a method described previously.[13] A detailed study of N_2O decline and CO_2 levels following N_2O administration, during this same experimental protocol, has been submitted for publication.[14]

Heart rate (HR), arterial blood pressure (BP), and respiratory rate (RR) were measured during inhalation of air, O_2, and N_2O using appropriate devices and were recorded on a Grass Model 79 polygraph. Skin temperature on the dorsum of the hand was monitored by a thermistor probe and recorded using a telethermometer (YSI Model 42SC). Digital blood flow (BF) was measured in a finger (digitus minimus) (of the hand in which skin temperature was recorded) by plethysmography[15] using a mercury in silastic strain gauge during control (air) and experimental (O_2 and N_2O-O_2) periods, and recorded on the polygraph during the last 30 seconds of each period (Fig. 1). The occlusion cuff was placed on the wrist of the same hand, and occlusion achieved with a cuff pressure of 60 torr applied for 5 seconds at the appropriate time. The length and circumference of a subject's finger were noted and used to calculate absolute digit blood flow as previously described.[15] Psychomotor performance tests, which were part of a companion study, were performed by the subjects before, during, and after N_2O administration. The results of these tests have been submitted for publication.[16]

Appropriate Student-t tests were used to compare within-group and between-group data for BF, BP, HR, RR, N_2O levels, skin temperature, and CO_2 levels. Significance was set at $p \leq 0.05$.

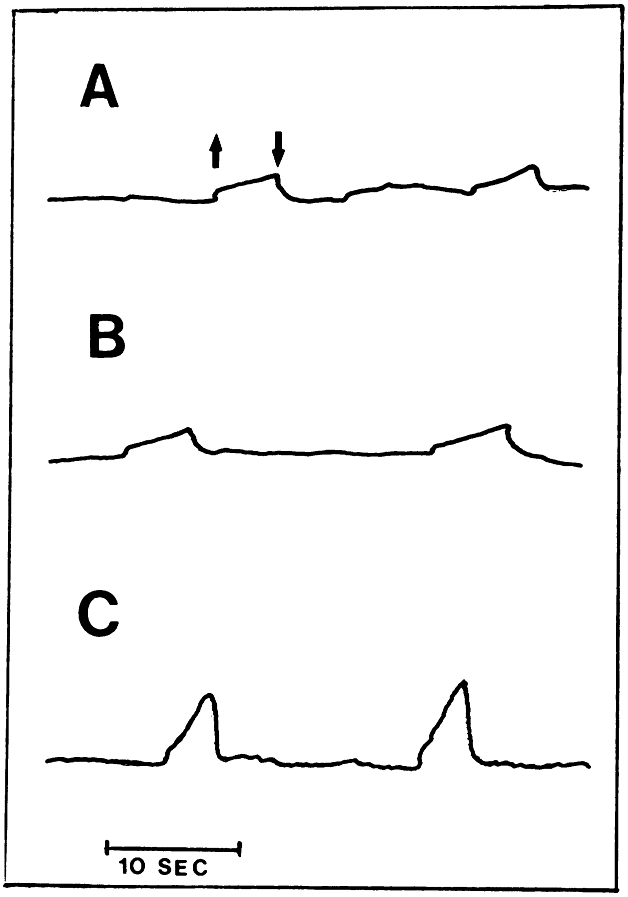

Fig. 1 — A typical polygraph tracing recorded from a digit plethysmograph, subject JH., age 22. A, air breathing control period; B, oxygen; C, N_2O; ↑, indicates start of venous occlusion; ↓, indicates end of venous occlusion. Increasing slope (N_2O compared to air and oxygen) of polygraph tracing indicates increased circumference of digit due to increased blood flow. Actual blood flow was calculated from these data using the method of Whitney[15], which involves calibration of each strain gauge such that actual length change of gauge and rate of change are used to determine digit flow (e.g., for this gauge 7.2 mm pen excursion represents 1 mm circumference change in the digit.

RESULTS

Average sedative N_2O concentrations ($\pm$ SEM) as determined by gas chromatography for he groups were: young, 33.3 $\pm$ 1.9%; elderly, 39.1 $\pm$ 4.3%. The levels required to achieve sedation varied widely for individuals in both groups (range: young 30-46%; elderly, 30-55%) but group means were not significantly different. The values determined chromatographically were slightly lower than machine gauge readings.

During the air-breathing control period mean digit blood flow in the elderly group was lower than that in the young, although this difference was not significant statistically (Table 1). Digit blood flow in both young and elderly groups increased significantly ($p < 0.05$) during the N_2O-O_2 period compared to both the control (air) and O_2 periods (Fig 2, Table 1). Calculated as a percent change from control, both groups consistently showed an increased BF (an average 2 to 3 times greater than control). There was wide individual variation in resting digital BF in both groups as well as wide variation in the magnitude of the BF response to N_2O. However, all subjects showed an increase in BF during N_2O inhalation. BF responses, i.e., degree of change, of the two groups during the N_2O period were not signifi-

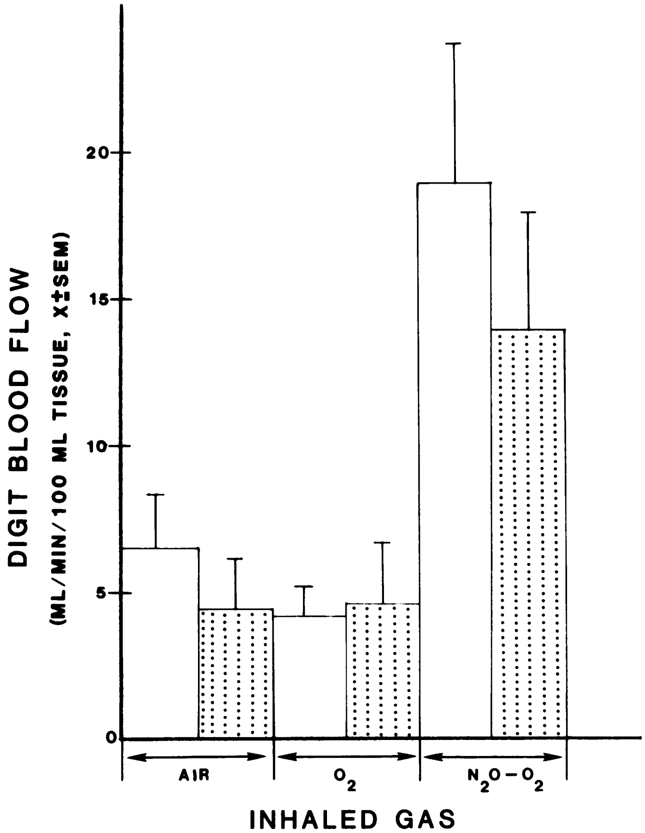

Fig. 2 — Digit blood flow response to O_2 and N_2O-O_2 inhalation in young (unshaded) and elderly (stippled) subjects.

cantly different from each other. Heart rate decreased slightly in both groups during both O_2 and N_2O periods, with values significantly different from the within-group control (Table 2). Respiratory rate decreased in both groups during the O_2 and N_2O periods, but the decrease was of a significant magnitude only in the young group.

No significant difference between groups was seen in mean end-tidal CO_2 levels during the N_2O period (young: 4.90 ± 0.12 (SEM) % CO_2; range 3.78-5.79%; elderly: 4.61 ± 0.31 (SEM) % CO_2, range 4.57-5.61%). Similarly, no significant changes were noted in skin temperatures within or between groups during the entire protocol. Arterial blood pressure showed no significant differences between groups in the various periods, except for systolic pressure during the O_2 period ($p < 0.05$, Table 2). Systolic BP was slightly higher in the elderly group as would be expected, but this overall elevation in pressure was not significantly different from the young group.

DISCUSSION

It must be emphasized at the outset that the aim of this study was to determine the effects of nitrous oxide on digit blood flow under conditions approximating the method of its administration in the dental office. Therefore, no attempt was made to establish dose-response curves by administering fixed doses, or to use a closed system to prevent the inevitable mouth-breathing that occurs with the nose-mask

TABLE 1. Digit Blood Flow (Absolute Flow in ml/min/100 ml Tissue; $\underline{X}$ ± Sem) and Skin Temperature (°C) in Young and Elderly Subjects Breathing Air, O_2, and N_2O-O_2.

Group		CONDITION		
		Control	O_2	N_2O
Young	BF	6.5 ± 1.8	4.2 ± 1.1	18.9 ± 4.7*
	Temp.	29.6 ± 0.5	29.7 ± 0.5	30.5 ± 0.6
Elderly	BF	4.4 ± 1.7	4.6 ± 1.9	13.9 ± 3.9*
	Temp.	29.2 ± 0.7	29.0 ± 0.7	29.7 ± 0.8

*Significantly different from both control and O_2 periods (Student's paired-t, $p \leq 0.05$).

TABLE 2. Heart-Rate, Arterial Blood Pressure, and Respiratory Rate ($\underline{X}$ ± Sem) in Young and Elderly Subjects Breathing Air, O_2, and N_2O-O_2.

	Young			Elderly		
	Control (Air)	O_2	N_2O	Control (AIR)	O_2	N_2O
Systolic B.P. (Torr)	122.3 ± 2.2	122.6 ± 2.0**	121.9 ± 2.1	128.4 ± 6.9	135.6 ± 6.7*	127.6 ± 5.4
Diastolic B.P. (TORR)	78.4 ± 1.7	76.9 ± 2.9	74.5 ± 2.2	72.5 ± 4.0	74.6 ± 3.2	76.3 ± 4.5
H.R. (beats/min)	72.4 ± 4.4	67.2 ± 4.9*	64.4 ± 3.0*	68.0 ± 1.6	64.6 ± 1.2*	61.4 ± 2.8
Resp. Rate (breaths/min)	17.4 ± 1.0	13.0 ± 1.0*	11.0 ± 1.0*	16.5 ± 1.3	15.3 ± 0.9	14.0 ± 0.9

*Significantly different from control, Student's paired-t, $P \leq 0.05$.

**Significant difference between groups, Student's unpaired-t, $P \leq 0.05$.

administration of N_2O as a sedative agent in the dental office. Ideally, studies of this type should include nitrogen-oxygen mixtures as comparative controls for the nitrous oxide-oxygen mixtures. However, since Kawamura et al.[5] have shown that no cardiovascular variable was significantly altered by breathing concentrations of N_2 up to 60% (with O_2) for periods of up to two hours, it was felt that these controls could be omitted.

The results indicate that the concentration of N_2O necessary to achieve subjective levels of sedation comparable to those sought in the dental office varied widely in both healthy young and healthy elderly individuals, and that there was no statistically significant difference in concentration required for one group compared to the other. Dundee[8] suggested that the use of all inhalation anesthetics in the elderly may be complicated by the fact that respiratory function declines with age. Also, there is evidence to support differences in responses of the elderly to other psychotropic drugs.[18,19] However, under the conditions of this study, which employed healthy subjects and mimiced the techniques of inhalation sedation used in dentistry, we found no significant differences between young and older subjects in the concentration of N_2O required for sedation or in the decline in N_2O concentrations following sedation.[14]

During the control period, digit blood flow in the elderly group was lower than that in the young group. Although this difference was not statistically significant in this study, others have shown a similar decrease in digit blood flow in elderly subjects.[17]

Sedative concentrations of N_2O-O_2 used in this study elicited an increase in digit blood flow in both the healthy young and the healthy elderly male subjects. Age did not appear to influence the digit blood flow response to N_2O in these subjects. When calculated as a percent change from the control period, blood flow increases in both groups in the N_2O period averaged 200-300%. The digit blood flow response to N_2O-O_2 inhalation observed in these subjects appeared to be due to N_2O, rather than to an effect of the inhaled O_2.

As was expected, RR decreased in both groups during N_2O inhalation, probably as a consequence of the calming and sedative effect of the gas. Age did not appear to effect HR, BP, RR, and skin temperature responses to inhaled N_2O in our experimental groups. As has been demonstrated by others using similar N_2O concentrations,[3,20] HR decreased significantly after both groups breathed N_2O for 30 minutes. Another study[5] showed no cardiovascular effect with 40% N_2O. No age-related effect of N_2O-O_2 inhalation on the level of alveolar CO_2 was noted. Taken together, these data suggest that, under the conditions of this experiment, the digit blood flow response and respiratory effect of sedative concentrations of inhaled N_2O-O_2 are virtually indistinguishable in healthy young and healthy elderly males.

Studies from other laboratories[3,21] have shown that N_2O, in concentrations of 40% and 70%, respectively, induces a decrease in forearm blood flow, with or without concurrent increases in arterial pressure or vascular resistance. These changes at higher levels of N_2O (>60%) may be due to increased sympathetic neural activity.[22] There is evidence to indicate that N_2O may induce a redistribution of forearm blood flow, with cutaneous vasodilation and skeletal muscle vasoconstriction.[26] The results of this study, i.e., an increase in digit blood flow in the absence of blood pressure changes, may reflect the fact that the forearm and digit have different ratios of muscle to skin. Others have shown that muscle and skin vascular beds respond differently in direction or degree to pharmacologic[23-25] and physiologic[26,27] stimuli.

Although changes were shown in total digit blood flow with N_2O, these results cannot be safely generalized either to the nailfold capillaries in the digit or to small vessels elsewhere, e.g., the dental pulp, gingiva, or the oral mucosa. Recently, it has been shown[28] that digit arterial blood flow velocity and nailfold capillary blood flow velocity in the same digit are complex and may not correlate at every instant. Thus, in order to obtain a complete picture of the effect of N_2O on cutaneous blood flow a necessary followup to the present study would be to monitor simultaneously nailfold capillary blood flow and total digit blood flow (in the same digit) while the subject breathes known, fixed mixtures of N_2O-O_2. This type of study is currently underway in our laboratory.

Given the dental clinical approach in this study, such that N_2O inhalation was limited to 30 min, the question of equilibration with N_2O must be addressed. It is well known that the vessel-rich group of highly perfused tissues, e.g., brain, heart, kidney, equilibrates rapidly with the arterial (alveolar) anesthetic concentration of N_2O, probably within 5-15 min of induction.[29,30] The muscle group, which includes muscle and skin, approaches equilibrium more slowly. Eger[31] has calculated time constants for the various tissue groups for N_2O, i.e., a time constant describing the rate of rise of a particular tissue group's partial pressure of inhaled anesthetic agent; he reported a time constant of 30 min for nitrous oxide in the muscle group. These data suggest that when BF measurements were made our subjects' central nervous systems were equilibrated with N_2O. Their digits, primarily composed of skin (with an abundant blood supply) plus small amounts of muscle and other tissue, were at or just reaching equilibrium. It is clear that the fat group (fatty tissue) and the vessel-poor group (bone, ligaments, cartilage) of tissues in our subjects were not yet equilibrated with N_2O when the BF measurements were made. To achieve equilibrium with these two tissue groups, a period of at least 2-2½ hours of N_2O inhalation would have been required. Thus, under the conditions of this study, it is safe to assume that sufficient inhalation of N_2O occurred to achieve either a direct effect on the blood vessels in the skin, or an indirect effect by way of the brain. The fact that the fat depots and the vessel-poor tissues were not yet equilibrated with N_2O when the flow measurements were made was of no consequences in this study, especially considering that none of the subjects in this study was obese.

The possibility that the increase in digit blood flow we observed during N_2O administration was caused by CO_2 must be considered, since CO_2 is a known vasodilator. Increases in alveolar concentrations of CO_2 during anesthesia have been attributed to a second gas effect[32] or to an increase in physiologic dead space,[33] although the exact mechanism is still a matter of controversy. Under the conditions of our experiment, however, it is unlikely that CO_2 was a factor. The average end-tidal CO_2 levels for both young and elderly groups during N_2O inhalation were well within the normal range for individuals breathing air; the subjects were not hypercapneic. Abramson[34] indicated that inhalation of 7% CO_2 resulted in a decrease in blood flow to the hand, regardless of whether blood pressure increased or remained the same. Further, the ratio in the digits of skin to muscle is large; the metabolism of skin is so low in relation to its vascularity that it is usually accepted that little or no metabolic autoregulation of blood flow occurs.[35] Burton[36] has estimated that a digit's oxygen requirement can be met by a flow of 0.8 ml/min/100 ml of digit skin tissue, which is a small fraction of total digit flow.

It has also been suggested that the primary controller of changes in digit flow is the sympathetic nervous system responding to thermal demands. Smith et al[21] have shown that the addition of 70% N_2O to halothane anesthesia results in a small but rapid rise in core body temperature. Similarly, skin temperature increased slightly in both young and elderly subjects in the present study, suggesting that the increase in digit blood flow may have involved thermoregulation.

The results of this study must be interpreted cautiously in terms of a possible mechanism for the large increase in blood flow observed in both groups. It has been shown previously[37] that anesthetic concentrations of N_2O produce a pattern of digit vasodilation leading to an increase in pulse waves and an increase in volume of the digit. The authors attribute this observation to central depression of the vasomotor center rather than to sympathetic blockade. However, it is well known that blockade of the sympathetic nerve supply to the hand causes a vasodilation, one that can be augmented only with direct, local heating.[38,39] A similar increase in flow can be caused by body heating and thus, has also been attributed to the removal of sympathetic constrictor tone. Much of this increase in total hand blood flow has been attributed to an increase in flow through arteriovenous anastomoses, most of which are located in the digits. Thus, it is possible that the increased digit blood flow observed in this study, in the absence of major arterial pressure alterations, was due to a central action of the gas leading to a decrease in sympathetic vasoconstrictor tone in the digits and an opening of A-V anastomoses. However, it is not possible at this time to rule out the possibility of a direct effect of the gas on the digit vessels.

The elderly subjects in this study are considered to be in the "young-old" category, since their mean age was approximately 65 years. Further, they were all active, in good general health, and not taking medications routinely. Therefore, it would be unwise to generalize the present findings to the "old-old" group, i.e., individuals 75 years old or older, or to those who are medically compromised. Further studies are required to extend the present study to these individuals.

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