

Autonomic Nervous System Responses during Sedative Infusions of Dexmedetomidine

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Background: The purpose of this study was to determine the effects of dexmedetomidine on systemic and cardiac autonomic reflex responses during rest and during thermal stress.

Methods: Volunteers received either placebo or low- or high-dose dexmedetomidine (target plasma concentrations 0.3 or 0.6 ng/ml, respectively) infusions in a prospectively randomized, double-blinded crossover study design. After 1 h, baroreflex sensitivity was assessed, and then core body temperature was raised to the sweating threshold and then lowered to the shivering threshold. Plasma catecholamines and blood pressure were measured, and cardiac autonomic responses were assessed by analysis of heart rate variability.

Results: Compared with placebo, plasma norepinephrine concentrations, blood pressure, heart rate, and some heart rate variability measures were lower after 1-h infusion of dexmedetomidine, but baroreflex responses did not differ significantly. Dexmedetomidine blunted the systemic and cardiac sympathetic effects of sweating observed during placebo infusion but had no effect on parasympathetic measures. Increases in blood pressure, and systemic catecholamines due to shivering were observed during placebo and dexmedetomidine, but these responses were less with dexmedetomidine. During shivering, dexmedetomidine infusion was associated with higher low-frequency and high-frequency heart rate variability power but lower heart rate compared with the sweating threshold and with the control period, suggesting nonreciprocal cardiac autonomic responses.

Conclusions: Infusion of dexmedetomidine results in compensated reductions in systemic sympathetic tone without changes in baroreflex sensitivity. Dexmedetomidine blunts heart rate and the systemic sympathetic activation due to sweating, but it is less effective in blunting cardiac sympathetic responses to shivering. During dexmedetomidine infusion, cardiac sympathetic and parasympathetic tone may have nonreciprocal changes during shivering.

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α_2 -ADRENERGIC receptor agonists bind to peripheral and central nervous system sites modulating autonomic nervous system function.¹⁻³ These effects may explain, in part, the clinically observed attenuation of sympathetically mediated responses to perioperative stress, including a reduced incidence of tachycardia and hypertension, in surgical patients given this class of drugs.⁴⁻⁷ α_2 Agonists have also been shown to attenuate sympathetic responses to thermal stress.^{8,9} Such stress may predispose surgical patients to myocardial ischemic and other complications.¹⁰⁻¹² While the sympatholytic effects of α_2 -adrenergic receptor agonists might benefit the increasingly aged surgical population at risk for fluctuations of body temperature and adverse perioperative cardiac outcomes, attenuation of sympathetic reflex responses to hemodynamic perturbations could predispose these patients to bradycardia and hypotension.^{1,4-7,13}

Dexmedetomidine is a highly selective α_2 -adrenergic receptor agonist recently approved by the FDA for sedation of critically ill patients.¹⁴ Clinical studies of the effect of dexmedetomidine on autonomic reflex responses have been mostly limited to measurement of systemic catecholamine concentrations.^{5,6} While these measurements provide an assessment of systemic sympathetic activation, they do not necessarily reflect end-organ sympathetic activation.¹⁵⁻²¹ Knowledge of the effect of dexmedetomidine administration on autonomic nervous system control of the heart would thus add to our understanding of its hemodynamic effects. Analysis of cardiac baroreflex function and heart rate variability (HRV) provide information about cardiac sympathetic and parasympathetic nervous system function.^{15,18-21} They therefore provide further evidence about the effects of dexmedetomidine on cardiac autonomic regulation than that obtained from systemic catecholamine concentrations and hemodynamic parameters alone. The purpose of this study was thus to determine the effects of two different doses of dexmedetomidine on systemic activation and cardiac autonomic reflex responses during rest and during thermal stress in unanesthetized volunteers.

Materials and Methods

With approval from the Committee on Human Research at the University of California, San Francisco, and written informed consent, we studied nine male volunteers. Exclusion criteria included a history of thyroid disease, dysautonomia, diabetes mellitus, Raynaud's syndrome, and hepatic or renal disease, tobacco use, history

of alcohol or drug abuse, use of any medication, and body weight greater than 115% of normal. These volunteers simultaneously participated in a thermoregulatory study.⁹

Treatment Protocol

Studies started near 8:00 AM and were scheduled so that all interventions were made at similar times each day to minimize circadian fluctuations. Catheters were inserted in a hand vein for fluid and drug administration, and in a radial artery for blood pressure measurement and blood sampling. Lactated Ringer's solution, 5 ml/kg, was given before administration of the study drug and was subsequently infused at $1.5 \text{ ml} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$.

The study was a randomized, double-blind, cross-over comparison of two doses of dexmedetomidine and placebo (normal saline). At least 7 days were allowed between treatments. The study drug was given by a computer-controlled infusion that targeted plasma dexmedetomidine concentrations of 0.3 and 0.6 ng/ml. This infusion pump (Harvard Apparatus 22; Harvard Apparatus, South Natick, MA) used STANPUMP software (generously provided by Steven Shafer, M.D., Department of Anesthesia, Stanford University, Palo Alto, CA); the software adjusted the infusion rate every 10 s, as necessary, based on pharmacokinetic data for dexmedetomidine. During the study, subjects rested in a supine position, and continuous electrocardiographic recordings for HRV analysis were collected. Care was taken throughout the protocol to minimize stimulation of the volunteers. Baroreflex testing was performed after 1 h of each drug or placebo infusion. After the baroreflex test and a subsequent rest period, volunteers' skin temperatures were increased until sweating was first detected (the sweating threshold) and then decreased until shivering was observed (the shivering threshold). Changes in temperature were kept at $3^\circ\text{C}/\text{h}$ or less to avoid triggering of dynamic thermoregulatory responses.²² Core temperature was measured from the tympanic membrane using thermocouple probes (Mallinckrodt Anesthesiology Products, Inc., St. Louis, MO) and recorded at 5-min intervals. Sweating was continuously quantified from the upper chest using a ventilated capsule as previously described.⁹ The sweating threshold was defined as sweating exceeding $40 \text{ g} \cdot \text{m}^{-2} \cdot \text{h}^{-1}$ for at least 5 min. Shivering was defined by a blinded observer as an increase in oxygen consumption for at least 5 min as measured with a metabolic monitor (Deltatrac; SensorMedics Corp., Yorba Linda, CA). Other details of the protocol have been previously described.⁹ The study drug infusion was discontinued once shivering was observed.

Measurements

Baroreceptor sensitivity was determined using a modification of the method of Smyth *et al.*²³ Briefly, intravenous nitroprusside (100–200 μg) was given to decrease

arterial blood pressure approximately 20 mmHg; this was followed 60 s later by phenylephrine (100–200 μg) to increase blood pressure by approximately 20 mmHg. Arterial blood pressure was measured from a radial artery cannula connected to a Transpac II transducer (Abbott Laboratories, North Chicago, IL). All heart rate and blood pressure responses were digitized at 128 Hz for off-line analysis with custom software. In addition, hemodynamic data were determined at 10-s intervals, and median values were determined over 3-min epochs.

Subjects underwent continuous electrocardiographic monitoring with AM Holter recorders (Marquette, series 8500, Milwaukee, WI) using leads CC5 and II. Holter monitoring was initiated at least 30 min before the study drug infusion was started and continued until 3 h after the end of the infusion period.

Dexmedetomidine, norepinephrine, and epinephrine plasma concentrations were determined from arterial blood samples collected 60 min after the start of the study drug infusion and at the onset of sweating and shivering. Blood samples were immediately placed in ice and were subsequently separated in a refrigerated centrifuge; plasma samples were stored at -70°C until analysis. Dexmedetomidine concentrations were assayed by gas chromatography and mass spectrometry. This method has a lower limit of detection of 20 pg/ml and coefficient of variation of 5.7% in the relevant concentration range (personal communication, Lauri Vuorilehto, M.Sc., Orion Corporation, Turku, Finland). Concentrations of epinephrine and norepinephrine in plasma were determined using high-performance liquid chromatography, with colometric electrochemical detection. The method has a lower limit of detection of 20 pg/ml and coefficients of variation near 10% in the relevant concentration ranges. When subject catecholamines values were below the limit of detection, values were interpolated to 10 pg/ml for data analysis purposes.

Data Analysis

To determine baroreflex sensitivity, cardiac interval (R-R interval from the electrocardiographic tracing) and mean arterial pressure were obtained for each cardiac cycle. The R-R interval was plotted as a function of the mean arterial pressure from the preceding cardiac cycle. The data on the linear portion of this relationship were analyzed using linear regression analysis. Baroreflex sensitivity was expressed as the slope of the linear regression line (in ms/mmHg).

Holter tape analysis was performed with a computerized scanner (Marquette 8000) with proprietary software (version 5.8) and standard QRS labeling techniques.²⁴ The electrocardiographic files were transferred to a computer workstation for secondary editing and HRV analysis. Frequency domain analysis of HRV, based on normal-to-normal sinus beats, was performed on 5-min segments

Table 1. Dexmedetomidine Concentrations, Systolic Blood Pressure, and Plasma Catecholamine Concentrations Results at the Control, Sweating, and Shivering Study Conditions for the Placebo and Low- and High-dose Dexmedetomidine Groups

	Control	Sweating	Shivering
Dexmedetomidine (pg/ml)			
Low dose (ng/ml)	0.42 ± 0.04	0.43 ± 0.03	0.48 ± 0.08
High dose (ng/ml)	0.83 ± 0.09	0.82 ± 0.09	0.83 ± 0.07
Systolic blood pressure (mmHg)			
Placebo	131 ± 12	126 ± 8	155 ± 16†‡
Low dose	116 ± 13*	110 ± 15*	130 ± 16*†‡
High dose	113 ± 15*	114 ± 16*	127 ± 15*†‡
Norepinephrine (ng/ml)			
Placebo	96 ± 10	111 ± 9†	234 ± 31†‡
Low dose	27 ± 8*	20 ± 6*	152 ± 33*†‡
High dose	22 ± 8*	15 ± 6*	120 ± 30*†‡
Epinephrine (ng/ml)			
Placebo	20 ± 11	31 ± 17	58 ± 41†‡
Low dose	19 ± 14	14 ± 7*	20 ± 16*
High dose	12 ± 5	12 ± 6*	15 ± 13*

Data are mean ± SD.

* $P \leq 0.05$ versus placebo. † $P \leq 0.05$ versus control. ‡ $P \leq 0.05$ versus sweating.

of data for the following periods: 55–60 min after the beginning of study drug infusion, and 5 min before sweating and shivering using fast Fourier transformation. Spectral analysis of HRV required greater than 80% of normal R-R intervals in the data set. HRV spectral power was computed over a frequency range from 0.0033×10^{-4} to 0.50 Hz. Power (in ms^2) for the heart rate spectrum was calculated in the low-frequency (LF; 0.04–0.15 Hz) and high-frequency (HF; 0.15–0.40 Hz) bands. The LF component of HRV reflects a combination of sympathetic and parasympathetic modulation of heart rate at the frequency associated with baroreflex activity.^{18–21}

Although sympathetic nerve activity has fluctuations in both the LF and HF bands, the time delay between changes in sympathetic activity and changes in cardiac ion channels is too great for change in the HF band to be affected. Therefore, at usual respiratory rates, the HF component of the HRV spectrum represents respiratory modulations of vagal cardiac nerve function only.^{18–21,25–29} Under conditions where the relationship between the sympathetic and parasympathetic arms of the autonomic nervous system is reciprocal, changes in the ratio of power of the LF and HF bands (the LF/HF ratio) can be interpreted as reflecting changes in autonomic balance. In those cases, an increase in the LF/HF ratio reflects greater sympathetic predominance and *vice versa*^{18–21,29}; the LF/HF ratio was therefore computed.

Because HF power is modulated by respiration, it is possible to estimate respiratory rates, especially when subjects are supine, by an autoregressive analysis of HRV. The order of the autoregressive fit is determined by maximizing the Akaike information criterion.²⁹ In addition, although the effect of respiratory rate on HF power is relatively small at normal respiratory rates, extremely fast or slow respiratory rates can significantly alter HF power.²⁹ To determine if changing respiratory rates confounded the autonomic response to drug or to heating or

cooling, respiratory rates for each 5-min period of interest were calculated.

Between-treatment and between-intervention comparisons of HRV and other continuous data were performed using paired *t* tests. Data were tested for normality using the Kolmogorov-Smirnov and Shapiro-Wilk tests. Non-normally distributed data were log transformed before analysis. When data could not be normalized by log transformation, a Wilcoxon nonparametric test was used. Data are reported as mean ± SD; $P < 0.05$ was considered statistically significant.

Results

Volunteers were 28 ± 5 yr old, 163 ± 24 cm tall, and weighed 74 ± 11 kg. Plasma dexmedetomidine concentrations slightly exceeded the targeted range during each study period (table 1). The effects of dexmedetomidine on thermoregulation has been previously described.⁹ During placebo infusion, sweating occurred at a tympanic membrane temperature of $36.9 \pm 0.3^\circ\text{C}$, which was not significantly different than during low-dose ($36.8 \pm 0.3^\circ\text{C}$) or high-dose ($36.8 \pm 0.3^\circ\text{C}$) dexmedetomidine. Shivering occurred at tympanic membrane temperatures of 37.0 ± 0.1 , 36.3 ± 0.3 , and $35.9 \pm 0.3^\circ\text{C}$ for the placebo, low-dose, and high-dose dexmedetomidine infusion days, respectively ($P = \text{NS}$).

Baroreflex Results (Control Period)

Baroreflex sensitivity results are listed in table 2. During the control period (*i.e.*, after 1-h infusion of placebo or dexmedetomidine), difference in mean baroreflex sensitivity to nitroprusside was not statistically significant between the different treatments. Mean baroreflex sensitivity to phenylephrine was shifted to the left (*i.e.*, lower heart rate at any given blood pressure) during the low- and high-dose dexmedetomidine infusions com-

Table 2. Baroreflex Sensitivity (ms/mmHg) Determined after 1-h Infusion of Placebo or Low- or High-dose Dexmedetomidine

	Nitroprusside Infusion	Phenylephrine Infusion
Placebo	15.0 ± 6.1 (5.7–23.3)	27.7 ± 14.2 (15.8–61.0)
Low dose	10.6 ± 4.6 (7.1–21.7)	39.9 ± 13.5 (22.4–59.4)
High dose	11.0 ± 7.3 (4.6–22.0)	39.8 ± 15.1 (23.8–72.8)

Data are mean ± SD (range).

pared with the placebo infusion, but this did not attain statistical significance either ($P = 0.16$).

Effects of Dexmedetomidine on Resting Supine Autonomic Function (Control Period)

Systolic blood pressure, heart rate, and HRV results are listed in tables 1 and 3. Respiratory rates during each infusion protocol are listed in table 4. Heart rate was normally distributed, but LF and HF power required log transformation to permit parametric statistical comparisons. The distribution of the LF/HF ratio could not be normalized by log transformation, so a nonparametric Wilcoxon test was used for statistical comparisons.

Both systolic blood pressure and plasma norepinephrine concentrations were significantly lower during dexmedetomidine infusions than during placebo, but plasma epinephrine concentrations, which were near the limit of detection on placebo, were not different. LF power was reduced for both low- and high-dose infusions, but heart rate and the LF/HF ratio were significantly reduced for high dose only. Respiratory rates were not affected by treatment with dexmedetomidine. These results together suggest reduced sympathetic activity with dexmedetomidine infusions during the con-

Table 3. Heart Rate and Heart Rate Variability Results during 5-min Period before Each Condition for Placebo and Low- and High-dose Dexmedetomidine

	Control	Sweating	Shivering
Heart rate (beats/min)			
Placebo	59 ± 7 (49–69)	68 ± 9† (56–82)	64 ± 8 (55–78)
Low dose	55 ± 8 (46–66)	59 ± 6* (52–67)	52 ± 5†‡ (43–58)
High dose	54 ± 8* (43–65)	59 ± 6*† (48–67)	48 ± 10*†‡ (29–63)
In LF power			
Placebo	7.37 ± 1.05	6.88 ± 0.82	7.58 ± 0.62‡
Low dose	6.80 ± 1.13*	6.32 ± 1.20†	8.35 ± 0.60†‡
High dose	6.68 ± 0.94*	6.02 ± 0.95*†	7.98 ± 1.20†‡
In HF power			
Placebo	7.02 ± 0.87	6.12 ± 0.79†	6.77 ± 0.84
Low dose	6.92 ± 1.16	6.52 ± 1.30	7.80 ± 0.65†‡
High dose	7.01 ± 1.00	6.61 ± 1.37	7.84 ± 1.02†‡
LF/HF ratio			
Placebo	1.59 ± 0.80	2.59 ± 1.50†	2.57 ± 1.32†
Low dose	1.02 ± 0.56	0.91 ± 0.48*	1.84 ± 0.63
High dose	0.81 ± 0.43*	0.67 ± 0.41*	1.57 ± 1.41

Data are mean ± SD (range). N = 9 for all conditions except N = 8 for heart rate variability indices for placebo shivering, low-dose sweating, and low-dose shivering because of technical problems resulting in less than 80% N = N intervals.

* $P \leq 0.05$ versus placebo. † $P \leq 0.05$ versus control. ‡ $P \leq 0.05$ versus sweating.

In LF = logarithm of low-frequency power (0.04–0.15 Hz); In HF = logarithm of high-frequency power (0.15–0.40 Hz).

Table 4. Respiratory Rates during 5-min Period before Each Condition for Placebo and Low- and High-dose Dexmedetomidine

	Baseline	Sweating	Shivering
Respiratory rate (breaths/min)			
Placebo	15.1 ± 1.6	16.1 ± 1.6	17.0 ± 1.9
Low dose	14.3 ± 1.1	15.0 ± 0.9	14.3 ± 1.4*
High dose	14.5 ± 1.7	14.7 ± 1.3*	14.2 ± 2.4*

Data are mean ± SD. N = 9.

* $P \leq 0.05$ versus placebo.

rol period compared with placebo treatment with little change in cardiac parasympathetic modulation.

Autonomic Findings at the Sweating Threshold Placebo Condition Compared with the Control Period. On placebo, blood pressure at sweating was unchanged from control, but there was an increase in mean heart rate (tables 1 and 3). Serum norepinephrine concentrations rose modestly, and the rise in serum epinephrine values was not significant (table 1). Heating to sweating did not significantly change LF power, but HF power decreased with a resultant increase in the LF/HF ratio (table 3). Respiratory rates did not change (table 4). Together, these results suggest mildly enhanced sympathetic and reduced vagal activity in association with sweating.

During Dexmedetomidine Treatment Compared with Placebo. Systolic blood pressure and serum catecholamine concentrations at sweating were significantly lower during dexmedetomidine infusions than during placebo (table 1). Heart rate (both doses) and LF power (high dose only) were significantly lower than on pla-

cebo (table 3). There were no significant differences in HF power between dexmedetomidine and placebo infusions at the sweating threshold, but the LF/HF ratio was lower during the dexmedetomidine treatment (table 3). Respiratory rates on high dose during sweating were significantly lower than on placebo (table 4).

During Dexmedetomidine Treatment Compared with the Control Period. During dexmedetomidine infusions, blood pressure at the sweating threshold and serum catecholamine concentrations were unchanged compared with the control period (table 1). During low-dose dexmedetomidine infusion, LF power was lower compared with the control period (table 3). During high-dose dexmedetomidine, mean heart rate was higher, and LF power was reduced compared with the control period (table 3). Respiratory rates were not different during sweating compared with the control period (table 4). Overall, the data are consistent with the blunting of the sympathetic activation associated with sweating and little or no effect on parasympathetic modulation of heart rate during the infusion of dexmedetomidine compared with the control conditions and with placebo.

Autonomic Findings at the Shivering Threshold

Placebo Condition Compared with the Control Period and Sweating Threshold. Cooling to shivering during placebo was associated with significant increases in systolic blood pressure and catecholamine concentrations compared with control and sweating (table 1). Heart rate tended to be higher than at control ($P = 0.06$) and lower than at sweating ($P = 0.075$) (table 3). The LF/HF ratio was higher compared with control, and LF power was higher than at the sweating threshold (table 3). These findings are indicative of enhanced sympathetic activity during shivering.

During Dexmedetomidine Treatment Compared With Placebo. At shivering, systolic blood pressure, serum catecholamines, and heart rate were significantly lower during dexmedetomidine treatment than during placebo, but there were no differences in HRV (tables 1 and 3). One subject developed 23% ventricular ectopic beats during shivering on low-dose dexmedetomidine during shivering. Respiratory rates were significantly lower on both doses of dexmedetomidine compared with placebo (table 4).

During Dexmedetomidine Treatment Compared with the Control Period and Sweating Threshold. At shivering, systolic blood pressure and serum norepinephrine concentrations were significantly higher than at control and at sweating (table 1). Heart rates were significantly lower than control for high dose and lower than at sweating for both doses (table 3). LF and HF power were significantly higher at shivering compared with the control period and with sweating (table 3). The LF/HF ratio, however, was not significantly different.

There was no significant difference in respiratory rates compared with control or with sweating. These combined results are consistent with a relative increase in sympathetic *and* vagal tone on dexmedetomidine at shivering compared both to control and to sweating.

Discussion

In this study of healthy volunteers, we found that dexmedetomidine at concentrations similar to those indicated for patient sedation decreases systolic blood pressure and heart rate. This was accompanied by an approximate 30% reduction in plasma concentrations of norepinephrine. Epinephrine concentrations, however, were not different between the placebo and dexmedetomidine treatment arms at the control period. Plasma norepinephrine and epinephrine concentrations reflect "spillover" of catecholamines from peripheral synapses and the adrenal medulla, but not necessarily end-organ sympathetic activation.¹⁵⁻¹⁷ We thus evaluated further measures of dexmedetomidine's effect on cardiac autonomic regulation. We found that despite dexmedetomidine-induced decreases in systolic blood pressure, baroreflex sensitivity was maintained. Heart rate and HRV results were consistent with a reduction in sympathetic activity but in addition suggested that dexmedetomidine infusions had little or no effect on cardiac parasympathetic activation at rest. Dexmedetomidine blunted the systemic and cardiac sympathetic effects of sweating observed during placebo infusion. Increases in blood pressure and systemic catecholamines induced by shivering were observed in both placebo and dexmedetomidine infusions and were of similar relative magnitudes compared with the control state, suggesting that the ability of the sympathetic nervous system to respond to perturbations was not affected. The absolute magnitude of sympathetic activation, however, was attenuated by dexmedetomidine.

Baroreflex Sensitivity

The unique pharmacology of α_2 -adrenergic receptor agonist drugs results in sedation and analgesia without depression of respiration.^{1,4} By attenuating surgical stress-induced sympathetic activation, these drugs also increase perioperative hemodynamic stability and decrease risk for myocardial ischemia.^{1,4-7} A concern with respect to the use of α_2 -adrenergic receptor agonists, though, is that the associated profound sympatholytic effects might attenuate clinical responses to hypovolemia or decreases in blood pressure induced by other causes. The effects of dexmedetomidine on baroreflex mediated changes in heart rate are thus of considerable clinical importance.

Clonidine, which is less specific for the α_2 -adrenergic receptor than dexmedetomidine, was found to either enhance or have no effect on baroreflex sensitivity to the pressor test with phenylephrine.³⁰ Ebert *et al.*⁸ found

that baroreflex mediated sensitivity to phenylephrine was augmented, while increases in heart rate in response to nitroprusside were not affected by dexmedetomidine. Our results during nitroprusside infusion are consistent with these findings. We found that dexmedetomidine either augmented or had little effect on baroreflex sensitivity to phenylephrine. One important difference between our study and the one by Ebert *et al.*⁸ is that while we conducted a three-way cross-over study with two doses of dexmedetomidine, Ebert *et al.*⁸ conducted their study with two, sequentially increased, dexmedetomidine concentrations. Serum dexmedetomidine concentrations in the experiment by Ebert *et al.*⁸ (0.7 and 1.3 ng/ml) were greater than in our study (0.42–0.45 and 0.83–0.85 ng/ml).

Autonomic Responses to Thermal Stress

Temperature fluctuations are common perioperatively, and these disturbances contribute to serious complications, including morbid myocardial outcomes.^{11,12} The sympathetic nervous system has an important role in modulating thermoregulatory responses, but these compensatory processes could have deleterious effects on myocardial oxygen balance, leading to adverse patient cardiac outcomes.^{10–12} Blunting autonomic responses to thermal stressors, thus, might help improve cardiac outcomes.

We assessed autonomic responses by measuring systemic catecholamine concentrations, blood pressure, and HRV. While the exact physiologic determinants of HRV remain incompletely known, under most circumstances (*e.g.*, orthostatic maneuvers, administration of vasodilating or vasoconstricting drugs) when changes HRV occur, they reflect autonomic perturbation when compared with recordings from muscle sympathetic nerves.^{18–21,25–29} Under conditions where the relationship between the sympathetic and parasympathetic nervous systems is reciprocal, changes in the ratio of the power of the LF and HF bands (the LF/HF ratio) can be interpreted as reflecting changes in cardiac sympathovagal balance.^{18–21,29} In those cases, an increase in the LF/HF ratio reflects greater sympathetic predominance. Interestingly, at the shivering threshold during dexmedetomidine infusion, both LF and HF increased and heart rate decreased compared with the control period and to the sweating threshold. Both the decrease in heart rate and the increase in HF power suggested increased parasympathetic modulation of heart rate, while the other data (increased systolic blood pressure and catecholamines) suggest increased sympathetic activity. A similar nonreciprocal relationship between sympathetic and vagal outflows occurs during facial immersion in cold water (“diving reflex”) when increased muscle sympathetic nerve activity and bradycardia occur simultaneously.^{29,31,32}

Fast respiratory rates reduce parasympathetic modulation of heart rate (*i.e.*, HF power), and low respiratory rates (< 10/min) can increase HF power by permitting sympathetic nervous system activity to affect heart rate at respiratory frequencies.³³ While respiratory rates were significantly reduced by dexmedetomidine during shivering, only two subjects had a sharp increase in HF power. Respiratory rates, however, remained greater than 10/min throughout, and thus can not explain our HRV findings.

The serum catecholamine, blood pressure, and HRV results, taken together, suggest that under placebo conditions, heating is associated with a modest increase in sympathetic nervous system activity that is attenuated by dexmedetomidine. Hypothermia is a more profound sympathetic stimulus. Even mild core hypothermia ($\approx 1.3^{\circ}\text{C}$) leads to peripheral vasoconstriction, increased blood pressure, and norepinephrine concentrations.^{34–36} Our data during the placebo infusions suggest that the LF/HF ratio which reflects cardiac sympathovagal balance is increased by both sweating and cooling to the shivering threshold. However, the similar LF/HF ratios during heating and cooling actually reflect quite different cardiac autonomic states, *i.e.*, “a relative sympathetic predominance” compared with the control period due to *decreased vagal* modulation of heart rate in the case of sweating and due to *increased sympathetic* modulation of heart rate in the case of shivering. This effect, during shivering, is mitigated but not eliminated by treatment with dexmedetomidine.

Limitations

This study was performed in healthy volunteers who did not have a history of cardiac disease and who were not taking cardiotoxic medications. Whether findings would be similar in patients with cardiac disease or other diseases is unclear. The perioperative state is accompanied by sympathetic activation, and whether this might influence autonomic reflex responses during dexmedetomidine infusions remains uncertain. A strength of this study is rigid control of experimental conditions that could confound the results. The sample size was small, but the cross-over design nonetheless provided reasonable statistical power.

There were considerable interindividual responses across study periods as well as intraindividual responses between study sessions, but no one subject responded in a manner consistently different from the others. This observation, therefore, might represent background “noise” in autonomic nervous system testing as might result from a multitude of factors that can affect these measurements, including day-to-day changes in psychological state. Dexmedetomidine binds to both central and peripheral α_2 -adrenergic receptors.¹ Binding to the latter may lead to vasoconstriction, especially at higher doses or with fast drug infusion. An additional explanation for the heterogeneity of the responses might be

varying central and peripheral α_2 -adrenergic binding between study periods and sessions. Enhanced vasoconstriction might thus promote differing autonomic responses than vasodilation associated with inhibition of central sympathetic outflow.

Clinical Significance

The sympatholytic effects of α_2 agonists are well documented. There has been some concern that perioperative hypotension and relative hypovolemia might go clinically unnoticed and/or result in a delayed clinical intervention because sympathetic responses are impaired by α_2 agonists. Our findings, that the potent α_2 agonist dexmedetomidine does not change baroreflex sensitivity (slope), suggest that patients will have a normal heart rate response to changes in blood pressure during administration of dexmedetomidine. Our data during the control period suggest that slowing of the heart rate observed during dexmedetomidine infusions results mostly from sympathetic withdrawal and not enhanced vagal activity. Further, while these data show that dexmedetomidine blunted autonomic responses to thermal stressors, these responses were not eliminated by the drug.

Hypothermia has been associated with a higher frequency of potentially life-threatening ventricular arrhythmias.^{11,12} Heightened sympathetic nervous system activity promotes ventricular arrhythmias, while enhanced vagal tone is protective.³⁷ Our findings, during dexmedetomidine infusion, that sympathetic and parasympathetic activation occurred in parallel at the shivering threshold and not in a reciprocal fashion, are of clinical interest in that heightened vagal tone under these conditions might reduce susceptibility to life-threatening ventricular arrhythmias.

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