

The Effects of Increasing Plasma Concentrations of Dexmedetomidine in Humans

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Background: This study determined the responses to increasing plasma concentrations of dexmedetomidine in humans.

Methods: Ten healthy men (20–27 yr) provided informed consent and were monitored (underwent electrocardiography, measured arterial, central venous [CVP] and pulmonary artery [PAP] pressures, cardiac output, oxygen saturation, end-tidal carbon dioxide [ET_{CO₂}], respiration, blood gas, and catecholamines). Hemodynamic measurements, blood sampling, and psychometric, cold pressor, and baroreflex tests were performed at rest and during sequential 40-min intravenous target infusions of dexmedetomidine (0.5, 0.8, 1.2, 2.0, 3.2, 5.0, and 8.0 ng/ml; baroreflex testing only at 0.5 and 0.8 ng/ml).

Results: The initial dose of dexmedetomidine decreased catecholamines 45–76% and eliminated the norepinephrine increase that was seen during the cold pressor test. Catecholamine suppression persisted in subsequent infusions. The first two doses of dexmedetomidine increased sedation 38 and 65%, and lowered mean arterial pressure by 13%, but did not change central venous pressure or pulmonary artery pressure. Subsequent higher doses increased sedation, all pressures, and calculated vascular resistance, and resulted in significant decreases in heart rate, cardiac output, and stroke volume. Recall

and recognition decreased at a dose of more than 0.7 ng/ml. The pain rating and mean arterial pressure increase to cold pressor test progressively diminished as the dexmedetomidine dose increased. The baroreflex heart rate slowing as a result of phenylephrine challenge was potentiated at both doses of dexmedetomidine. Respiratory variables were minimally changed during infusions, whereas acid–base was unchanged.

Conclusions: Increasing concentrations of dexmedetomidine in humans resulted in progressive increases in sedation and analgesia, decreases in heart rate, cardiac output, and memory. A biphasic (low, then high) dose–response relation for mean arterial pressure, pulmonary arterial pressure, and vascular resistances, and an attenuation of the cold pressor response also were observed. (Key words: Adrenoceptor agonists; autonomic; α_2 receptor; baroreceptor; cardiovascular; cold pressor test; memory.)

THE α_2 receptors are involved in regulating the autonomic and cardiovascular systems. α_2 Receptors are located on blood vessels, where they mediate vasoconstriction, and on sympathetic terminals, where they inhibit norepinephrine release.^{1,2} α_2 receptors also are located within the central nervous system,³ and their activation leads to sedation, a reduction of tonic levels of sympathetic outflow, and an augmentation of cardiac vagal activity.^{4–6} This can result in a decrease in heart rate (HR) and cardiac output (CO).^{7,8} The use of α_2 agonists in the perioperative period has been associated with reduced anesthetic requirements and attenuated HR and blood pressure (BP) responses to stressful events.^{9–12} In addition, α_2 receptors within the spinal cord modulate pain pathways, thereby providing some degree of analgesia.^{13–15}

Clonidine is the prototypical α_2 agonist and has been studied for more than a decade. It has sedative and analgesic properties that reduce anesthetic¹⁶ and analgesic^{13,17} requirements during the perioperative period. The routine use of clonidine as an anesthetic adjuvant has been limited by its relatively long half-life of 6–10 h,¹⁸ although its ability to combine sedation with preservation of respiratory function suggests that it may be useful for prolonged postoperative sedation. The recently described adrenoceptor agonist dexmedetomi-

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dine has a half-life of only 2.3 h, and is 8- to 10-fold more potent than clonidine for the α_2 receptor. By virtue of this potency, dexmedetomidine is considered to be a full agonist of the α_2 receptor, which might permit its application in relatively high doses for sedation and analgesia without the unwanted vascular effects from activation of α_1 receptors. There have been a number of studies of lower doses of dexmedetomidine as an adjunct to anesthesia in cardiac and noncardiac patients undergoing cardiac and noncardiac surgical procedures.^{9,11,19-21} However, there have been no studies of the dose-response relation of continuous infusions of high concentrations of dexmedetomidine on the autonomic and cardiovascular responses of humans not receiving anesthetic drugs. It is unclear whether autonomic or direct peripheral vascular effects, or both, might limit the use of high concentrations of dexmedetomidine. Human studies that have used intravenous boluses of dexmedetomidine show decreases in BP and CO after small boluses (0.25–1 $\mu\text{g}/\text{kg}$), whereas the response to larger boluses (1–4 $\mu\text{g}/\text{kg}$) has been a transient increase in BP and a sometimes profound reflex bradycardia.^{8,22} The current study of healthy volunteers determined the autonomic, cardiovascular, and sedative responses to increasing steady state plasma concentrations of dexmedetomidine.

Materials and Methods

After approval of the protocol by the Human Research Review Committee of The Medical College of Wisconsin and the VA Medical Center, 10 healthy men provided written informed consent and were enrolled in the study. All 10 met entrance criteria that included normal history and physical examination results, 12-lead electrocardiography [ECC], urinalysis, and blood chemistry screening (complete blood count [CBC], electrolytes, liver function tests, hepatitis, and human immunodeficiency virus [HIV]), all of which were obtained within the 14 days preceding the study period. Subjects fasted at least 8 h before arrival at the laboratory. HR was monitored from leads II and V_5 of the electrocardiograph, and respiratory function was monitored with use of an abdominal bellows (respiratory rate [RR]), a nasal cannula (end-tidal carbon dioxide), and a pulse oximeter (oxygen saturation). A 20-gauge catheter was inserted into a radial artery for direct determination of arterial blood pressure and blood gases, and an 18-gauge catheter was inserted into a forearm vein for fluid maintenance and

drug administration. Lactated Ringer's solution was infused at a rate of 1.5 $\text{ml} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$. A pulmonary artery catheter was inserted into the right internal jugular vein for blood sampling and the measurement of central venous pressure (CVP), pulmonary artery pressure (PAP), pulmonary capillary wedge pressure (PCWP), and CO. The volunteers participated in the following tests: visual analog scale for sedation ($\text{VAS}_{\text{sedation}}$); picture recall memory test (MEM); and cold pressor (CP) test, after which they rated their pain with use of another visual analog scale (VAS_{pain}). In addition, the investigator rated the subject's level of alertness or sedation with use of the Observer's Assessment of Alertness/Sedation scale (OAA/S).

The $\text{VAS}_{\text{sedation}}$ is a 100-mm ruler with end points of "very alert" (0) and "very sedated" (100); the subject moves a sliding indicator line to identify their level of alertness. A score of 100 was used if subjects could not be aroused. The OAA/S comprises four scales that the researcher uses to assess alertness or sedation: speech responsiveness, facial expression, and eyes. A score of 100 on all four scales correlates with maximum alertness, and a composite score is determined by summing the scores of all four scales. The reliability and validity of the OAA/S have been established previously.²³ The picture recall memory test consisted of showing the subject a non-emotion-evoking picture of a familiar object and having the subject identify the object. A different picture (random order) was shown at each steady state time point. Therefore, each subject had the potential to see a total of eight objects. *Memory recall* was the number of objects recalled the morning after study drug administration, and "recognition" was the number of correct identifications from among 16 displayed pictures after the recall determination. The CP test consisted of immersion of the hand up to the wrist in continuously agitated ice water for 1 min, followed by a subjective assessment of pain with use of a sliding VAS_{pain} (0 = no pain, 100 = excruciating pain).

The following baseline measurements were obtained after a 30-min stabilization period following catheter insertion: BP, HR, PAP, CVP, PCWP, and CO. A blood sample was taken from the proximal port of the pulmonary artery catheter for determination of plasma norepinephrine, epinephrine, and dexmedetomidine levels. Alertness or sedation was assessed by the observer (OAA/S) and by the subject ($\text{VAS}_{\text{sedation}}$), after which the picture recall memory test and the CP tests were performed. HR and BP were averaged over the last 15 s of the test, and the subject rated pain using the VAS_{pain} scale. A blood sample was obtained immediately after

the test for norepinephrine and epinephrine determination. Five minutes after the CP test, a baroreceptor stress test was performed by use of intravenous injection of a 100- μ g bolus of sodium nitroprusside, followed 60 s later with a 200- μ g bolus of phenylephrine to restore and increase BP above baseline for 1 to 2 min. This process produces a range of BP perturbations (-20 to +15%), so that the sensitivity of the baroreceptor reflex regulation of HR can be adequately described.²⁴ Linear regression analyses were performed off-line to determine the slope ("sensitivity") of the HR increase to decreasing BP (depressor test) and the HR slowing in response to BP increases (pressor test).²⁴

After baseline data were recorded, dexmedetomidine was administered intravenously using a computer-controlled infusion pump (STANPUMP, Palo Alto, CA). The pump infused the study drug according to pharmacokinetic models to achieve, within 5 min, the following seven, ascending, targeted, plasma concentrations: 0.5, 0.8, 1.25, 2.0, 3.2, 5.0, and 8.0 ng/ml. Each infusion step lasted exactly 40 min. Measurements and tests performed at baseline (cardiovascular data, blood sampling, and psychometric and CP tests) were repeated beginning 15 min after each infusion step began and during predicted steady state (baroreflex testing was repeated only during the first two doses of dexmedetomidine). The timing of measurements and tests during each 40-min infusion period are displayed in table 1. Cardiopulmonary data were collected over 5-min and averaged. CO was determined from the average of three measurements.

The infusion of study drug was discontinued and re-

covery began when any one of the following criteria was observed: 30% increase from baseline in mean arterial BP (MAP), systolic BP, mean PAP or systolic PAP sustained for more than 5 min; 30% decrease in CO from baseline (subsequently amended to 35%, see Discussion); MAP less than 50 mmHg sustained for more than 5 min; CVP or PCWP greater than 12 mmHg; HR during infusion 40 beats/min or fewer sustained for more than 5 min; disturbances in cardiac conduction; or inability of investigator to maintain airway patency and oxygen saturation as measured by pulse oximetry (Sp_{O_2}) with head or chin repositioning. The subjects were monitored for 4 h after discontinuation of dexmedetomidine infusion (table 1). Invasive monitoring was halted 4 h after discontinuing the dexmedetomidine infusion, and, thereafter, noninvasive BP, HR, and Sp_{O_2} were monitored during an overnight recovery period. Subjects were discharged the morning after the study.

Analytical Methods

Off-line analysis was performed for 5-min segments (a baseline and during min 15-20 of each infusion period) of HR data to determine HR variability by use of power spectral analysis. A fast Fourier transform (FFT) was applied to the cardiac intervals, and the power in the high-frequency range (0.15-0.4 Hz) was determined. An index of cardiac-vagal activity has been determined as the percent of total HR power (0-0.5 Hz) that occurs in the high-frequency range of 0.15-0.4 Hz.²⁵

Dexmedetomidine concentrations were determined by use of gas chromatography-mass spectroscopy (GC/MS).²⁶ The lower limit of quantification was 10 pg/ml.

Table 1. Schedule of Measurements during Each 40-min Dexmedetomidine Infusion Step and during 4-h Recovery

Measurement*	Infusion	Recovery
	Sampling times (min after start of infusion or recovery)	
BP, PAP, HR, CVP, RR, Sp_{O_2}	5, 15	Every 30 min
Dexmedetomidine	14, 38	10, 19, 30, 45, 60, 120, 180, 240
CO, PCWP	20	25, 55, 115
NE, Epinephrine	25, after each CP test	30, 60
ABG	25	
VAS, OAA/S, MEM	26	Every 30 min
CP test	29	210 (in last five subjects)
BRT	35 (steps 1 and 2 only)	215 (in last five subjects)

* All measurements also were taken before dexmedetomidine infusions in a 40-min sequence identical to infusion. Times are minutes after starting dexmedetomidine infusions.

ABG = arterial blood gases; BP = blood pressure; BRT = baroreceptor reflex test; CO = cardiac output; CP test = cold pressor test; CVP = central venous pressure; HR = heart rate; MEM = memory test; NE = norepinephrine; OAA/S = observer's assessment of alertness/sedation; PAP = pulmonary artery pressure; PCWP = pulmonary capillary wedge pressure; RR = respiratory rate; Sp_{O_2} = oxygen saturation; VAS = visual analog scale.

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and the within-day and interday coefficients of variation were less than 15%. Epinephrine and norepinephrine were determined with use of the standard high-performance liquid chromatography method. The sensitivity of the system was 20–25 pg/200 μ l injectant, with a 68% recovery of epinephrine and a 98.5% recovery of norepinephrine.

Statistical Methods

Cardiorespiratory variables with full numerical strength were analyzed using regression analysis to relate the response of the variable to the average plasma level of dexmedetomidine during each infusion dose. The analysis allowed for random subject-effects because repeated measurements were made for the same subject. The regression model incorporated a possible discrete “drop” or “jump” in the response as the plasma level of dexmedetomidine changed from zero (baseline) to a positive value, followed by a functional relation of the remaining responses to the plasma levels of dexmedetomidine. This function was taken as the sum of a linear term and a square root term in the concentration of the drug, leading to the following equation:

$$Y = B_0 + B_1 \cdot \text{PLASMADC} + B_2 \cdot (\text{PLASMADC})^{0.5} + B_3 \cdot \text{PZERO}$$

where Y is the mean response, PLASMADC is the plasma concentration of dexmedetomidine, PZERO is an indicator variable equaling 1 at baseline (zero dose) and 0 otherwise, B_0 is the y -intercept, B_1 is the parameter for plasma dexmedetomidine concentration, B_2 is the pa-

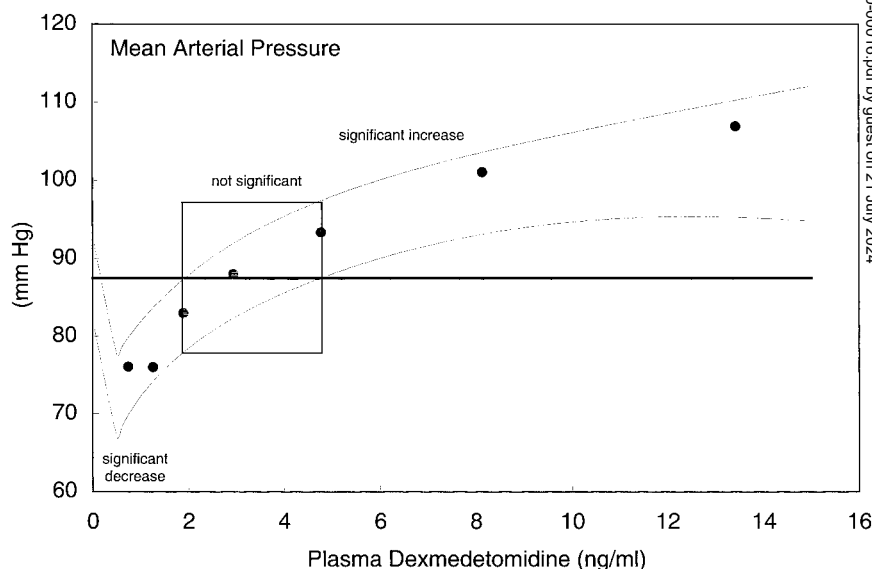
rameter for the square root of the plasma dexmedetomidine concentration, and B_3 is the parameter for PZERO. The regression line and the 95% confidence limits of the line were calculated for each variable. The response of that variable during dexmedetomidine infusion was considered to be significantly different from baseline whenever the 95% confidence limits exceeded or decreased below the baseline value (fig. 1).

Recovery period responses were similarly analyzed using regression analysis to relate the response to time and the plasma level of dexmedetomidine at the beginning of the recovery period. The analysis allowed for random subject-effects because repeated measurements were made for the same volunteers. The regression model incorporated the starting level of dexmedetomidine and the functional relation of mean response to time.

Nonparametric Tests

Four of the measured variables are on a scale of less than complete numerical strength and they were analyzed by use of a nonparametric procedure. These measured variables include the observer's assessment of alertness and sedation (OAA/S), $\text{VAS}_{\text{sedation}}$, VAS_{pain} during the CPT, and SpO_2 . Taking differences between successive available measurements for each subject, significance tests were performed to detect trends with increasing drug concentration. Recall and recognition were evaluated with use of the Mantel-Haenszel chi-square test. Significance was assigned if $P < 0.05$.

Fig. 1. A representation of the model and the technique to derive statistical significance. The model is shown for mean arterial pressure (MAP) and describes the mean and 95% confidence intervals for MAP as a function of the plasma concentration of dexmedetomidine. Statistical significance is achieved if the 95% confidence interval is outside the baseline value (before infusion of dexmedetomidine) of the measured variable.



Results

The average age was 24 yr (range, 20–27 yr), average height was 177 cm (range, 170–185 cm), and average weight was 78 kg (range, 68–88 kg). Plasma dexmedetomidine levels measured at 14 and 34 min after the beginning of each infusion step did not differ; therefore, plasma dexmedetomidine levels are reported as the average of both measurements. At each step, achieved dexmedetomidine levels exceeded targeted levels, and the gradient increased with each higher targeted level. Specifically, targeted:mean achieved dexmedetomidine levels were as follows (ng/ml, \pm SD): 0.5:0.7 \pm 0.22; 0.8:1.2 \pm 0.22; 1.2:1.9 \pm 0.23; 2.0:3.2 \pm 0.48; 3.2:5.1 \pm 0.64; 5.0:8.4 \pm 0.82; and 8.0:14.7 \pm 0.78 ng/ml.

Plasma levels of norepinephrine decreased significantly by 66% during the first infusion step and remained 60–85% below baseline during subsequent infusion steps (fig. 2). Norepinephrine levels did not show any significant recovery toward preinfusion baseline at 1 h after discontinuation of dexmedetomidine. Similarly, plasma epinephrine levels decreased 40% during the first infusion step and remained 40–60% below baseline during subsequent infusion periods (fig. 2). The index of cardiac-vagal activity (percent of total HR power [0–0.5 Hz] in the high-frequency range of 0.15–0.4 Hz) tended to increase throughout the infusion steps, but there was considerable individual variability, and significance was only achieved at infusion step 5 and at 2 h into recovery.

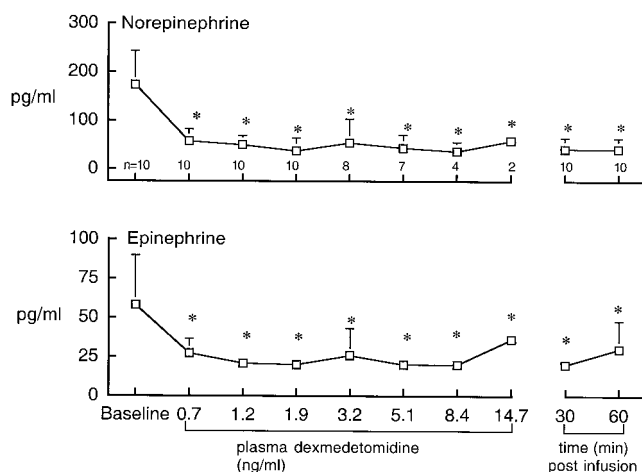


Fig. 2. The catecholamine responses to target, controlled infusions of dexmedetomidine. Plasma levels of norepinephrine and epinephrine (mean \pm SD) both decreased substantially after the first dose and remained suppressed throughout the infusion period and into the recovery period. *Significant change from preinfusion baseline value, $P < 0.05$.

Cardiovascular and Respiratory Effects

There was a biphasic BP response to increasing plasma levels of dexmedetomidine. The first two infusion steps of dexmedetomidine significantly lowered MAP by 13%, whereas higher concentrations of dexmedetomidine resulted in progressive increases in MAP, with average peak individual increases averaging 12% more than baseline. Increasing plasma concentrations of dexmedetomidine resulted in decreases in HR (average maximum decrease = 29%), progressive decreases in CO (average maximum decrease = 35%), and no decrease in stroke volume until infusion step 5 (fig. 3). The first two infusion steps did not significantly change CVP, PCWP, mean PAP, or calculated pulmonary or systemic vascular resistances. However, the third infusion step, which increased plasma levels of dexmedetomidine to 1.9 ng/ml was associated with significant increases in these variables that were sustained throughout subsequent infusion steps (fig. 4). The average individual maximum percent increases were as follows: CVP = 195%, PCWP = 89%, mean PAP = 44%, pulmonary vascular resistance = 155%, and systemic vascular resistance = 67%.

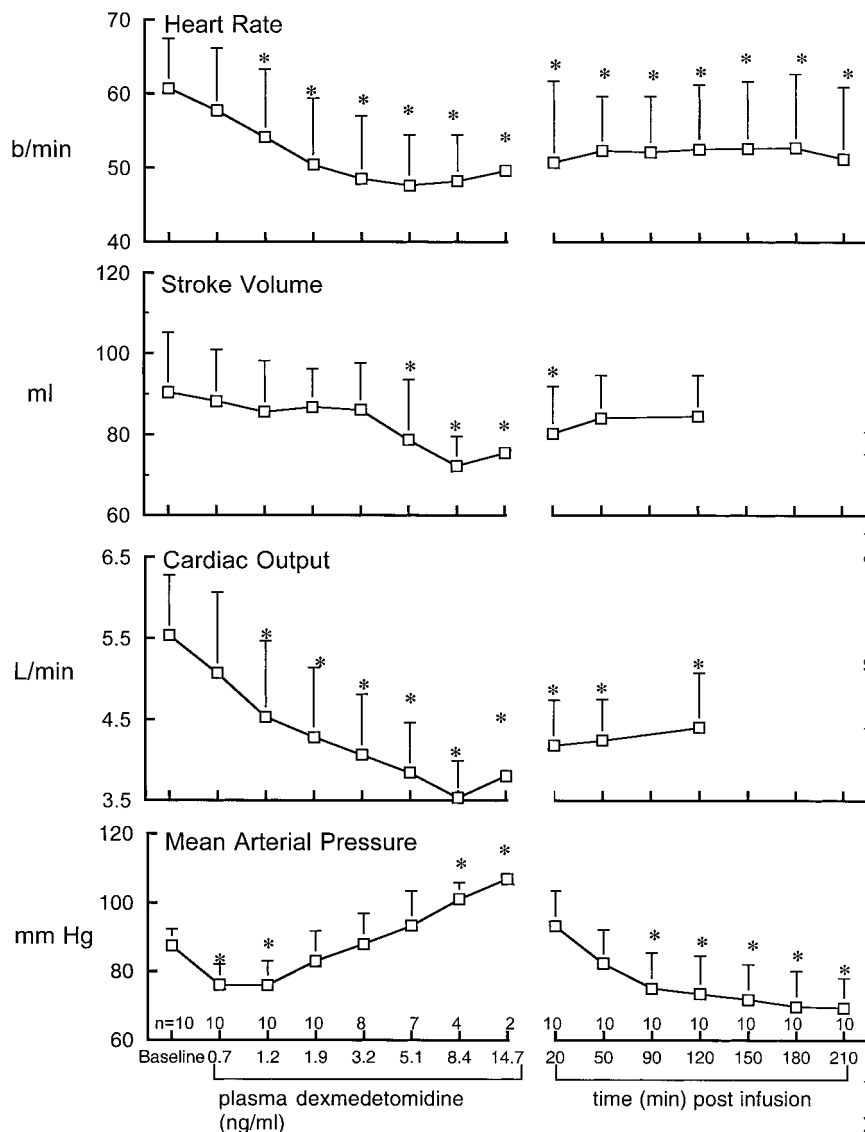
Based on clinical criteria, the respiratory system remained relatively uncompromised, even at high doses of dexmedetomidine (table 2). Arterial oxygenation was not significantly altered at any infusion dose. There were decreases in pH with increasing target doses that were statistically significant but not clinically important. There also was a gradual and statistically significant increase in the arterial carbon dioxide (P_{aCO_2}) during the stepwise infusions. However, even after the seventh step, P_{aCO_2} was 46.5 and 47.1 mmHg in the two volunteers in whom this dose was achieved. The respiratory rate gradually increased from 14 breaths/min at baseline to 23 breaths/min at the sixth infusion step to 25 breaths/min at the seventh infusion step ($n = 2$). Baseline bicarbonate values were 26.29 ± 1.61 mm and they did not significantly decrease during the dexmedetomidine infusions (range, 26.26–25.45 during infusions).

Sedation and Memory

The measures of sedation (OAA/S , VAS_{sedation}) were significantly changed during infusions ($P < 0.004$), as shown in figure 5. Sedation increased progressively with increasing dexmedetomidine concentrations (fig. 5). The mean (\pm SD) baseline VAS_{sedation} score was 4 (\pm 11). An increase in the VAS_{sedation} score of 36 (\pm 27) was seen after the first targeted dose. During the second dose, the mean increase from baseline was 62 (\pm 18). Thereafter, sedation levels continued to gradually in-

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Fig. 3. The hemodynamic response (mean \pm SD) to target, controlled infusions of dexmedetomidine. There were significant changes in cardiac output and heart rate after infusion step 1. Stroke volume remained unchanged until higher doses. Mean arterial blood pressure (MAP) showed a biphasic (low, then high) response to increasing infusions of dexmedetomidine. *Significant change from preinfusion baseline, $P < 0.05$.



crease. The two volunteers who received the highest incremental dose (infusion step 7) could not be aroused, even by very vigorous shaking. In addition, one subject could not be aroused at step 3, two at step 4, and three at steps 5 and 6. The VAS_{sedation} score recovered gradually over the 4-h postinfusion observation period, after which time it was not significantly different from baseline level.

In the memory test 1 day after study initiation, all volunteers recalled and recognized the picture they had been shown at baseline. Recall and recognition both were well-preserved for the picture shown during the first infusion step (8 of 10 and 10 of 10 volunteers,

respectively), and thereafter recall and recognition both decreased (fig. 6). The third dose of dexmedetomidine totally abolished recall (0%), and recognition was only 20% (2 of 10).

Cold-pressor Testing

The CP test in the preinfusion (baseline) period resulted in a 15% increase in MAP and a 28% increase in norepinephrine (fig. 7). Dexmedetomidine at all infusion steps prevented a significant norepinephrine response to the CP test. Increasing dexmedetomidine infusions progressively diminished the MAP response to the CP test until it was essentially abolished after the second

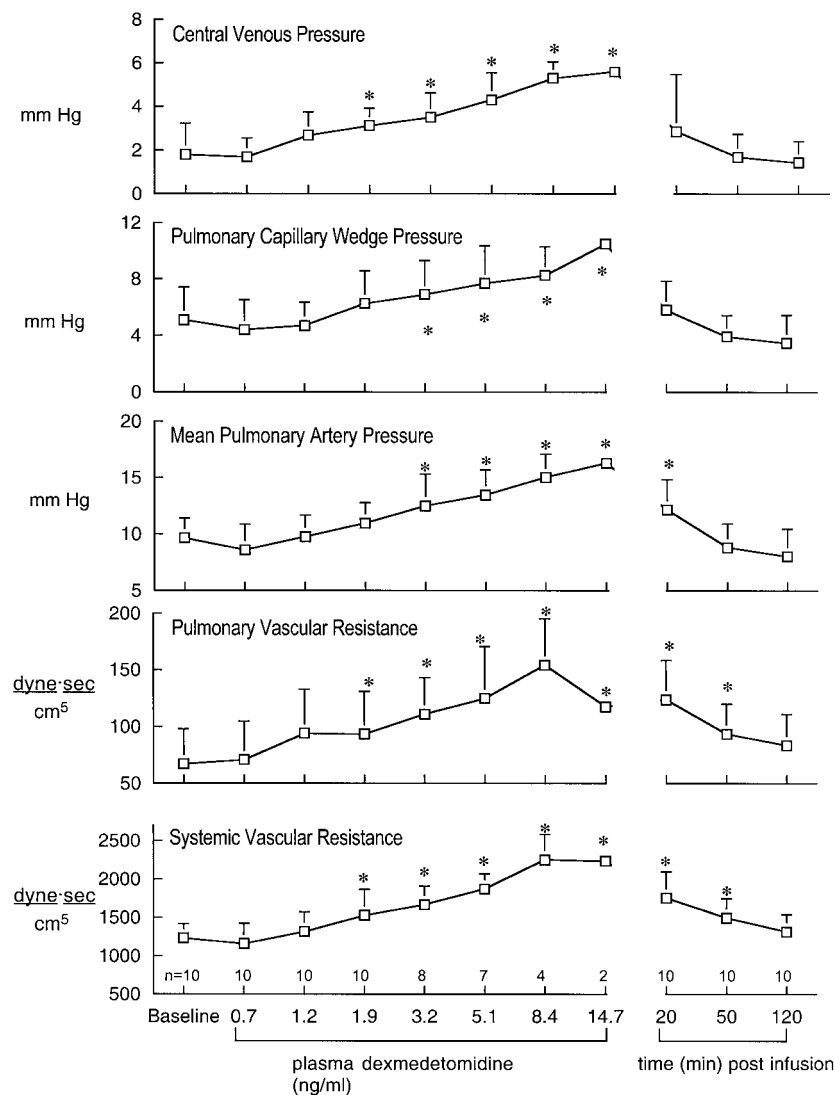


Fig. 4. Additional hemodynamic responses (mean \pm SD) to target, controlled infusions of dexmedetomidine. Low doses of dexmedetomidine did not change central hemodynamics or systemic vascular resistance, but larger doses increased all variables. These increases were sustained throughout remaining infusion steps. *Significant change from preinfusion baseline, $P < 0.05$.

infusion step, at which plasma levels exceeded 1.2 ng/ml. The epinephrine response to the CP test was not influenced by dexmedetomidine infusions.

The VAS_{pain} scores after CP test decreased significantly during dexmedetomidine infusion (fig. 7). These decreases represent data from subjects who were able to score their pain ($n = 7$, step 4; $n = 4$, step 5; $n = 1$, step 6), and from subjects who were asleep and did not awaken during the CP test. Their pain was scored as zero ($n = 1$, step 4; $n = 3$, step 5; $n = 3$, step 6). These doses were not achieved in the remaining subjects. The two subjects in whom dose 7 was achieved were asleep and were not aroused during the CP test, and their pain response was scored as 0.

Baroreceptor Reflex Testing

In response to the depressor test (sodium nitropruside), the reflex gain of HR during hypotension was unchanged during dexmedetomidine infusions (fig. 8). The reflex gain of HR from the pressor test (phenylephrine) was significantly increased during both dexmedetomidine infusion steps.

Recovery

Recovery data for all variables have been included in the figures, when available. Recovery began from different levels of plasma dexmedetomidine. Specifically, the two people in whom the highest dexmedetomidine dose was achieved (20% of the sample) recovered more

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Table 2. Respiratory and Acid-Base Variables during Infusion of Dexmedetomidine

Infusion step	Baseline	1 0.5*	2 0.8*	3 1.25*	4 2.0*	5 3.2*	6 5.0*	7 8.0*
n	10	10	10	10	9	7	4	2
Pa _{O₂} (mmHg)	92 ± 2	94 ± 3	95 ± 2	100 ± 4	101 ± 6	92 ± 2	87 ± 3	100 ± 21
Pa _{CO₂} (mmHg)	43 ± 1	44 ± 1	45 ± 1†	45 ± 1	46 ± 1†	46 ± 1†	46 ± 1	47 ± 0
pH	7.39 ± 0.003	7.38 ± 0.004†	7.37 ± 0.005†	7.37 ± 0.004†	7.36 ± 0.004†	7.36 ± 0.009†	7.35 ± 0.009	7.35 ± 0.012
Respiration rate (breaths/min)	14 ± 1	16 ± 1	16 ± 1	18 ± 1†	19 ± 1†	20 ± 1†	23 ± 1	25 ± 0
Oxygen saturation (%)	98 ± 0.2	97 ± 0.2†	97 ± 0.2†	97 ± 0.2†	97 ± 0.6	97 ± 0.4	96 ± 0.7	96 ± 0.5

Data are mean ± SEM.

* Target dexmedetomidine (ng/ml).

†P < 0.05 compared with baseline values.

slowly than did the remaining 80% of the study population. Recovery data are presented as group means, and the greater variation in these samples is most likely explained by the variation in plasma levels of dexmedetomidine.

Discontinuation Criteria

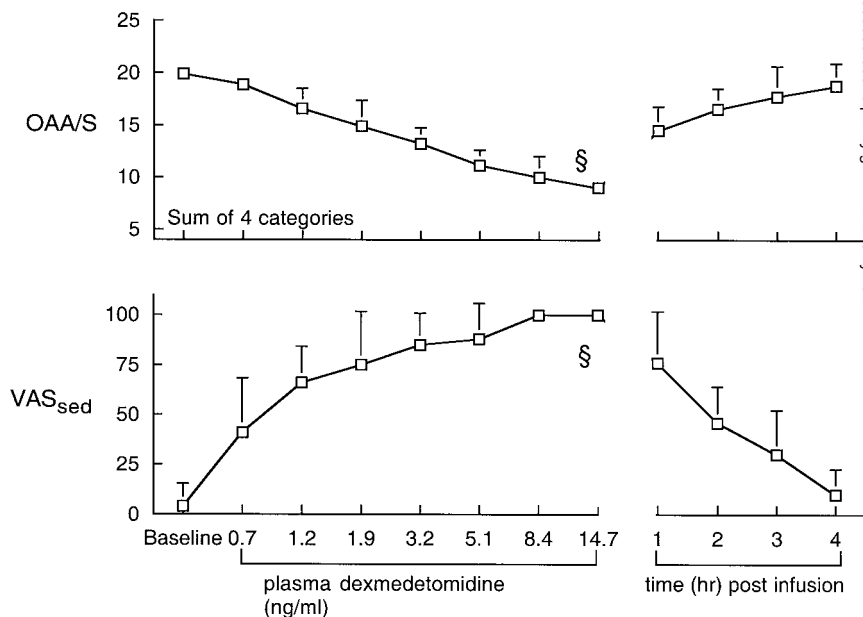
In the first three subjects, study drug discontinuation was based on a 30% decrease in CO, although acid-base status and stroke volume were well-maintained. In the remaining seven subjects, modified discontinuation criteria required at least a 35% decrease in CO or an HR ≤ 40 beats/min, or both, associated with other signs of circulatory compromise (change in acid-base status or Sp_{O₂}) as determined by the investigator. This permitted the evaluation of higher plasma concentrations of

dexmedetomidine without compromising the subject. In two people, infusions were discontinued because of MAP that exceeded 30% of baseline, and, in another two people, discontinuation occurred because mean PAP increased 30% above baseline value. In one subject, the infusions were halted because of relatively profound and unexplainable agitation. The subject's restlessness prevented reliable data collection, which necessitated quiet resting conditions. This discontinuation occurred during the fourth infusion step at a plasma level of 3.6 ng/ml.

Discussion

The α₂ agonists have a number of properties that may prove to be useful for treating the patient undergoing

Fig. 5. Sedation scores (mean ± SD) in response to target, controlled infusions of dexmedetomidine. The composite Observer Assessment of Alertness/Sedation score can range from 9 to 20, with 20 indicating maximum alertness. VAS_{sedation} (VAS_{sed}) is a visual analog scale with end points of very alert (0) to very sedated (100). §Significant change in variable during increasing dexmedetomidine infusions, determined with use of non-parametric statistics.



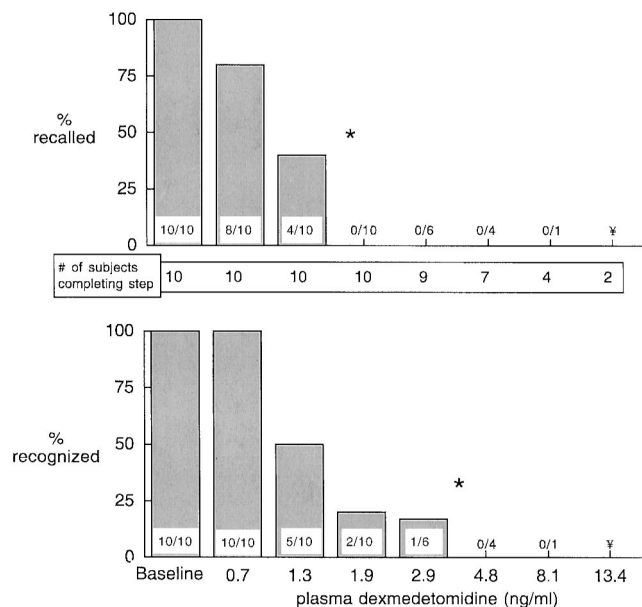


Fig. 6. Bar graph of percent of correct responses to the memory test at each infusion step. The number of subjects that correctly recalled or recognized the picture over the number of subjects participating in the test at each infusion step is indicated within the box in each bar (No. recalled/No. participating). Beginning with infusion step 4, the number of subjects that received dexmedetomidine no longer corresponds to the number of subjects that were shown a picture. The difference is the number of subjects that could not be aroused. † Indicates that no pictures were shown at this step because both subjects who received this dose could not be aroused. **P* < 0.05, significant trend during dexmedetomidine infusions compared with baseline, Mantel-Haenszel test.

painful surgical procedures. Administration in lower concentrations as adjuvants during the intraoperative period has resulted in a reduced requirement for other anesthetic agents, fewer interventions to treat tachycardia, and a reduction in the incidence of myocardial ischemia.^{9,27,28} However, this use has been limited by a number of side effects, such as the increased need for fluid supplementation and the greater need for pharmacologic rescue therapy for bradycardia and hypotension.^{19,20,29} These side effects may be attributed to the combined properties of the volatile anesthetics (vasodilation and myocardial depression) and α_2 agonists (sympathoinhibition). Another potential use for the newer, more specific α_2 agonists would be as “complete” anesthetics when used in high concentrations. Concerns related to high concentrations of dexmedetomidine include the potential for systemic and pulmonary hypertension because of direct peripheral vascular effects or the potential to compromise myocardial function or

blood pressure, or both, as a result of profound autonomic effects.

The current study indicates that increased concentrations of dexmedetomidine in humans result in decreases in HR, progressive decreases in cardiac output, a biphasic (low, then high) dose-response relation for blood pressure and vascular resistance, and an attenuation of the CP test response. At all plasma concentrations up to 8 ng/ml, the metabolic demands of the subjects were met based on a preservation of acid-base balance. Lower plasma concentrations of dexmedetomidine provided sedation-analgesia, while preserving recall and recognition. Higher concentrations of dexmedetomidine caused systemic and pulmonary hypertension, without respiratory compromise, and resulted in profound sedation, analgesia, and memory impairment.

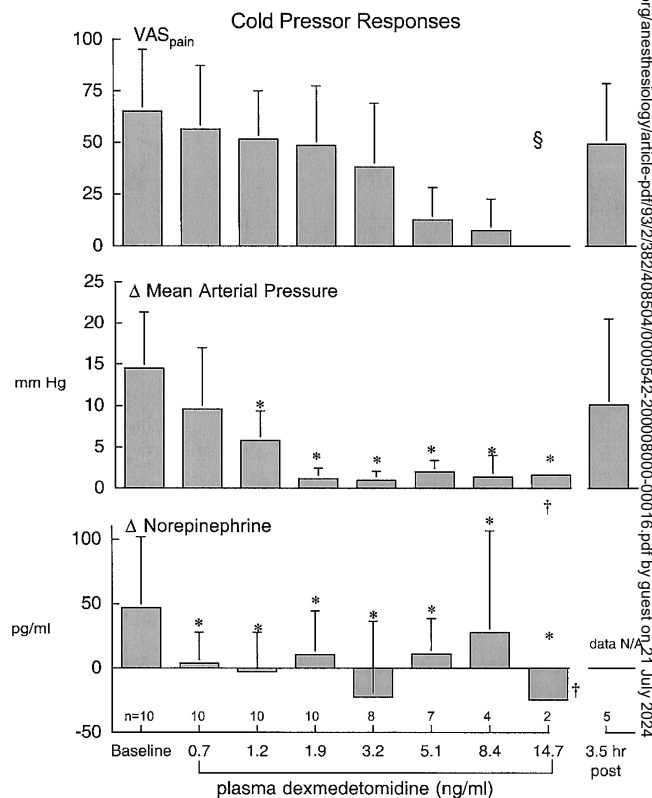


Fig. 7. The change in mean arterial pressure (MAP), norepinephrine (NE), and pain responses (VAS_{pain}) (mean $\Delta \pm$ SD) to the cold-pressor test. This test was applied before (preinfusion), during each infusion of dexmedetomidine, and one time in the recovery period (n 5 for recovery). The VAS_{pain} scale rates pain from 0 no pain to 100 excruciating pain. Perception of pain was significantly reduced during the infusions (response evaluated with use of nonparametric statistics). The MAP and norepinephrine responses also were attenuated at all infusion steps. *Significant change from preinfusion baseline, *P* < 0.05.

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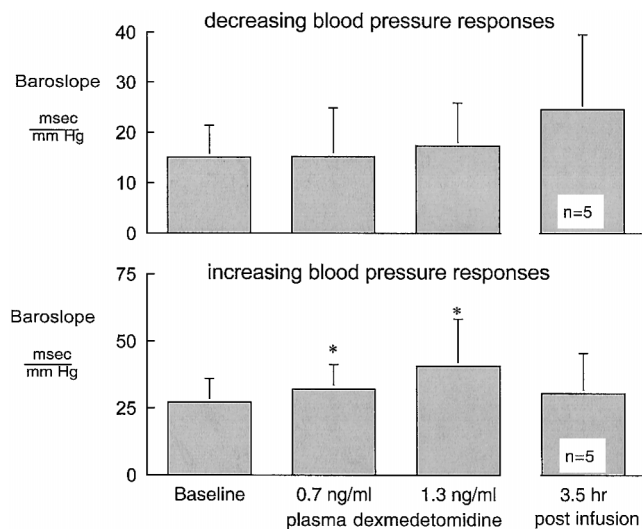


Fig. 8. Baroreflex sensitivity (mean \pm SD) during increasing plasma dexmedetomidine levels (n 10). Sensitivity was calculated from the slope of the relation between R-R interval (R-RI) and mean arterial pressure (MAP) during sodium nitroprusside (decreasing pressure) and during phenylephrine (increasing pressure). Baroreflex sensitivity was tested only at baseline and infusion steps 1 and 2. There was a significant potentiation of the response to phenylephrine at both doses of dexmedetomidine. *Significant change from preinfusion baseline, $P < 0.05$.

Cardiovascular Effects

Lower Plasma Concentrations. The first two infusion periods resulted in average plasma concentrations of dexmedetomidine of 0.7 and 1.2 ng/ml, which decreased plasma norepinephrine by more than 50%. These infusions lowered BP but did not significantly alter SVR or CVP. Although PCWP did not change during the initial three infusion doses, it significantly increased throughout subsequent infusions. These results suggest that the initial two concentrations were below the threshold to produce significant peripheral vaso- or venoconstriction or that the sympatholytic effects of dexmedetomidine offset any direct effect on the peripheral vasculature. HR and CO both were decreased during the first several infusion steps, and this most likely contributed to the reduction of BP. It is now reasonably clear that sympatholysis from dexmedetomidine is importantly involved in slowing of HR because patients prescribed β -receptor blocking drugs do not experience HR slowing when receiving dexmedetomidine.¹⁹ A second mechanism for reducing HR during dexmedetomidine may be by increasing cardiac vagal activity, as suggested by others.⁶ The current study used HR variability to obtain an indirect evaluation of cardiac-vagal activity.³⁰ However, this measurement provided highly vari-

able changes, such that no consistent significant effects were observed.

We avoided bolus dosing of dexmedetomidine. A previous study⁸ indicated that when dexmedetomidine was administered in a 1- μ g/kg bolus (which resulted in plasma levels of 0.9 ng/ml, similar to the lower concentrations in this study), a transient increase in BP and a reflex decrease in HR were noted. Findings in animals indicate that the pressor response to bolus doses of α_2 -agonists are enhanced after autonomic denervation.³ This suggests that, when sympathetic inhibition from the central actions of the α_2 agonists are absent, the peripheral vascular action (vasoconstriction) is unmasked.

Higher Plasma Concentrations. At plasma concentrations of dexmedetomidine that exceed 1.9 ng/ml progressive increases in BP, SVR, and PVR and further decreases in CO were observed. The decrease in CO was caused by further decreases in HR and, at higher doses, stroke volume, but possibly not from further decreases in sympathetic outflow because norepinephrine concentrations showed no significantly greater decreases from the value at the 1.9-ng/ml concentration of dexmedetomidine. It is unlikely that the further reduction in CO can be attributed to a direct effect of dexmedetomidine on the myocardium because several investigations in animal models have shown that dexmedetomidine has no direct myocardial effects.^{7,32} We cannot rule out the possibility that some of the CO reduction is caused by an increased afterload or a reduction in the metabolic demands of the body.

At higher concentrations of dexmedetomidine, there also were significant and progressive increases in PCWP and CVP. This is probably related to both the decreased CO and the increased PAP. In addition, α_2 -mediated venoconstriction could have contributed to these changes.

Respiratory Effects

We observed only minimal effects of dexmedetomidine on the respiratory system throughout a broad range of plasma concentrations. Minute volume was not measured, but Pa_{O_2} was well-maintained throughout. However, more pronounced respiratory effects have been reported when dexmedetomidine is rapidly infused to high concentrations. A dose of 1 or 2 μ g/kg dexmedetomidine administered to volunteers over 2 min (achieving peak plasma levels of 0.9 and 2.3 ng/ml) resulted in irregular breathing and short episodes of apnea and, in some cases, mild hypoxemia and hypercapnia.⁵ Apnea, airway obstruction, and hypoxemia did not occur in our

study, in which bolus dosing was avoided. Because the α_2 adrenoceptor does not have an active role in the respiratory center,³³ the very mild respiratory depression that was observed is more probably secondary to profound sedation.

Sedation and Cognition

Dexmedetomidine administered by computer-controlled, target infusion was associated with dose-related sedation and analgesia based on VAS_{sedation} and OAA/S measures and the VAS_{pain} score in response to a CP test. Recall and recognition decreased with increasing dose ($P < 0.05$), but only substantially decreased (100% decrease in recall and 80% decrease in recognition) when the target level of 1.25 ng/ml (mean plasma level 1.9 ng/ml) was achieved.

The sedative properties of α_2 -adrenergic agonists are well-documented, with the majority of work focused on clonidine.^{17,34,35} In the current study, the inability to "wake up" volunteers was not a criterion for drug discontinuation. Rather, discontinuation criteria included inability to maintain airway patency and oxygenation. Because these were not compromised at any dose, extremely high plasma concentrations of dexmedetomidine were achieved in some volunteers. This resulted in deep sedation associated with unresponsiveness to loud verbal stimuli and vigorous shaking. Four hours after discontinuation of infusions, sedation scores had recovered and were not significantly different from baseline scores.

Despite dose-related sedation, recall and recognition were not severely impaired until the third incremental infusion step. This may have implications when using dexmedetomidine as an anesthetic adjuvant or for postoperative sedation.‡ Target doses of dexmedetomidine of 0.5–1.25 ng/ml (plasma concentration 0.7–1.9 ng/ml) produce sedation, with preservation of memory (free recall and recognition) and a modest level of analgesia.

Analgesic Effects

There was a 14% decrease in the pain score to the CP test after the first incremental dose of dexmedetomidine, accompanied by a significant decrease in the MAP response to the CP. Increasing doses lead to linearly decreasing pain sensation and MAP response to the CP. In

five subjects, the CP test was repeated at 3.5 h post dexmedetomidine infusions and VAS_{pain} was still reduced by 35% from baseline. Several mechanisms have been postulated for the analgesia noted with α_2 -adrenergic agonists. Supraspinal,³⁶ ganglionic,³⁷ spinal,³⁸ and peripheral actions³⁹ have been shown. Large intravenous doses of clonidine have a direct spinal effect,⁴⁰ and the high plasma concentrations in this study might have resulted in some spinal analgesic effect.

Baroreflex Responses

Baroreflex testing was performed at baseline and at the two lower doses of dexmedetomidine. The initial study design was to evaluate reflex function at higher concentrations of dexmedetomidine. This was abandoned because of concerns that profound bradycardia or asystole might occur during the phenylephrine portion of the test sequence. With dexmedetomidine, we noted a preservation of the reflex tachycardia during the depressor portion of the test. Therefore, reflex increases in cardiac sympathetic outflow or withdrawal of cardiac-vagal tone that occur during hypotension could still be effectively achieved against a background of centrally mediated sympathoinhibition (and possible vagal potentiation) from dexmedetomidine. In contrast, the reflex HR slowing to the pressor stimulus was augmented during dexmedetomidine. Our previous work⁴ with oral clonidine in human volunteers indicated that, despite reduction in basal sympathetic outflow, clonidine preserved but did not augment the ability of the reflexes to adjust HR and sympathetic nerve activity.

Limitations

Because this study necessitated invasive procedures and a long period of supine positioning (up to 12 h), a placebo-infused comparator group was not used. Our experiences with studies of unsedated volunteers suggest restlessness alone modifies hemodynamics and catecholamines. In general, other adjuvants for sedation such as propofol or midazolam, are not associated with increasing systemic pressure or PAP when used in high doses (presuming respiratory function is controlled). Because of the relatively long half-life of dexmedetomidine, we were unable to randomize the dose in this single experimental session. A study design of different doses on different days was not considered because of concerns related to repeated invasive intervention, daily variability, and the potential for subject dropouts. Study drug discontinuation criteria prevented a true representation of all hemodynamic variables at higher doses. For

‡ Abbott Laboratories (Abbott Park, Illinois) is seeking Food and Drug Administration approval to use dexmedetomidine at plasma concentrations of 1 ng/ml or less for sedation in the intensive care unit.

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example, average MAP and PAP may have been higher had we not discontinued some subjects because their MAP or PAP exceeded the predefined end points (> 30% increase).

In summary, lower plasma concentrations of dexmedetomidine may be useful to provide sedation and mild analgesia while preserving memory and cardiovascular and respiratory functions. Increasing concentrations of dexmedetomidine resulted in decreases in HR, progressive decreases in CO, and a biphasic (low, then high) dose-response relation for BP and vascular resistances. Higher concentrations of dexmedetomidine resulted in systemic and pulmonary hypertension. Although high concentrations of dexmedetomidine resulted in further sedation and analgesia with minimal respiratory changes, the observed cardiovascular effects might limit the usefulness of high concentrations of dexmedetomidine when used in a less healthy patient population.

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