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Effect of Dexmedetomidine on Cerebral Blood Flow Velocity, Cerebral Metabolic Rate, and Carbon Dioxide Response in Normal Humans

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Background: **Dexmedetomidine reduces cerebral blood flow (CBF) in humans and animals. In animal investigations, cerebral metabolic rate (CMR) was unchanged. Therefore, the authors hypothesized that dexmedetomidine would cause a decrease in the CBF/CMR ratio with even further reduction by superimposed hyperventilation. This reduction might be deleterious in patients with neurologic injuries.**

Methods: **Middle cerebral artery velocity (CBFV) was recorded continuously in six volunteers. CBFV, jugular bulb venous saturation ($Sjvo_2$), CMR equivalent (CMRe), and CBFV/CMRe ratio were determined at six intervals before, during, and after administration of dexmedetomidine: (1) presedation; (2) presedation with hyperventilation; at steady state plasma levels of (3) 0.6 ng/ml and (4) 1.2 ng/ml; (5) 1.2 ng/ml with hyperventilation; and (6) 30 min after discontinuing dexmedetomidine. The slope of the arterial carbon dioxide tension ($Paco_2$)–CBFV relation was determined presedation and at 1.2 ng/ml.**

Results: **CBFV and CMRe decreased in a dose-related manner. The CBFV/CMRe ratio was unchanged. The CBFV response to carbon dioxide decreased from 1.20 ± 0.2 $cm \cdot s^{-1} \cdot mm\ Hg^{-1}$ presedation to 0.40 ± 0.15 $cm \cdot s^{-1} \cdot mm\ Hg^{-1}$ at 1.2 ng/ml. $Sjvo_2$ was statistically unchanged during hyperventilation at 1.2 ng/ml *versus* presedation (50 ± 11 *vs.* 43 ± 5%). Arousal for hyperventilation at 1.2 ng/ml resulted in increased CBFV (30 ± 5 to 38 ± 4) and Bispectral Index (43 ± 10 to 94 ± 3).**

Conclusions: **The predicted decrease in CBFV/CMRe ratio was not observed because of an unanticipated reduction of CMRe and a decrease in the slope of the $Paco_2$–CBFV relation. CBFV and Bispectral Index increases during arousal for hyperventilation at 1.2 ng/ml suggest that CMR–CBF coupling is preserved during dexmedetomidine administration. Further evaluation of dexmedetomidine in patients with neurologic injuries seems justified.**

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DEXMEDETOMIDINE is a highly selective α_2 agonist for which the labeled indication is intensive care unit sedation. It can produce a state of "cooperative sedation" associated with minimal respiratory depression and some analgesia. Those properties make it potentially attractive in many clinical situations, including the sedation of intensive care unit patients in whom the ability to perform frequent neurologic evaluations is of clinical importance. In addition, those same clinical properties might be advantageous in central nervous system–related procedures performed outside the intensive care unit, including awake craniotomy, carotid endarterectomy during regional anesthesia, carotid angioplasty and stenting, and other neurointerventional procedures.

However, there is a significant and unresolved issue with respect to the safety and suitability of dexmedetomidine for use in patients who have or who are at risk for neurologic injuries. That issue is the matter of the uncertainty as to the effect of dexmedetomidine on the ratio of cerebral oxygen supply to cerebral oxygen demand, *i.e.*, the ratio of cerebral blood flow (CBF) to cerebral metabolic rate (CMR). The concern arises because the limited existing body of information suggests that dexmedetomidine might result in a reduction of the CBF/CMR ratio. The available information indicates that dexmedetomidine causes a reduction of CBF in humans.[1,2] The effect of dexmedetomidine on CMR is less well documented. The only relevant investigations, performed in dogs anesthetized with isoflurane or halothane, reported no effect whatsoever of dexmedetomidine on CMR.[3,4] Reduction of CBF with no change in CMR would result in a reduction of the CBF/CMR ratio. The current era is one in which clinicians involved in anesthesia for neurosurgery and neurologic critical care have restricted the use of hyperventilation as a result of the concern that imposing a potent vasoconstrictive stimulus (hypocapnia) on marginally perfused brain will result in ischemia. The parallel concern is that dexmedetomidine might similarly cause CBF reduction without a parallel change in CMR and thereby compromise cerebral oxygen delivery. On the basis of the existing CBF and CMR information, we hypothesized that the administration of dexmedetomidine to healthy subjects would result in reduction of the CBF/CMR ratio and that the superimposition of hypocapnia would further decrease that ratio to a near–physiologically threatening degree. The following investigation was undertaken to test that hypothesis.

Materials and Methods

After approval by the institutional review boards of the University of California, San Diego and the Veterans Affairs Medical Center, San Diego, six healthy males aged 33–57 yr provided written informed consent and were enrolled in the study. None was receiving psychoactive or antiseizure medications, and all were free of neurologic and cardiac disorders. All subjects were classified as American Society of Anesthesiologists physical status I or II. None had had previous exposure to dexmedetomidine. Subjects fasted for at least 8 h and abstained from caffeine ingestion for the 12 h before the study session. None of the subjects used tobacco products.

The studies were conducted in the Simulation Center at the Veterans Affairs Medical Center, San Diego. Subjects were asked to void before the start of the study to avoid placement of a urinary catheter. Monitors were applied, vascular catheters were inserted, and the study was conducted with the subjects in a comfortable supine position. Sequential compression devices were applied to both lower legs. Bispectral Index (BIS XP®; Aspect Medical Systems, Inc., Norwood, MA) and near-infrared spectroscopy (NIRS) (INVOS® Cerebral Oximeter; Somanetics, Troy, MI) electrodes were placed on the left and right forehead, respectively. The NIRS was used to provide early warning of potentially hazardous degrees of reduction of the CBF/CMR ratio that we anticipated might occur with hyperventilation during dexmedetomidine administration. When the function of the BIS and NIRS electrodes had been confirmed, transcranial Doppler probes (Pioneer TC8080 and Companion III; Nicolet-Viasys Health Care, Madison, WI) were placed to insonate middle cerebral artery velocity (CBFV) bilaterally. The probes were secured and maintained in a constant position using an adjustable circumferential head holder. The side that yielded the highest quality signal was used for the subsequent data collection. Oxygen saturation (pulse oximeter), electrocardiogram (leads II and V5), heart rate, end-tidal carbon dioxide (ET_{CO_2}; nasal cannula), and respiratory rate (from the capnogram) were monitored continuously. Oxygen was delivered at 1 l/min by nasal cannula. A 20-gauge catheter was inserted into a peripheral upper extremity vein for fluid (0.9% normal saline) and dexmedetomidine administration. A 20-gauge catheter was inserted into a radial artery for continuous arterial blood pressure monitoring and intermittent blood gas sampling. An 18-gauge, 6-inch catheter (Arterial line Kit/1 Lot No. 99520245; Argon Medical Devices, Athens, TX) was introduced into the right internal jugular vein, using ultrasound guidance, at approximately the level of the cricothyroid membrane and passed retrogradely into the jugular bulb. Placement at the base of the skull or within the jugular bulb was verified objectively by ultrasound and subjectively by confirmation of middle ear/retromastoid sensation by the subjects. Blood samples for jugular venous oxygen saturation (Sjv_{O_2}) determination were collected intermittently by aspiration of blood at a rate of not greater than 1.5 ml/min. This approach should limit extracerebral blood contamination to an insignificant amount.[5,6] All catheter placements were performed using sterile technique and local infiltration with 1% lidocaine.

Cerebral (BIS, NIRS, CBFV) and cardiorespiratory parameters (mean arterial pressure, arterial oxygen saturation, ET_{CO_2}, respiratory rate, heart rate) were observed continuously throughout the study period. In addition, at six predetermined intervals, simultaneous samples of arterial and jugular venous blood were obtained for blood gas determination. The six intervals were presedation, presedation with hyperventilation (presedation–HV), steady state dexmedetomidine plasma level 0.6 ng/ml (0.6 ng/ml), steady state dexmedetomidine plasma level 1.2 ng/ml (1.2 ng/ml), steady state dexmedetomidine plasma level 1.2 ng/ml with hyperventilation (1.2 ng/ml–HV), and 30 min after discontinuation of dexmedetomidine infusion (recovery). After placement of the right internal jugular catheter, the room lighting was lowered, and 10 min of undisturbed stabilization ensued. Thereafter, the presedation arterial and venous samples and physiologic data were obtained. The subject was then asked to hyperventilate voluntarily (aided by a metronome for respiratory rate pacing) to achieve an ET_{CO_2} of 20 mm Hg. When a stable ET_{CO_2} level of 20 mm Hg had been maintained for 5 min, the presedation–HV blood samples and data were obtained. Thereafter, the subject was allowed to breathe at a spontaneous rate for 5 min. Dexmedetomidine was then administered intravenously using a STANPUMP infusion protocol# to achieve a steady state drug plasma dexmedetomidine concentration of 0.6 ng/ml in 40 min. Forty-five minutes after initiation of the infusion, the 0.6 ng/ml blood specimens and physiologic data were obtained. The infusion protocol was then adjusted to achieve a serum level of 1.2 ng/ml after an additional 40 min. Five minutes thereafter, the 1.2 ng/ml data were obtained. Every attempt was made to avoid disturbing the subject during data collection at the 0.6 and 1.2 ng/ml intervals. When the latter data had been obtained, the subject was aroused in anticipation of the second hyperventilation phase. Immediately upon arousal, CBFV and BIS were noted, and immediately thereafter, the subject was asked to hyperventilate, again with metronome pacing. No attempt was made to achieve a sustained "steady state" before hyperventilation. During hyperventilation, the dexmedetomidine infusion continued to maintain the 1.2 ng/ml serum level. When an ET_{CO_2} of 20 mm Hg had been maintained for 5 min, the 1.2 ng/ml–HV data were obtained. The dexmedetomidine infusion was

STANPUMP program. Available at: http://anesthesia.stanford.edu/pkpd/. Accessed February 2007.

Table 1. Modified Observer's Assessment of Alertness/Sedation Scale

Score	Responsiveness	Speech	Facial Expression	Eyes
5	Awake and alert; responds to normal tone	Normal	Normal	Clear
4	Lethargic response to normal tone	Mild slowing	Mildly relaxed	Mild ptosis
3	Responds only to loud and/or repeated voice	Moderate slowing or slurred	Very relaxed	Severe ptosis or eyes closed
2	Responds only to mild shaking	Incoherent	—	—
1	Does not respond to mild shaking	—	—	—

Maximum score of 20 with sum of all categories.

then discontinued, and the subject was left undisturbed. Thirty minutes later, the recovery interval data were obtained.

The CMR equivalent (CMRe) was calculated at each of the six intervals as follows:

$$\text{CMRe} = \text{CBFV} \times (\text{Cao}_2/\text{ml} - \text{Cjvo}_2/\text{ml}) \text{ (relative units)}.$$

The CBFV/CMRe ratio was also determined at each interval.

The slope of the arterial carbon dioxide tension ($Paco_2$)–CBFV relation (CO_2R) was calculated presedation and at the 1.2 ng/ml steady state plasma level as follows:

$$CO_2R = \Delta\text{CBFV}/\Delta Paco_2 \text{ (cm}\cdot\text{s}^{-1}\cdot\text{mm Hg}^{-1}\text{)}.$$

For each subject, CBFV at 1.2 ng/ml was corrected to the presedation $Paco_2$ value based on the CO_2R as determined at 1.2 ng/ml steady state serum level. (Both CBFV and corrected CBFV data are provided.)

For each subject, a modified Observer's Assessment of Alertness/Sedation (OAA/S) scale score was recorded after data collection at the presedation, 0.6 ng/ml, and 1.2 ng/ml intervals. The OAA/S is comprised of four subscales (speech, responsiveness, facial expression, and eye opening), with a maximum score of 20 (table 1).

Statistical Analyses

All data are presented as mean ± SD. The effect of dexmedetomidine administration and hyperventilation on each recorded parameter (mean arterial pressure, heart rate, arterial carbon dioxide partial pressure, respiratory rate, oxygen saturation, CBFV, CMRe) were analyzed using a repeated-measures analysis of variance with Bonferroni corrections as appropriate (KaleidaGraph 4.0; Synergy Software, Reading PA). Student *t* tests for paired data were used to compare carbon dioxide response at presedation and 1.2 ng/ml. *P* values of less than 0.05 were considered significant.

Results

Five of the six male volunteers had no pertinent medical history, and one reported a history of mild hypertension for which he was taking 10 mg lisinopril daily. All subjects were asked to stop any prescribed or over-the-counter medications for a period of at least 24 h before the study session. The population demographics are in table 2.

Dexmedetomidine administration was associated with clinically obvious sedation in all subjects. The sedation was a sleep-like state from which arousal was achieved easily. Neither euphoria nor disinhibition was evident. Once aroused, the subjects were able to follow hyperventilation instructions without difficulty, and when that task was completed, all reverted quickly to the sleep-like state. The clinically apparent sedation was reflected by decreases in both BIS and OAA/S scores. BIS decreased from 95 ± 3 presedation to 54 ± 9 and 43 ± 10 at 0.6 ng/ml and 1.2 ng/ml, respectively (fig. 1A). OAA/S values decreased from 20 (presedation) to 18 ± 0.7 and 15 ± 1.6 at 0.6 ng/ml and 1.2 ng/ml, respectively (fig. 1B). The three subjects with the lowest BIS scores were the most difficult to arouse for hyperventilation at the 1.2 ng/ml level. With arousal of the subjects for hyperventilation at the 1.2 ng/ml level, BIS scores immediately increased to approximately presedation values (table 3).

Dexmedetomidine administration was associated with the biphasic effect on mean arterial pressure that has been observed by others,[7] consisting of a decrease at 0.6 ng/ml with some recovery at the 1.2 ng/ml interval. After discontinuation of dexmedetomidine, mean arterial pressure again decreased (table 4). Increasing plasma levels of dexmedetomidine were associated with a dose-related reduction in heart rate (table 4), also as observed by others.[1,7,8]

Dexmedetomidine administration was not associated with significant changes in respiratory rate, arterial oxygen saturation, or $Paco_2$ (table 5). A consistent, although modest, dose-related increase in $Paco_2$ occurred between the presedation (37 ± 6 mm Hg) and 1.2 ng/ml (45 ± 4 mm Hg) intervals ($P < 0.05$; table 5). Two of the six subjects required occasional jaw-lift maneuvers to relieve partial airway obstruction.

Table 2. Population Demographics

	Subjects (n = 6)
Age, yr	46.5 ± 7.3 (33–57)
Height, cm	178 ± 11
Weight, kg	84.7 ± 10

Data are presented as mean ± SD.

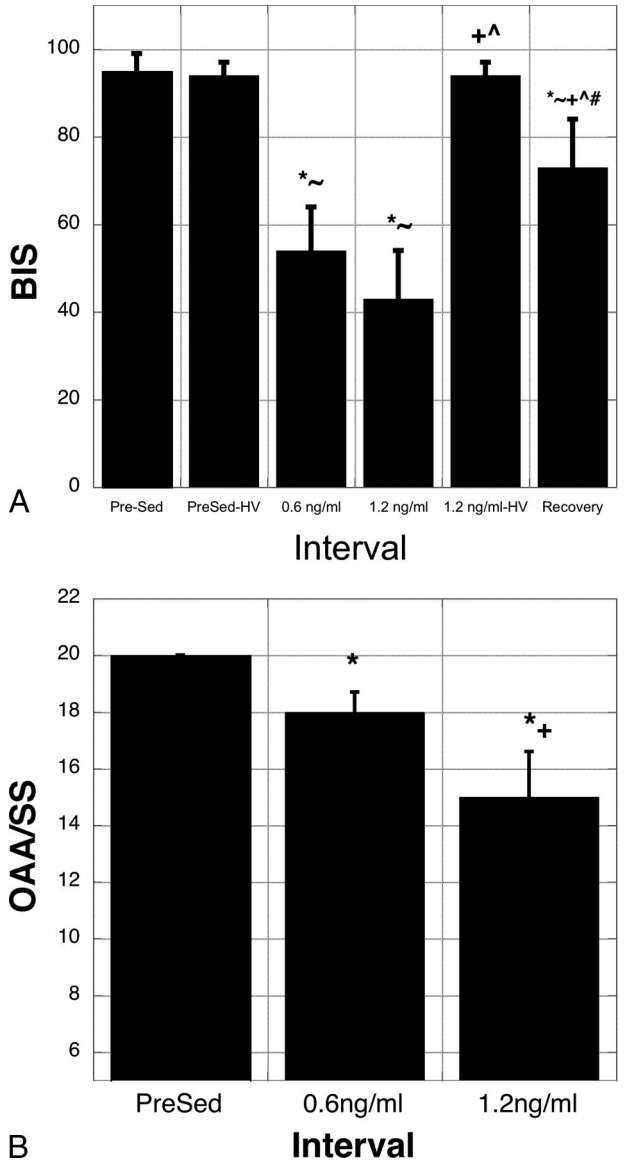

Fig. 1. Sedation scores before, during, and after infusion of dexmedetomidine. (*A*) A dose-related reduction in the Bispectral Index (BIS) was observed with increased dexmedetomidine plasma concentrations. Arousal for hyperventilation at the 1.2 ng/ml plasma level resulted in an immediate return of the BIS to presedation (PreSed) values with a reduction when subjects were allowed to return to a sedative state (recovery) after hyperventilation at 1.2 ng/ml level. (*B*) A subjective measure of sedation using a modified Observer's Assessment of Alertness/Sedation scale (OAA/SS) showed a dose-related reduction in alertness (increase in sedation) with increasing dexmedetomidine plasma concentrations. Data are presented as mean ± SD. * $P < 0.05$ *versus* PreSed. ~ $P < 0.05$ *versus* PreSed–HV. + $P < 0.05$ *versus* 0.6 ng/ml. ^ $P < 0.05$ *versus* 1.2 ng/ml. # $P < 0.05$ *versus* 1.2 ng/ml–HV. HV = hyperventilation.

Dexmedetomidine administration resulted in a dose-related decrease in CBFV (fig. 2). CBFV decreased by approximately 18% and 32% (both statistically significant) from the baseline value when the plasma dexmedetomidine concentration was increased to 0.6 ng/ml and 1.2 ng/ml, respectively (table 3). A similar dose-related reduction in CMRe occurred simultaneously (fig. 2 and table 3). CMRe decreased by 26% and 41% (*vs.* presedation) at the 0.6 ng/ml and 1.2 ng/ml serum levels, respectively. The combined effect of these changes in CBFV and CMRe was that there was no statistically significant change in the CBFV/CMRe ratio in association with dexmedetomidine administration, although there was a trend toward increases in that ratio (table 3). The increase in $Paco_2$ that occurred at 1.2 ng/ml level inevitably contributed to the increased CBFV/CMRe ratio, 22 ± 11, at that interval. Accordingly, a corrected CBFV was calculated using the slope of the $Paco_2$–CBFV response curve determined at the 1.2 ng/ml level (0.40 $cm \cdot s^{-1} \cdot mm\ Hg^{-1}$, see below). The corrected CBFV/CMRe ratio, 20 ± 9, remained numerically (but not statistically) greater than the presedation value.

In the non–steady state condition, immediately after arousal of the subjects for hyperventilation at the 1.2 ng/ml serum level, CBFV increased from 30 ± 5 to 38 ± 4 cm/s and BIS increased from 43 ± 10 to 94 ± 3 (table 3).

There was no significant change in $Sjvo_2$ from baseline during dexmedetomidine administration in the absence of hyperventilation. During hyperventilation, both presedation and at 1.2 ng/ml, $Sjvo_2$ decreased significantly in comparison with the immediately preceding nonhyperventilated control condition. Although the differences were not statistically significant, there seemed to be a trend toward higher $Sjvo_2$ values during 1.2 ng/ml–HV (50 ± 11%) than during presedation–HV (43 ± 5%). At the recovery interval, 30 min after discontinuation of dexmedetomidine administration, at which time sedation was still clinically apparent, CBFV, CMRe, and BIS had all increased toward, but had not yet reached, presedation levels. NIRS values were unchanged at all study intervals. (For technical reasons, NIRS data were obtained in only five of the six subjects.)

Hyperventilation resulted in no statistically significant change in CMRe (table 3). Hyperventilation both presedation and at 1.2 ng/ml resulted in a significant decrease in the CBFV/CMRe ratio *versus* the respective prehyperventilation states. However, the CBFV/CMRe ratios were not statistically different at presedation–HV and 1.2 ng/ml–HV, though there was an apparent trend toward a greater ratio during the latter (table 3). The slope of the $Paco_2$–CBFV response curve decreased from 1.20 ± 0.2 $cm \cdot s^{-1} \cdot mm\ Hg^{-1}$ before administration of dexmedetomidine to 0.40 ± 0.15 $cm \cdot s^{-1} \cdot mm\ Hg^{-1}$ at the 1.2 ng/ml level ($P < 0.0002$).

Discussion

The data obtained in the current investigation led to the rejection of the original hypothesis. We had surmised that dexmedetomidine would result in "pharmacologic hyperventilation," *i.e.*, CBF reduction without a parallel reduction in CMR. However, the decreases in the

Table 3. Effects of Dexmedetomidine on Cerebral Parameters

Interval	CBFV, cm/s	CO_2R, $cm \cdot s^{-1} \cdot mm\ Hg^{-1}$ of $Paco_2$	CMRe, Relative Units	CBFV/CMRe	$Sjvo_2$, %	NIRS	BIS
PreSed	44 ± 4		2.7 ± 0.3	16 ± 3	64 ± 4	74 ± 3	95 ± 3
PreSed–HV	24 ± 5*	1.2 ± 0.2	2.5 ± 0.4	9.5 ± 1*	43 ± 5*	71 ± 3	94 ± 3
0.6 ng/ml	36 ± 5*†		2.0 ± 0.5	19 ± 6	65 ± 7†	74 ± 4	54 ± 9*†
1.2 ng/ml	30 ± 5*†‡		1.6 ± 0.6*†	22 ± 11	68 ± 9†	73 ± 3	43 ± 10*†
1.2 ng/ml–Arousal	38 ± 4†					73 ± 3	94 ± 3
1.2 ng/ml–HV	22 ± 3*§‖	0.4 ± 0.2˜	1.9 ± 0.5*	12 ± 3	50 ± 11*§	70 ± 3	94 ± 3†
Recovery	37 ± 5*†§#		20 ± 5		66 ± 6†#	74 ± 3	73 ± 10*†§‖#

Data are presented as mean ± SD. CBFV corrected (CBFVc) from arterial carbon dioxide tension ($Paco_2$) 45 mm Hg to 37 mm Hg (table 3) = 27 ± 4 cm/s at 1.2 ng/ml. CBFVc/CMRe = 20 ± 9 at 1.2-ng/ml interval.

* $P < 0.05$ *vs.* PreSed. † $P < 0.05$ *vs.* PreSed–HV. ‡ $P < 0.05$ *vs.* 0.6 ng/ml. § $P < 0.05$ *vs.* 1.2 ng/ml. ‖ $P < 0.05$ *vs.* 1.2 ng/ml–Arousal. # $P < 0.05$ *vs.* 1.2 ng/ml–HV.

0.6 ng/ml = 0.6 ng/ml plasma dexmedetomidine concentration; 1.2 ng/ml = 1.2 ng/ml plasma dexmedetomidine concentration; 1.2 ng/ml–HV = 1.2 ng/ml plasma dexmedetomidine concentration with hyperventilation; BIS = Bispectral Index; CBFV = cerebral blood flow velocity; CMRe = cerebral metabolic rate equivalent; CO_2R = carbon dioxide response (CBFV/Δ $Paco_2$); NIRS = near-infrared spectroscopy; PreSed = presedation; PreSed–HV = presedation with hyperventilation; recovery = 30 min after discontinuation of dexmedetomidine infusion; $Sjvo_2$ = jugular venous oxygen saturation.

CBFV/CMR ratio that were anticipated were not observed during either normocapnia or hypocapnia. The explanation is twofold. The primary reason is that dexmedetomidine, contrary to the anticipation derived from the previous canine investigations,[3,4] did, in fact, result in substantial reduction of CMR in our population of healthy volunteers. Second, there was a significant reduction in the slope of the $Paco_2$–CBFV relation during administration of dexmedetomidine.

Although a decrease in CBF in association with administration of dexmedetomidine in humans has been reasonably well documented previously, the current investigation is the first to examine the effects on CMR in man. The only previous investigations of CMR effects were performed in dogs.[3,4] In the investigation by Zornow *et al.*,[3] which used a cerebral venous outflow technique, the dose-related CMR responsiveness of the preparation was first confirmed by incremental administration of isoflurane in concentrations up to 2.2 minimal alveolar concentration (MAC). Thereafter, a decrease in isoflurane concentration to 0.5 MAC was accompanied by a concomitant increase in CMR. Dexmedetomidine administered immediately thereafter in a dose of 10 μg/kg over 10 min resulted in a reduction of CBF of almost 50% but no change in CMR. The reason for the difference between these observations and the current CMR data is not apparent. Given the substantial CBF response observed in the dogs, the differences seem unlikely to be a function of either inadequate dosage or a deterioration of the preparation. The use of isoflurane as the background anesthetic might, by antecedent CMR depression, have reduced the latitude for dexmedetomidine to reduce CMR. However, at only 0.5 MAC isoflurane, that seems unlikely to explain the complete absence of a CMR effect. The investigation by Karlsson *et al.*[4] was similar. The administration of 10 μg/kg dexmedetomidine to dogs anesthetized with 1.0 MAC halothane was associated with a reduction of CBF with no change in CMR. When halothane concentration was reduced to 0.1 MAC, CMR increased, confirming the CMR responsiveness of the model. Again, there is no apparent explanation for the absence of a CMR effect by dexmedetomidine. Species difference is left as the remaining explanation. That convenient and oft-used explanation is nonetheless somewhat unsatisfactory in that such a dramatic interspecies difference in the relative CBF and CMR effects of an anesthetic agent is without precedent.

By contrast, the CBFV effects that we observed are consistent with all of the CBF observations previously reported for dexmedetomidine. At the highest drug plasma concentration level achieved in the current investigation (1.2 ng/ml), there was a reduction in CBF velocity of approximately 35%. Prielipp *et al.*,[1] using positron emission tomography, observed a global reduction in CBF of approximately 33% in healthy human volunteers during clinically significant dexmedetomidine-induced sedation. Zornow *et al.*[2] observed dose-related reductions in CBFV of up to 28% in human volunteers during administration of dexmedetomidine.

Table 4. Effects of Dexmedetomidine on Hemodynamic Parameters

Interval	MAP, mm Hg	HR, beats/min
PreSed	99 ± 7	60 ± 3
PreSed–HV	99 ± 6	81 ± 12*
0.6 ng/ml	76 ± 8*	51 ± 2*†
1.2 ng/ml	87 ± 10	49 ± 3*†
1.2 ng/ml–HV	86 ± 8	66 ± 10‡
Recovery	80 ± 10*	50 ± 2*†§

Data are presented as mean ± SD.

* $P < 0.05$ *vs.* PreSed. † $P < 0.05$ *vs.* PreSed–HV. ‡ $P < 0.05$ *vs.* 1.2 ng/ml. § $P < 0.05$ *vs.* 1.2 ng/ml–HV.

0.6 ng/ml = 0.6 ng/ml plasma dexmedetomidine concentration; 1.2 ng/ml = 1.2 ng/ml plasma dexmedetomidine concentration; 1.2 ng/ml–HV = 1.2 ng/ml plasma dexmedetomidine concentration with hyperventilation; HR = heart rate; MAP = mean arterial blood pressure; PreSed = presedation; PreSed–HV = presedation with hyperventilation; recovery = 30 min after discontinuation of dexmedetomidine infusion.

Table 5. Effects of Dexmedetomidine on Respiratory Parameters

Interval	RR, breaths/min	Pa_{O_2}, mm Hg	Sp_{O_2}, %	Pa_{CO_2}, mm Hg	pH
PreSed	14 ± 2	119 ± 20	99 ± 1	37 ± 6	7.42 ± 0.03
PreSed–HV	20*	122 ± 14	100	18 ± 4*	7.66 ± 0.03*
0.6 ng/ml	15 ± 1	114 ± 21	98 ± 1	41 ± 2†	7.38 ± 0.02†
1.2 ng/ml	16 ± 1	113 ± 17	98 ± 1	45 ± 4*†	7.36 ± 0.03*†
1.2 ng/ml–HV	21 ± 4*	120 ± 16	99 ± 1	22 ± 5*‡	7.60 ± 0.06*‡
Recovery	14 ± 2	123 ± 27	98 ± 1	44 ± 4*†§	7.37 ± 0.02†§

Data are presented as mean ± SD.

* $P < 0.05$ *vs.* PreSed. † $P < 0.05$ *vs.* PreSed–HV. ‡ $P < 0.05$ *vs.* 1.2 ng/ml. § $P < 0.05$ *vs.* 1.2 ng/ml–HV.

0.6 ng/ml = 0.6 ng/ml plasma dexmedetomidine concentration; 1.2 ng/ml = 1.2 ng/ml plasma dexmedetomidine concentration; 1.2 ng/ml–HV = 1.2 ng/ml plasma dexmedetomidine concentration with hyperventilation; Pa_{CO_2} = arterial carbon dioxide partial pressure; Pa_{O_2} = arterial oxygen partial pressure; PreSed = presedation; PreSed–HV = presedation with hyperventilation; recovery = 30 min after discontinuation of dexmedetomidine infusion; RR = respiratory rate; Sp_{O_2} = arterial oxygen saturation.

The precise mechanism of the reduction of CBF by dexmedetomidine cannot be ascertained from the current results. Direct vasoconstriction and vasoconstriction as a consequence of the coupling of CMR and CBF may both contribute. With respect to the former, α_2 receptors are known to be widely distributed within the cerebral vasculature.[9,10] The vasoconstrictive effect that they mediate seems to occur principally at the level of smaller caliber cerebral arteries (distal to the circle of Willis), *i.e.*, pial arterioles.[9] Activation of intrinsic noradrenergic neural pathways originating in the locus ceruleus and projecting to the microvasculature of the central nervous system may also contribute.[9,11] The extent to which coupling contributed to the CBF reduction is uncertain. However, indirect evidence from the current observations suggests that that phenomenon may have made some contribution. When the subjects were aroused for hyperventilation after data collection at 1.2 ng/ml, CBFV and BIS increased abruptly from 30 ± 5 to 38 ± 4 cm/s and 43 ± 10 to 94 ± 3, respectively, and CMRe (as determined during the immediately ensuing hyperventilation) increased by 19% (although that increase was not statistically significant). The parallel increases in CBFV and CMRe suggest that coupling is operative to at least some extent during administration of dexmedetomidine.

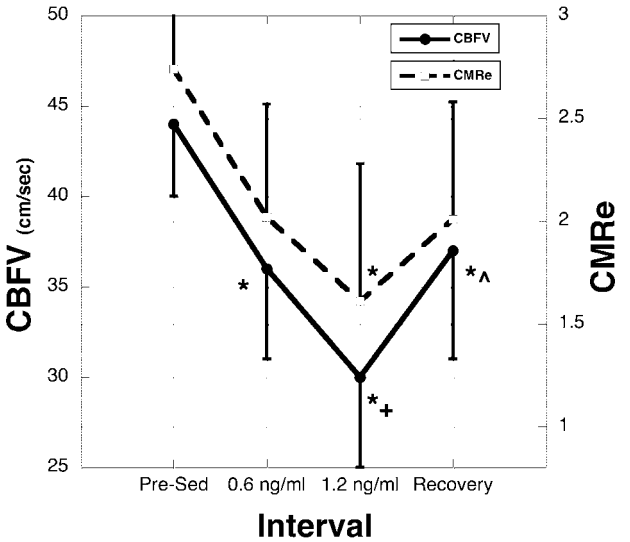

Fig. 2. The effect of dexmedetomidine on cerebral blood flow velocity (CBFV; cm/s) and cerebral metabolic rate equivalent (CMRe). Data are presented as mean ± SD. * $P < 0.05$ *versus* presedation (PreSed). + $P < 0.05$ *versus* 0.6 ng/ml. ^ $P < 0.05$ *versus* 1.2 ng/ml. Recovery = 30 min after discontinuation of dexmedetomidine infusion.

The data reveal that the reduction in the CBFV/CMRe ratio that we had anticipated clearly did not occur. In fact, although the differences were not statistically significant, there seems to have been, if anything, a trend toward increases in the CBFV/CMRe ratio during dexmedetomidine administration. That same trend is evident in the comparison of the CBFV/CMRe ratios during hyperventilation presedation and at 1.2 ng/ml (9.5 ± 1 and 12 ± 3, respectively). Although we report that this latter difference was not statistically significant, the statistical correction for multiple comparisons has probably obscured a true difference. The CBFV/CMRe ratio was greater in all six subjects at 1.2 ng/ml–HV than at presedation–HV. Using the Student *t* test for paired data to compare those two intervals in isolation, the difference is significant at $P = 0.04$. The explanation for the apparent increase in CBFV/CMRe ratio at 1.2 ng/ml–HV in part resides in the observation of a reduction in the slope of the Pa_{CO_2}–CBFV relation during the administration of dexmedetomidine, *i.e.*, the reduction in CBFV per unit change in Pa_{CO_2} was less during dexmedetomidine administration than in the unsedated state. This latter observation may not represent any unique attribute of dexmedetomidine because the general pattern in carbon dioxide response determinations has been that the less the baseline flow, the less the slope of the Pa_{CO_2}–CBF relationship. The Sjv_{O_2} and NIRS data are consistent with the absence of any physiologically threatening changes in CBFV/CMRe ratios.

The current study is subject to some limitations. The first is that it was conducted in volunteers who were free of neurologic disease and who were receiving no other sedative, analgesic, or hypnotic medications. It is possible that the effect of dexmedetomidine on CBF, CMR,

and the CBF/CMR ratio will be different in patients whose physiologic responses are disordered as a result of various cerebral injuries and who may have received medications that have produced antecedent suppression of CMR. The current results nonetheless seem to justify cautious and systematic exploration of the use of dexmedetomidine in patients with cerebral injuries, ideally with concurrent monitoring of Sjv_{O_2} and/or intraparenchymal (brain tissue) oxygen partial pressure.

The subjects in this investigation were all male. Although it is possible that female subjects would demonstrate different physiologic responses to dexmedetomidine, it seems unlikely. First, females have not been observed to respond differently to dexmedetomidine in terms of systemic physiology. Second, there are no precedents for significantly different cerebral physiologic responses between males and females among other anesthetic or sedative agents.

Both the CBFV and the CMRe methodologies involve some assumptions. For CBFV to bear a linear relation to CBF, the diameter of the insonated vessel must remain constant. The linearity of the relation between CBF and CBFV has been confirmed for some situations.[12,13] However, although human middle cerebral arteries have been shown *in vitro* not to constrict in response to the α_2 agonist clonidine,[14] the validity of the assumption of constant middle cerebral artery diameter has not been confirmed *in vivo* for dexmedetomidine. The vasoconstriction caused by dexmedetomidine is thought to occur at vessels of smaller caliber distal to those in and near the circle of Willis.[9,15] However, if some reduction of vessel diameter does occur in the middle cerebral artery, it would lead to an artifactual increase in CBFV and a proportional overestimate of CMR during dexmedetomidine administration. Although the data might in that event yield overestimates of both CBF and CMR, those parallel overestimates should not invalidate the observations about the important endpoint, *i.e.*, the CBF/CMR ratio.

Our CMR equivalent calculation entails the assumption that the middle cerebral artery blood flow and the jugular venous drainage domains are the same or, at a minimum, remain relatively unchanged, during dexmedetomidine administration and during hyperventilation. There can be no certainty that this assumption is absolutely valid. However, the concordance of our data for CBFV/CMRe, Sjv_{O_2}, and NIRS suggests that it is reasonable. Furthermore, the observation that the CMRe did not change during hyperventilation in the presedation state supports the notion that the relative CBF and venous drainage territories were not altered by hypocapnia.

Our investigation did not include a control group, *i.e.*, a group in which vascular catheters and the various noninvasive monitors were placed, in which subjects underwent hyperventilation but did not receive dexmedetomidine. Such a group would serve to confirm that no exclusively time-related change in cerebral physiology contributed to the effects that we herein attribute to dexmedetomidine. The invasive nature of the investigation argued against submitting subjects to a control limb of this nature. The large existing human experience with jugular venous catheters and episodic hyperventilation does not contain any suggestion that produces changes in CBF, CMR, or the slope of the Pa_{CO_2}–CBF relation.

Our investigation provided some incidental observations about BIS or OAA/S monitoring during dexmedetomidine administration. The relation between BIS or OAA/S and dexmedetomidine serum concentration was not examined quantitatively. Nonetheless, there was an apparently reasonable correlation between both BIS and OAA/S scores and clinical sedation. In addition, with arousal (for hyperventilation) at the 1.2 ng/ml serum level, BIS increased to presedation levels (OAA/S not recorded), whereas CMRe increased to only 70% of that observed presedation. This suggests that although BIS may serve as a useful monitor of dexmedetomidine sedation, the level of which is very stimulation dependent, it cannot be used as a surrogate marker of the CMR effects of dexmedetomidine.

In summary, dexmedetomidine caused a dose-related reduction in both CBF and CMR in healthy subjects. The anticipated adverse effects of dexmedetomidine on the cerebral oxygen supply–demand relation, *i.e.*, the CBF/CMR ratio, were not apparent during either normocapnia or hypocapnia. The data contradict those of previous investigations in dogs that indicated that dexmedetomidine does not cause a reduction in CMR. The results do not give assurance that dexmedetomidine will not cause adverse effects on the CBF/CMR ratio in patients with neurologic injuries. However, they seem to justify cautious and systematic exploration of the use of dexmedetomidine in patients with cerebral injuries, ideally with concurrent monitoring of Sjv_{O_2} and/or intraparenchymal (brain tissue) oxygen partial pressure.

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