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Dexmedetomidine Weakens Dynamic Cerebral Autoregulation as Assessed by Transfer Function Analysis and the Thigh Cuff Method

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Background: **Dexmedetomidine, which is often used in intensive care units in patients with compromised circulation, might induce further severe decreases in cerebral blood flow (CBF) with temporal decreases in arterial pressure induced by various stimuli if dynamic cerebral autoregulation is not improved. Therefore, the authors hypothesized that dexmedetomidine strengthens dynamic cerebral autoregulation.**

Methods: **Fourteen healthy male subjects received placebo, low-dose dexmedetomidine (loading, 3 $\mu g \cdot kg^{-1} \cdot h^{-1}$ for 10 min; maintenance, 0.2 $\mu g \cdot kg^{-1} \cdot h^{-1}$ for 60 min), and high-dose dexmedetomidine (loading, 6 $\mu g \cdot kg^{-1} \cdot h^{-1}$ for 10 min; maintenance, 0.4 $\mu g \cdot kg^{-1} \cdot h^{-1}$ for 60 min) infusions in a randomized, double-blind, crossover study. After 70 min of drug administration, dynamic cerebral autoregulation was estimated by transfer function analysis between arterial pressure variability and CBF velocity variability, and the thigh cuff method.**

Results: **Compared with placebo, steady state CBF velocity and mean blood pressure significantly decreased during administration of dexmedetomidine. Transfer function gain in the very-low-frequency range increased and phase in the low-frequency range decreased significantly, suggesting alterations in dynamic cerebral autoregulation in lower frequency ranges. Moreover, the dynamic rate of regulation and percentage restoration in CBF velocity significantly decreased when a temporal decrease in arterial pressure was induced by thigh cuff release.**

Conclusion: **Contrary to the authors' hypothesis, the current results of two experimental analyses suggest together that dexmedetomidine weakens dynamic cerebral autoregulation and delays restoration in CBF velocity during conditions of decreased steady state CBF velocity. Therefore, dexmedetomidine may lead to further sustained reductions in CBF during temporal decreases in arterial pressure.**

DEXMEDETOMIDINE reduces steady state cerebral blood flow (CBF) by augmentation of cerebrovascular resistance[1–3] *via* α_{2B}-mediated vascular smooth muscle constriction and *via* stimulation of intrinsic neural pathways innervating cerebral vasculature.[1,4,5] This may lead to a reduction in the reserve of cerebral oxygen supply with alterations in cerebral autoregulation, although whether this reduction in steady state CBF is accompanied by a decrease in cerebral metabolic rate of oxygen is controversial.[1,4–7]

In addition to changes in steady state CBF, it is generally accepted that CBF also changes briskly in response to transient changes in arterial pressure during normal conditions.[8–12] The ability of the cerebral vascular bed to buffer changes in CBF induced by "transient" changes in arterial pressure is referred to as dynamic cerebral autoregulation, this being estimated by transfer function analysis,[10–12] transient hyperemic response test,[9] and the thigh cuff method.[8,13] Transfer function analysis between arterial pressure oscillations and CBF fluctuations reveals a frequency dependent property of dynamic cerebral autoregulation, different frequency components having different mechanisms for the regulation of CBF.[10,11,14] In contrast, the thigh cuff method estimates functioning of the cerebral vasodilatory response to a physical and temporal decrease in arterial pressure[8] and measures the rate of restoration of CBF.[13] Therefore, combined use of both methods would be able to provide detailed information on dynamic cerebral autoregulation.

Dexmedetomidine is often administered to patients in intensive care units who may have compromised circulatory stability. When arterial pressure decreases temporally in response to various stimuli, further severe decreases in CBF would occur during the conditions of decreased steady state CBF induced by dexmedetomidine, unless dynamic cerebral autoregulation is improved by dexmedetomidine. However, the effect of dexmedetomidine on dynamic cerebral autoregulation has not been studied. Hence, we attempted to evaluate dynamic cerebral autoregulation during administration of dexmedetomidine to test our hypothesis that dexmedetomidine strengthens dynamic cerebral autoregulation, preventing a severe decrease in CBF. To this end, dynamic cerebral autoregulation was estimated using both transfer function analysis and the thigh cuff method.

Materials and Methods

The institutional review board of Nihon University School of Medicine (Itabashi-Ku, Tokyo, Japan) approved this study. All study participants provided written informed consent as well as a medical history, and were screened based on a physical examination including electrocardiography and blood pressure measurements. Volunteers were excluded if CBF velocity signals in the middle cerebral artery could not be obtained by

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transcranial Doppler ultrasonography. We investigated 14 healthy, normotensive, males with a median age of 21 yr (range, 18–23 yr), a median height of 173 cm (range, 163–182 cm), and a median weight of 65 kg (range, 57–79 kg).

All participants fasted for at least 2 h before the experiments, and refrained from heavy exercise and consumption of caffeinated or alcoholic beverages for at least 24 h before the experiments. All participants were familiarized with the measurement techniques and experimental conditions before starting the study.

Participants lay supine in a comfortable bed, in an environmentally controlled experimental room, at an ambient temperature of 23°–25°C. An electrocardiograph, pulse oximeter, nasal cannula (Life scope BSM-5132; Nihon Kohden, Tokyo, Japan), and Bispectral Index monitor (BIS XP®; Aspect Medical Systems, Inc., Norwood, MA) were applied. Continuous arterial pressure was measured in the radial artery using tonometry with a noninvasive arterial pressure monitor at the heart level on a beat-to-beat basis, and was calibrated by intermittent blood pressure measured using the oscillometric method with a sphygmomanometer cuff placed over the brachial artery (JENTOW 7700; Colin, Aichi, Japan). The CBF velocity in the middle cerebral artery was continuously measured by transcranial Doppler ultrasonography (WAKI; Atys Medical, St. Genislaval, France). A 2-MHz probe was placed over the temporal window and fixed at a constant angle with a probe holder customized to fit individual facial bone structure and ear.[15] Each waveform of continuous arterial pressure, CBF velocity, and electrocardiography were recorded at a sampling rate of 1 kHz using commercial software (Notocord-hem 3.3; Notocord, Paris, France) throughout the experiment. For the thigh cuff method, large cuffs were placed around both thighs of all the participants. A 22-gauge catheter was inserted into a forearm vein for drug administration.

The study was a randomized, double-blind, crossover comparison between two doses of dexmedetomidine and placebo (normal saline). At least 7 days were allowed between experiments. High-dose dexmedetomidine was administered as an initial loading dose of 6 $\mu g \cdot kg^{-1} \cdot h^{-1}$ for 10 min, followed by 0.4 $\mu g \cdot kg^{-1} \cdot h^{-1}$ for 60 min (High-DEX). The dose of dexmedetomidine for low-dose was half that of high-dose dexmedetomidine (Low-DEX: an initial loading dose of 3 $\mu g \cdot kg^{-1} \cdot h^{-1}$ for 10 min; with a maintenance dose of 0.2 $\mu g \cdot kg^{-1} \cdot h^{-1}$ for 60 min). These doses and periods of infusion were chosen to obtain dexmedetomidine plasma concentrations of approximately 0.6 and 0.3 ng/ml respectively, as described in the manufacturer's material (Hospira Japan K.K., Osaka, Japan). Moreover, these infusion regimens were similar to those used in previous studies[16,17] including dexmedetomidine plasma concentrations.[5] An equal volume of normal saline per hour was administered as placebo (fig. 1). Infusion of drugs was continued during measurement of data. All subjects received all three types of infusions.

Seventy minutes after commencement of administration of dexmedetomidine or placebo (loading, 10 min; maintenance, 60 min), 6-min data of continuous arterial pressure, CBF velocity, and electrocardiography waveforms were obtained and used for spectral and transfer function analyses during spontaneous respiration of room air. Respiratory rate, end-tidal carbon dioxide pressure (ET_{CO_2}), and arterial oxygen saturation (Sp_{O_2}) were recorded every minute during this period. Mean values for steady state mean blood pressure (MBP), CBF velocity, heart rate, respiratory rate, ET_{CO_2}, and Sp_{O_2} were obtained by averaging data of the 6-min segments. In addition, cerebrovascular resistance was expressed as cerebral vascular resistance index (CVRi), where

$$CVRi = MBP/CBF\ velocity.$$

After measuring 6-min data of these waveforms, thigh cuffs were inflated to 30 mmHg above the subject's systolic blood pressure by using a rapid cuff inflator (E20 Rapid Cuff Inflator; Hokanson, Inc., Bellevue, WA). This instrument inflates a large cuff to 50 mmHg in less than 0.3 s and deflates it again in less than 0.2 s. After 2 min of inflation, the cuffs were deflated rapidly to produce at least 10-mmHg decreases in arterial pressure. If this decrease in arterial pressure could not be achieved, data on the subject was excluded from group-averaged thigh cuff data for statistical analysis. After data measurements, infusion of the drugs was discontinued.

Beat-to-beat values of MBP and CBF velocity were obtained by integrating signals within each cardiac cycle using personal computer–based Notocord-hem 3.3 software for spectral and transfer function analyses that were based on the Welch algorithm. Using previously validated algorithms,[10–12,18,19] beat-to-beat data for MBP and CBF velocity were then linearly interpolated and resampled at 2 Hz. Fast Fourier transform and transfer function analysis were performed using a Hanning window on 256-point segments with 50% overlap, this process resulting in five segments over 6 min of data recordings. This data were then analyzed using DADiSP software (DSP Development, Cambridge, MA). The spectral power of MBP and CBF velocity, mean value of transfer function gain, phase and coherence function were calculated in the very-low-frequency (0.02–0.07 Hz), low-frequency (0.07–0.20 Hz), and high-frequency (0.20–0.30 Hz) ranges (figs. 2 and 3). These ranges were specifically selected to reflect different patterns of the dynamic pressure–flow relation,[10,11,14] while including sufficient time for autoregulatory responses to be initiated.[20] Coherence function between 0 and 1 reflects the linear relation between MBP and CBF velocity. Phase reflects the temporal relation between the two variables. A phase decreases during conditions of compromised ce-

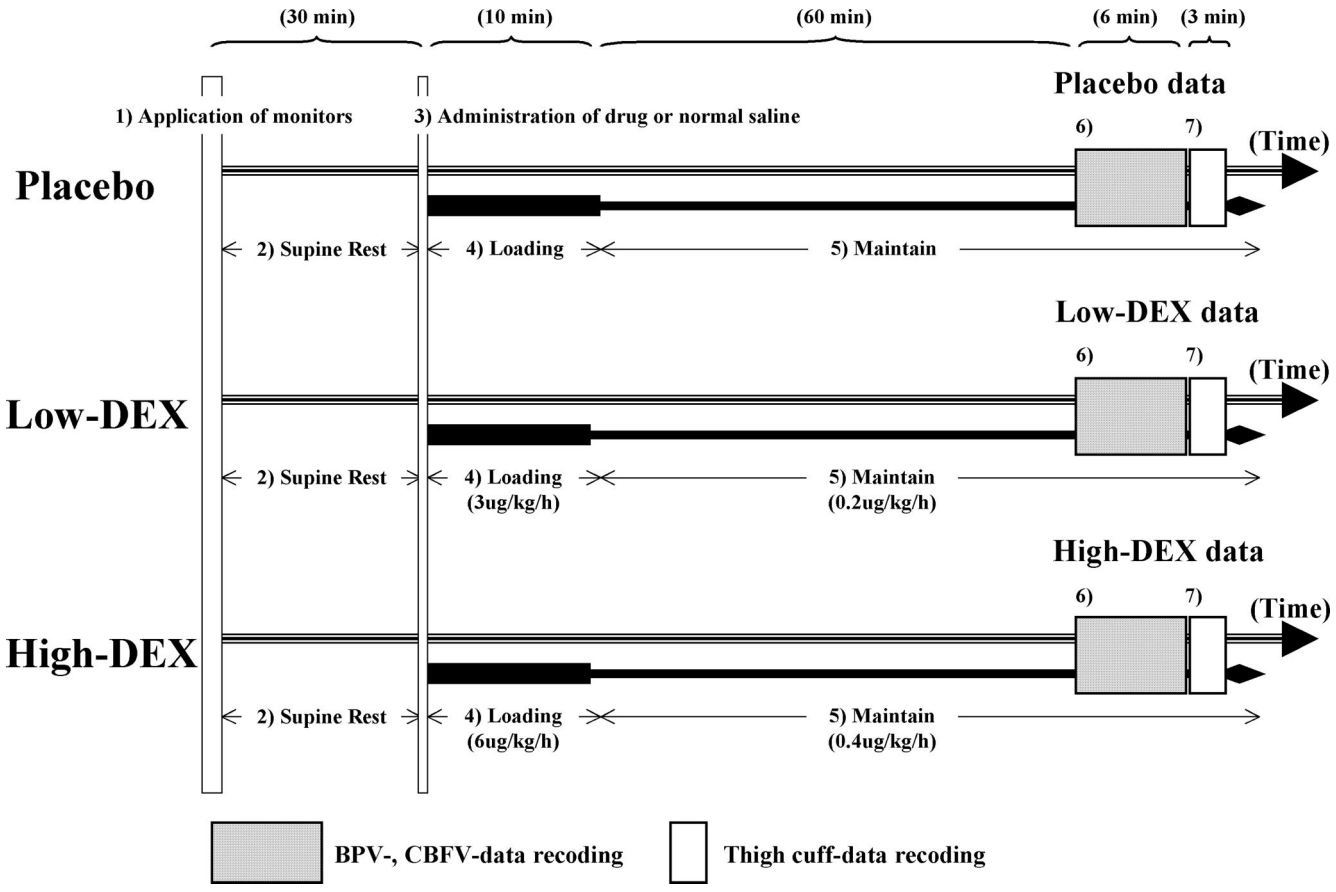

Fig. 1. Experimental protocol. The study consisted of the following phases: (1) arrival at the environmentally controlled experimental room and application of monitors; (2) adequate period of rest (approximately 30 min); (3) administration of drug or normal saline; (4) loading dose for 10 min; (5) maintenance dose for 60 min; (6) measurement of blood pressure variability (BPV) and cerebral blood flow velocity variability (CBFV) data; and (7) measurement of thigh cuff data. *Gray boxes* = measurement of BPV and CBFV data; *open boxes* = measurement of thigh cuff data. DEX = dexmedetomidine.

rebral circulation.[10,12,21–23] Transfer function gain reflects the ability of the cerebrovascular bed to buffer changes in CBF velocity induced by transient changes in arterial pressure at different frequencies. A larger gain indicates that any given change in pressure leads to a larger change in flow, implying impaired autoregulation,[11,12,21–23] although the magnitude of impairment is difficult to determine from transfer function gain and phase.

Transfer function gain at cardiac frequencies close to the heart rate was also examined.[24] For calculation of this frequency, continuous arterial pressure and CBF velocity waveforms were resampled at 10 Hz, and fast Fourier transform and transfer function analysis were performed. Transfer function gain in the cardiac frequency indicates the passive transmission of pressure to flow, because autoregulatory mechanisms are unlikely to have had sufficient time to respond.[24]

Next, the rate of restoration of CBF velocity after a temporal decrease in arterial pressure induced by deflation of the large cuffs applied around both thighs was determined.[8,13] Using refinements of previously established algorithms,[8] the CBF velocity response to decreases in arterial pressure was fitted to a series of curves to determine the dynamic rate of regulation (dROR). Briefly, continuous arterial pressure and CBF velocity waveforms were resampled at 25 Hz for this analysis, these traces being smoothed by regressive moving average at 1-s intervals to dampen the harmonics of the pulse wave (fig. 4).[25,26] Baseline values of arterial blood pressure (ABP) and CBF velocity were obtained by calculating their averages during the 4 s before thigh cuff release. Baseline values were obtained for all three types of infusions. Values of CVRi were obtained by dividing ABP by CBF velocity for each time point. The magnitude of the step decrease was calculated by subtracting baseline ABP from averaged ABP of the interval from 1 to 3.5 s after thigh cuff release. This value was then divided by baseline ABP to obtain the relative step decrease, ΔABP (percentage decrease in arterial pressure). During the interval from 1 to 3.5 s after thigh cuff release, CVRi changed with time (T) in an approximately linear fashion. The slope of this regression line (ΔCVRi/ΔT) defines the rate at which CVRi changed. This rate depends on ΔABP. Full restoration of CBF velocity would theoretically occur if

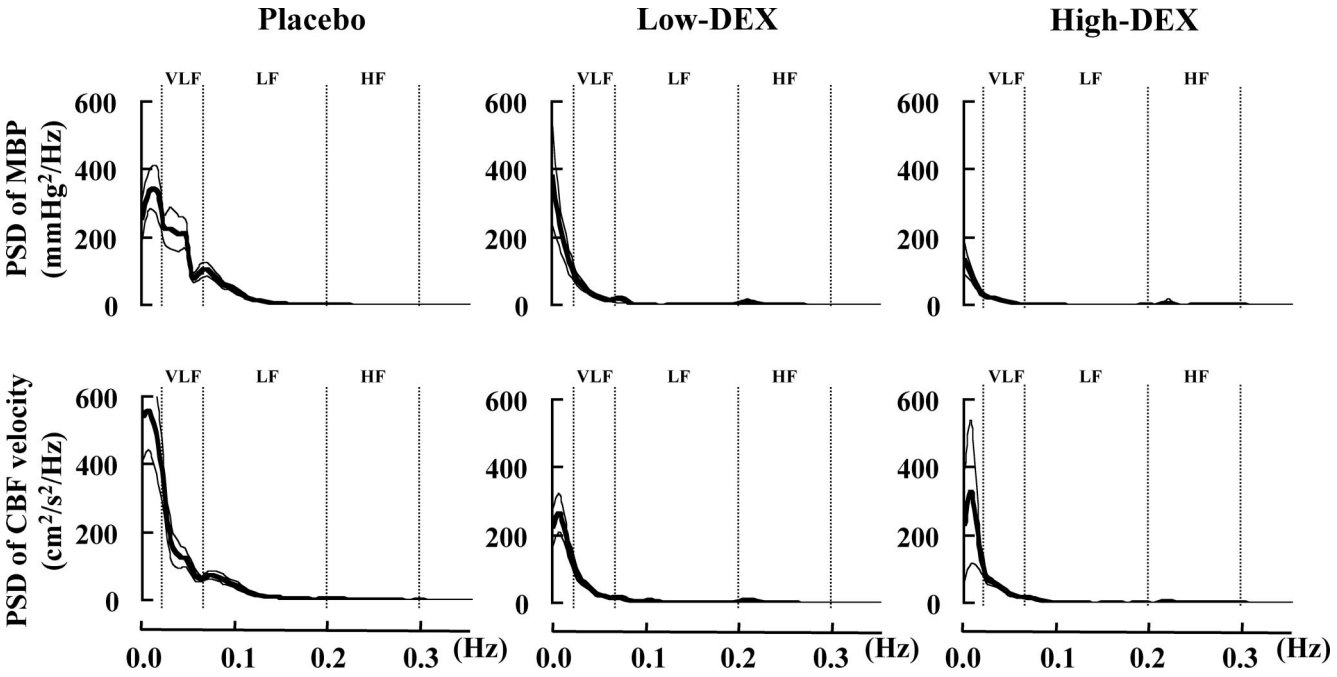

Fig. 2. Group-averaged spectral power density of mean blood pressure (MBP) and cerebral blood flow (CBF) velocity with placebo and two doses of dexmedetomidine (DEX). *Thick lines* = averaged estimates; *thin lines* = SEMs. HF = high-frequency range (0.20–0.30 Hz); LF = low-frequency range (0.07–0.20 Hz); PSD = power spectral density; VLF = very-low-frequency range (0.02–0.07 Hz).

ΔCVRi were equal to ΔABP. Therefore, dROR was defined as:

$$\text{dROR} = (\Delta\text{CVRi}/\Delta\text{T})/\Delta\text{ABP}.$$

Therefore, dROR reflects the early part (1–3.5 s) of the vasodilatory response of dynamic cerebral autoregulation. Normal dROR has been reported to be approximately 20%/s (range, 15–30%/s).[8] In addition, percentage restoration in CBF velocity is expressed as:

$$\text{Percentage restoration in CBF velocity} = \text{restoration/reduction} \times 100 = \frac{(\text{Recovery} - \text{Minimum})}{(\text{Baseline} - \text{Minimum})} \times 100,$$

where Baseline is the average CBF velocity during the 4 s before thigh cuff release; Minimum is the lowest value of CBF velocity after thigh cuff release; and Recovery is the average CBF velocity measured in the 4-s interval between 6 and 10 s after thigh cuff release, this being the predicted time by which recovery of CBF velocity after thigh cuff release is almost complete during normal conditions. Percentage restoration measures the latter part (6–10 s) of CBF velocity restoration.

Statistical Analysis

Interdose variables were compared using one-way repeated-measures analysis of variance for each dose level of placebo, Low-DEX, and High-DEX. To determine where significant differences occurred, the Bonferroni *post hoc* test was used for all pairwise comparisons. Regarding data of the thigh cuff method, statistical analyses were performed on only 11 of the subjects at each dose (total 33 analyses) by one-way (non–repeated-measures) analysis of variance, followed by Bonferroni *post hoc* test, because three different subjects at each dose did not achieve a 10-mmHg decrease in ABP on thigh cuff release. A P value of less than 0.05 was considered statistically significant. The analyses were performed using personal computer–based software (SigmaStat; Systat Software, Inc., CA). Data are presented as mean ± SD.

Results

Table 1 shows the average values of steady state hemodynamic and respiratory data with each infusion dose. Compared with placebo, steady state MBP and CBF velocity decreased significantly with Low-DEX and High-DEX. CVRi increased significantly with Low-DEX and High-DEX. Heart rate decreased significantly with Low-DEX and tended to decrease with High-DEX. Although respiratory rate and ET_{CO_2} remained unchanged, Sp_{O_2} showed a slight decrease with Low-DEX and High-DEX, this slight decrease being statistically significant but probably clinically insignificant. Bispectral Index tended to decrease in association with an increase in the dexmedetomidine dose (analysis of variance, $P = 0.08$). The values of all these indices were not significantly different between Low-DEX and High-DEX.

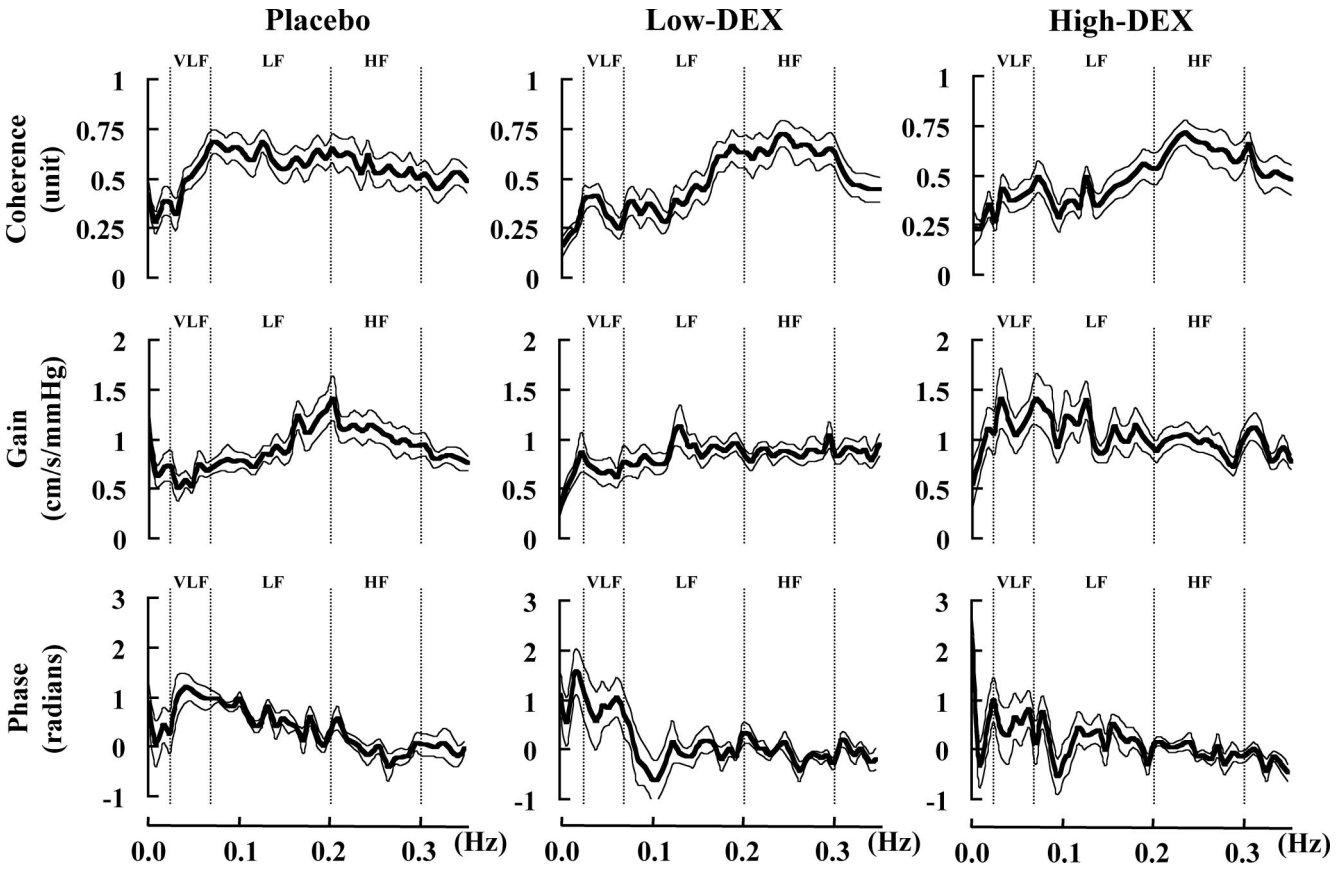

Fig. 3. Group-averaged transfer function analysis between mean blood pressure (MBP) and cerebral blood flow (CBF) velocity with placebo and two doses of dexmedetomidine (DEX). *Thick lines* = averaged estimates; *thin lines* = SEMs. Coherence = coherence function; Gain = transfer-function gain between MBP and CBF velocity; HF = high-frequency range (0.20–0.30 Hz); LF = low-frequency range (0.07–0.20 Hz); Phase = phase relation between MBP and CBF velocity; VLF = very-low-frequency range (0.02–0.07 Hz).

Table 2 shows average frequency domain data with each infusion dose. Figures 2 and 3 show group-averaged power spectral density and transfer function analysis of beat-to-beat changes in MBP and CBF velocity. Compared with placebo, the spectral power of MBP variability and CBF velocity variability at the very-low-frequency range decreased significantly with Low-DEX and High-DEX. Coherence in this range remained below 0.5 with Low-DEX and High-DEX. Transfer function gain in this range increased significantly with High-DEX as compared with placebo and Low-DEX. Phase in this range did not change significantly.

The low-frequency power of MBP variability and CBF velocity variability decreased significantly with Low-DEX and High-DEX, coherence in this range also decreasing significantly below 0.5 with these drug doses. Although transfer function gain in this range did not change significantly, phase in this range decreased significantly with Low-DEX and tended to decrease with High-DEX.

The high-frequency power of MBP variability and CBF velocity variability did not change with Low-DEX and High-DEX. Coherence in the high-frequency range was above 0.5 with all infusion doses, including placebo. Transfer function gain and phase in this range did not change significantly with Low-DEX and High-DEX.

Transfer function gains in the cardiac frequency, as an index of passive transmission of pressure to flow, were 0.89 ± 0.1, 0.82 ± 0.1, and 0.79 ± 0.2 cm $\cdot$ s^{-1} $\cdot$ mmHg^{-1} with placebo, Low-DEX, and High-DEX, respectively, the gain tending to decrease with High-DEX as compared with placebo ($P = 0.051$).

Table 3 shows the average values of restoration of CBF velocity using the thigh cuff method. Averaged and smoothed tracings from the entire series are presented in figure 4. Minimum CBF velocity, dROR, and percentage restoration of CBF velocity in the interval from 6 to 10 s after thigh cuff release all decreased significantly with Low-DEX and High-DEX as compared with placebo. These indices were not significantly different between Low-DEX and High-DEX.

Discussion

In the current study, where steady state CBF velocity decreased by augmentation in CVRi during administration of dexmedetomidine, transfer function gain in the very-low-frequency range increased and phase in the low-frequency range decreased with administration of dexmedetomidine. These results suggest that dexme-

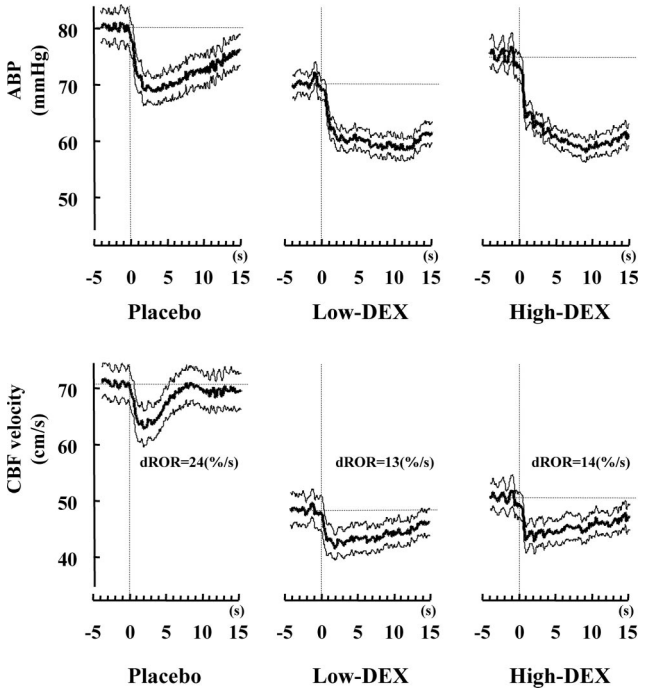

Fig. 4. Group-averaged arterial blood pressure (ABP) and cerebral blood flow (CBF) velocity during the thigh cuff method. Thigh cuffs were released at time 0. *Thick lines* = averaged estimates; *thin lines* = SEMs. DEX = dexmedetomidine; dROR = dynamic rate of regulation.

detomidine may alter dynamic cerebral autoregulation in the lower frequency ranges. In addition, dROR significantly decreased during administration of both doses of dexmedetomidine when temporal decreases in arterial pressure were induced by thigh cuff deflation, suggesting a decline in the rapid vasodilatory response of dynamic cerebral autoregulation. Moreover, percentage restoration in CBF velocity was less than half that of placebo, even during administration of low-dose dexmedetomidine. Considered together, the results of these two experimental analyses suggest that dexmedetomidine weakens dynamic cerebral autoregulation.

Table 1. Steady State Hemodynamics and Respiratory Conditions

	Placebo	Low-DEX	High-DEX
MBP, mmHg	79 ± 9	65 ± 6*	69 ± 6*
CBF velocity, cm/s	69 ± 10	49 ± 8*	49 ± 10*
CVRi, mmHg · cm^{-1} · s^{-1}	1.2 ± 0.2	1.4 ± 0.3*	1.5 ± 0.3*
HR, beats/min	57 ± 6	53 ± 6*	53 ± 7†
RR, breaths/min	13 ± 3	13 ± 2	14 ± 2
ET_{CO_2}, mmHg	41 ± 5	41 ± 6	41 ± 5
Spo_2, %	98 ± 1	97 ± 1*	97 ± 0*
BIS	86 ± 5	85 ± 8	80 ± 9

Values are mean ± SD.

* $P < 0.05$ *vs.* placebo. † $P = 0.06$ *vs.* placebo.

BIS = Bispectral Index; CBF = cerebral blood flow; CVRi = cerebral vascular resistance index; DEX = dexmedetomidine; ET_{CO_2} = end-tidal carbon dioxide pressure; HR = heart rate; MBP = mean blood pressure; RR = respiratory rate; Spo_2 = arterial oxygen saturation.

Table 2. Spectral and Transfer Function Analysis of Blood Pressure and CBF Velocity

	Placebo	Low-DEX	High-DEX
VLF_{MBP}, mmHg^2	7.04 ± 4.91	1.55 ± 1.28*	0.57 ± 0.42*
VLF_{vel}, cm^2/s^2	5.20 ± 3.72	1.72 ± 0.87*	1.60 ± 0.85*
CohVLF, units	0.48 ± 0.19	0.35 ± 0.11	0.38 ± 0.13
GainVLF, cm · s^{-1} · mmHg^{-1}	0.64 ± 0.32	0.72 ± 0.34	1.19 ± 0.68*†
PhaseVLF, radians	0.95 ± 0.90	0.95 ± 1.23	0.63 ± 1.17
LF_{MBP}, mmHg^2	2.89 ± 1.42	0.52 ± 0.98*	0.22 ± 0.21*
LF_{vel}, cm^2/s^2	2.98 ± 2.21	0.68 ± 0.97*	0.50 ± 0.29*
CohLF, units	0.62 ± 0.18	0.43 ± 0.17*	0.43 ± 0.15*
GainLF, cm · s^{-1} · mmHg^{-1}	0.91 ± 0.32	0.88 ± 0.20	1.13 ± 0.47
PhaseLF, radians	0.62 ± 0.19	−0.03 ± 0.72*	0.07 ± 1.00‡
HF_{MBP}, mmHg^2	0.25 ± 0.24	0.43 ± 0.47	0.41 ± 0.38
HF_{vel}, cm^2/s^2	0.45 ± 0.31	0.39 ± 0.31	0.42 ± 0.23
CohHF, units	0.55 ± 0.18	0.62 ± 0.14	0.60 ± 0.16
GainHF, cm · s^{-1} · mmHg^{-1}	1.02 ± 0.32	0.88 ± 0.16	0.95 ± 0.28
PhaseHF, radians	0.01 ± 0.22	−0.03 ± 0.08	−0.07 ± 0.16

Values are mean ± SD.

* $P < 0.05$ *vs.* placebo. † $P < 0.05$ *vs.* Low-DEX. ‡ $P = 0.07$ *vs.* placebo.

CBF = cerebral blood flow; CohHF = coherence in the high-frequency range; CohLF = coherence in the low-frequency range; CohVLF = coherence in the very-low-frequency range; DEX = dexmedetomidine; GainHF = transfer function gain in the high-frequency range; GainLF = transfer function gain in the low-frequency range; GainVLF = transfer function gain in the very-low-frequency range; HF_{MBP} = high-frequency component of the mean blood pressure variability; HF_{vel} = high-frequency component of the CBF velocity variability; LF_{MBP} = low-frequency component of the mean blood pressure variability; LF_{vel} = low-frequency component of the CBF velocity variability; PhaseHF = phase in the high-frequency range; PhaseLF = Phase in the low-frequency range; PhaseVLF = Phase in the very-low-frequency range; VLF_{MBP} = very-low-frequency component of the mean blood pressure variability; VLF_{vel} = very-low-frequency component of CBF velocity variability.

Cerebral autoregulation maintains CBF at relatively constant levels despite sustained perfusion pressures between 60 and 150 mmHg, guaranteeing cerebral oxygen supply.[20] However, CBF velocity responds briskly to "transient" changes in arterial pressure even during normal conditions.[8–12] The regulation of these rapid changes in CBF is recognized as dynamic cerebral autoregulation. Dexmedetomidine is a sedative drug that is used in intensive care unit patients who are likely to have compromised circulatory stability. In these patients, dynamic cerebral autoregulation assumes even

Table 3. Restoration in Cerebral Blood Flow Assessed by Thigh Cuff Method

	Placebo	Low-DEX	High-DEX
dROR, %/s	24 ± 1	13 ± 1*	14 ± 1*
min-CBFv, cm/s	62 ± 12	43 ± 9*	45 ± 8*
%restoration-CBFv, %	91 ± 57	43 ± 37*	29 ± 11*

Values are mean ± SD.

* $P < 0.05$ *vs.* placebo.

%restoration-CBFv = percentage restoration in cerebral blood flow velocity in the interval from 6 to 10 s after thigh cuff release; DEX = dexmedetomidine; dROR = dynamic rate of regulation; min-CBFv = minimum values of cerebral blood flow velocity after thigh cuff release.

greater significance than during normal conditions, serving to prevent further decreases in CBF velocity that may be induced by temporal decreases in arterial pressure. When arterial pressure decreases temporally by postural changes or operative stimuli, further severe decreases in CBF would occur during the conditions of decreased steady state CBF induced by dexmedetomidine, unless dynamic cerebral autoregulation is improved. Therefore, the current study estimated dynamic cerebral autoregulation during dexmedetomidine sedation using two methods.

Transfer function analysis quantifies the ability of the cerebral vessels to respond to beat-to-beat arterial pressure changes and yields insight into dynamic, frequency-dependent properties of cerebral autoregulation.[10,11,14] For example, short-term fluctuations in CBF velocity at high frequencies ($>$ 0.2 Hz, or faster than 5 s/cycle), closely match those observed in arterial pressure. In contrast, slow fluctuations (below approximately 0.07 Hz, or slower than 14 s/cycle) in CBF velocity are relatively independent of changes in arterial pressure, indicating that dynamic cerebral autoregulation is more effective at lower frequency ranges. Therefore, the buffering capacity of the cerebral vascular bed is dependent on the frequency of fluctuations in perfusion pressure, different frequency components being regulated by different mechanisms, such as metabolic, myogenic, neural, and/or other mechanisms.[10,11,14,20] Moreover, several previous studies examining the effects of various interventions on dynamic cerebral autoregulation have shown that each intervention alters the dynamic relation or dependence of CBF fluctuations on arterial pressure oscillations in a specific frequency interval.[14,27–30] This transfer function approach, however, relies solely on the relation between spontaneous oscillations in arterial pressure and fluctuations in CBF velocity, although with the advantage that this analysis has enabled estimations of dynamic cerebral autoregulation without either drug administration or mechanical stimuli. Therefore, diminution of spontaneous oscillations may affect analysis of the transfer function approach, together with the concern that information about variables such as vasomotor tone is not included in the determination of coherence between arterial blood pressure and CBF velocity.

In the current evaluation of the dynamic relation between MBP oscillations and CBF fluctuations using transfer function analysis, coherence in the very-low- and low-frequency ranges was below 0.5 during administration of dexmedetomidine, with remarkable reduction in MBP variability. Because small coherence suggests any one of three possible mechanisms, *i.e.*, (1) a nonlinear relation between changes in pressure and velocity, (2) the presence of a low signal-to-noise ratio, or (3) a weak relation between the two signals, *i.e.*, effective autoregulation,[10,11] the current study cannot reveal which process led to the small coherence. Many previous studies have estimated transfer function gain and phase as interpretable indices even if coherence was small.[19,24,31–33] Moreover, changes in transfer function gain and phase are unlikely to be induced solely by alterations in arterial pressure variability.[14,34] Therefore, increases in transfer function gain in the very-low-frequency range and phase decreases in the low-frequency range during administration of dexmedetomidine may be interpretable, although decreases in signal-to-noise ratio may reduce reliability of gain and phase. During conditions of compromised cerebral circulation,[10,12,21–23] transfer function gain increased and/or phase decreased, implying impaired dynamic cerebral autoregulation. Therefore, the changes in transfer function gain and phase observed in the current study suggest impairment of dynamic cerebral autoregulation. Because dynamic cerebral autoregulation in the lower frequency ranges may include autonomic, myogenic, and metabolic mechanisms,[11,14] it is possible that dexmedetomidine alters dynamic cerebral autoregulation *via* changes in these autoregulatory mechanisms. In fact, MBP variability in the lower frequency ranges, including peripheral vasomotor sympathetic activity, decreased in the current study, with several other studies also reporting that dexmedetomidine causes a reduction in sympathetic activity[35] and contraction of vascular smooth muscle.[1,4] However, autoregulatory mechanisms in the high-frequency range were not influenced by dexmedetomidine, because transfer function indices in this range did not change. However, transfer function gain in the cardiac frequency as an index of the passive transmission of pressure to flow tended to decrease with administration of high-dose dexmedetomidine. It is possible that this decrease was due to an altered vascular state.[24] Arteriolar constriction *via* dexmedetomidine could change the transduction characteristics of the vascular bed. Therefore, the current results from transfer function analysis provided information about two physiologic states that may be altered by dexmedetomidine, autoregulatory mechanisms, and cerebrovascular state.

The thigh cuff method estimates functioning of the cerebral vasodilatory response to physical decreases in arterial pressure in dynamic situations.[8] Therefore, this method examines how quickly cerebral vessels dilate and CBF velocity returns to baseline when ABP remains decreased for a short period, as dynamic cerebral autoregulation. The dROR describes the rapid vasodilatory response of cerebral vessels and the early part of restoration in CBF velocity.[8,13] As a method of determining the dROR, the instrument used a special algorithm with several refinements compared with the one used by Aaslid *et al.*[8] The time course of cerebrovascular resistance was calculated from arterial pressure and CBF velocity recordings, and dROR was determined as the normalized change in cerebrovascular resistance per second during the 2.5-s period immediately after a temporal decrease in arterial pressure. The reference point for

normalization was the calculated change in cerebrovascular resistance that would have nullified the effects of the temporal decrease in arterial pressure.[8] In the current study, dROR significantly decreased during administration of dexmedetomidine, suggesting a decline in the early part of the vasodilatory response of dynamic cerebral autoregulation. This decline is probably due to antagonism of cerebral vasodilation by the vasoconstriction caused by dexmedetomidine. In addition, in the current study, the latter part of restoration in CBF velocity was estimated as percentage restoration in CBF velocity. The assumption that percentage restoration in CBF velocity should be almost complete within 6–10 s of cuff deflation was based on predictions that CBF velocity is almost restored within this time with normal autoregulation.[8,13] The percentage restoration in CBF velocity during administration of dexmedetomidine decreased significantly compared with placebo. CBF velocity was almost completely restored within 10 s after thigh cuff release with placebo infusion, though it was restored by only 30–40% within 10 s with low- and high-dose dexmedetomidine. Therefore, dexmedetomidine seems to compromise restoration of CBF *via* weakened dynamic cerebral autoregulation.

Therefore, contrary to our hypothesis, the current results of all four indices of dynamic cerebral autoregulation (transfer function gain and phase in the lower frequency ranges, dROR, and percentage restoration in CBF velocity) concur that dexmedetomidine weakens rather than strengthens dynamic cerebral autoregulation, delaying restoration in CBF velocity during conditions of decreased steady state CBF velocity. This further and sustained decrease in CBF may exceed the reserve of cerebral oxygen supply. However, it is as yet unclear whether dexmedetomidine induces global cerebral ischemia *via* weakened dynamic cerebral autoregulation[36,37] and whether dexmedetomidine reduces the cerebral metabolic rate.[1,4,6,7] The decrease in steady state CBF velocity is apparently not accompanied by a proportionate reduction of cerebral metabolic rate in animals,[1,4,6] whereas another study reported that coupling of flow and metabolism occurs in humans.[7] However, because dynamic cerebral autoregulation plays an important role when arterial pressure decreases temporally by postural changes or operative stimuli, further decreases and delays in restoration of CBF should be cautioned against as a clinical problem regardless of the coupling of steady state flow and metabolism.

The primary limitation of the current study is the use of transcranial Doppler ultrasonography for measurements of middle cerebral artery blood flow. This approach is based on the assumption that the diameter of the middle cerebral artery remains relatively constant, as has been shown by others.[38–40] However, the current study could not exclude the possibility that the middle cerebral artery itself was constricted by dexmedetomidine, because the effects and distribution of α_2-adrenergic receptors on large cerebral arteries are unclear despite known constrictive effects on cerebral arterioles.[41]

Interpretation of indices of dynamic cerebral autoregulation is also a limitation of the current study. In the transfer function analysis, interpretation of the small coherence (< 0.5) in the lower frequency range remains controversial. Although remarkable reduction in arterial pressure variability induces small coherence with decrease in signal-to-noise ratio,[10,14,29] there is the possibility that small coherence in the lower frequency ranges may imply a weak relation between changes in pressure and velocity. To clarify the origin of the small coherence observed on transfer function analysis and increase reliability of gain and phase, further studies normalizing arterial pressure variability using the mechanical method (oscillatory lower body negative pressure) may be needed.[14,34] In the thigh cuff method, measurements often have a high variation. Therefore, we were unable to obtain thigh cuff data in 3 of the 14 subjects at each dose level in the current study. To diminish variation of thigh cuff data and to reduce missing data, we should have repeated measurements three times and used the average of the three measurements. Further, ABP during administration of dexmedetomidine remained low during the 10-s period after thigh cuff release, suggesting diminished vaso- and/or cardiac-baroreflex function. In the calculation of dynamic cerebral autoregulation, sustained decreases in ABP did not influence dROR because data from the 3.5-s periods immediately after thigh cuff release was used for calculation of dROR, although it may be one factor accounting for the decrease in the percentage restoration in CBF velocity. In addition, it is possible that the decrease in ABP decreased below the lower limit of the autoregulatory curve. However, if this was true, we would expect the recovery of CBF velocity to follow that of arterial pressure (*i.e.*, flow would passively increase with pressure). In the current study, CBF velocity increased before arterial pressure began to return.

There are two other limitations with our study protocol. Potential instability in the plasma concentration of dexmedetomidine and changes in arterial carbon dioxide cannot be excluded as possible confounding factors of our results because we did not measure them. However, the current doses and periods of dexmedetomidine infusion were consistent with those administered in previous clinical and experimental studies as light and moderate sedation.[5,16,17] These previous studies indicated that dexmedetomidine levels reached steady state values within approximately 1 h after its administration, as did hemodynamic variables such as heart rate, MBP, respiratory status, and sedation depth, irrespective of the loading dose. Therefore, we speculated that the current regimens produced steady state plasma concentrations and hemodynamics as in these previous studies.[5,16,17]

Arterial carbon dioxide generally increases by approximately 4 mmHg during light and/or moderate dexmedetomidine sedation.[2,7] Arterial carbon dioxide in the current study might also have increased to this level and may have partly affected dynamic cerebral autoregulation. However, the remarkable decrease in dROR in the current study cannot be explained merely by this level of increase in arterial carbon dioxide.[8]

The current study investigated the effects of dexmedetomidine on dynamic cerebral autoregulation assessed by transfer function analysis and the thigh cuff method. The results suggest that dexmedetomidine might weaken dynamic cerebral autoregulation and delay restoration in CBF velocity during temporal decreases in arterial pressure, under conditions with decreases in steady state CBF velocity. Therefore, we caution that even low-dose dexmedetomidine can lead to further and sustained reductions in CBF when arterial pressure decreases temporally with postural changes or release of avascularization.

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