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ORIGINAL ARTICLE

The effect of dexmedetomidine on arterial-cardiac baroreflex function assessed by spectral and transfer function analysis

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Abstract
Purpose The α_2-adrenergic receptor agonist dexmedetomidine reportedly weakens heart rate (HR) responses to 'rapid' (during a few seconds) reduction in arterial pressure, but does not affect HR responses to 'gradual' (during 60 s) reduction in arterial pressure. As the speed of neurotransmission along the parasympathetic nerve is relatively rapid, alteration of parasympathetic-mediated arterial-cardiac baroreflex function plays a more important role in HR responses to 'rapid' changes in arterial pressure. We therefore hypothesized that dexmedetomidine attenuates parasympathetic-mediated arterial-cardiac baroreflex function.
Methods Twelve healthy men received placebo, low-dose (loading, 3 μg/kg/h for 10 min; maintenance, 0.2 μg/kg/h for 60 min) (low-DEX), or moderate-dose (loading, 6 μg/kg/h for 10 min; maintenance, 0.4 μg/kg/h for 60 min) (moderate-DEX) dexmedetomidine infusions in a randomized, double-blind, crossover study. Before and after 70 min of infusion, arterial-cardiac baroreflex function was assessed by spectral and transfer function analysis between arterial pressure variability and HR variability.
Results The high-frequency power of systolic arterial pressure (SAP) variability increased significantly with low-DEX and moderate-DEX infusions (significant interaction effects, $P = 0.005$), whereas the high-frequency power of R-wave–R-wave interval (RRI) variability (as an index of cardiac parasympathetic activity) did not change significantly at any dose infusions. Then, transfer function gain in the high-frequency range (as an index of parasympathetic arterial-cardiac baroreflex) decreased significantly with low-DEX and moderate-DEX infusions (significant interaction effects, $P = 0.007$).
Conclusions The present results suggest that dexmedetomidine attenuates parasympathetic-mediated arterial-cardiac baroreflex function, implying weakened HR response to 'rapid' reduction in arterial pressure.

Keywords Dexmedetomidine · Autonomic baroreflex regulation · Autonomic nerve activity · Spectral analysis · Transfer function analysis

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Introduction

Dexmedetomidine, a highly selective α_2-adrenergic receptor agonist, is often used for sedation in the operating theater and intensive care unit [1–3]. Many studies have reported various effects of dexmedetomidine on the autonomic nervous system or cardiovascular system [4–9]. Thus, the effects of dexmedetomidine on heart rate (HR) responses to reduction in arterial pressure are controversial [4, 6, 9]. A few studies have examined HR responses to a 'gradual' (during 60 s) decrease in arterial pressure by nitroprusside administration during dexmedetomidine infusion [4, 6]. These previous studies concluded that dexmedetomidine has no effect on baroreflex sensitivity. Conversely, our previous study evaluated cardiovascular reflex responses to 'rapid' (during a few seconds) reduction in arterial pressure after thigh cuff deflation during dexmedetomidine infusion [9]. Our previous research

demonstrated that dexmedetomidine weakens HR responses to temporal reduction in arterial pressure, implying attenuated baroreflex function. The discrepancy between our study and other previous studies may be explained by the difference in the speed of neurotransmission between sympathetic and parasympathetic regulatory mechanisms [10] responding to different speeds of reduction in arterial pressure. Because the parasympathetic nerve with fast neurotransmission can modulate HR more rapidly than the sympathetic nerve [10], alteration of parasympathetic arterial-cardiac baroreflex function would probably play a more important role in HR responses to 'rapid' changes in arterial pressure during dexmedetomidine sedation.

We therefore hypothesized that dexmedetomidine attenuates parasympathetic arterial-cardiac baroreflex function. Spectral and transfer function analysis between arterial pressure variability and HR variability can distinguish parasympathetic arterial-cardiac baroreflex function from other functions [11–14]. By using these analyses, arterial-cardiac baroreflex function was estimated in the same subjects as in our previous study [9].

Methods

The institutional review board of Nihon University School of Medicine approved this study. All study volunteers provided written informed consent as well as a medical history and were screened by a physical examination including electrocardiography (ECG) and arterial pressure measurements. We investigated 12 healthy, normotensive males with a mean age of 21 years (range, 18–23 years), a mean height of 173 cm (163–182 cm), and a mean weight of 66 kg (57–79 kg). The present study is a follow-up on two earlier articles on dexmedetomidine research [9, 15] and is based on reanalysis of the data obtained from the same subjects in a previous study on cardiovascular reflexes during dexmedetomidine infusion [9].

The present experiment protocol was the same as the description provided in our previous reports [9, 15]. Briefly, an analog ECG and continuous arterial pressure waveforms obtained from a 3-lead ECG (Life scope BSM-5132; Nihon Kohden, Tokyo, Japan) and tonometry (JENTOW 7700; Colin, Aichi, Japan) were recorded at a sampling rate of 1 kHz using commercial software (Notocord-hem 3.3; Notocord, Paris, France) throughout the experiment. A pulse oximeter, nasal cannula (Life scope BSM-5132; Nihon Kohden), and bispectral index monitor (BIS XP; Aspect Medical Systems, Norwood, MA, USA) were applied. All participants received placebo (normal saline), low-dose dexmedetomidine (low-DEX; loading dose of 3 μg/kg/h for 10 min; maintenance dose of 0.2 μg/kg/h for 60 min), or moderate-dose dexmedetomidine (moderate-DEX; loading dose of 6 μg/kg/h for 10 min; maintenance dose of 0.4 μg/kg/h for 60 min) infusions in a randomized, double-blind, crossover study. 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, Osaka, Japan). Moreover, these infusion regimens were similar to those used in previous studies [16, 17], including dexmedetomidine plasma concentrations [18]. At least 7 days were allowed between experiments. Drugs were administered after recording baseline data for 6 min after at least 30 min of rest. Seventy minutes after commencement of infusion of dexmedetomidine or placebo (loading, 10 min; maintenance, 60 min), 6-min data of ECG and continuous arterial pressure waveforms were analyzed for spectral and transfer function analyses. Before each 6-min data acquisition, sedation depths were assessed by the modified Observer's Assessment of Alertness/Sedation (OAA/S) scale [19]. Bispectral index (BIS) was used to confirm the stability of sedation depth during data acquisition. Steady-state values of HR, systolic arterial pressure (SAP), and diastolic arterial pressure (DAP) were obtained by averaging the 6 min of data. Steady-state values of arterial oxygen saturation (SpO_2), respiratory rate, and BIS that were manually recorded every minute were averaged over this 6-min time interval. After the data measurements, infusion of the drugs was discontinued.

Beat-to-beat values of SAP and R-wave–R-wave interval (RRI) were obtained using PC-based Notocord-hem 3.3 software to assess arterial-cardiac baroreflex function. Using previously validated algorithms [13, 20, 21], these data were linearly interpolated and resampled at 2 Hz to create an equidistant time series for spectral and transfer function analysis. The time series of SAP and RRI were first de-trended with third-order polynomial fitting and then subdivided into 256-point segments with a 50% overlap. This process resulted in five segments of data over a 6-min period of data collection. Fast Fourier transform analysis was implemented with each Hanning-windowed data segment and then averaged to calculate the autospectra of SAP and RRI. The minimal resolution of these spectra is $\sim$0.0078 Hz. High-frequency powers of SAP variability and RRI variability in the range of 0.15–0.50 Hz and low-frequency power in the range of 0.04–0.15 Hz were calculated from integration of the autospectra [20, 21]. This data acquisition and processing strategy conforms to the recommendations of international consensus panels for the assessment of cardiovascular variability [21]. Transfer function gain, phase, and coherence (squared coherence function) between SAP and RRI variability were estimated using the cross-spectral method [11–14] as mean values of high and low frequency in the ranges of 0.15–0.35 and 0.04–0.15 Hz, respectively. Transfer function gain between

SAP and RRI variability reflects changes in RRI variability in response to changes in SAP mediated by baroreflex function, whereas the estimated phase reflects the time relationship between these two variables. The assumption of linearity and reliability of the transfer function estimation were evaluated by coherence $\geq$0.4 [22, 23]. Transfer function estimates in the high-frequency range are predominantly determined by parasympathetic modulation, whereas estimates of transfer function in the low-frequency range are influenced by both sympathetic and parasympathetic modulation [11–14]. Data were analyzed using PC-based software (DADiSP; DSP Development, Cambridge, MA, USA).

Variables were compared using two-way repeated-measures analysis of variance (ANOVA) with stage (baseline and drug administration) × dose (placebo, low-DEX, and moderate-DEX). If the spectral power estimates were not normally distributed, transformation into the square root was performed before the ANOVA. The interaction effect was considered the most relevant for differences occurred. To determine where significant difference occurred, a Student–Newman–Keuls post hoc test was used for all pairwise comparisons. $P < 0.05$ was considered statistically significant. The analyses were performed using PC-based software (SigmaStat; Systat Software, Chicago, IL, USA). Data are presented as mean ± SEM.

Results

Because continuous measurement of BIS at baseline was not stable with the electromyogram in two subjects, these values were excluded from the group-averaged data for statistical analysis. The average values of steady-state hemodynamic and respiratory data with each infusion dose are presented in Table 1. HR decreased significantly with low-DEX and moderate-DEX infusions (significant interaction effects, $P < 0.001$). SAP and DAP decreased significantly with low-DEX and moderate-DEX infusions (significant interaction effects, $P < 0.001$ and $P = 0.005$, respectively). SpO_2 and respiratory rate did not change significantly at any dose infusions. The OAA/S score decreased significantly with moderate-DEX (significant interaction effects, $P = 0.008$), whereas BIS did not change significantly at any dose infusions.

Group-averaged power spectral density and transfer function indices of beat-to-beat changes in SAP and RRI are presented in Fig. 1 and Table 2. The high-frequency power of SAP variability increased significantly with low-DEX and moderate-DEX (significant interaction effects, $P = 0.005$), whereas the high-frequency power of RRI variability (as an index of cardiac parasympathetic activity) did not change significantly. Transfer function gain in the high-frequency range (as an index of parasympathetic arterial-cardiac baroreflex) decreased significantly with low-DEX and moderate-DEX (significant interaction effects, $P = 0.007$). The values of all these indices were not significantly different between low-DEX and moderate-DEX infusions.

The low-frequency powers of SAP variability (as an index of sympathetic vasomotor activity) decreased significantly with low-DEX and moderate-DEX (significant interaction effects, $P < 0.001$). The low-frequency powers of RRI variability (as an index of cardiac sympatho-vagal activity) decreased significantly with moderate-DEX (significant interaction effects, $P = 0.021$). Transfer function gain in the low-frequency range (as an index of sympathetic and parasympathetic baroreflex) increased significantly with moderate-DEX compared with baseline (significant

Table 1 Steady-state hemodynamics and respiratory conditions

	Placebo		Low-DEX		Moderate-DEX	
	Baseline	Drug administration	Baseline	Drug administration	Baseline	Drug administration
HR (beats/min)	59 ± 2	58 ± 2	61 ± 1	53 ± 2*	60 ± 3	53 ± 2*
SAP (mmHg)	114 ± 3	117 ± 4	113 ± 3	98 ± 3*,#	117 ± 3	102 ± 3*,#
DAP (mmHg)	58 ± 1	62 ± 3	56 ± 1	51 ± 1#	61 ± 2	54 ± 2*,#
SpO_2 (%)	98 ± 0	98 ± 0	98 ± 0	97 ± 0	98 ± 0	97 ± 0
Resp-R (breath/min)	13 ± 1	13 ± 1	12 ± 1	13 ± 1	12 ± 1	14 ± 1
OAA/S score	4.8 ± 0.1	4.7 ± 0.2	4.8 ± 0.0	4.3 ± 0.3	4.8 ± 0.1	3.3 ± 0.2*,#,†
BIS	84 ± 2	86 ± 2	88 ± 1	84 ± 2	86 ± 3	78 ± 2

Values are means ± SEM

Low-DEX low-dose dexmedetomidine, *moderate-DEX* moderate-dose dexmedetomidine, *HR* heart rate, *SAP* systolic arterial pressure, *DAP* diastolic arterial pressure, *SpO_2* arterial oxygen saturation, *Resp-R* respiratory rate, *OAA/S* Observer's Assessment of Alertness/Sedation Score (*OAA/S score of 5* responds readily to name spoken in normal tone, *OAA/S score of 4* lethargic response to name spoken in normal tone, *OAA/S score of 3* responds only after name is called loudly and/or repeatedly), *BIS* bispectral index

*$P < 0.05$ (vs. each baseline), #$P < 0.05$ (vs. placebo in drug administration), †$P = 0.052$ (vs. low-DEX in drug administration)

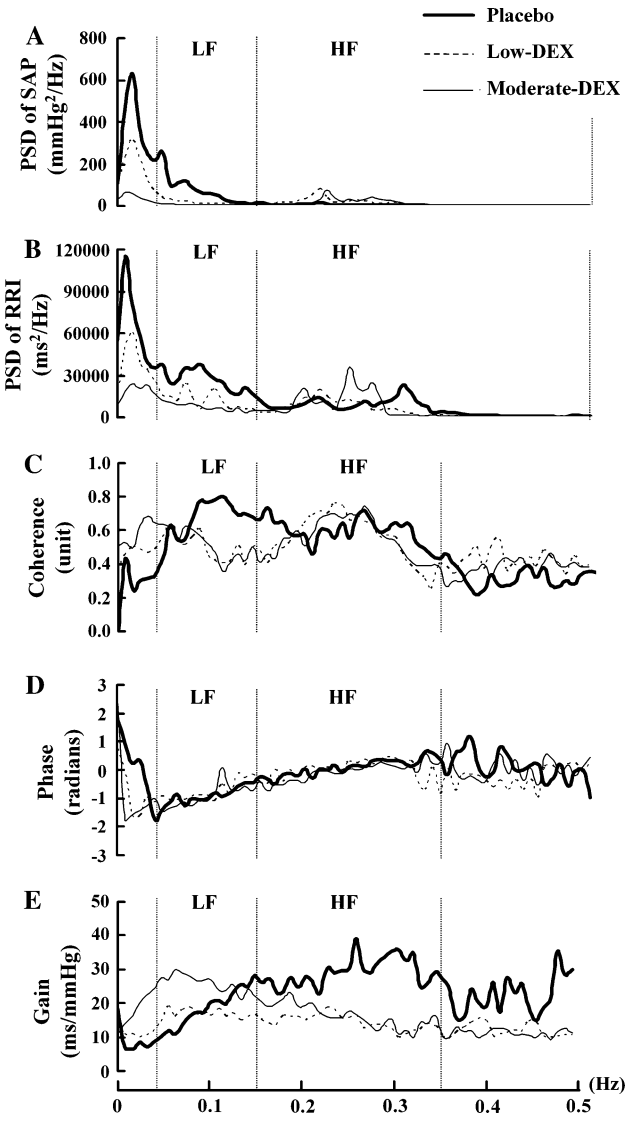

Fig. 1 Group-averaged power spectral density (PSD) and transfer function indices between systolic arterial pressure (SAP) and R-wave–R-wave interval (RRI) during administration of placebo and two doses of dexmedetomidine (DEX). **a** PSD of SAP. **b** PSD of RRI. **c** Coherence function. **d** Phase between SAP and RRI. **e** Transfer function gain between SAP and RRI. *LF* low-frequency range, *HF* high-frequency range. Placebo data (placebo), *thick line*; low-dose dexmedetomidine data (low-DEX), *dotted line*; moderate-dose dexmedetomidine data (moderate-DEX), *thin line*

main effect of time, $P = 0.027$). Coherence in the high- and low-frequency ranges was above 0.5 with all infusions, and phase in these frequency ranges did not change significantly at any dose infusions.

Discussion

The main findings of the present study were as follows: RRI variability in the high-frequency range (as an index of cardiac parasympathetic activity) remained unchanged despite increase in SAP variability with dexmedetomidine infusion. Then, transfer function gain in this range, representing the parasympathetic component of autonomic baroreflex regulation, decreased significantly with dexmedetomidine infusion. As expected, the present results suggest that dexmedetomidine attenuates parasympathetic arterial-cardiac baroreflex function.

In the previous studies, dexmedetomidine has been reported to weaken heart rate (HR) responses to 'rapid' reduction in arterial pressure resulting from thigh cuff deflation [9], but does not affect HR responses to 'gradual' reduction in arterial pressure induced by nitroprusside administration [4, 6]. This discrepancy may result from differences in the regulatory mechanisms responding to different speeds of reduction in arterial pressure. We therefore speculated that HR responses to 'rapid' reduction in arterial pressure would consist primarily of parasympathetic baroreflex.

In the present study, we used spectral and transfer function analysis between SAP variability and RRI variability to assess autonomic baroreflex regulation of the heart. RRI variability includes output signals of arterial-cardiac baroreflex [11, 24]. In other words, a change in SAP variability as input would influence estimation of RRI variability as output. In fact, both the low- and high-frequency powers of SAP variability changed significantly with dexmedetomidine infusions in the present study, possibly influencing RRI variability. To further understand the changes in autonomic circulatory control [11, 25], investigation of not only RRI variability but also SAP variability and transfer function between these two variables was applied in the present study. Transfer function analysis estimates the relationship between SAP variability as input and RRI variability as output, and transfer function gain between these two variables represents autonomic baroreflex regulation of the heart [11–14]. Moreover, transfer function analysis would be able to provide detailed information on autonomic baroreflex regulation by considering their frequency region: for example, the estimates of transfer function in the high-frequency range (0.15–0.35 Hz or 3–7 s) are primarily determined by parasympathetic modulation [11–14].

In the present results, RRI variability in the high-frequency range remained unchanged with dexmedetomidine infusion, suggesting unchanged cardiac parasympathetic activity. This result is consistent with previous reports that investigated the effects of dexmedetomidine on autonomic nervous activity assessed by spectral analysis of HR variability [6]. However, SAP variability in the high-frequency range (as input on the baroreflex arc) significantly increased with dexmedetomidine infusion. It is likely that dexmedetomidine induces capacitive vessel dilatation, leading to relative central hypovolemia.

Table 2 Autonomic nerve activity and arterial-cardiac baroreflex function

	Placebo		Low-DEX		Moderate-DEX	
	Baseline	Drug administration	Baseline	Drug administration	Baseline	Drug administration
HF_{SAP} ($mmHg^2$)	1.2 ± 0.2	1.1 ± 0.3	1.6 ± 0.3	3.9 ± 0.7*,#	1.4 ± 0.3	4.0 ± 0.7*,#
HF_{RRI} (ms^2)	1950 ± 813	2055 ± 1023	1235 ± 341	1567 ± 600	1937 ± 646	2088 ± 900
Gain-HF (ms/mmHg)	30.1 ± 5.7	29.2 ± 6.0	21.5 ± 2.7	14.5 ± 2.3*,#	29.0 ± 4.9	16.6 ± 3.8*,#
LF_{SAP} ($mmHg^2$)	6.7 ± 1.0	7.7 ± 1.4	5.5 ± 0.7	1.9 ± 0.7*,#	6.0 ± 1.0	0.6 ± 0.1*,#
LF_{RRI} (ms^2)	1592 ± 491	2856 ± 955*	983 ± 181	1291 ± 786#	1963 ± 508	932 ± 398*,#
Gain-LF (ms/mmHg)	15.3 ± 3.1	17.2 ± 3.1	12.2 ± 0.8	16.5 ± 1.4*	20.1 ± 4.4	26.0 ± 4.7*,†

Values are means ± SEM

Low-DEX low-dose dexmedetomidine, *Moderate-DEX* moderate-dose dexmedetomidine, HF_{SAP} power in high-frequency range of systolic arterial pressure variability, HF_{RRI} power in high-frequency range of R-wave–R-wave interval variability, *Gain-HF* transfer function gain in high-frequency range, LF_{SAP} power in low-frequency range of systolic arterial pressure variability, LF_{RRI} power in low-frequency range of R-wave–R-wave interval variability, *Gain-LF* transfer function gain in low-frequency range

*$P < 0.05$ (vs. each baseline), #$P < 0.05$ (vs. placebo in drug administration), †$P = 0.052$ (vs. low-DEX in drug administration)

Therefore, the increased SAP variability in this range would be caused by augmented effects of pleural pressure by respiration under the relative central hypovolemia. For precise interpretation of autonomic circulatory control as already stated, the present study also evaluated transfer function between these two variables. As expected, transfer function gain in the high-frequency range significantly decreased with dexmedetomidine infusions, suggesting attenuation of parasympathetic arterial-cardiac baroreflex function. Therefore, we consider that the attenuated parasympathetic baroreflex would weaken HR responses to rapid changes in arterial pressure, and this speculation is consistent with our previous report [9].

In the low-frequency range, SAP variability and RRI variability decreased significantly with dexmedetomidine infusions, suggesting diminished sympathetic vasomotor activity and cardiac sympatho-vagal activity. However, transfer function gain in this range, as an index of both sympathetic and parasympathetic arterial-cardiac baroreflex function, remained unchanged with low-dose dexmedetomidine or increased with moderate-dose dexmedetomidine infusions in the present study. This finding may imply augmentation of sympathetic baroreflex function, which has a relatively slow rate of neurotransmission [10], because of attenuation of parasympathetic baroreflex function as already stated. This dissociation between diminution of sympathetic vasomotor activity and maintenance of baroreflex function in the low-frequency range is consistent with the previous study, which reported decreased muscle sympathetic nerve activity and unchanged baroreflex function as estimated by vasoactive drug injection during clonidine administration [26]. Thus, there is a possibility that dexmedetomidine may have different effects on sympathetic and parasympathetic baroreflex regulation. The complex effects may relate to discrepant alterations of baroreflex function between previous studies [4, 6, 9].

Dexmedetomidine reportedly produces complex dose-dependent responses in the systemic circulation at a wide range of plasma concentrations (0.7–14.7 ng/ml) [4]. For example, HR and cardiac output decrease progressively with increasing concentrations of dexmedetomidine. Mean arterial pressure and vascular resistance show a biphasic dose–response relationship. Moreover, plasma levels of norepinephrine and epinephrine decreased substantially after the first dose and remained suppressed until high plasma concentrations of dexmedetomidine. In the present results, transfer function gain in the high-frequency range decreased with low-dose dexmedetomidine and remained at the same low-dose level even with moderate-dose dexmedetomidine. This change may be a similar type of dose-dependent response as plasma levels of catecholamines and does not indicate a simple linear dose-dependent response. Also, transfer function gain in the low-frequency range increased only with moderate-dose dexmedetomidine, implying a possible threshold for this alteration. The present study used low and moderate clinical doses of dexmedetomidine, probably equivalent to plasma concentrations of 0.3 and 0.6 ng/ml [15]. To provide a complete overview of dose-dependent effects of dexmedetomidine on autonomic baroreflex regulation, a wider range of infusion doses should be used in future studies.

The primary limitation of the present study is that autonomic circulatory control was estimated by the variable output of a complex system passing through a target organ, namely, the heart and arterioles. SAP variability and RRI variability are only indirect indices of autonomic nerve activity, being influenced by many other factors such as respiratory condition and reactivity of the heart and arterioles [27], although dexmedetomidine sedation produces little respiratory depression [28]. In addition, the steady-state changes in SAP or HR might affect the spontaneous arterial-cardiac baroreflex function, i.e.,

transfer function gain. Generally, the steady-state changes in SAP or HR lead to movement of the operating point on the static stimulus–response curve of the arterial-cardiac baroreflex, shift of static stimulus–response curve itself, or modification of the shape of the curve. Because SAP and HR in the present study decreased with dexmedetomidine infusions, some alteration of static stimulus–response relationship should occur. However, the present study cannot reveal which alterations of the static stimulus–response relationship occurred. Also, transfer function analysis cannot estimate the buffering capacity of the stimulus–response relationship. On the other hand, the transfer function analysis can show the dynamic properties of baroreflex function around the operating point. The gain (slope) around the operating point is dependent on the speed of changes in SAP, that is, the dynamic properties of baroreflex function. The present study revealed differences in dynamic properties of baroreflex function with speed of changes in SAP (gain-LF vs. gain-HF) during dexmedetomidine infusions.

The present protocol has limitations. In this study, no power analysis for baroreflex function indices was performed before the experiment because the present study was a follow-up analysis on our earlier article that investigated the effects of dexmedetomidine on cerebral circulation [15]. Because the sample size is small, there is a possibility that the present study could not show significant differences between low-DEX and moderate-DEX infusions (type II error).

In conclusion, the present study determined the effects of dexmedetomidine on arterial-cardiac baroreflex function assessed by spectral and transfer function analysis between SAP variability and RRI variability. Dexmedetomidine may have complex effects on autonomic circulatory control, but such effects would lead to simple attenuation of parasympathetic arterial-cardiac baroreflex function at low and moderate doses.

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