British Journal of Anaesthesia **103 (4):** 561–5 (2009)
doi:10.1093/bja/aep210 Advance Access publication August 13, 2009

BJA

NEUROSCIENCES AND NEUROANAESTHESIA

Cardiovascular reflex responses to temporal reduction in arterial pressure during dexmedetomidine infusion: a double-blind, randomized, and placebo-controlled study

J. Kato[1], Y. Ogawa[2]*, W. Kojima[1], K. Aoki[2], S. Ogawa[1] and K. Iwasaki[2]

[1]Department of Anesthesiology and [2]Division of Hygiene, Department of Social Medicine, Nihon University School of Medicine, 30-1 Oyaguchi-Kamimachi, Itabashi-Ku, Tokyo 173-8610, Japan

**Corresponding author. E-mail: yojiro@med.nihon-u.ac.jp*

Background. The low and moderate doses of dexmedetomidine reduce arterial pressure and heart rate (HR), suggesting attenuation of sympathetic activity and dominance of cardiac-vagal activity. These autonomic responses under dexmedetomidine sedation may attenuate cardiovascular reflex responses to temporal reduction in arterial pressure, inducing a severe hypotension. We therefore investigated the effects of dexmedetomidine on cardiovascular reflex responses to temporal reduction in arterial pressure induced by the thigh cuff method.

Methods. Twelve healthy men received placebo, low-dose (loading 3 $\mu g\ kg^{-1}\ h^{-1}$ for 10 min; maintenance 0.2 $\mu g\ kg^{-1}\ h^{-1}$ for 60 min), and moderate-dose (loading 6 $\mu g\ kg^{-1}\ h^{-1}$ for 10 min; maintenance 0.4 $\mu g\ kg^{-1}\ h^{-1}$ for 60 min) dexmedetomidine infusions in a randomized, double-blind, crossover study. After 70 min of drug infusion, systolic arterial pressure (SAP) and HR responses after thigh cuff deflation were evaluated as indices of cardiovascular reflex.

Results. Reduction in SAP (ΔSAP) [placebo 8 (4), low 12 (4), moderate 19 (5) mm Hg] after thigh cuff deflation was significantly greater in dexmedetomidine than placebo infusions, in a dose-dependent manner. The change in HR (ΔHR), ΔHR/ΔSAP, and the percentage restoration of SAP were lower with dexmedetomidine compared with placebo.

Conclusions. The present results indicated that dexmedetomidine weakens arterial pressure preservation and HR responses after thigh cuff deflation, suggesting attenuated cardiovascular reflexes. Therefore, it must be cautioned that dexmedetomidine can lead to further and sustained reduction in arterial pressure during transient hypotension induced by postural changes, haemorrhage, and/or other stresses.

Br J Anaesth 2009; **103**: 561–5

Keywords: anaesthetics i.v.; arterial pressure, drug effects; arterial pressure, hypotension; cardiovascular system, responses; sedation

Accepted for publication: June 4, 2009

The α_2-receptor agonist dexmedetomidine is often used in the anaesthetic setting[1–4] and the intensive care unit.[5 6] Dexmedetomidine has a biphasic dose–response relationship to arterial pressure.[7] Clinical doses of dexmedetomidine reduce arterial pressure,[8 9] because low and moderate doses of dexmedetomidine may be below the threshold required to produce significant peripheral vasoconstriction or because the sympatholytic effects of dexmedetomidine may offset direct effects on the peripheral vasculature.[7] Moreover, dexmedetomidine reduces heart rate (HR) by a reduction of tonic levels of sympathetic outflow[10] and a dominance of cardiac-vagal activity.[11] These autonomic responses under dexmedetomidine sedation may attenuate cardiovascular reflex responses to transient hypotension induced by postural changes or haemorrhage. However, no study has investigated the effects of dexmedetomidine on cardiovascular reflex responses to temporal reductions in arterial pressure.

To test our hypothesis that dexmedetomidine attenuates cardiovascular reflex responses to transient hypotension, we investigated arterial pressure and HR responses after thigh cuff deflation.

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 and also a medical history, and were screened by a physical examination including ECG and arterial pressure measurements. We investigated 12 healthy, normotensive males with a mean (range) age 21 (18−23) yr, height 173 (163−182) cm, and weight 66 (57−79) kg. These subjects were a subset of the group of subjects previously studied by us during an investigation on cerebral autoregulation.[12]

All participants fasted for at least 2 h before the experiments, and refrained from heavy exercise and consuming 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 ECG, pulse oximeter, nasal cannula (Life scope BSM-5132; Nihon Kohden, Tokyo, Japan), and bispectral index monitor (BIS XP®; Aspect Medical Systems, Inc., Norwood, MA, USA) were applied. Continuous arterial pressure was measured in the radial artery using tonometry with a non-invasive arterial pressure monitor at the heart level on a beat-to-beat basis, and calibrated by intermittent arterial pressure measured using the oscillometric method with a sphygmomanometer cuff placed over the brachial artery (JENTOW 7700; Colin, Aichi, Japan). Each waveform of ECG and continuous arterial pressure 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 G catheter was inserted into a forearm vein for drug infusion.

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. Moderate-dose dexmedetomidine was infused as an initial loading dose of 6 μg kg^{-1} h^{-1} for 10 min, followed by 0.4 μg kg^{-1} h^{-1} for 60 min (Moderate DEX). The dose of dexmedetomidine for low-dose infusion was half that of moderate-dose dexmedetomidine (Low DEX: an initial loading dose of 3 μg kg^{-1} h^{-1} for 10 min; with a maintenance dose of 0.2 μg kg^{-1} h^{-1} for 60 min). These doses and periods of infusion were chosen to obtain dexmedetomidine plasma concentrations of ∼0.6 and 0.3 ng ml^{-1} 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.[8 9 13] An equal volume of normal saline per hour was infused as placebo. Infusion of drugs was continued during the measurements. All subjects received all three types of infusions.

Seventy minutes after commencement of infusion of dexmedetomidine or placebo (loading 10 min; maintenance 60 min), 6 min worth of data of ECG and continuous arterial pressure waveforms were obtained for steady-state data. Ventilatory frequency, end-tidal carbon dioxide pressure (E'_{CO_2}), and arterial oxygen saturation (Sp_{O_2}) were recorded every minute during this period. Steady-state values of systolic arterial pressure (SAP), diastolic arterial pressure (DAP), HR, ventilatory frequency, E'_{CO_2}, and Sp_{O_2} were averaged over the 6 min time interval before thigh cuff inflation. After measuring steady-state data of these waveforms, thigh cuffs were inflated to 30 mm Hg above the subject's SAP by using a rapid cuff inflator (E20 Rapid Cuff Inflator; Hokanson, Inc., Bellevue, WA, USA). This instrument inflates a large cuff to 50 mm Hg in <0.3 s and deflates it again in <0.2 s. After 2 min of inflation, the cuffs were rapidly deflated to produce temporal reductions in arterial pressure.

The cardiovascular reflex after release of the large cuffs applied around both thighs was determined. Using previously validated algorithms,[14–17] beat-to-beat values of SAP and HR were obtained using PC-based Notocord-hem 3.3 software (Notocord-hem 3.3; Notocord, Paris, France). The computer then plotted curves as presented in Figure 1. Baseline values of SAP and HR were obtained by calculating their averages during the 10 s before thigh cuff release. Baseline values were obtained for all three types of infusions. Reduction in SAP (ΔSAP) was calculated by subtracting the lowest value of SAP after thigh cuff release (minimum SAP) from baseline SAP, whereas change in HR (ΔHR) was calculated by subtracting baseline HR from the highest value of HR after thigh cuff release (maximum HR). Then, an increase in HR in response to reduction in SAP (ΔHR/ΔSAP), as an index of arterial cardiac reflex, was calculated. In addition, percentage restoration of SAP was expressed as:

$$\text{Percentage restoration of SAP} = \frac{\text{restoration}}{\text{reduction}} \times 100 = \frac{(\text{recovery SAP} - \text{minimum SAP})}{(\text{baseline SAP} - \text{minimum SAP})} \times 100(\%),$$

where recovery SAP is the average SAP measured in the 10 s interval between 20 and 30 s after thigh cuff release, this being the predicted time by which recovery of SAP after thigh cuff release is complete or overshoots baseline levels under normal conditions.[17]

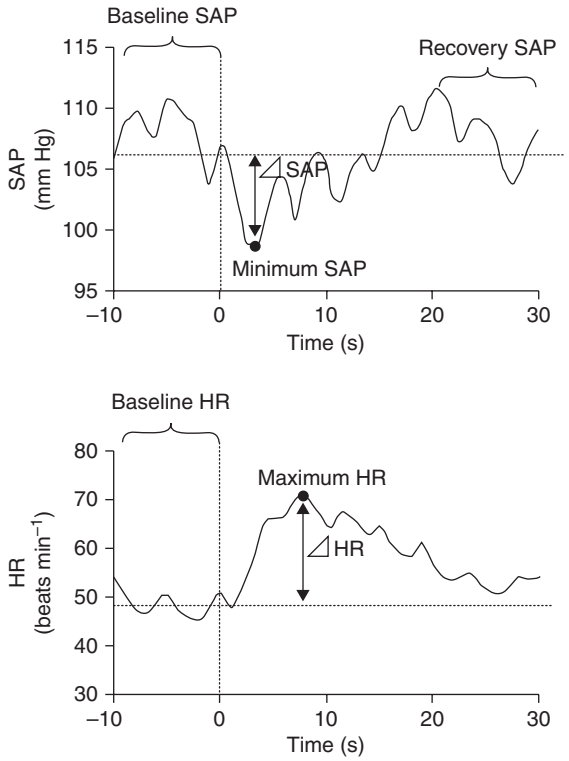

Fig 1 Representative changes in SAP and HR induced by thigh cuff deflation. Thigh cuffs were released at time 0. Baseline SAP was the average SAP during the 10 s before thigh cuff release. Minimum SAP was the lowest value of SAP after thigh cuff release. ΔSAP was the difference between baseline SAP and minimum SAP. Recovery SAP was the average SAP measured in the 10 s interval between 20 and 30 s after thigh cuff release. Baseline HR was the average HR during the 10 s before thigh cuff release. Maximum HR was the highest value of HR after thigh cuff release. ΔHR was the difference between baseline HR and maximum HR.

Inter-dose variables were compared using one-way repeated-measures analysis of variance (ANOVA) (placebo, Low DEX, and Moderate DEX). To determine where significant differences occurred, the Student–Newman–Keuls *post hoc* test was used for all pairwise comparisons. A P-value of <0.05 was considered statistically significant. The analyses were performed using PC-based software (SigmaStat; Systat Software, Inc., San Jose, CA, USA). Data are presented as mean (SD).

Results

The average values of steady-state haemodynamic and respiratory data with each infusion dose are presented in Table 1. Steady-state SAP, and DAP with Low DEX and Moderate DEX were significantly lower than with the placebo. HR tended to decrease in association with an increase in the dexmedetomidine dose (ANOVA, $P=0.063$). Although Sp_{O_2} with Low DEX and Moderate DEX was slightly but significantly lower than with placebo, ventilatory frequency and E'_{CO_2} were not significantly different among the three infusions. Bispectral index tended to decrease in association with an increase in the dexmedetomidine dose (ANOVA, $P=0.057$). The values of all these indices were not significantly different between Low DEX and Moderate DEX.

Table 1 Steady-state haemodynamics and respiratory conditions before thigh cuff deflation. SAP, systolic arterial pressure; DAP, diastolic arterial pressure; HR, heart rate; Sp_{O_2}, arterial oxygen saturation; Resp-R, ventilatory frequency; E'_{CO_2}, end-tidal carbon dioxide pressure; BIS, bispectral index. Values are means (SD). *$P<0.05$ (*vs* placebo)

	Placebo	Low DEX	Moderate DEX
SAP (mm Hg)	117 (13)	98 (10)*	102 (9)*
DAP (mm Hg)	62 (9)	51 (6)*	54 (5)*
HR (beats min^{-1})	58 (6)	53 (6)	53 (8)
Sp_{O_2} (%)	98 (1)	97 (1)*	97 (1)*
Resp-R (bpm)	13 (3)	13 (2)	14 (2)
E'_{CO_2} (kPa)	5.3 (0.8)	5.3 (0.8)	5.5 (0.7)
BIS	86 (5)	83 (7)	78 (8)

Table 2 Arterial pressure and HR after thigh cuff deflation. ΔSAP, the reduction in SAP after thigh cuff release; ΔHR, the response in HR after thigh cuff release; ΔHR/ΔSAP, increase of HR in response to reduction of SAP after thigh cuff release; %Restoration of SAP, percentage restoration of SAP in the interval from 20 to 30 s after thigh cuff release. Values are mean (SD). *$P<0.05$ (*vs* placebo); #$P<0.05$ (*vs* Low DEX)

	Placebo	Low DEX	Moderate DEX
ΔSAP (mm Hg)	8 (4)	12 (4)*	19 (5)*,#
ΔHR (beats min^{-1})	16 (8)	12 (4)*	11 (4)*
ΔHR/ΔSAP (beats min^{-1} mm Hg^{-1})	3.3 (4)	1.1 (1)*	0.6 (0)*
%Restoration of SAP	189 (171)	82 (31)*	50 (8)*

The average values of cardiovascular reflex indices assessed by the thigh cuff method are presented in Table 2. Averaged tracings from the entire series are presented in Figure 2. A decrease in SAP (ΔSAP) with Low DEX and Moderate DEX was significantly larger than with placebo; this decrease also being significantly larger with Moderate DEX when compared with Low DEX. The response of HR (ΔHR), ΔHR/ΔSAP, and the percentage restoration of SAP were significantly lower with Low DEX and Moderate DEX than with placebo.

Discussion

The primary finding of the present study was that when temporal reduction in arterial pressure was induced by thigh cuff deflation, the reduction in SAP was significantly greater during dexmedetomidine infusion than with placebo, in a dose-dependent manner. Also, change in HR, ΔHR/ΔSAP, and the percentage restoration of SAP were lower in dexmedetomidine infusions when compared with placebo, even with low-dose dexmedetomidine infusion. These results indicate that dexmedetomidine weakens arterial pressure preservation and HR responses after thigh cuff deflation.

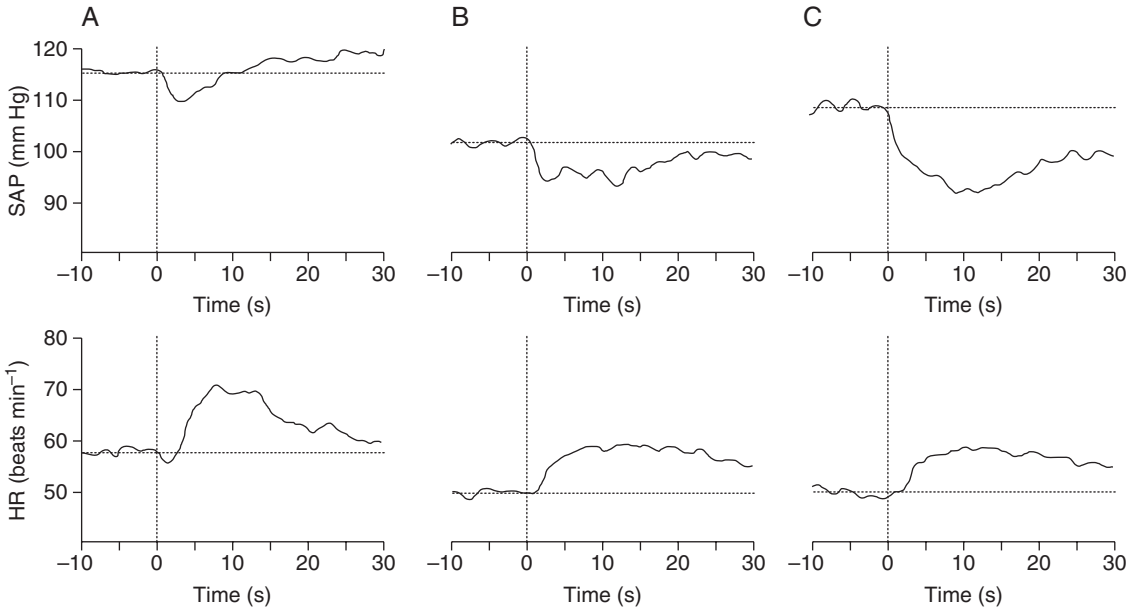

Fig 2 Group-averaged SAP and HR during the thigh cuff method. Placebo (A); low-dose dexmedetomidine: low DEX (B); and moderate-dose dexmedetomidine: moderate DEX (C). Thigh cuffs were released at time 0.

The present results of steady-state haemodynamics indicated a decrease in arterial pressure and HR similar to that observed in previous studies,[8 9 13] implying diminution of sympathetic activity and dominance of cardiac-vagal activity.[7 10 11] The autonomic effects of small doses of dexmedetomidine may compromise cardiovascular reflexes, namely increases in HR and augmentation of peripheral vascular resistance that occur in response to the transient hypotension by postural changes, haemorrhage, vasodilatation by heating, epidural bolus drug injection, or lifting patients for transfer from the intensive care unit beds to transporters.

The present study induced transient hypotension using the thigh cuff method. This method provides a temporal reduction in arterial pressure and a transient increase in HR by rapid deflation of the thigh cuff after temporary ischaemia in the lower limbs with cuff inflation.[14–17] In previous studies, it has been presented that circulatory occlusion of resting skeletal muscles with thigh cuff inflation does not evoke either cardiovascular metaboreflexes or mechanoreflexes,[14–16] suggesting that the cuff inflation used in the present study caused no interference with cardiovascular reflexes. Thus, use of the thigh cuff method during dexmedetomidine sedation would aid in evaluation of cardiovascular reflex responses to simulated haemodynamic changes without any autonomic effects by administration of vasoactive drugs.

A representative change after thigh cuff deflation (Fig. 1) had three phases with different characteristics, similar to that observed in a previous study.[17] In phase 1, after thigh cuff release, arterial pressure decreased rapidly. In response to this decrease in arterial pressure, HR increased after a slight time delay. In phase 2, in association with the restoration of arterial pressure from the nadir to the level before thigh cuff release, HR continuously increased with simultaneous increases in arterial pressure. In phase 3, arterial pressure overshot predeflation levels, HR decreased from maximal responses and recovered to the level before thigh cuff release in association with a recovery of arterial pressure. Thus, phases 1, 2, and 3 of cardiovascular reflexes after thigh cuff release would be indicated by the indices used in the present study (ΔSAP, ΔHR, and percentage restoration in SAP), respectively. Also, the ΔHR/ΔSAP was estimated as an index of cardiac reflexes. Consequently, the present results of all these indices suggest together that dexmedetomidine attenuated cardiovascular reflex.

Dexmedetomidine has beneficial effects in the anaesthetic setting, including sedation, analgesia, anxiolysis, and reduction in opioid, and inhalation anaesthetic requirement.[3 4 10 18 19] Moreover, sedation with dexmedetomidine is efficacious in critically ill patients in the intensive care unit.[5 6] These previous studies have also reported that dexmedetomidine prevents incidences of detrimental haemodynamic changes in the operating theatre and the intensive care unit. However, the present study found that cardiovascular reflex index to temporal reductions in arterial pressure was attenuated during dexmedetomidine sedation. From the present results, it must be cautioned that when transient hypotension is induced by postural changes, haemorrhage, and/or other stresses, dexmedetomidine administration can lead to further and sustained reduction of arterial pressure.

The present regimen would produce steady-state plasma concentration, but potential instability cannot be excluded.[12] The plasma concentration of dexmedetomidine

should have been measured for more precise study. Then, the SD in percentage restoration of SAP was very large in the placebo infusion, because the index includes not only the complete recovery but also the overshoot in SAP.[17] Indeed, a subject who overshot extensively relative to reduction of SAP indicates 673% in percentage restoration of SAP.

We investigated the effects of dexmedetomidine on cardiovascular reflex responses to temporal reductions in arterial pressure induced by the thigh cuff method. Dexmedetomidine weakens arterial pressure preservation and HR responses after thigh cuff deflation, suggesting attenuated cardiovascular reflexes. Therefore, dexmedetomidine infusion can lead to further and sustained reduction in arterial pressure when transient hypotension occurs in the perioperative period.

Funding

This work was supported by institutional funding and Hospira Japan K.K. (Osaka, Japan).

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