J Anesth (2011) 25:818–822
DOI 10.1007/s00540-011-1215-3

ORIGINAL ARTICLE

Dexmedetomidine can stabilize hemodynamics and spare anesthetics before cardiopulmonary bypass

Takayuki Kunisawa · Megumi Ueno · Atsushi Kurosawa · Michio Nagashima · Dai Hayashi · Tomoki Sasakawa · Akihiro Suzuki · Osamu Takahata · Hiroshi Iwasaki

Received: 7 January 2011 / Accepted: 11 August 2011 / Published online: 8 September 2011

Abstract
Purpose We previously confirmed the effectiveness of dexmedetomidine (DEX) for stabilizing hemodynamics as well as sparing anesthetics during anesthetic induction in patients undergoing cardiac surgery (Kunisawa et al. in J Clin Anesth 21:194–199, 1). In this study, we investigated whether these effects of DEX continue until the start of cardiopulmonary bypass (CPB).
Methods Twenty-two patients with mild to moderate cardiovascular disease were randomized into two groups [DF2 group: DEX dose of 0.7 μg/kg/h after initial dose and effect-site concentration (ESC) of fentanyl of 2 ng/ml; PF4 group: saline and ESC of fentanyl of 4 ng/ml]. Propofol was administered for anesthetic induction and maintenance. Hemodynamics, cardiovascular drugs, ESC of propofol, and cardiovascular responses to skin incision (SI) and sternotomy (St) were measured or calculated.
Results Blood pressure (BP) at the pre-/post-SI periods was higher in the DEX group (137 ± 17/140 ± 16 mmHg) than in the placebo group (85 ± 9/109 ± 24 mmHg). Percent increases in cardiovascular response to SI or St were lower in the DEX group than in the placebo group (for example, 1.9 ± 2.2 vs. 27.4 ± 19.9% in systolic BP due to SI). ESCs of propofol at SI and St in the DEX group were lower than those in the placebo group.
Conclusions DEX combined with 2 ng/ml fentanyl before CPB can suppress the decrease in blood pressure at the pre- and post-SI periods, can blunt the cardiovascular responses to SI and St, and can spare the required ESC of propofol despite fentanyl concentration, which was half of that in the placebo group.

Keywords Dexmedetomidine · Anesthetic-sparing effect · Adjuvant · Before cardiopulmonary bypass

Introduction

Hypotension caused by anesthesia and hypertension resulting from surgical stimuli should be avoided because these conditions can cause undesirable events leading to severe complications. Previously, we reported that dexmedetomidine (DEX) combined with anesthetic drugs suppressed the decrease in blood pressure (BP) during anesthetic induction (AI) and blunted the cardiovascular response to tracheal intubation [1]. From the results in this report, the effect of DEX on BP preservation is expected to continue after AI, and the effect of DEX on blunting the cardiovascular response to noxious stimuli is also expected to occur at skin incision (SI) and sternotomy (St). Moreover, it was reported that DEX, an anesthetic adjunct in coronary artery bypass grafting, spares inhalation of anesthetics and narcotic drugs [2]. Therefore, we hypothesized that the expansion of our protocol into starting cardiopulmonary bypass (CPB) would stabilize hemodynamics and spare propofol before CPB.

Thus, the present pilot study had three goals: (1) to confirm that dexmedetomidine preserves BP before CPB, (2) to confirm that dexmedetomidine blunts the cardiovascular response to SI and St, and (3) to investigate the

Presented at First World Congress of Total Intravenous Anesthesia (TCI), Venice, Italy, September–November 28, 2007.

T. Kunisawa (✉) · M. Ueno · A. Kurosawa · M. Nagashima · D. Hayashi · T. Sasakawa · A. Suzuki · O. Takahata · H. Iwasaki
Department of Anesthesiology and Critical Care Medicine, Asahikawa Medical College, 2-1-1-1 Midorigaoka-higashi, Asahikawa, Hokkaido 0788510, Japan
e-mail: taka.kunisawa@nifty.ne.jp

extent to which our protocol can spare propofol before CPB.

Materials and methods

The study was approved and monitored by the Research Ethics Committee of Asahikawa Medical College, and informed consent was obtained from each patient. The study population consisted of 22 patients, aged 46–79 years, who were scheduled to undergo cardiovascular surgery (coronary artery bypass grafting, valve replacement, or replacement of the total aortic arch) for ischemic heart disease, valvular disease, or aneurysm of the aortic arch. The exclusion criteria were severe cardiovascular disease [New York Heart Association (NYHA) class 4 or less than 30% left ventricular ejection fraction], or concurrent systemic disorders (e.g., patients with a severe liver dysfunction or those with chronic renal failure on hemodialysis). Patients with arrhythmias such as atrial fibrillation or disturbance in the conduction system and those on α-methyldopa or clonidine treatment were also excluded from this study. This study was controlled, double blinded, and randomized based on a sealed envelope technique. The patients were randomized into one of two groups, the DF2 or PF4 group, based on the administration of dexmedetomidine or placebo combined with anesthetics and the fentanyl effect-site concentration (ESC).

The patients received no premedication. After arrival of the patient in the operating room (OR), standard monitoring was performed using IntelliVue M8010A (Philips Electronics Japan, Tokyo, Japan) during general anesthesia. The radial artery was cannulated during local anesthesia using a 20-gauge catheter. Dexmedetomidine (Precedex, 200 μg/2 ml; Hospira Japan, Japan) was diluted with saline to obtain a concentration of 0.1 μg/kg/ml. Patients received either the diluted dexmedetomidine or placebo saline at a rate of 60 ml/h for 10 min before anesthetic induction, followed by a continuous infusion at a rate of 7 ml/h. In the DF2 group, the initial dose of dexmedetomidine was 1.0 μg/kg for 10 min, and the continuous infusion dose was 0.7 μg/kg/h. Anesthetic management was performed using propofol and fentanyl with vecuronium as a muscle relaxant. Propofol was administered using a target-controlled infusion (TCI) pump (TE-371; Terumo, Tokyo, Japan) and adjusted to keep the bispectral index (BIS) value in the BISmonitor (Aspect, BIS Monitor A-2000; Nihon Kohden, Tokyo, Japan) within 40–60. Fentanyl was administered using a syringe pump (Graseby 3500; Graseby Medical, Watford, UK) operated by STANPUMP software (available at http://opentci.org/doku.php; accessed on 1 March 2010) with Shafer's parameter setting [3] using either the fixed target ESC of 2 ng/ml in the DF2 group or 4 ng/ml in the PF4 group. The TCI system was located at a distance from the anesthesiologist and investigator so that the target concentration could not be seen. Vecuronium was administered at a dose of 0.1 mg/kg to facilitate the intubation, and additional vecuronium was administrated as needed. The pharmacological intervention protocol was as follows. If hypotension [systolic blood pressure (SBP) <90 mmHg] occurred with a heart rate less than 50 bpm, 5 mg ephedrine was to be administered intravenously (i.v.). If hypotension (SBP $<$ 90 mmHg) occurred with a heart rate of 50 bpm or more, 50 μg phenylephrine was administered i.v. In the case of bradycardia [heart rate (HR) $<$ 40 bpm], 0.5 mg atropine was administrated. Hypertension (SBP $\geq$ 160 mmHg)

Table 1 Patient demographics and surgical condition

	DF2 group	PF4 group	*P* value
Number of patients	11	11	
Age (years)	68 ± 6	69 ± 9	0.979
Gender (M/F)	8/3	7/4	0.647
Weight (kg)	57 ± 8	58 ± 11	0.865
Height (cm)	158 ± 8	155 ± 8	0.456
ASA physical status, II/III	2/9	3/8	0.619
Case (IHD/Val D/Vas D)	4/5/2	5/4/2	0.895
LVEF (%)	64 ± 10	59 ± 14	0.296
Duration from AI to SI (min)	107 ± 18	113 ± 12	0.409
Duration from AI to St (min)	144 ± 40	151 ± 35	0.695
Duration from SI to St (min)	37 ± 35	38 ± 26	0.951

Data are presented as mean ± SD or number of patients

ASA, American Society of Anesthesiologists; DF2 group, dexmedetomidine with a fentanyl effect-site concentration (ESC) of 2 ng/ml; PF4 group, placebo with a fentanyl ESC of 4 ng/ml; ASA, American Society of Anesthesiologists; IHD, ischemic heart disease; Val D, valvular disease; Vas D, vascular disease; LVEF, left ventricular ejection fraction as estimated by transthoracic echocardiography; AI, anesthetic induction; SI, skin incision; St, sternotomy

was intended to be treated with 0.5 mg nicardipine and tachycardia (HR $\geq$ 100 bpm) was intended to be treated by 5 mg esmolol.

The doses of the cardiovascular agents were recorded. HR was monitored by electrocardiography. The values of the hemodynamic parameters measured during a stable state immediately before the administration of dexmedetomidine or placebo saline were recorded at the pre-AI period. The values measured immediately before SI or St were recorded as values at the pre-SI and pre-St periods, respectively. The highest values, monitored in real time, during the 0–5 min after the SI or St were recorded as the post-SI and post-St values, respectively.

Gender, the American Society of Anesthesiologists-Physical Status (ASA-PS) score, the number of patients, and the number of drugs administered were analyzed using the chi-square test. The other demographic parameters, i.e., surgical condition, percent changes in the hemodynamic values due to SI or St, and ESC of propofol, were analyzed using an unpaired *t* test. The hemodynamic values were analyzed using repeated-measures analysis of variance (ANOVA) followed by unpaired *t* test to analyze intergroup differences in the same periods and Dunnett test to be compared with the pre-AI period value within the group. Data were expressed as mean $\pm$ SD, and a *P* value less than 0.05 was considered statistically significant.

Results

The demographics and surgical conditions are shown in Table 1. There were no intergroup differences in the patients' demographic characteristics or in the three durations (AI to SI, AI to St, and SI to St).

The hemodynamic values at each period are presented in Fig. 1. SBP in the PF4 group at all periods was significantly lower than the pre-AI value. In contrast, SBP in the DF2 group at the pre-/post-St periods was lower than that at pre-AI period. The SBP values at the pre-SI (137 $\pm$ 17 mmHg) period and the post-SI period (140 $\pm$ 16 mmHg) in the DF2 group were significantly higher than the corresponding values (85 $\pm$ 9 and 109 $\pm$ 24 mmHg, respectively) in the PF4 group. Diastolic blood pressure (DBP) values at the pre-SI, post-SI, and pre-St periods in the PF4 group were significantly lower than those values at the pre-AI period; however, there were no significant differences between pre-AI values and those from the other periods within the DF2 group. HR values at the pre- and post-SI periods in the PF4 group were lower than those values at the pre-AI period, and the HR values at all periods in the DF2 group were lower than those recorded at the pre-AI period. There was a single intergroup difference in HR at the post-St period (DF2, 58 $\pm$ 9 bpm vs. PF4, 67 $\pm$ 10 bpm).

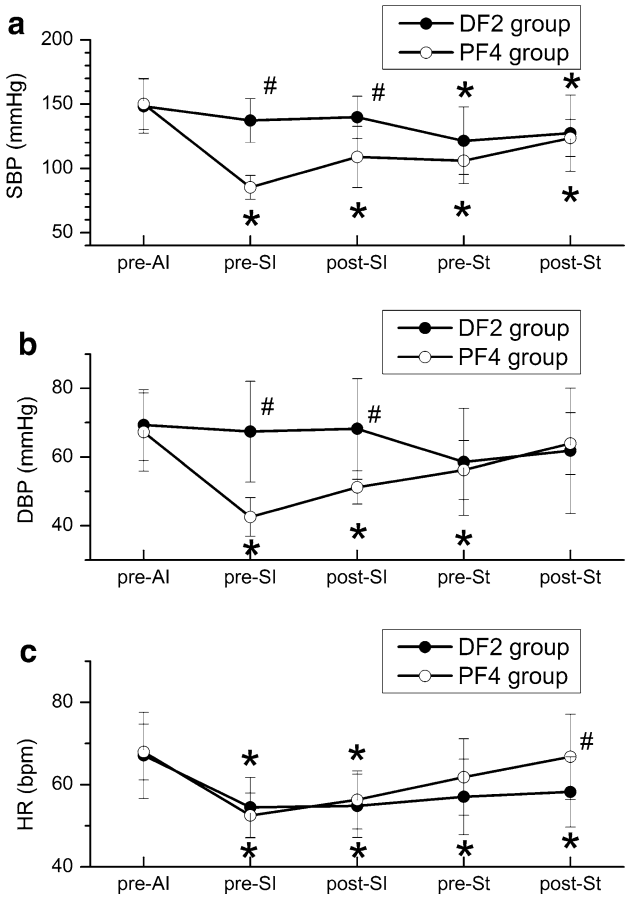

Fig. 1 The hemodynamic data for each period. **a** Systolic blood pressure (SBP) in the PF4 group [placebo with a fentanyl effect-site concentration (ESC) of 4 ng/ml] at all periods was significantly lower than that at pre-AI within the same group; however, SBP in the DF2 group (dexmedetomidine with a fentanyl ESC of 2 ng/ml) only at the pre- and post-St periods was lower than that at pre-AI. SBP values at the pre-/post-SI periods in the DF2 group were higher than the corresponding value in the PF4 group. **b** The diastolic blood pressure (DBP) value shows the same tendency as the SBP value except (1) in the pre-/post-St periods in the DF2 group and (2) in the post-St period in the PF4 group. **c** The heart rate (HR) values at all periods were significantly lower than that at the anesthetic induction (AI) period within the DF2 group. In contrast, HR values at the pre-/post-SI periods were significantly lower than that at the AI period within the PF4 group. HR at the post-St period in the PF4 group was higher than the corresponding value in the DF2 group. $^{*}P < 0.05$ when compared with the value at the pre-AI period within the same group; $^{\#}P < 0.05$ when compared with the PF4 group at the same period. DF2 group, dexmedetomidine with a fentanyl effect-site concentration (ESC) of 2 ng/ml; PF4 group, placebo with a fentanyl ESC of 4 ng/ml; SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate; AI, anesthetic induction; SI, skin incision; St, sternotomy

Cardiac responses to SI or St are demonstrated in Fig. 2. Percentage increase in the PF4 group was significantly higher than the corresponding values in the DF2 group [for example, the percentage increase in SBP due to SI was 1.9 $\pm$ 2.2% (DF2) vs. 27.4 $\pm$ 19.9% (PF4)].

The drugs administered and ESC of propofol are listed in Table 2. There were no significant intergroup difference

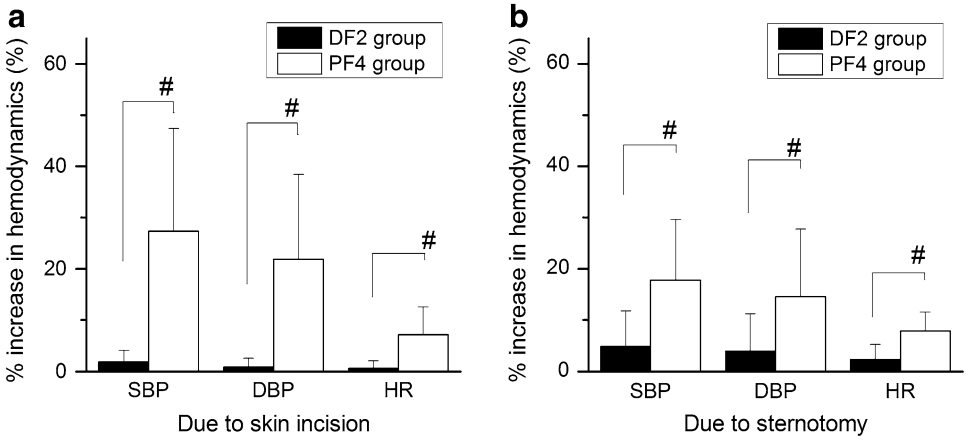

Fig. 2 Percent increase in the hemodynamic values resulting from skin incision and sternotomy. a The percent increases in SBP, DBP, and HR were significantly lower in the DF2 group than in the PF4 group. b The percent increases in SBP, DBP, and HR were also significantly lower in the DF2 group than in the PF4 group. $^{\#}P < 0.05$ when compared with the PF4 group. DF2 group, dexmedetomidine with a fentanyl effect-site concentration (ESC) of 2 ng/ml; PF4 group, placebo with a fentanyl ESC of 4 ng/ml; SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate

Table 2 Frequency and dose of cardiovascular agents administered and effect-site concentration (ESC) of propofol

		DF2 group	PF4 group	*P* value
Ephedrine	Frequency (%)	55	73	0.375
	Dose (mg)	4.09 ± 4.37 (0–10)	9.09 ± 7.69 (0–20)	0.075
Phenylephrine	Frequency (%)	55	45	0.670
	Dose (μg)	81.8 ± 84.5 (0–200)	100.0 ± 130.4 (0–300)	0.702
Atropine	Frequency (%)	0	0	–
	Dose (mg)	0	0	1.000
Nicardipine	Frequency (%)	0	18	0.138
	Dose (mg)	0	0.23 ± 0.52 (0–1.5)	0.161
Esmolol	Frequency (%)	0	0	–
	Dose (mg)	0	0	1.000
ESC of propofol	at skin incision (μg/ml)	1.76 ± 0.39	2.83 ± 0.61	<0.001*
	at sternotomy (μg/ml)	1.80 ± 0.31	2.81 ± 0.54	<0.001*

Data are presented as mean ± SD (range) or frequencies

DF2 group, dexmedetomidine with a fentanyl effect-site concentration (ESC) of 2 ng/ml; PF4 group, placebo with a fentanyl ESC of 4 ng/ml

* *P* value less than 0.05 was considered statistically significant

in both frequency and dose of ephedrine or phenylephrine. Atropine and esmolol were not administered in any of the groups. Nicardipine was only administered in the PF4 group; however, there were no significant intergroup differences in the frequency or dose.

Discussion

The strong effect of DEX as an adjuvant was proved in our previous study, in which hemodynamic parameters did not significantly change in the DF2 group in response to tracheal intubation despite the fentanyl concentration, which was half of that in the PF4 group [1]. In the present study, the strong effect was also proven by the lower percent increase in all hemodynamic parameters in the DF2 group than in the PF4 group, despite using only half of the fentanyl concentration used in the PF4 group. Three observations from our study showed stress response to noxious stimuli in the PF4 group: the first was the cardiovascular response to SI or St, the second was that HR at post-St in the PF4 group was significantly higher than that in the DF2 group, and the third was the existence of the case in which nicardipine administration was needed. In other words, these data indicate that DEX suppresses sufficiently stress response to noxious stimuli.

Although many studies have reported that DEX could cause hypotension [2, 4–6], the effect of DEX on

preserving BP during anesthetic induction was demonstrated in our previous study [1]. The reason for this was thought to be as follows: because the sympatholytic effect of DEX could be masked by the drugs used for AI, the peripheral vasoconstrictive effect of DEX became more pronounced. These phenomena are also thought to be the reason, in the present study, why the SBP and DBP in the DF2 group at the pre- and post-SI periods were higher than the corresponding values in the PF4 group when intergroup comparisons were performed at the same period (# in Fig. 1) and why there were significant differences in BP at only 2 of 8 points when compared with the values at the AI period within the DF2 group in contrast to 7 of 8 points when compared with the values at the AI period in the PF4 group (* in Fig. 1).

The HR in the DF2 group was stable at the low rate because of the effect of DEX and synergy with fentanyl; this finding was consistent with that of a previous report [1, 7]. As already mentioned, the HR in the PF4 group gradually increased and was higher than that in the DF2 group at the post-St period because 4 ng/ml fentanyl could not suppress the catecholamine release resulting from noxious stimuli. However, DEX with 2 ng/ml fentanyl could suppress the cardiovascular response to noxious stimuli, thereby suggesting that this combination of DEX and fentanyl sustained the low HR in the DF2.

The anesthetic-sparing effects of DEX are well known, even in the field of cardiothoracic anesthesia, and some studies have shown the effects as follows. Jalonen et al. [2] reported that the total fentanyl dose and end-tidal concentration of enflurane were reduced approximately 25%, respectively, during coronary artery bypass grafting. Kanda et al. [8] reported that advancing the start time of DEX administration caused both an approximate 24% and 28% reduction in ESC of propofol and fentanyl, respectively, in cardiovascular surgery. In the present study, an approximate 37% reduction of propofol was also demonstrated despite the fentanyl concentration in the DF2 group being half of that in the PF4 group; this finding was consistent with that of previous studies.

There were no significant intergroup differences with any of the cardiovascular drugs. First, wide-range criteria for pharmacokinetic treatment are not thought to change the incidence of use of cardiovascular agents, but result in differences in hemodynamics. Second, there were some causes for BP preservation. In the DF2 group, as mentioned above, DEX functioned in BP preservation because the sympatholytic effect of DEX was masked. Moreover, the decrease in propofol ESC might facilitate BP preservation, which can be a benefit of the anesthetic-sparing effect of DEX. On the other hand, because the effect of fentanyl against noxious stimuli was not thought to be enough, this insufficient effect of fentanyl may contribute toward preserving BP.

Limitations of this study included the small sample size and limited population. We cannot address the efficiency for patients with severe complications such as heart failure, conduction disturbance, or no complications. Further studies with a large sample size should be conducted to determine the usefulness of DEX in combination with fentanyl for patients with a broad range of complications and their varying surgeries.

DEX with a twofold-reduced fentanyl concentration could preserve BP before CPB, could blunt the cardiovascular response to SI and St, and could reduce the required propofol concentration before CPB.

Acknowledgments Support was provided solely from institutional and/or departmental sources.

References

1. Kunisawa T, Nagata O, Nagashima M, Mitamura S, Ueno M, Suzuki A, Takahata O, Iwasaki H. Dexmedetomidine suppresses the decrease in blood pressure during anesthetic induction and blunts the cardiovascular response to tracheal intubation. J Clin Anesth. 2009;21:194–9.
2. Jalonen J, Hynynen M, Kuitunen A, Heikkila H, Perttila J, Salmenpera M, Valtonen M, Aantaa R, Kallio A. Dexmedetomidine as an anesthetic adjunct in coronary artery bypass grafting. Anesthesiology. 1997;86:331–45.
3. Shafer SL, Varvel JR, Aziz N, Scott JC. Pharmacokinetics of fentanyl administered by computer-controlled infusion pump. Anesthesiology. 1990;73:1091–102.
4. Carollo DS, Nossaman BD, Ramadhyani U. Dexmedetomidine: a review of clinical applications. Curr Opin Anaesthesiol. 2008;21:457–61.
5. Talke P, Li J, Jain U, Leung J, Drasner K, Hollenberg M, Mangano DT. Effects of perioperative dexmedetomidine infusion in patients undergoing vascular surgery. The Study of Perioperative Ischemia Research Group. Anesthesiology. 1995;82:620–33.
6. Biccard BM, Goga S, de Beurs J. Dexmedetomidine and cardiac protection for non-cardiac surgery: a meta-analysis of randomised controlled trials. Anaesthesia. 2008;63:4–14.
7. Ebert TJ, Hall JE, Barney JA, Uhrich TD, Colinco MD. The effects of increasing plasma concentrations of dexmedetomidine in humans. Anesthesiology. 2000;93:382–94.
8. Kanda H, Kunisawa T, Kurosawa A, Nagashima M, Suzuki A, Takahata O, Iwasaki H. Effect of dexmedetomidine on anesthetic requirements in cardiovascular surgery (in Japanese with English abstract). Masui (Jpn J Anesthesiol). 2009;58:1496–500.