RESEARCH

Effects of dexmedetomidine on cardiac electrophysiology in patients undergoing general anesthesia during perioperative period: a randomized controlled trial

Chao Tan[1†], Shiting Yan[1,2†], Jie Shen[3†], Hao Wu[1], Leyang Yu[1,2], Ying Wang[1,2], Shunping Tian[1], Wei Zhou[1], Yong Wu[3] and Zhuan Zhang[1*]

Abstract

Background: Dexmedetomidine has controversial influence on cardiac electrophysiology. The aim of this study was to explore the effects of dexmedetomidine on perioperative cardiac electrophysiology in patients undergoing general anesthesia.

Methods: Eighty-one patients were randomly divided into four groups: groups D_1, D_2, D_3 receiving dexmedetomidine 1, 1, 0.5 µg/kg over 10 min and 1, 0.5, 0.5 µg/kg/h continuous infusion respectively, and control group (group C) receiving normal saline. Twelve-lead electrocardiograms were recorded at the time before dexmedetomidine/normal saline infusion (T_1), loading dose finish (T_2), surgery ending (T_6), 1 h (T_7) after entering PACU, 24 h (T_8), 48 h (T_9), 72 h (T_{10}) and 1 month (T_{11}) postoperatively. Cardiac circulation efficiency (CCE) were also recorded.

Results: Compared with group C, QTc were significantly increased at T_2 in groups D_1 and D_2 while decreased at T_7 and T_8 in group D_3 ($P < 0.05$), iCEB were decreased at T_8 ($P < 0.05$). Compared with group D_1, QTc at T_2, T_6, T_7, T_9 and T_{10} and iCEB at T_8 were decreased, and CCE at T_2-T_4 were increased in group D_3 significantly ($P < 0.05$). Compared with group D_2, QTc at T_2 and iCEB at T_8 were decreased and CCE at T_2 and T_3 were increased in group D_3 significantly ($P < 0.05$).

Conclusions: Dexmedetomidine at a loading dose of 0.5 µg/kg and a maintenance dose of 0.5 µg/kg/h can maintain stability of cardiac electrophysiology during perioperative period and has no significant adverse effects on CCE.

Trial registration: ClinicalTrials.gov NCT04577430 (Date of registration: 06/10/2020).

Keywords: Dexmedetomidine, General anesthesia, Cardiac electrophysiology, Cardiac function

†Chao Tan, Shiting Yan and Jie Shen contributed equally to this work.

*Correspondence: zhangzhuancg@163.com

¹ Department of Anesthesiology, the Affiliated Hospital of Yangzhou University, Yangzhou 225012, China
Full list of author information is available at the end of the article

Background

Dexmedetomidine is a highly selective α_2-adrenergic receptor agonist, which can inhibit the activity of sympathetic nervous system and exert predictable sedative and analgesic effects without obvious respiratory depression [1, 2]. Previous studies [3–6] reported that dexmedetomidine could change the permeability of ion channels to affect cardiac electrophysiology balance and cardiac function during perioperative period. A previous study

Tan *et al. BMC Anesthesiology* (2022) 22:271

Page 2 of 14

discovered that dexmedetomidine could intensify the efferent impulse of vagus nerve, prolong the effective refractory period of myocardial cells, decrease myocardial autonomy, and shorten the abnormally prolonged QTc [7]. While researchers found that dexmedetomidine could also prolong the QTc [8], inhibit the function of sinus and atrioventricular (AV) node in children [9, 10], and even induce refractory cardiogenic shock [6]. The commonly used anesthetics, propofol and remifentanil, for general anesthesia have little significant impacts on cardiac electrophysiology [11–17].

In the current study, dexmedetomidine was applied to patients undergoing elective surgeries for 1–3 h under total intravenous general anesthesia with continuous infusion of propofol and remifentanil. The first aim was to observe its influences on cardiac electrophysiology and function perioperatively. The secondary aim was to probe into the optimum dosage of dexmedetomidine that had minimum negative effects on electrocardia action and cardiac function during perioperative period.

Material and methods

Study design and approval

This prospective, double-blind, randomized controlled study was abided by the Consolidated Standards of Reporting Trials (CONSORT) regulations and conducted after gaining approval from the ethics committee of the Affiliated Hospital of Yangzhou University (2020-YKL09-025, China). Written informed consent following the principles of Declaration of Helsinki was obtained from all the subjects included in the study. The trial was registered before patient enrollments at clinicaltrials.gov (NCT04577430).

Totally 81 gender-neutral patients undergoing elective surgeries for 1–3 h under total intravenous anesthesia, aged 18–65 years of age, body mass index (BMI) 18.5–30.0 kg/m^2, American Society of Anesthesiologists (ASA) status I or II, were eligible for study recruitment regulations. Exclusion criteria were as follows: refusal; hypersensitivity to study medication; diabetes; preoperative QTc prolongation (male $\geq$ 440 ms, female $\geq$ 460 ms); abnormal cardiac conduction and other arrhythmia; history of heart disease, such as pacemaker implantation, coronary heart disease, congestive heart failure, and heart valve disease, etc.; use of antiarrhythmic drugs that affect the QT interval, such as β-receptor blockers and calcium channel blockers, etc.; non-sinus rhythm, severe sinus bradycardia [Heart rate (HR) $\leq$ 50 beats/min]; electrolyte abnormalities before surgery; liver and kidney function abnormalities; or surgical procedures with cardiovascular, malignant, thoracic and other procedures lasting longer than 3 h.

The patients were assigned to four groups using a computer-generated number table randomly: dexmedetomidine loaded with 1 μg/kg and maintained with 1 μg/kg/h (group D_1), 1 μg/kg and 0.5 μg/kg/h (group D_2), 0.5 μg/kg and 0.5 μg/kg/h (group D_3), and normal saline loaded with 50 ml/h for 10 min and maintained with 10 ml/h (group C). The loading dose of dexmedetomidine was infused intravenously at a constant speed with an infusion pump for 10 min.

Study procedure

No patient received preoperative medication. All patients were monitored routinely with electrocardiogram (ECG), non-invasive blood pressure (NBP) and pulse oxygen saturation (S_pO_2) after entering the operating theater. Venous access was established in a wrist cephalic vein with a 20-G intravenous cannula (B. Braun, Melsungen, Germany). Ringer's solution was transfused at a rate of 10–15 ml/kg/h. For those with normal Allen's test results, the left radial artery was punctured under ultrasound guidance after local anesthesia to monitor the invasive blood pressure (IBP). IBP and cardiac function monitoring equipment (Most-care, Projecta Engineering Co., Ltd, Italy) was connected to the arterial line. Dexmedetomidine or normal saline loading dose was initiated after 5 min's rest. In each group, the loading dose was infused intravenously for 10 min before induction of anesthesia, and then the maintenance dose was initiated. An anesthetist took charge of the preparation of dexmedetomidine and saline, which were covered with a towel when on the infusion pump. Another anesthetist who was blinded to the drugs and group allocations was responsible for data collection and intraoperative management. The patients and surgeons were both blinded to group allocations. All research data were recorded at 8.00 a.m. - 12.00 a.m.

Total intravenous general anesthesia was induced with midazolam 0.05 mg/kg, propofol 1.0–2.0 mg/kg, sufentanil 0.2–0.4 μg/kg and rocuronium 0.6 mg/kg. After sufficient muscle relaxation, the tracheal tube was inserted and fixed and then mechanical ventilation was performed. The ventilator parameters were set at inhaled oxygen concentration 60%, tidal volume 6–8 ml/kg, respiratory rate 12–14 times/min, inspiration/expiration ratio 1:2, positive end-expiratory pressure 3 cmH$_2$O, and end-tidal carbon dioxide pressure 35–45 mmHg (1 mmHg = 0.133 kPa). General anesthesia was maintained with intravenous propofol 4–12 mg/kg/h, remifentanil 5–15 μg/kg/h, and dexmedetomidine/normal saline with the corresponding doses in each group. Muscle relaxation was maintained with intermittent intravenous injection of rocuronium. The depth of anesthesia was monitored with Narcotrend monitoring (MT Monitortechnik

Tan *et al. BMC Anesthesiology*   (2022) 22:271

Page 3 of 14

GmbH&Co.KG, Germany), the stage of which was maintained between D2 to E1 (sedation index 20 – 46) in all groups. Propofol and remifentanil were infused until surgery ending, and dexmedetomidine/saline and rocuronium stopped infusion at about 30 min before the end of surgery. Propofol and remifentanil doses were adjusted according to anesthesia depth from the Narcotrend monitoring. If mean arterial pressure (MAP) decreased > 20% of baseline value, ephedrine or phenylephrine was used. If HR decreased > 20% of basic value, atropine was injected. Cases were excluded if vasoactive drugs or atropine was used. Patients were called their names every 1 min until eyes opening after surgery finish. The tracheal tube was removed when the patient met extubation indications. All subjects were then transferred to the post-anesthesia care unit (PACU).

Cardiac circulation efficiency (CCE), maximum pressure gradient (dp/dt), HR, MAP, and systemic vascular resistance (SVR) were recorded at the following time points: just before dexmedetomidine infusion (T_1), dexmedetomidine loading dose finish (T_2), surgery beginning (T_3), 30 min after surgery beginning (T_4), 1 h after surgery beginning (T_5), surgery ending (T_6) and 1 h after transferring to PACU (T_7). The twelve-lead ECG was measured at T_1, T_2, T_6, T_7, 24 h (T_8), 48 h (T_9), 72 h (T_{10}) and 1 month (T_{11}) postoperatively using the digital electrocardiograph (aECG-12PWL, Xiamen Nalong Technology Co., Ltd, China) with ECG paper speeding at 25 mm/s and the gain at 10 mm/mv. Measurements and analyzation of the ECG were manipulated by an electrophysiologist who was blinded to group allocations. Each ECG in leads II and V5 was measured for 3 complete P-QRS-T cycles, and the averages were recorded respectively. The PR in lead II interval was measured, and the intervals of QRS, QT, QTc and Tp-e were measured in lead V5. The QT interval was measured from the start of QRS complex to the T wave ending, and the T wave ending was the intersection of the descending branch tangent and the baseline. If U waves appeared, the T wave ending was regard as the nadir of the curve between T and U waves. QTc was calculated based on the Bazett formula [18], in which $QTc = QT/\sqrt{RR}$. The Tp-e was measured from the peak to the T wave ending. The index of cardiac electrophysiological balance (iCEB) was calculated according to $iCEB = QT/QRS$. Electrolyte concentrations were tested at T_1, T_2, T_5, T_6 and T_7, and changes in potassium (K^+) and ionized calcium (iCa^{2+}) levels were recorded. The surgery time, duration of anesthesia (the time from dexmedetomidine or normal saline loading dose infusion to tracheal tube removal) and waking time from surgery were recorded, respectively. The dosages of propofol and remifentanil, total fluid intake from entering the operating theater to PACU and use of vasoactive drugs were recorded. The occurrence of arrhythmia during perioperative period was also recorded.
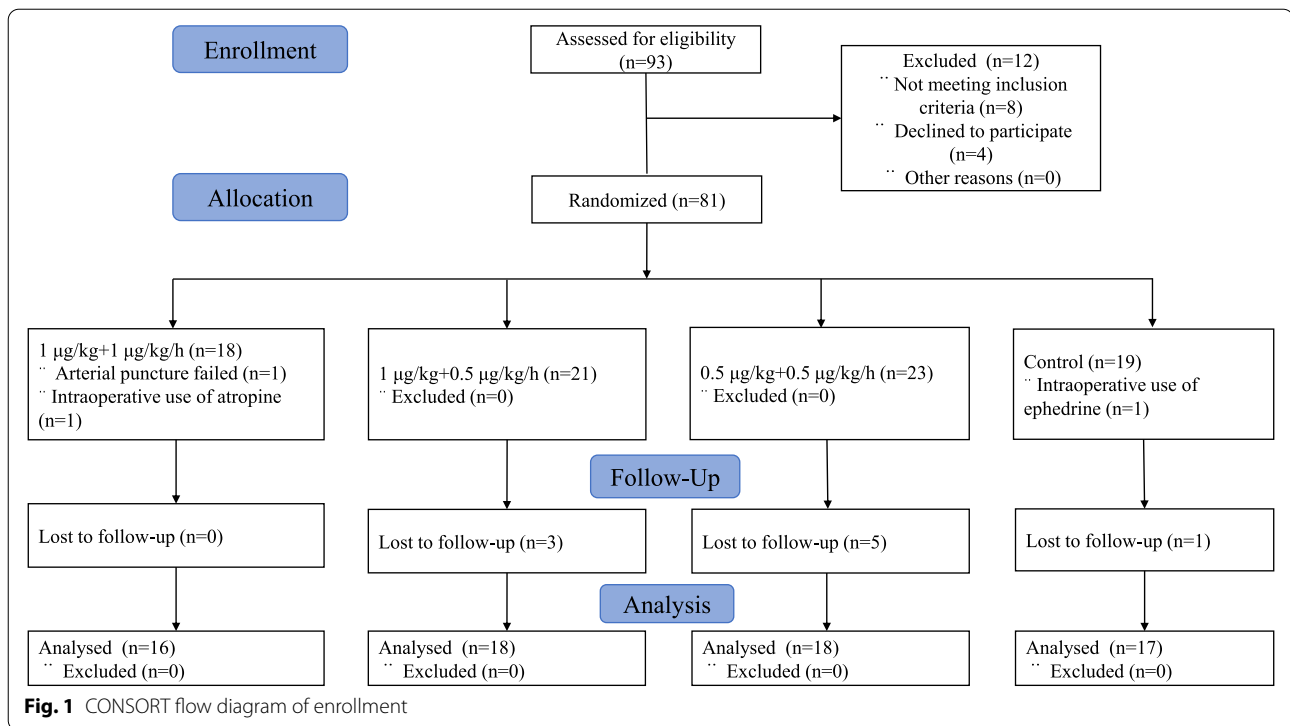
Statistical analysis

PASS 15.0 (NCSS Llc., USA) was applied to sample size calculation in this research. QTc was the main research indicator, showing a mean ± standard deviation (SD) of 1.0 ± 12.2 ms after dexmedetomidine loading dose used in our pilot study. As a result, at least 15 patients should be included in every group to reach a power of 80% ($\beta = 0.2$) with two-tailed significance level of less than 0.05. An additional 20% was added to make up loss by protocol violations, 18 patients were recruited per group to minimize the impact of missing data consequently.

SPSS 23.0 (IBM Corporation, USA) was used for complete statistical analysis. Data with normal distributions were expressed as means ± SD. One-way analysis of variance (ANOVA) was used for comparisons between groups (variance homogeneity), and Welch's ANOVA was used for variance nonhomogeneity. Repeated measurement ANOVA was used for repeated measurements data in groups, and categorical data were compared by chi-square (χ^2) test or Fisher's exact test. Bonferroni correction was used for group differences between baseline and each time point. Two-sided *P* values of less than 0.05 were considered to be significant.

Results

Of 93 patients originally recruited, 12 patients were excluded for refusal and failure to meet inclusion criteria. Therefore, 81 subjects were allocated randomly in this study, and data of 69 (33 males and 36 females) were available for the analysis finally. Figure 1 presents participants inclusion, reasons for exclusion, allocations and study procedures. The demographic characteristics of all subjects were presented in Table 1, and there were no significant differences among the four groups (*P* > 0.05). No significant differences were observed in clinical characteristics including surgery time, duration of anesthesia, waking time from surgery, total fluid intake from the operating theater to the PACU or patients with hypertension (*P* = 0.710, *P* = 0.462, *P* = 0.123, *P* = 0.631, *P* = 0.708, respectively) (Table 2). Compared with group C, the dosages of propofol and remifentanil in groups D_1, D_2 and D_3 decreased significantly (*P* = 0.042, *P* < 0.001, respectively) (Table 2). No significant differences in changes of K^+ and iCa^{2+} concentrations existed in any group (*P* > 0.05) (Table 3).

Tan *et al. BMC Anesthesiology*   (2022) 22:271

Page 4 of 14

Fig. 1 CONSORT flow diagram of enrollment

Table 1 Patients' demographic data

	Group D$_1$	Group D$_2$	Group D$_3$	Group C	*P* value
Gender (Male/Female)	8/8	9/9	8/10	8/9	0.985
Age (years)	49.1 ± 9.6	49.4 ± 11.2	43.1 ± 10.3	47.2 ± 9.9	0.237
Weight (kg)	64.5 ± 10.9	67.3 ± 7.6	65.4 ± 6.3	68.2 ± 8.1	0.553
Height (cm)	165.2 ± 8.2	166.8 ± 7.8	166.2 ± 7.3	166.2 ± 8.8	0.951
BMI (kg/m^2)	23.6 ± 2.7	24.2 ± 1.9	23.7 ± 1.9	24.7 ± 2.3	0.452
ASA status I/II	9/7	9/9	13/5	11/6	0.549

Data are expressed as numbers or mean ± SD

BMI body mass index, *ASA* American Society of Anesthesiologists

Table 2 Clinical characteristics in the four groups during perioperative period

	Group D$_1$	Group D$_2$	Group D$_3$	Group C	*P* value
Duration of Surgery (min)	100.6 ± 30.5	91.1 ± 35.7	88.6 ± 25.8	93.5 ± 31.6	0.710
Duration of anesthesia (min)	129.9 ± 33.0	115.3 ± 38.8	113.3 ± 26.2	118.1 ± 30.6	0.462
Waking time from surgery (min)	10.9 ± 3.5	9.7 ± 3.1	9.3 ± 2.5	8.4 ± 2.9	0.123
Total fluid intake from entering the operating theater to PACU (ml)	1171.9 ± 414.3	1180.6 ± 394.8	1030.0 ± 297.9	1152.4 ± 438.3	0.631
Patients with hypertension, n(%)	4 (25.0%)	2 (11.1%)	3 (16.7%)	2 (11.8%)	0.708
Dosage of propofol (mg/kg/h)	5.1 ± 1.0△	5.2 ± 1.0△	5.5 ± 1.1	6.1 ± 1.4	0.042
Dosage of remifentanil (μg/kg/h)	6.5 ± 2.4*	5.8 ± 1.7*	6.3 ± 2.2*	8.4 ± 1.4	< 0.001

Data are expressed as numbers or mean ± SD

PACU Post-anesthesia care unit

△ $P < 0.05$, * $P < 0.01$, compared with group C

Tan *et al. BMC Anesthesiology*   (2022) 22:271

Page 5 of 14

Table 3 Electrolyte concentrations of K^+ and iCa^{2+} in the four groups

		GroupD$_1$ ($n=16$)	GroupD$_2$ ($n=18$)	GroupD$_3$ ($n=18$)	GroupC ($n=17$)	P^a	P^b	P^c	P^d	P^e	P^f
K^+ (mmol/L)	T_1	3.73 ± 0.20	3.72 ± 0.23	3.68 ± 0.18	3.80 ± 0.19	0.968	0.547	0.286	0.562	0.255	0.090
	T_2	3.78 ± 0.19	3.76 ± 0.21	3.74 ± 0.20	3.82 ± 0.21	0.778	0.606	0.615	0.810	0.422	0.299
	T_5	3.83 ± 0.21	3.79 ± 0.23	3.71 ± 0.18	3.81 ± 0.20	0.669	0.098	0.855	0.202	0.805	0.134
	T_6	3.85 ± 0.21	3.85 ± 0.23	3.72 ± 0.24	3.82 ± 0.29	>0.99	0.120	0.759	0.109	0.752	0.204
	T_7	3.88 ± 0.26	3.88 ± 0.30	3.83 ± 0.20	3.91 ± 0.25	0.969	0.587	0.733	0.604	0.696	0.368
	P_{T1-2}	0.841	>0.99	0.474	>0.99						
	P_{T1-5}	0.282	0.903	>0.99	>0.99						
	P_{T1-6}	0.104	0.057	>0.99	>0.99						
	P_{T1-7}	0.172	0.121	0.153	0.760						
	P_{T2-5}	>0.99	>0.99	>0.99	>0.99						
	P_{T2-6}	>0.99	0.334	>0.99	>0.99						
	P_{T2-7}	0.739	0.280	0.916	0.827						
iCa^{2+} (mmol/L)	T_1	1.15 ± 0.07	1.14 ± 0.03	1.13 ± 0.06	1.14 ± 0.04	0.434	0.193	0.515	0.588	0.900	0.510
	T_2	1.15 ± 0.06	1.14 ± 0.04	1.14 ± 0.06	1.14 ± 0.02	0.510	0.488	0.389	0.972	0.826	0.856
	T_5	1.15 ± 0.05	1.13 ± 0.04	1.13 ± 0.06	1.12 ± 0.02	0.327	0.247	0.148	0.852	0.614	0.749
	T_6	1.15 ± 0.04	1.14 ± 0.04	1.15 ± 0.06	1.12 ± 0.03	0.752	0.833	0.151	0.588	0.244	0.091
	T_7	1.16 ± 0.05	1.15 ± 0.04	1.14 ± 0.06	1.13 ± 0.03	0.677	0.148	0.085	0.285	0.174	0.756
	P_{T1-2}	>0.99	>0.99	0.201	>0.99						
	P_{T1-5}	>0.99	>0.99	>0.99	0.747						
	P_{T1-6}	>0.99	>0.99	0.306	0.573						
	P_{T1-7}	>0.99	0.828	>0.99	>0.99						
	P_{T2-5}	>0.99	>0.99	>0.99	0.878						
	P_{T2-6}	>0.99	>0.99	>0.99	0.435						
	P_{T2-7}	>0.99	>0.99	>0.99	>0.99						

Data are expressed as mean $\pm$ SD

T_1 before dexmedetomidine infusion, T_2 dexmedetomidine loading dose finish, T_5 1 h after surgery beginning, T_6 surgery ending, T_7 1 h after entering PACU

P_{T1-2}, P_{T1-5}, P_{T1-6}, P_{T1-7} for comparisons between T$_1$ and T$_2$, T$_5$, T$_6$, T$_7$; P_{T2-5}, P_{T2-6}, P_{T2-7} for comparisons between T$_2$ and T$_5$, T$_6$, T$_7$; P^a, P^b, P^c, P^d, P^e and P^f for comparisons between groups D$_1$ and D$_2$, groups D$_1$ and D$_3$, groups D$_1$ and C, groups D$_2$ and D$_3$, groups D$_2$ and C, and groups D$_3$ and C, respectively

PR data

PR intervals in all groups were normal at T_1. Compared with T_1, the PR intervals were prolonged significantly at T_2, T_6 and T_7 in group D$_1$ (T_2: $P<0.001$, T_6: $P<0.001$, T_7: $P=0.009$), at T_2 in group D$_2$ ($P<0.001$), and prolonged at T_2, T_6, and T_7 (T_2: $P=0.007$, T_6: $P=0.007$, T_7: $P=0.014$) but shortened significantly at T_{10} ($P=0.008$) in group D$_3$. Compared with T_2, the PR intervals were shortened significantly at T_{8-11} in groups D$_1$ and D$_2$ (D$_1$, D$_2$: $P<0.001$, respectively) and at T_{9-11} in group D$_3$ (T_9: $P<0.001$, T_{10}: $P<0.001$, T_{11}: $P=0.004$).

Compared with group C, the PR intervals were prolonged significantly at T_2 in groups D$_1$ and D$_2$ ($P<0.001$). Compared with groups D$_1$ and D$_2$, the PR intervals were shortened significantly at T_2 in group D$_3$ ($P=0.032$, $P=0.019$, respectively).

QRS data

There were no significant differences in QRS intervals within and among the four groups ($P>0.05$).

QTc data

QTc values in all groups were normal and no differences existed at T_1. Compared with T_1, QTc was prolonged significantly at T_2, T_6 and T_7 in group D$_1$ ($P<0.001$), at T_2 and T_6 in group D$_2$ (T_2: $P<0.001$, T_6: $P=0.023$), and at T_{6-8} in group C ($P<0.01$), while shortened significantly at T_2 and T_{10} in group D$_3$ (T_2: $P=0.039$, T_{10}: $P=0.005$). Compared with T_2, QTc decreased significantly at T_{10} and T_{11} in group D$_1$ (T_{10}: $P=0.019$, T_{11}: $P=0.001$), at T_{9-11} in group D$_2$ (T_9: $P=0.010$, T_{10}: $P=0.001$, T_{11}: $P=0.019$), while increased significantly at T_6 in group D$_3$ ($P=0.001$) and at T_{6-8} in group C (T_6: $P<0.001$, T_7: $P=0.014$, T_8: $P=0.025$).

Compared with group C, QTc in groups D$_1$ and D$_2$ were significantly prolonged at T_2 ($P=0.001$, $P=0.003$, respectively), while shortened significantly at T_7 and T_8 in group D$_3$ ($P=0.040$, $P=0.021$, respectively). QTc in group D$_3$ was shortened significantly at T_2, T_6, T_7, T_9 and T_{10} compared with group D$_1$ (T_2: $P<0.001$, T_6: $P=0.044$, T_7: $P=0.001$, T_9: $P=0.016$, T_{10}: $P=0.027$),

Tan *et al. BMC Anesthesiology*　　(2022) 22:271

Page 6 of 14

and shortened significantly at T_2 compared with group D_2 ($P < 0.001$).

Tp-e data
Tp-e values in all groups were normal and no differences existed at T_1 and T_2. There were no statistical differences among the four groups both at T_1 and T_2 ($P > 0.05$).

Compared with group C, Tp-e at T_8 in group D_1 was prolonged significantly ($P = 0.007$) while shortened significantly in group D_3 ($P = 0.032$). Tp-e in group D_3 was shortened significantly at T_{7-9} compared with group D_1 (T_7: $P = 0.032$, T_8: $P < 0.001$, T_9: $P = 0.002$) and at T_8 and T_9 compared with group D_2 (T_8: $P < 0.001$, T_9: $P = 0.007$).

iCEB data
iCEB values at T_1 among the four groups were comparable. Compared with T_1, iCEB at T_2, T_{6-8} in groups D_1 and D_2 (D_1: $P < 0.001$, D_2: $P < 0.001$, $P < 0.001$, $P = 0.022$, $P = 0.010$, respectively), at T_6 in group D_3 ($P < 0.001$), and at T_6 and T_7 in group C (T_6: $P < 0.001$, T_7: $P = 0.011$) were significantly prolonged. Compared with T_2, iCEB at T_{10} in groups D_1 and D_2 were significantly shortened ($P = 0.008$, $P = 0.001$, respectively), at T_6 was prolonged and at T_8 was shortened significantly in group D_3 (T_6: $P = 0.038$, T_8: $P = 0.031$), and at T_6 and T_7 in group C was significantly shortened (T_6: $P < 0.001$; T_7: $P = 0.044$).

iCEB at T_8 in group D_3 was significantly shortened compared with groups C, D_1 and D_2 ($P = 0.047$, $P = 0.043$, $P = 0.024$, respectively) (Table 4) (Fig. 2).

Perioperative cardiac function and hemodynamic parameters
Compared with T_1, CCE decreased significantly in groups D_1 and D_2 at T_3 ($P = 0.001$, $P = 0.037$). Compared with group C, CCE decreased significantly at T_2 in groups D_1 and D_2 ($P = 0.021$, $P = 0.047$), and at T_3 in group D_1 ($P = 0.005$). Compared with group D_1, CCE increased significantly in group D_3 at T_{2-4} (T_2: $P = 0.003$, T_3: $P = 0.001$, T_4: $P = 0.046$). Compared with group D_2, CCE increased significantly in group D_3 at T_2 and T_3 (T_2: $P = 0.007$, T_3: $P = 0.037$) (Fig. 3).

Compared with T_1, dp/dt decreased significantly at T_{2-7} in groups D_1 and D_2, at T_{2-6} in group D_3 (D_1: $P < 0.001$, D_2: $P < 0.001$, $P < 0.001$, $P < 0.001$, $P < 0.001$, $P < 0.001$, $P = 0.001$, D_3: $P = 0.010$, $P = 0.001$, $P < 0.001$, $P < 0.001$, $P < 0.001$, respectively), and at T_{3-6} in group C ($P = 0.020$, $P < 0.001$, $P < 0.001$, $P < 0.001$). Compared with T_2, dp/dt decreased significantly at T_{4-7} in group D_1 ($P < 0.001$) and at T_{4-6} in groups D_2, D_3 and C (D_2: $P < 0.001$, $P = 0.013$, $P = 0.018$, D_3: $P < 0.001$, C: $P < 0.001$, respectively). Compared with group C, dp/dt decreased significantly in group D_1 at T_7 and in D_2 at T_4 and T_7 (D_1: $P = 0.005$, D_2: $P = 0.044$, $P = 0.020$, respectively). Compared with groups

D_1 and D_2, dp/dt increased significantly in group D_3 at T_7 ($P = 0.010$, $P = 0.039$) (Fig. 3).

Compared with T_1, HR decreased significantly at T_{2-7} in each dexmedetomidine group ($P < 0.001$), and at T_{3-7} in group C (T_{3-6}: $P < 0.001$; T_7: $P = 0.012$). Compared with T_2, HR decreased significantly at T_4 in group D_1 ($P = 0.014$), and at T_{3-6} in group C ($P < 0.001$). Compared with group C, HR decreased significantly at T_2 in each dexmedetomidine group (D_1: $P = 0.005$, D_2: $P = 0.001$, D_3: $P = 0.004$, respectively), and at T_4 in group D_1 ($P = 0.013$) (Fig. 3).

Compared with T_1, MAP in group D_1 increased at T_2 ($P = 0.003$) and decreased at T_6 ($P = 0.024$) significantly, increased at T_2 ($P < 0.001$) and decreased at T_{5-6} in group D_2 (T_5: $P = 0.002$, T_6: $P = 0.012$) significantly, decreased significantly at T_2, T_5 and T_6 in group D_3 ($P < 0.001$, $P = 0.003$, $P < 0.001$), and decreased significantly at T_5 in group C ($P = 0.006$). Compared with T_2, MAP in groups D_1 at T_{5-7}, D_2 at T_{4-7}, D_3 at T_6, and C at T_5 decreased significantly (D_1: $P < 0.001$, D_2: $P < 0.001$, D_3: $P < 0.001$, C: $P = 0.005$, respectively). Compared with group C, MAP in group D_1 increased significantly at T_{2-5} ($P = 0.002$, $P = 0.001$, $P = 0.009$, $P = 0.016$), in group D_2 increased significantly at T_2 ($P = 0.047$). Compared with groups D_1, MAP in group D_3 decreased significantly at T_2 and T_3 (T_2: $P < 0.001$, T_3: $P = 0.013$). Compared with groups D_2, MAP in group D_3 decreased significantly at T_2 ($P = 0.033$) (Fig. 3).

Compared with T_1, SVR in groups D_1 and D_2 was significantly higher at T_2 ($P < 0.001$, $P < 0.001$, respectively). Compared with T_2, SVR in groups D_1 and D_2 was significantly lower at T_6 and T_7 (D_1: $P = 0.002$, $P < 0.001$, D_2: $P = 0.031$, $P = 0.002$, respectively). Compared with group C, SVR was significantly increased at T_2, T_4 and T_5 in group D_1 (T_2: $P = 0.008$, T_4: 0.019, T_5: $P = 0.048$), and at T_2 in group D_2 ($P = 0.047$). Compared with group D_1, SVR was significantly lower at T_{2-5} in group D_3 ($P < 0.001$, $P = 0.003$, $P = 0.005$, $P = 0.037$). Compared with group D_2, SVR in group D_3 was significantly lower at T_2 and T_3 (T_2: $P < 0.001$, T_3: $P = 0.016$). No arrhythmia occurred during perioperative period in the four groups (Fig. 3).

Discussion
Dexmedetomidine contains the imidazole ring, which has agonistic effects on α_{2A} and I_1 imidazoline receptors [19], inhibits cardiac sympathetic nerve activity, and converts rapid ventricular and supraventricular arrhythmias [20]. It inhibits the activity of voltage-gated sodion (Na^+) channel subtype α—Nav1.5 specifically expressed in cardiac tissues in a dose-dependent manner [21] to decrease the Na^+ channel continuous current (I_{Nap}) peak values under stress state, thus reduces effects on myocardial repolarization dispersion and the occurrence

Tan *et al. BMC Anesthesiology* (2022) 22:271

Page 7 of 14

Table 4 Comparison of ECG indicators in the four groups

		GroupD$_1$ ($n=16$)	GroupD$_2$ ($n=18$)	GroupD$_3$ ($n=18$)	GroupC ($n=17$)	P^a	P^b	P^c	P^d	P^e	P^f
PR (ms)	T$_1$	147.4±17.5	154.7±15.6	149.2±17.9	149.9±17.9	0.223	0.763	0.678	0.342	0.415	0.903
	T$_2$	170.6±12.0	171.4±14.5	158.0±19.6	149.6±19.2	0.878	0.032	0.001	0.019	<0.001	0.141
	T$_6$	164.6±18.5	163.7±13.4	161.4±21.3	157.7±20.3	0.888	0.621	0.290	0.715	0.343	0.555
	T$_7$	161.6±18.6	165.9±17.4	162.1±23.2	156.4±18.1	0.515	0.942	0.446	0.552	0.151	0.390
	T$_8$	154.9±13.5	150.0±16.1	152.7±19.9	157.9±16.3	0.393	0.701	0.608	0.627	0.165	0.359
	T$_9$	147.1±18.9	150.0±13.9	143.8±21.1	155.1±19.5	0.646	0.614	0.220	0.322	0.423	0.078
	T$_{10}$	146.1±17.1	148.2±14.1	141.6±15.7	150.9±19.5	0.707	0.439	0.403	0.238	0.631	0.102
	T$_{11}$	145.8±16.6	148.7±15.6	145.6±17.1	150.9±17.3	0.619	0.964	0.385	0.577	0.695	0.348
	P_{T1-2}	<0.001	<0.001	0.007	>0.99						
	P_{T1-6}	<0.001	0.153	0.007	0.523						
	P_{T1-7}	0.009	0.059	0.014	>0.99						
	P_{T1-8}	0.801	>0.99	>0.99	0.465						
	P_{T1-9}	>0.99	>0.99	>0.99	>0.99						
	P_{T1-10}	>0.99	0.052	0.008	>0.99						
	P_{T1-11}	>0.99	0.696	>0.99	>0.99						
	P_{T2-6}	>0.99	0.160	>0.99	0.134						
	P_{T2-7}	0.219	>0.99	>0.99	>0.99						
	P_{T2-8}	<0.001	<0.001	>0.99	0.364						
	P_{T2-9}	<0.001	<0.001	<0.001	>0.99						
	P_{T2-10}	<0.001	<0.001	<0.001	>0.99						
	P_{T2-11}	<0.001	<0.001	0.004	>0.99						
QRS (ms)	T$_1$	88.5±7.9	88.6±10.5	86.2±9.8	84.0±9.4	0.973	0.477	0.179	0.973	0.443	0.156
	T$_2$	89.3±10.6	87.7±10.9	87.5±12.1	84.2±8.4	0.666	0.634	0.175	0.963	0.335	0.359
	T$_6$	88.9±9.7	87.3±8.9	84.7±10.7	84.5±8.4	0.632	0.216	0.196	0.432	0.395	0.940
	T$_7$	90.3±9.6	88.7±9.0	85.4±9.5	85.1±7.2	0.617	0.128	0.113	0.288	0.257	0.931
	T$_8$	90.1±10.5	88.4±11.8	86.2±9.2	85.4±8.6	0.973	0.476	0.353	0.484	0.356	0.814
	T$_9$	87.6±7.7	87.7±10.3	84.5±9.2	84.6±8.1	0.989	0.313	0.333	0.292	0.313	0.977
	T$_{10}$	87.3±8.5	87.7±9.8	82.7±7.9	86.6±7.7	0.891	0.127	0.826	0.088	0.714	0.184
	T$_{11}$	87.2±6.6	85.9±8.7	84.9±9.8	85.8±8.5	0.673	0.437	0.634	0.712	0.951	0.763
	P_{T1-2}	>0.99	>0.99	>0.99	>0.99						
	P_{T1-6}	>0.99	>0.99	>0.99	>0.99						
	P_{T1-7}	>0.99	>0.99	>0.99	>0.99						
	P_{T1-8}	>0.99	>0.99	>0.99	>0.99						
	P_{T1-9}	>0.99	>0.99	>0.99	>0.99						
	P_{T1-10}	>0.99	>0.99	0.830	>0.99						
	P_{T1-11}	>0.99	>0.99	>0.99	>0.99						
	P_{T2-6}	>0.99	>0.99	0.247	>0.99						
	P_{T2-7}	>0.99	>0.99	>0.99	>0.99						
	P_{T2-8}	>0.99	>0.99	>0.99	>0.99						
	P_{T2-9}	>0.99	>0.99	>0.99	>0.99						
	P_{T2-10}	>0.99	>0.99	0.061	>0.99						
	P_{T2-11}	>0.99	0.804	>0.99	>0.99						

Tan *et al. BMC Anesthesiology*   (2022) 22:271

Page 8 of 14

Table 4 (continued)

		GroupD$_1$ ($n=16$)	GroupD$_2$ ($n=18$)	GroupD$_3$ ($n=18$)	GroupC ($n=17$)	P^a	P^b	P^c	P^d	P^e	P^f
QTc (ms)	T$_1$	413.8±11.1	414.4±12.2	416.2±14.7	409.2±15.5	0.882	0.605	0.341	0.703	0.259	0.134
	T$_2$	427.0±11.7	425.2±12.6	408.1±17.3	410.0±14.9	0.719	<0.001	0.001	0.001	0.003	0.690
	T$_6$	429.9±9.5	423.8±10.1	419.6±21.0	424.5±14.3	0.228	0.044	0.292	0.389	0.888	0.323
	T$_7$	428.7±11.0	419.1±13.9	413.3±15.3	422.2±9.0	0.031	0.001	0.148	0.171	0.468	0.040
	T$_8$	419.2±9.2	419.0±13.4	413.0±14.7	422.8±10.6	0.965	0.147	0.398	0.148	0.361	0.021
	T$_9$	418.0±12.5	411.2±16.2	405.7±14.8	411.4±13.9	0.174	0.016	0.192	0.258	0.970	0.250
	T$_{10}$	413.8±8.8	410.1±12.7	404.0±12.9	410.2±15.0	0.397	0.027	0.419	0.151	0.977	0.149
	T$_{11}$	408.1±15.0	411.3±13.3	412.1±17.7	407.4±16.5	0.554	0.457	0.897	0.874	0.464	0.375
	$P_{T1\text{-}2}$	<0.001	<0.001	0.039	>0.99						
	$P_{T1\text{-}6}$	<0.001	0.023	>0.99	<0.001						
	$P_{T1\text{-}7}$	<0.001	>0.99	>0.99	0.002						
	$P_{T1\text{-}8}$	>0.99	>0.99	>0.99	0.004						
	$P_{T1\text{-}9}$	>0.99	>0.99	0.068	>0.99						
	$P_{T1\text{-}10}$	>0.99	>0.99	0.005	>0.99						
	$P_{T1\text{-}11}$	>0.99	>0.99	>0.99	>0.99						
	$P_{T2\text{-}6}$	>0.99	>0.99	0.001	<0.001						
	$P_{T2\text{-}7}$	>0.99	>0.99	>0.99	0.014						
	$P_{T2\text{-}8}$	>0.99	>0.99	>0.99	0.025						
	$P_{T2\text{-}9}$	0.727	0.010	>0.99	>0.99						
	$P_{T2\text{-}10}$	0.019	0.001	>0.99	>0.99						
	$P_{T2\text{-}11}$	0.001	0.019	>0.99	>0.99						
Tp-e (ms)	T$_1$	84.3±13.2	81.7±8.0	79.6±8.8	82.5±10.3	0.462	0.183	0.629	0.535	0.803	0.390
	T$_2$	87.3±14.7	82.1±6.9	82.2±7.7	81.9±10.5	0.149	0.158	0.141	0.974	0.961	0.936
	T$_6$	85.5±9.6	83.8±8.7	82.2±9.1	85.9±9.5	0.588	0.296	0.906	0.602	0.502	0.237
	T$_7$	85.9±8.7	83.4±8.7	79.7±8.0	84.2±7.3	0.380	0.032	0.567	0.183	0.761	0.108
	T$_8$	91.9±11.0	87.4±8.9	75.4±10.0	82.5±8.4	0.179	<0.001	0.007	<0.001	0.140	0.032
	T$_9$	87.1±11.2	85.3±9.7	76.6±8.8	81.2±7.0	0.578	0.002	0.076	0.007	0.203	0.146
	T$_{10}$	83.1±10.8	82.6±5.9	77.5±7.5	81.9±7.2	0.853	0.056	0.671	0.061	0.803	0.108
	T$_{11}$	81.9±9.2	78.9±8.8	81.8±10.1	80.5±8.2	0.344	0.975	0.673	0.345	0.596	0.687
	$P_{T1\text{-}2}$	>0.99	>0.99	>0.99	>0.99						
	$P_{T1\text{-}6}$	>0.99	>0.99	>0.99	>0.99						
	$P_{T1\text{-}7}$	>0.99	>0.99	>0.99	>0.99						
	$P_{T1\text{-}8}$	0.160	0.733	>0.99	>0.99						
	$P_{T1\text{-}9}$	>0.99	>0.99	>0.99	>0.99						
	$P_{T1\text{-}10}$	>0.99	>0.99	>0.99	>0.99						
	$P_{T1\text{-}11}$	>0.99	>0.99	>0.99	>0.99						
	$P_{T2\text{-}6}$	>0.99	>0.99	>0.99	>0.99						
	$P_{T2\text{-}7}$	>0.99	>0.99	>0.99	>0.99						
	$P_{T2\text{-}8}$	>0.99	>0.99	0.222	>0.99						
	$P_{T2\text{-}9}$	>0.99	>0.99	0.666	>0.99						
	$P_{T2\text{-}10}$	>0.99	>0.99	0.358	>0.99						
	$P_{T2\text{-}11}$	0.115	>0.99	>0.99	>0.99						

Tan *et al. BMC Anesthesiology* (2022) 22:271

Page 9 of 14

Table 4 (continued)

		GroupD$_1$ ($n=16$)	GroupD$_2$ ($n=18$)	GroupD$_3$ ($n=18$)	GroupC ($n=17$)	P^a	P^b	P^c	P^d	P^e	P^f
iCEB	T$_1$	4.40±0.48	4.51±0.62	4.69±0.69	4.70±0.58	0.599	0.172	0.164	0.383	0.365	0.964
	T$_2$	4.85±0.67	4.96±0.69	4.83±0.85	4.70±0.57	0.666	0.936	0.537	0.598	0.284	0.579
	T$_6$	4.92±0.62	4.97±0.55	5.13±0.64	5.22±0.55	0.807	0.312	0.149	0.428	0.214	0.641
	T$_7$	4.81±0.53	4.82±0.51	4.96±0.60	5.04±0.38	0.962	0.426	0.219	0.440	0.223	0.643
	T$_8$	4.75±0.54	4.87±0.68	4.48±0.61	4.93±0.46	0.980	0.047	0.807	0.043	0.782	0.024
	T$_9$	4.59±0.50	4.70±0.64	4.58±0.62	4.78±0.59	0.587	0.983	0.364	0.560	0.701	0.339
	T$_{10}$	4.47±0.54	4.51±0.53	4.73±0.57	4.48±0.44	0.819	0.160	0.988	0.224	0.829	0.158
	T$_{11}$	4.57±0.39	4.69±0.51	4.69±0.60	4.60±0.49	0.503	0.499	0.866	0.995	0.611	0.607
	P_{T1-2}	<0.001	<0.001	0.876	>0.99						
	P_{T1-6}	<0.001	<0.001	<0.001	<0.001						
	P_{T1-7}	0.001	0.022	0.095	0.011						
	P_{T1-8}	<0.001	0.010	0.968	0.624						
	P_{T1-9}	0.989	>0.99	>0.99	>0.99						
	P_{T1-10}	>0.99	>0.99	>0.99	0.875						
	P_{T1-11}	>0.99	0.849	>0.99	>0.99						
	P_{T2-6}	>0.99	>0.99	0.038	<0.001						
	P_{T2-7}	>0.99	>0.99	>0.99	0.044						
	P_{T2-8}	>0.99	>0.99	0.031	0.947						
	P_{T2-9}	0.317	0.253	0.319	>0.99						
	P_{T2-10}	0.008	0.001	>0.99	0.647						
	P_{T2-11}	0.331	0.304	>0.99	>0.99						

Data are expressed as mean ± SD

ECG Electrocardiogram, *QTc* Corrected QT, *Tp-e* Interval between the peak and the end of the electrocardiographic T wave, *iCEB* index of cardiac electrophysiological balance, T_1 before infusion of dexmedetomidine, T_2 dexmedetomidine loading dose finish, T_6 surgery ending, T_7 1 h after transferring to PACU, T_8 24 h postoperatively, T_9 48 h postoperatively, T_{10} 72 h postoperatively, T_{11} 1 month postoperatively
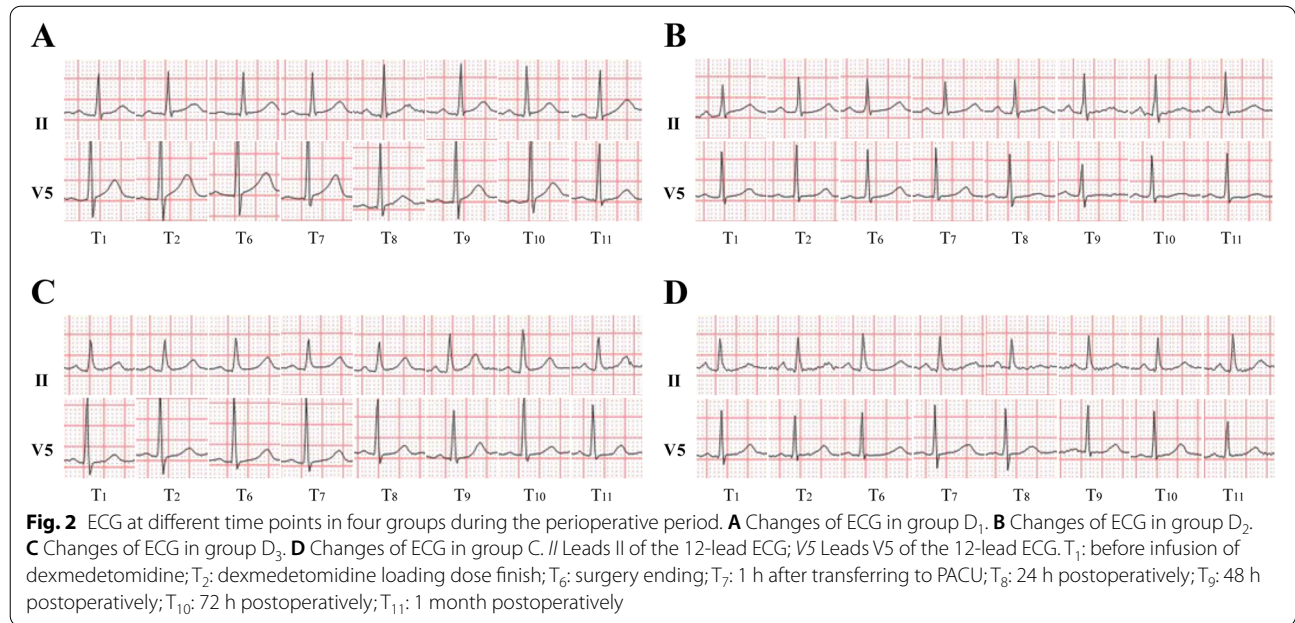
P_{T1-2}, P_{T1-6}, P_{T1-7}, P_{T1-8}, P_{T1-9}, P_{T1-10}, P_{T1-11} for comparisons between T_1 and T_2, T_6, T_7, T_8, T_9, T_{10}, T_{11}; P_{T2-6}, P_{T2-7}, P_{T2-8}, P_{T2-9}, P_{T2-10}, P_{T2-11} for comparisons between T_2 and T_6, T_7, T_8, T_9, T_{10}, T_{11}; P^a, P^b, P^c, P^d, P^e and P^f for comparisons between groups D_1 and D_2, groups D_1 and D_3, groups D_1 and C, groups D_2 and D_3, groups D_2 and C, and groups D_3 and C, respectively

rates of malignant arrhythmia. Previous studies reported that dexmedetomidine could prolong the action potential duration of cardiomyocytes, reduce the incidence of early afterdepolarization, and decrease the autonomy of cardiomyocytes.

PR interval reflects AV conduction. In this study, the PR intervals in each dexmedetomidine group were significantly prolonged after loading dose, indicating that dexmedetomidine had inhibitory effects on AV conduction, which was consistent with the conclusion of Ergul et al.'s study [7]. The PR intervals in groups D_1 and D_2 were significantly prolonged than these in groups D_3 and C when dexmedetomidine loading dose finish, and no significant difference existed between groups D_3 and C. It indicated that the incidence of AV conduction block induced by

dexmedetomidine might be related to its dose, that is, higher dose might produce higher incidence of AV conduction block. PR intervals recovered to normal levels at 48 h, 72 h and 1 month postoperatively in each dexmedetomidine group.

Abnormal prolongation of QTc usually indicates increased sensitivity to arrhythmia. In this study, the QTc intervals in groups D_1 and D_2 were significantly longer than the baseline values, while in group D_3 shortened significantly after dexmedetomidine loading dose injection, suggesting that dexmedetomidine loading dose 1 μg/kg injected in 10 min could prolong ventricular repolarization duration and interfere with cardiac conduction system significantly, which was not conducive to cardiac electrophysiological stability. QTc in groups D_1

Tan *et al. BMC Anesthesiology*   (2022) 22:271

Page 10 of 14

Fig. 2 ECG at different time points in four groups during the perioperative period. **A** Changes of ECG in group D_1. **B** Changes of ECG in group D_2. **C** Changes of ECG in group D_3. **D** Changes of ECG in group C. *II* Leads II of the 12-lead ECG; *V5* Leads V5 of the 12-lead ECG. T_1: before infusion of dexmedetomidine; T_2: dexmedetomidine loading dose finish; T_6: surgery ending; T_7: 1 h after transferring to PACU; T_8: 24 h postoperatively; T_9: 48 h postoperatively; T_{10}: 72 h postoperatively; T_{11}: 1 month postoperatively

and D_2 was significantly prolonged than those in groups D_3 and C when dexmedetomidine loading dose finish. Meanwhile, QTc in group D_3 was significantly shorter than those in groups D_1 and C at surgery ending, 1 h in PACU, 24 h and 48 h postoperatively. It indicated that dexmedetomidine in group D_3 could reduce myocardial electrophysiological heterogeneity [22], suggesting that lower dose of dexmedetomidine could reduce the risk of myocardial electrical activity imbalance associated with increased sympathetic efferent stimulation during perioperative period [7, 23, 24]. Our research was different from Hammer et al.'s [8], which concluded that QTc was prolonged by dexmedetomidine, the reason might be related to the different inclusion criteria and medication scheme.

Tp-e is an indicator of the synchronization of myocardial cells repolarization and can be used as a predictor of torsades de pointes. Matthias et al. [25] found that dexmedetomidine loading doses of 0.25, 0.5, and 0.75 μg/kg injected in 1 min after general anesthesia induction had no significant influences on Tp-e intervals at 60 s after the injection. In our study, compared with group C, Tp-e

at 24 h postoperatively in group D_1 was significantly prolonged, while in group D_3 shortened significantly, indicating an increased risk of desynchronization of myocardial cells repolarization existed in group D_1, and suggesting that the effects of dexmedetomidine on ventricular transmembrane repolarization might be related to its dose. It has been reported that the Tp-e interval may be prolonged in response to sympathetic hyperactivity [26]. The shorter Tp-e interval in group D_3 compared with group C in our study might be related to the balanced vagal efference and sympathetic activity originating from the lower dose of dexmedetomidine [27].

iCEB is an index that can reflect cardiac electrophysiological balance quickly and intuitively, which predicts the risk of arrhythmias, including torsades de pointes (TdP) and non-TdP ventricular tachycardia/ventricular fibrillation [28, 29]. The higher the iCEB values, the more likely imbalanced the electrophysiological homeostasis. In this study, iCEB in groups D_1 and D_2 increased significantly at dexmedetomidine loading dose finish, surgery ending and 24 h postoperatively compared with baseline values. Although iCEB in group D_3 increased significantly

(See figure on next page.)

Fig. 3 Cardiac function and hemodynamic indexes at different time points in the four groups. **A** Bar graphs of quantification of CCE change levels. **B** Bar graphs of quantification of dp/dt change levels. **C** Bar graphs of quantification of HR change levels. **D** Bar graphs of quantification of MAP change levels. **E** Bar graphs of quantification of SVR change levels. *CCE* cardiac circulation efficiency; *dp/dt* maximum pressure gradient; *HR* heart rate; *MAP* mean arterial blood pressure; *SVR* systemic vascular resistance. T_1: before dexmedetomidine infusion; T_2: dexmedetomidine loading dose finish; T_3: surgery beginning; T_4: 30 min after surgery beginning; T_5: 1 h after surgery beginning; T_6: surgery ending; T_7: 1 h after transferring to PACU. [a] $P < 0.05$, [c] $P < 0.01$, compared with T_1; [b] $P < 0.05$, [d] $P < 0.01$, compared with T_2; [△] $P < 0.05$, [*] $P < 0.01$, compared with group C; [#] $P < 0.05$, [▲] $P < 0.01$, compared with group D_1; [※] $P < 0.05$, $P < 0.01$, Compared with group D_2

Tan *et al. BMC Anesthesiology*   (2022) 22:271

Page 11 of 14
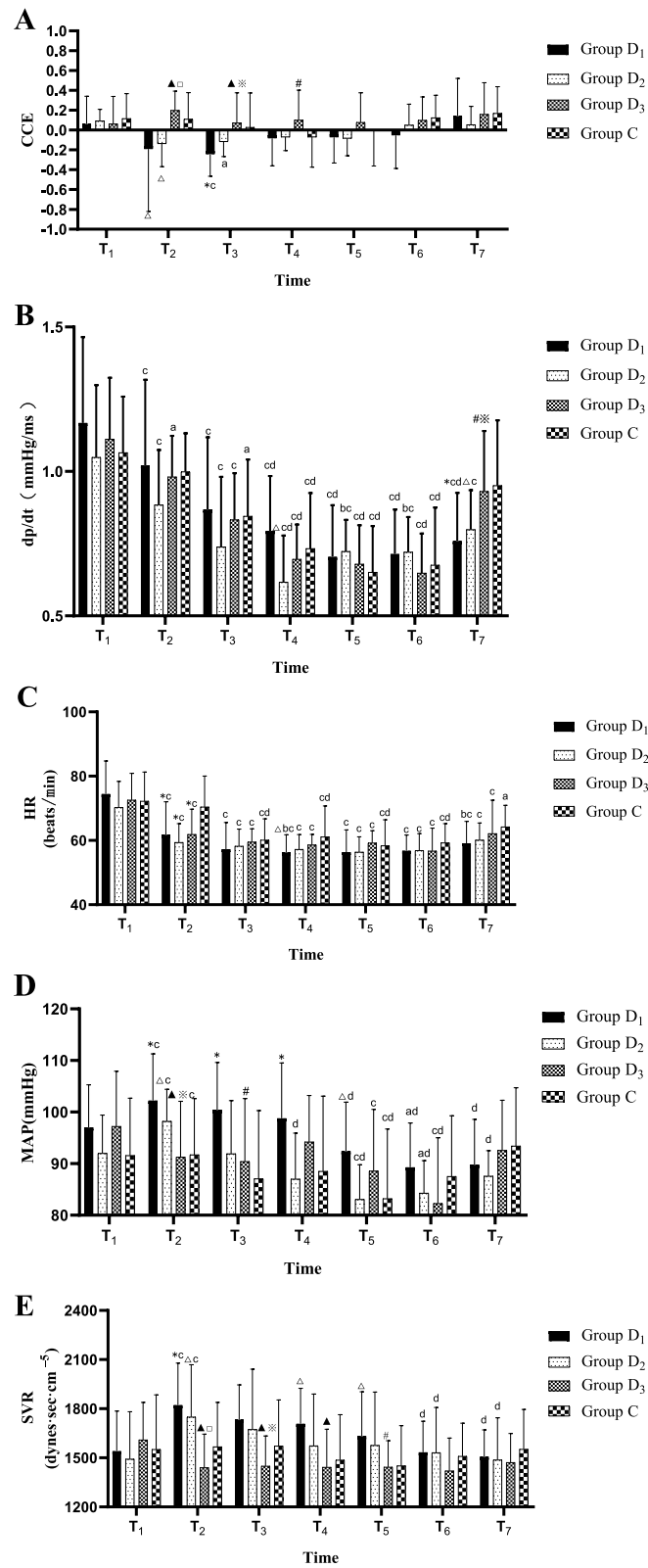
Fig. 3 (See legend on previous page.)

compared with the baseline at surgery ending, it returned to the baseline at 24 h postoperatively and was significantly lower than groups D_1, D_2 and C, suggesting that higher dose of dexmedetomidine might not be beneficial to cardiac electrophysiological stability and lower dose of dexmedetomidine in D_3 was more conducive to keep cardiac electrophysiological balance during perioperative period. Studies have shown [28] that abnormal iCEB elevations may be associated with excessive sympathetic activation and opening of cardiomyocyte cation channels, leading to drastic fluctuations in ion flow of action potential. The results of this study suggest that lower doses of dexmedetomidine are more advantageous than other doses applied.

In groups D_1 and D_2, SVR and MAP increased significantly compared to baseline values and were higher than groups C and D_3 when dexmedetomidine loading doses completed, suggesting that dexmedetomidine at higher dose of 1 μg/kg infused for 10 min could stimulate the α_{2B} receptors on vascular smooth muscle cells and contract resistance blood vessels [30–32]. Meanwhile, dp/dt in groups D_1 and D_2 were significantly lower than basic values, which indicated that the cardiac ejection function was influenced to a certain extent.

CCE is the cardiac circulation efficiency, which reflects the work efficiency of the heart for maintaining the circulation dynamic balance. The higher the CCE, the greater the efficiency, which is negatively correlated with the sudden death rate [33]. In this study, CCE in groups D_1 and D_2 after dexmedetomidine loading dose were significantly lower than those in groups C and D_3, indicating that dexmedetomidine loading dose 1 μg/kg might produce inhibitory effect on cardiac function. The reason might be related to the significantly increased SVR and cardiac afterload [34], producing a restrictive influence on cardiac function [35]. Dp/dt is the maximum pressure gradient, which is positively correlated with myocardial contraction function. In the current study, dp/dt in each dexmedetomidine group was significantly lower than the basic values after dexmedetomidine loading dose use, indicating that loading doses of 1 or 0.5 μg/kg could both inhibit myocardial contractility. While the dp/dt in group D_3 was significantly higher than those in groups D_1 and D_2 at 1 h in PACU and had no significant difference compared with that in group C, illustrating that lower dose of dexmedetomidine at 0.5 μg/kg/h significantly improve the cardiac prognosis, which was consistent with the previous studies [36–38]. Hence, lower dose dexmedetomidine in D_3 had no significant adverse effects on myocardial function during perioperative period.

In vitro studies [3, 39], dexmedetomidine reduced the I_{Ca-L} of cardiomyocytes significantly at a concentration of 10 ng/ml and above, that is, time of the ion channel inactivation was prolonged. In this study, HR in each dexmedetomidine group decreased significantly than the basic values and that in group C when the loading dose was completed. The reason might be related to the changes of Ca^{2+} ion channel inactivation [40]. Since catecholamines and cortisol had certain effects on cardiac electrophysiology, all research data in the current study were completed in the morning between 8 a.m. to 12 a.m. to avert the influences of day-night changes on cardiac electrophysiology [23]. Furthermore, basic values of K^+ and iCa^{2+} were comparable with standard values to avoid adverse effects on QTc, PR and QRS intervals [41].

Our study still has certain limitations. Considering that sevoflurane might prolong QTc intervals [42], this study only included patients under totally intravenous general anesthesia. The effects of dexmedetomidine on cardiac electrophysiology under combined intravenous and inhalational general anesthesia needs further study. Secondly, subjects with hypertension were not excluded in this study. Myocardial hypertrophy resulted from long-term hypertension might have certain impacts on myocardial repolarization and hemodynamics. Thirdly, we did not collect the intraoperative twelve-lead ECG limited by surgery manipulation. The effects of dexmedetomidine on electrocardia action and cardiac function still need to be proved by a multicenter and large-scale study.

Conclusions

In summary, dexmedetomidine at a loading dose of 0.5 μg/kg and a maintenance dose of 0.5 μg/kg/h could maintain the stability of cardiac electrophysiology during perioperative period and has no significant adverse effects on CCE.

Tan *et al. BMC Anesthesiology*   (2022) 22:271

Page 13 of 14

Declarations

Ethics approval and consent to participate
This study was approved by the the ethics committee of the Affiliated Hospital of Yangzhou University (2020-YKL09-025). Written informed consent following the principles of Declaration of Helsinki was obtained from all the subjects.

Consent for publication
Not applicable.

Competing interests
The authors declared that they had no competing interests.

Author details
[1]Department of Anesthesiology, the Affiliated Hospital of Yangzhou University, Yangzhou 225012, China. [2]Graduate School, Dalian Medical University, Dalian 116000, China. [3]Department of Cardiac Function, the Affiliated Hospital of Yangzhou University, Yangzhou 225012, China.

References
1. Kleiman AM, Johnson KB. Untapped potential of dexmedetomidine. Anesth Analg. 2019;129(6):1450–3.
2. Keating GM. Dexmedetomidine: a review of Its use for sedation in the intensive care setting. Drugs. 2015;75(10):1119–30.
3. Zhao J, Zhou CL, Xia ZY, Wang L. Effects of dexmedetomidine on l-type calcium current in rat ventricular myocytes. Acta Cardiol Sin. 2013;29(2):175–80.
4. Burns KM, Greene EA. Long QT syndrome unmasked by dexmedetomidine: a case report. Congenit Heart Dis. 2014;9(1):E11-15.
5. Yang L, Gong YQ, Tan Y, Wu L, Witman N, Zheng JJ, et al. Dexmedetomidine exhibits antiarrhythmic effects on human-induced pluripotent stem cell-derived cardiomyocytes through a Na/Ca channel-mediated mechanism. Ann Transl Med. 2021;9(5):399.
6. Sichrovsky TC, Mittal S, Steinberg JS. Dexmedetomidine sedation leading to refractory cardiogenic shock. Anesth Analg. 2008;106(6):1784–6.
7. Ergul Y, Unsal S, Ozyilmaz I, Ozturk E, Carus H, Guzeltas A. Electrocardiographic and electrophysiologic effects of dexmedetomidine on children. Pacing Clin Electrophysiol. 2015;38(6):682–7.
8. Hammer GB, Drover DR, Cao H, Jackson E, Williams GD, Ramamoorthy C, et al. The effects of dexmedetomidine on cardiac electrophysiology in children. Anesth Analg. 2008;106(1):79–83 table of contents.
9. Char D, Drover DR, Motonaga KS, Gupta S, Miyake CY, Dubin AM, et al. The effects of ketamine on dexmedetomidine-induced electrophysiologic changes in children. Paediatr Anaesth. 2013;23(10):898–905.
10. Tirotta CF, Nguyen T, Fishberger S, Velis E, Olen M, Lam L, et al. Dexmedetomidine use in patients undergoing electrophysiological study for supraventricular tachyarrhythmias. Paediatr Anaesth. 2017;27(1):45–51.
11. Safaeian R, Hassani V, Mohseni M, Ahmadi A, Ashraf H, Movaseghi G, et al. Comparison of the effects of propofol and sevoflurane on QT interval in pediatrics undergoing cochlear implantation: a randomized clinical trial study. Anesth Pain Med. 2019;9(4):e88805.
12. Staikou C, Stamelos M, Stavroulakis E. Impact of anaesthetic drugs and adjuvants on ECG markers of torsadogenicity. Br J Anaesth. 2014;112(2):217–30.
13. Park JH, Lee KY, Choi YD, Lee J, Shin HJ, Han DW, et al. Effect of different general anaesthetics on ventricular repolarisation in robot-assisted laparoscopic prostatectomy. Acta Anaesthesiol Scand. 2020;64(9):1243–52.
14. Oji M, Terao Y, Toyoda T, Kuriyama T, Miura K, Fukusaki M, et al. Differential effects of propofol and sevoflurane on QT interval during anesthetic induction. J Clin Monit Comput. 2013;27(3):243–8.
15. Keating S, Fries R, Kling K, Graham L, Clark-Price S, Schaeffer DJ. Effect of methadone or hydromorphone on cardiac conductivity in dogs before and during sevoflurane anesthesia. Front Vet Sci. 2020;7:573706.
16. Yilmaz CF, Elboğa G, Altunbaş G, Vuruşkan E, Uğur BK, Sucu M. Evaluation of ventricular repolarization features with Tp-e, Tp-e/QTc, JTc and JTd during electroconvulsive therapy. J Electrocardiol. 2018;51(3):440–2.
17. Sen S, Ozmert G, Boran N, Turan H, Caliskan E. Comparison of single-breath vital capacity rapid inhalation with sevoflurane 5% and propofol induction on QT interval and haemodynamics for laparoscopic surgery. Eur J Anaesthesiol. 2004;21(7):543–6.
18. Hoimark L, Uhrskov SL, Vukelic AL. Plasma concentrations of antipsychotics and QTc prolongation: a pilot study. Nord J Psychiatry. 2020;74(5):374–9.
19. Cobos-Puc LE, Aguayo-Morales H, Silva-Belmares Y, González-Zavala MA, Centuriónet D. alpha2A-adrenoceptors, but not nitric oxide, mediate the peripheral cardiac sympatho-inhibition of moxonidine. Eur J Pharmacol. 2016;782:35–43.
20. Tsutsui K, Hayami N, Kunishima T, Sugiura A, Mikamo T, Kanamori K, et al. Dexmedetomidine and clonidine inhibit ventricular tachyarrhythmias in a rabbit model of acquired long QT syndrome. Circ J. 2012;76(10):2343–7.
21. Stoetzer C, Reuter S, Doll T, Foadi N, Wegner F, Leffler A, et al. Inhibition of the cardiac Na+ channel alpha-subunit Nav1.5 by propofol and dexmedetomidine. Naunyn Schmiedebergs Arch Pharmacol. 2016;389(3):315–25.
22. Odening KE, Van DLHJ, Ackerman MJ, Volders PGA, Ter Bekke RMA. Electromechanical reciprocity and arrhythmogenesis in long-QT syndrome and beyond. Eur Heart J. 2022;21:ehac135.
23. Kim Y, Kim SY, Lee JS, Kong HJ, Han DW. Effect of dexmedetomidine on the corrected QT and Tp-e intervals during spinal anesthesia. Yonsei Med J. 2014;55(2):517–22.
24. Ellermann C, Brandt J, Wolfes J, Willy K, Wegner FK, Leitz P, et al. Safe electrophysiologic profile of dexmedetomidine in different experimental arrhythmia models. Sci Rep. 2021;11(1):23940.
25. Gorges M, Sherwin ED, Poznikoff AK, West NC, Brodie SM, Whyte SD. Effects of dexmedetomidine on myocardial repolarization in children undergoing general anesthesia: a randomized controlled trial. Anesth Analg. 2019;129(4):1100–8.
26. Kaya H, Suner A, Koparal M, Yucetas SC, Kafadar S. Evaluation of Tp-e interval, Tp-e/QT ratio and index of cardiac-electrophysiological balance in patients with tinnitus. BMC Cardiovasc Disord. 2021;21(1):415.
27. Huang SS, Song FX, Yang SZ, Hu S, Zhao LY, Wang SQ, et al. Impact of intravenous dexmedetomidine on postoperative bowel movement recovery after laparoscopic nephrectomy: a consort-prospective, randomized, controlled trial. World J Clin Cases. 2021;9(26):7762–71.
28. Robyns T, Lu HR, Gallacher DJ, Garweg C, Ector J, Willems R, et al. Evaluation of Index of Cardio-Electrophysiological Balance (iCEB) as a new biomarker for the identification of patients at increased arrhythmic risk. Ann Noninvasive Electrocardiol. 2016;21(3):294–304.
29. Liu Y, Fu X, Gao H, Ren Y, Li H, He Y, et al. Effects of different concentrations of desflurane on the index of cardiac electrophysiological balance in gynecologic surgery patients. Can J Physiol Pharmacol. 2020;98(5):332–5.
30. Hongo M, Fujisawa S, Adachi T, Shimbo T, Shibata S, Ohba T, et al. Age-related effects of dexmedetomidine on myocardial contraction and coronary circulation in isolated guinea pig hearts. J Pharmacol Sci. 2016;131(2):118–25.
31. Talke P, Anderson BJ. Pharmacokinetics and pharmacodynamics of dexmedetomidine-induced vasoconstriction in healthy volunteers. Br J Clin Pharmacol. 2018;84(6):1364–72.
32. Ashraf MW, Uusalo P, Scheinin M, Saari TI. Population modelling of dexmedetomidine pharmacokinetics and haemodynamic effects after intravenous and subcutaneous administration. Clin Pharmacokinet. 2020;59(11):1467–82.
33. Romagnoli S, Franchi F, Ricci Z, Scolletta S, Payen D. The Pressure Recording Analytical Method (PRAM): technical concepts and literature review. J Cardiothorac Vasc Anesth. 2017;31(4):1460–70.
34. Ok SH, Kwon SC, Baik J, Hong JM, Oh J, Han JY, et al. Dexmedetomidine-induced contraction involves CPI-17 Phosphorylation in Isolated Rat Aortas. Int J Mol Sci. 2016;17(10):1663.

35. Lee K, Hwang HJ, Kim OS, Oh YJ. Assessment of dexmedetomidine effects on left ventricular function using pressure-volume loops in rats. J Anesth. 2017;31(1):18–24.
36. Li H, Liu J, Shi H. Effect of dexmedetomidine on perioperative hemodynamics and myocardial protection in thoracoscopic-assisted thoracic surgery. Med Sci Monit. 2021;27:e929949.
37. Tan XL, Chen YY, Hu B, Zhou QM, Shao WD, Xu B, et al. Dose-response relationship of dexmedetomidine combined with sufentanil for postoperative intravenous analgesia in video-assisted thoracoscopic surgery. Zhongguo Yi Xue Ke Xue Yuan Xue Bao. 2019;41(3):373–8 [in Chinese].
38. Duncan D, Sankar A, Beattie WS, Wijeysundera DN. Alpha-2 adrenergic agonists for the prevention of cardiac complications among adults undergoing surgery. Cochrane Database Syst Rev. 2018;3(3):CD004126.
39. Evdokimovskii EV, Jeon R, Park S, Pimenov OY, Alekseev AE. Role of alpha2-adrenoceptor subtypes in suppression of L-Type Ca^{2+} Current in Mouse Cardiac Myocytes. Int J Mol Sci. 2021;22(8):4135.
40. Shuplock JM, Smith AH, Owen J, Van Driest SL, Marshall M, Saville B, et al. Association between perioperative dexmedetomidine and arrhythmias after surgery for congenital heart disease. Circ Arrhythm Electrophysiol. 2015;8(3):643–50.
41. Chrysostomou C, Komarlu R, Lichtenstein S, Shiderly D, Arora G, Orr R, et al. Electrocardiographic effects of dexmedetomidine in patients with congenital heart disease. Intensive Care Med. 2010;36(5):836–42.
42. Liu Y, Gao H, Wang G, An L, Yi J, Fu X, et al. A comparison of the effect of sevoflurane and propofol on ventricular repolarisation after preoperative cefuroxime infusion. Biomed Res Int. 2019;2019:8978906.

Publisher's Note