Effect of dexmedetomidine on hemodynamic changes and inflammatory responses in patients undergoing off-pump coronary-artery bypass grafting

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Abstract. The aim of the present study was to determine the effect of dexmedetomidine on hemodynamic changes and inflammatory responses in patients undergoing off-pump coronary artery bypass grafting (OPCABG). A total of 300 patients about to receive OPCABG were randomized evenly into the control group (n=116) and study group (n=123). Intravenous dexmedetomidine pump infusion was administered to patients in the study group at a rate of 0.4 μg.kg^{-1}.h^{-1}. The control group received physiological saline at the same infusion speed. Changes in hemodynamic parameters and inflammatory indices were compared between the two groups. Hemodynamic parameters, such as the heart rate and mean arterial pressure, were lower in patients from the study group, compared with that in the control group (both P<0.05). The levels of pro-inflammatory factors, such as interleukin (IL)-6, tumor necrosis factor-α and C-reactive protein, were also reduced in the study group (P<0.05). The observed levels of IL-10 were lower in the control group compared with that in the study group, although a statistically significant difference was not achieved. Thus, the administration of dexmedetomidine in patients undergoing OPCABG stabilized hemodynamics and reduced inflammation. The present study was registered at the Chinese Clinical Trial Registry, under the trial registration number ChiCTR-OOC-15005978 (2015).

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Introduction

Coronary artery disease (CAD) is a major cardiovascular disease that affects the global population. CAD is a major cause of death in developed and developing countries (1). With advances in medical technology, effective medication and interventional therapy, off-pump coronary artery bypass grafting (OPCABG) has become increasingly available for patients with coronary heart disease in Asia. OPCABG can be achieved with a low mortality and a good medium to long term survival. OPCABG is associated with fewer post-operative complications and comparable late coronary interventions (2). However, in the majority of patients who suffer from severe myocardial ischemia, surgery can activate the sympathetic nerves, triggering the release of catecholamine. This subsequently causes adverse cardiovascular reactions, such as elevated blood pressure and increased heart rate, directly affecting the prognosis of patients (3,4). Therefore, anesthesiologists should select appropriate anesthetic drugs to create safe and comfortable conditions for surgery, reduce the post-operative inflammatory response and have little impact on the hemodynamic indices.

Dexmedetomidine is a novel and highly selective α-2 adrenergic receptor agonist, with an $\alpha2$:$\alpha1$ receptor affinity of 1620:1 (5). It has analgesic, sedative and anxiolytic properties, with a mild inhibitory effect on respiratory function (6-8). Dexmedetomidine is used as a sedative in critical illness and may serve anti-inflammatory effects (9). Hence the present study investigated the effects of dexmedetomidine on the hemodynamics and inflammatory response of 239 patients undergoing OPCABG surgery.

Materials and methods

Patient selection. A total number of 300 patients undergoing OPCABG, aged 55-75 years old, weighing 55-85 kg and with American Society of Anesthesiology II-III (10), were included in the present study regardless of their sex and education level (Table I). Patients with neurological/mental health conditions or organs (including brain, lung, liver and kidney) dysfunction were excluded. All subjects were well-informed and provided

written informed consent before accepting anesthesia. The present study was approved by The Ethics Committee of Tianjin Chest Hospital (approval no. 2012KY-001-01) and was registered at the Chinese Clinical Trial Registry, under trial registration number ChiCTR-OOC-15005978 (2015).

Randomization and study blinding. Patients were randomly assigned into the control group (group C), in which no intraoperative intravenous pump infusion of dexmedetomidine was used. In the dexmedetomidine group (group D), dexmedetomidine was infused at a rate of $0.4 \mu g.kg^{-1}.h^{-1}$, starting from endotracheal intubation to the end of the surgery. The dosage and ratio of dexmedetomidine were calculated according to the recommended dosage in combination with the body weight of the patient. Based on the findings from retrospective studies (11,12), a total of 127 patients were required in each group with an α-level of 0.05 and power of 0.8. Assuming a 20% withdrawal rate during the course of the clinical trial, including study design deviation and consent withdrawal, 150 patients were enrolled into each group.

During the study period, 300 patients were screened, and 279 of these met the inclusion criteria (including undergoing OPCABG, an age of 55-75 years old, weighing 55-85 kg and with an American Society of Anesthesiology score of II-III), leaving 135 patients in group C and 144 patients in group D. Among the enrolled patients, 40 were excluded due to the following reasons: i) Intraoperative switch to extracorporeal circulation; ii) intraoperative massive bleeding and blood perfusion; iii) second surgery within a short time following initial surgery; iv) lengthy postoperative mechanical ventilation support; v) lost to follow-up post-operatively; and vi) death. Thus, 239 patients were enrolled in the present study, 116 and 123 in groups C and D, respectively (Fig. 1).

The results of randomization were sealed in envelopes with serial numbers and placed in the study center under the supervision of the clinical research coordinator (GW). Randomization was performed 30-60 min prior to surgery, which was 30-60 min following the provision of informed consent from the patients. The clinical research coordinator was not blinded to the grouping results. The responsibilities of the clinical research coordinator included assigning the patients to randomized groups, distributing medicine, providing instructions to the anesthesiologists regarding the intraoperative measures, conducting the study protocol under strict guidelines, collecting the data and coordinating the entire study. The anesthesiologists responsible for intraoperative management were blinded to the grouping results. Strict blinding during the follow-up was ensured. In addition, the medical team providing postoperative care in the intensive care unit (ICU) and the wards, the investigators, patients, statisticians, and data and safety oversight committees were all blinded to the grouping results.

Anesthesia management. Identical anesthesia induction with 0.03-0.05 mg/kg midazolam, 0.15-0.3 mg/kg etomidate, 0.5-1 μg/kg sufentanil and 0.6 mg/kg rocuronium was adopted for all the enrolled patients. After anesthesia induction, oral endotracheal intubation (tidal volume, 6-8 ml/kg; respiratory rate, 13/min) was performed, and a radial artery puncture for

central venous catheter placement or Swan-Ganz catheter placement was performed. The parameters, including the heart rate, mean arterial pressure, oxygen saturation, end-tidal CO_2, brain spectral index (BIS), central venous pressure, cardiac output and pulmonary artery pressure were monitored. During anesthesia maintenance, supplementation with identical general anesthetics, analgesics and muscle relaxants was performed, namely propofol and sevoflurane, sufentanil and cis-atracurium. The vasoactive drugs utilized included norepinephrine, nicardipine, milrinone, and esmolol. Following surgery, the patient was transferred to the ICU.

Outcome measures. Venous blood was collected at pre-incision (t1), immediately following sternal closure (t2), then 4, 12 and 24 h postoperatively (t3, t4 and t5, respectively). ELISA kits (all, Abcam) were used to detect interleukin (IL)-6 (cat. no. ab46027), tumor necrosis factor-α (cat. no. ab181421), C-reactive protein (CRP; cat. no. ab260058) and IL-10 (cat. no. ab185986) levels. BIS values were recorded a intraoperatively at the t1 and t2 time points. Hemodynamic parameters (HR and MAP) at each time point, both intraoperatively and postoperatively were also recorded.

Statistical analysis. The SPSS v21.0 software (IBM Corp.) was used for data analysis. Continuous data are presented as the mean ± SD and were analyzed using a t-test. $P<0.05$ was considered to indicate a statistically significant difference.

Results

Comparison of clinical data and surgical records. No significant difference in the general condition, complications, cardiac function and surgical records was observed between the two groups (Tables I and II). No significant difference was also detected in the intraoperative doses of the vasoactive drugs between the two groups (Table III).

Comparison of hemodynamic parameters and BIS values at each time point. Patients in the group D had a significantly slower heart rate at t2, t3, and t4, compared with that in group C (Fig. 2). A significantly lower mean arterial pressure was also observed in patients in group D at the t2 and t3 time points (Fig. 3), while BIS values at t1 and t2 in both groups ranged from 40-55 indicating that the depth of anesthesia in both the patients was moderate. However, no significant difference was observed in BIS values between the two groups at these time points (Fig. 4).

Comparison of biochemical indices. Differences were observed in the levels of IL-6, TNF-α, CRP and IL-10 between the two groups. TNF-α levels were significantly lower in group D compared with that in group C at the t2 and t3 time points (Fig. 5). IL-6 levels were also significantly reduced at the t2 time point compared with that in group C (Fig. 6), while the levels of CRP were significantly reduced in group D compared with that in group C, at the t3, t4 and t5 time points (Fig. 7). Furthermore, the amount of IL-10 in group C was marginally reduced, compared with that on group D, at the t3, t4 and t5 time points; however, this difference was not statistically significant (Fig. 8).

Table I. Baseline characteristics.

|	Group		
Variable	C, n=116	D, n=123	P-value
Mean age ± SD, years	66±4.5	67±3.6	0.352
Mean education duration ± SD, years	10.6±3.1	10.6±3.2	0.961
Sex, female, n (%)	53 (47)	56 (46)	0.498
Sex, male, n (%)	63 (53)	67 (54)	0.924
Mean height ± SD, cm	171±8.3	170±8.5	0.723
Mean weight ± SD, kg	73±5.2	73±5.9	0.998
Hypertension, n (%)	103 (78)	105 (85)	0.721
Diabetes mellitus, n (%)	86 (74)	91 (74)	0.145
Previous myocardial infarction, n (%)	58 (50)	50 (41)	0.235
Meanpreoperative EF ± SD	55±4.6	54±5.1	0.535

EF, ejection fraction.
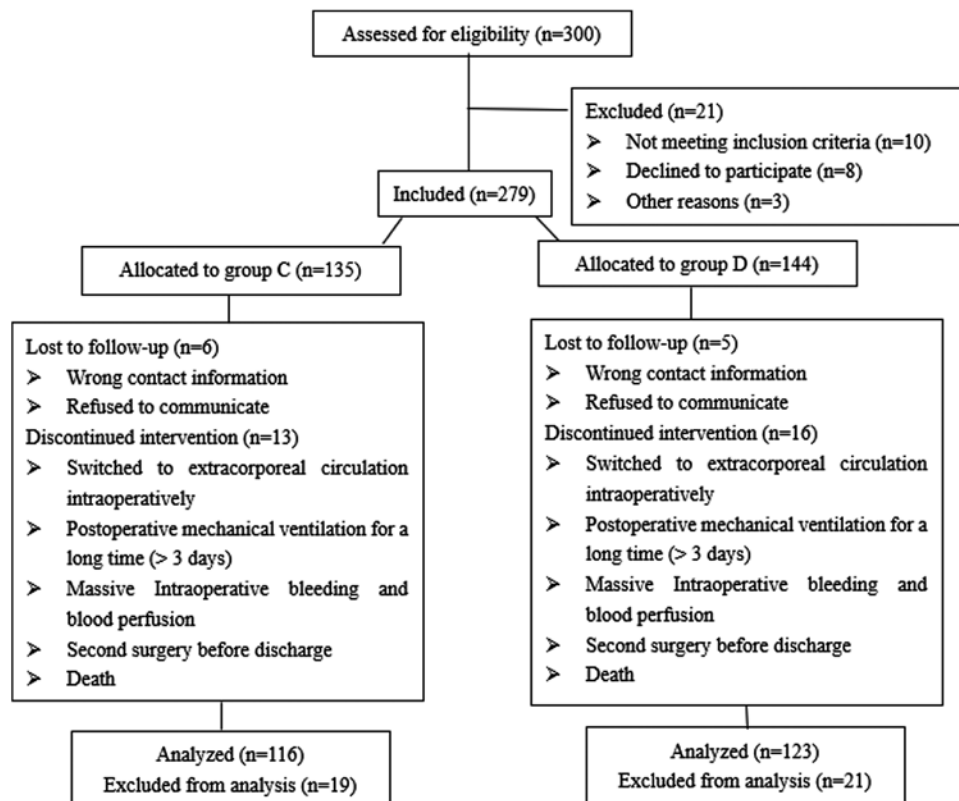
Figure 1. Flow chart of patient enrollment and exclusion.

Discussion

In the USA, the Food and Drug Administration (FDA) has approved the use of dexmedetomidine for short-term sedation (24 h) in ICUs for patients undergoing mechanical ventilation and endotracheal intubation. In October 2008, the FDA extended the use of this drug for sedation of non-intubated patients prior to and during surgical and non-surgical procedures (3).

In the present study, the effects of intraoperative use of dexmedetomidine on hemodynamics and inflammatory responses were evaluated during OPCABG surgery. Previous studies have demonstrated the anti-inflammatory effect of dexmedetomidine in clinical practice, yet few have documented this effect in OPCABG (13-16). Furthermore, unlike previous studies (11,12), the clinical trial described in the present study combined clinical indicators and measurement of inflammatory factors to jointly describe the anti-inflammatory effect of dexmedetomidine and its potential clinical benefit.

Dexmedetomidine was found to reduce the mean arterial pressure and heart rate, suggesting a stabilizing effect on

Table II. Clinical record.

Variable	Group		P-value
	C, n=116	D, n=123	
Number of grafts ± SD	3±0.5	3±0.6	0.984
Mean duration of anesthesia ± SD, h	3.8±0.6	4.1±0.7	0.845
Mean time spent in ICU ± SD, days	2.2±0.2	2.0±0.1	0.624
Mean time spent in hospital ± SD, days	8.3±1.2	7.2±1.3	0.397

ICU, intensive care unit.

Table III. Vasoactive drugs.

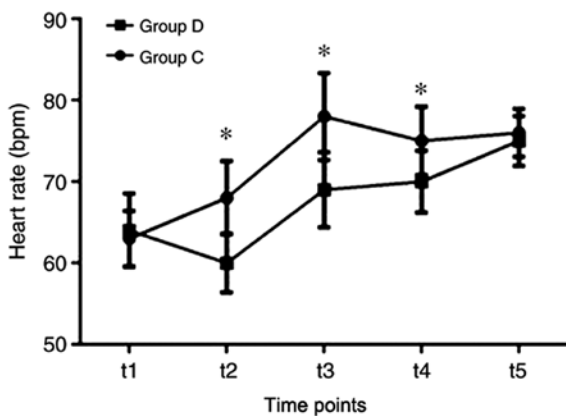| Variable	Group		P-value
	C, n=116	D, n=123	
Premedication			
Dose of μorphine ± SD, mg	5±0.9	5±1.0	0.922
Dose of σcopolamine ± SD, mg	0.3±0.05	0.3±0.06	0.987
Positive inotropic drugs			
Mean level of dopamine ± SD, mg/kg/min	3.82±0.71	4.03±0.55	0.367
Mean level of milrinone ± SD, mg/kg/min	0.35±0.02	0.39±0.03	0.201
Mean level of norepinephrine ± SD, μg/kg/min	0.41±0.06	0.37±0.06	0.145

Figure 2. Heart rate in the D and C groups. Heart rates were measured at pre-incision (t1), immediately following sternal closure (t2), then 4, 12 and 24 h postoperatively (t3, t4 and t5, respectively), and compared between each group at the same time points. Data are presented as the mean ± SD. *$P<0.05$ vs. control. D, dexmedetomidine; C, control; t, time.
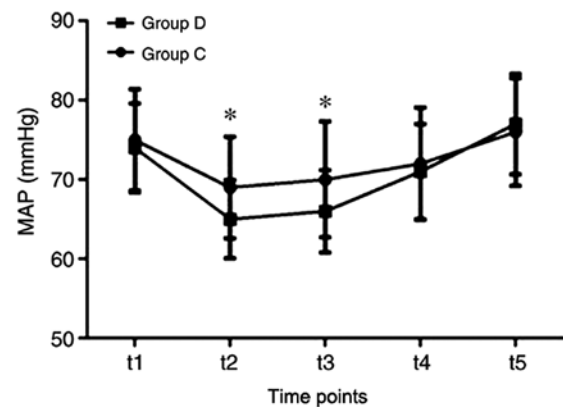

Figure 3. Comparisons of MAP between the two groups at each time point. MAP was measured at pre-incision (t1), immediately following sternal closure (t2), then 4, 12 and 24 h post-operatively (t3, t4 and t5, respectively), and compared between each group at the same time points. Data are presented as the mean ± SD. *$P<0.05$ vs. control. D, dexmedetomidine; C, control; MAP, mean arterial pressure; t, time.

hemodynamics (17-20). This could be attributed to the ability of dexmedetomidine to reduce sympathetic nerve activity, inhibit the release of sympathetic impulses, and relieve nerve tension primarily according to the highly selective nature of the drug (21). In previous studies, dexmedetomidine did not demonstrate any myocardial inhibition and even exhibited cardioprotection, neuroprotection, and renoprotection by reducing inflammation (22-24). A previous study suggested that the use of dexmedetomidine reduced the requirement for

propofol and improved the hemodynamic stability in patients with BIS-guided sedation (25). Consistent with this previous study, the present findings also confirmed that administration of dexmedetomidine did not decrease the BIS values and demonstrated effective stability during anesthetic maintenance at the sedation level.

Trauma and postoperative pain following cardiac surgery contribute to the inflammatory response in patients (26). Inflammatory responses occur intraoperatively, but can
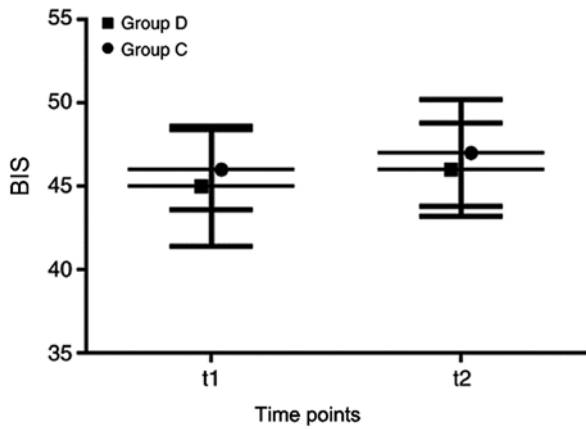
Figure 4. Comparisons of BIS between the two groups at t1 and t2 time points. BIS values were measured at pre-incision (t1), immediately following sternal closure (t2), and compared between each group at the same time points. Data are presented as the mean ± SD. D, dexmedetomidine; C, control; t, time.
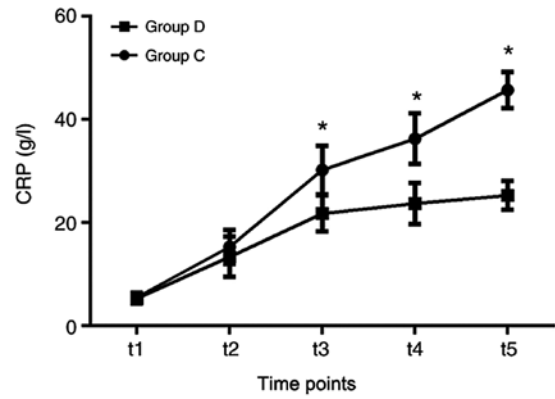

Figure 7. Comparisons of CRP between the two groups at each time point. CRP levels were measured at pre-incision (t1), immediately after sternal closure (t2), then 4, 12 and 24 h postoperatively (t3, t4 and t5, respectively), and compared between each group at the same time points. Data are presented as the mean ± SD. *P<0.05 vs. control. D, dexmedetomidine; C, control; CRP, C-reactive protein; t, time.
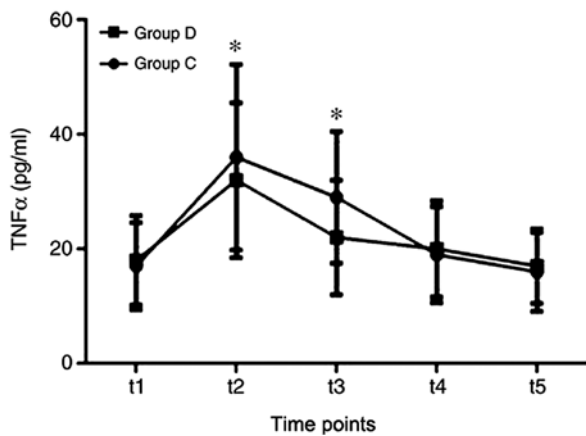

Figure 5. Comparisons of TNF-α between the two groups at each time point. TNF-α levels were measured at pre-incision (t1), immediately following sternal closure (t2), then 4, 12 and 24 h postoperatively (t3, t4 and t5, respectively), and compared between each group at the same time points. Data are presented as the mean ± SD. *P<0.05 vs. control. D, dexmedetomidine; C, control; TNF-α, tumor necrosis factor-α; t, time.
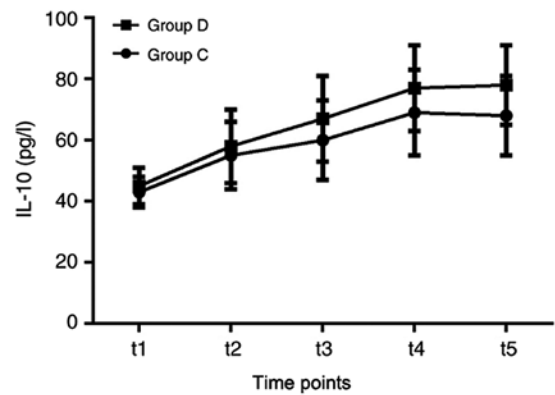

Figure 8. Comparisons of IL-10 between the two groups at each time point. IL-10 levels were measured at pre-incision (t1), immediately after sternal closure (t2), then 4, 12 and 24 h postoperatively (t3, t4 and t5, respectively), and compared between each group at the same time points. Data are presented as the mean ± SD. D, dexmedetomidine; C, control; IL, interleukin; t, time.
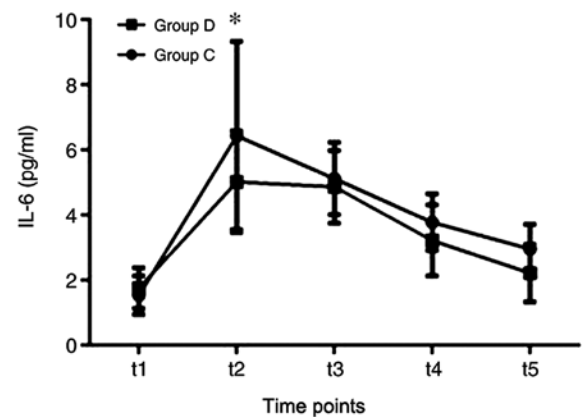

Figure 6. Comparisons of IL-6 between the two groups at each time point. IL-6 levels were measured at pre-incision (t1), immediately following sternal closure (t2), then 4, 12 and 24 h postoperatively (t3, t4 and t5, respectively), and compared between each group at the same time points. Data are presented as the mean ± SD. *P<0.05 vs. control. D, dexmedetomidine; C, control; IL, interleukin; t, time.

also persist postoperatively. Hyperinflammatory responses damage particular organs, including the lung, heart and kidney, and in turn, trigger unfavorable pathological changes, including tissue and cell degeneration, necrosis, changes in hemodynamics (inflammatory hyperemia), increased vascular permeability (inflammatory exudation), fluid exudation and cellular exudation (inflammatory infiltration) resulting in systemic inflammatory response syndrome. This leads to secondary multiple organ injury and dysfunction, affecting postoperative outcomes (including prolonged hospitalization and increased medical costs) and quality of life (27). The postoperative use of dexmedetomidine in patients in ICU effectively inhibits the release of inflammatory mediators, reducing the incidence rate of systemic inflammatory response syndrome (28-31). Dexmedetomidine also significantly suppresses the production of lipopolysaccharide-induced proinflammatory mediators, including TNF-α, IL-6, and CRP, both *in vivo* and *in vitro* (31-34). IL-10 is an anti-inflammatory cytokine that inhibits the production of IL-6 and TNF-α (35). The present findings also suggested that the use

of dexmedetomidine during surgery significantly reduced the intraoperative and short-term post-operative levels TNF-α and IL-6. Moreover, dexmedetomidine also reduced the postoperative levels of CRP. Thus, it may be hypothesized that dexmedetomidine activates the central nervous system, as well as the peripheral α2 adrenergic receptor, to reduce sympathetic nerve activity and plasma catecholamine concentration, which then reduces perioperative inflammatory responses (36,37). Indeed, dexmedetomidine has previously been demonstrated to reduce sympathetic tone and indirectly improve parasympathetic tone, which may inhibit systemic inflammatory responses (38). Yang and Hong (39) also suggested that dexmedetomidine could inhibit nuclear factor-κB activity and activate cholinergic anti-inflammatory pathways. Chen *et al* (40) investigated whether dexmedetomidine served an anti-inflammatory effect on myocardial ischemia-reperfusion injury in patients who underwent coronary artery bypass graft surgery (CABG) with CPB. The study demonstrated that dexmedetomidine inhibited the increase in cardiac troponin I and creatine kinase isoenzymes, attenuated the production of pro-inflammatory cytokines TNF-α, IL-6 and IL-8, and promoted anti-inflammatory cytokine IL-10 production. The results demonstrated that dexmedetomidine regulated the anti-inflammatory response and provided myocardial protection in CABG with CPB (40). Thus, dexmedetomidine could maintain the perioperative hemodynamic stability in patients receiving OPCABG, alleviate the perioperative inflammatory response, and might be beneficial to patients during postoperative recovery.

However, only a single-dose intravenous pump infusion of dexmedetomidine was evaluated in the present study. The study confirmed that dexmedetomidine stabilized hemodynamic parameters in patients undergoing OPCABG surgery; however, the study design could not establish whether the dose used produced an optimal result on coronary indices. Furthermore, follow-up information regarding the short and long-term postoperative outcomes, including the mortality rate and complications, were unavailable. In addition, the use of dexmedetomidine during time spent in the ICU and whether this could also improve patient outcomes was not assessed. The present study also lacked a positive control group, as anti-inflammatory drugs used are not approved for surgery in China, with the exception of ulinastatin. Thus, the findings of the present study should be validated in future studies and the limitations addressed.

In conclusion, anesthesia with dexmedetomidine during OPCABG surgery effectively alleviated stress-induced responses, promoted hemodynamic stability and produced an effective sedative action. Thus, dexmedetomidine may be a potentially suitable anesthetic for clinical use.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

WZ analyzed the data and wrote the manuscript. LY assisted with cardiac surgery and performed the post-operative follow-up of patients. PS and JH implemented anesthesia and recorded intraoperative data. YL collected patient blood samples and conducted ELISA. GW designed and supervised the trial. All authors read and approved the final manuscript.

Ethics approval and consent to participate

This study was approved by the Ethics Committee of Tianjin Chest Hospital (approval no. 2012KY-001-01) and was registered at the Chinese Clinical Trial Registry with the trial registration number ChiCTR-OOC-15005978 (2015). All subjects were well informed and provided written informed consent.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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