Does Dexmedetomidine Provide Cardioprotection in Coronary Artery Bypass Grafting With Cardiopulmonary Bypass? A Pilot Study

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Objective: **The purpose of this pilot study was to evaluate whether dexmedetomidine has a cardioprotective effect during coronary artery bypass graft surgery with cardiopulmonary bypass (CPB).**

Design: **A prospective, double-blind, randomized controlled trial.**

Setting: **A university hospital.**

Participants: **Thirty-eight patients undergoing coronary artery bypass graft surgery.**

Interventions: **Patients were randomized into 2 groups: dexmedetomidine and placebo groups. In the dexmedetomidine group, dexmedetomidine infusion was started by a loading dose of 0.5 μg/kg/10 min, followed by a continuous infusion of 0.5 μg/kg/h. The placebo group received the same volume of saline. Measurements of central venous pressure, mean pulmonary artery pressure (MPAP) and cardiac index were performed before and after dexmedetomidine loading dose and 2, 24 and 48 hours after CPB. Simultaneously, arterial blood was sampled for CK-MB, cardiac troponin T, and N-terminal probrain natriuretic peptide.**

Measurements and Main Results: **CK-MB, cardiac troponin T and N-terminal probrain natriuretic peptide values were elevated in the periods after CPB in both groups ($p < 0.05$) and there were no statistically significant differences between groups. MPAP was decreased in the dexmedetomidine group at the 2nd, 24th and 48th hour after CPB ($p < 0.001$, $p < 0.001$, $p = 0.002$, respectively). Higher cardiac index values were seen earlier in the dexmedetomidine group than in the placebo group ($p < 0.05$).**

Conclusions: **Myocardial damage was not reduced by administration of 0.5 μg/kg loading dose and 0.5 μg/kg/h infusion of dexmedetomidine. However MPAP tended to be lower in the dexmedetomidine group. Large-scale clinical outcome studies are indicated to confirm the effect of dexmedetomidine.**

KEY WORDS: dexmedetomidine, cardioprotective effect, coronary artery bypass grafting, cardiopulmonary bypass

CORONARY ARTERY BYPASS GRAFTING (CABG) with cardiopulmonary bypass (CPB) may result not only in ischemic injury but also in reperfusion injury. The extent of these injuries is directly proportional to cardiac biomarker release. The increase in these biomarkers is an indicator of cell death. Cardiac troponin (cTn) is a sensitive and specific biomarker for assessing cardiac injury.[1] In addition to the use of cTn to monitor active myocardial damage, there is growing evidence that measuring brain natriuretic peptide (BNP) may be effective to monitor myocardial stretch as a result of volume overload, eg, in cardiac dysfunction,[2] and as a good marker for complications after cardiac surgery.[3]

Dexmedetomidine (Precedex; Abbott Laboratories Inc, Abbott Park, IL) is a selective and specific α-2 adrenoreceptor agonist. The α-2 adrenoreceptors are involved in regulating the autonomic and cardiovascular systems. The α-2 adrenoreceptors are located in the blood vessels, where they mediate vasoconstriction, and in sympathetic terminals, where they inhibit the release of norepinephrine.[4]

Guo et al and Okada et al reported that dexmedetomidine exerted a cardioprotective effect on left ventricular dysfunction caused by hypoxia reoxygenation and global ischemia in an isolated rat heart.[5,6] They demonstrated that this cardioprotective effect of dexmedetomidine was mediated by α-2 adrenergic stimulation.

Cardioprotective effects of dexmedetomidine have not been reported in a clinical study of cardiac surgery patients. The aim of this pilot study was to assess whether dexmedetomidine has a cardioprotective effect during CABG with CPB.

METHODS

After approval by the institutional ethics committee, informed consent was obtained from all the patients. Thirty-eight patients between the age of 39 to 80 years undergoing elective CABG surgery, were enrolled in the study. Exclusion criteria were as follows: concurrent valvular surgery or presence of valvular disease, redo surgery, unstable angina or elevated levels of cardiac enzyme (≥0.06 ng/mL, cTnI) within 48 hours of surgery, ejection fraction <40%, the need for inotropic agents or an intra-aortic balloon pump preoperatively, chronic renal insufficiency (creatinine >1.6 mg/dL) or chronic renal failure, and moderate-to-severe chronic obstructive pulmonary disease.

Patients were premedicated with 5 mg of diazepam administered orally on the night before surgery. Standard monitoring was achieved in all the patients. Anesthesia was induced with 2 to 5 μg/kg of fentanyl (total dose of 5 μg/kg before surgical incision), 0.2 to 0.3 mg/kg of etomidate, and 1 mg/kg of rocuronium and was maintained with 5 μg/kg/h of fentanyl, 0.5% to 2% of sevoflurane in 40% to 60% oxygen-air mixture, and rocuronium. After the induction of anesthesia, a femoral artery catheter was inserted. A central venous catheter and a pulmonary artery catheter (Swan-Ganz CCOmbo Pulmonary Artery Catheter, Edwards Lifesciences LLC) were inserted through the right internal jugular vein. For the suppression of CPB-related inflammatory response, 30 mg/kg of methylprednisolone was injected. No antifibrinolytic drug was used during the surgery. Anticoagulation was maintained with 350 U/kg of unfractionated heparin for CPB. The kaolin-activated coagulation time was measured every 30 minutes, and if the activated coagulation time was less than 480 seconds, additional heparin (100 U/kg) was administered during CPB. After the termination

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of CPB, 1.3 mg of protamine sulfate per 100 U of heparin was given to all the patients.

Patients were divided randomly into 2 groups: the dexmedetomidine group (Group D, n = 18) or the placebo group (Group P, n = 20), using the sealed envelope method. An independent person performed randomization and prepared the solution containing either 2 μg/mL of dexmedetomidine or normal saline (SP) with a total volume of 100 mL. The dexmedetomidine group received a loading dose of 0.5 μg/kg/10 min of dexmedetomidine via a central venous catheter followed by a continuous infusion of 0.5 μg/kg/h of dexmedetomidine. The infusion was discontinued at the end of the surgery. The placebo group received the same volume of SP.

Hemodynamic data were recorded before induction of anesthesia, after endotracheal intubation, before and after study drug (or SP) loading dose, and at 2, 24, and 48 hours after separation from CPB. Hemodynamic data included heart rate (HR), systolic arterial pressure (SAP), mean pulmonary artery pressure (MPAP), central venous pressure (CVP), and cardiac index (CI). Blood samples for biochemical markers were obtained at 5 time intervals: before and after study drug (or SP) loading dose and at 2, 24, and 48 hours after separation from CPB. Samples were centrifuged immediately and stored at −80°C until assayed.

Serum concentration of cTn T (cTnT) was determined using an Elecsys cTnT kit with a COBAS e 411 (Roche Diagnostics, GmbH, Mannheim, Germany) analyzer, and the serum concentration of CK-MB was determined using an Olympus CK-MB kit with an Olympus analyzer. Plasma N-terminal probrain natriuretic peptide (NT-proBNP) concentrations also were determined using a Human NT-proBNP ELYSA kit (EIAab & USCNLIFE—Wuhan EIAab Science Co, Ltd, Houston, TX).

In all the patients, nitroglycerin infusion was started at 0.2 μg/kg/min and titrated to maintain a mean perfusion pressure of 50 to 80 mmHg during CPB. An additional dose of 0.1 mg/kg of midazolam, 1 to 1.5 mg/kg of lidocaine, and 0.3 mg/kg of rocuronium was provided during rewarming from CPB. Hematocrit levels were kept above 22% on CPB and above 28% postoperatively. Hypertension was treated by increasing the concentration of sevoflurane or by the administration of nitroglycerin, if increasing the depth of anesthesia was ineffective. Hypotension was corrected using volume replacement or ephedrine, as clinically indicated. After weaning from CPB, inotropic support (dobutamine or dopamine, both of them ≥5 μg/kg/min) was initiated for a CI <2.0 L/min/m^2 or a mean arterial pressure <60 mmHg, or both despite optimization of preload, afterload, and HR as the routine practice. When these medications were insufficient, ephedrine (≥0.2 μg/min) was added. Propofol sedation (2-5 mg/kg/h) was started in the intensive care unit (ICU) and was continued until weaning from ventilatory support was initiated.

Data were analyzed by the use of the SPSS 15.0 statistical program. Statistical comparisons of the demographic and perioperative data (HR, SAP, CVP, MPAP, SpO_2, and CI) were performed by the Student t-test, chi-square, or Fisher exact test when appropriate. A repeated measure of analysis of variance was used for serial data. Data were determined not to be distributed normally by the Shapiro-Wilk test for normality of the underlying population. Therefore, these data (CK-MB, cTnT, and NT-proBNP) were reported as median and range. They were compared within groups across time using the Friedman repeated-measures analysis of variance. Between the groups, comparisons were made using the Mann-Whitney U test. A p value <0.05 was considered statistically significant.

RESULTS

The demographic data are summarized in Table 1. There were no significant differences in terms of age, height, body weight, body surface area, sex, diabetes mellitus, hypertension, ejection fraction, and smoking history. No differences between the groups were observed with respect to the number of bypasses, cross-clamping (81.95 ± 23.05 and 70.57 ± 25.85 min in Group P and Group D, respectively) and CPB (133.95 ± 34.49 and 120.84 ± 35.92 min in Group P and Group D, respectively) time, inotrope usage, time on ventilator, and length of ICU stay. There was only a significant difference in terms of surgery time ($p = 0.005$) (Table 2).

There were no statistically significant differences between the groups with respect to HR, SAP, CVP, and CI values. MPAP values were lower in Group D than in Group P at 48 hours after CPB ($p = 0.02$). In Group D, lower MPAP values were recorded at the 2nd hour, 24th hour, and 48th hour after CPB than before infusion MPAP value ($p < 0.05$). In Group P, higher CI value was seen only at the 48th h after CPB than before infusion value, whereas in Group D, higher CI values were seen at the 24th hour (3.48 ± 0.8 L/min/m^2) and 48th hour (3.59 ± 0.76 L/min/m^2) after CPB than before infusion value (2.96 ± 0.84 L/min/m^2; $p < 0.05$) (Table 3). CK-MB, cTnT, and NT-proBNP values were higher in both the groups in the periods after CPB ($p < 0.05$). CK-MB and cTnT values peaked at the 2nd hour after CPB in both the groups. NT-proBNP values peaked at the 24th hour (4.62 ng/mL, as median) after CPB in Group D. No significant differences were observed between the groups in CK-MB, cTnT, and NT-proBNP values for all measurement intervals (Figs 1-3, respectively).

DISCUSSION

In this study, reversible increases in the serum CK-MB, cTnT, and NT-proBNP concentrations starting with CPB were observed in both the groups. Myocardial damage during CPB was not reduced by administration of a 0.5 μg/kg/10 min loading dose and a 0.5 μg/kg/h infusion dose of

Table 1. Demographic Data

	Placebo Group (n = 20)	Dexmedetomidine Group (n = 18)	p Value
Age (y)	63.60 ± 8.33	60.36 ± 11.12	0.31
Height (cm)	166.55 ± 6.44	166.31 ± 7.76	0.91
Weight (kg)	75.40 ± 11.82	77.52 ± 13.73	0.50
Body surface area (m^2)	1.81 ± 0.15	1.86 ± 0.17	0.43
Sex (male/female), n	14/6	13/5	0.81
Diabetes, n (%)	7 (35)	7 (38.9)	0.83
Hypertension, n (%)	13 (65)	12 (66.7)	0.83
Ejection fraction (%)	55 ± 8.93	55.52 ± 8.98	0.85
Smoker, n (%)	6 (30)	5 (27.8)	0.43

NOTE. Values are mean ± SD or number of patients (%). There were no significant differences between the groups.

Table 2. Intraoperative and Postoperative Data

	Placebo Group (n = 20)	Dexmedetomidine Group (n = 18)	p Value
Surgery time (m)	329.50 ± 47.20	**282.94 ± 49.94***	**0.005**
No. of bypasses (n)	3.35 ± 0.81	3.15 ± 0.95	0.50
LIMA (n)	16	15	1.0
Cross-clamp time (m)	81.95 ± 23.05	70.57 ± 25.85	0.15
CPB time (m)	133.95 ± 34.49	120.84 ± 35.92	0.25
Inotropes (n)			
Dopamine	5	5	0.78
Dopamine + Dobutamine	3	4	0.69
Ephedrine	1	2	0.34
Time on ventilator (h)	9.20 ± 3.26	7.96 ± 2.70	0.21
Length of ICU stay (h)	83.05 ± 15.86	67.23 ± 8.10	0.36

NOTE. Values are mean ± SD or number of patients.
Abbreviations: LIMA, left internal mammary artery; CPB, cardiopulmonary bypass; ICU, intensive care unit.
*$p < 0.05$ between the groups.

dexmedetomidine. However, higher CI values were seen earlier in Group D than in Group P. Furthermore, MPAP tended to be lower in Group D than in Group P.

Okada et al studied an isolated rat heart model to determine the myocardial effect of dexmedetomidine on left ventricular function, coronary flow, and infarct size. They reported that the administration of dexmedetomidine before ischemia exerted a cardioprotective effect against ischemia/reperfusion injury.[5] This effect occurred via the α-2 adrenergic stimulation caused by dexmedetomidine. To the best of the authors' knowledge, there is no clinical trial investigating whether or not dexmedetomidine has a cardioprotective effect. As a first clinical study, Jalonen et al used dexmedetomidine as an anesthetic adjunct in CABG surgery and they reported that dexmedetomidine decreased the plasma norepinephrine level and attenuated hyperdynamic responses to anesthesia and surgery but increased the propensity toward hypotension.[7] They used a higher loading dose of dexmedetomidine than that used in the present study. Their dexmedetomidine doses were 1.5 μg/kg/30 min as the loading and 0.42 μg/kg/h as the maintenance dose. A lower loading dose was chosen because of bradycardia and the hypotensive side effects of dexmedetomidine. There were no differences between the groups in terms of bradycardia and hypotension.

In the present study, serum cardiac isoenzymes (CK-MB and cTnT) were used for assessing myocardial damage. In addition, serum NT-proBNP levels were measured for monitoring myocardial stretch as a result of volume overload. Although cTnT values in particular were lower in Group D at periods 2, 24, and 48 hours after CPB, the differences were not statistically significant.

In the literature, there were only a few clinical studies investigating the myocardial protective effect of nonvolatile anesthetic agents during CABG with CPB in humans.[8-10] Xia et al reported that a large dose of propofol during CPB attenuated myocardial damage as compared with isoflurane or small-dose propofol anesthesia.[8] They thought that this effect was achieved through the antioxidant properties of propofol. In their study, CK-MB, troponin T, and troponin I values were measured preoperatively and at 8 hours, 24 hours, and 48 hours after CPB. These values were significantly lower in the large-

Table 3. Hemodynamic Data

	Before Induction	Before Infusion	After Infusion	2 h After CPB	24 h After CPB	48 h After CPB
HR (beats/min)						
Placebo	83 ± 15	71 ± 19*	76 ± 16	81 ± 14	96 ± 11*	98 ± 16*
Dexmedetomidine	84 ± 16	79 ± 16	76 ± 12*	82 ± 18	99 ± 17*	100 ± 14*
SAP (mmHg)						
Placebo	153 ± 25	127 ± 21	124 ± 30	105 ± 18	119 ± 14	125 ± 13
Dexmedetomidine	155 ± 20	131 ± 31	106 ± 24	105 ± 18	126 ± 13	126 ± 16
CVP (mmHg)						
Placebo		10 ± 2	9 ± 3	7 ± 3	7 ± 2	8 ± 2
Dexmedetomidine		12 ± 3	10 ± 3	7 ± 2	7 ± 3	7 ± 3
MPAP (mmHg)						
Placebo		20 ± 3	17 ± 5	19 ± 4	17 ± 4	21 ± 4
Dexmedetomidine		22 ± 3	19 ± 5	16 ± 5†	17 ± 4†	17 ± 4†,‡
CI (L/min/m2)						
Placebo		2.87 ± 0.6	2.53 ± 0.73	2.73 ± 0.72	3.22 ± 0.75	3.39 ± 0.66†
Dexmedetomidine		2.96 ± 0.84	2.58 ± 1.14	2.71 ± 0.53	3.48 ± 0.8†	3.59 ± 0.76†

*$p < 0.05$ compared with before induction value.
†$p < 0.05$ compared with before infusion value.
‡$p = 0.02$ between the groups.

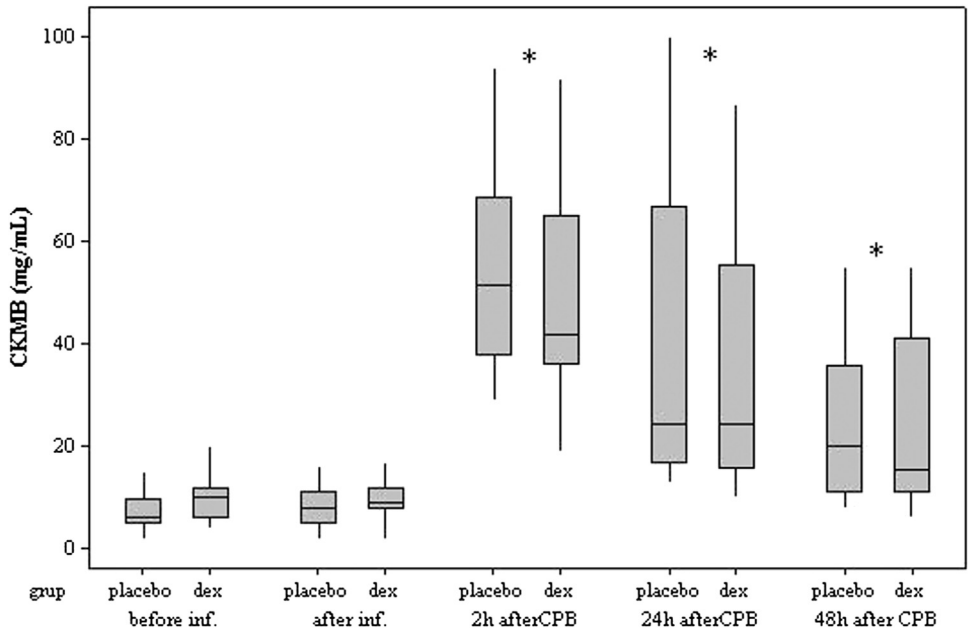

Fig 1. Changes in the CK-MB concentrations of the 2 groups before placebo or dexmedetomidine infusion (before inf.), after placebo or dexmedetomidine infusion (after inf.), 2, 24, and 48 hours after CPB; $^{*}p < 0.05$ compared with before infusion and after infusion values in 2 groups. Values are expressed as median with 25th and 75th percentiles.

dose propofol group compared with the small-dose propofol and isoflurane group. Murphy et al studied the effect of the choice of intraoperative opioid (morphine *v* fentanyl) on the recovery of myocardial function after CABG surgery.[9] They evaluated all echocardiographic data and blood samples for biochemical markers in 46 patients. They observed that the myocardial performance index values were improved significantly 15 minutes post-CPB and at the end of the surgery in the morphine group. Inversely, myocardial performance index significantly worsened in the fentanyl group in the same time periods. cTn I concentrations were increased from baseline values at 24 and 48 hours but were not different significantly between groups. Similarly, in the 2 groups, marked increase was observed at 24 and 48 hours in BNP measurements, but there

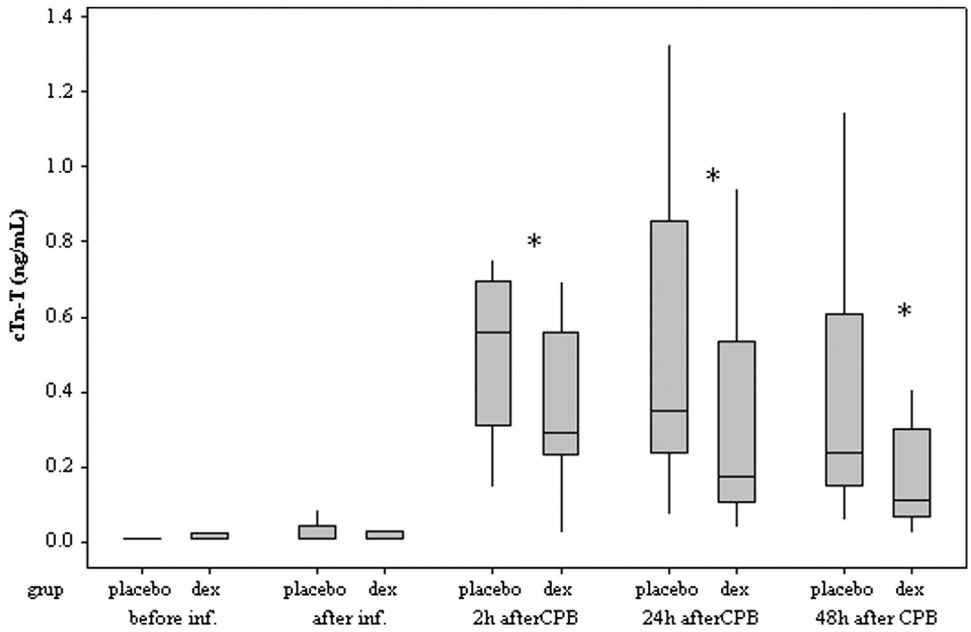

Fig 2. Changes in the cTnT concentrations of the 2 groups before placebo or dexmedetomidine infusion (before inf.), after placebo or dexmedetomidine infusion (after inf.), 2, 24, and 48 hours after CPB; $^{*}p < 0.05$ compared with before infusion and after infusion values in 2 groups. Values are expressed as median with 25th and 75th percentiles.

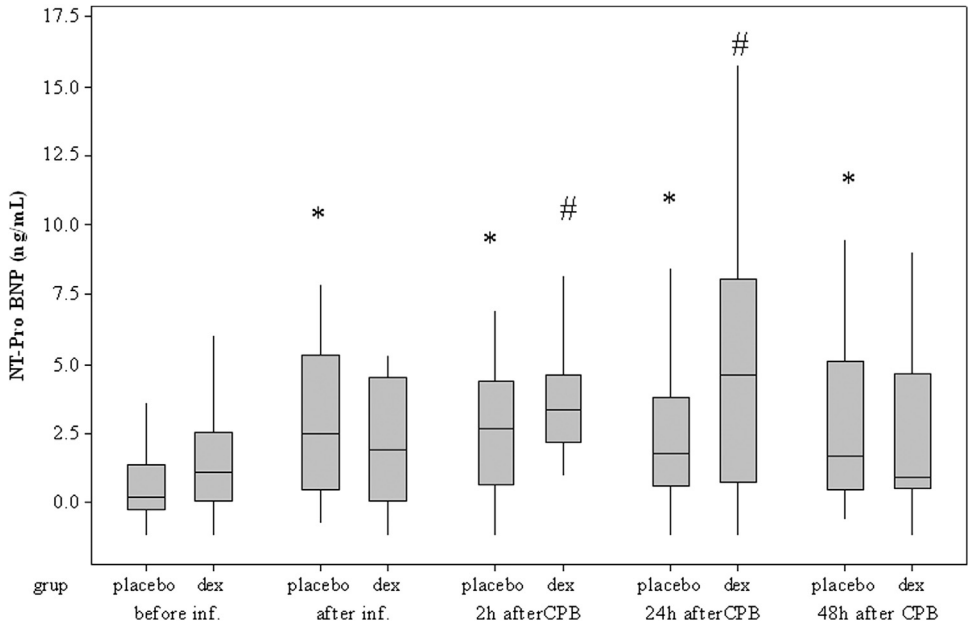

Fig 3. Changes in the NT-proBNP concentrations of the 2 groups before placebo or dexmedetomidine infusion (before inf.), after placebo or dexmedetomidine infusion (after inf.), 2, 24, and 48 hours after CPB; $^{*}p < 0.05$ compared with before infusion value in Group P; $^{\#}p < 0.05$ compared with before infusion, after infusion, and 48 hours after CPB values in Group D. Values are expressed as median with 25th and 75th percentiles.

were no significant differences between the groups. In the present study, the same result as that in the study of Murphy et al was recorded in terms of biochemical markers. CK-MB, cTnT, and NT-proBNP values were higher in both the groups at 2, 24, and 48 hours after CPB. Conversely, no significant differences were observed between the groups in CK-MB, cTnT, and NT-proBNP values. Malagon et al investigated the relationship between midazolam (0.2 mg/kg/h), propofol (6-8 mg/kg/h), and sevoflurane (end-tidal concentration of 2%-3%) throughout the surgery as the main anesthetic agent during pediatric cardiac surgery and postoperative cTnT production. They showed that postoperative production of cTnT in pediatric patients undergoing CPB is similar with midazolam, propofol, or sevoflurane anesthesia.[10]

In the present study, plasma NT-proBNP concentrations also were evaluated during and after surgery. There were no statistically significant differences between the 2 groups in terms of NT-proBNP concentrations. However, NT-proBNP levels gradually increased after the CPB period in both the groups and peaked at the 24th hour in Group D (4.62 ng/mL as median). In Group P, such a peak was not observed in plasma NT-proBNP concentrations. Berendes et al[11] showed that BNP concentrations peaked at 24 hours after surgery. Crescenzi et al[12] studied the postoperative plasma NT-proBNP levels and their correlation with major clinical endpoints, such as mortality and length of ICU stay after CABG surgery. They reported that NT-proBNP concentrations (median) increased from 270 pg/mL preoperatively to 1,664 pg/mL on postoperative day 1 and all postoperative values were higher than the preoperative ones. In this study, all the postoperative NT-proBNP concentrations also were higher than the preoperative ones. They concluded that postoperative NT-proBNP levels were associated with in-hospital mortality and prolonged ICU stay after CABG surgery.

In this study, there was no significant difference in terms of MPAP between the groups, but MPAP tended to be lower in Group D. But et al[13] studied the effect of preoperative dexmedetomidine infusion on hemodynamics in patients with pulmonary hypertension undergoing mitral valve replacement surgery. In their study, the authors used loading and infusion doses of 1 μg/kg and 0.4 μg/kg/h of dexmedetomidine, respectively. Drug infusion was stopped when the surgery began. The authors concluded that preoperative dexmedetomidine effectively reduced mean arterial pressure, MPAP, and pulmonary capillary wedge pressure when compared with the placebo group in patients with pulmonary hypertension undergoing mitral valve replacement surgery. Lazol et al[14] studied the effect of dexmedetomidine on pulmonary artery pressure after congenital heart disease surgeries in children. This prospective observational pilot study consisted of 22 patients. Measurements of the pulmonary artery systolic pressure in these patients were assessed echocardiographically. They reported that dexmedetomidine might be associated with a decrease in pulmonary artery systolic pressure in this patient population. There was no control group in their study, and they had no direct cardiac output measurements. The present study had a control group and direct cardiac output measurements. Different volume status and inotropic support usage in patients may influence MPAP. However, there were no differences between the groups in the use of inotropic support and CVP in the study. Nonetheless, dexmedetomidine was used at low doses in the present study. If this study had a moderate dose of dexmedetomidine and a large

study group, there could be significant results in favor of dexmedetomidine. High-dose dexmedetomidine resulted in increases in pulmonary and systemic vascular resistances and a decrease in cardiac output in prior studies.[15,16]

In the present study, surgery time was shorter in the group receiving dexmedetomidine. However, there was no difference between the groups in terms of duration of CPB and cross-clamp. For this reason, this difference was thought to be noncardiac in origin. This group might have had a shorter duration of hemostasis. However, this topic is beyond the scope of this work. Nonetheless, Durmus et al[17] reported that using dexmedetomidine intraoperatively reduced bleeding during middle ear surgery and septorhinoplasty surgeries. Ayoglu et al[18] also showed that dexmedetomidine was helpful as an adjuvant agent in improving visibility of the operative field and in reducing bleeding and bleeding scores in septoplasty surgeries.

The limitations of this pilot study were it was a small-scale clinical trial, only 1 dose of dexmedetomidine was used, and there were no dose-response data. Another limitation of the study was the lack of effort to keep the end-tidal sevoflurane concentration constant. The differences between groups might have been minimized by using unsteady end-tidal sevoflurane concentration.

In conclusion, the administration of low-dose dexmedetomidine, 0.5 μg/kg/10 min of loading and 0.5 μg/kg/h of infusion dose, did not reduce myocardial damage during CABG with CPB. However, MPAP tended to be lower in the dexmedetomidine group. More studies with larger numbers of patients and using moderate doses of dexmedetomidine are needed to confirm the effect of dexmedetomidine.

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