The Effects of Dexmedetomidine on Myocardial Function Assessed by Tissue Doppler Echocardiography During General Anesthesia in Patients With Diastolic Dysfunction

A CONSORT-Prospective, Randomized, Controlled Trial

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Abstract: Dexmedetomidine is a commonly used sedative and adjuvant agent to general anesthesia. The present was designed to evaluate the effects of dexmedetomidine on myocardial function by using tissue Doppler echocardiography during general anesthesia in patients with diastolic dysfunction.

Forty patients undergoing orthostatic surgery with ejection fraction preserved diastolic dysfunction grade 2 or 3 were randomly allocated to the Control and Dex group (n = 20, each). In the Dex group, dexmedetomidine was given as an initial loading dose of 1.0 μg/kg over 10 minutes followed by a maintenance dose of 0.5 μg/kg/h. The ratio of peak early diastolic transmirtal or transtricuspid inflow velocity to early diastolic mitral or tricuspid annular velocity (LV or RV E/e0) and left or right ventricular myocardial performance index (LV or RV MPI) were measured at before and after the administration dexmedetomidine or saline.

The Dex group showed significant decrease of heart rate (P = 0.038), and increase of mean blood pressure (P < 0.001), LV E/e0 (P = 0.025), and LV MPI (P < 0.001) compared to those of the Control group on a linear mixed model analysis. Also, the Dex group showed significant increase of RV E/e0 (P < 0.001) and RV MPI (P = 0.028) compared to those of the Control group.

Intraoperative dexmedetomidine administration during general anesthesia was appeared to deteriorate biventricular function in patients with diastolic dysfunction. We suggest careful consideration and a need for reducing dosage when administering dexmedetomidine in patients with diastolic dysfunction.

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Abbreviations: BIS = bispectral index, Dex = dexmedetomidine group, EF = ejection fraction, FAC = fractional area change, HR =

INTRODUCTION

Dexmedetomidine is a highly selective α2-adrenoreceptor agonist that has gained popularity in the intensive care unit, cardiovascular intervention and endoscopic procedures, and as an adjuvant to general anesthesia for its sedative and analgesic effects. Although there have been studies suggesting the use of perioperative dexmedetomidine in cardiac surgery improved postoperative morbidity and mortality,5,6 there is also conflict in literature that have reported adverse cardiovascular effects of dexmedetomidine including hypotension or hypertension, bradycardia, and even cardiac arrest.5,6 Even with the amounting evidence that dexmedetomidine has critical cardiovascular effects, few studies have investigated the direct effects of dexmedetomidine on cardiac function. Although our previous study7 presented evidence that dexmedetomidine administration had minimal effects on cardiac function in young healthy patients, there are no current studies assessing the effects of dexmedetomidine administration on biventricular function in patients with cardiac dysfunction. In a recent study,8 64.1% of patients over 65 years were assessed with diastolic dysfunction. Regardless, the importance of diastolic dysfunction has been underestimated in comparison to systolic dysfunction. Because preoperative diastolic dysfunction is highly affiliated with overall postoperative prognosis,9 mortality after acute coronary syndrome,10 and adverse postoperative outcome of patients with myocardial infarction,11 undermining diastolic dysfunction may be a critical mistake. As dexmedetomidine becomes a more ubiquitous agent in the clinical field, we believe a true evaluation of dexmedetomidine on cardiac function in patients with cardiac dysfunction is critically essential.

Tissue Doppler indices are more reliable in estimating cardiac function than 2-dimensional or conventional Doppler echocardiography in patients with preexisting left ventricle (LV) relaxation impairment. The ratio (E/e0) of peak early diastolic transvalvular inflow velocity (E) to early diastolic valvular annular velocity (e0) is a valuable tool in diagnosing diastolic dysfunction independent of preload, in patients with preserved LV ejection fraction (EF) and impaired LV relaxation.12 Tissue Doppler imaging derived myocardial performance index (MPI), estimates combined systolic and diastolic performance to
evaluate global cardiac function. Its most prominent use is to assess diastolic function. In contrast to Doppler-assessed transvalvular blood flow, tissue Doppler imaging derived MPI is relatively independent of heart rate (HR) and loading conditions.

In this randomized, double-blind, and placebo-controlled trial, we investigated the effects of dexmedetomidine on myocardial function in patients with diastolic dysfunction by using tissue Doppler imaging derived indices including MPI and E/e' during general anesthesia.

METHODS

Study Population

This study received approval from the institutional review board of Severance Hospital, Yonsei University Health System, Seoul, South Korea (Ref. 4-2015-0284) on May 2015 and was registered at Clinical Trials.gov (NCT02490072). All participants provided written informed consent before participation. Patients undergoing orthopedic surgery in supine position were included. The inclusion criteria were American Society of Anesthesiologists physical status of class II or III, over 40 years of age, and patients with sinus rhythm lateral mitral valvular (MV) e' velocity <10 cm/s or septal MV e' velocity <8 cm/s and averaged LV E/e' ≥9 on preoperative transthoracic echocardiographic evaluation. Averaged LV E/e' = 9–12 was defined as diastolic dysfunction grade 2, and LV E/e' ≥13 was defined as diastolic dysfunction grade 3. The patients with LV systolic function preserved (LV EF ≥50%) diastolic dysfunction were enrolled in this study. For patients without preoperative echocardiographic examination, we performed a transthoracic echocardiographic prior to surgery. The patients with lateral MV e' velocity <10 cm/s or septal MV e' velocity <8 cm/s were enrolled in our study (Figure 1). The exclusion criteria were the patients with severe functional liver or kidney disease, diagnosed heart failure, regional wall motion abnormality of LV, history of arrhythmia or treatment with antiarrhythmic drugs, bradycardia (HR <45 beats/min) patients provided written informed consent before participation. Patients undergoing orthopedic surgery in supine position were included. The inclusion criteria were American Society of Anesthesiologists physical status of class II or III, over 40 years of age, and patients with sinus rhythm lateral mitral valvular (MV) e' velocity <10 cm/s or septal MV e' velocity <8 cm/s and averaged LV E/e' ≥9 on preoperative transthoracic echocardiographic evaluation. Averaged LV E/e' = 9–12 was defined as diastolic dysfunction grade 2, and LV E/e' ≥13 was defined as diastolic dysfunction grade 3. The patients with LV systolic function preserved (LV EF ≥50%) diastolic dysfunction were enrolled in this study. For patients without preoperative echocardiographic examination, we performed a transthoracic echocardiographic prior to surgery. The patients with lateral MV e' velocity <10 cm/s or septal MV e' velocity <8 cm/s were enrolled in our study (Figure 1). The exclusion criteria were the patients with severe functional liver or kidney disease, diagnosed heart failure, regional wall motion abnormality of LV, history of arrhythmia or treatment with antiarrhythmic drugs, bradycardia (HR <45 beats/min) or atrioventricular block, and severe chronic obstructive lung disease. Enrolled patients were randomly allocated to the Control or dexmedetomidine group (Dex group) using a randomized sequence

![FIGURE 1. Algorithm used for diastolic dysfunction grading. LV = left ventricle, MV e' = peak early diastolic mitral annulus velocity, MV E = peak early diastolic transmural inflow velocity.](image)

Anesthetic Management

After each patient arrived to the operating room, normal saline 5 mL/kg was administrated to replace the fluid deficit. Patients were not premedicated. Blood pressure, oxygen saturation, electrocardiography, and bispectral index (BIS; A-200 bispectral index monitor, Aspect Medical System Inc., Newton, MA) were monitored noninvasively. Anesthesia was induced by propofol and remifentanil through a target-controlled infusion system (Orchestra; Base Primera, Fresenius Vial, Brezins, France). Following the loss of consciousness, rocuronium 0.8 mg/kg was administered to facilitate tracheal intubation. During the surgery, the dose of propofol and remifentanil were adjusted to maintain BIS range between 40 and 50 in both groups. The effect site concentration and total dose of each administered propofol and remifentanil were recorded. Hemodynamic instability was treated as follows: atropine was administered when the HR decreased to <45 beats/min, while β1-adrenergic antagonist was administered when HR increased to ≥120 beats/min. When mean blood pressure (MBP) decreased to below 20% of baseline value, phenylephrine (50 μg) was administered. When MBP increased up to 120 mmHg, calcium channel blocker (500 μg) was administered. In cases of vasoactive drug administration, measurement was not performed within 5 minutes to minimize its influence on the echocardiographic evaluation.

Echocardiographic Measurements

The blinded anesthesiologist inserted a 4–7 MHz multiplane transoesophageal echocardiography (TEE) probe (6TC; GE, Vingmed Ultrasound AS, Horten, Norway) via the oesophagus and connected it to a cardiac ultrasound system (Vivid E9; GE, Vingmed Ultrasound AS, Horten, Norway). The echocardiographic examination was performed by the same anesthesiologist. To assess LV and right ventricle (RV) diastolic function, pulsed-wave Doppler ultrasoundography was used to measure transmitral and tricuspid fluid flow at mid-oesophageal 4-chamber views. The peak early diastolic transmural inflow velocity (MV E), peak early diastolic (MV e'), and systolic (MV s') mitral annular velocity were measured at the lateral and septal annular by tissue Doppler imaging. Average LV E/e' was obtained by averaging the total of lateral and septal LV E/e'. Peak early diastolic (TV e') and systolic (TV s') tricuspid annular velocity were also measured at lateral tricuspid annular. The ratio (RV E/e') of peak early diastolic
output was calculated: Cardiac output output was assessed by stroke volume using pulsed-wave 

dine or saline. 20, 40, and 60 minutes after the administration dexmedetomi-
eamination were measured after the patient became hemo-
tration of propofol and remifentanil, MBP, HR, BIS, and TEE

and their 95% confidence intervals (Table 1). The concen-
readings divided by their mean and expressed as a percentage

calculated as the mean absolute differences between the 2

gator and once to a 2nd investigator. The variabilities were

entered twice to a 1st investigator. The variabilities were

determined by 1 anesthesiologist who was blinded to the group assignments. To determine intra- and

observer variability, a random sample of 25% of all echocardiographic data was submitted twice to a 1st investi-
gator and once to a 2nd investigator. The variabilities were calculated as the mean absolute differences between the 2

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Statistical Analysis

For justification of numbers, the primary outcome measure

was defined as the LV E/e′. A difference of 3.0 between the Control and Dex group was taken as clinically significant in the preliminary results for the 1st 10 patients. Previously, our studies7 have also found a standard deviation (SD) of 3.2 for

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TABLE 1. Inter- and Intra-observer Variability

|               | Intra-observer Variability | Inter-observer Variability |
|---------------|----------------------------|----------------------------|
| MV e′         | 1.8 (1.2–2.5)              | 2.1 (1.1–2.8)              |
| EF            | 6.4 (2.6–7.8)              | 6.0 (3.4–8.2)              |
| LV FAC        | 2.3 (1.7–2.9)              | 2.2 (1.4–2.8)              |
| LV MPI        | 1.3 (0.7–2.3)              | 1.5 (0.8–2.2)              |
| MV s′         | 1.7 (1.3–2.4)              | 2.3 (1.4–3.1)              |
| TV e′         | 2.0 (1.2–2.8)              | 2.6 (1.8–3.5)              |
| TAPSE         | 6.0 (3.8–8.2)              | 6.1 (4.6–8.6)              |
| TV s′         | 2.0 (1.4–2.7)              | 2.2 (1.3–2.9)              |
| RV MPI        | 1.5 (1.0–2.3)              | 1.7 (1.2–2.5)              |

Values are expressed as percentages (95% confidence intervals). EF = ejection fraction, FAC = fractional area change, LV MPI = left ventricular myocardial performance index, MV e′ = peak early diastolic mitral annular velocity, MV s′ = peak systolic mitral annular velocity, RV MPI = right ventricular myocardial performance index, TAPSE = tricuspid annular plane systolic excursion, TV e′ = peak early diastolic tricuspid annular velocity, TV s′ = peak systolic tricuspid annular velocity.

DISCUSSION

In this study, the administration of dexametomidine to the patients with preexisting diastolic dysfunction resulted in a decrease of HR and increase of MBP, MPI, and E/e′ during general anesthesia. Therefore, dexametomidine administration during general anesthesia deteriorated biventricular function in patients with underlying diastolic dysfunction.
E/e' is a relatively load-independent indicator used to estimate LV filling pressure in patients with EF preserved diastolic dysfunction. MPI is a comprehensive way to evaluate systolic and diastolic cardiac function within 1 cardiac cycle. In our results, the baseline MPI was prolonged, and dexmedetomidine further augmented biventricular MPI prolongation. Also, LV EF, and MV s' significantly decreased in the Dex group. In patients with EF preserved diastolic dysfunction, dexmedetomidine significantly depressed systolic function as well as diastolic function. Accordingly, when administering dexmedetomidine to patients with diastolic dysfunction, we propose the need to adjust drug dosage and further study is needed to evaluate the relationship between decreased dosage of dexmedetomidine and cardiac function. In our previous study of healthy young patients without cardiac dysfunction, transient blood pressure elevation occurred only directly after dose loading of dexmedetomidine. Moreover, the transient increase of blood pressure after loading dexmedetomidine did not affect biventricular diastolic and systolic function. In comparison, in our current study on patients with diastolic dysfunction, the increase of blood pressure persisted throughout the entire dexmedetomidine administration. With this sort of hemodynamic change, dexmedetomidine could induce a rise of LV afterload and have effects on LV relaxation and filling in patients with diastolic dysfunction, which is evidenced by the decrease of e' and increase of E/e'. These results can be explained by the physiology of diastolic dysfunction. In a diastolic impaired heart, the increased afterload delays onset of relaxation and increases isovolumic relaxation time. Although a normal heart is able to react to elevated afterload without change in LV end-systolic volume, a heart with decreased afterload reservoir shows marked deterioration of LV relaxation in response to even a slight increase of afterload, thus resulting in an increase of LV systolic and diastolic volume.

Interestingly, this study revealed that most patients with LV diastolic dysfunction also accompanied RV systolic and diastolic dysfunction. In patients with LV diastolic dysfunction, decreased TV e' (7.1 ± 1.3 at baseline; normal value, 14.5 ± 3.5) represents a depressed RV diastolic function. Because RV is a thin-walled and retrosternal structure, it is difficult to completely visualize RV in a single echocardiographic view. The parameters derived from tissue Doppler imaging are valuable in estimating RV function, especially RV MPI can be considered to have powerful prognostic value. RV diastolic dysfunction is due to ventricular interdependence as the geometric shape of 1 ventricle directly affects the contralateral ventricle through the septum. Elevated LV end-diastolic pressure in patients with chronic LV diastolic dysfunction causes pulmonary venous hypertension and the raised pulmonary vascular resistance causes pulmonary artery hypertension. Pulmonary artery hypertension evokes a rise in RV afterload and subsequently results in RV systolic failure. Unfortunately, our study was clinically based, thus we could not evaluate pulmonary artery pressure. Therefore, we were unable to confirm this systematic mechanism of impaired RV function after dexmedetomidine administration.
TABLE 2. Baseline Demographic and Clinical Characteristics

|                          | Dex (n = 20)          | Control (n = 20) | P     |
|--------------------------|-----------------------|-----------------|-------|
| Age, y                   | 70.5 ± 6.0            | 71.0 ± 5.5      | 0.684 |
| Sex (male/female)        | 9 (45.0)/11 (55.0)    | 9 (45.0)/11 (55.0) | > 0.99|
| Body mass index, kg/m²   | 23.5 ± 3.4            | 24.4 ± 2.7      | 0.736 |
| ASA classification II/III| 11 (55.0)/9 (45.0)    | 10 (50.0)/10 (50.0) | 0.751 |
| Grade of diastolic dysfunction 2/3 | 10 (50.0)/10 (50.0)    | 10 (50.0)/10 (50.0) | > 0.99 |
| Hypertension, n          | 11                    | 8               | 0.34  |
| RAAS inhibitor           | 7                     | 6               | 0.73  |
| Calcium channel blocker  | 5                     | 1               | 0.076 |
| β-adrenergic antagonists | 2                     | 0               | 0.147 |
| Furosemide               | 3                     | 2               | 0.632 |
| Diabetes mellitus, n     | 4                     | 2               | 0.375 |

Intraoperative data

|                          | Dex (n = 20)          | Control (n = 20) | P     |
|--------------------------|-----------------------|-----------------|-------|
| Total administered dose of propofol during study, mg | 407.5 ± 68.6⁺       | 508.0 ± 73.0    | < 0.001 |
| Total administered dose of remifentanil during study, µg | 437.5 ± 76.9       | 412.0 ± 115.6   | 0.741 |
| Total administered dose of dexmedetomidine, µg | 97.2 ± 16.1          | -               |       |
| Anesthesia time, minutes | 132.1 ± 22.3          | 129.8 ± 31.4    | 0.082 |
| Operation time, minutes  | 107.9 ± 23.6          | 113.8 ± 41.2    | 0.064 |
| Intake fluid, mL         | 630.4 ± 36.7          | 642.7 ± 40.2    | 0.314 |
| Urine output, mL         | 100.9 ± 22.3          | 97.6 ± 31.9     | 0.216 |
| Estimated blood loss, mL | 44.7 ± 23.6           | 57.2 ± 18.6     | 0.062 |

Type of surgery, n

|                          | Dex (n = 20)          | Control (n = 20) | P     |
|--------------------------|-----------------------|-----------------|-------|
| Total knee replacement    | 4                     | 3               | > 0.99 |
| Total hip replacement     | 6                     | 2               | 0.432 |
| Open or closed reduction and internal fixation of femur | 3               | 5               | 0.695 |
| Open or closed reduction and internal fixation of upper limb | 5               | 6               | > 0.99 |
| Open or closed reduction and internal fixation of lower limb | 2               | 4               | 0.661 |

Data are presented as the mean ± SD, or number (percentage). ASA = American Society of Anesthesiologists, RAAS = renin-angiotensinaldosterone system.
⁺ P < 0.001 compared with Control group.

TABLE 3. Effect Site Concentration of Anesthetics, Hemodynamics, and BIS Score

|                          | Baseline | 20 minutes | 40 minutes | 60 minutes | P_{group×time} |
|--------------------------|----------|------------|------------|------------|----------------|
| Propofol conc., µg/mL    | 3.4 ± 0.7| 2.0 ± 0.3**,**,** | 1.9 ± 0.3**,**,** | 2.0 ± 0.3**,**,** | 0.022 |
| Control                  | 3.5 ± 0.5| 3.2 ± 0.4 | 3.3 ± 0.4 | 3.0 ± 0.3 | 0.785 |
| Remifentanil conc., µg/mL| 2.8 ± 0.9| 3.2 ± 0.7 | 3.2 ± 0.6 | 3.2 ± 0.6 | < 0.001 |
| Control                  | 2.7 ± 0.6| 3.1 ± 1.0 | 3.1 ± 0.7 | 3.0 ± 0.6 | 0.038 |
| MBP, mm Hg               | 78.6 ± 10.6| 93.0 ± 12.3**,**,** | 89.5 ± 12.3**,**,** | 90.0 ± 11.9**,**,** | 0.027 |
| Control                  | 77.2 ± 14.1| 80.4 ± 13.6 | 79.0 ± 7.9 | 77.2 ± 10.0 | 0.027 |
| HR, beats/min            | 75.8 ± 11.5| 61.8 ± 9.1**,**,** | 56.4 ± 10.4**,**,** | 59.7 ± 8.9**,**,** | 0.027 |
| Control                  | 71.8 ± 9.7| 72.2 ± 12.6 | 72.2 ± 11.3 | 71.0 ± 10.4 | 0.027 |
| BIS                      | 44.8 ± 4.6| 41.6 ± 3.9**,**,** | 40.8 ± 2.4**,**,** | 41.4 ± 2.1**,**,** | 0.027 |
| Control                  | 45.6 ± 5.5| 46.1 ± 5.6 | 47.5 ± 7.1 | 45.8 ± 6.7 | 0.027 |

Data are expressed as mean ± SD. 20 = 20 minutes after dexmedetomidine administration, 40 = 40 minutes after dexmedetomidine administration, 60 = 60 minutes after dexmedetomidine administration. Baseline = before administration of dexmedetomidine, BIS = bispectral index, Control = control group, Dex = dexmedetomidine group, HR = heart rate, MBP = mean blood pressure, Propofol conc. = effect site concentration of propofol, Remifentanil conc. = effect site concentration of remifentanil.

⁺⁺⁺ P < 0.05 compared with Control group.
⁺⁺⁺⁺ P < 0.01 compared with Control group.
** P < 0.05 compared with Baseline.
Another interesting finding made through this study was that the Dex group presented more cases of increased MBP requiring nocardipine administration compared to the Control. It is known that the initial transient increase of blood pressure induced by dexmedetomidine mainly involves vasoconstriction due to vascular smooth muscle contraction by the activation of peripheral α_{2B}-adrenoceptors.25 This contraction state of the vascular smooth muscles is regulated by Ca^{2+}-dependent29 or Ca^{2+}-sensitization mechanism.30 The vasodilation induced by dexmedetomidine is due to the action of endothelial nitric oxide synthase (eNOS) within the vascular endothelium, and the vasodilation negates the initial vasoconstriction during dexmedetomidine administration.31 However, in patients with diastolic dysfunction, there is a deficit of NO production or action.32 A recent experimental study revealed a deficit in eNOS is largely related to diastolic dysfunction.33 Thus, while the responses to dexmedetomidine of the endothelial components of the blood vessels are suppressed, the response of Ca^{2+}-dependent peripheral vasoconstriction is sustained during dexmedetomidine administration. In literature, there were conflicts of results in changes of blood pressure due to dexmedetomidine administration. In a meta-analysis of randomized, controlled trials of dexmedetomidine in noncardiac surgery, incidence of perioperative hypotension increased.34 On the contrary, in a large cohort study, dexmedetomidine administration did not inflict significant intraoperative hypotension.35 However, these previous studies did not characterize cardiac function of the participants. Therefore, further studies are needed to evaluate the hemodynamic impact of dexmedetomidine administration on not only patients with diastolic dysfunction but atherosclerosis, diabetes and other diseases correlated with abnormal NO production.

The present study might have several limitations. First, since this study was aimed to evaluate the net cardiac performance during dexmedetomidine administration, we minimally controlled the changes of blood pressure within clinically acceptable ranges. We could not differentiate whether dexmedetomidine directly impaired cardiac function or indirectly depressed cardiac function by increase of afterload according to the increase of blood pressure through this study. Thereby, further study regarding the causal relationship between the 2 issues is needed. Second, in this study, dexmedetomidine was used as an adjuvant agent to general anesthesia. Thus, we cannot generalize the results of this study to assume the same results on cardiac function in the case of dexmedetomidine as the sole sedative. We applied general anesthesia using propofol and remifentanil as the baseline anesthetics and monitored the depth of anesthesia by BIS. There is controversy in the effects of intravenous anesthetics on diastolic dysfunction. Propofol administration has been shown to depress MV e’ and subsequently lead to impaired diastolic function in patients with normal cardiac function.36 However, in patients with preexisting diastolic dysfunction, propofol administration did not further aggravate diastolic function.37 Remifentanil did not impair systolic or diastolic function in healthy patients.38 Further study is needed to evaluate the effects of dexmedetomidine as the sole sedative on cardiac function. Third, we could not calculate pulmonary vascular resistance and pulmonary wedge pressure, since we were unable to insert a pulmonary artery catheter due to ethical issues. Therefore, we could not confirm whether decrease in RV function was due to the changes of pulmonary vascular resistance or to direct RV depressant effects of dexmedetomidine. Further study will be needed to assess the direct effects of dexmedetomidine on pulmonary vasculature.

In conclusion, intraoperative dexmedetomidine administration during general anesthesia induced a sustained increase of blood pressure and a deterioration of biventricular function.
as assessed by tissue Doppler imaging, in patients with diastolic dysfunction. Since dexmedetomidine administration has the possibility of aggravating cardiac function in patients with diastolic dysfunction, we suggest careful consideration of its use or a need for reducing its dosage when administering dexmedetomidine in patients with diastolic dysfunction.

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