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Dexmedetomidine *vs.* propofol sedation reduces the duration of mechanical ventilation after cardiac surgery – a randomized controlled trial

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Abstract. – OBJECTIVE: The aim of our study was to compare the clinical effects of sedation with dexmedetomidine *vs.* propofol in patients undergoing cardiac surgery and analyze their effects on the duration of mechanical ventilation (MV), length of stay in the intensive care unit (ICU), and total hospital stay.

PATIENTS AND METHODS: The study included 120 patients who were randomized in a 1:1 ratio into two groups of 60 patients. The first group was sedated with continuous dexmedetomidine in doses 0.2-0.7 mcg/kg/h. The second group was sedated with propofol in doses 1-2 mg/kg/h.

RESULTS: Patients sedated with dexmedetomidine required 2.2 hours less time on MV ($p<0.001$). There was a positive correlation between the duration of MV and the ICU length of stay ($r=0.368$; $p<0.001$), as well as between the duration of MV and the total hospital stay ($r=0.204$; $p=0.025$). Delirium occurred in the postoperative period in 25% of patients sedated with propofol, while in the dexmedetomidine group it was only 11.7% ($p=0.059$). Patients who developed delirium had a significantly longer duration of MV (12.6±5.4 *vs.* 9.3±2.5 hours, $p=0.010$).

CONCLUSIONS: Postoperative sedation with dexmedetomidine, compared to propofol, reduces the duration of MV, but does not influence the length of stay in the ICU and length of hospitalization after open heart surgery.

Key Words:
Dexmedetomidine, Mechanical ventilation, Cardiac surgery, Postoperative delirium, Sedation.

Introduction

According to the lately developed Early Recovery After Surgery (ERAS) concept[1], one of the main goals of the postoperative strategy is earlier extubation and a shorter duration of mechanical ventilation (MV) with adequate sedation. Patients undergoing open heart surgery should be on MV and sedated from one to six hours after surgery[1,2]. Prolonged MV is associated with numerous complications, eventually leading to longer stay in the intensive care unit (ICU), longer hospital stay, and higher morbidity and mortality. This can cause permanent harm, disadvantages, and loss of independence. Apart from the impeded health and disrupted quality of life of both patients and their families, this leads to higher treatment costs and increases the economic burden[1,3-5].

Sedation during MV enables the patient's synchronization with the ventilator, prevents agitation, reduces hemodynamic instability, and reduces subjective discomfort6. Specific measures are recommended to reduce the duration of sedation and MV, improve outcomes and reduce complications in ICU patients[6,7]. These include the selection of an adequate sedative, daily sedation interruption, and spontaneous breathing trials. Dexmedetomidine and propofol are the most widely used sedatives with distinct pharmacological features that make them suitable for sedation after cardiac surgery[4,8-11].

Dexmedetomidine is a potent α2 agonist with anxiolytic, sedative, analgesic, and sympatholytic effects. Continuous dexmedetomidine infusion causes hypnosis and sedation without respiratory depression, so it can provide earlier postoperative extubation and prevent blood oxygen level variations[1,3,4,12]. Due to the analgesic effect, dexmedetomidine use reduces the need for opioids[13,14].

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The most common side effects[8,9,14] of dexmedetomidine include bradycardia and hypotension, which are attributed to the sympatholytic effect.

Propofol has represented the gold standard for sedation after cardiac surgery for decades, due to the rapid onset of action, fast recovery after discontinuation, and relatively low cost. Nonetheless, its use has been restricted due to common hemodynamic instability and respiratory depression, observed even with regular doses of propofol[3,8,13-16].

The aim of the present study was to compare the clinical effects of sedation with dexmedetomidine *vs.* propofol in patients undergoing cardiac surgery, and analyze their effects on the duration of MV, length of stay in the ICU, and total hospital stay.

Patients and Methods

This was a prospective, randomized, single-blinded, controlled clinical trial. The study was conducted at the Clinic for Cardiovascular Surgery of the Institute of Cardiovascular Diseases Vojvodina between 01 March 2022 and 30 September 2022. The study protocol complied with the Declaration of Helsinki and was approved by the Ethics Committee of the Institute of Cardiovascular Diseases Vojvodina. Informed consent was obtained from all individual participants included in the study. The study was registered at ClinicalTrials.gov (NCT05849597).

Study Population

The study included patients of both sexes scheduled for elective cardiac surgery with the use of cardiopulmonary bypass (CPB) (including coronary artery bypass grafting, valve repair/replacement, and combined). The study included adult patients, older than 18 years, with a left ventricular ejection fraction (LVEF) >40%. Patients with preoperative atrial fibrillation, previous history of interventionally treated arrhythmias, second- and third-degree atrioventricular block, bradycardia with heart rate ≤50/min, pacemaker, renal or hepatic insufficiency, or undergoing emergency procedures were excluded from the study. Patients with a history of serious mental illness, delirium, and severe dementia were excluded as well.

A total of 620 patients were screened, of whom 465 were excluded due to exclusion criteria, and 30 declined to participate in the study. From 125 patients that were selected, 5 patients subsequently requested to be excluded from the study (Figure 1). After inclusion, all the patients filled in an epidemiological questionnaire which included general and demographic data, and information about alcohol and cigarette consumption. Blood laboratory analyses and hemodynamic parameters were recorded for all the patients as well.

Anesthesia and CPB Management

Anesthesia was induced with combination of sufentanil, midazolam, propofol, and rocuronium bromide. After intubation, the lungs were mechanically ventilated with an oxygen/air mixture of 50:50. Anesthesia was maintained with sevoflurane, analgesia with a continuous infusion of sufentanil, and muscle relaxation with intermittent administration of rocuronium bromide. Perioperative and postoperative monitoring included continuous arterial and central venous pressure measurement, electrocardiography (ECG), oxygen saturation (pulse oximetry), body temperature measured in the nasopharynx, and diuresis. Arterial blood gas analyses were performed intermittently. The heart rate and blood pressure were maintained within 25% of the baseline values. Anticoagulation was achieved with heparin to maintain an activated clotting time above 480 s.

Management of CPB included mild hypothermia (32-34°C) and targeted mean perfusion pressure between 60 and 80 mmHg. Myocardial protection was achieved with antegrade intermittent cold (extracellular crystalloid or blood) cardioplegia. Before separation from CPB, patients were rewarmed to 36° to 37°C. After separation from CPB, heparin was neutralized with protamine sulfate, 1 mg/100 U heparin, to achieve an activated clotting time under 130 s. All patients were transferred to the ICU after completing surgery.

Study Design

All 120 patients included in the study were randomized in 1:1 ratio, using computer-generated numbers, into two groups of 60 patients. Upon arrival at the ICU, vital parameters were measured. The first group of patients was sedated with continuous dexmedetomidine infusion in doses 0.2-0.7 mcg/kg/h. Dexmedetomidine infusion was discontinued before weaning from MV and extubation. For patients requiring MV longer than 24 hours, dexmedetomidine infusion was substituted with propofol. The second group of patients was sedated with continuous propofol infusion in doses 1-2 mg/kg/h. Propofol infusion was also discontinued before weaning from MV and extubation.

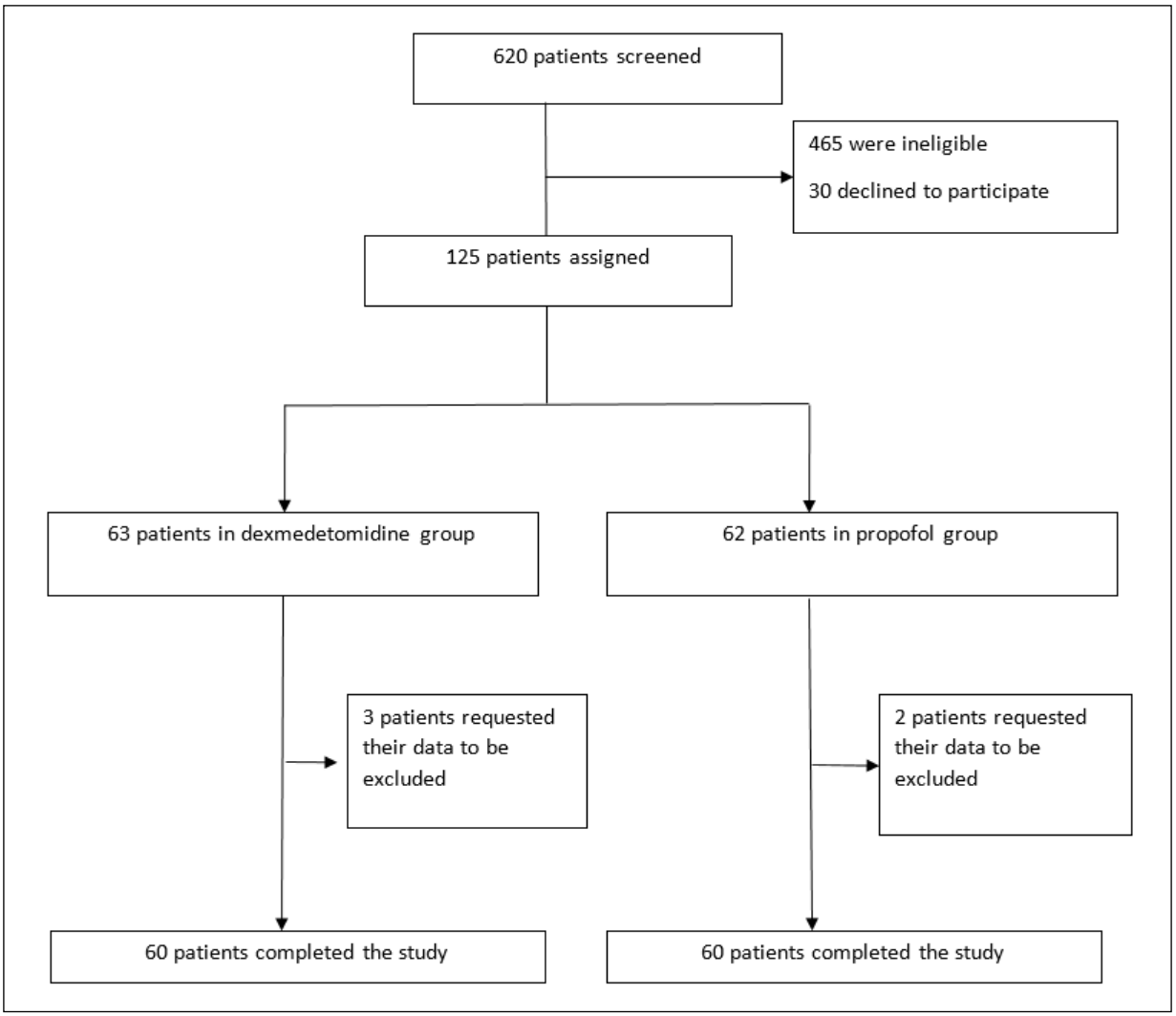

Figure 1. Flow diagram of the study.

The sedation level was assessed using the Richmond Agitation and Sedation Scale (RASS) every two hours. Postoperative analgesia was managed according to the protocol (opioid analgesics, non-steroid anti-inflammatory drugs, paracetamol), with pain level assessment using a visual analog scale (0 - no pain; 10 - unbearable pain).

The following data were observed: age, sex, body mass index (BMI), hemoglobin, heart rate, and LVEF. Among the postoperative parameters, the following were analyzed: duration of MV (in hours), extubation time, ICU and hospital length of stay (in days), postoperative hemoglobin, blood product transfusion rates, occurrence of atrial fibrillation, and assessment of delirium. Assessment of delirium was performed using the confusion assessment method for ICU (CAM-ICU) every 12 hours during five postoperative days.

Statistical Analysis

At the moment of trial design, on the basis of previously published literature, we assumed an average duration (12.8 hours) of MV in patients after open heart surgery with standard sedation. The recruitment of 109 patients with 1:1 randomization was required for a significant reduction in the duration of MV to provide a power of 80% with α=0.05.

Continuous variables were expressed as arithmetic mean ± standard deviation, while categorical variables were expressed as absolute numbers and percentages. Two groups were compared using the independent samples *t*-test or Mann-Whitney U test for continuous variables, and the Chi-square test for categorical variables. Statistical significance for all of the tests was set at the *p*-value <0.05. All the

analyses were performed using SPSS, version 20.0 (IBM Corp., Armonk, NY, USA).

Results

There were no significant differences between dexmedetomidine and propofol group in age and gender distribution and other baseline characteristics (Table I). Both dexmedetomidine and propofol groups had similar preoperative hemoglobin levels (135.8±15.7 *vs.* 131.1±16.1 g/l, p=0.112), heart rate (68.1±10.6 *vs.* 70.6±12.7 bpm, p=0.236), and left ventricular ejection fraction (57.3±6.6 *vs.* 57.7±6.6 %, p=0.780). CPB time (69.2±26.9 *vs.* 76.6±27.5 min; p=0.143) and aortic cross-clamp time (59.9±23.7 *vs.* 66.3±24.4 min; p=0.144) were similar in dexmedetomidine and propofol group.

Patients sedated with dexmedetomidine required 2.2 hours shorter time on MV compared to patients sedated with propofol, which represents a 20% reduction (p<0.001) (Figure 2). There were two patients in the propofol group who required mechanical ventilation beyond 24 hours, while there were no such patients in the dexmedetomidine group.

There was a significant positive correlation between the duration of MV and the ICU length of stay (r=0.368; p<0.001), as well as between the duration of MV and the total hospital length of stay (r=0.204; p=0.025). There was no significant correlation between CPB time (r=0.053; p=0.566) and aortic cross-clamp time (r=0.063; p=0.494) with the duration of MV.

The length of stay in the ICU was 1 day for the majority of patients in both groups, and the total hospital stay was slightly over 7 days for both groups (Table II). There were no patients with fatal outcomes in either group.

Delirium in the postoperative period assessed with the CAM-ICU score was observed in one-quarter of patients sedated with propofol, while patients sedated with dexmedetomidine experienced delirium only half as much. Although the level of significance was slightly beyond the threshold (p=0.059), the difference is indicative. Patients who developed delirium had a significantly longer duration of MV (12.6±5.4 *vs.* 9.3±2.5 hours, p=0.010) (Figure 3).

The two groups had a similar number of patients with new-onset atrial fibrillation, as well as patients requiring red blood cell transfusions in the postoperative period (Table II).

Discussion

The current study is a prospective randomized clinical trial confirming that dexmedetomidine-based postoperative sedation reduces the

Table I. Baseline characteristics of the study population.

	Dexmedetomidine	Propofol	*p*-value
Age, years	63.5±9.8	66.3±11.1	0.153
Males, n (%)	39 (65.0%)	38 (63.3%)	0.849
Body mass index, kg/m^2	27.5±3.9	27.5±4.0	0.927
Smokers, n (%)	20 (33.3%)	18 (30.0%)	0.695
Alcohol consumption, n (%)			
Every day	6 (10.0%)	4 (6.7%)	0.145
Few times per week	8 (13.3%)	4 (6.7%)	
Few times per year	8 (13.3%)	3 (5.0%)	
No alcohol consumption	38 (63.3%)	49 (81.7%)	

Table II. Summary of the study results.

	Dexmedetomidine	Propofol	*p*-value
Duration of MV, hours	8.8±2.0	11.0±4.2	<0.001*
ICU length of stay, days	1.1±0.5	1.2±0.6	0.425
Hospital length of stay, days	7.4±2.0	7.4±2.0	1.000
Postoperative delirium, n (%)	7 (11.7%)	15 (25.0%)	0.059
Postoperative atrial fibrillation, n (%)	16 (26.7%)	20 (33.3%)	0.426
Postoperative transfusion, n (%)	32 (53.3%)	39 (65.0%)	0.194

*The difference is statistically significant.

duration of MV after open heart surgery in compared to sedation with propofol. Our results demonstrated that longer MV is associated with longer stays in the ICU, more postoperative hospital days, and increased incidence of postoperative delirium in patients after cardiac surgery.

MV of the lungs represents an integral part of the postoperative recovery after cardiac surgery. Leaving behind the concept of opioid anesthesia has enabled faster postoperative recovery and earlier weaning from MV and extubation. Today, the majority of patients after cardiac surgery are extubated within 6 hours after surgery. However, 6-20% of patients require prolonged MV[17,18], which is associated with higher morbidity and mortality, increased length of stay in the ICU, longer total hospital stay, worse quality of life and higher economic burden[19,20].

Factors influencing the length of postoperative MV include the patient's preoperative condition, comorbidities, type of cardiac surgery, and type of anesthesia. Nevertheless, recovery after surgery is also influenced by the selection of medications used for postoperative sedation. Sedation based on benzodiazepines was used as a standard globally up until 2018. Due to the extended sedative effects, benzodiazepines were associated with prolonged MV and longer stays in the ICU. Their use was also associated with a higher incidence of postoperative delirium[21].

The 2018 Clinical Practice Guidelines for the Prevention and Management of Pain, Agitation/Sedation, Delirium, Immobility and Sleep Disruption in Adult Patients in the Intensive care unit (ICU)[22] recommended the use of dexmedetomidine and propofol, instead of benzodiazepines, for sedation in mechanically ventilated patients. Both dexmedetomidine and propofol are two short-acting agents that are widely used. Although both of them are first-line agents, there are only few studies in literature directly comparing their effects and outcomes in patients after cardiac surgery.

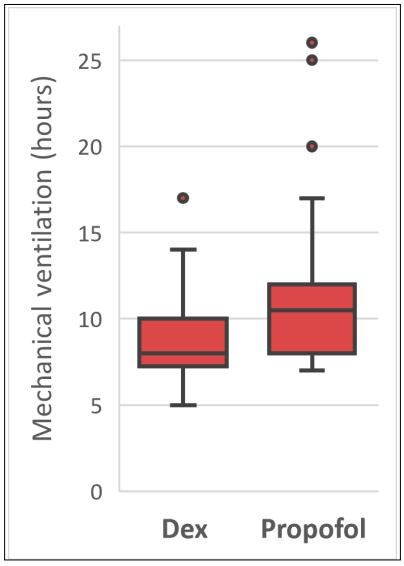

Figure 2. Duration of mechanical ventilation was significantly shorter in patients receiving dexmedetomidine *vs.* propofol (p<0.001). Median values with interquartile ranges are displayed. Dex, dexmedetomidine.

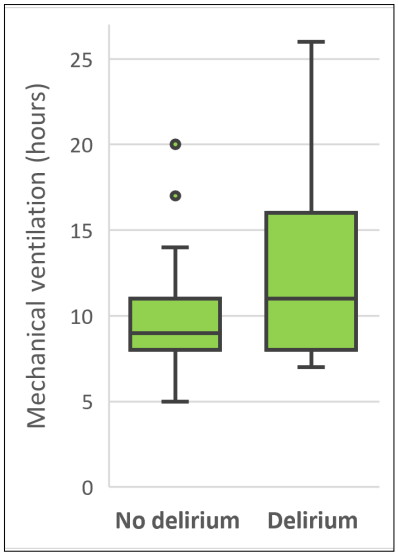

Figure 3. Patients who developed delirium had a significantly longer duration of mechanical ventilation (p=0.010). Median values with interquartile ranges are displayed.

A recently published large retrospective study by Hu et al[20] included 1,388 patients after coronary artery bypass graft surgery. The authors demonstrated that patients sedated with dexmedetomidine had fewer postoperative respiratory complications and a shorter duration of MV compared to propofol, which is similar to what we observed in our study. Hu et al20 also showed shorter stay in the ICU and shorter hospital stay in the group of patients sedated with dexmedetomidine. In contrast, our results did not show a difference in the time spent in the ICU and total hospital stay. This can be explained by the local practice of our hospital to discharge the patients without serious complications of open-heart surgery from the ICU on the first postoperative day. This is important because transferring patients to regular departments enables them better day-night rhythm, noise reduction, earlier mobilization, and the ability to feed themselves and take care of personal hygiene. Most importantly, this provides early contact with family and their inclusion

in the patients' recovery. Furthermore, our local practice is to discharge patients home routinely on the sixth postoperative day after open heart surgery if they are recovering well and their postoperative course is uneventful. This enables them to return to their families, familiar surroundings and daily activities as soon as possible. Evidence clearly demonstrates that all of these methods represent crucial measures for the prevention of postoperative delirium and can reduce postoperative morbidity and mortality[23-28].

Another retrospective study published by Wanat et al[4] also demonstrated a shorter duration of MV in patients sedated with dexmedetomidine after cardiac surgery. The explanation for such results most probably lies in the fact that dexmedetomidine does not cause respiratory depression. Also, due to the analgesic effect of dexmedetomidine, the patients require fewer opioids, which further reduces respiratory depression. Additionally, dexmedetomidine expresses a favorable hemodynamic profile[29]. In contrast, propofol significantly lowers arterial blood pressure through the reduction in cardiac output and vasodilation[15]. Furthermore, dexmedetomidine suppresses pulmonary oxidative stress and inflammatory response, thus reducing the severity of acute lung injury induced by the remote organ ischemia-reperfusion[30,31]. Similar to our results, the aforementioned study by Wanat et al[4] did not demonstrate a difference between dexmedetomidine and propofol sedation in the ICU length stay and total hospital stay.

On the contrary, a randomized controlled trial by Eremenko and Chemova[32], who also compared the effects of dexmedetomidine and propofol for postoperative sedation after cardiac surgery, failed to show the difference in the duration of postoperative MV. Nevertheless, they did demonstrate a significantly shorter length of stay in the ICU in the dexmedetomidine group. Although the dexmedetomidine dose range used for sedation was the same as in our study (0.2-0.7 mcg/kg/h), we generally used minimal doses of dexmedetomidine, which were sufficient for light but adequate sedation without hemodynamic compromise. The wide dose range for dexmedetomidine might have allowed the application of relatively higher doses in the trial by Eremenko and Chemova[32], which might explain the longer MV duration due to potential deeper postoperative sedation.

The results of our study indicate that postoperative delirium develops twice as much with propofol sedation *vs.* dexmedetomidine. The group sedated with propofol had 25% postoperative delirium, compared to only 12% in the dexmedetomidine group, with a statistical difference slightly above the threshold (p=0.059). This is consistent with the literature, as most of the studies have demonstrated a lower incidence of postoperative delirium in patients postoperatively sedated with dexmedetomidine compared to patients sedated with propofol and midazolam[33,34].

A large meta-analysis by Wu et al[35], including 1,387 cardiac surgery patients from 10 different trials, showed that the risk of delirium was lowered by 54% in patients receiving dexmedetomidine, which is consistent with our results. However, there are also large trials[4,36] whose results did not show a reduction in the incidence of postoperative delirium with dexmedetomidine sedation compared to other sedatives. We hypothesize that this could be attributed to hypotension and bradycardia, the most common side effects associated with dexmedetomidine.

Limitations

The primary limitation of our study is that additional medications that were prescribed during sedation were not analyzed, such as antipsychotics or opioids, which may have altered the patients' level of sedation and affected their time on MV and other outcomes.

The secondary limitation is the fact that all patients with a history of serious mental illness, delirium, and severe dementia were excluded from the study, as were patients with hepatic or renal dysfunction and heart failure with LVEF <40%. These patients represent the most vulnerable groups with increased risk for the development of postoperative delirium, hence the exclusion of such individuals might diminish the significance of dexmedetomidine for the prevention of postoperative delirium.

Future scopes should be focused on identifying patients with increased risk of prolonged MV and associated complications and implementing prevention measures in these individuals. Moreover, although the protocols for the prevention of postoperative delirium have been established, clinical trials investigating their use and results in routine clinical practice are still missing. Further investigations are required to validate the efficacy and safety of pharmacological prevention, as well as non-pharmacological measures, such as the open-door policy in the ICU, digital contact with family and friends, and other alternative methods.

Conclusions

Postoperative sedation with dexmedetomidine, compared to propofol, reduces the duration of MV but does not influence the length of stay in the ICU and length of hospitalization after open heart surgery. Postoperative delirium is less common in patients sedated with dexmedetomidine.

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Authors' Contributions
All authors had major roles in the conception, design, planning, and carrying out of the study. All authors contributed to the analysis of the data and the writing and editing of the manuscript.

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Conflict of Interest
The authors declare that they have no conflict of interest to declare.

Data Availability
The datasets generated during and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Ethics Approval
Ethics Committee of the Institute of Cardiovascular Diseases Vojvodina approved the study protocol and gave ethical clearance with number 612-1/1.

Informed Consent
Informed consent was obtained from all individual participants included in the study.

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