

# Effect of Dexmedetomidine on Pulmonary Artery Pressure in Children with Congenital Heart Disease and Pulmonary Hypertension

## Abstract

**Background:** This study was undertaken to determine the effects of dexmedetomidine on pulmonary artery pressure (PAP) in children with congenital heart disease (CHD) and pulmonary hypertension (PH) undergoing cardiac catheterization with and without a planned intervention during monitored anesthetic care using midazolam and ketamine. **Materials and Methods:** Children (<18 years) with known CHD and PH who were scheduled for cardiac catheterization and interventional procedures were included in the study. The procedures were performed under monitored anesthesia. After obtaining baseline PAPs, an intravenous (IV) infusion of dexmedetomidine (1 µg/kg) was given for over 10 min. During infusion, heart rate (HR), blood pressure (BP), respiratory rate (RR), and peripheral arterial oxygen saturation (SPO<sub>2</sub>) were recorded every 2 min until completion of dexmedetomidine infusion, 15 min later, and when the procedure was completed. In addition, pulmonary artery systolic and diastolic pressures, and mean pulmonary artery pressure (MPAP) were recorded and the pulmonary artery systolic pressure (PASP)/systolic blood pressure (BP) ratio was calculated. **Results:** All children tolerated the procedure without adverse events. The HR decreased significantly over time during dexmedetomidine infusion. The changes in systemic systolic BP and PAPs were not significantly different from the baseline value at all points of measurement as was the ratio between the systolic pulmonary artery and systolic systemic BPs. **Conclusions:** Administration of dexmedetomidine in a dose of 1 µg/kg over 10 min did not significantly alter the PAP in children with CHD and PH. There was a decrease in the HR that was not clinically significant. The children tolerated dexmedetomidine without adverse events.

**Keywords:**  $\alpha$ 2-agonist, congenital heart disease, dexmedetomidine, mean pulmonary artery pressure, pulmonary artery systolic pressure, pulmonary hypertension

## Introduction

For many years, cardiac catheterization was the standard workup for obtaining both anatomical and physiological data in children with heart disease. Rubio-Alvarez performed a cardiac interventional procedure in 1954 for the treatment of pulmonary stenosis.<sup>[1]</sup> Consequently, balloon atrial septostomy for palliation of transposition of the great vessels was described by Rashkind and Miller.<sup>[2]</sup> There has been a dramatic increase in the number and scope of transcatheter interventions in the recent two decades. Anesthesiologists have been involved in providing optimal conditions for cardiac catheterization and interventional procedures on neonates, infants, and children with congenital heart disease (CHD). A variety of agents have been used to provide general anesthesia (GA) and sedation, such as

thiopentone, propofol, ketamine, pethidine, barbiturates, and antihistamines.<sup>[3,4]</sup> As early as 1958, Smith *et al.* at the Hospital for Sick Children in Toronto used the “cocktail” (chlorpromazine, pethidine, and promethazine) for sedation.<sup>[5]</sup> This sedative cocktail was used intramuscularly, but it has now been superseded by shorter-acting intravenous (IV) agents for understandable reasons. Many centers worldwide use GA during cardiac catheterization for the care of children, but this is not universal. GA with positive pressure ventilation may alter the intracardiac pressure, systemic/pulmonary vascular resistance, and shunt fraction. Therefore, moderate to deep sedation with analgesia in a spontaneously breathing child may be preferable. Currently, a combination of agents, such as midazolam, ketamine, propofol, and dexmedetomidine, have been used to provide analgesia, anxiolysis, and amnesia during cardiac catheterization and

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interventional procedures in children. Such a combination is often tailor-made to ensure spontaneous unobstructed breathing, acid-base balance, and normothermia with minimal disturbance in pathophysiology. Most techniques adopt methods to provide a quick and smooth recovery.

Dexmedetomidine is a alpha ( $\alpha$ )-2 adrenergic agonist with sedative, anxiolytic, and analgesic properties and without significant central respiratory depression. It is frequently used in pediatric patients because of its efficacy and lack of side effects. This study was undertaken to determine the effects of dexmedetomidine on pulmonary artery pressure (PAP) in children with CHD and pulmonary hypertension (PH), undergoing cardiac catheterization with and without a planned intervention during monitored anesthetic care using midazolam and ketamine.

## Materials and Methods

After obtaining approval from the institutional review board (IRB) and informed consent from the parents, children up to 12 years of age with baseline pulmonary artery systolic pressure (PASP) greater than 30 mmHg and mean pulmonary artery pressure (MPAP) more than 22 mmHg undergoing elective cardiac catheterization with or without a planned interventional procedure were enrolled for the study. Patients with fixed pulmonary artery stenosis and right ventricular outflow tract obstruction, single ventricle and pulmonary stenosis, known arrhythmias, contraindication to monitored anesthesia care using ketamine, and those who refused to give consent were excluded from the study. The PAPs were measured by echocardiography data; hence, the pulmonary vascular resistance data were unavailable. The children were not receiving specific treatment for PH in the form of phosphodiesterase inhibitors, endothelin receptor antagonists, or prostacyclin analogs. The American Society of Anesthesiologists (ASA) guidelines for procedural sedation were followed. A standard protocol for monitored anesthetic care was followed, which was described elsewhere.<sup>[6]</sup> Patients were put on a fast prior to intervention with clear water and fluids allowed up to 2 h, breast-milk up to 4 h, and solid food up to 6 h. The preanesthesia evaluation included chest X-ray, echocardiogram, and hemoglobin and serum creatinine estimation. A warming unit was used for infants and small children. Glycopyrrolate, midazolam, and ketamine in all cases for procedural sedation intravenously were used. After obtaining IV access, glycopyrrolate 4  $\mu$ g/kg, midazolam 0.05 mg/kg, and ketamine 1 mg/kg were administered. The protocol included the use of supplemental ketamine 0.5 mg/kg IV as a bolus, if necessary. The cardiologists placed a pulmonary artery catheter through the femoral vein after infiltration of the groin with 1% lignocaine. After the placement of the pulmonary artery catheter, an infusion of dexmedetomidine at a rate of 1  $\mu$ g/kg was started and infused over 10 min and continued at a rate of 0.3  $\mu$ g/kg until the end of the

cardiac catheterization procedure. Monitoring of the patient included electrocardiography (ECG) for heart rate (HR) and rhythm, peripheral arterial oxygen saturation (SpO<sub>2</sub>), noninvasive BP/direct arterial BP, also respiration was monitored and recorded every 5 min throughout the procedure. The postprocedure care consisted of the following:

- i. Nasal O<sub>2</sub> at 2 LPM
- ii. Fluid administration at 2ml/kg/h
- iii. Monitoring of HR, SpO<sub>2</sub> (continuously), RR, and BP every 5 min
- iv. Bradycardia was defined as HR that was below the normal range for the age, i.e., less than 100 bpm for infants, less than 80 bpm for toddlers, less than 70 bpm for school children, and less than 60 for adolescents. Bradycardia was treated with atropine 20  $\mu$ g/kg
- v. Hypotension was defined as fall in the systolic BP by 20% of the baseline value and treated by volume infusion of 10 ml/kg and boluses of phenylephrine at 5–10  $\mu$ g/kg at the discretion of the anesthesiologist
- vi. Ventricular fibrillation was treated with defibrillation of 2 J/kg and IV adrenaline at a dose of 10  $\mu$ g/kg and chest compression at 100/min, depth  $\geq 1/3^{\text{rd}}$  anteroposterior diameter of the chest.

For the purpose of the study, HR, systolic arterial BP (SABP), diastolic arterial BP (DABP), mean arterial pressure (MAP), pulmonary arterial systolic, mean and diastolic pressures (PASP, MPAP and DPAP), respiratory rate (RR), and peripheral arterial oxygen saturation (SpO<sub>2</sub>) were recorded at the following time periods:

- i. Prior to initiation of the anesthetic care (A)
- ii. After ketamine administration (B)
- iii. Prior to dexmedetomidine (C)
- iv. During dexmedetomidine infusion every 2 min (D1 to D5)
- v. At the end of procedure (E).

Arterial blood gases were estimated during the procedure and recorded. The University of Michigan Sedation Scale (UMSS) score<sup>[7]</sup> was recorded every 30 min after anesthesia till the patient was fully awake (UMSS score was as follows: Score 0 = Awake and alert; Score 1 = Minimally sedated, may appear tired/sleepy, responds to verbal conversation and or sound; Score 2 = Moderately sedated, somnolent/sleeping, easily aroused with light tactile stimulation or simple verbal command—also known as “conscious sedation”; Score 3 = Deep sedation, deep sleep, aroused only with deep or significant physical stimulation; and Score 4 = Unarousable).

## Statistical analysis

Statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS) software, version 16.0 (SPSS Inc., Chicago, IL) and Microsoft Office Excel 2007. For analysis of data among nine different time points, we used the SPSS univariate general linear model

for repeated measures analysis of variance (ANOVA). As per the requirement of repeated measures ANOVA, the minimum sample size of 10+ number of dependent variables (nine times) = 19 was satisfied. For comparison of data between two-time points, student's paired *t*-test with two-tailed distribution, assuming unequal variances, was used. Statistical tests were two-sided and  $P < 0.05$  was considered statistically significant.

## Results

There were 25 children with CHD with PH in this group who underwent monitored anesthetic care for cardiac catheterization/intervention. Their age was  $5.4 \pm 1.1$  (mean  $\pm$  standard deviation [SD]) years and weight was  $13.5 \pm 4.8$  kg (mean  $\pm$  SD). These patients underwent device closure (atrial septal defect,  $n = 4$ ; ventricular septal defect,  $n = 4$ ; patent ductus arteriosus,  $n = 13$ ) or diagnostic cardiac catheterization for complex CHD ( $n = 4$ ). All children tolerated the procedures without adverse events. No patient was required break-through sedation during the study period. The HR decreased significantly from  $111 \pm 21$  bpm prior to dexmedetomidine infusion to  $101.8 \pm 19.4$  bpm at the end of 10 min period of infusion ( $P < 0.01$ ; Figure 1). This decrease in HR was not clinically significant and did not qualify for any treatment. There was a significant increase in systolic blood pressure from  $103 \pm 19.8$  mmHg to  $111 \pm 21.7$  mmHg at 2 min,  $109 \pm 18.9$  mmHg at 4 min and  $108.5 \pm 18.0$  mmHg after the completion of dexmedetomidine infusion but this increase in systolic blood pressure was not clinically significant ( $P = 0.201$ ; Figure 2). There were no significant changes in systemic diastolic, mean arterial pressure and PAPs nor in the ratio between the systolic pulmonary artery and systolic systemic blood pressures ( $P = 0.164$ ; Figure 3 and  $P = 0.269$ ; Figure 4). The complete parameters measured were described in Table 1. The breathing

frequency was unaffected during dexmedetomidine infusion. There was no incidence of respiratory depression or airway obstruction. Intraoperative arterial blood gases showed a mean PaO<sub>2</sub> of  $204 \pm 135$  mmHg, PaCO<sub>2</sub> of  $36 \pm 4$  mmHg, pH of  $7.36 \pm 0.03$ , Hb of  $15.4 \pm 3$  g% and BE of  $4.7 \pm 1.7$  mMol/L.

## Discussion

Dexmedetomidine is chemically active dextro-isomer of the imidazole compound, medetomidine. Its pharmacology and mechanism of action have been extensively reviewed elsewhere.<sup>[8,9]</sup> Dexmedetomidine is a valuable adjunct for adult procedural sedation as well as pediatric patients.<sup>[10,11]</sup> Several reports were reported of its safe and effective use in the pediatric ICU.<sup>[12,13]</sup> Kristin *et al.*<sup>[14]</sup> have reported that invasive procedures may be performed using dexmedetomidine 1-3 mcg/kg alone or with a combination of low dose ketamine in spontaneously breathing children with different congenital heart defects. Ulgey *et al.*<sup>[15]</sup> performed a study where 60 children undergoing cardiac catheterization were divided into two groups: One group received ketamine-propofol and the other group received ketamine-propofol-dexmedetomidine. Ketamine was given in a dose of 1 mg/kg, propofol was given in a dose of 1 mg/kg, and dexmedetomidine was added at 1  $\mu$ g/kg for 5 min as an infusion. The study revealed that the addition of dexmedetomidine decreased consumption of propofol without cardiorespiratory depression, lowered airway complications and reduced the time recovery time of patients. In a retrospective cohort study, Mester *et al.*<sup>[16]</sup> showed that 16 patients who underwent pediatric cardiac catheterization under sedation with dexmedetomidine (1  $\mu$ g/kg) after ketamine (2 mg/kg) for induction, exhibited effective sedation with less depression of respiratory and cardiovascular function.

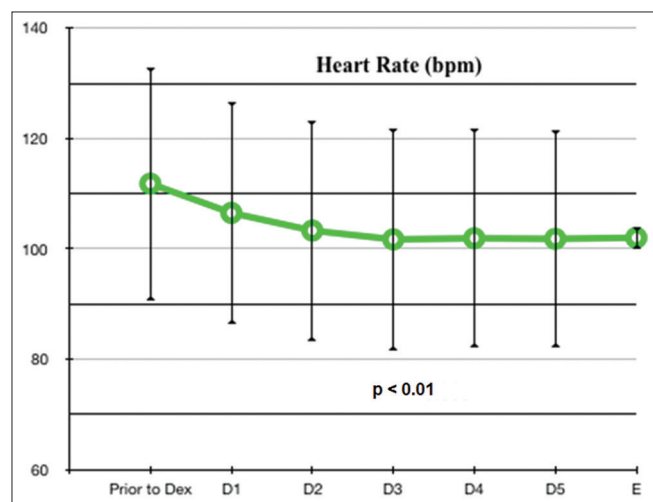


Figure 1: Heart rate changes during Dex (dexmedetomidine) infusion. Dex = Dexmedetomidine; bpm = Beats per minute; D1, D2, D3, D4, D5 = Every 2 min during bolus of dexmedetomidine infusion; E = At the end of procedure

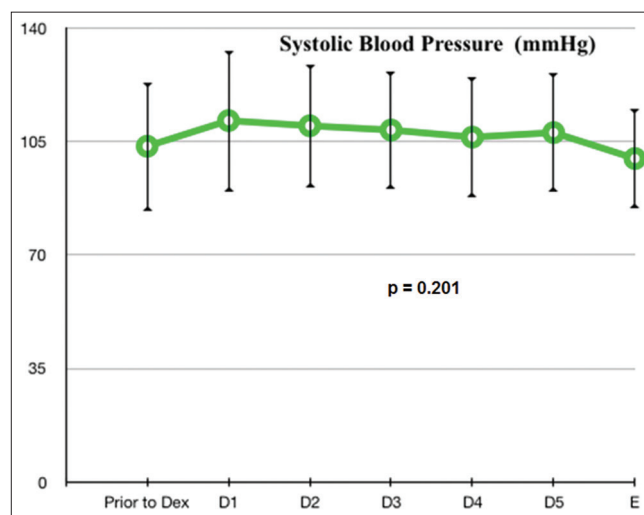
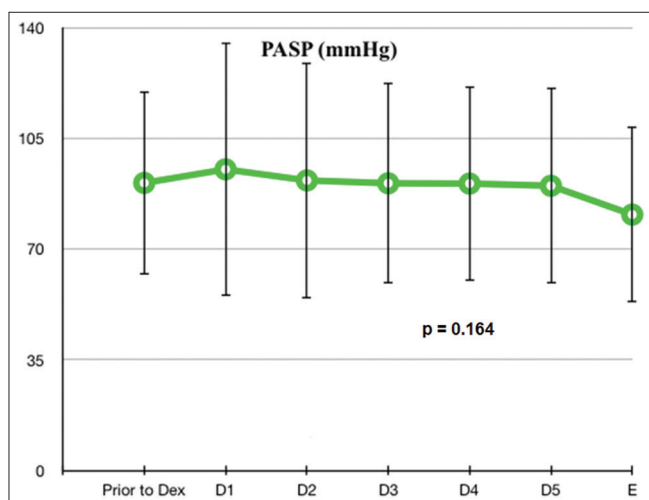


Figure 2: Systolic blood pressure changes during Dex (dexmedetomidine) infusion. Dex = Dexmedetomidine; bpm = Beats per minute; D1, D2, D3, D4, D5 = Every 2 min during bolus of dexmedetomidine infusion; E = At the end of procedure; SpO<sub>2</sub> = Peripheral arterial oxygen saturation

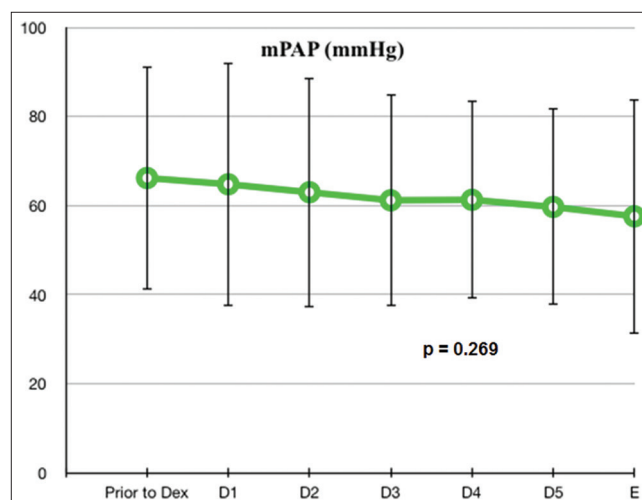
**Table 1: Monitored parameters in children undergoing diagnostic/interventional catheterization procedures during the study period**

	HR (bpm)	Systolic BP (mmHg)	Diastolic BP (mmHg)	Mean BP (mmHg)	PASP (mmHg)	PADP (mmHg)	mPAP (mmHg)	PASP/SAP ratio	RR (breaths/min)	SpO <sub>2</sub> (%)
Initial	118.8±23.4	111.6±12.5	68.4±14.3	82.7±11.7	NA	NA	NA	NA	27.8±7.9	92.7±7.0
After Ketamine	119.1±23.2	107.0±12.9	65.5±14.6	79.7±12.2	NA	NA	NA	NA	27.9±7.8	95.8±5.7
Prior to Dex	111.8±21.1	103.5±19.8	61.5±17.5	78.9±18.5	90.9±29.0	49.1±27.6	66.2±25.1	0.9	27.6±6.6	95.4±5.0
D1	106.5±20.0	111.4±21.7*	67.0±19.5	85.7±21.1	95.2±39.9	45.0±29.3	64.8±27.4	0.9	27.9±6.9	96.8±5.3
D2	103.3±19.9*	109.8±18.9*	64.9±17.1	84.2±18.5	91.7±37.4	43.3±27.5	63.0±25.8	0.8	28.6±8.6	96.8±5.2
D3	101.7±20.2*	108.5±18.0*	64.0±15.7	79.4±17.3	90.8±31.7	41.8±26.2	61.2±23.7	0.8	30.1±10.0	97.0±4.7
D4	101.9±19.8*	106.3±18.5*	62.0±15.3	81.7±17.6	90.7±30.8	42.1±26.7	61.3±22.2	0.9	30.4±11.7	97.1±4.8
D5	101.8±19.4*	107.7±18.4*	63.5±16.2	82.8±17.6	90.0±30.9	41.1±26.6	59.7±22.1	0.8	30.0±10.3	97.3±4.5*
E	102.0±2.0*	99.7±15.2	60.5±15.5	74.6±13.6	80.9±27.7	36.66±24.9	57.6±26.3	0.8	29.7±9.8	97.9±4.1*

\* $P < 0.05$  when compared with prior to dexmedetomidine infusion. Dex=Dexmedetomidine; HR=Heart rate, bpm=Beats per minute; BP=Blood pressure; RR=Respiratory rate, D1, D2, D3, D4, D5=Every 2 min during bolus of dexmedetomidine infusion; E=At the end of procedure; SpO<sub>2</sub>=Peripheral arterial oxygen saturation; PASP=Pulmonary artery systolic blood pressure; mPAP=Mean pulmonary artery pressure; PADP=Pulmonary artery diastolic blood pressure



**Figure 3: Pulmonary artery systolic blood pressure (PASP) changes during dexmedetomidine infusion. Dex = Dexmedetomidine; bpm = Beats per minute; D1, D2, D3, D4, D5 = Every 2 min during bolus of dexmedetomidine infusion; E = At the end of procedure; PASP = Pulmonary artery systolic blood pressure**



**Figure 4: Mean pulmonary artery pressure (mPAP) changes during dexmedetomidine infusion. Dex = Dexmedetomidine; bpm = Beats per minute; D1, D2, D3, D4, D5 = Every 2 min during bolus of dexmedetomidine infusion; E = At the end of procedure; mPAP = Mean pulmonary artery pressure; PADP = Pulmonary artery diastolic blood pressure**

In a randomized study conducted by Tosun *et al.*<sup>[17]</sup> 44 patients underwent pediatric cardiac catheterization; these patients were divided into ketamine-propofol (KP) and ketamine-dexmedetomidine (KD) groups. The study showed that the HR was lower in the KD group than in the KP group; however, recovery time duration was longer in the KD group than in the KP group (49 and 23 mins, respectively). Li BL, *et al.*<sup>[18]</sup> in a prospective study enrolled 115 children scheduled for transthoracic echocardiography below three years of age. All children were sedated with intranasal dexmedetomidine at 3 mcg/kg. The results showed that additional oxygen was required only in one child; however, all the other children experienced sufficient comfort and proper sedation with normal hemodynamic signs. Koroglu *et al.*<sup>[19]</sup> in a study where 60 pediatric patients undergoing MRI were divided into dexmedetomidine (initial dose 1 mcg/kg)

and propofol (initial dose of 3 mg/kg) groups. The study reported that in spite of adequately achieving sedation in most patients of both groups, children were prone to desaturation and hypotension in the propofol group.

In a prospective open-label study, William *et al.* evaluated the effects of ketamine in children with increased pulmonary vascular resistance undergoing cardiac catheterization under sevoflurane anesthesia. They demonstrated that ketamine did not increase pulmonary vascular resistance in spontaneously breathing children with PH in the presence of sevoflurane.<sup>[20]</sup> Dexmedetomidine has been used extensively for sedation and analgesia of critically ill and mechanically ventilated patients, invasive and noninvasive procedural sedation, as an adjunct to general anesthesia and treatment of withdrawal symptoms from opioids and benzodiazepines. However, the effect of dexmedetomidine on PAP is not clear. In an observational

study, children undergoing cardiac catheterization received an infusion of dexmedetomidine was associated with systemic vasoconstriction and hypertension but no significant changes in PAP or vascular resistance.<sup>[21]</sup> This is of interest in patients with both univentricular and biventricular physiology, more so in patients who are prone to develop pulmonary hypertensive crisis perioperatively such as patients with atrioventricular septal defects, truncus arteriosus, obstructed total anomalous pulmonary venous connection and those undergoing Glenn and Fontan procedures. The present study was attempted to study the effect of dexmedetomidine on pulmonary arterial pressure in infants and children with known PH and undergoing cardiac catheterization and interventional procedures under monitored anesthetic care using ketamine.

In a study done by Judith *et al.*, the effect of dexmedetomidine on PAP after cardiac surgery was investigated.<sup>[22]</sup> The results were similar to the findings of our study. They suggested that Dexmedetomidine might have had an exaggerated beneficial sympatholytic effect during the post CPB period, which is characterized by a hyperadrenergic state. The patients in Judith's study did not have preoperative PAH. This study included patients with CHD with PAH to determine the effects of dexmedetomidine on PAP. Twenty-one of patients in this study had left to right shunt. The PAH in this condition is caused by increased pulmonary blood flow. All our children received supplemental nasal oxygen of 2 LPM during the study. The PAP's were not measured in the absence of oxygen. Hence, we are not sure if the PAP was reduced by oxygen administered alone or dexmedetomidine with oxygen resulted in increased flow through the shunt. However, there was no measurable decrease in PAP.

It can also be postulated that dexmedetomidine decreases the systemic blood pressure, thus decreasing the shunt and hence the pulmonary blood flow and PAP. Qp/Qs were not measured in our study. Thus, whether the decrease in PAP was secondary to a decrease in PBF or to decrease in PVR is not known. Ketamine was used in all the patients. Its average dose was 2 mg/kg. This was similar to a study done by Kristin where dexmedetomidine was used as a primary sedative during invasive procedures in infants and toddlers with CHD.<sup>[14]</sup> Ketamine counters the decrease in blood pressure and HR caused by dexmedetomidine and has an additive effect with dexmedetomidine.<sup>[23]</sup>

The limitation of our study was that pulmonary vascular resistance and cardiac output were not measured which could have affected the PASP. However, there was no evidence of acidosis or hemodynamic fluctuations to suggest any change in cardiac output. There was no control group for comparison of hemodynamics, sedation and analgesia. In addition, the sample size was small, but we completed all the procedures successfully with minimal side effects. These results can be used to design a larger,

randomized controlled study to determine the effects of dexmedetomidine on PAP and vascular resistance.

## Conclusions

We conclude that dexmedetomidine in the doses used did not exert a significant effect on PAP in children undergoing cardiac catheterization procedures after sedation with glycopyrrolate, midazolam and ketamine analgesia. Dexmedetomidine had no effect on respiratory parameters. We suggest that it can be used safely in patients with pulmonary artery hypertension undergoing cardiac catheterization procedures in spontaneously breathing patients.

## Ethical statement

The institutional review board and ethics committee approved this study.

## Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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## Conflicts of interest

There are no conflicts of interest.

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