Dosing and efficacy of intranasal dexmedetomidine sedation for pediatric transthoracic echocardiography: a retrospective study

Posologie et efficacité de la sédation intranasale à base de dexmédétomidine pour l'échocardiographie transthoracique chez l'enfant: une étude rétrospective

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Abstract

Purpose We designed this retrospective observational study on the use of α_2 -agonist dexmedetomidine to determine the optimum intranasal dose to achieve sedation for pediatric transthoracic echocardiography and to identify any dose-related adverse effects.

Methods Outpatient children aged three months to three years with diverse diagnoses of congenital heart disease, including cyanotic cardiac defects, underwent transthoracic echocardiography under dexmedetomidine sedation. Aerosolized intranasal dexmedetomidine was administered with initial doses ranging from 1–3 $\mu\text{g}\cdot\text{kg}^{-1}$. A rescue dose of 1 $\mu\text{g}\cdot\text{kg}^{-1}$ was administered if adequate sedation was not achieved within 45 min following the first dose. The primary study outcome was the achievement of adequate sedation to allow transthoracic

echocardiography (TTE) scanning, including subxiphoid and suprasternal probe manipulation.

Results Sedation with intranasal dexmedetomidine for transthoracic echocardiography was successful in 62 of the 63 (98%) patients studied, with an intranasal rescue dose required in 13 (21%) patients. Intranasal doses of dexmedetomidine 2.5–3.0 $\mu\text{g}\cdot\text{kg}^{-1}$ were required for tolerating TTE probe placement, including subxiphoid and suprasternal manipulation, with minimal response and a 90% success rate. Excluding patients who required a second dose of dexmedetomidine, the mean (standard deviation) time from administration to achieving such sedation (onset time) was 26 (8) min for low-dose (1–2 $\mu\text{g}\cdot\text{kg}^{-1}$) dexmedetomidine and 28 (8) min for moderate-dose (2.5–3.0 $\mu\text{g}\cdot\text{kg}^{-1}$) dexmedetomidine ($P = 0.33$). Time from administration of low-dose dexmedetomidine to discharge, including TTE scan time, was 80 (14) min, and it increased with moderate-dose dexmedetomidine to 91 (22) min ($P = 0.05$). Mild to moderate bradycardia and hypotension were observed, but no interventions were required.

Conclusion We found that aerosolized intranasal dexmedetomidine offers satisfactory conditions for TTE in children three months to three years of age with an optimal dose of 2.5–3.0 $\mu\text{g}\cdot\text{kg}^{-1}$ administered under the supervision of a pediatric cardiac anesthesiologist.

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Résumé

Objectif Nous avons conçu cette étude observationnelle rétrospective sur l'utilisation de la dexmédétomidine, un agoniste des récepteurs α_2 , afin de déterminer la dose intranasale optimale pour obtenir une sédation pour l'échocardiographie transthoracique chez l'enfant et d'identifier tout effet secondaire néfaste lié à la dose.

Méthode Des enfants en clinique externe, âgés de trois mois à trois ans et présentant divers diagnostics de cardiopathie congénitale, notamment des malformations cardiaques cyanogènes, ont eu une échocardiographie transthoracique avec sédation à la dexmédétomidine. De la dexmédétomidine intranasale en aérosol a été administrée, les doses initiales allant de $1\text{--}3\text{ }\mu\text{g}\cdot\text{kg}^{-1}$. Une dose de sauvetage de $1\text{ }\mu\text{g}\cdot\text{kg}^{-1}$ a été administrée si une sédation adéquate n'avait pas été obtenue au cours des 45 min suivant l'administration de la première dose. Le principal critère d'évaluation de l'étude était l'obtention d'une sédation adéquate afin de permettre un examen par échocardiographie transthoracique (ETT), y compris une manipulation sous-xiphoïdienne et suprasternale de la sonde.

Résultats La sédation par dexmédétomidine intranasale pour l'échocardiographie transthoracique a réussi chez 62 des 63 (98 %) patients à l'étude, et une dose de sauvetage intranasale a été requise chez 13 (21 %) patients. Des doses intranasales de dexmédétomidine de l'ordre de $2,5\text{--}3,0\text{ }\mu\text{g}\cdot\text{kg}^{-1}$ ont été nécessaires pour tolérer le positionnement de la sonde d'ETT, notamment la manipulation sous-xiphoïdienne et suprasternale, avec une réaction minimale et un taux de réussite de 90 %. En excluant les patients ayant nécessité une seconde dose de dexmédétomidine, le temps moyen (écart type) entre l'administration et l'obtention d'une telle sédation (début d'action) était de 26 (8) min pour une faible dose ($1\text{--}2\text{ }\mu\text{g}\cdot\text{kg}^{-1}$) de dexmédétomidine et de 28 (8) min pour une dose modérée ($2,5\text{--}3,0\text{ }\mu\text{g}\cdot\text{kg}^{-1}$) de dexmédétomidine ($P = 0,33$). Le temps entre l'administration d'une faible dose de dexmédétomidine et le congé, incluant le temps d'examen d'ETT, était de 80 (14) min. Ce temps a augmenté avec une dose modérée de dexmédétomidine à 91 (22) min ($P = 0,05$). Une bradycardie et une hypotension légères à modérées ont été observées, mais aucune intervention n'a été nécessaire.

Conclusion Selon nos observations, la dexmédétomidine intranasale en aérosol procure des conditions satisfaisantes pour l'ETT chez des enfants âgés de trois mois à trois ans, avec une dose optimale de $2,5\text{--}3,0\text{ }\mu\text{g}\cdot\text{kg}^{-1}$ administrée sous la supervision d'un anesthésiologiste cardiaque pédiatrique.

Accurate transthoracic echocardiography (TTE) is a mainstay for the diagnosis and periodic surveillance of congenital cardiac disease. Most pediatric TTE exams can be accomplished with patient cooperation; however, sedation is often required for detailed TTE exams in some infants and toddlers.¹ While chloral hydrate and pentobarbital are oral sedatives used extensively for TTE,

their administration depends on patient cooperation, they possess relatively long biological half-lives, and they have been found to be potentially deleterious to brain structures in experimental models.² Moreover, chloral hydrate has limited availability in some countries, including the United States.³

Dexmedetomidine, an α_2 -agonist with sedative properties and greater receptor selectivity than clonidine,⁴ may be an alternative choice for sedation during TTE in young children. Dexmedetomidine has recently gained popularity for intravenous sedation in children, including those with congenital cardiac disease.⁵ Importantly, dexmedetomidine can be administered intranasally with minimal patient cooperation and without intravenous access. It also seems devoid of the local discomfort frequently associated with intranasal administration of midazolam, rendering it very attractive for brief sedation during echocardiography.^{6–9} The bioavailability of orally administered dexmedetomidine is very poor at 16% (12–20%) with a peak at two hours¹⁰; however, the intranasal route has shown to be more effective than the buccal (i.e., sublingual) route of administration when using equal doses of dexmedetomidine premedication in children.¹¹ Indeed, in one study, buccal dosing resulted in a peak dexmedetomidine serum concentration in 90 min, while intranasal dosing gave a peak serum level at 38 min.^{10,12}

Nevertheless, the appropriate dose of intranasal dexmedetomidine to facilitate sedation for TTE is not known. Moreover, the hemodynamic side effects of dexmedetomidine, which could be dose-dependent and especially prevalent in children with congenital heart disease, have not been adequately explored in this patient population. Accordingly, we performed a retrospective review of our quality assurance data and sedation records for patients undergoing TTE examinations under intranasal dexmedetomidine sedation.

This aim of this study was to identify the dose of intranasal dexmedetomidine required to achieve satisfactory conditions for TTE and to determine any adverse effects of this newer sedation technique. This information will be valuable for improving clinical practice in sedating young children with congenital heart disease and for directing future prospective research.

Methods

The Institutional Review Board of Cincinnati Children's Medical Center (CCHMC) waived the requirement for written informed consent to analyze these quality assurance data (ID: 2014-7583; under IND no. 76-346 for pediatric use of dexmedetomidine), and the Pharmacy and Therapeutics Committee of CCHMC previously approved

the use of intranasal dexmedetomidine as described in this report. We used a convenience non-probability sample for this study.

We defined the range of intranasal dexmedetomidine dosing as low dose ($1\text{--}2\text{ }\mu\text{g}\cdot\text{kg}^{-1}$) and moderate dose ($2.5\text{--}3.0\text{ }\mu\text{g}\cdot\text{kg}^{-1}$); we did not employ higher initial doses (greater than $3.0\text{ }\mu\text{g}\cdot\text{kg}^{-1}$).^{6,7,13} The primary outcome of the study was the achievement of a level of sedation adequate to allow TTE scanning, including subxiphoid and suprasternal probe manipulation.

A pediatric cardiologist and a pediatric cardiac anesthesiologist routinely evaluate and triage children who present to our institution for TTE. Patients deemed unable to remain motionless while requiring a complete detailed TTE, which may include critical measurements of gradients or detailed visualization of anatomic structures, were generally referred for sedation.

An attending pediatric cardiac anesthesiologist supervised all cases of sedation and anesthetics in the echocardiography suite. In 2014, 560 of 3,208 (17%) patients under one year of age, 295 of 612 (48%) patients one to two years of age, and 128 of 518 (25%) patients two to three years of age were sedated for their examinations using oral pentobarbital or general anesthesia using sevoflurane and/or propofol. In 2014, two of ten rotating pediatric cardiac anesthesiologists began using intranasal dexmedetomidine sedation instead of oral pentobarbital or general anesthesia.

Patients were fasted for at least six hours for formula, four hours for breast milk, and two hours for clear liquids. No patients received aerosolized intranasal dexmedetomidine if they presented with intravenous access (i.e., in-hospital patients), were taking digoxin or beta-blockers, or had second-degree heart block. With the parents present, a trained pediatric cardiac sedation nurse administered dexmedetomidine (Precedex, Hospira, Inc. Lake Forest, IL, USA) intranasally using a mucosal atomizer (LMA MAD NasalTM, Teleflex Research Triangle Park, NC, USA) after dilution with 0.9% saline to a total volume of 0.5 mL (see Electronic Supplementary Material for a video example of a pediatric patient receiving intranasal dexmedetomidine for sedation during a transthoracic echocardiographic examination).

We defined adequate sedation (i.e., the primary outcome) for TTE examination as minimal response to subxiphoid and suprasternal TTE probe placement. This was considered similar to a Ramsay sedation score of 4–5, which was previously found to allow successful TTE examinations.¹⁴ If adequate sedation was not achieved within 45 min of the initial administration, additional intranasal (i.e., “rescue”) dexmedetomidine ($1\text{ }\mu\text{g}\cdot\text{kg}^{-1}$) was administered. No mechanical restraints were used during the TTE examinations.

Pre-sedation heart rate (HR) and oxygen saturation (SpO_2) were documented, as was patient weight. Blood pressure (BP) measurement was deferred if patients resisted. During onset of sedation, patients were monitored by continuous pulse oximetry and observation by a pediatric cardiac sedation nurse. Electrocardiographic and BP monitoring (every five minutes if tolerated) commenced upon attaining adequate sedation. Study data during sedation were captured with automated electronic monitoring.

The treatment of bradycardia or hypotension was at the discretion of the sedation providers who were guided by comparisons of measurements taken on arrival to the echocardiography suite as well as patient norms for age. For this retrospective study, bradycardia was defined in accordance with the Pediatric Advanced Life Support (PALS) guidelines for this age range, with moderate bradycardia defined as a $\text{HR} < 80\text{ beats}\cdot\text{min}^{-1}$ at rest and substantial bradycardia defined as a $\text{HR} < 60\text{ beats}\cdot\text{min}^{-1}$.^{15,16} Hypotension was also based on the PALS guidelines and defined as $< 70\text{ mmHg}$ for systolic BP in this age range of three years or less.¹⁶ Oxygen desaturation was defined as a $\text{SpO}_2 < 92\%$ for normoxic patients or as $\geq 5\%$ below awake admission values for cyanotic patients.^{17,18}

Following completion of the echocardiographic exam, patients were evaluated and discharged according to previously published discharge criteria for pentobarbital sedation in our institution.¹⁴ These criteria included being easily awakened, a lack of respiratory distress or airway compromise, and HR, BP, respiratory rate, and SpO_2 within normal ranges for age or the patient’s awake values on admission. Most patients were discharged to the cardiology clinic for same-day follow-up visits with their pediatric cardiologist, followed later by discharge to home.

Statistical analyses

Data are presented as mean [standard deviation (SD)] with a 95% confidence interval (CI) where indicated or, if data were highly skewed, as median (interquartile range [IQR]). The Shapiro-Wilk test was used to check normality of the data. Normally distributed continuous data were compared with Student’s *t* test or one-way analysis of variance, where appropriate. Non-parametric data were compared using the Kruskal-Wallis test. Group comparisons of categorical variables utilized Chi square or Fisher’s exact test, as appropriate. Multiple normal or logistic linear regression modelling was used depending on continuous or binary outcomes to adjust the effects for other factors. All reported *P* values are two sided.

The statistical analysis was performed with SAS® version 9.3 (NC, USA) or GraphPad Prism 6.0 for Mac (GraphPad Software, La Jolla, CA, USA).

Results

Sixty-three outpatients with diverse diagnoses of congenital heart disease, including cyanotic heart disease, received intranasal dexmedetomidine sedation for TTE from January 21, 2014 to December 31, 2014 (Table 1). Patients' mean (SD) age was 17.8 (8.2) mth, weight was 10.2 (2.7) kg, and American Society of Anesthesiologists' physical status ranged from I-III (Table 2).

Patients received initial dexmedetomidine doses ranging from 1–3 $\mu\text{g}\cdot\text{kg}^{-1}$ (Figure). With respect to our primary outcome, a low initial dexmedetomidine dose (mean, 1.6 $\mu\text{g}\cdot\text{kg}^{-1}$; 95% CI, 1.4 to 1.8) provided adequate sedation for 22 of 32 (69%) patients, while an initial moderate dose (mean, 2.6 $\mu\text{g}\cdot\text{kg}^{-1}$; 95% CI, 2.5 to 2.7) resulted in successful sedation without the need for intranasal rescue dosing in 28 of 31 (90%) cases. Accordingly, an initial moderate dose of dexmedetomidine lowered the risk of needing an intranasal “rescue” dose by 69% (relative risk [RR], 0.31; 95% CI, 0.09 to 1.02; $P = 0.05$). These estimates were obtained from a modified Poisson regression approach for binary outcomes.¹⁹ We observed that age had a significant quadratic effect on the need for rescue sedation, with younger patients requiring less rescue dexmedetomidine ($P = 0.05$ for the linear and quadratic effects for age). After adjusting for this age effect, we found that increasing the dexmedetomidine from a low to a moderate dosage reduced the risk of needing a rescue dose by 74% (RR, 0.26; 95% CI, 0.08 to 0.83; $P = 0.02$). In the above models, the initial dose was categorized as low or moderate at the dose level of 2.15 $\mu\text{g}\cdot\text{kg}^{-1}$ where we observed the minimum P value for testing the null hypothesis of no difference in initial dose on the probability of rescue dosing.

Table 3 shows the onset and duration of sedation. Excluding patients who required a second dose of dexmedetomidine, the mean (SD) time from administration to achieving adequate sedation (onset time) was 26 (8) min for low-dose dexmedetomidine and 28 (8) min for moderate-dose dexmedetomidine ($P = 0.33$). The multiple linear regression model for the time of onset indicated that increasing patient age was a significant covariate for onset time (regression coefficient = 0.55; $P = 0.02$), but patient weight and initial dexmedetomidine dose were not significant covariates ($P = 0.31$ and $P = 0.54$, respectively).

The mean (SD) TTE examination times for the low- and moderate-dose dexmedetomidine groups were 37 (13) min and 39 (16) min, respectively, without differences between groups ($P = 0.83$). Once adequate sedation was achieved, none of the patients required additional medication to treat premature awakening during the TTE exam.

The mean (SD) times from the administration of low- and moderate-dose dexmedetomidine to discharge,

Table 1 Primary cardiac diagnoses

Diagnosis	Count
VSD	11
Screening for cardiac murmur	12
Aortic valve disease, coarctation	8
Atrial communication (ASD, PFO)	4
TGA (following ASO)	5
PA hypertension	4
Univentricular lesions (following bidirectional Glenn operation)	4
TOF (repaired), PS	4
PDA	3
Screening for Kawasaki's syndrome	5
Miscellaneous (MS, AVC, TAPVR)	3
Total	63

Prevalence of primary cardiac diagnoses, most patients had more than one anatomic lesion. ASD = atrial septal defect; ASO = arterial switch operation; AVC = atrioventricular canal; MS = mitral stenosis; PA = pulmonary artery; PDA = patent ductus arteriosus; PFO = patent foramen ovale; PS = pulmonary stenosis; TAPVR = total anomalous pulmonary venous return; TGA = transposition of the great vessels variants; TOF = tetralogy of Fallot; VSD = ventricular septal defect

including TTE scan time, were 70 (15) min and 91 (22) min, respectively ($P = 0.04$ by Welch's unequal variances Student's t test)^A (Table 3). Although tolerating oral fluids was not required, 46 (72%) patients were documented to have taken oral fluids prior to discharge. In a follow-up phone call 24 hr following the examination, all patients were reported to have recovered uneventfully from sedation and did not require any interventions or readmissions. There were no reports of post-sedation irritability or vomiting after aerosolized intranasal dexmedetomidine.

Heart rate in all patients decreased approximately 25% from awake (i.e., on admission) values during sedation without differences between dosing groups (Table 4). Seven patients (11%) who received only one dose of dexmedetomidine experienced moderate bradycardia (HR < 80 beats·min⁻¹), and one patient who received a rescue dose (total dose, 3 $\mu\text{g}\cdot\text{kg}^{-1}$) also experienced moderate bradycardia. The multiple logistic regression model showed that age, dexmedetomidine dose (initial and total), and need for intranasal rescue dosing had no significant association with the incidence of bradycardia ($P > 0.05$). Nevertheless, HR < 80 beats·min⁻¹ was associated with lower awake (on admission) HR ($P = 0.02$). No hemodynamic interventions were needed, and the HR in all patients increased to age-appropriate normal ranges upon arousal and prior to discharge.

^A Shapiro-Wilk normality test $P = 0.48$ and $P = 0.15$, respectively.

Table 2 Patient characteristics

	Study population (n = 63)	DEX 1 - 2 $\mu\text{g}\cdot\text{kg}^{-1}$ (n = 32)	DEX 2.5 - 3.0 $\mu\text{g}\cdot\text{kg}^{-1}$ (n = 31)
Age (months)	17.5 (7.9)	16.9 (8.2)	18.1 (7.6)
Weight (kg)	10.1 (2.7)	9.9 (2.9)	10.3 (2.6)

Data are presented as mean (standard deviation). DEX = dexmedetomidine

Figure Dose response curve. Initial doses of intranasal dexmedetomidine 2.5 or 3.0 $\mu\text{g}\cdot\text{kg}^{-1}$ provided successful sedation for approximately 90% of children aged three to 36 mth undergoing echocardiography, as defined by tolerating the exam within 45 min following the initial dose without requiring additional medication. The graph shows the percentage of children tolerating echocardiography, including subxiphoid and suprasternal probe placement, following initial doses of intranasal dexmedetomidine ranging from 1-3 $\mu\text{g}\cdot\text{kg}^{-1}$ without the need for additional sedation. Numbers above each data point represent the total number of children receiving the respective initial dose and the number of children requiring an additional intranasal “rescue” dose of 1 $\mu\text{g}\cdot\text{kg}^{-1}$ to tolerate the exam. Bars indicate lower 95% confidence intervals

Table 3 Dexmedetomidine dose onset and discharge times

DEX Dose $\mu\text{g}\cdot\text{kg}^{-1}$	n	Onset (min)	Initial Dose to Discharge (min)	End of TTE to Discharge (min)
1.0	5	33 [19 - 37]	80 [64 - 98]	19 [15 - 30]
1.5	7	25 [20 - 29]	80 [67 - 85]	16 [12 - 20]
2.0	12	27 [23 - 30]	78 [69 - 94]	14 [10 - 17]
2.5	18	28 [21 - 31]	87 [75 - 101]	15 [10 - 23]
3.0	8	32 [23 - 40]	89 [77 - 103]	17 [10 - 38]
		$P = 0.46$	$P = 0.64$	$P = 0.66$

Data are presented a median [interquartile range]. Thirteen patients are not included because they required two doses of sedation (“rescue”). P value by the Kruskal-Wallis test. DEX = dexmedetomidine; TTE = transthoracic echocardiography

Blood pressure in all patients remained at awake values or decreased slightly during sedation (Table 4). Hypotension (systolic BP < 70 mmHg) was seen in five

(8%) patients. None of the patients had received a rescue dose of intranasal dexmedetomidine. The multiple logistic regression model indicated no significant association between age, weight, initial dexmedetomidine dose, *nil per os* time, or lowest sedated HR and a systolic BP < 70 mmHg ($P > 0.05$). None of the patients showed clinical evidence of poor perfusion or new cardiac dysfunction on echocardiography; therefore, no treatment was instituted for the hypotension. All patients with this relatively mild hypotension took oral clear fluids upon arousal and were discharged upon return of BP to normal limits within 30 min of scan completion.

None of the patients in this study required administration of supplemental oxygen or interventions such as insertion of an oral or intranasal airway, shoulder roll placement, neck extension beyond neutral, or other airway maneuvers. The lowest measured peripheral oxygen saturation SpO_2 in acyanotic patients was 94%. Two of four chronically cyanotic patients with bidirectional cavopulmonary anastomoses had a reduction in $\text{SpO}_2 > 5\%$ (absolute) from awake admission values without apparent airway obstruction. Both of these patients had received a second dose of dexmedetomidine (1 $\mu\text{g}\cdot\text{kg}^{-1}$) for inadequate levels of sedation following an initial dose of 2 $\mu\text{g}\cdot\text{kg}^{-1}$. The anesthesiologist elected to continue monitoring these patients without supplemental oxygen administration or airway manipulations; their SpO_2 reverted to awake values upon emergence.

Discussion

Intranasal dexmedetomidine can be effectively used as a sedative for TTE in young children with congenital heart disease. An initial moderate dose of aerosolized intranasal dexmedetomidine 2.5-3.0 $\mu\text{g}\cdot\text{kg}^{-1}$ was needed to achieve successful sedation in 90% of infants with congenital cardiac disease with an onset time of approximately 30 min. Compared with low-dose dexmedetomidine (1-2 $\mu\text{g}\cdot\text{kg}^{-1}$), these doses provided greater success but did not hasten the onset of sedation. Furthermore, the relatively higher doses did not increase adverse effects pertaining to HR, BP, or SpO_2 .

Intranasal dexmedetomidine is an attractive sedative for facilitating detailed TTE in otherwise uncooperative infants and toddlers. Its use does not necessitate intravenous cannulation or patient cooperation with swallowing medication, and minimal respiratory depression or airway obstruction is expected.²⁰ Patients under dexmedetomidine sedation are generally arousable with moderate stimulation,²¹ which should allow for expeditious discharge. Dexmedetomidine has a relatively short plasma half-life of two hours compared with that of chloral hydrate

Table 4 Vital signs during dexmedetomidine sedation

Vital Sign	DEX 1-2 $\mu\text{g}\cdot\text{kg}^{-1}$ ($n = 22$)	DEX 2.5-3.0 $\mu\text{g}\cdot\text{kg}^{-1}$ ($n = 28$)	<i>P</i> value
Change in HR (beats·min ⁻¹)	-29 (11) (26%)	-31 (14) (25%)	0.50
Patients with HR < 80 beats·min ⁻¹	3 (9.4%)	4 (12.9%)	0.71
Change in SBP (mmHg)*	-9 [5 - 14]	-13 [4 - 26]	0.41
Patients with SBP < 70 mmHg	3 (9.4%)	2 (6.5%)	0.67

Data are presented as mean (SD) and (percentage reduction) for change in heart rate from vital signs taken on admission to the echocardiography suite and as absolute number of patients with vital sign changes and percentages of their respective group. DEX = dexmedetomidine; HR = heart rate; SBP = systolic blood pressure

*Data are presented as median [interquartile range] and were analyzed with Mann-Whitney test, as they failed normality test. All other data were compared with unpaired Student's *t* test

or pentobarbital (both ~ 24 hr),²² suggesting the potential for fewer late post-sedation complications. Conversely, hypertension and bradycardia have ensued after rapid intravenous boluses of dexmedetomidine, followed by vasodilation and moderate hypotension.²³⁻²⁵ Dexmedetomidine is also known to inhibit sinoatrial and atrioventricular node function, which can lead to bradycardia, especially in children with rhythm disturbances.^{26,27} While speculative, use of a drug that provides sedation by a distinctly different mechanism from that of traditional gamma-aminobutyric acid agonist or N-methyl-D-aspartate antagonist sedatives and anesthetics could potentially avoid the neurocognitive abnormalities described following repeated exposures to these agents.²⁸

Before recommending dexmedetomidine for sedation in infants and toddlers with congenital heart disease, it is important to determine the dose that will provide adequate levels of sedation with acceptable cardiorespiratory parameters and allow for quick recovery to facilitate safe imaging studies. In children, intranasal dexmedetomidine has been utilized for sedation in doses ranging from 1-4 $\mu\text{g}\cdot\text{kg}^{-1}$.^{6,7,13} Intranasal dexmedetomidine has also been studied as “rescue” sedation after failed oral chloral hydrate (50 mg·kg⁻¹) administration.⁶ A recent study suggested that intranasal dexmedetomidine sedation 3 $\mu\text{g}\cdot\text{kg}^{-1}$ was effective for infant (ages 1-37 months) echocardiography.²⁹ Nasal dexmedetomidine has also been administered in combination with intranasal midazolam for pediatric TTE scans,¹³ which may be an option in some sedation-resistant patients or for a further decrease in onset time. Nevertheless, the overall success rate reported with this combination may only marginally improve the already high success rate of intranasal dexmedetomidine 2.5-3.0 $\mu\text{g}\cdot\text{kg}^{-1}$ used in our study.

Previous studies have reported relative bradycardia with intravenous administration of dexmedetomidine, which did not require a response from the clinician.^{27,30} Our results extend these findings to dexmedetomidine administered by the intranasal route. Heart rate < 80 beats·min⁻¹, the lower

limit of normal pulse rate at rest in this age group,¹⁵ was found in 13% of patients after intranasal administration of the drug. Nevertheless, we detected no concomitant hypotension, hypoperfusion, or decreased contractility on echocardiogram in any of these patients; therefore, the sedation team did not initiate any interventions. Importantly, the observed relative bradycardia was not associated with increased dexmedetomidine doses or with patient weight, but it was associated with older age and lower HR on admission before medication.

Dexmedetomidine not only leads to decreases in HR but also gives rise to initial hypertension, as previously observed in small children following intravenous administration.³¹ Nevertheless, we did not observe any hypertensive response in our patients following intranasal administration, which could have been due to the dissimilar routes of administration. A reduction in systolic BP to < 70 mmHg during sedation for children in this age group occurred in 8% of patients, including those who received a second dose. This reduction in BP was not associated with total dose of dexmedetomidine, age, or weight. No interventions for low BP were initiated. Since no intravenous access was present during these outpatient procedures, we could not easily administer a fluid bolus in response to hypotension, as has been suggested.³² Minimizing pre-procedural fasting, withholding antihypertensive medications, and more liberally allowing oral clear liquids prior to sedation with dexmedetomidine might ameliorate these hemodynamic abnormalities. Awakening and oral fluid intake immediately after echocardiography allowed BP to return to normal range in all our patients.

Dexmedetomidine has previously been found to have only limited effects on upper airway calibre or respiratory drive during sedation,²⁰ and accordingly, we did not observe decreases in peripheral oxygen saturations below normal in any of our non-cyanotic children.

Although the onset time for dexmedetomidine sedation is approximately 30 min, expedited discharge was possible

in the stated dose range as patients were easily arousable and had unobstructed airways and intact swallowing mechanisms, which allowed for discharge. The cost to acquire generic dexmedetomidine at our institution is approximately \$4 for 30 µg, while the cost for 50 mg of pentobarbital is approximately \$27 to sedate a 10-kg child (personal communication, CCHMC pharmacy, December 2014). In comparison, the cost and charges for vapour-based or total intravenous anesthetic are much higher. Further studies comparing intranasal dexmedetomidine with other sedatives and general anesthesia will be useful for comparing costs and procedural times.

Our report does have some limitations. The retrospective design of this study introduces several limitations, the most obvious being that choice of sedative and dose were not randomized but left to the discretion of the anesthesiologist. This may have introduced selection bias as experience was gained during the introduction of this drug to our practice. Moreover, since our data set did not include a control group, randomized prospective studies would be required to compare dexmedetomidine with other sedatives. As a rule, blood pressure measurement was not initiated until sedation was achieved so as not to arouse the child; therefore, any potential initial hypertensive response could have gone undetected. It should be emphasized that experienced cardiac sedation nurses performed dexmedetomidine sedation in our cohort under the supervision of a pediatric cardiac anesthesiologist in the echocardiography suite. Large prospective studies are required to comment on the safety of administering intranasal dexmedetomidine in this setting or before recommending this technique for use by a wider group of practitioners. An additional point for further discussion is sedation of children with congenital heart disease without establishing intravenous access. Finally, since all doses were targeted at achieving sedation, a complete dose-response relationship could not be examined.

In conclusion, an initial dose of aerosolized intranasal dexmedetomidine in the range of 2.5–3.0 µg·kg⁻¹ offers satisfactory conditions for TTE in children three months to three years of age. Nevertheless, trained personnel may need to monitor its use in this patient population.

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