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REVIEW ARTICLE

Dexmedetomidine: a review of applications for cardiac surgery during perioperative period

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Abstract Cardiac surgery is associated with a high incidence of cardiovascular and other complications during the perioperative period that translate into increased mortality and prolonged hospital stays. Safe comprehensive perioperative management is required to eliminate these adverse events. Dexmedetomidine is a selective α_2-adrenoreceptor agonist that has been described as an ideal medication in the perioperative period of cardiac surgery. The major clinical effects of dexmedetomidine in this perioperative period can be summarized as attenuating the hemodynamic response, cardioprotective effects, antiarrhythmic effects, sedation in the ICU setting, treatment of delirium, and procedural sedation. Although there are some side effects of dexmedetomidine, it is emerging as an effective therapeutic agent in the management of a wide range of clinical conditions with an efficacious, safe profile. The present review serves as an overview update in the diverse applications of dexmedetomidine for cardiac surgery during the perioperative period.

Keywords Dexmedetomidine · Sedation · Cardiac surgery

Introduction

Dexmedetomidine is a highly selective α_2-adrenergic receptor agonist that has been shown to have both analgesic and sedative effects. Compared with clonidine, which is an α_2-agonist that has been used for the treatment of hypertension, dexmedetomidine is considered a complete agonist with an α_2:α_1 specificity ratio of 1,600:1 [1]. The elimination half-life of dexmedetomidine is 2 h versus 8 h for clonidine, and the α-half-life of dexmedetomidine is 6 min. The short half-life of dexmedetomidine makes it available as a preparation intended for intravenous administration.

The original Food and Drug Administration (FDA)-approved indication for dexmedetomidine was the provision of short-term sedation (24 h) for adult patients in the intensive care unit (ICU) setting who were receiving mechanical ventilation with endotracheal intubation. On October 17, 2008, dexmedetomidine received FDA approval for monitored anesthesia care in adults [2]. Recently, dexmedetomidine was approved in Europe for sedation of adult ICU patients requiring a sedation level not deeper than arousal in response to verbal stimulation [3]. To date, several papers have described its use in patients with heart disease in the operating room, in the catheterization laboratory, in magnetic resonance imaging (MRI) suites, and in the intensive care unit (ICU). This article reviews the cardioprotective properties of dexmedetomidine as well as reports outlining its applications for the perioperative period in cardiac surgery.

Attenuating the hemodynamic response

Hypotension caused by anesthesia and hypertension resulting from surgical stimuli should be avoided because these conditions can cause undesirable events leading to severe complications. Tracheal intubation and surgical stimulants cause a hyperdynamic hemodynamic condition because of a reflex increase in sympathetic and sympathoadrenal activity. This increased sympathoadrenal

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activity may result in hypertension, tachycardia, and arrhythmias, consequently leading to an increase in myocardial oxygen consumption and ischemia [4]. Hemodynamic depression is common during anesthetic induction and surgery, especially in patients with hypertension or myocardial insufficiency. A variety of drugs have been used to control these hemodynamic responses, such as vasodilators, beta blockers, calcium channel blockers, α_2-agonists, opioids, and vasoconstrictors. However, no modality was devoid of drawbacks and limitations. Recently, several studies have described the positive effects of dexmedetomidine on cardiovascular stability in cardiac operations.

In a published randomized control trial, Sulaiman et al. [5] evaluated the effects of dexmedetomidine on attenuation of stress response to endotracheal intubation in patients undergoing elective off-pump coronary artery bypass grafting. Sixty adult patients were randomly allocated to dexmedetomidine group or to a saline group. Fifteen minutes before induction of anesthesia, a single dose of dexmedetomidine 0.5 mg/kg was administered intravenously using a syringe pump over 10 min. The same amount of saline was administered to the patients in the control group. Better control of heart rate and blood pressure was observed in the dexmedetomidine group than in the control group ($p < 0.05$). Except at 5 min post intubation, pulmonary artery pressures were similar between the two groups. Also, no incidences of hypotension, arrhythmias, or other electrocardiography were observed during the study period in any group. Similarly, Menda et al. [6] and Kunisawa et al. [7] reported that dexmedetomidine as an adjunct to anesthetic induction blunts the hemodynamic response to endotracheal intubation in patients undergoing cardiac surgery.

The intraoperative hemodynamic effect of dexmedetomidine has also been studied. Kunisawa et al. [8] in their subsequent study reported dexmedetomidine combined with 2 ng/ml fentanyl before cardiopulmonary bypass (CPB) can suppress the decrease in blood pressure at the pre- and post-skin incision periods, can blunt cardiovascular responses to skin incision and sternotomy, and can spare the required effect-site concentration of propofol despite fentanyl concentration, which was half of that in the placebo group. Other studies also reported dexmedetomidine can provide stable hemodynamics for both adults and children during cardiac surgery [9, 10].

Although the most common adverse effects with dexmedetomidine were bradycardia and hypotension, its proper use has been demonstrated to be a valuable aid in these situations because it can decrease perioperative catecholamine concentrations and promote perioperative hemodynamic and adrenergic stability.

Cardioprotective effects

Perioperative cardiac events are always associated with myocardial oxygen supply–demand imbalance and myocardial injury [11, 12]. Furthermore, myocardial injury is unavoidable in open heart surgery under CPB. To decrease the incidence of cardiovascular complications in high-risk surgical patients, perioperative administration of dexmedetomidine has been already used in clinical practice, but this intervention is still controversial.

To date, a series of studies suggested that dexmedetomidine has a protective effect against myocardial ischemia injury in animal and clinic use. Okada et al. [13] used an isolated buffer-perfused rat heart model to assess the specific myocardial effects of dexmedetomidine on left ventricular (LV) function, coronary flow (CF), and infarct size. Dexmedetomidine was administered during the preischemic period with three different concentrations (0.1, 1, and 10 nM). As a result, dexmedetomidine improved the infarct size at each concentration: 45.3 ± 3.6 %, 30.2 ± 3.3 %, and 21.2 ± 2.3 % of total left ventricular mass for 0.1, 1, and 10 nM dexmedetomidine, respectively. This study demonstrated a cardioprotective effect of dexmedetomidine on global ischemia in the isolated rat heart model, which was mediated by α_2-adrenergic stimulation. In a clinical observation study, Riha et al. [14] demonstrated that ketamine-dexmedetomidine anesthesia during elective coronary artery bypass grafting (CABG) resulted in lower postoperative levels of cTnI and CK-MB compared with sevoflurane-sufentanil anesthesia.

Subsequent studies have evaluated the direct protective effects of dexmedetomidine on ischemia-reperfused myocardium in various scenarios. In a study by Yoshitomi et al. [15], 39 pigs were randomized to receive intracoronary infusion of dexmedetomidine at a rate of 1 ng/ml (group LD, $n = 9$), 10 ng/ml (group MD, $n = 9$), or 100 ng/ml (group HD, $n = 9$) of coronary blood flow or vehicle (group C, $n = 12$) for 30 min before ischemia. Myocardial stunning was produced by 12-min ischemia of the perfused area of the left anterior descending (LAD) coronary artery and 90-min reperfusion. The study showed that intracoronary infusion of dexmedetomidine significantly improves regional myocardial contractility after ischemia and reperfusion of the perfused area of LAD in a dose-dependent manner and suppresses the increase in plasma norepinephrine concentration after reperfusion in anesthetized pigs. These effects may result from preventing an increase in myocardial norepinephrine level in the ischemic region through cardiac presynaptic α_2-adrenoreceptor stimulation, but this is not centrally mediated. Similarly, another study by Ibacache et al. [16] demonstrated the relevance of cardiac survival kinases for dexmedetomidine preconditioning and dexmedetomidine peri-insult administration-induced

cardioprotection against regional ischemia/reperfusion injury in in vivo and ex vivo rat heart models.

In contrast to the studies already mentioned, a recent randomized control trial found dexmedetomidine did not provide cardioprotection in coronary artery bypass grafting with cardiopulmonary bypass [17]. Thirty-eight patients were randomized into two groups in the study. In the dexmedetomidine group, dexmedetomidine infusion was started by a loading dose of 0.5 μg/kg/10 min, followed by a continuous infusion of 0.5 μg/kg/h. The placebo group received the same volume of saline. No significant differences were observed between the groups in CK-MB, cTnT, and NT-proBNP values for all measurement intervals. However, mean pulmonary artery pressure tended to be lower in the dexmedetomidine group.

Antiarrhythmic effects

The adverse effects of dexmedetomidine that have been highlighted in the adult population, and those which continue to provide the most concern, are hypotension and bradycardia. In particular, morbidity and even potential mortality related to the negative chronotropic and dromotropic effects of dexmedetomidine have received the most attention in the adult literature [18–21]. However, anecdotal experience with dexmedetomidine in the pediatric population has demonstrated its potential therapeutic applications in the treatment of tachyarrhythmias.

The electrophysiological properties of dexmedetomidine have been assessed in a few pediatric studies [22–24]. Hammer et al. [23] evaluated the effect of dexmedetomidine on sinus node, atrioventricular node, and conduction pathways, and found a decrease in heart rate (HR) with significant depression of sinus and atrioventricular nodal function in a clinical study in pediatric patients undergoing electrophysiological study. Chrysostomou et al. [22], in a prospective observational controlled study in pediatric patients with congenital heart disease, reported changes in various electrophysiological parameters on the surface electrocardiogram; however, they determined that the changes were related to changes in HR and not related to a direct effect of dexmedetomidine on cardiac conduction tissues. In another study, Char et al. [24] tested concurrent administration of ketamine to mitigate the adverse effects on the conduction system associated with dexmedetomidine use in children. They found that increase in mean arterial pressure, decrease in heart rate, sinus node recovery time, QT, and AV nodal effective refractory period were impaired after dexmedetomidine, followed by a return to baseline after coadministration of ketamine.

The antiarrhythmic mechanism of dexmedetomidine action is not completely understood, and to date, the negative chronotropic effects of dexmedetomidine have been used as a therapeutic maneuver in various clinical scenarios. Chrysostomou et al. [25] were the first authors to use dexmedetomidine with the intention of treating tachyarrhythmias in congenital cardiac surgery. In this retrospective study, 14 pediatric patients received dexmedetomidine for atrial and junctional tachyarrhythmias. In 13 (93 %) of 14 patients, conversion to normal sinus rhythm (NSR) or a sufficient decrease in HR to improve hemodynamic function was found. Four patients experienced adverse effects. Nine patients, including patients with junctional ectopic tachycardia (JET) and junctional accelerated rhythm (JAR), were transiently paced with atrial (seven) or AV sequential (two) pacing during the administration of dexmedetomidine to improve AV synchrony. In another prospective cohort study of pediatric patients undergoing cardiothoracic surgery [26], the same

Table 1 Additional anecdotal experience with dexmedetomidine used to treat perioperative tachyarrhythmias

References	Demographics and arrhythmia	Treatment and outcomes
Ohsugi et al. [28]	A 3-year-old with corrected TGA, status post total cavopulmonary connection; SVT was unresponsive to antiarrhythmic therapy and cardioversion with undesirable hemodynamic status	Dexmedetomidine resulted in slowing of the HR and a return to NSR; patient then was weaned from extracorporeal life support
Parent et al. [29]	A 12-year-old with recurrent VT secondary to a dilated cardiomyopathy; arrhythmia was unresponsive to amiodarone	Dexmedetomidine was administered (loading dose of 0.5 μg/kg during 20 min) and resulted in conversion to NSR with a significant improvement in hemodynamic status
Delwadia et al. [30]	A 5-year-old boy with a 1-year history of SVT for surgical repair of a large ASD; the intraoperative episodes of SVT failed to respond to cardioversion and adenosine	Dexmedetomidine dosing included a loading dose of 1 μg/kg during 10 min followed by an infusion of 1 μg/kg/h; before completion of the loading dose, conversion to NSR was noted
LeRiger et al. [31]	A 6-week-old, 4-kg infant for TOF repair; JET occurred after cross-clamp release while the infant was still undergoing CPB	Conversion to SR occurred within 15 min of increasing the dexmedetomidine infusion from 0.5 to 3 μg/kg/h

VT ventricular tachycardia, *NSR* normal sinus rhythm, *TGA* transposition of the great arteries, *HR* heart rate, *SVT* supraventricular tachycardia, *ASD* atrial septal defect, *TOF* tetralogy of Fallot, *JET* junctional ectopic tachycardia, *CPB* cardiopulmonary bypass

investigators evaluated the preemptive antiarrhythmic effects of dexmedetomidine and found perioperative use of dexmedetomidine may reduce the incidence of both ventricular (0 % vs. 25 %) and supraventricular tachyarrhythmias (6 % vs. 25 %)without significant adverse effects. A third study by Chrysostomou et al. [27] provided additional information regarding the potential efficacy of dexmedetomidine in the acute treatment of AV nodal-dependent reentrant tachyarrhythmias in pediatric patients compared with adenosine. As noted by the authors, administration of dexmedetomidine (0.7 ± 0.3 μg/kg) successfully terminated 26 episodes of SVT (96 %) at a median time of 30 s (20–35 s). Although adenosine, the current drug of choice, is very effective, dexmedetomidine may prove to possess a more favorable therapeutic profile with increased effectiveness and fewer side effects. Additional anecdotal experience with dexmedetomidine used to treat perioperative tachyarrhythmias has also been reported in some cases (Table 1) [28–31].

The exact mechanism of this antiarrhythmic effect is not known. Current evidence supports a primary parasympathomimetic effect that results in alteration of the Ca^{2+} current across the myocyte cell membrane and a secondary or additive central sympatholytic effect. Although the negative chronotropic effects of dexmedetomidine have been shown by its novel effect on antiarrhythmias, it is important for the clinician to select the appropriate patients and clinical settings for its safest use. Current data support its use only by experienced personnel including intensivist care physicians, anesthesiologists, and emergency room physicians in a monitored care setting. Although hypotension and bradycardia are the most common adverse effects and can be largely avoided by careful patient selection and dose titration, significant hemodynamic adverse events still may occur in specific patient populations [32, 33]. Rapid intravenous boluses or large doses should be used with caution in various patient populations and in clinical scenarios including significantly depressed left ventricular function and hemodynamic instability, recent high-degree AV block, premature neonates, volume depletion, hepatic disease, and significant hypoalbuminemia.

Sedation in the ICU setting

Sedation, used to reduce stress response and facilitate adequate mechanical ventilation, is an important component of postoperative management following cardiac surgery [34, 35]. However, ideal pharmacotherapy strategies for pain and sedation have not been identified in the postoperative cardiac surgery population. To find an optimal sedation and analgesia therapy, several studies have evaluated the clinical effect of dexmedetomidine therapy in postoperative cardiac surgery patients.

Dexmedetomidine versus GABA agonists

In the early studies, dexmedetomidine appears to offer no advantage over propofol as the initial sedative. Anger et al. [36], in a prospective, descriptive study of clinical practice, evaluated the clinical effect of dexmedetomidine versus propofol-based therapy in 56 postoperative cardiac surgery patients. All mechanically ventilated adult patients admitted to the cardiac surgery ICU postoperatively who were receiving propofol and met inclusion criteria were matched 1:1 by procedure within 48 h of each dexmedetomidine enrollment. The results showed that patients receiving dexmedetomidine had no difference in duration of mechanical ventilation and length of stay, with a higher incidence of hypotension and analgesic consumption. In another retrospective cohort study, Barletta et al. [37] determined the impact of dexmedetomidine on analgesic requirements, sedation, length of mechanical ventilation, adverse drug events, and sedation-related costs after coronary artery bypass graft surgery or valvular surgery. A significant decrease in the amount of opioid required was only seen during the sedative infusion period and did not continue for the duration of the ICU stay. The length of mechanical ventilation, quality of sedation, and adverse events did not significantly differ between the two groups. Sedation-related costs were significantly higher with dexmedetomidine ($p < 0.001$).

Conversely, recent studies demonstrated the different results of dexmedetomidine-based sedation in cardiac surgery patients. Curtis et al. [38] conducted a retrospective study of 582 patients to evaluate the effects between propofol-based and dexmedetomidine-based sedation in cardiac surgery patients. There was a reduced length of ICU stay in the dexmedetomidine group compared with the propofol group, but it did not reach statistical significance (43.9 vs. 52.5 h, $p = 0.067$).

Dexmedetomidine versus morphine

In our routine practice, cardiac surgery patients in ICU are usually given morphine infusion and additional intermittent intravenous midazolam as a sedative agent. However, more and more studies have evaluated the efficacy and safety of dexmedetomidine in comparison to morphine in postoperative cardiac surgery patients. In a smaller, open-label study, Abd Aziz et al. [39] randomized 28 adult, mechanically ventilated patients undergoing open-heart surgery to receive continuous infusions of dexmedetomidine or morphine at the cardiothoracic intensive care unit.

Sedative dosage was adjusted to a goal sedation score of 2–4 using the Modified Ramsay Sedation Scale, and there were no significant differences in scores on either scale between two groups, except heart rate, which was significantly lower in the dexmedetomidine group (86 ± 2.7 vs. 92 ± 1.5 beats/min, $p = 0.028$). Dexmedetomidine showed no difference in safety and efficacy compared with continuous morphine therapy.

A similar study conducted by Lam et al. [40] described its use in pediatric patients with heart failure in the cardiac intensive care unit (CICU). In this retrospective observational study, 47 pediatric patients were randomized into two groups: the DEX group of 21 patients, who received a DEX infusion together with conventional agents, and the control group of 23 patients, who only received conventional sedation agents. Heart rate, mean arterial pressure (MAP), and inotrope score did not significantly differ between the two groups at the termination of infusion. The numbers of daily sedation and analgesic rescue boluses were significantly lower in the DEX group throughout infusion than in the control group ($p = 0.04$). Administration of DEX for children with heart failure in the CICU appears to be safe, but it should be used cautiously. Furthermore, DEX use is associated with decreased conventional sedation agents.

Treatment of delirium

Delirium is a very common complication in older people who undergo cardiac surgery. In recent studies, the incidence of delirium after cardiac surgery ranged from 3 % to 52 %, with even higher numbers among those in intensive care units (ICUs) [41–49]. The impact of delirium following cardiac surgery places a substantial burden on both patients and healthcare systems as a result of increased morbidity, decline in long-term cognitive function, and higher mortality rates [50, 51]. Thus, the prevention of delirium is desirable for both patients and caregivers. Intervention strategies have also been shown to reduce hospital costs [51, 52]. Dexmedetomidine has been found to significantly reduce rates of delirium because of the its lack of cholinergic or γ-aminobutyric acid effect and improved sleep architecture [53, 54]. Furthermore, with the beneficial factor of decreasing need for opioids, it has been previously associated with delirium precipitation [55, 56].

A randomized study by Maldonado et al. [57] investigated the effects of postoperative sedation on the development of delirium in patients undergoing cardiac valve operations with cardiopulmonary bypass (CPB). After successful weaning from CPB, 118 patients were started on one of three randomly assigned, postoperative sedation protocols: dexmedetomidine (loading dose 0.4 μg/kg, followed by a maintenance drip of 0.2–0.7 μg/kg/h), propofol drip (25–50 μg/kg/min), or midazolam drip (0.5–2 mg/h). The presence of delirium was determined by DSM-IV diagnostic criteria during the first 3 postoperative days. Dexmedetomidine was found to decrease the incidence of delirium to 3 % when compared to a 50 % incidence when using propofol or midazolam. Shehabi et al. [58] assessed the effect of dexmedetomidine-based therapy, compared to a morphine-based regimen, on the prevalence of delirium, ventilation time, and hemodynamic profile in postcardiac patients. They found that the duration of delirium was shorter in patients receiving dexmedetomidine. However, there was no difference in incidence between the two groups.

A large meta-analysis on the efficacy of dexmedetomidine as a sedative and analgesic by Tan and Ho included a smaller analysis of five postoperative studies consisting of 1,200 patients. Within these studies, 67 % of the patients were postoperative cardiac patients, and no significant effect of dexmedetomidine on the incidence of delirium was found [59]. Another meta-analysis by Lin et al. [60] determined the risk factors of delirium after cardiac surgery in 25 controlled trials or cohort studies. This meta-analysis showed that several risk factors are associated with postoperative delirium and that sedation with dexmedetomidine may decrease the incidence of delirium in cardiac surgical patients.

Although the body of evidence supporting dexmedetomidine prophylaxis in preventing delirium is growing, the evidence supporting such treatment in patients undergoing elective cardiac surgery is relatively weak. Further studies are needed to define its role in large numbers of patients.

Treatment of withdrawal

The increase in the use of benzodiazepines and opioids administered to provide effective sedation and anxiolysis during acute illnesses has resulted in new issues that must be addressed, including tolerance, physical dependency, and withdrawal [61]. Regardless of whether dexmedetomidine is responsible for withdrawal, the potential role of the agent in treating such problems is supported by animal studies [62–64], case reports of adults and children [65–69], and some retrospective case series [70, 71].

Finkel et al. [67] outlined the successful use of dexmedetomidine to treat withdrawal of two pediatric patients after cardiac transplantation. Baddigam et al. [65] reported the successful use of dexmedetomidine to treat withdrawal of three patients after prolonged ICU stays following cardiac surgery. The former report included a 6-month-old

infant with pulmonary atresia who had a 3-month exposure to high-dose opioids and benzodiazepines and a 7-year-old boy who had been sedated while undergoing extracorporeal membrane oxygenation for 3 weeks before transplantation. The latter report included an adolescent patient who had a history of ethanol, tobacco, cannabinoid, and intravenous drug abuse and two pediatric-age patients who had been sedated to facilitate adequate mechanical ventilation after cardiac surgery for a long time in the ICU. Dexmedetomidine allowed successful rapid withdrawal from opioids and benzodiazepines while maintaining hemodynamic stability in the presence of denervated hearts. The largest reported series regarding the use of dexmedetomidine to control withdrawal in a pediatric population is a retrospective review of seven infants ranging in age from 3 to 24 months, four of whom had congenital heart disease (CHD) [70].

With its rapid titration by intravenous infusion, dexmedetomidine is an ideal agent to use as a sedative adjunct or as means of controlling withdrawal from other medications. Despite its potential benefits, dexmedetomidine can have deleterious effects on cardiorespiratory function, which mandates close observation, especially in spontaneously ventilating patients.

Procedural sedation

As the demand for optimal sedation and analgesia in pediatric patients undergoing cardiac catheterization has increased, a number of providers have gained experience in providing for the sedation and analgesia of these patients. To simplify calculations of shunt fraction and enable accurate cardiac output measurements, supplemental oxygen administration should be minimized, and as many advocate, these anesthetic agents are sometimes used at a lower dose, resulting in incomplete sedation. This decreased sedation can increase the risk of pneumothorax or hemothorax during procedures that require precision such as central venous line placement and decrease the overall success. Furthermore, traditional sedative agents can have a negative effect on cardiac function, can alter cardiac conduction, and can cause respiratory depression that warrants rescue positive-pressure ventilation. Dexmedetomidine has sedative properties, provides an analgesic effect, and preserves spontaneous ventilation. These properties make dexmedetomidine a useful sedative during invasive procedures that require spontaneous ventilation [72]. To date, only a few studies have investigated the utility of dexmedetomidine in this scenario.

Table 2 Anecdotal experience with dexmedetomidine for sedation of patients with heart disease during perioperative period

References	Type of study and cohort size	Outcomes
Barton et al. [77]	Case series of six children with CHD ranging from 3 days to 29 months who received sedation for an invasive procedure including central venous catheter placement, chest tube insertion, fiberoptic bronchoscopy, and femoral vein cutdown for placement of a Broviac catheter were breathing spontaneously throughout their procedure	Dexmedetomidine was used as the primary agent for sedation while supplemental sedation with ketamine was provided for three of the patients; dexmedetomidine was administered as a bolus (mean dose 1.5 μg/kg; range, 1–3 μg/kg). Two infants required supplementation with a single dose of ketamine (either 0.3 or 0.5 mg/kg); one patient who underwent a more prolonged procedure required a second bolus dose of dexmedetomidine (1 μg/kg) and a total ketamine dose of 1.5 mg/kg
Munro et al. [78]	Single patient case report of a 12-year-old boy with a diagnosis of idiopathic pulmonary hypertension and a behavioral disorder, undergoing diagnostic cardiac catheterization	Dexmedetomidine was administered at 1 μg/kg/h with the patient breathing spontaneously followed by a loading dose of ketamine 1 mg/kg and dexmedetomidine 1 μg/kg; the procedure was completed successfully without change in hemodynamic status
Kunisawa et al. [79]	Two adults with mental retardation were sedated with high-dose dexmedetomidine alone during diagnostic cardiac catheterization; one had been diagnosed with valvular disease and VSD, the other one was diagnosed with Fallot and ASD	High-dose dexmedetomidine was administered and the maximum predicted plasma concentration of dexmedetomidine was up to 4.3 ng/ml; in both cases, dexmedetomidine provided proper sedation and no respiratory system complications occurred despite inspiration of room air even when a high dose was administered
Kunisawa et al. [80]	A toddler was scheduled to undergo interventional cardiac catheterization after intracardiac repair. Dexmedetomidine was administered at the dose of 1–15 μg/kg/h to maintain the BIS value between 40 and 70 and to keep the patient immobile	Maximum pCp of dexmedetomidine and mean pCp were calculated as 6.1 and 4.1 ng/ml, respectively. A high dose of dexmedetomidine was found to be useful in some cases because the morphological assessment could be performed without the need for oxygen supply or mechanical ventilation and because no respiratory trouble occurred despite the procedure being performed around the neck

CHD congenital heart disease, *VSD* ventricular septal defect, *ASD* atrial septal defect, *pCp* predicted plasma concentration, *BIS* bispectral index

Initial work to compare the effects of dexmedetomidine–ketamine and propofol–ketamine combinations on hemodynamics, sedation level, and the recovery period in pediatric patients undergoing cardiac catheterization, reported by Tosun et al. [73], showed that the dexmedetomidine–ketamine combination was not superior to the propofol–ketamine combination because of insufficient sedation and analgesia and a longer recovery time.

A more recent study by Munro et al. [74] reported their initial experience using dexmedetomidine for diagnostic and interventional catheterization in children and suggested that dexmedetomidine, with or without the addition of propofol, may be a suitable alternative for sedation in spontaneously breathing patients undergoing cardiac catheterization.

In contrast to the study of Tosun et al. [73], a continuous ketamine infusion was not used in another study conducted by Mester et al. [75] This retrospective analysis evaluated the efficacy of a dexmedetomidine–ketamine sedation during diagnostic and interventional cardiac catheterization for 16 pediatric patients. Only minimal changes in heart rate and blood pressure were noted. They demonstrated that the combination of ketamine and dexmedetomidine provides effective sedation for cardiac catheterization in infants and children without significant effects on cardiovascular or ventilatory function.

The latest prospective cohort study examined the feasibility and safety of transcatheter aortic valve replacement (T-AVR) under monitored anesthesia care [76]. Ninety-two consecutive patients undergoing T-AVR were divided into two groups: I, monitored anesthesia care ($n = 70$; 76.1 %) and II, intubation ($n = 22$; 23.9 %). Monitored anesthesia care was given by anesthesiologists in one of two protocol regimens: ketamine and propofol or dexmedetomidine. Although eight patients (11.4 %) with monitored anesthesia care were converted to general anesthesia, there was a trend to lower median intensive care unit stay and hospital stay in the monitored anesthesia care group. Further, the monitored anesthesia care group had significantly lower median procedure duration, and there was no significant difference in procedural complications between the two groups. Additional anecdotal experience with dexmedetomidine for procedural purposes in infants and children also has demonstrated its potential utility during the perioperative period of cardiac surgery (Table 2) [77–80].

Safety profile

There are a few side effects of dexmedetomidine, which should always be kept in mind before choosing the patients for its use. The most common adverse effects with dexmedetomidine were bradycardia and hypotension, in some cases severe enough to warrant the use of vasoactive support. These temporary effects have been managed with atropine, ephedrine, and volume infusion. Caution should be taken in those clinical situations in which the sympatholytic actions of α_2-receptor agonists prove detrimental, such as in patients with left ventricular dysfunction and when administered to patients who are volume depleted, vasoconstricted, or have severe heart block [81]. Other adverse cardiovascular effects reported, owing primarily to the initial α_2-receptor effects on systemic circulation followed by central α_2-receptor agonism, included tachycardia, hypertension with the need for intervention, a cardiovascular Sequential Organ Failure Assessment score >1, an increase in arrhythmias, and cardiac arrest [82]. These potentially deleterious effects have significant implications for the safe use of these drugs in the critically ill, when multiple factors with negative chronotropic influences convene in a clinical setting, and underline the importance of adequate patient selection for the safe use of dexmedetomidine.

Adverse noncardiovascular events included dry mouth, nausea, desaturation, pulmonary edema, and atelectasis. Long-term infusions of dexmedetomidine may result in upregulation of receptors, leading to the development of withdrawal syndrome on abrupt discontinuation manifesting as nervousness, agitation, headaches, and hypertensive crisis. The teratogenic effects of dexmedetomidine have not been adequately studied at this time, but the drug does cross the placenta and should be used during pregnancy only if the benefits justify the risk to the fetus [83]. Therefore, large-scale randomized controlled trials are still needed to establish various effects of dexmedetomidine and to clearly define its safety profile.

Conclusion

Dexmedetomidine has been shown to be safe in short-term sedation. Although hypotension and bradycardia are the most significant side effects, these effects are currently being explored as a therapeutic option for the treatment of hemodynamic response and perioperative tachyarrhythmias in patients with heart disease. Given its favorable sedative and anxiolytic properties together with its limited effects on hemodynamic and respiratory function, there is growing interest in the use of dexmedetomidine for the perioperative period of cardiac surgery. These applications include its use as an agent to attenuate the hemodynamic response, as cardioprotection therapy for myocardial ischemic injury, as a therapeutic option for tachyarrhythmias, as sedation during mechanical ventilation, as treatment for withdrawal, as procedural sedation, and to prevent emergence delirium. It is apparent that dexmedetomidine has several beneficial

cardiovascular and neuroprotective properties. Therefore, there is an urgent need to confirm these beneficial effects in well-designed studies to establish its place in cardiac anesthesia.

Conflict of interest The author has no conflict of interest to declare in relationship to the information contained in this article.

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