A comparison between the effect of ketamine versus dexmedetomidine infusion on the frequency of spells during Fallot repair: a randomized controlled trial

Mai A.F. Madkour, Mohamed Elayashy, Mohamed Maher

Department of Anesthesia, Surgical Intensive Care, and Pain Management, Faculty of Medicine, Cairo University, Cairo, Egypt

Correspondence to Mohamed E. Mohamed, MD, 7 El-Shishiny Street, El-Maryotia, Faisal, Giza - 12131, Egypt Tel: 0020235941134; Mobile: 00201001833155; e-mail: mohamedelayashy@kasralainy.edu.eg

Received 26 February 2017
Accepted 4 May 2017

The Egyptian Journal of Cardiothoracic Anesthesia 2017, 11:1–7

Background
Patients with tetralogy of Fallot experience changes in the dynamics of right ventricular outflow tract obstruction, or changes in systemic vascular resistance cause a decrease in the systemic arterial oxygen saturation. Dexmedetomidine use is not yet approved in pediatric patients, but its effects have been studied in pediatric patients during cardiac surgery, which showed a decrease in the incidence of arrhythmias after bypass. In this study, we postulate that dexmedetomidine may have potential benefits on the pulmonary vascular resistance, which may play a role in decreasing the incidence of tet spells during Fallot repair.
Patients and methods
This randomized controlled study was conducted in Cairo university pediatric hospitals, where patients were randomly allocated to two equal groups, 30 patients in each group between 6 months and 12 years of age. Patients were allocated to two groups to receive two different anesthesia maintenance regimens: group 1 (the ketamine group, n=30) received isoflurane 0–1% together with ketamine infusion 1 mg/kg/h, and group 2 (the dexmedetomidine group, n=30) received isoflurane 0–1% together with dexmedetomidine 0.25 μg/kg/h. Mean arterial pressure, heart rate, and oxygen saturation were recorded. Arterial blood gases, glucose and lactate levels, and number of tet spells, which is the primary outcome in our study, were evaluated.
Results
Our primary finding was the number of spells, which was 2 (range: 0–4) in the KET group compared with 0 (range: 0–2) in the DEX group ($P<0.001$). Intraoperative heart rate decreased more in the DEX group than in the KET group at all times of measurement but with a significant difference at T2 and T3. Mean arterial pressure also decreased in the DEX group with a significant difference between the two groups at T1, T2, and T3.
Conclusion
Dexmedetomidine infusion as an adjuvant to anesthesia decreased the number of spells in the prebypass period significantly better than ketamine infusion in children undergoing Fallot repair.

Keywords:
dexmedetomidine, Fallot, ketamine, spells

Egypt J Cardiothorac Anesth 11:1–7

1687-9090

Introduction

Patients with tetralogy of Fallot experience changes in the dynamics of right ventricular outflow tract obstruction, or changes in systemic vascular resistance cause a decrease in the systemic arterial oxygen saturation [1].

Intraoperative decrease in systemic vascular resistance due to hypotension or an increase in right ventricular outflow tract obstruction due to increased sympathetic stimulation is associated with an increase in right-to-left shunting and a decrease in systemic arterial hemoglobin oxygen saturation, producing a hypoxemic or 'tet' spell during anesthesia and surgery [2].

Dexmedetomidine is a highly selective α_2-adrenergic agonist approved for sedation in adults. Although not approved in the pediatric population, an increasing number of reports described its use in pediatric patients during intraoperative period. Le Reiger *et al.* [3] used dexmedetomidine for the control of junctional ectopic rhythm after weaning from cardiopulmonary bypass in pediatric patients undergoing repair of tetralogy of Fallot. Conversion to normal sinus rhythm occurred 15 min of increasing dexmedetomidine infusion from 0.5 to 3 μg/kg/h [3].

There is an increasing need nowadays for dexmedetomidine in clinical practice for pediatric patients, including the use of dexmedetomidine intraoperatively as a part of balanced anesthetic technique, its use in sedation during mechanical ventilation in ICU, and its use in invasive and noninvasive procedural sedation in catheterization laboratory or during computed tomography and MRI [4].

Dexmedetomidine also was effective in patients when other agents (midazolam and/or chloral hydrate) failed. Koroglu *et al.* [5] compared dexmedetomidine and propofol for MRI. Although both propofol and dexmedetomidine provided effective sedation, more hemodynamic and respiratory effects were seen with propofol including tachycardia, decreased mean arterial pressure (MAP), and hypoxemia. Although likely to be of little clinical significance in the majority of patients, these differing effects may be of clinical consequence in patients with cyanotic congenital heart disease in whom a decrease in MAP may increase right-to-left shunt or who may tolerate hypoxemia less easily compared with patients without comorbid diseases [5].

Munro *et al.* [6] were the first to report their experience with dexmedetomidine for sedation during cardiac catheterization in pediatric patients. Their technique involved premedication with oral midazolam followed by inhalation induction with sevoflurane to facilitate the placement of vascular access. This was followed by discontinuation of the sevoflurane and the transition to intravenous dexmedetomidine administered as a bolus of 1 μg/kg administered over 10 min followed by a continuous infusion starting at 1 μg/kg/h [6].

The effect of dexmedetomidine on pulmonary vascular resistance is not clear [4], although transient pulmonary hemodynamic changes were found in adult healthy volunteers with dexmedetomidine infusion [7] compared with placebo. Dexmedetomidine attenuates the increase in MAP, mean pulmonary artery pressure, and pulmonary capillary wedge pressure in adults with pulmonary hypertension undergoing mitral valve replacement [8].

There are also very limited data available describing the impact of dexmedetomidine on patients with single-ventricle, for whom chronotropic variability also are important. These patients have poor clinical outcomes when atrioventricular synchrony is lost [4].

The potential benefits of dexmedetomidine in providing postoperative sedation in infants and children with congenital heart disease undergoing mechanical ventilation also have been studied. Chrysostosmou *et al.* [9] retrospectively reviewed their experience with postoperative dexmedetomidine infusion in pediatric patients undergoing cardiac and thoracic surgery. Dexmedetomidine was administered after the surgical procedure as a continuous infusion of 0.1–0.5 μg/kg/h and continued for 3–26 h.

Patients and methods

This randomized controlled study was conducted in Cairo university pediatric hospitals after obtaining our Institute Ethical Committee approval. Written informed consent was obtained from the guardians. Randomization was carried out using a computer-generated sequence and concealed in opaque envelopes. Patients were randomly allocated to two equal groups comprising 30 patients in each group between 6 months and 12 years of age. Pediatric patients with Fallot tetralogy who were between 4 months and 12 years of age and weighing more than 6 kg scheduled for total repair were included in this study. Patients with congestive heart failure or those who underwent Blalock–Taussig shunt or redo Fallot repair were excluded.

After sedation with ketamine 3–5 mg/kg intramuscularly, an intravenous catheter was inserted and infusion of Ringer solution was started. The patient was connected to five-lead ECG, pulse oximetry, and noninvasive pressure cuff.

Anesthesia was induced using ketamine 1 mg/kg and fentanyl 10–15 μg/kg, and tracheal intubation was facilitated using pancuronium 0.1 mg/kg. Mechanical ventilation was started with tidal volume 6 ml/kg, inspiratory-to-expiratory time ratio 1 : 2, and positive end-expiratory pressure 5 cmH_2O, and respiratory rate was adjusted to maintain $EtCO_2$ between 35 and 40 cmH_2o; a radial arterial catheter was inserted followed by a central venous catheter in the internal jugular vein.

Patients were allocated to two groups to receive two different anesthesia maintenance regimens (randomization numbers were provided in sealed envelopes): group 1 (n=30) received isoflurane 0–1% together with ketamine infusion 1 mg/kg/h prepared by adding 100 mg ketamine to 25 ml normal saline to have a concentration of 4 mg/ml, and group 2 (n=30) received isoflurane 0–1% together with dexmedetomidine 0.25 μg/kg/h prepared by adding 1 mg of dexmedetomidine to 25 ml normal saline to have a concentration of 4 μg/ml.

All infusions were prepared by an anesthesia nurse. Infusion rates were adjusted to maintain arterial pressure within 25% of baseline .When MAP was less than 25% of baseline, maintenance agents were discontinued temporarily until restoration of blood pressure. Unresponsive hypotension was treated with calcium gluconate 50 mg/kg followed by dopamine infusion 5 μg/kg/min. Pancuronium boluses of 0.01 mg/kg were given when needed, and FiO_2 was maintained at 1 during the study period.

Number of tet spells was our primary outcome. It is defined as an attack of desaturation and hypotension. MAP, heart rate (HR), oxygen saturation, arterial blood gases, and glucose and lactate levels were recorded. All data were obtained simultaneously at three intervals: T1: 10 min after intubation; T2: 10 min after sternotomy; and T3: at completion of cannulation before initiation of cardiopulmonary bypass. All operations were performed by same surgeon.

Statistical analysis

Categorical data were presented as frequency (%) and analyzed using χ^2. Continuous data were presented as mean and SDs and analyzed using the unpaired *t*-test. Nonparametric data presented as median and range and were analyzed using the Mann–Whitney test. Repeated measures were analyzed using the analysis of variance test for repeated measures. *P* value less than or equal to 0.05 was considered statistically significant, and *P* value less than or equal to 0.01 was considered highly significant. SPSS (version 15) software and Microsoft Excel 2016 were used for analysis.

Sample size

The primary outcome in our study was the number of tet spells 'periods of hypotension and desaturation' during procedure. We calculated the sample size using version 15.0 (MedCalc Software, Ostend, Belgium) to detect a difference of 35% between the two study groups. Having a study power of 80% and an α error of 0.05, a minimum number of 25 patients was needed for each group; we increased the number by 20% to be 30 patients per group to compensate for possible dropouts [7].

Results

A total of 60 patients with Fallot disease were enrolled in our study, 30 patients in each group (43 patients were on β-blockers and 17 were not, but all patients had a history of spells; moreover, 43 patients were blue tets and 16 were pink). Patients' demographic data are presented in Table 1.

Our primary finding was the number of spills, which was 2 (range: 0–4) in the KET group compared with 0 (range: 0–2) in the DEX group. There was a significant difference with *P* value less than 0.001.

Intraoperative hemodynamics (HR and MAP) (Figs 1 and 2) are presented as mean±SD. HR decreased more in the DEX group than in the KET group at all times of measurement but with a significant difference at T2 and T3. MAP also decreased in the DEX group with a significant difference between the two groups at T1, T2, and T3.

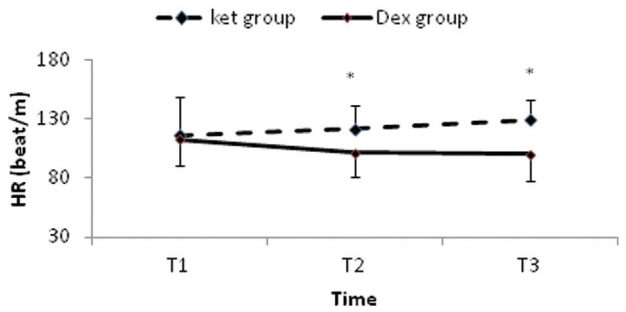
As regards blood gases, pH, $PaCO_2$, and PaO_2 are presented in Figs 3–5. There was a significant difference in pH at T3 with decreased pH in the KET group at all times. There was a significant difference in $PaCO_2$ at T2 with increased CO_2 in the KET group. PaO_2 was higher in the DEX group with a significant difference at all times of measurement.

There was no significant difference between the two groups as regards lactate level and glucose level at all times of measurements (Figs 6 and 7).

Table 1 Demographic data

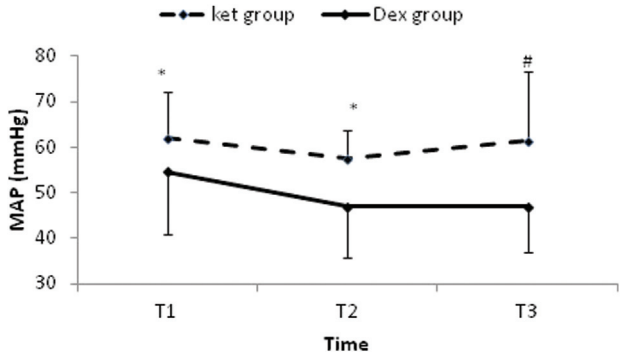
	Group 1 (*n*=30) [*n* (%)]	Group 2 (*n*=30) [*n* (%)]	*P* value
Age	2.36±1.31	1.91±0.91	0.4
Sex			0.8
Male	17 (56)	15 (50)	
Female	13 (44)	15 (50)	
Weight (kg)	12±2.73	11.7±2.13	0.65
β-Blocker			0.7
On β-blocker	22 (73.3)	21 (70)	
No β-blocker	8 (26.7)	9 (30)	
Tets			0.7
Blue tets	22 (73.3)	21 (70)	
Pink tets	8 (26.7)	9 (30)	

Figure 1



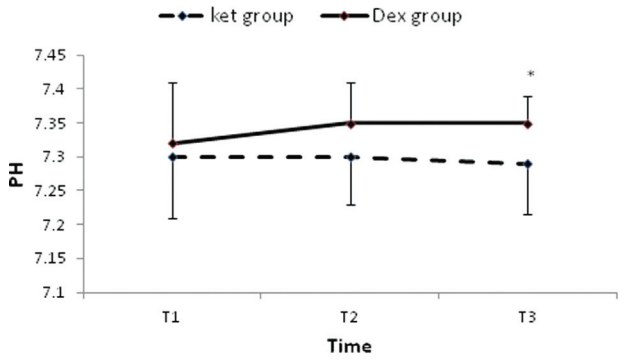
Mean±SD of heart rate (HR). T1=10 min after induction. T2=10 min after sternotomy. T3=before start of bypass. *$P<0.01$

Figure 2



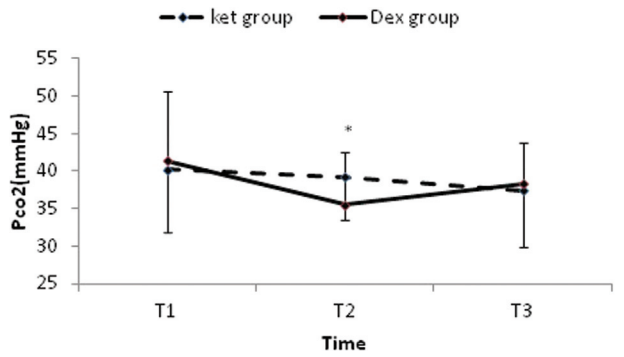
Mean±SD of mean arterial pressure (MAP). T1=10 min after induction. T2=10 min after sternotomy. T3=before start of bypass. *$P<0.05$, #$P<0.01$

Figure 3



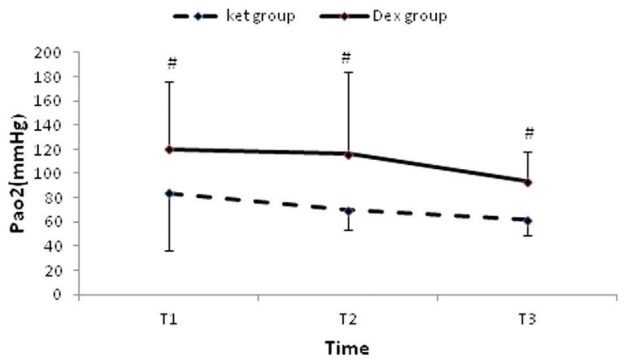
Mean±SD of pH. T1=10 min after induction. T2=10 min after sternotomy. T3=before start of bypass. $P<0.05$

Figure 4



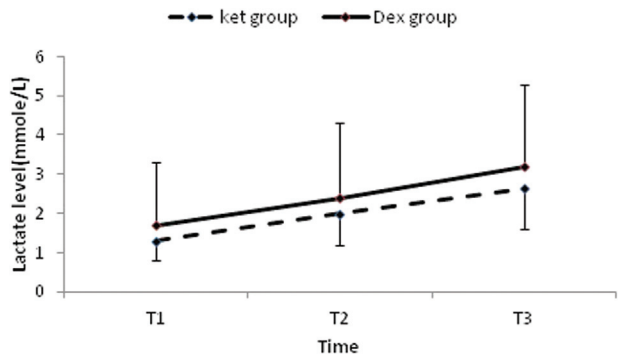
Mean±SD of $PaCO_2$. T1=10 min after induction. T2=10 min after sternotomy. T3=before start of bypass. *$P<0.05$

Figure 5



Mean±SD of PaO_2. T1=10 min after induction. T2=10 min after sternotomy. T3=before start of bypass. #$P<0.01$

Figure 6



Mean±SD of lactate level. T1=10 min after induction. T2=10 min after sternotomy. T3=before start of bypass

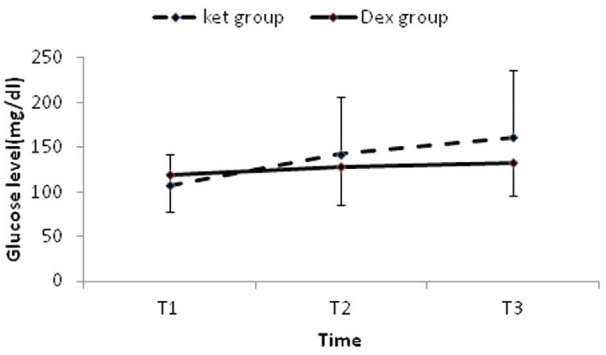
Discussion

Dexmedetomidine infusion as an adjuvant to anesthesia decreased the number of spells in the prebypass period significantly better than ketamine infusion in children undergoing Fallot repair.

Depth of anesthesia plays a role in the development of intraoperative tet spells; light plane of anesthesia causes a secondary spell caused by increased sympathetic activity leading to tachycardia and right ventricular outflow tract obstruction [1].

In a study by Baranky *et al.* [10], an increase in the depth of anesthesia using a combination of sufentanil and flunitrazepam has maintained hemodynamic stability and prevented plasma elevations of epinephrine and

Figure 7



Mean±SD of glucose level. T1=10 min after induction. T2=10 min after sternotomy. T3=before start of bypass

norepinephrine during surgical stimulation, thus decreasing the frequency of spells during the repair of Fallot.

In our study we compared the effect of both ketamine and dexmedetomidine on hemodynamic stability and the level of glucose and lactate during surgical stimulation. We also compared their role in decreasing the frequency of spells intraoperatively.

Both of the drugs have completely different effects on systemic vasculature; ketamine increases the systemic vascular resistance, thus antagonizing the vasodilatation caused by the inhalational anesthetics. In this group of patients, the resistance of right ventricular outflow causes venous return flow from the right to the left across the ventricular septal defect, producing arterial desaturation. Because of the large ventricular septal defect, systemic and pulmonary circuits are parallel, and changes in systemic vascular resistance affect pulmonary blood flow [11–13].

The most unaccepted effect of ketamine is that it increases the pulmonary vascular resistance as well, especially in children [14], and hence it acts only through one mechanism to decrease desaturation, which is increasing the systemic vascular resistance; this explains the continuity of spells with ketamine infusion.

Ketamine is one of the anesthetic drugs of choice in Fallot repair due to its beneficial cardiovascular effects of increasing systemic vascular resistance and the resulting decrease in right-to-left shunt. Furthermore, by increasing pulmonary blood flow, it improves oxygenation. In a study, intravenous or intramuscular ketamine as induction agents did not significantly decrease SaO_2% in patients with Fallot's tetralogy [15].

Ketamine appears as a good choice for induction and maintenance in patients with congenital heart disease where it preserves intraoperative and postoperative hemodynamic stability.

Dexmedetomidine is a highly specific α2-receptor agonist that is used increasingly in children, although not yet Food Drug and Administration approved in pediatric patients [16]. Activation of presynaptic α2 receptors on sympathetic nerves and the central nervous system induces sympatholysis, whereas activation of vascular postsynaptic receptors causes both vasoconstriction (activation of α2 receptors on vascular smooth muscle cells) and vasodilatation (activation of α2 receptors on endothelial cells). Although there are several studies evaluating the effect of dexmedetomidine on the systemic blood pressure, there is very limited information on its effects on the pulmonary vascular resistance, particularly in pediatric patients undergoing cardiothoracic surgery [16].

The study by Lazol *et al.* [17], which investigated the effect of dexmedetomidine on pulmonary vascular resistance in pediatric patients undergoing various cardiac surgeries such as Norwood, Glenn, and Fontan operations, showed that administration of dexmedetomidine at the usual therapeutic doses is not associated with any increase in the pulmonary vascular resistance. On the contrary, there was evidence that its use may be associated with a modest decrease in the pulmonary vascular resistance [16].

The mechanism of action of dexmedetomidine is due its ability to block sympathetic stress response, decrease analgesic and anesthetic requirements, decrease respiratory depression and bradycardia, and decrease the incidence of arrhythmias [18].

We assume that the significant decrease in the cyanotic spells in the DEX group compared with the KET group is due to the absence of interference in pulmonary vascular resistance in this group, whereas in the KET group it is highly increased together with the increase in systemic vascular resistance causing masking of its beneficial effects in cyanotic children.

A study by Mukhtar *et al.* [19] has demonstrated that dexmedetomidine has a significant sympatholytic effect blunting the endogenous catecholamine release in response to surgical trauma in pediatric patients undergoing cardiopulmonary bypass and surgery for congenital heart disease. A total of 30 infants and children were randomized to receive placebo or

dexmedetomidine (bolus of 1 mg/kg over 10 min followed by infusion at 0.5 mg/kg/h) after anesthetic induction. The concentrations of plasma cortisol, norepinephrine, epinephrine, and glucose increased after sternotomy and cardiopulmonary bypass in both groups; however, the increase in glucose was not significant in the DEX group [19].

We found that there was no difference as regards lactate level in both study groups. Animal studies [20,21] have shown direct myocardial preserving effect of dexmedetomidine by lowering stress response, lowering anti-ischemic responses such as lactate production, thus raising resistance to developing arrhythmias, and promoting protective mechanisms during hypoxia and reoxygenation.

The undesired hemodynamic effects of dexmedetomidine in pediatric patients are bradycardia, sinus arrhythmias, and hypotension [16], which are absent with ketamine. These hemodynamic effects are exaggerated in the presence of inhalational anesthesia and are of special importance in children with congenital heart diseases, where they may affect also the pulmonary blood flow. Although we omitted the use of a loading dose of dexmedetomidine for these reasons, we found a significant decrease in HR and mean arterial blood flow in the DEX group at both T2 and T3 compared with the KET group. These effects were treated instantly when becoming unfavorable by discontinuing the drug and then with vasopressors if needed. Further, if more sedation was needed a bolus of 1 ml of the infused drug was given.

In our study there were blue tets patients and pink tets patients. In addition, there were patients on β-blockers and other patients were not. These factors did not affect our result as there was no significant difference as regards their distribution in each group.

We think the main limitation of our study was that the depth of anesthesia was not compared between the two groups using a bispectral index; however, the use of inhalational anesthetic may have affected the comparison between the two drugs.

Further studies are recommended to assess the role of dexmedetomidine in non-Fallot congenital cardiac patients and whether it has adverse events in these cases.

Conclusion

The importance of preventing the tet spells associated with desaturation in Fallot patients makes the use of dexmedetomidine favorable in those pediatric patients. All of its undesirable side effects can be prevented by not using a loading dose for infusion or by decreasing the infusion rates or even the use of low dose of vasopressors, which are normally used in congenital heart surgery.

Financial support and sponsorship
Nil.

Conflicts of interest
There are no conflicts of interest.

References

1 William JG, Thomas ES, Ross MU, Joseph AK. Intraoperative hypoxemic spells in tetralogy of Fallot. An echocardiographic analysis of diagnosis and treatment. Anesth Analg 1989; 68:8159.

2 Hickey PR, Wessel D Treatment of congenital heart disease. In: Kaplan A, editor. Cardiac anesthesia. New York, NY: Grune & Stratton; 1987. pp. 625–723.

3 LeReiger M, Naguib A, Gallantowicz M, Tobias JD. Dexmedetomidine controls junctional ectopic tachycardia during tetralogy of Fallot in an infant. Anna Card Anesth 2015; 15:224–228.

4 Tobias JD. Dexmedetomidine: applications in pediatric critical care and pediatric anesthesiology. Pediatr Crit Care Med 2007; 8:115–131.

5 Koroglu A, Teksan H, Sagir O, Yucel A, Toprak H, Ersoy OM. Comparison of the sedative, hemodynamic, and respiratory effects of dexmedetomidine and propofol in children undergoing magnetic resonance imaging. Anesth Analg 2006; 103:63–67.

6 But AK, Ozgul U, Erdil F, Gulhas N, Toprak HI, Durmus M, Ersoy MO. The effects of preoperative dexmedetomidine infusion on hemodynamics in patients with pulmonary hypertension undergoing mitral valve replacement surgery. Acta Anaesthesiol Scand 2006; 50:1207–1212.

7 Bloor BC, Ward DS, Belleville JP, Maze M. Effects of intravenous dexmedetomidine in humans: II. Hemodynamic changes. Anesthesiology 1992; 77:1134–1142.

8 Koroglu A, Teksan H, Sagir O, Yucel A, Toprak H, Ersoy OM. A comparison of the sedative, hemodynamic, and respiratory effects of dexmedetomidine and propofol in children undergoing magnetic resonance imaging. Anesth Analg 2006; 103:63–67.

9 Munro HM, Tirotta CF, Felix DE, Lagueruela RG, Madril DR, Zahn EM, Nykanen DG. Initial experience with dexmedetomidine for diagnostic and interventional cardiac catheterization in children. Paediatr Anaesth 2007; 17:109–112.

10 Baranky A, Richter JA, Henze R, Mitto P, Spath P. Total intravenous anesthesia for infants and children undergoing correction of tetralogy of Fallot: sufentanil versus sufentanil-flunitrazepam technique. J Cardiothorac Vascu Anesth 1992; 6:185–189.

11 Tuğrul M, Çamci E, Pembeci K, Telci L, Akpir K. Ketamine infusion versus isoflurane for the maintenance of anesthesia in the prebypass period in children with tetralogy of Fallot. J Cardiothorac Vasc Anesth 2000; 14:557–561.

12 Traber DL, Wilson RD, Priano LL. The effects of alpha-adrenergic blockade on the cardiopulmonary response to ketamine. Anesth Analg 1971; 50:737–742.

13 Traber DL, Wilson RD. Involvement of sympathetic nervous system in the pressor response to ketamine. Anesth Analg 1969; 48:248–252.

14 Hickey PR, Hansen DD, Cramolini GM, Vincent RN, Lang P. Pulmonary and systemic hemodynamic responses to ketamine in infants with normal and elevated pulmonary vascular resistance. Anesthesiology 1985; 62:287–293.

15 Tavakollian AR, Allahyary E. The comparison of the effect of three anesthetic induction regimens on the arterial oxygen saturation in children with tetralogy of Fallot undergoing cardiac surgery. Iran Red Crescent Med J 2011; 13:702–706.

16 Easley RB, Tobias JD. Pro: dexmedetomidine should be used for infants and children undergoing cardiac surgery. J Cardiothorac Vasc Anesth 2008; 22:147–151.

17 Lazol JP, Lichtenstein SE, Jooste EH, Shiderly D, Nivedit A, Tatum GH, *et al.* Effect of dexmedetomidine on pulmonary artery pressure after congenital cardiac surgery: a pilot study. Pediatr Crit Care Med 2010; 11: 589–592.

18 Kristen L. Dexmedetomidine infusion as an adjunct anesthetic for tetralogy of Fallot repair during a pediatric cardiac mission in Jamaica: a case report. AANA J 2012; 80:385–391.

19 Mukhtar AM, Obayah EM, Hassona AM. The use of dexmedetomidine in pediatric cardiac surgery. Anesth Analg 2006; 103:52–56.

20 Kamibayashi T, Mammoto T, Hayashi Y, Yamatodani A, Takada K, Sasaki S, Yoshiya I. Further characterization of the receptor mechanism involved in the antidysrhythmic effect of dexmedetomidine on halothane/epinephrine dysrhythmias in dogs. Anesthesiology 1995; 83:1082–1089.

21 Guo H, Takahashi S, Cho S, Hara T, Tomiyasu S, Sumikawa K. The effects of dexmedetomidine on left ventricular function during hypoxia and reoxygenation in isolated rat hearts. Anesth Analg 2005; 100:629–635.