

Dexmedetomidine: What is its role in the pediatric cardiac patient?

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I TOLD YOU I'M NOT SICK! WHAT'S THAT? WILL IT HURT?
IT'S A TONGUE DEPRESSOR. IT WON'T HURT AT ALL.
WHAT'S THAT? WILL IT HURT?
IT'S A STETHOSCOPE. IT WON'T HURT AT ALL.
3-31
WHAT'S THAT? WILL IT HURT?
IT'S A CATTLE PROD. IT HURTS A LITTLE LESS THAN A BRANDING IRON.
LITTLE KIDS HAVE NO SENSE OF HUMOR.
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WATTERSON

Panacea – goddess of all cures





Woodcut by Veronese physician Joseph Gazola, 1716

Asclepius and the family





Dexmedetomidine

- Maybe not a panacea.

- But a useful tool in the anesthetic and critical care management of children with congenital heart disease

Disclosures



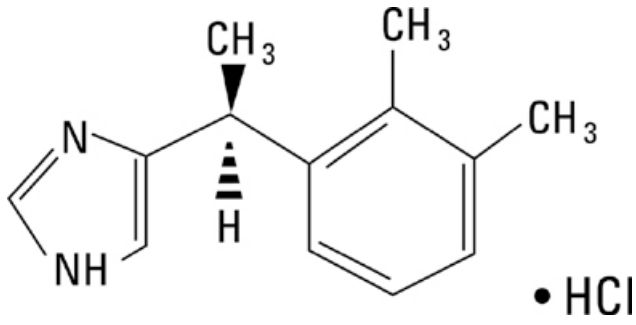
Objectives

- Participants will:

- Understand the pharmacology of dexmedetomidine
- Discuss the clinical utility of dexmedetomidine in the pediatric cardiac patient population
- Recognize the limitations of using dexmedetomidine in children with congenital heart disease
- Explore potential benefits of dexmedetomidine as presented in basic science literature

Dexmedetomidine

- α_2-adrenergic receptor agonist
- α_2:α_1 selective binding 1600:1
  - 7x more selective than clonidine



- α phase, redistribution half-life= 7 mins
- *B* phase, terminal elimination half life = 2 hrs
- Clearance 15 mL/kg/min
- Shorter half-life than clonidine
  - Allows for infusion titration

Dexmedetomidine

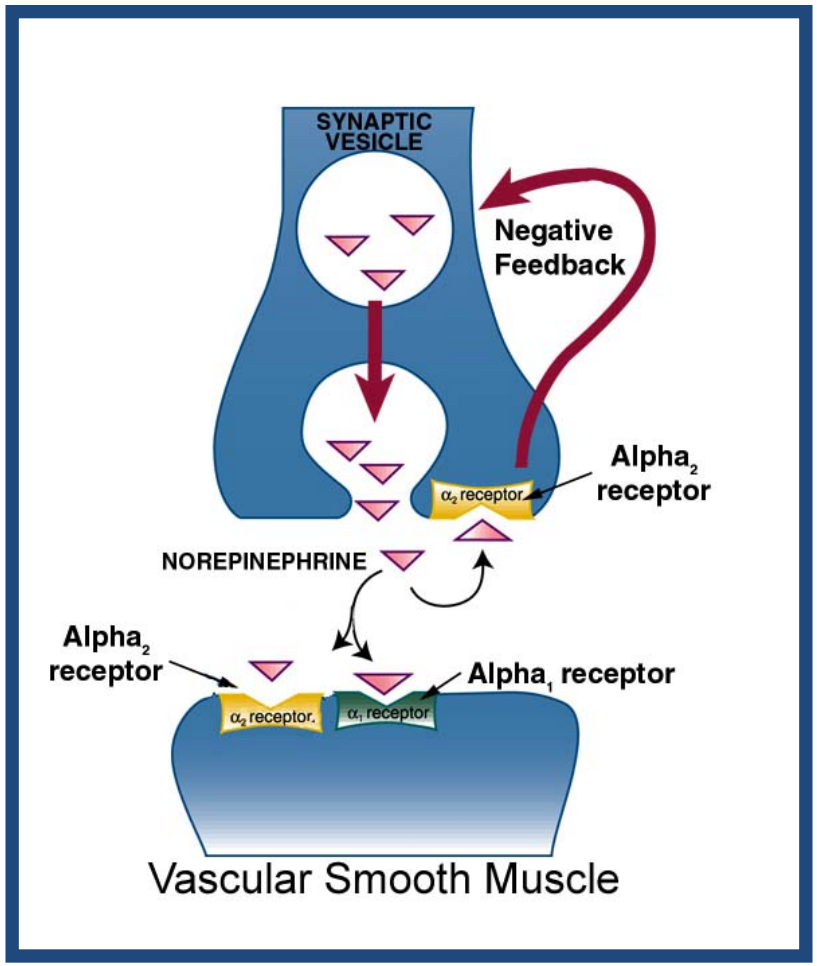
- Hepatic metabolism – similar to morphine and acetaminophen
  - Inactive metabolites
  - 85% glucuronidation
    - Uridine-5-diphosphate (UDP)-glucuronyltransferase
  - 15% cytochrome p450
- Maturation of clearance at 1 year of age
  - 85% of adult clearance

PK considerations in CHD children

- Clearance increases
  - Weight, age, single ventricle physiology
- Clearance decreases
  - Total cardiopulmonary bypass time

- Potts, *Ped Anesth,* 2009
- Su, *Anes & Anal,* 2010

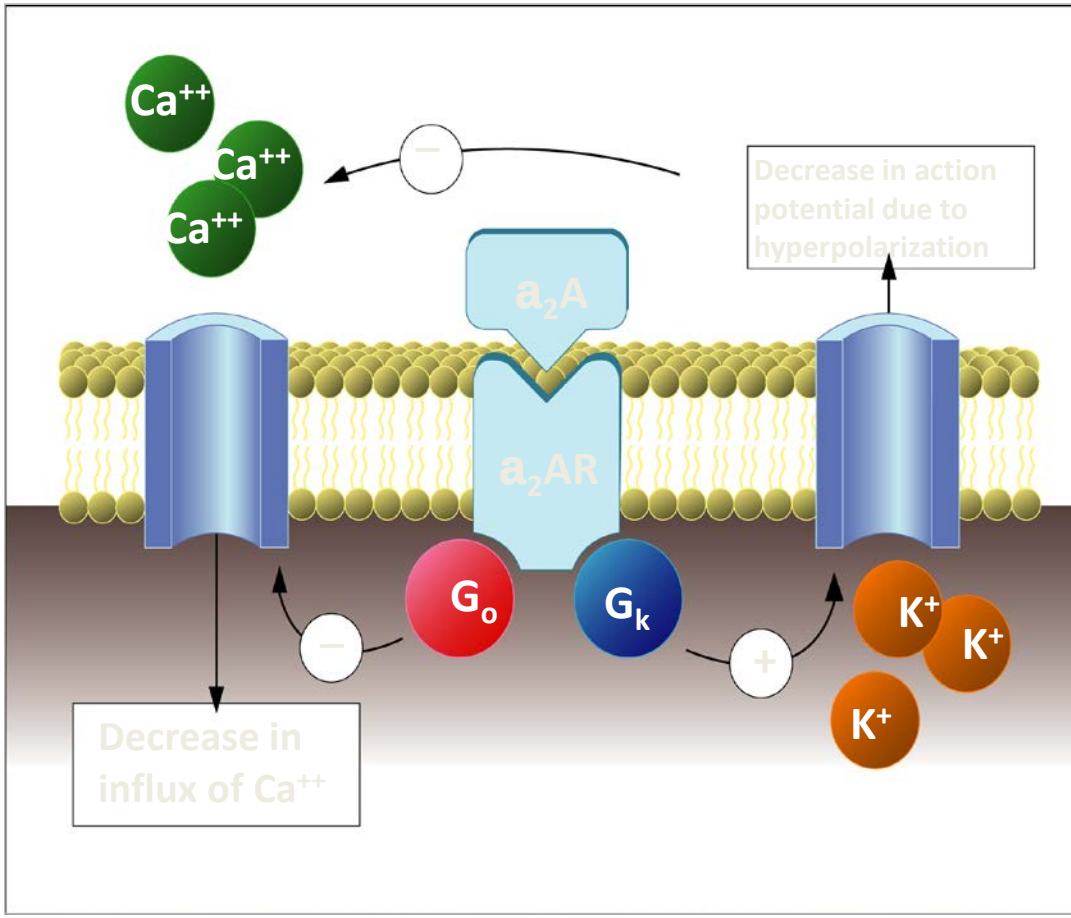
Cellular Mechanism of the α_2-Adrenergic Agonists



- Alpha-2 receptor provides negative feedback to inhibit NE release
- Decrease sympathetic response
- Clinical effectiveness tied to selectivity for alpha-2

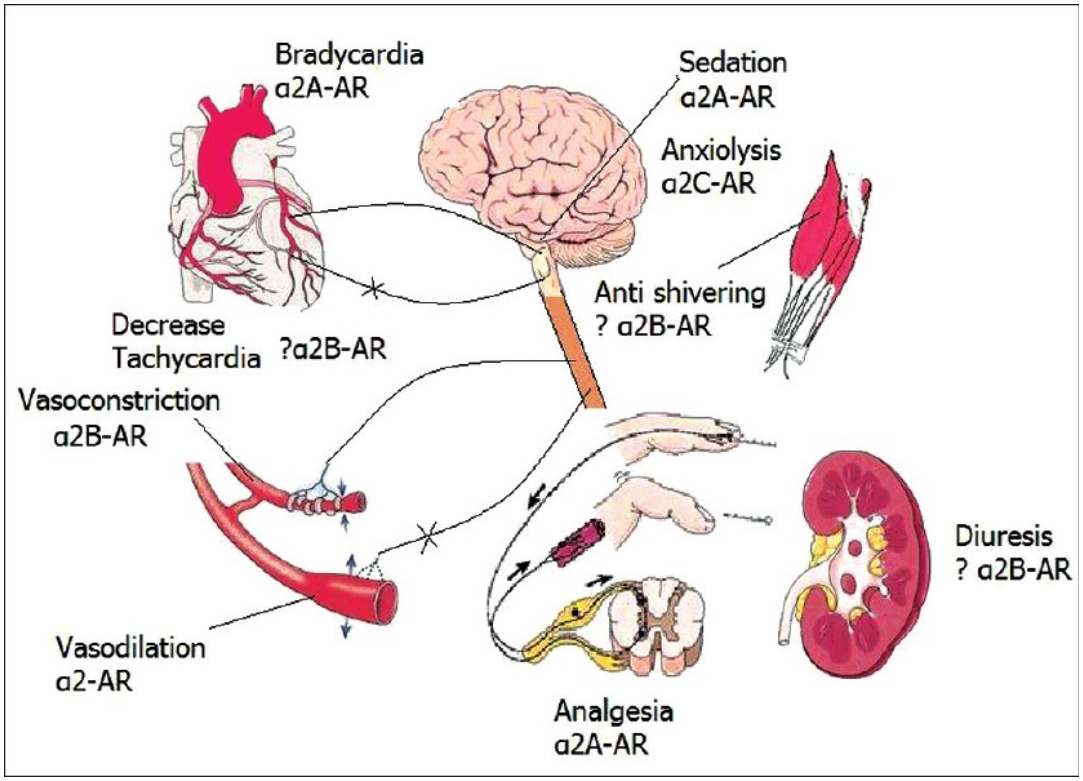
Cellular Mechanism of the α_2-Adrenergic Agonists

- Alpha-2 agonist binds to receptor
- G-protein coupling
- Decrease cell membrane potential
  - Decrease Ca influx
  - Increase K efflux
- Hyperpolarized membrane less likely to fire
- Noradrenergic neuron does not release NE, inhibiting histamine release
- SLEEP



End organ effects of Dexmedetomidine

- Neurologic
- Hemodynamics
- Respiratory



End Organ Effects - Neurologic

- Sedation via selective binding α_2 receptors in the locus ceruleus
  - Decreased noradrenergic output $\rightarrow$ increased GABA firing
  - Natural, non-REM sleep
    - Animal studies
    - Pediatric EEG



Nelson, *Anesth,* 2003

Mason, *Ped Anes, 2009*

End Organ Effects - Neurologic

- No effect on ICP
- Decrease CBF, CMRO2
- Possible neuroprotection during ischemia
- Preserves SSEP, MEP
- Thermoregulation
  - Decreases shivering, heat production, lipolysis

End Organ Effect - CV

- Cardiovascular effects via central and peripheral adrenoreceptors
- Hypotension
- Hypertension
- Bradycardia
- Electrophysiology
- PA Pressures

End Organ Effect - CV

- Hypotension
  - Low dose causes sympatholysis
  - Up to 30% from baseline
  - Dose/Bolus association
  - Attenuated with dose of Ketamine
- Hypertension
  - Large dose causing peripheral vasoconstriction
  - Bolus dose/frequency
  - More frequent in infants
  - Transient, self-resolving (30 mins)

End Organ Effect - Bradycardia

- Decrease up to 30% of baseline with loading dose
- More common in infants
- Ketamine may attenuate response
- Glycopyrrolate
  - Pretreatment does not attenuate
  - Treatment may cause significant hypertension
- Caution
  - AV node dysfunction
  - Sinus node dysfunction
  - HR altering drugs: *B*-blockers, digoxin
- Treatment (when present with hypotension, decreased perfusion)
  - Discontinue drug
  - Stimulation
  - Inotropic agents

End Organ Effect - Respiratory

- Maintains airway patency
- Maintains ventilation
- Respiratory rate, SaO2, EtCO2 all remain unchanged
- Makes the drug very attractive in the ICU and for procedural sedation





- FDA approval in adults (December 1999)
  - mechanically ventilated ICU patients, 24 hours
  - monitored anesthesia care
- Currently labeled dosing for ICU sedation
  - loading dose: 1.0 µg/kg over 10 minutes
  - maintenance dose: 0.2 to 0.7 µg/kg/hr
- 2008 FDA added surgical/medical procedures in adults without intubation outside the OR

- **Not approved for children**

- Ji, et al. *Circulation,* 2013
  - Retrospective cohort, 1260 CABG/valve surgery pts.
  - 50% perioperative infusion of dexmedetomidine
  - Mortality % (AOR)

	In-Hospital	30 Day	1 year
Non Dexmed	4.59	5.12	7.95
Dexmed	1.23 (0.34)	3.17 (0.39)	3.17 (0.47)

- Wijeysundera, *The Cochrane Collaboration, 2009*
  - α_2-AR agonists reduced mortality and myocardial ischemia; RR 0.66 and 0.68

- Barr, et al. *CCM,* 2013
  - New SCCM guidelines favoring use of non-benzodiazepine and non-opioid drugs, including dexmedetomidine, for ICU sedation.
  - Category B evidence of improve outcomes, decreased delirium

Use in pediatric cardiac patients

- Preoperative sedative
- Procedural sedation
- Anesthesia management during surgical repair of CHD
- Anesthesia management during cardiac catheterization
- CICU sedation
- Anti-arrhythmia therapy
- Treatment of post-anesthesia shivering



- Chrysostomou, *"Use of dexmedetomidine in children after cardiac and thoracic surgery,"* PCCM 2006

- Chrysostomou, "*Dexmedetomidine use in a pediatric cardiac intensive care unit: Can we use it in infants after cardiac surgery?"* PCCM 2009

- Lam, "*Hemodynamic effects of dexmedetomidine in critically ill neonates and infants with heart disease,"* Ped Cardio 2012

- Lam, "*Safety and efficacy of dexmedetomidine in children with heart failure,"* Ped Cardio 2013

A Dose-Response Study of Dexmedetomidine Administered as the Primary Sedative in Infants Following Open Heart Surgery

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Objective: To evaluate the dose-response relationship of dexmedetomidine in infants with congenital heart disease postoperative from open heart surgery.
Design: Prospective open-label dose-escalation pharmacokinetic-pharmacodynamic study.
Setting: Tertiary pediatric cardiac ICU.
Patients: Thirty-six evaluable infants, 1–24 months old, postoperative from open heart surgery requiring mechanical ventilation.
Interventions: Cohorts of 12 infants were enrolled sequentially to one of the three IV loading doses of dexmedetomidine (0.35, 0.7, and 1 mcg/kg) over 10 minutes followed by respective continuous infusions (0.25, 0.5, and 0.75 mcg/kg/hr) for up to 24 hours.
Measurements and Main Results: Dexmedetomidine plasma concentrations were obtained at timed intervals during and following discontinuation of infusion. Pharmacodynamic variables evaluated included sedation scores, supplemental sedation and analgesia medication administration, time to tracheal extubation, respiratory function, and hemodynamic parameters. Infants achieved a deeper sedation measured by the University of Michigan Sedation Scale score (2.6 vs 1) despite requiring minimal supplemental sedation (0 unit doses/hr) and fewer analgesic medications (0.07 vs 0.15 unit doses/hr) while receiving dexmedetomidine compared with the 12-hour follow-up period. Thirty-one patients were successfully extubated while receiving the dexmedetomidine infusion. Only one patient remained intubated due to oversedation during the infusion. While receiving dexmedetomidine, there was a decrease in heart rate compared with baseline, 132 versus 161 bpm, but there was an increase in heart rate compared with postinfusion values, 132 versus 128 bpm. There was no statistically or clinically significant change in mean arterial blood pressure.
Conclusions: Dexmedetomidine administration in infants following open heart surgery can provide improved sedation with reduction in supplemental medication requirements, leading to successful extubation while receiving a continuous infusion. The postoperative hemodynamic changes that occur in infants postoperative from open heart surgery are multifactorial. Although dexmedetomidine may play a role in decreasing heart rate immediately postoperative, the changes were not clinically significant and did not fall below postinfusion heart rates. (*Pediatr Crit Care Med* 2013; 14:499–507)
Key Words: congenital heart disease; dexmedetomidine; infant; pharmacodynamics; sedation

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The authors have disclosed that they do not have any conflicts of interest.
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Dexmedetomidine is a sedative-anxiolytic α_2 agonist administered off label to pediatric patients in ICUs and operating rooms both as a single sedative-analgesic agent and as an adjunct to other sedative-analgesic regimens. It has gained increasing popularity for sedation in ICUs due to its limited effects on respiratory function. In the general pediatric population, the administration of dexmedetomidine is most commonly associated with decreased heart rate (HR) and/or blood pressure during continuous infusion and hypertension during rapid infusion or loading dose administration. Although these hemodynamic changes are commonly observed, clinically significant bradycardia and hypotension are infrequent (1–5).

Infants postoperative from open heart surgery are particularly vulnerable to adverse cardiorespiratory side effects associated with sedatives and analgesics. Retrospective studies of dexmedetomidine administered to children postoperative from cardiac surgery report bradycardia in 0% to 12.5%

- Prospective Study
  - 3 cohorts of 12 infants (1-24 mos.)
  - Loading dose 0.35/0.7/1 mcg/kg over 10 mins
  - gtt 0.25/0.5/0.75 mcg/kg/hr
- Results
  - Deeper sedation
  - Less supplementation
  - 31 extubated on dexmed
    - Decreased time to extubation with higher dosing
  - Decrease HR – not clinically significant
    - Dose dependent
  - No difference in MAP from baseline
- Conclusion
  - Improved sedation
  - Successful extubation
  - Hemodynamically safe

In the OR



The Use of Dexmedetomidine in Pediatric Cardiac Surgery

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We tested dexmedetomidine, an α_2 agonist, for its ability to decrease heart rate, arterial blood pressure, and neuroendocrinal responses during pediatric cardiac surgery. In a randomized, placebo-controlled study, 30 pediatric patients undergoing open heart surgery were randomly assigned to one of two equal groups. The control group received saline, whereas the treatment group (DEX group) received an initial bolus dose of dexmedetomidine (0.5 $\mu g/kg$) over 10 min, followed immediately by a continuous infusion of 0.5 $\mu g \cdot kg^{-1} \cdot h^{-1}$. Arterial blood pressure, heart rate, and sequential concentrations of circulating cortisol, epinephrine, norepinephrine, and blood glucose were measured. Relative to baseline, arterial blood pressure and heart rate decreased significantly after the administration of dexmedetomidine through skin incision. In the control group, patients' heart rate and arterial blood pressure measures increased after skin incision until the end of bypass ($P < 0.05$). In both groups, plasma cortisol, epinephrine, norepinephrine, and blood glucose increased significantly relative to baseline, after sternotomy, and after bypass. However, the values were significantly higher in the control group compared with the DEX group ($P < 0.05$). In conclusion, intraoperative dexmedetomidine infusion attenuated the hemodynamic and neuroendocrinal response to surgical trauma and cardiopulmonary bypass in pediatric patients undergoing corrective surgery for congenital heart disease.

(Anesth Analg 2006;103:52–6)

The stress response is the term given to the hormonal and metabolic changes that occur after injury or trauma. This is part of a systemic reaction to injury that encompasses a wide range of endocrinological, immunological, and hematological effects. It is initiated by neuronal activation of the hypothalamo-pituitary-adrenal axis (1). The stress response to surgery is characterized by increased secretion of pituitary hormones and activation of the sympathetic nervous system (2,3). Attenuation of the cardiovascular, neuroendocrine, and inflammatory responses to surgery may improve outcome by beneficial effects on organ function (1,4).

Dexmedetomidine is a highly specific, potent, and selective α^2 adrenoceptor agonist (5). It has a relatively high ratio of α^2/α^1 activity (1620:1 as compared to 220:1 for clonidine) (6) and is therefore considered a full agonist of the α^2 receptor. This ratio ensures that its potent action is selective for the central nervous system, without unwanted cardiovascular effects from α^1 receptor activation (6). Dexmedetomidine has activity at the imidazoline receptors involved in central arterial blood pressure control (7,8). It causes a dose-dependent decrease in mean arterial blood pressure (MAP) and heart rate (HR) (9) and a reduction in sympathetic nervous system activity (9,10). Dexmedetomidine is an imidazole compound, and therefore, it has the potential to exert similar inhibitory effects to etomidate on cortisol synthesis (11).

This is the first study to report the sympatholytic effects of a continuous intraoperative infusion of dexmedetomidine on cardiovascular function and stress hormones (cortisol and catecholamine) in pediatric cardiac surgery patients. The hypothesis that dexmedetomidine would attenuate the increase in HR, MAP, and plasma catecholamine concentrations in pediatric patients undergoing corrective surgery for congenital heart disease was investigated.

METHODS

After approval of the local Ethics Committee and obtaining written informed consent from the guardians of all patients, the study was designed to include 30 patients, aged 1–6 yr, scheduled for congenital heart disease repair surgery using cardiopulmonary bypass (CPB) between January 2004 and September 2004. Patients undergoing re-operations, deep hypothermia, those with low cardiac output, and those with nonpalpable peripheral pulses before surgery (e.g., accompanying coarcta-

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In the cath lab



- Provides good level of sedation when compared to propofol.
- Maintains airway patency and spontaneous ventilation
- May require propofol rescue bolus

Munro, *Ped Anesth,* 2006

Dexmedetomidine + Ketamine

Mester, AJ of Ther, 2008

- Bolus
  - Dexmedetomidine 1 mcg/kg
  - Ketamine 2 mg/kg
- Infusion
  - 2 mcg/kg/hr → 1 mcg/kg/hr
- Rescue
  - Ketamine 0.5 mcg/kg

- 16 patients
- Balanced hemodynamics
  - No clinical change in HR or BP
  - Opposing effects of the 2 drugs
- No change in respiratory parameters
- No movement to local infiltration
- Rescue
  - 3/16 required ketamine

Safe in pulmonary HTN

- 21 OHT patients, 21 PHTN patients
- 10 minute infusion dose
  - 1, 0.75, 0.5 mcg/kg
- HD response
  - Decrease HR
  - Increase MAP, SVRi
  - Small increase PAP in OHT, not seen in PHTN
  - No change in PVRi
- α_2 vasoconstrictor effect seen in peripheral vasculature, does not appear active in pulmonary vasculature



ANESTHESIA & ANALGESIA

The Hemodynamic Response to Dexmedetomidine Loading Dose in Children With and Without Pulmonary Hypertension

Robert H. Friesen, MD,* Christopher S. Nichols, MD,* Mark D. Twite, MBChB,* Kathryn A. Cardwell, BS,* Zhaoxing Pan, PhD,† Biagio Pietra, MD,† Shelley D. Miyamoto, MD,† Scott R. Auerbach, MD,† Jeffrey R. Darst, MD,† and D. Dunbar Ivy, MD†

BACKGROUND: Dexmedetomidine, an α-2 receptor agonist, is widely used in children with cardiac disease. Significant hemodynamic responses, including systemic and pulmonary vasoconstriction, have been reported after dexmedetomidine administration. Our primary goal of this prospective, observational study was to quantify the effects of dexmedetomidine initial loading doses on mean pulmonary artery pressure (PAP) in children with and without pulmonary hypertension.
METHODS: Subjects were children undergoing cardiac catheterization for either routine surveillance after cardiac transplantation (n = 21) or pulmonary hypertension studies (n = 21). After anesthetic induction with sevoflurane and tracheal intubation, sevoflurane was discontinued and anesthesia was maintained with midazolam 0.1 mg/kg IV (or 0.5 mg/kg orally preoperatively) and remifentanil IV infusion 0.5 to 0.8 μg/kg/min. Ventilation was mechanically controlled to maintain P_{ETCO_2} 35 to 40 mm Hg. When end-tidal sevoflurane was 0% and fraction of inspired oxygen (F_{IO_2}) was 0.21, baseline heart rate, mean arterial blood pressure, PAP, right atrial pressure, pulmonary artery occlusion pressure, right ventricular end-diastolic pressure, cardiac output, and arterial blood gases were measured, and indexed systemic vascular resistance, indexed pulmonary vascular resistance, and cardiac index were calculated. Each subject then received a 10-minute infusion of dexmedetomidine of 1 μg/kg, 0.75 μg/kg, or 0.5 μg/kg. Measurements and calculations were repeated at the conclusion of the infusion.
RESULTS: Most hemodynamic responses were similar in children with and without pulmonary hypertension. Heart rate decreased significantly, and mean arterial blood pressure and indexed systemic vascular resistance increased significantly. Cardiac index did not change. A small, statistically significant increase in PAP was observed in transplant patients but not in subjects with pulmonary hypertension. Changes in indexed pulmonary vascular resistance were not significant.
CONCLUSION: Dexmedetomidine initial loading doses were associated with significant systemic vasoconstriction and hypertension, but a similar response was not observed in the pulmonary vasculature, even in children with pulmonary hypertension. Dexmedetomidine does not appear to be contraindicated in children with pulmonary hypertension. (Anesth Analg 2013;XXX:00–00)

The pulmonary vascular effects of many anesthetic drugs have been inadequately investigated. The lack of knowledge of these effects can create uncertainty in the delivery of clinical anesthetic care, particularly in children with congenital heart disease and/or pulmonary hypertension, who frequently require anesthesia or sedation for diagnostic or therapeutic procedures.

Dexmedetomidine, an α-2 and imidazole receptor agonist, is widely used in pediatrics for procedural and therapeutic sedation and as a component of surgical anesthesia. Experience with dexmedetomidine in children with congenital heart disease is growing.[1–6] A cardiac catheterization study of children with transplanted hearts demonstrated a significant but transient increase in pulmonary artery pressure (PAP) in response to dexmedetomidine bolus,[7] but studies of its hemodynamic effects in children with pulmonary hypertension are lacking. The purpose of this study was to document the pulmonary vascular hemodynamic effects of dexmedetomidine in children with and without pulmonary hypertension undergoing cardiac catheterization.

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Conflict of Interest: See Disclosures at the end of the article.

Reprints will not be available from the authors.

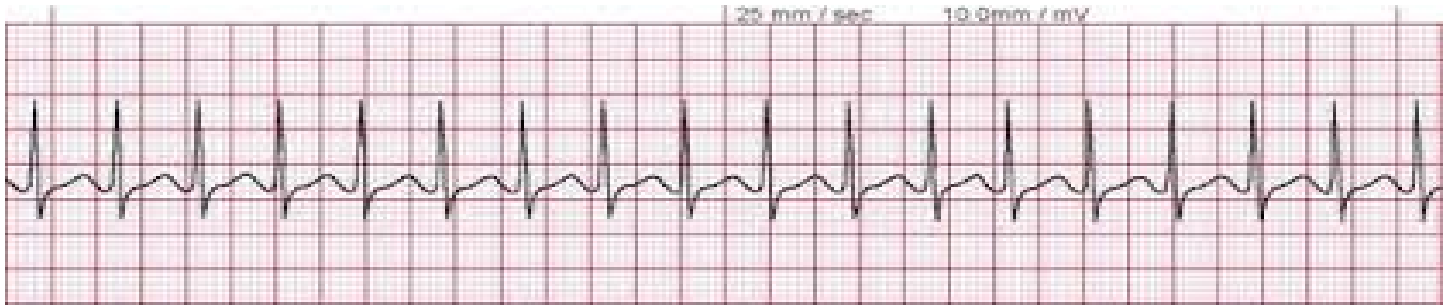
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METHODS

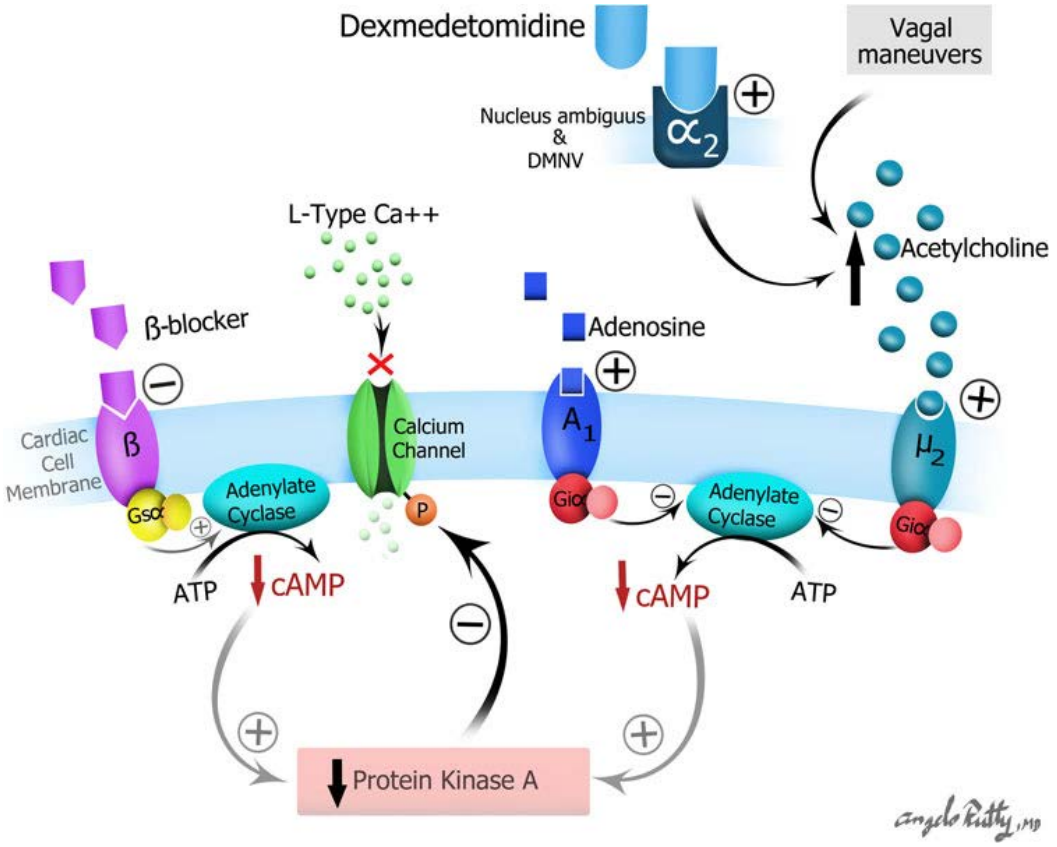
This prospective descriptive study was approved by the hospital's IRB. Written informed consent was obtained from the parents or guardians of the subjects, and written assent was obtained from children aged 7 years or older. Subjects were included if they were between 1 and 14 years of age and were scheduled to undergo elective cardiac catheterization for either postcardiac transplant surveillance or periodic pulmonary hypertension assessment. Pulmonary hypertensive subjects were patients known to have pulmonary hypertension (mean PAP pressure >25 mm Hg) documented by prior cardiac catheterization and/or current

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- Anti-arrhythmic properties of dexmedetomidine
- Chrysostomou, et al, Children's Hospital of Pittsburgh
- Decrease incidence and successful treatment
  - SVT
  - A-flutter
  - V-tach
  - JET
  - sinus tachycardia

Proposed antiarrhythmic mechanism



Tobias & Chrysostomou, *Ped Cardio, 2013*

The effects of dexmedetomidine on cardiac electrophysiology in children

Hammer, et al, A&A, 2008

- 12 children with SVT presenting for EPS
- 1 mcg/kg 10 mins, 0.7 mcg/kg/hr

- Results
  - Increased sinus node cycle length
  - Increased sinus node recovery time
  - AV node depression
    - Wenckeback cycle length prolongation
    - Prolong PR interval

- Avoid in EPS
- Caution in patient at risk for heart block, bradycardia

Other clinical uses

- Preoperative sedation
- Treatment of post-anesthesia shivering
- Procedural sedation
- MRI, radiology
- Anterior mediastinal mass
- Difficult airway
- Bronchoscopy
- Sedated echocardiography
- Sleep studies
- EEG
- Narcotic withdrawal
- Emergence delirium

Organ protection?

- Decrease post-bypass acute kidney injury (adults)

  Ji, *PLoS One,* 2013

- Protection against contrast induced nephropathy by decreasing endothelin-1 and renin

  Bayram, *Ped Anes,* 2014

Organ Protection?

- Decrease in histological inflammation and multiple inflammatory molecules in VILI (dogs)

  Chen, *J Surg Res,* 2013

- Inhibit inflammation in lung of septic rats by suppressing TRL4/NF-κB pathway, decrease IL-6 and TNF-α (rats)

  Wu, *Mediators Inflamm,* 2013

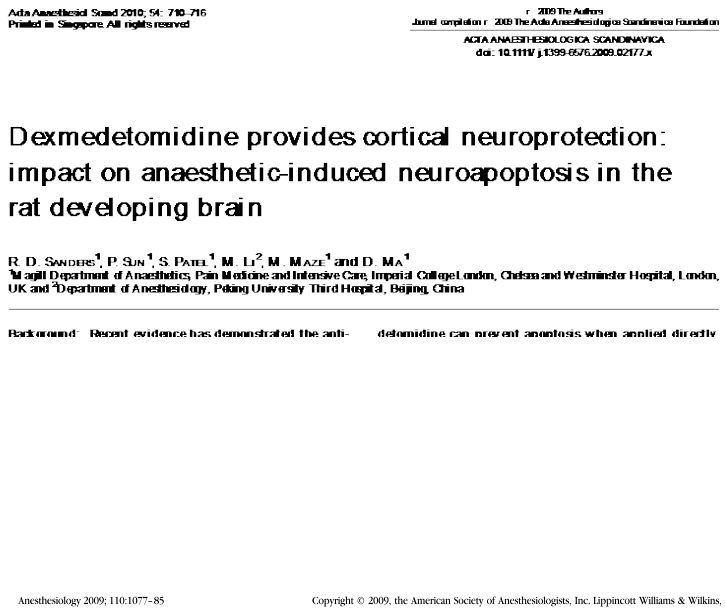
- Decrease mortality and inhibit pro-inflammatory cytokines during polymicrobial sepsis (mice)

  Xu, *Inflamm Res,* 2013

- Protective mechanism against ischemia-reperfusion lung injury (rats)

  Jiang, *Mol Med Rep,* 2014

Neuroprotection



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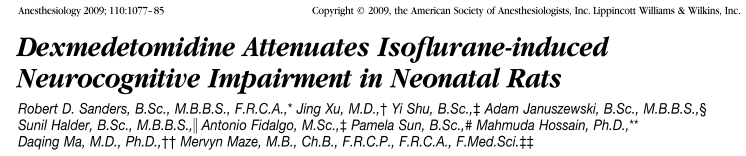
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Dexmedetomidine provides cortical neuroprotection: impact on anaesthetic-induced neuroapoptosis in the rat developing brain

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[1]Imperial Department of Anaesthetics, Pain Medicine and Intensive Care, Imperial College London, Chelsea and Westminster Hospital, London, UK and [2]Department of Anesthesiology, Peking University Third Hospital, Beijing, China

Background: Recent evidence has demonstrated the anti- dexmedetomidine can prevent apoptosis when applied directly



Anesthesiology 2009; 110:1077–85

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Dexmedetomidine Attenuates Isoflurane-induced Neurocognitive Impairment in Neonatal Rats

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- α_2-AR thought to play trophic role in CNS signaling
- Isoflurane caused apoptosis and cognitive dysfunction in neonatal rats
- Inhibition of isoflurane-induced apoptosis
- Preserved long-term memory and cognitive function

Which do you choose?



