Alpha-2 Adrenergic Agonists (dexmedetomidine)

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Medonex

Outline

- Overview of alpha-2 adrenoceptors and alpha-2 agonists
- Selected clinical effects
  - Sedation
  - Hemodynamics
  - Ventilation
- Other effects mediated by alpha-2 agonists
- Practical points (Dosing)
- Discussion

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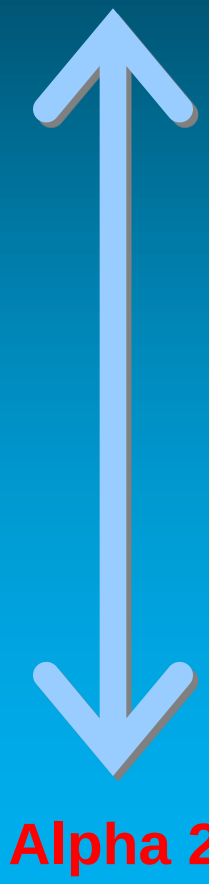
Nine Adrenoceptors

- Alpha-1a, Alpha-1b and Alpha-1d
- Beta-1, Beta-2, Beta-3
- Alpha-2a, Alpha-2b and Alpha-2c

Adrenoceptors

- Alpha-1a, Alpha-1b and Alpha-1d
- Beta-1, Beta-2, Beta-3
- Alpha-2a, Alpha-2b and Alpha-2c
  - Central – Peripheral
  - Presynaptic – Postsynaptic
  - Extrasynaptic (vascular)

Alpha-Adrenoceptor Agonists

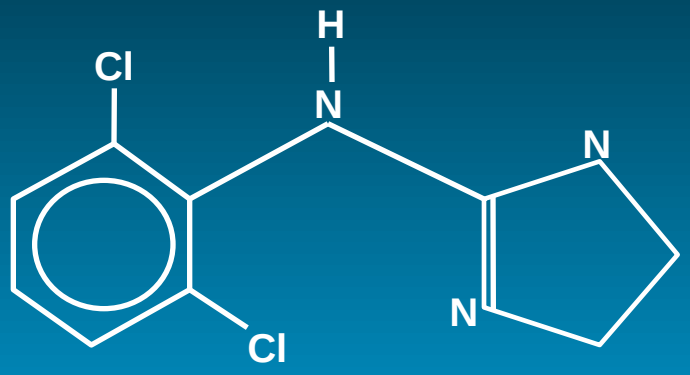


- Norepinephrine
- Epinephrine
- Dopamine
- Tizanidine

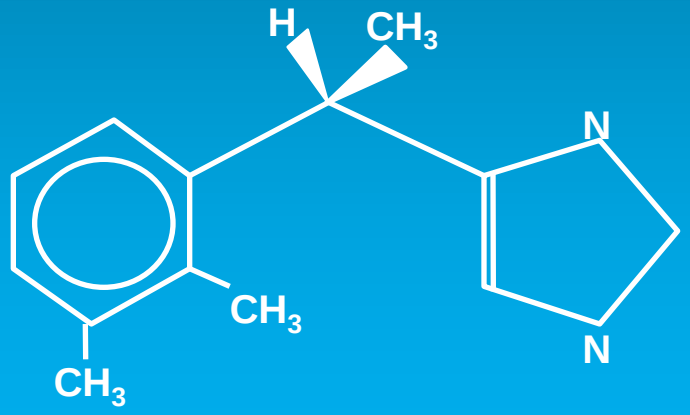
- Clonidine

- Mivazerol
- Guanfacine
- Medetomidine
- Dexmedetomidine

Alpha-2 Agonists



Clonidine



Dexmedetomidine

α_2 Agonists

Clonidine

- Selectivity: α_2:α_1 250:1
- Imidazole derivate 16:1
- Elimination half-life 10 hrs
- 2.5 L/kg
- PO, patch, epidural
- Antihypertensive
- Epidural formulation Duraclon 1,000 ug/vial, IV

Dexmedetomidine

- Selectivity: α_2:α_1 1620:1
- Imidazole derivate 31:1
- Elimination half-life β 2 hrs
- V_{ss} 118 L (gets everywhere)
- 94% protein bound
- Eliminated by liver/kidney
- Effects own PK (V1?CO?)
- Sedative
- Only available in IV form
- Precedex 200 ug/vial

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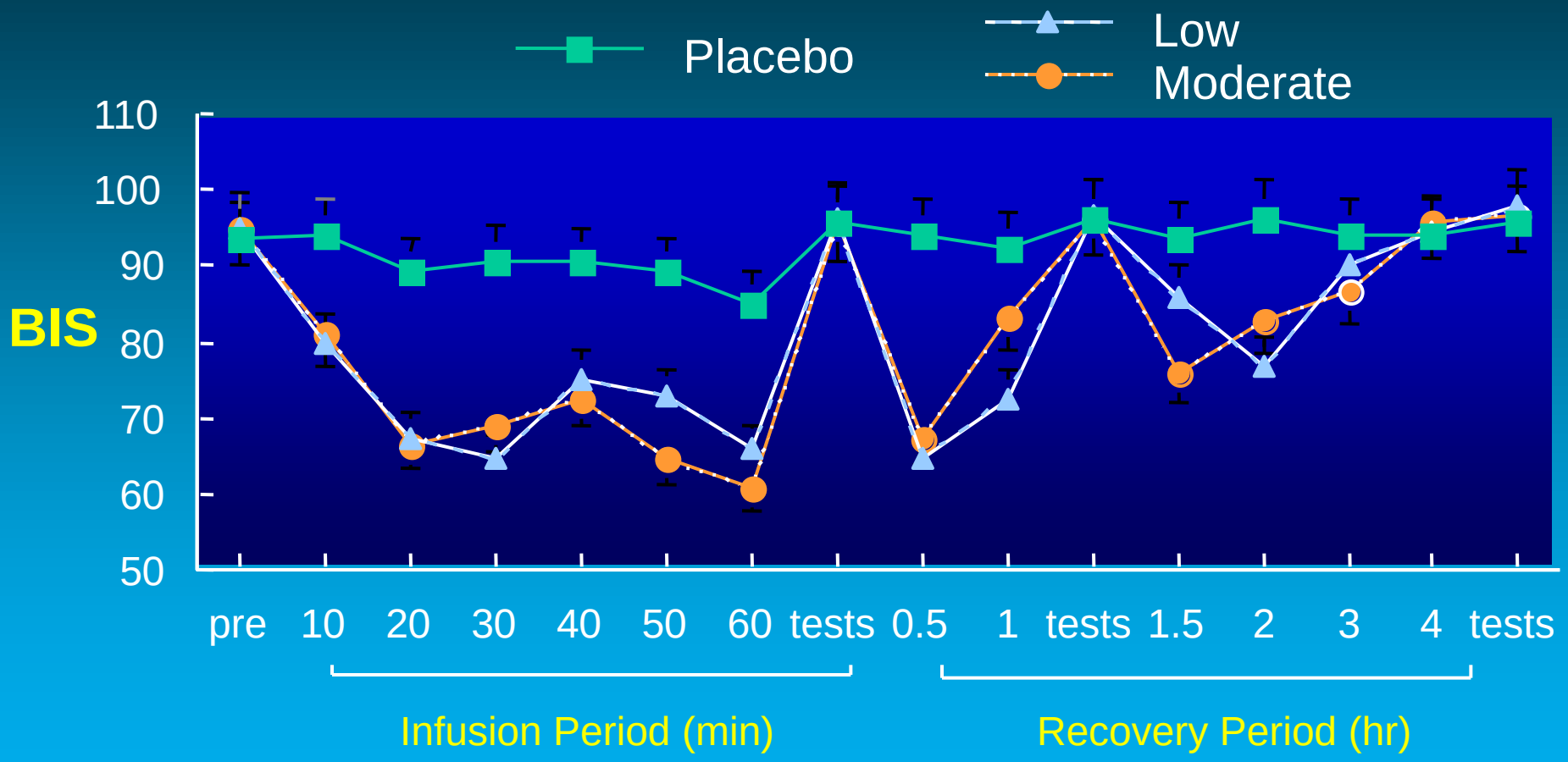
Sedation

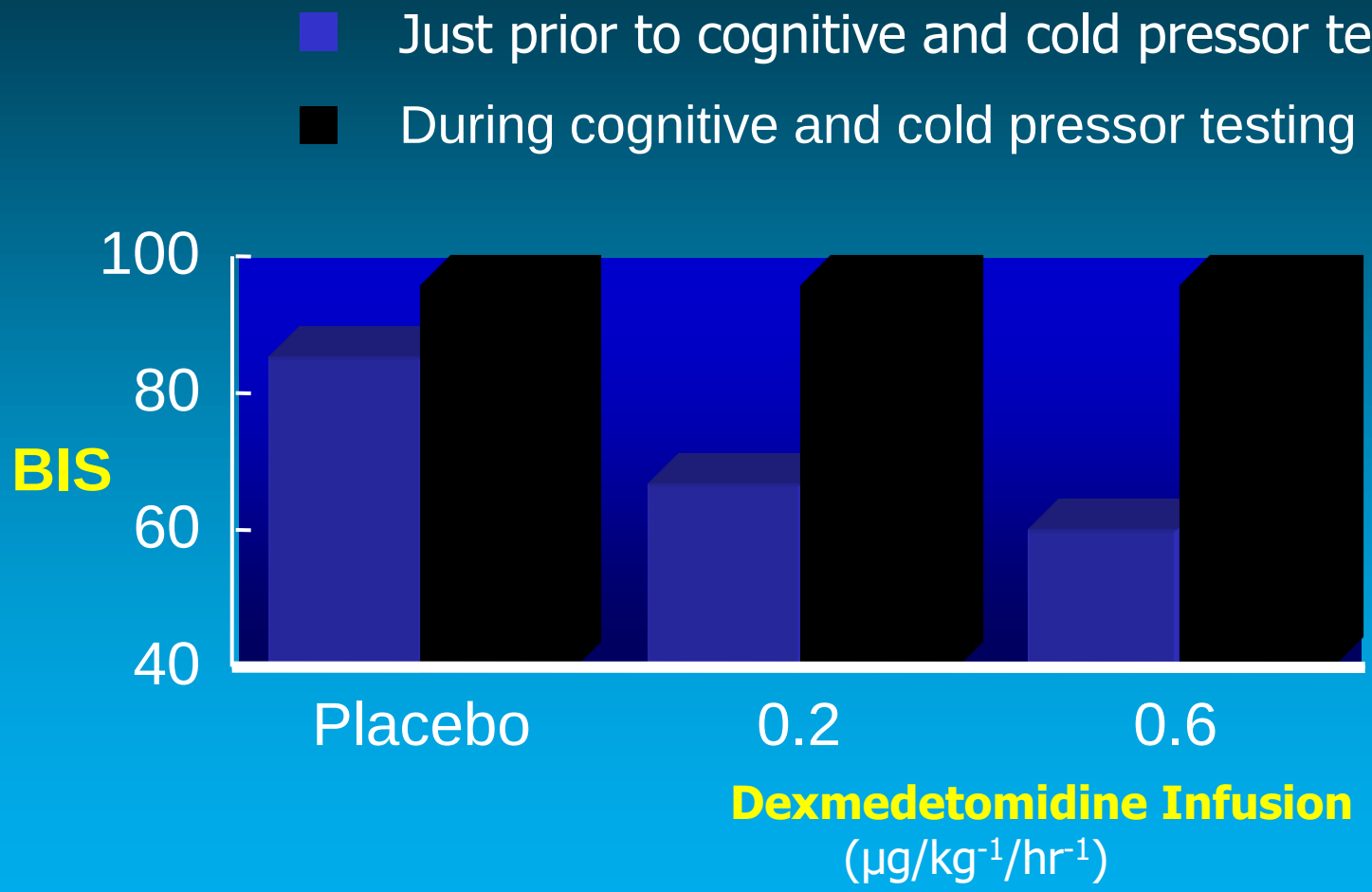
- Dose dependent
- Minimal respiratory depression
- Arousable
- Known action
  - Hyperpolarization of LC neurons
  - α_2A-receptor subtype
- Resembles natural sleep (ICU?)
- Reversible (atipamezole)
- Amnesia?

Arousability From Sedation During Dexmedetomidine Infusion



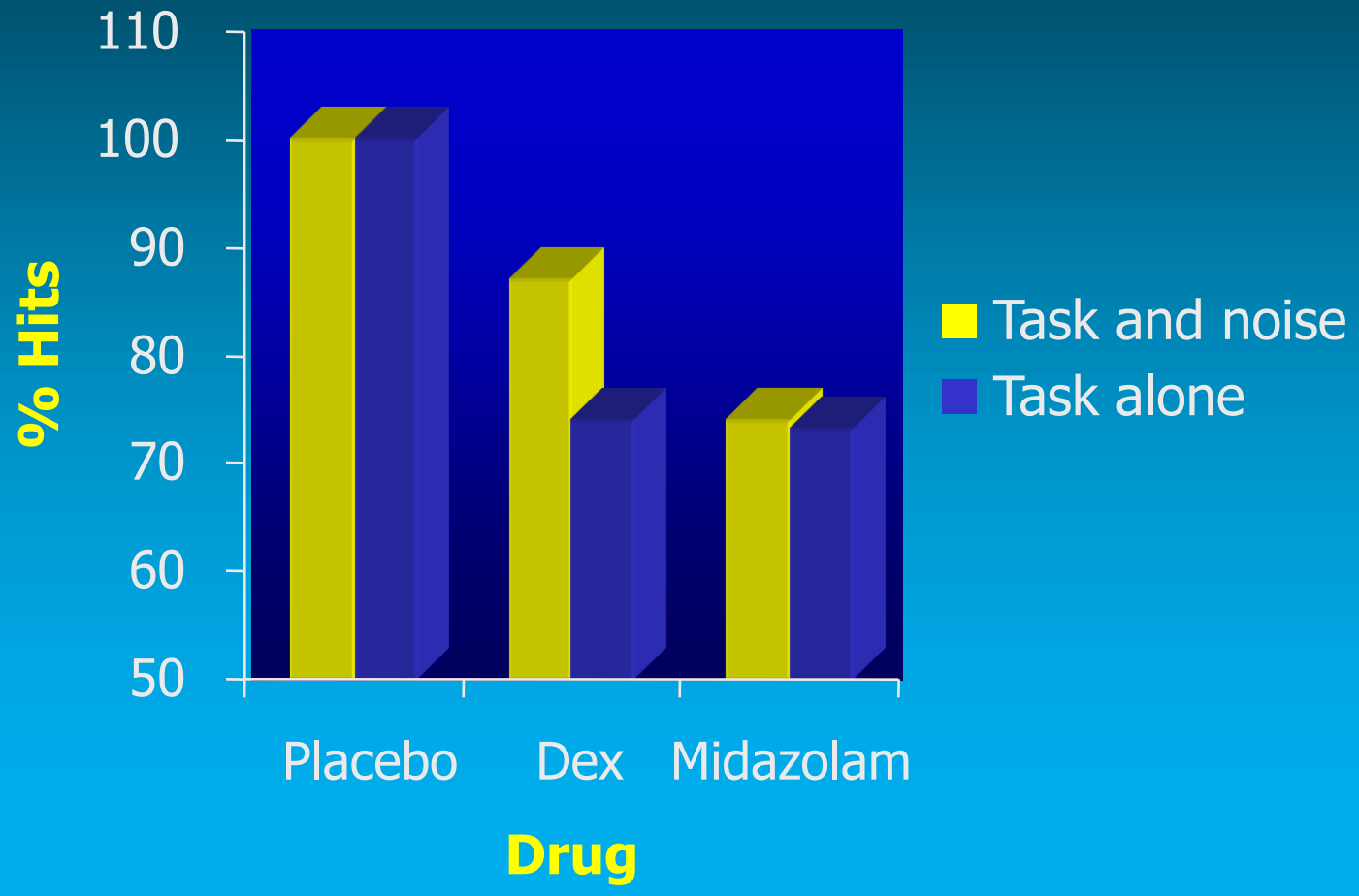
Hall. *Anesth Analg*. 2000;90:701.

Arousability From Sedation During Dexmedetomidine Infusion



Hall. *Anesth Analg*. 2000;90:701.

Comparison of Equi-Sedative Doses of Midazolam and Dexmedetomidine on Task Performance in Humans



Sedation

- Goal is to have a comfortable, calm patient who is arousable and cooperative
- Patient who is not arousable should have the dose reduced.
- Arousability a test for appropriate sedation (EEG/BIS)
- Patient too awake - needs more (clonidine)

Sedation

- No central respiratory depression. However sedation may cause upper airway obstruction.
- Very synergistic with other sedatives
- Length of infusion: 24 hr vs ?? tolerance, cortisol, rebound.

Sedation

- Typical doses (target plasma levels 0.3-1.2 ng/ml):
  - 0.5 ug/kg load, 0.5 ug/kg/hr infusion
  - 1.0 ug/kg load, 0.7 ug/kg/hr infusion
  - Increase dose by bolus/infusion
  - Load only - short procedures
  - Patients with high sympathetic activity may need very high doses. Most PD, dosing studies done in unstimulated volunteers.

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- Physiologic effects mediated by alpha-2 agonists
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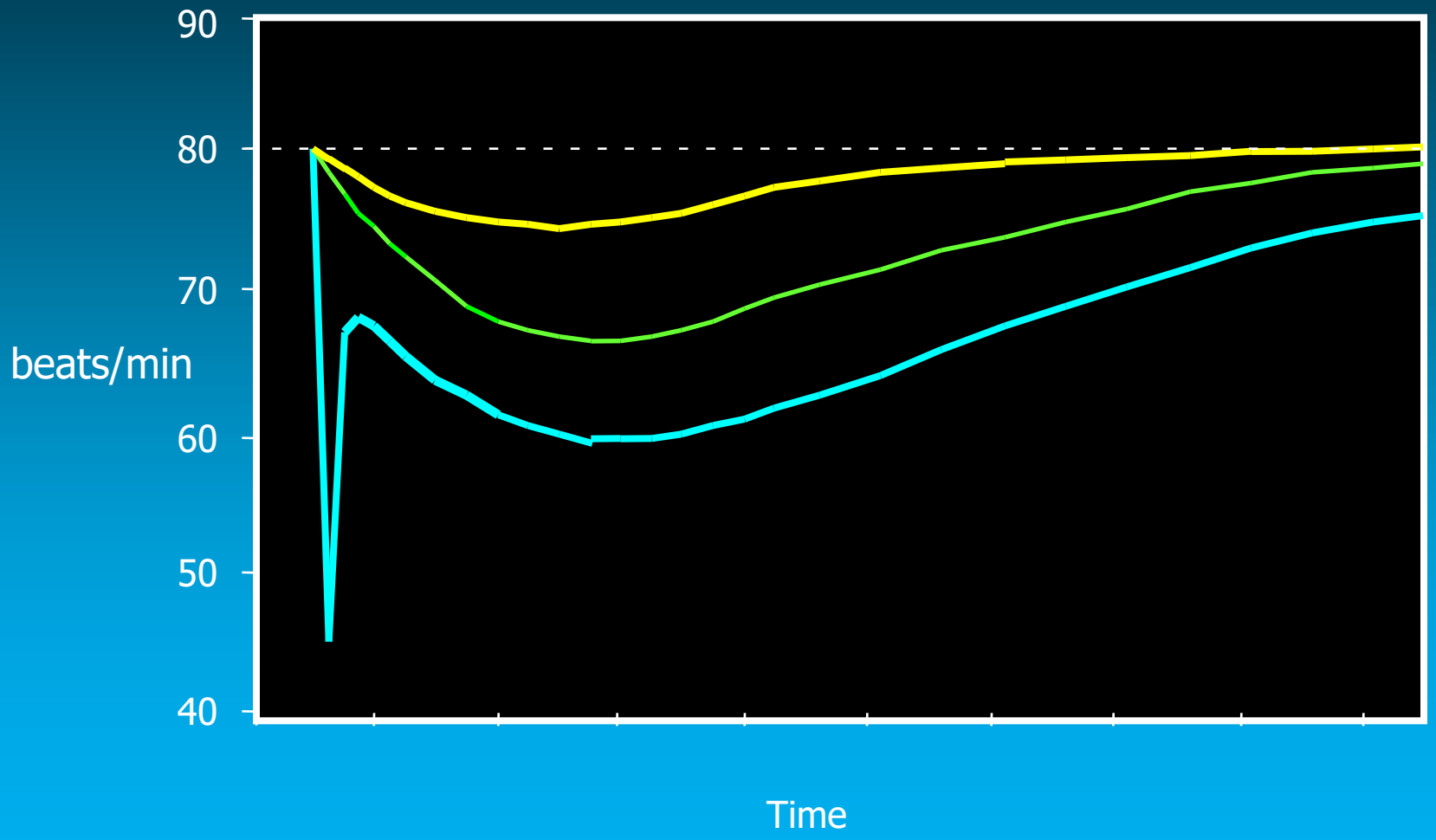
Hemodynamic effects

- Combination of effects mediated by:
  - Reduction of central SNS activity (alpha-2a)
  - Reduction of presynaptic NE release (alpha-2a and c)
  - Stimulation of VSM cells (alpha-2b)
  - Stimulation of endothelium
  - Stimulation of central imidazoline receptors
  - Some vagomimetic activity

Heart Rate Response



HR effects

- Bradycardia does not typically progress to a clinically significant problem, unless patient has coexisting disease and will not tolerate bradycardia.
- Like total spinal. Once the SNS activity is gone…
- Baroreflexes are reset, but intact - hypertension will reduce HR further.
- Observed asystole/sinus pauses have developed in healthy unstimulated volunteers at any dex plasma level, after a vagal stimulus. Unopposed vagal stimulus.

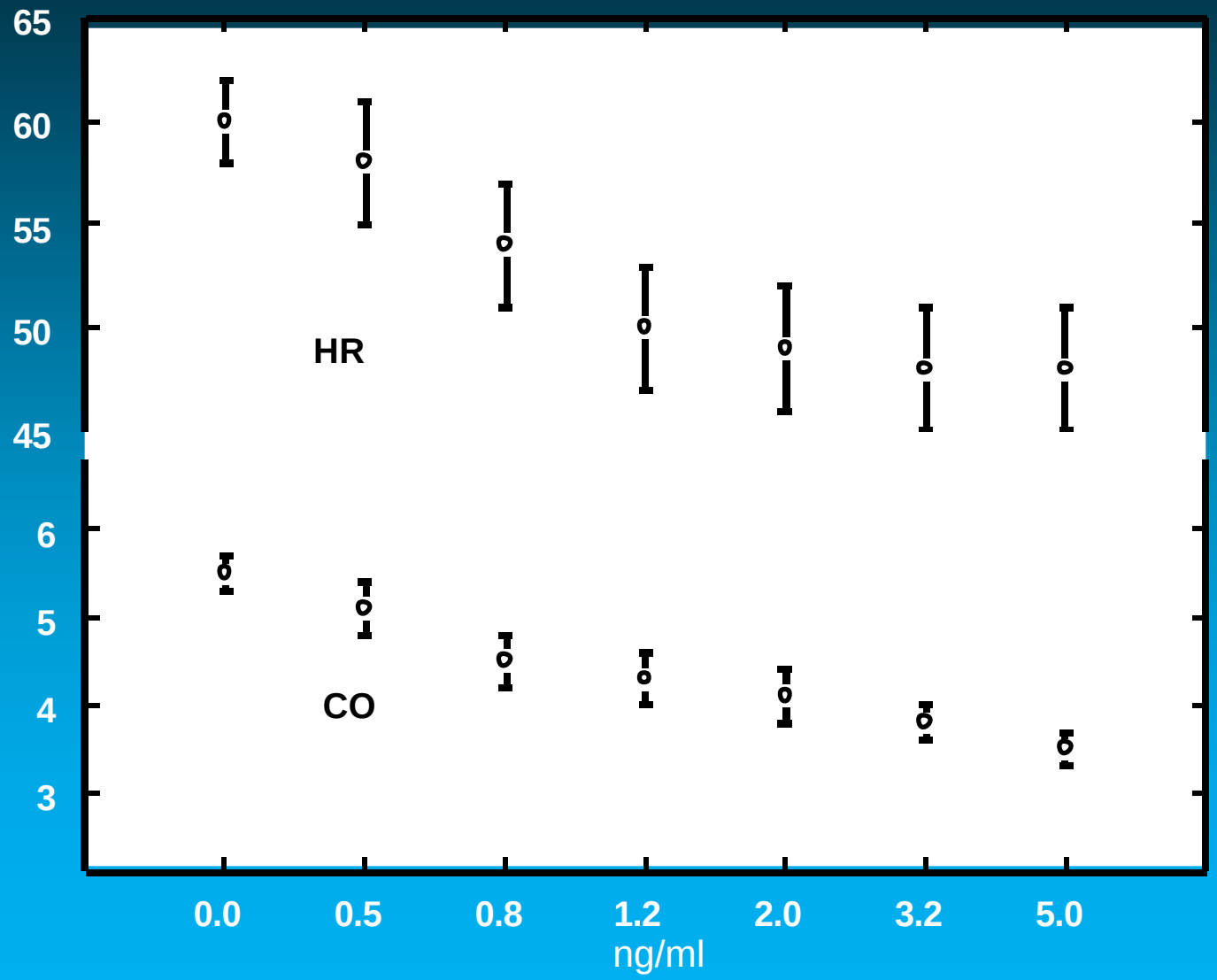
HR effects

- Intraoperative use of dexmedetomidine have resulted in increased treatment of bradycardia.
- Heart blocks have been observed intraoperatively (no catechols?)
- Postoperative treatment of bradycardia is rare (catechols)

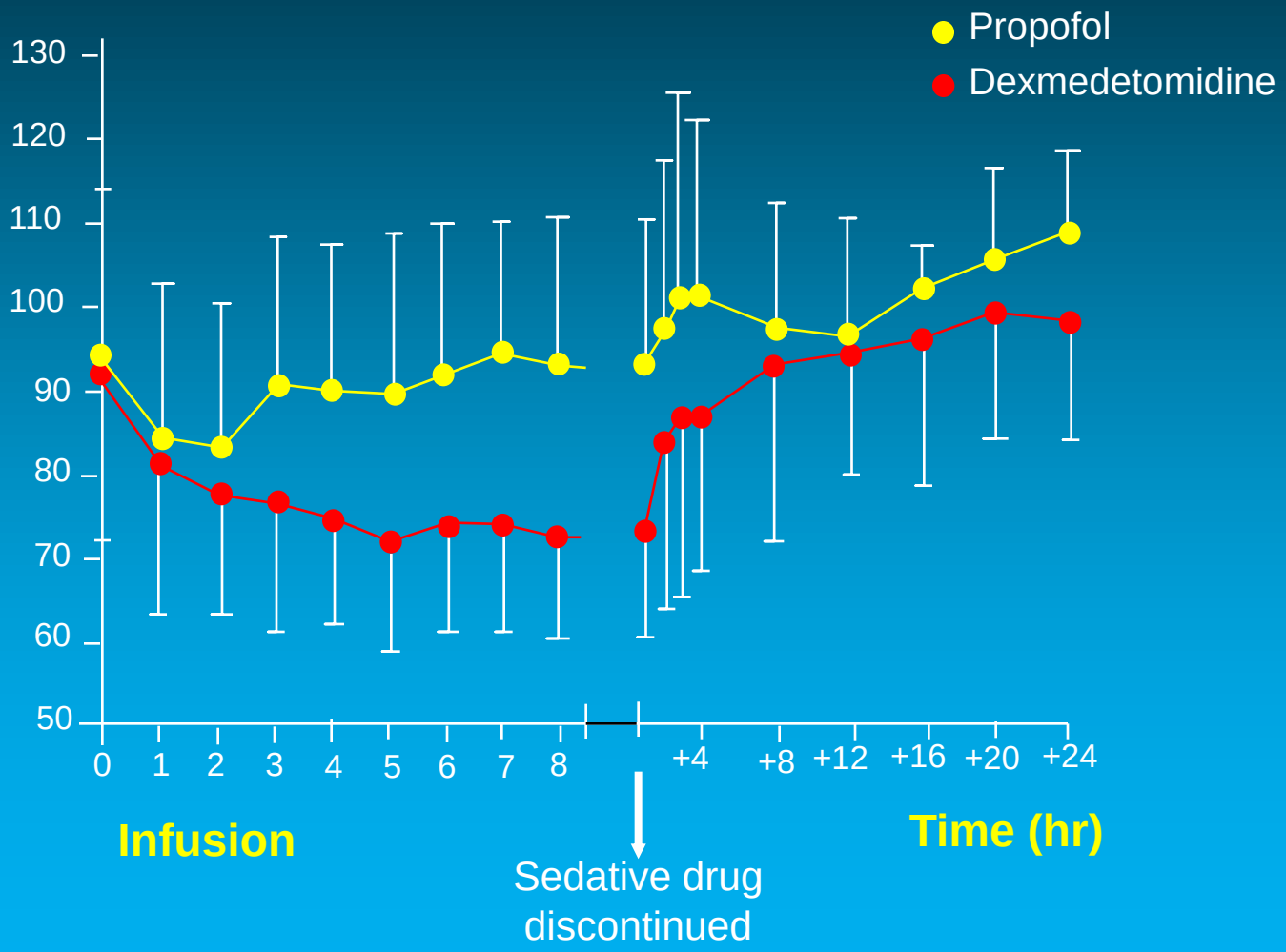
HR effects

- Average response is a 20% reduction in HR
- Volunteers with low resting heart rates have smaller HR responses than patients with high HRs
- Treatment of bradycardia:
  - Normal response to atropine and glycopyrrolate
  - Be cautious-coronary perfusion.

Heart rate Response MTD

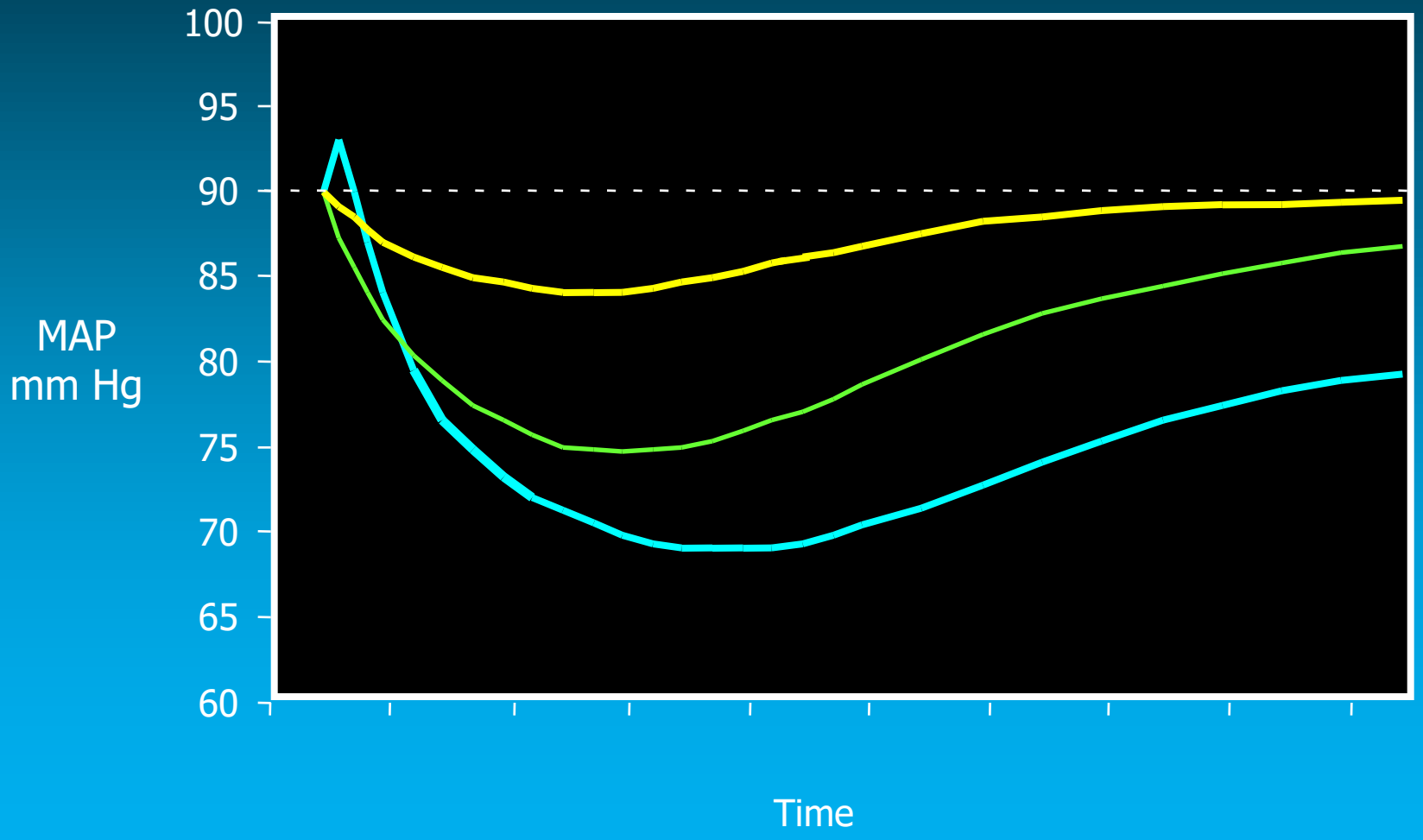


Effect on Heart Rate

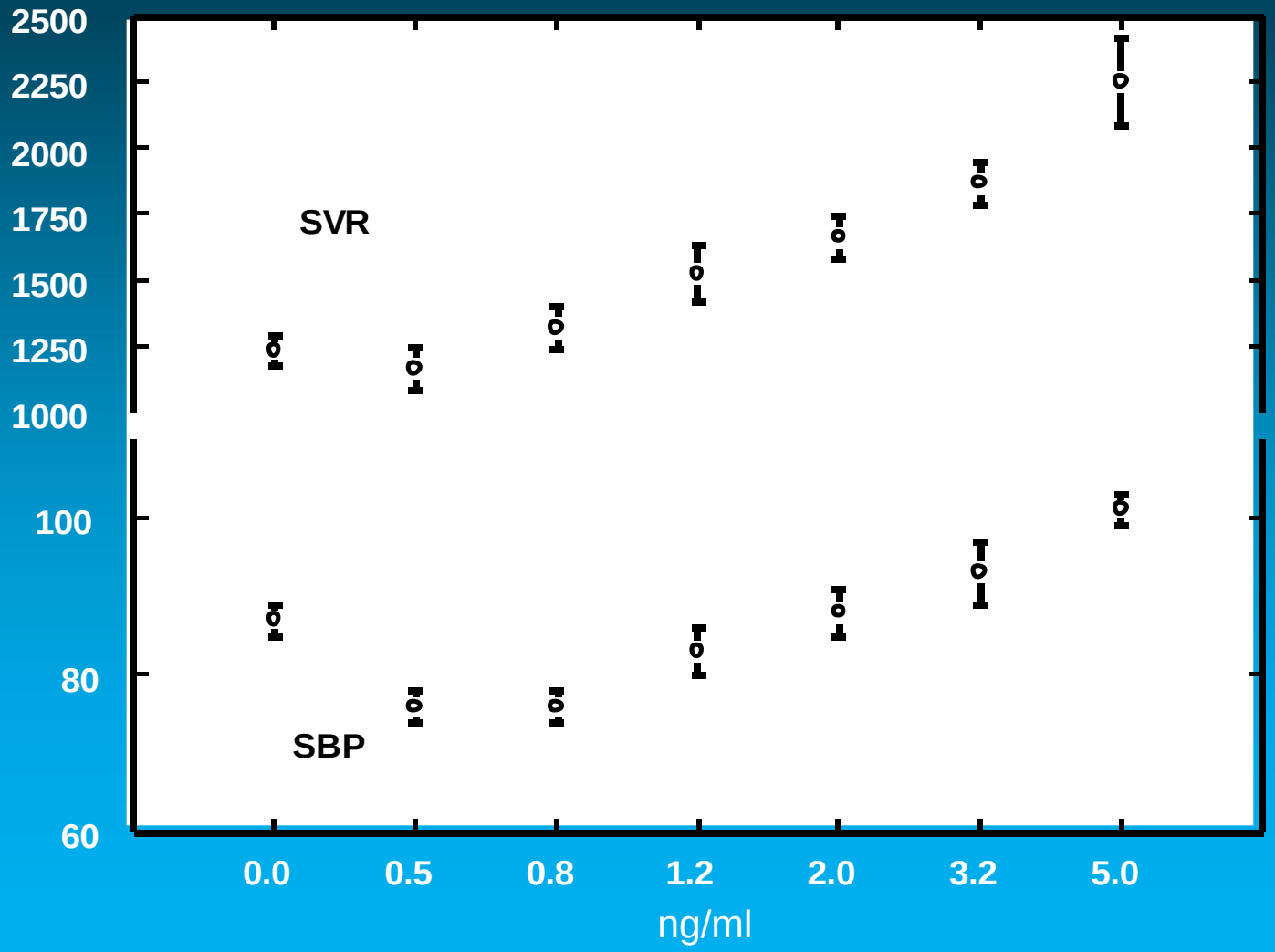


Venn RM, Grounds RM. *Br J Anaesth*. 2001;87:684-690.

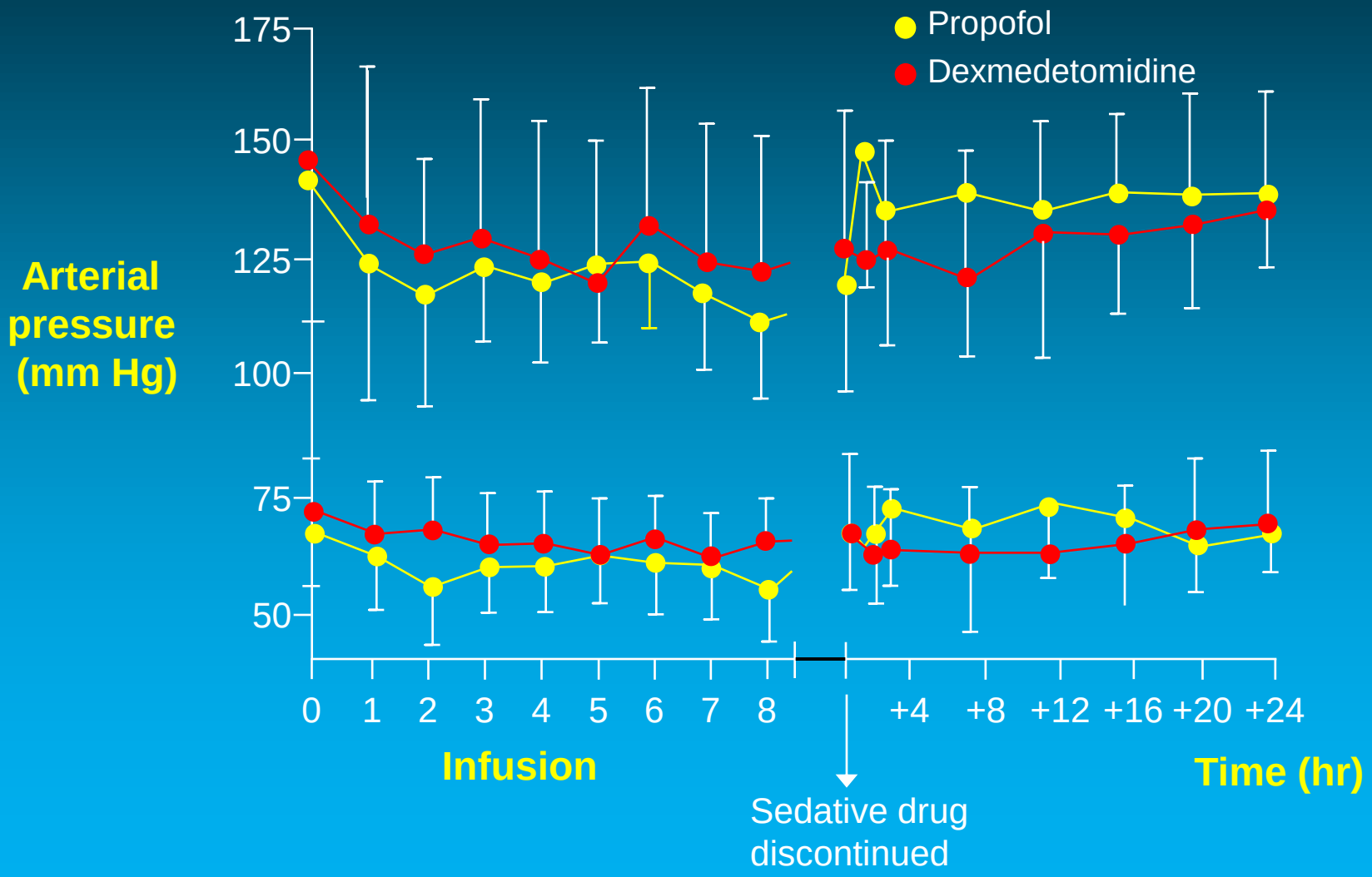
Blood Pressure Response



Hemodynamic Response MTD



Effect on Blood Pressure



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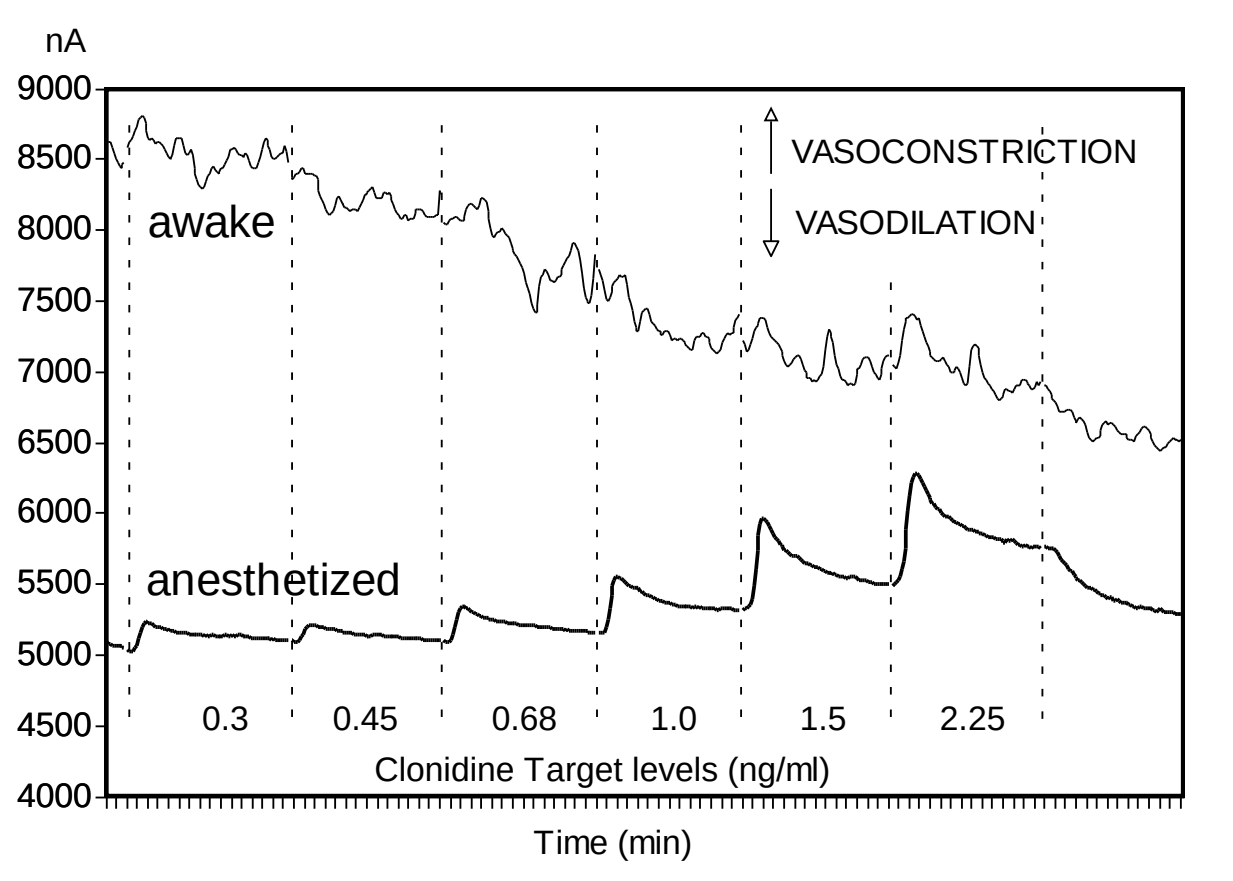
Alpha-2b / Vasoconstriction

- Alpha-2b adrenoceptors at vascular smooth muscle cells mediate vasoconstriction
- Inverse relationship between arterial diameter and alpha-2 ARs.
- “instantaneous” compared to the central sympatholytic effect

Clonidine/ General anesthesia



Common observation

- BP increased when I gave dex, What should I do?
- Why: Propofol, general anesthesia, epidurals reduce SNS activity/tone. Thus, vasoconstriction may dominate.
- Either reduce the dose or switch to another drug.

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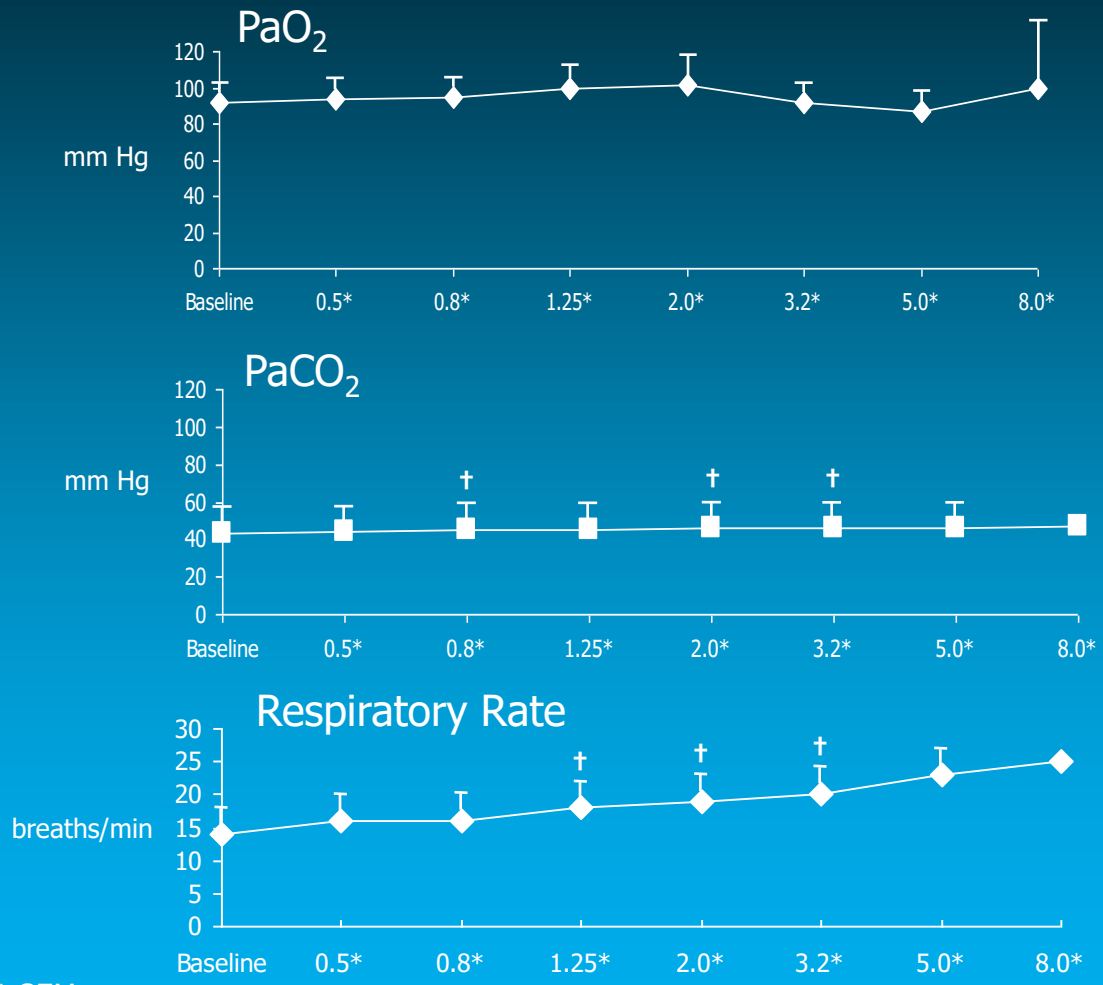
Effect on Ventilation (Alpha-2)

- Clonidine, dexmedetomidine
  - Minimal effect on RR, V_E, Pa CO_2,
  - Small decrease in V_E/ET CO_2
- No potentiation of opioid-induced respiratory depression
- Sedation: upper airway obstruction
- Irregular RR with large boluses

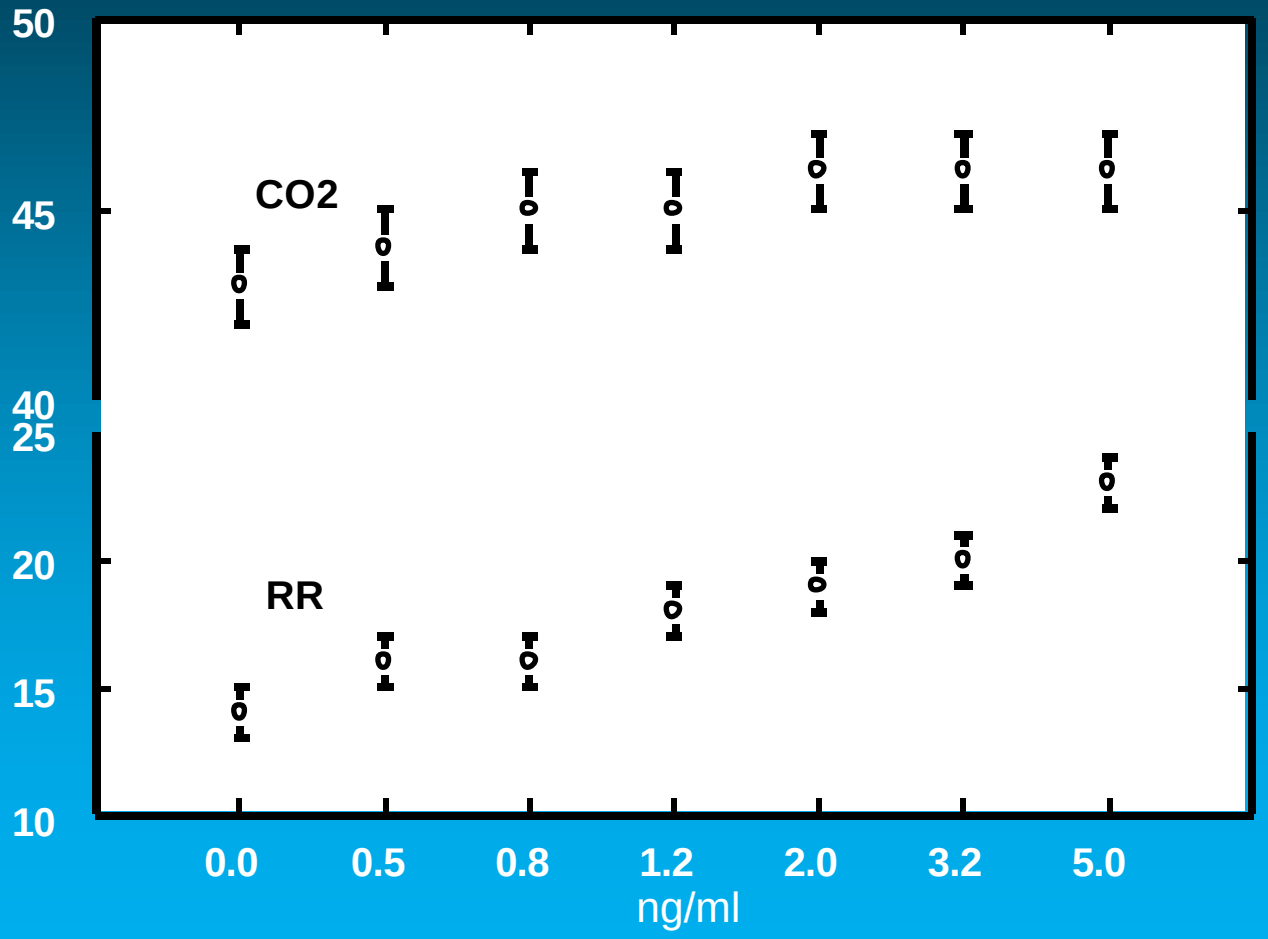
Respiratory Response

Maximum Tolerable Dose Study



Data are mean ± SEM.
*Target dexmedetomidine (ng/mL).
†$P<0.05$ compared with baseline values.
Adapted from Ebert et al. *Anesthesiology.* 2000;93:389.

Respiratory Response MTD



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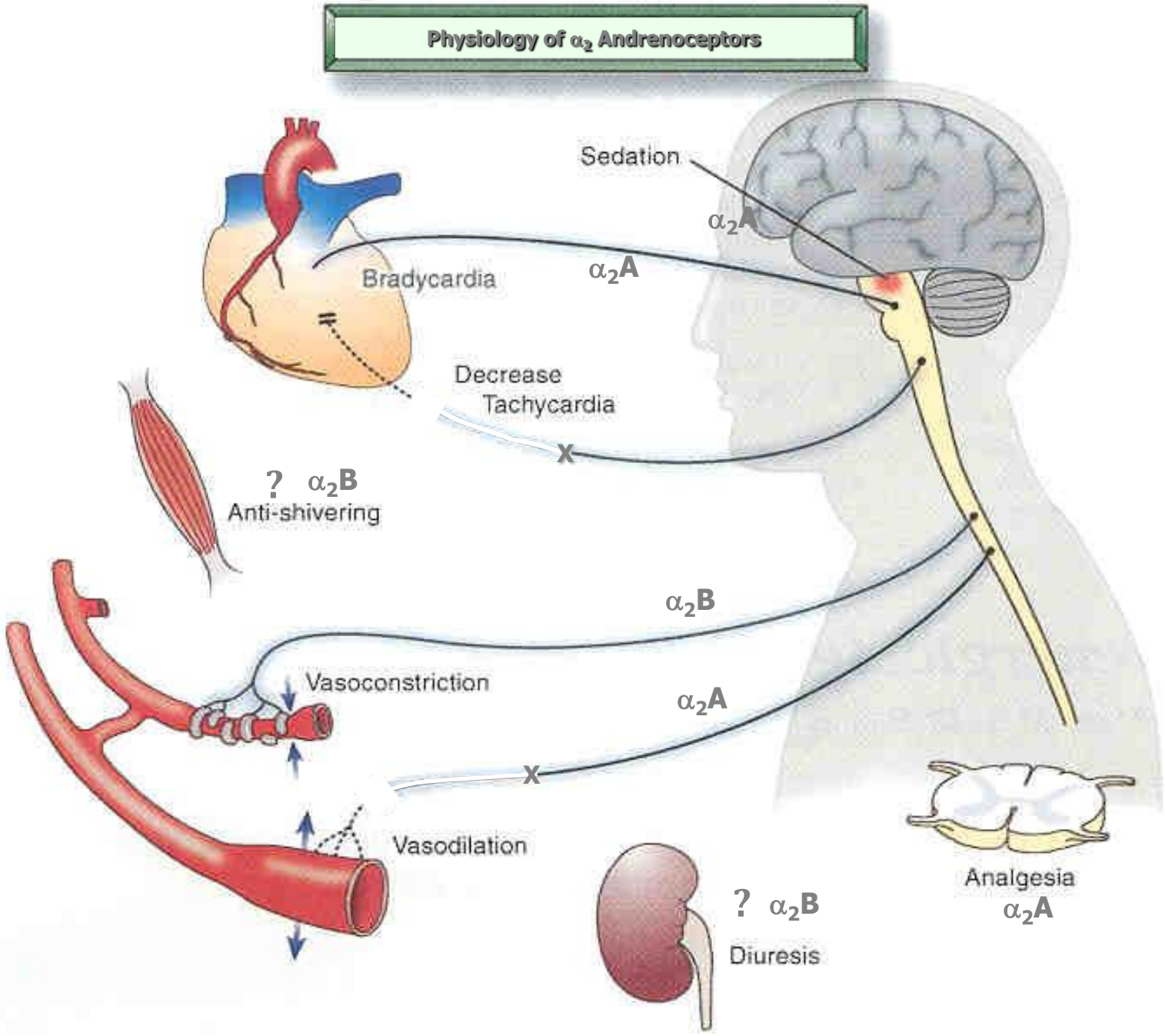
Alpha-2 AR Mediated Responses

- Numerous alpha-2 AR mediated responses
- Different dose response curve for each

α_2-Receptor Subtypes



Effects of Alpha-2 Agonists

- Endocrine
  - ↓ NE release
  - ↓ insulin release
  - ↓ cortisol release
  - ↑ GH release
- Baroreflexes stay intact (reset)
- Normal response to vasoactive drugs
- Attenuates stress response

Effects of Alpha-2 Agonists

- No effect on ICP
- Reduces IOP
- No effect on relaxants
- Prolongs local anesthetic action
- Decreases metabolism
- Decreases oxygen consumption

Effects of Alpha-2 Agonists

- Dry mouth (awake fibers)
- Decreases bowel motility
- Decreases psychomotor performance
- Not amnestic
- Slows EEG
- Prevents opioid induced rigidity
- Neuro/cardiac protection?

Side Effects

- Sinus pause/arrest
- Orthostatic hypotension
- Dry mouth
- Vasoconstriction

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Patient Selection

- High sympathetic activity
- Agitated/anxious
- With discomfort

NOT

- Low blood pressure
- Hypovolemic/shock
- Conduction defects

Dosing

- Dexmedetomidine
  - 10 min loading infusion 0.5-1.0 ug/kg
  - 0.2-0.7 ug/kg/hr infusion
  - Effects in 5-10 min, reduced in 30-60 min
- Clonidine
  - 10 min loading infusion 3-5 ug/kg
  - 0.3 ug/kg/hr infusion
  - Effects in 5-10 min iv, in 60-90 min po

My favourite use

- Transition from intraop to postop period by administering dexmedetomidine during the last 30 min of surgery, while reducing other anesthetics
- Limited by PACU/ICU nurses who are unfamiliar with managing the infusion
- NOT a do all drug! Still need some narcotics. No cross tolerance with opioids

Alpha-2 agonist development
(where to look for the literature)

- Clonidine 1960 (nasal decongestant)
- Medetomidine (vetenary use, early literature)
  - Levomedetomidine inactive
- Dexmedetomidine 1980's (lots of studies):
  - Premedication
  - Anti-ischemic agent
  - Anesthetic adjunct (intraop)
  - ICU sedation
- Mivazerol (development stopped)
- MPV 2426 (polar compound for pain)
- Future: Subtype selective agonists/antagonists