VASOPRESSORS AND INOTROPES

COMMUNITY OF PRACTICE ASSIGNMENT

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PHARM D. CANDIDATE, 2017

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WHAT ARE VASOPRESSORS AND INOTROPES

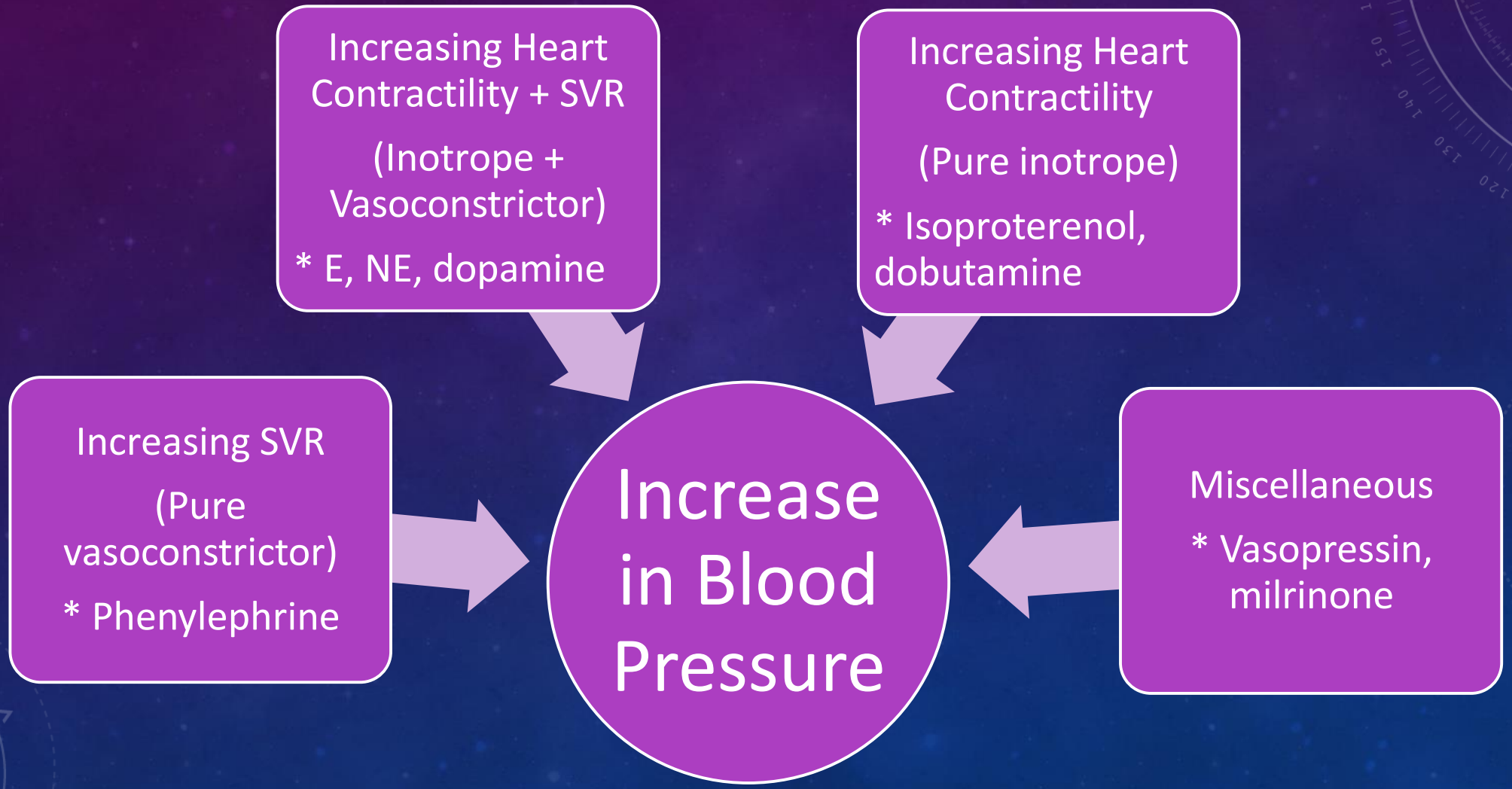
Definitions

- Vasopressors: Anti-hypotensive agents that cause ***vasoconstriction*** leading to increased systemic or pulmonary vascular resistance (SVR or PVR)
- Inotropes: Agents that alter the ***contractility*** and ***rate*** of the heart
- Chronotropes: Agents that alter the ***rate*** at which the heart beats

IN WHICH SITUATIONS DO WE USE VASOPRESSORS AND INOTROPES?

- Shock and severe hypotension
- Symptomatic bradycardia
- Low cardiac output (CO)
- Heart block
- Bradyarrhythmia (i.e. TdP)
- Peri-operatively

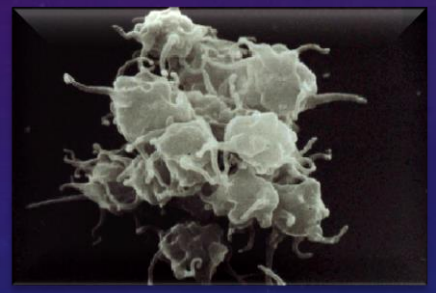
INOTROPES, VASOPRESSORS AND THEIR EFFECTS



EXAMPLES OF INOTROPES AND VASOPRESSORS

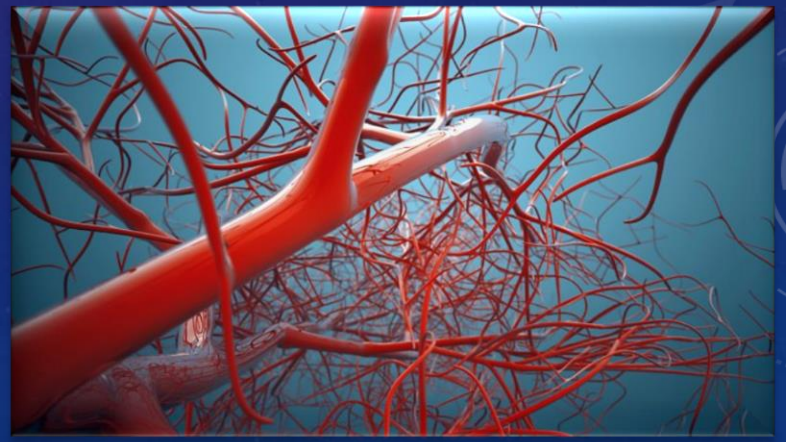
• Epinephrine	• $\alpha_1 > \beta_1 > \beta_2$
• Norepinephrine	• $\alpha_1 > \beta_1 > \beta_2$
• Dobutamine	• $\beta_1 > \beta_2 > \alpha_1$
• Dopamine	• DA $> \beta_1 > \alpha_1 > \beta_2$
• Isoproterenol	• $\beta_1 = \beta_2$
• Phenylephrine	• α_1 only
• Vasopressin (ADH)	• $V_1 = V_2$
• Phosphodiesterase inhibitors (PDE_3I)	• N/A

HOW DO INOTROPES AND VASOPRESSORS WORK?



Inotropes and vasopressors act on receptors:

- α_1 – Located in the vascular smooth muscle
  - Stimulation results in vasoconstriction and increased SVR
- α_2 – Located on sympathetic neurons, platelets, and pancreatic β -cells
- β_1 – Located (mostly) in cardiac tissue
  - Stimulation results in increased cardiac contraction and heart rate
- β_2 – Located in the vascular smooth muscle
  - Stimulation causes smooth muscle relaxation and vasodilation

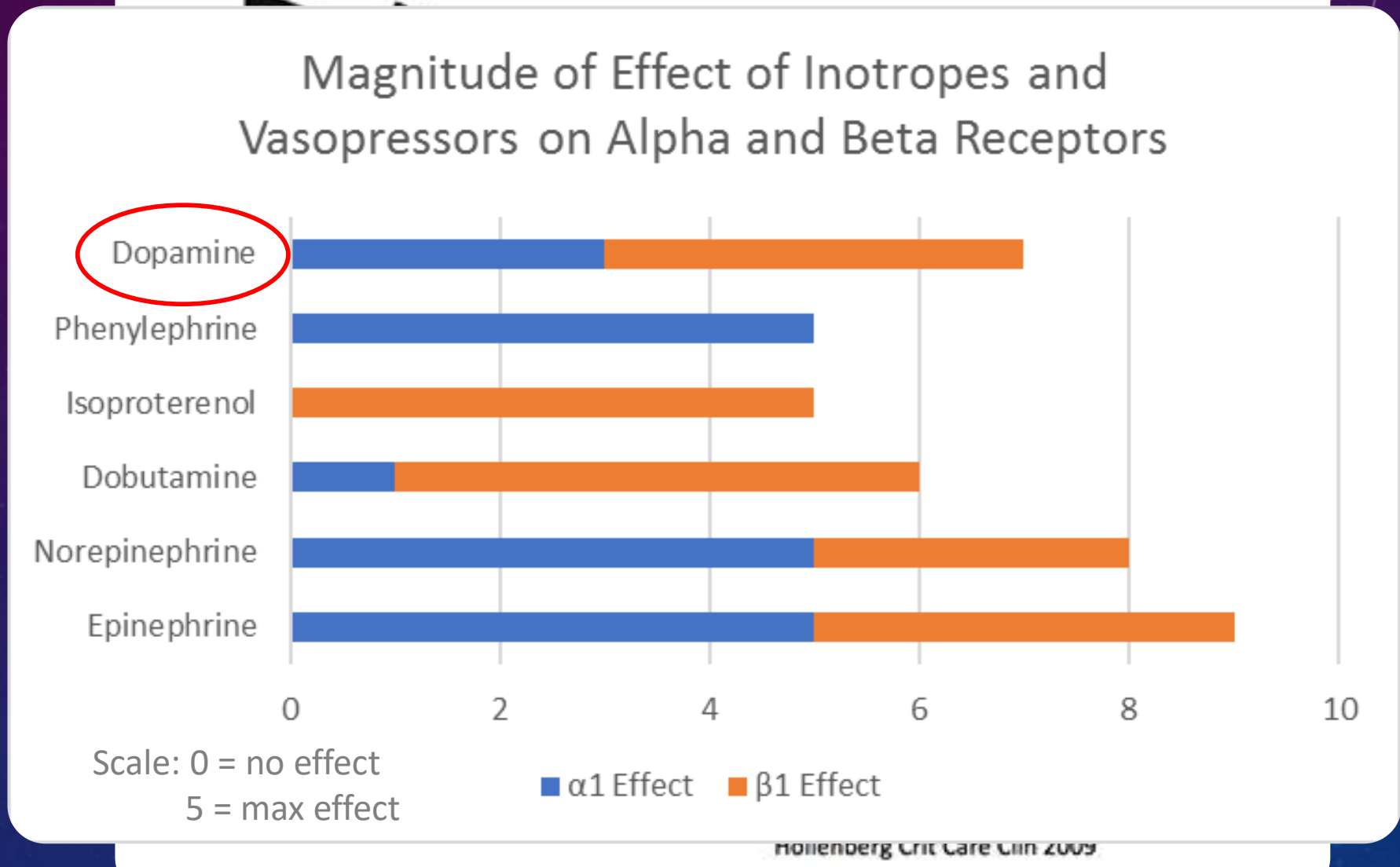


Based on this information, which of might we target for treatment of hypotension?

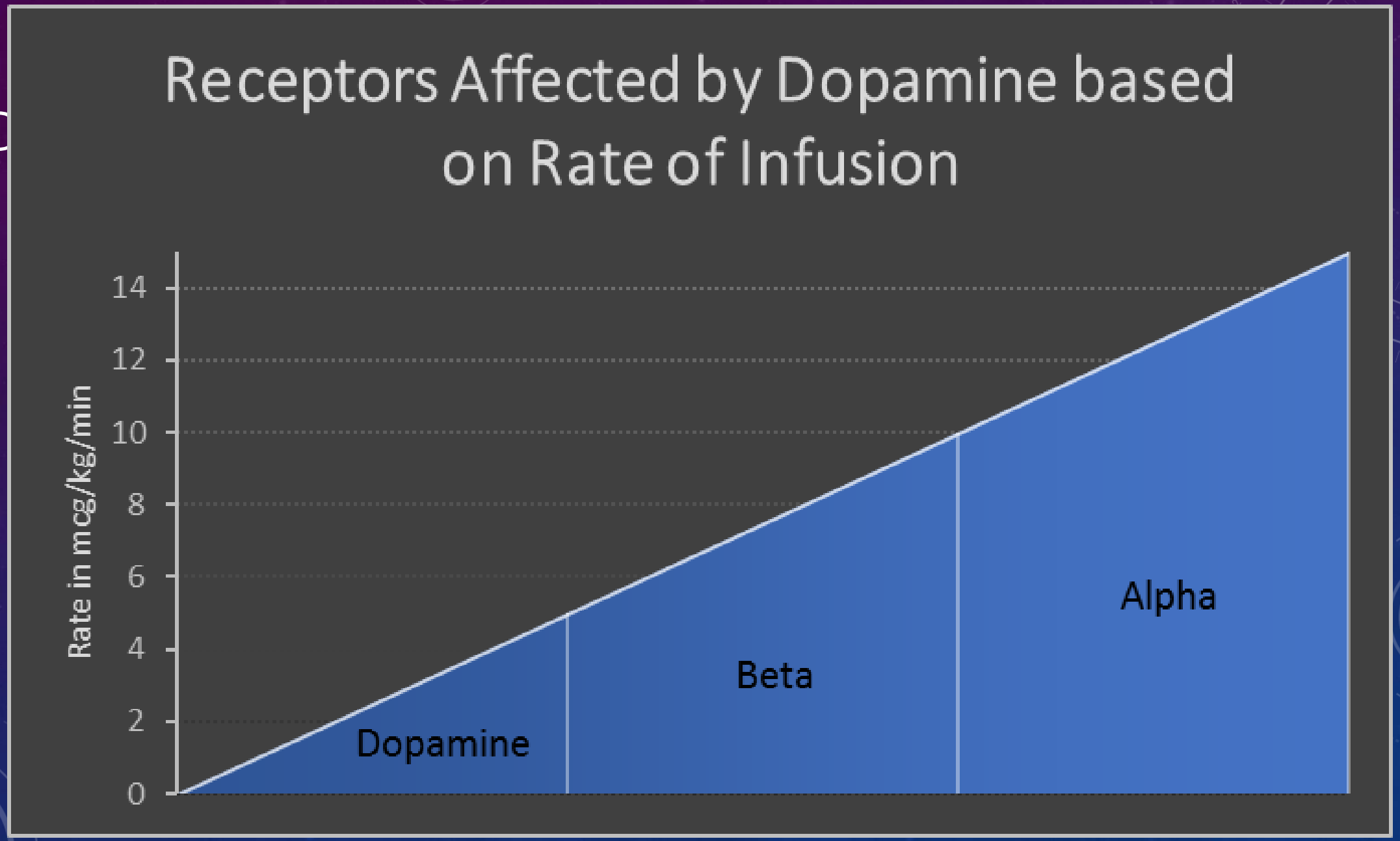
INOTROPE AND VASOPRESSOR FORMULAS

$$Cardiac\ Output\ (CO) = Stroke\ Volume\ (SV) \times Heart\ Rate\ (HR)$$

- How is CO related to inotropes and vasopressors?
  - Pure α_1 stimulation *reduces CO*
  - β_1 increases contractility = more blood pumping out = increased stroke volume
  - β_1 also increases HR
- HR and SV increasing means *CO also increases*

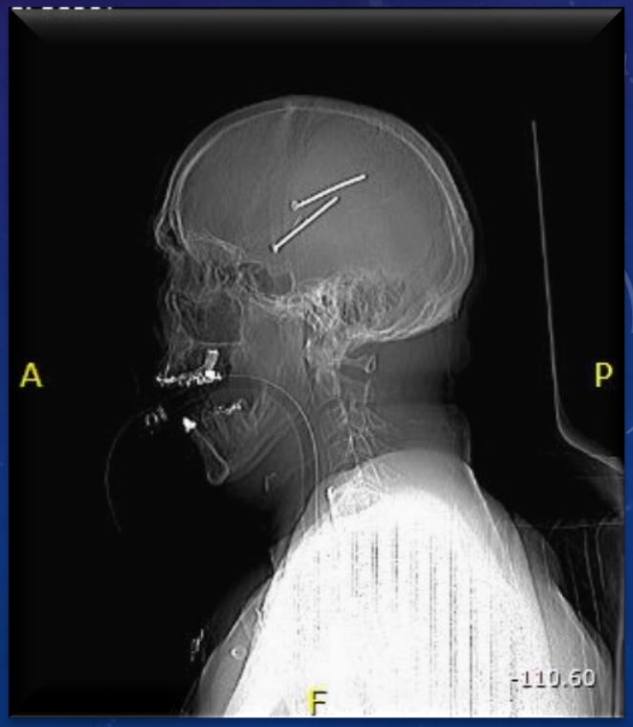

Magnitude of Effect of Inotropes and Vasopressors on Alpha and Beta Receptors
Dopamine
Phenylephrine
Isoproterenol
Dobutamine
Norepinephrine
Epinephrine
0
2
4
6
8
10
Scale: 0 = no effect
5 = max effect
α1 Effect
β1 Effect

D


Receptors Affected by Dopamine based on Rate of Infusion
Rate in mcg/kg/min
0
2
4
6
8
10
12
14
Dopamine
Beta
Alpha

CASES 1.0 AND 1.5

- See Student Rounds Presentations May to June 2017

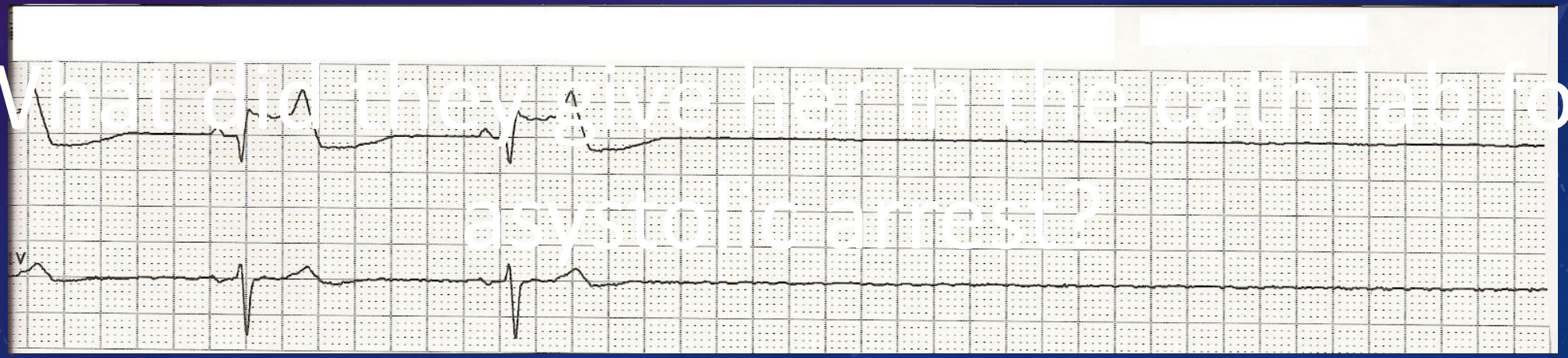


CASE 2.0

- 64-year old female
  - Admitting diagnosis: ACS
  - PMH: T2DM, HTN, CAD
    - Refuses to take anti-platelets and beta blockers
  - HPI: Ongoing chest pain off/on for 2 days, troponin 1.5, RBBB, non-specific ST changes, K+ 5.1, SCr 61
  - Unremarkable social and family history

CASE 2.0 CONTINUED…

- Patient underwent angiogram after initial refusal
  - Underwent asystolic arrest



What did they have in the cath lab for asystolic arrest?

MANAGEMENT OF SHOCK

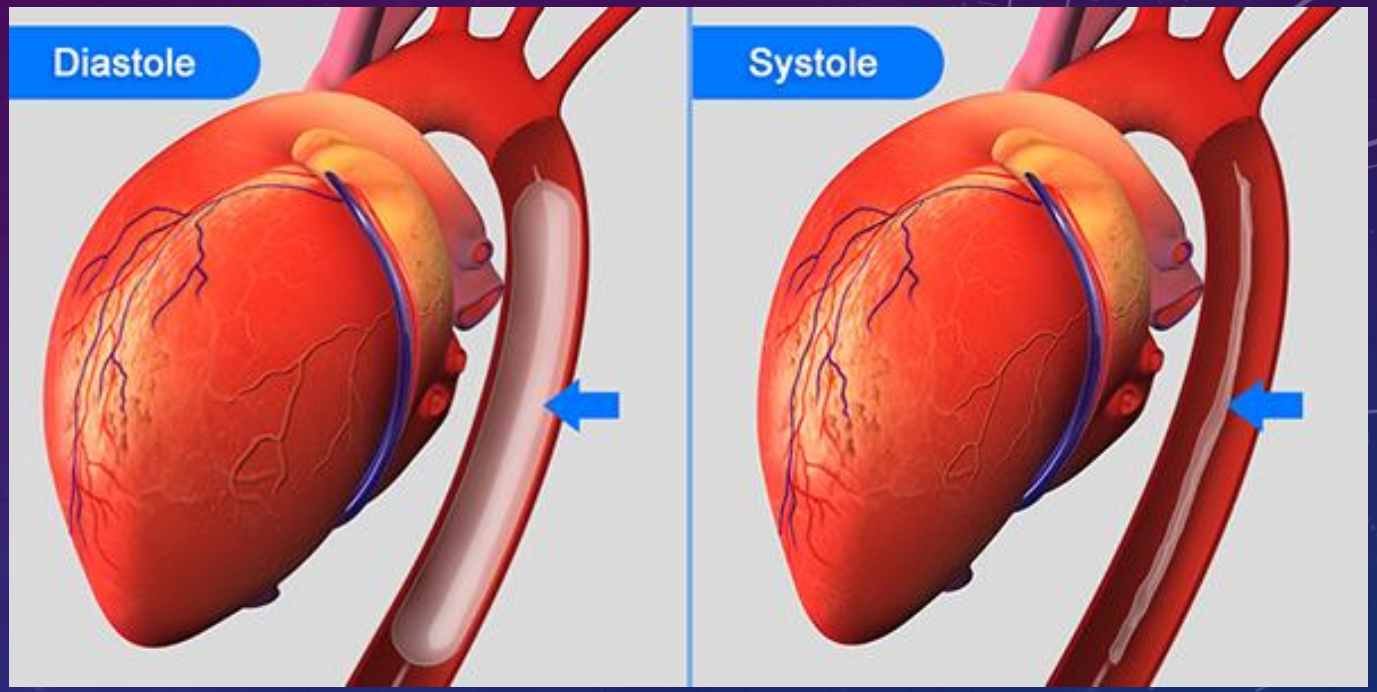
- How do we manage a shock patient?
- We give them the ***VIP* treatment**
  - **V**entilate (oxygen administration)
  - **I**nfuse (fluid resuscitate)
  - **P**ump (vasoactive/inotropic agents)
- Vasoactive agents are given if fluid resuscitation is not effective
  - May be administered during fluid resuscitation as well

SELECT TREATMENT ALGORITHMS

- Asystolic Arrest
  - 1st line – CPR
  - 1st line – Epinephrine every 5 minutes
    - Vasopressin shows no benefit over epinephrine
    - Atropine + epinephrine shows benefit for return of spontaneous circulation

CASE 2.0 CONTINUED…

- Patient received:
  - Prompt CPR ✓
  - Epinephrine and atropine ✓
  - Aortic balloon pump
    - Plus IV heparin
  - Dobutamine ($\beta_1 > \beta_2 > \alpha_1$) infusion
    - Grade 4 LV dysfunction present
    - Ejection fraction of approximately 20%



CASE 2.0 CONTINUED…

- Patient underwent subsequent CABG x 3
  - Was admitted to ICU post-OR
  - Intra-aortal balloon pump still in place
- Inotropes and vasopressors post-OR:
  - Epinephrine ($\alpha_1 > \beta_1 > \beta_2$)
  - Norepinephrine ($\alpha_1 > \beta_1 > \beta_2$)
  - Dobutamine ($\beta_1 > \beta_2 > \alpha_1$)
- Ventilated

CASE 2.0 CONTINUED…

- Patient became oliguric and SCr increased to 372 µmol/L
- Dialysis required
  - Hemodynamically unstable; likely unable to tolerate IHD
  - SLEDD (Sustained Low Efficiency (Daily) Dialysis) performed initially
- Tracheostomy performed due to prolonged ventilation

CASE 2.0 CLOSED

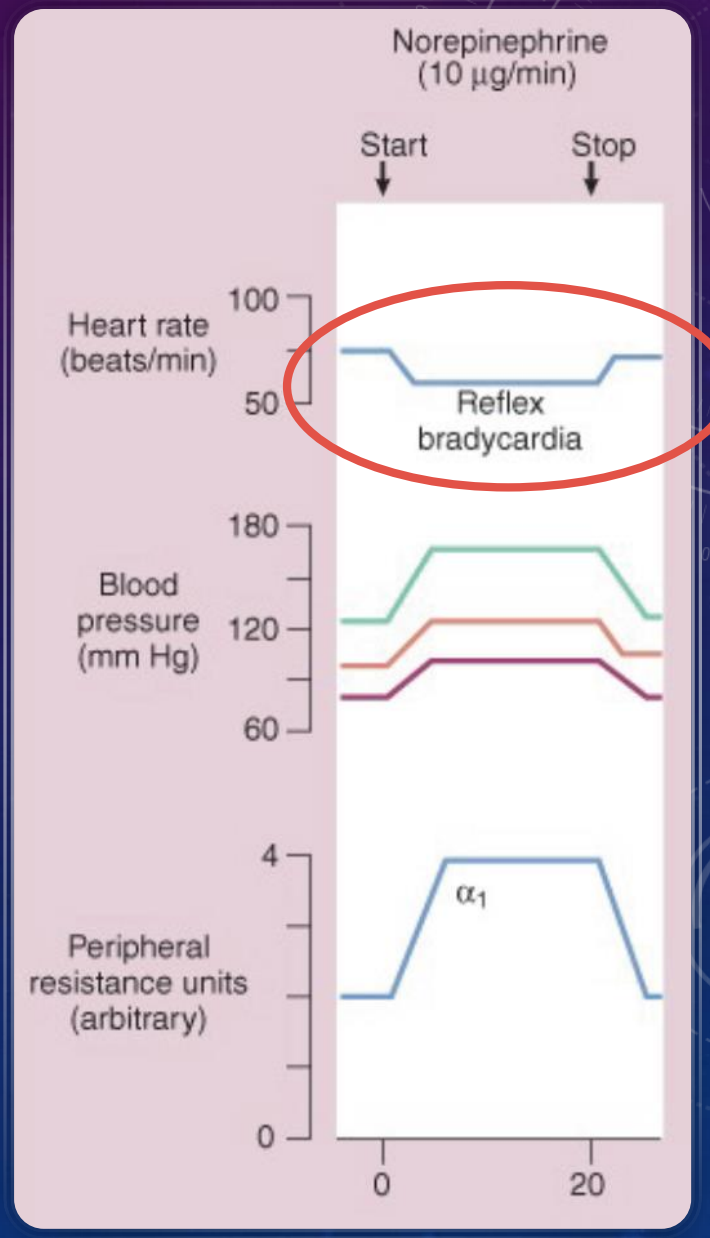
- Patient remains hemodynamically stable, but very weak
- Vasopressors are being weaned off and are only being used intermittently
- Prognosis does not foresee patient leaving the hospital in her lifetime

THE “MEDICAL” SIDE OF THINGS

- Continuous blood pressure monitoring REQUIRED for use of inotropes and vasopressors
  - Done through an arterial line setup
- Administration of inotropes and vasopressors done through a central venous catheter
- Administer the lowest possible dose for the shortest period of time to minimize ADRs

SIDE EFFECTS OF VASOPRESSORS

- Increased myocardial oxygen demand
- Ventricular arrhythmia
- Contraction band necrosis (in cardiogenic shock)
- Infarct expansion (in cardiogenic shock)
- Increased mortality (CHF)
- Lactic acidosis (with NE post-cardiopulmonary bypass)
- **Reflex bradycardia with NE ($\alpha_1 > \beta_1 > \beta_2$)**
- **Dermal necrosis**



SELECT TREATMENT ALGORITHMS

- Bradyarrhythmia
  - 1st line – Dobutamine (β1> β2> α1), isoproterenol (β1= β2), dopamine (DA> β1> α1> β2)
    - Use if atropine ineffective
    - May be used until pacemaker can be installed
    - Can be used in Torsades de Pointes

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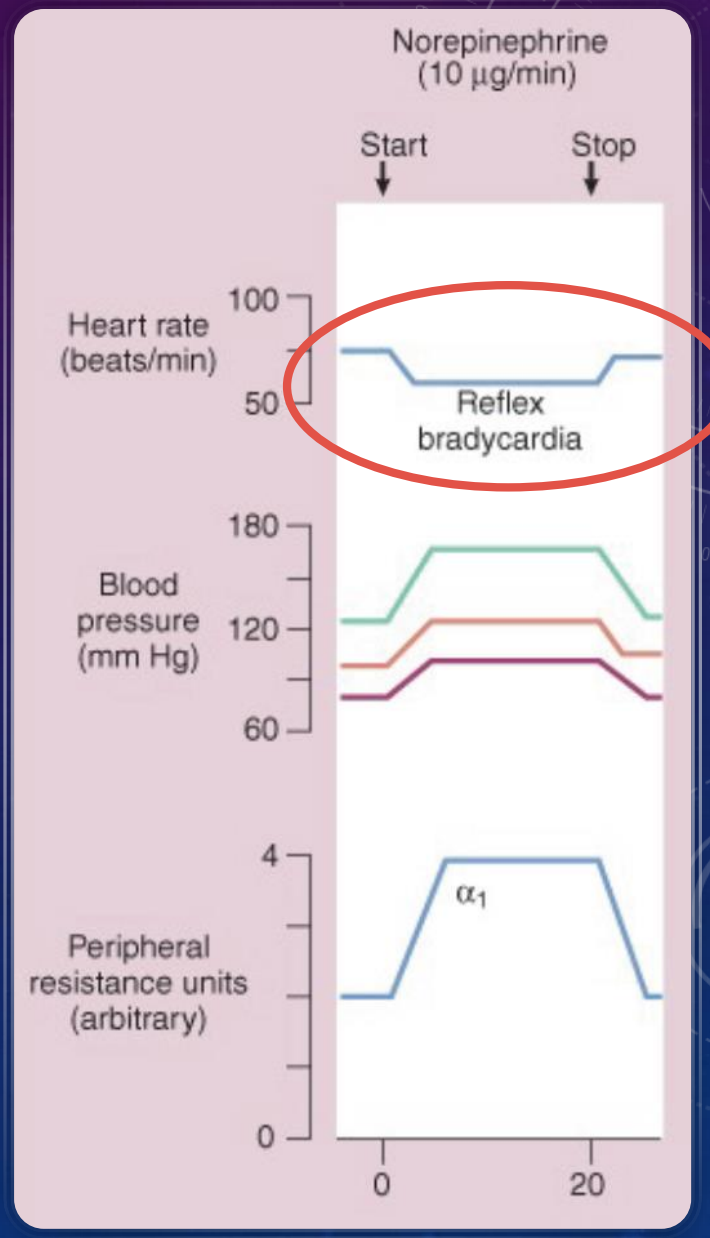

PHENTOLAMINE

- Phentolamine is an antidote for extravasation of epinephrine and norepinephrine
  - Dermal necrosis occurs in tissue due to intense vasoconstriction
  - Phentolamine injected around the area to minimize the spread of necrosis
  - Mechanism of action: Complete (non-selective) α-blockade

SELECT TREATMENT ALGORITHMS

- Cardiogenic Shock complicating Acute MI
  - 1st line – Dobutamine ($\beta_1 > \beta_2 > \alpha_1$) if no shock symptoms and SBP 70-100
  - 1st line – Dopamine ($DA > \beta_1 > \alpha_1 > \beta_2$) if shock symptoms and SBP 70-100
    - These agents AVOID excessive α_1 stimulation which can lead to end-organ ischemia
    - They maximize the use of inotropy
  - 2nd line – Use NE when SBP < 70 or as add-on therapy with inadequate response to 1st line agents
  - 2nd line – Vasopressin may be used in late shock/NE-resistant shock
    - Vasopressin levels are high during early shock but deplete with time

SELECT TREATMENT ALGORITHMS

- Heart Failure
  - 1st line – Avoid vasopressors!
    - Diminished peripheral perfusion, pulse pressure and worsening kidney function (avoid α_1)
    - High SVR despite hypotension (avoid α_1)
    - Positive inotropes increase mortality (avoid β_1)
  - Refractory HF – Dobutamine (β1> β2> α1), dopamine (DA> β1>A1> β2), milrinone (PDE3i = vasodilation in vascular smooth muscle + inotropy)
    - Decreases afterload, increases force of contractility

SUMMARY

- Inotrope = increase HR and contractility
- Vasopressor = constriction of vessels
- MOA: α or β agonism leading to vasoconstriction or inotropy
- $CO = SV \times HR$
- **V**entilate, **I**nfuse, **P**ump
- Least amount of inotropes vasopressors for the shortest period of time

THE END

THANK YOU FOR ATTENDING STUDENT ROUNDS MAY-JUNE 2017

SINCERELY,

Jillian Belanger

and

Jonathan Gbedemah

METHYLENE BLUE??

- Hypotension can be present in the peri-operative period
  - Can be partially due to the effects of endothelial nitric oxide synthase (eNOS)
- Methylene blue directly inhibits eNOS
  - Prevents the synthesis of nitric oxide which is vasodilatory
  - Also blocks production of cGMP which is a pro-vasodilatory molecule
- Administered as a single dose at 1.5 – 2 mg/kg
- Use is unsupported in septic shock

MILRINONE

- Phosphodiesterase 3 (PDE3) enzymes are located largely in the heart
  - PDE3 works to decrease the amount of cAMP in the heart
  - cAMP causes increased contractility
  - Thus, PDE3Is inhibit the breakdown of cAMP leading to increased contractility
- Used as inotropic support in CHF
- Given as a loading dose 50 µg/kg (dependent on renal function) plus a maintenance dose

TO DO

- Comb through presi and change all alpha/A and beta/B to symbols
- Change order of slides

METABOLISM OF INOTROPES AND VASOPRESSORS

- Endogenous inotropes and vasopressors are metabolized by:
  - Catechol-O-Methyltransferase (COMT)
  - Monoamine oxidase (MAO)
- Thus, theoretical interactions exist between their use and COMT inhibitors (i.e. entacapone) and MAO inhibitors (i.e. phenelzine (Nardil) and selegiline) due to decreased clearance
  - Small studies have found that NE + entacapone shows no increased effect on BP
    - One case of ventricular tachycardia
  - Other small studies found that NE + phenelzine have no increase in BP

WHY IS NOREPINEPHRINE 1ST LINE IN SEPTIC SHOCK?

- NE has A1 effects + modest B1 leading to increased SVR and maintaining CO
- Compared to epinephrine, NE has decreased rate of arrhythmia as well as better effects on serum lactate and splanchnic blood flow
- Compared to dopamine, NE has less death

SUGGESTIONS

- Outline for presentation
  - Graphically outline what I will be presenting
  - Ensure all points are hit
- GRAPHICS (large)
- Cases
  - Use overlap graph in cases to allow for explanation of why certain pressors were used
  - PB
    - Dob/dop
    - 23 Bed
- Questions to ponder (bridging slides)