MAYO CLINIC

Red or Blue: Which One for You?

Hydroxocobalamin or Methylene Blue for Refractory Vasoplegic Shock

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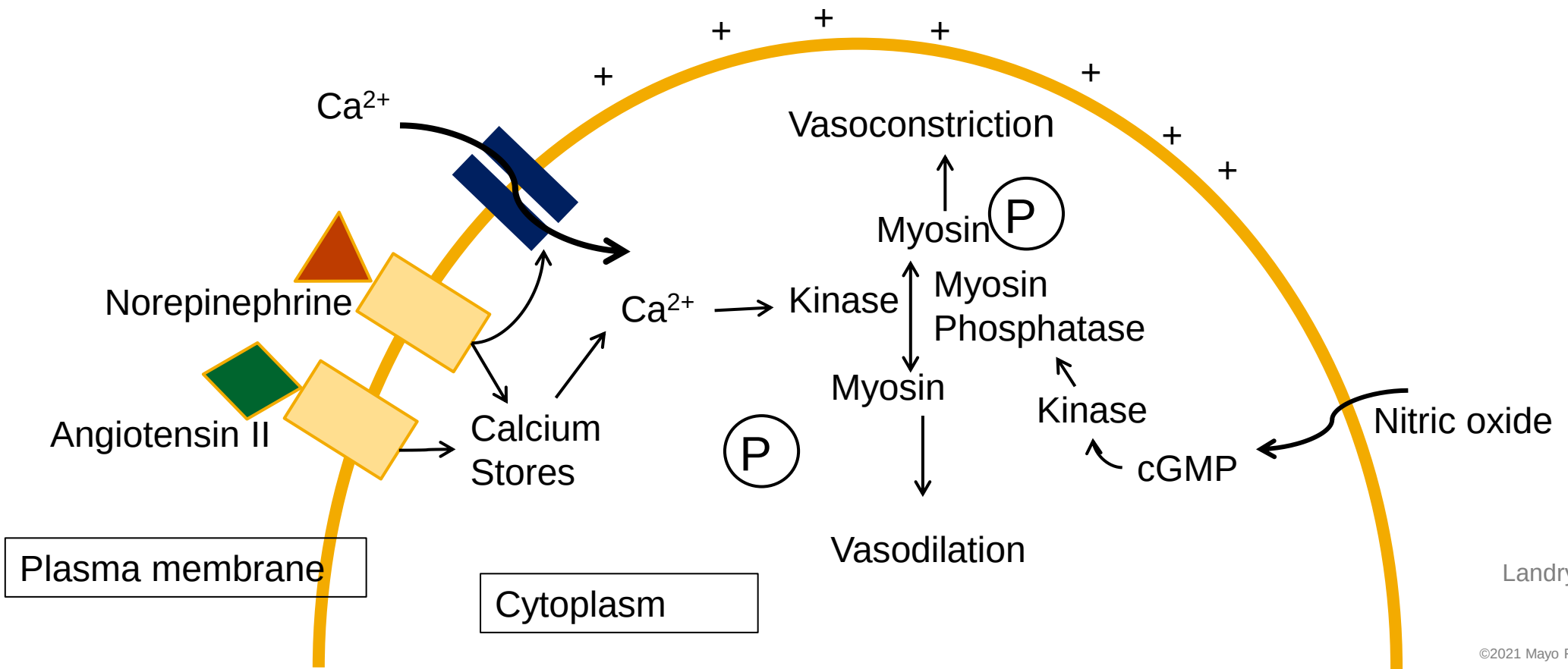
Pharmacy Grand Rounds
February 2nd, 2021

LEARNING OBJECTIVES

1. Describe the pathophysiology of refractory vasoplegic shock
2. Examine literature detailing use of methylene blue and hydroxocobalamin for refractory vasoplegic shock
3. Identify appropriate use of methylene blue or hydroxocobalamin in refractory vasoplegic shock

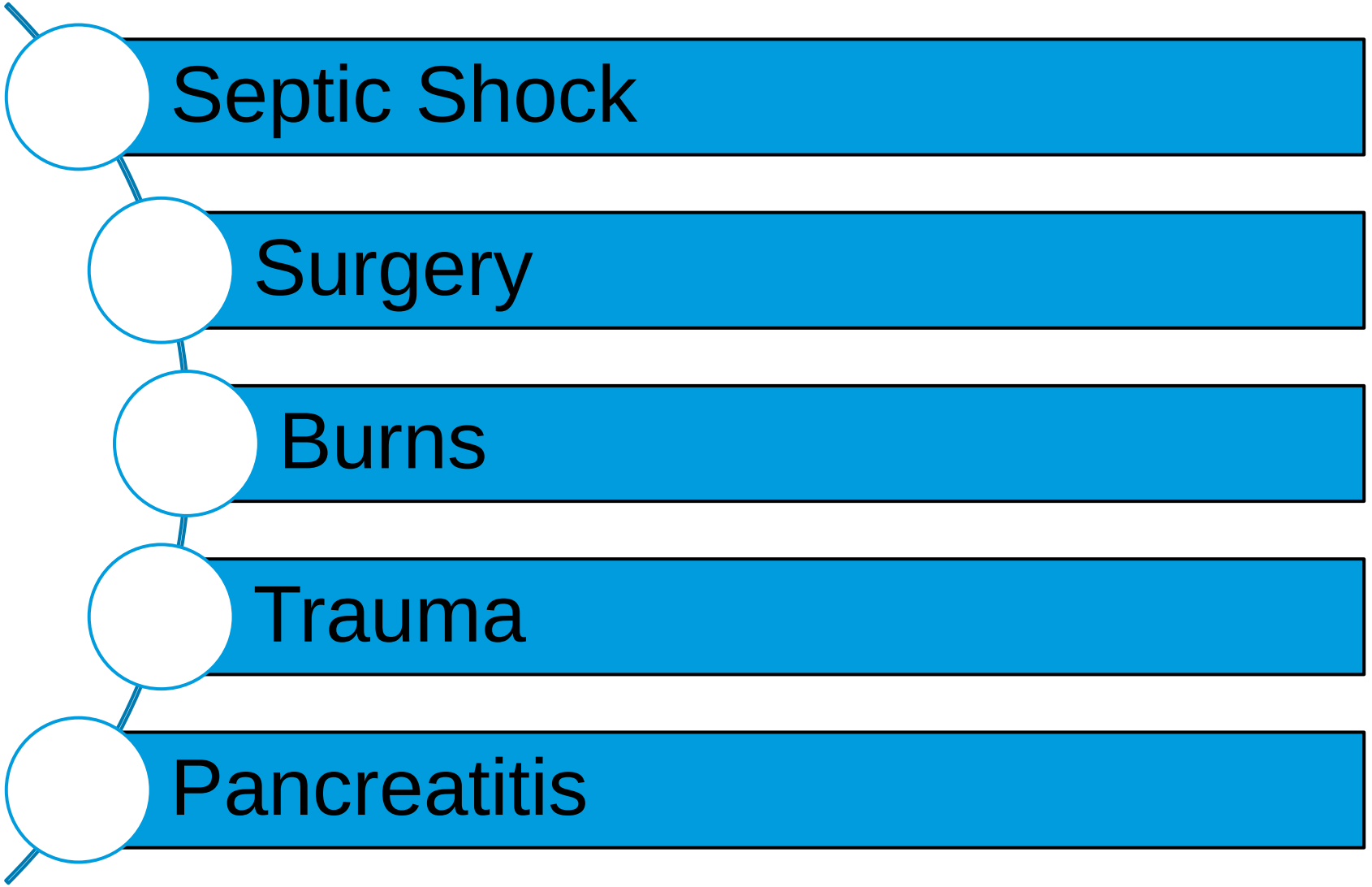
1 PATHOPHYSIOLOGY OF VASOPLEGIC SHOCK

NORMAL PATHOPHYSIOLOGY



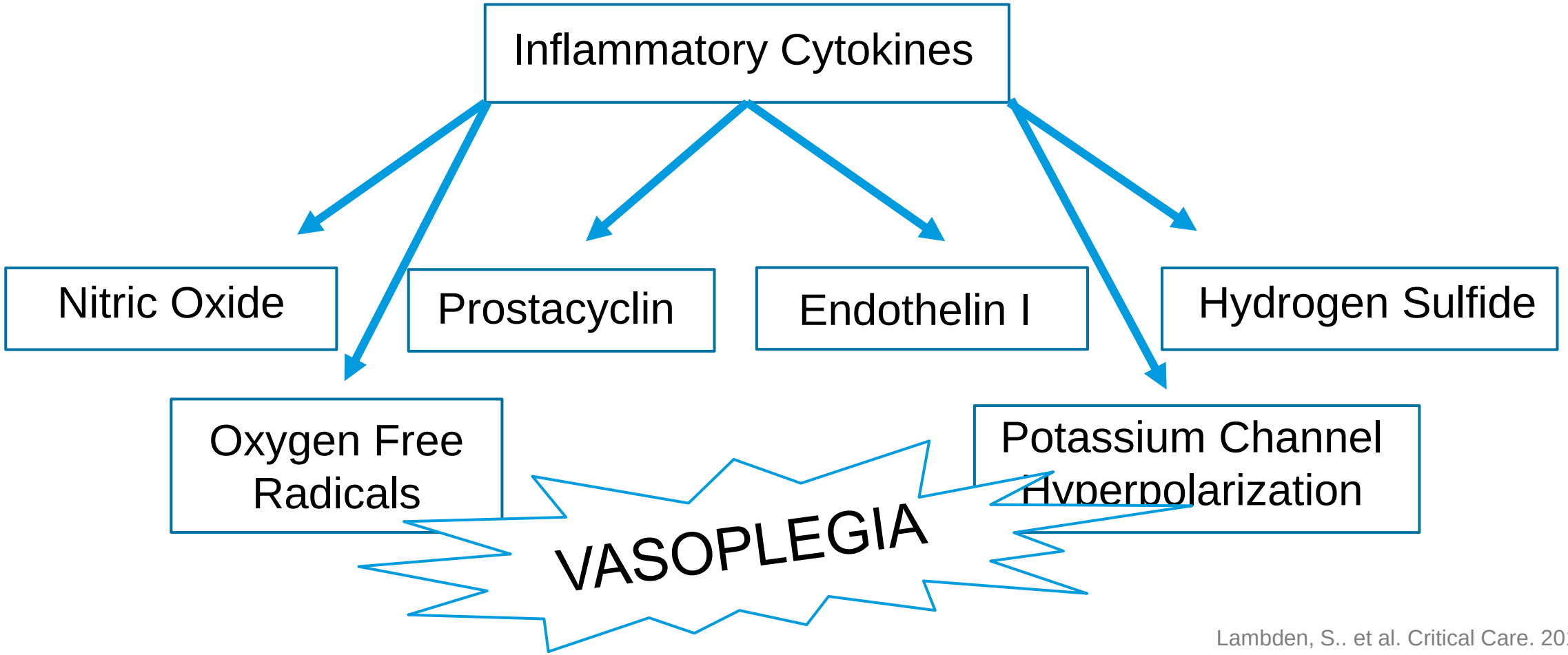
Landry, D.W. et al. N Engl J Med. 2001

CAUSES OF VASOPLEGIC SHOCK

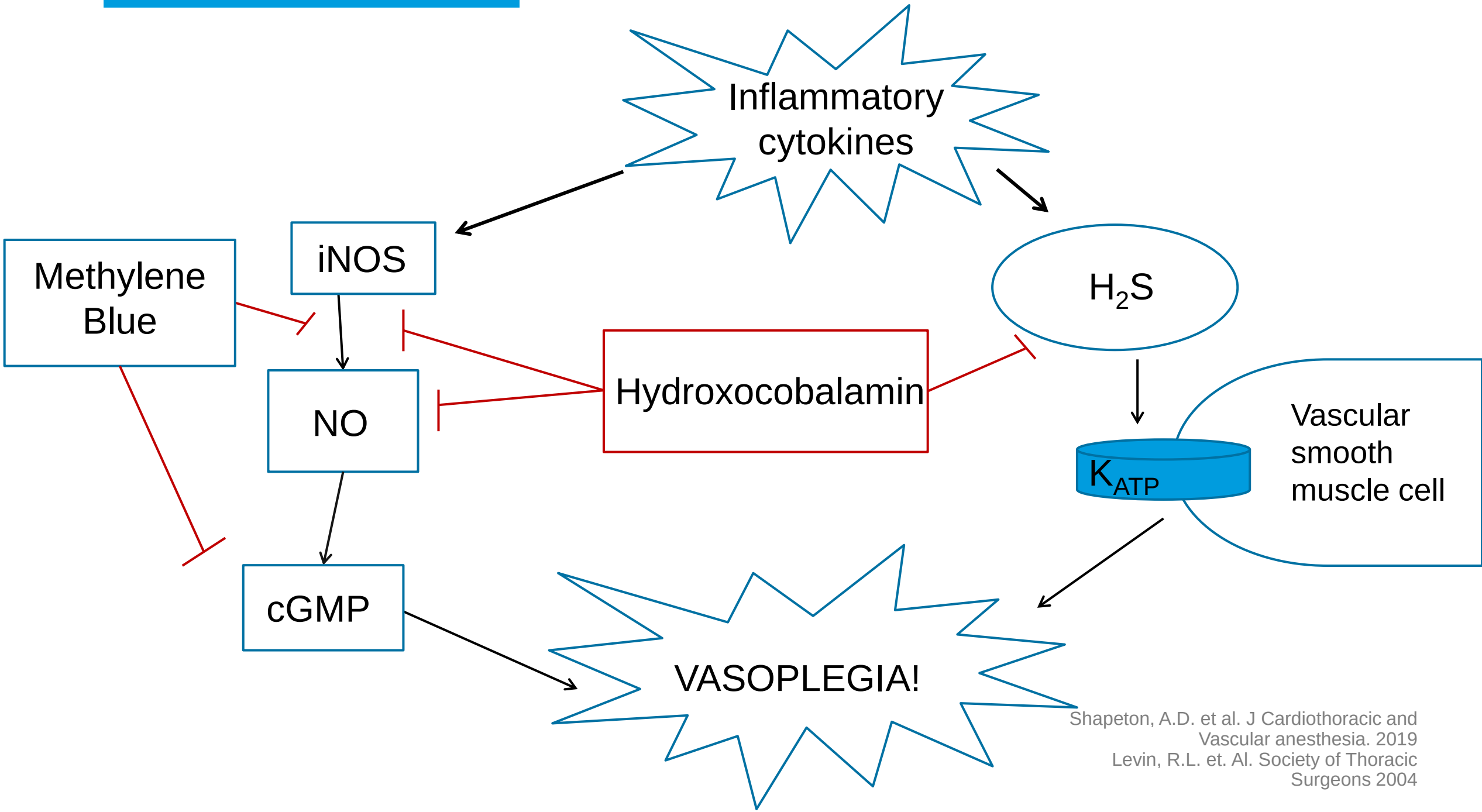


Lambden, S.. et al. Critical Care. 2018

PATHOPHYSIOLOGY OF REFRACTORY VASOPLEGIC SHOCK



Lambden, S.. et al. Critical Care. 2018



Shapeton, A.D. et al. J Cardiothoracic and Vascular anesthesia. 2019
Levin, R.L. et. Al. Society of Thoracic Surgeons 2004

WHAT ENZYME OR CO-FACTOR IS ACTIVATED TO START THE CASCADE LEADING TO VASOPLEGIA IN THE NITRIC OXIDE PATHWAY?

A. Nitric oxide

B. Inducible nitric oxide synthase

C. Nitric oxide reductase

D. Hydrogen sulfide

2 EVIDENCE FOR METHYLENE BLUE

METHYLENE BLUE

Mechanism of Action

- Restores vascular tone by inhibiting nitric oxide synthase with oxidation of enzyme-bound ferrous iron
- Blocks the formation of cyclic guanosine monophosphate (cGMP)

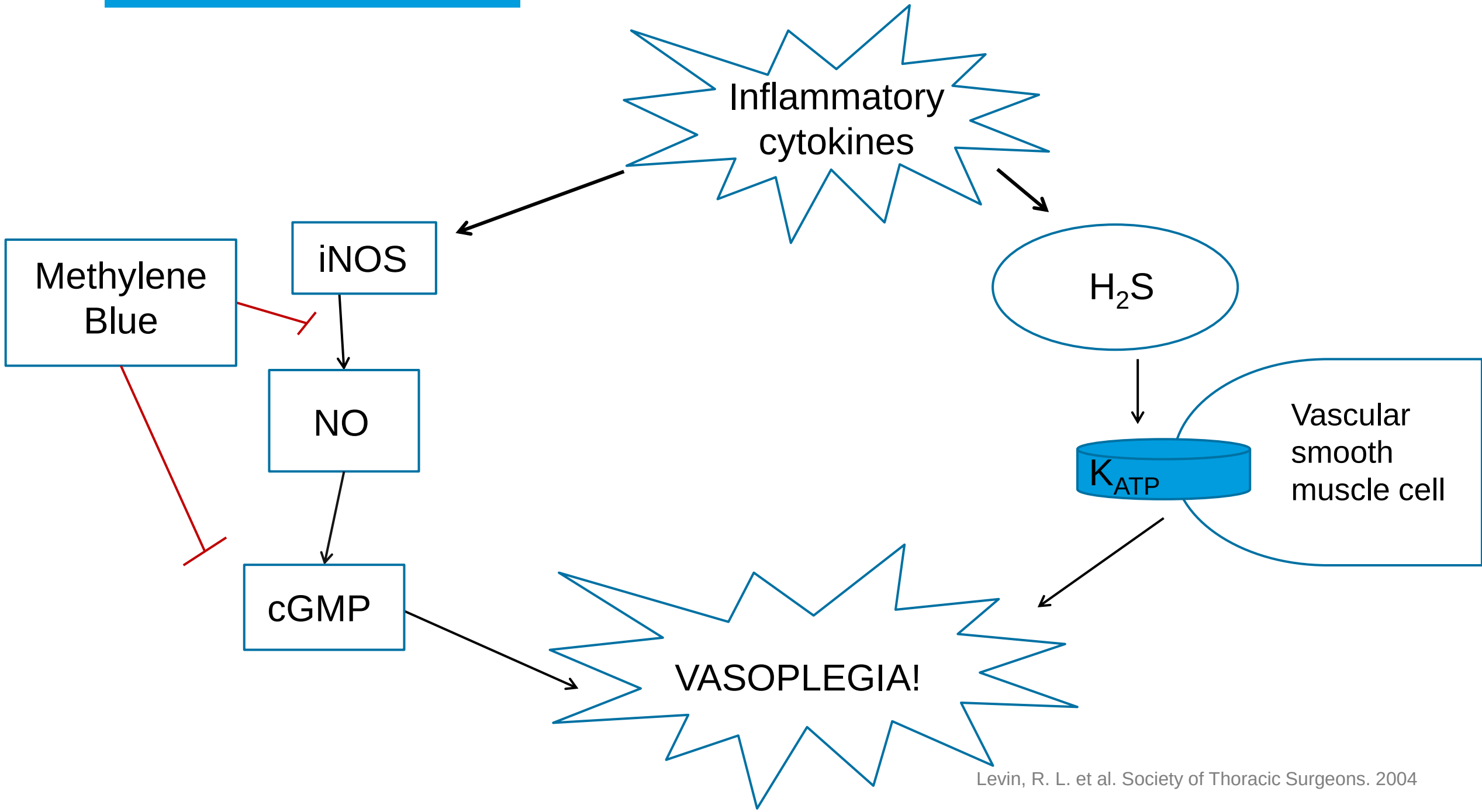
Side Effects

- Limb pain
- Skin and urine discoloration
- Syncope
- Chest discomfort
- Methemoglobinemia

Contraindications

- Patients with glucose-6-phosphate dehydrogenase deficiency (G6PD)
- Taking serotonergic medications
  - FDA boxed warning: Avoid use with MAOIs, SNRIs, SSRIs → serotonin syndrome

Levin, R. L. et al. Society of Thoracic Surgeons. 2004
Methylene blue. Package Insert. Accessed January 31st, 2021



Levin, R. L. et al. Society of Thoracic Surgeons. 2004

RANDOMIZED CONTROLLED TRIAL WITH METHYLENE BLUE

Patients

- Included
  - Vasoplegic patients undergoing cardiac surgery
- Excluded
  - Off-pump coronary artery bypass
  - Bacterial endocarditis
  - Aortic dissection
  - Urgent or emergent procedures

Definition of Vasoplegia

- Hypotension
- MAP <50 mmHg
- High or normal cardiac index >2.5 L/min/m^2
- Systemic vascular resistance (SVR) <800 dyn/s/cm^{-5}
- Vasopressor requirements

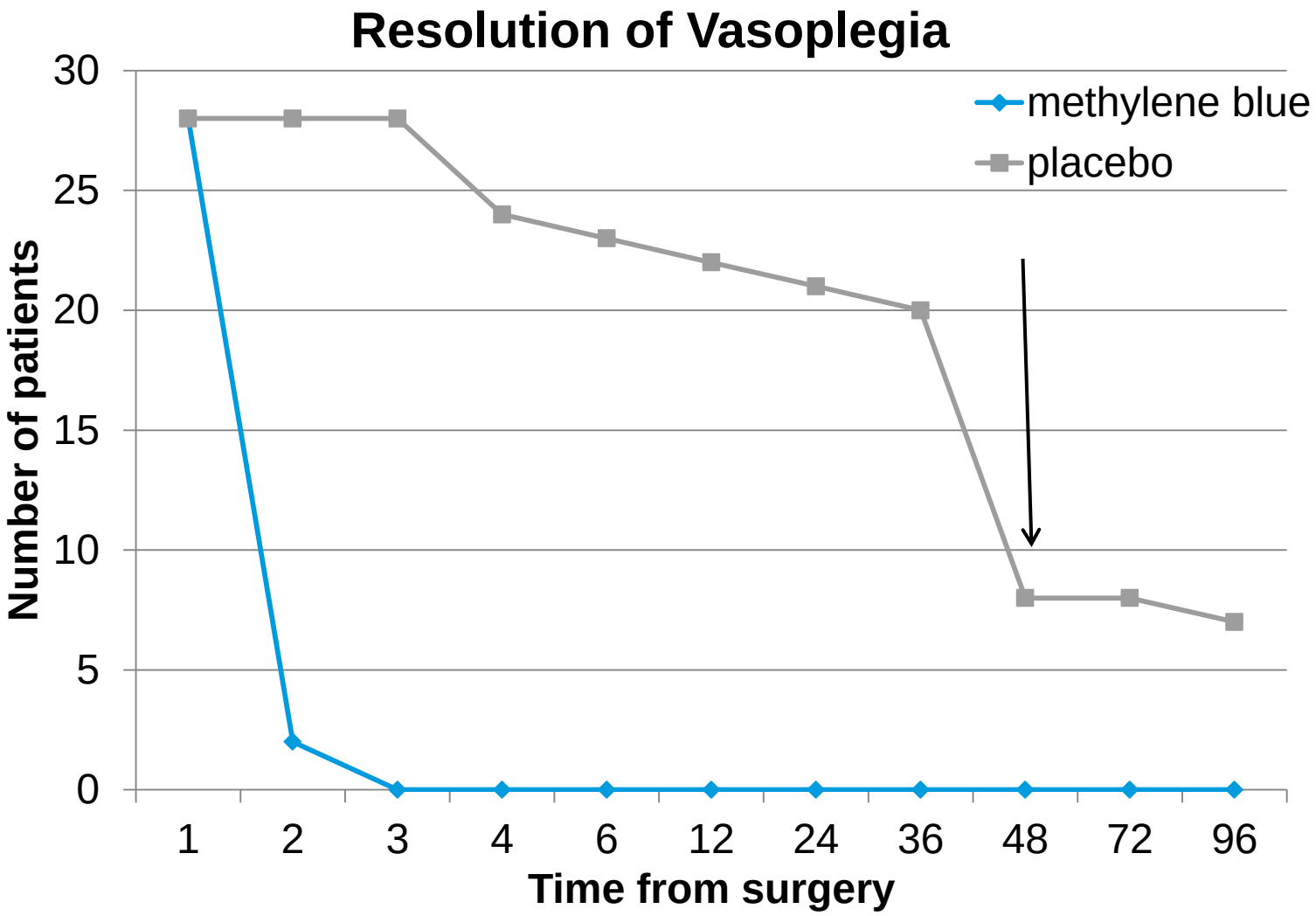
Randomization

- 1:1
- Methylene blue 1.5 mg/kg over 1 hour
- Placebo

Levin, R. L. et al. Society of Thoracic Surgeons. 2004

RESULTS

- 8.8% (56/638) patients met criteria for vasoplegia
- 28 patients in each arm, no differences in baseline characteristics
- Overall mortality: 27/638 patients (4.2%)
  - 6 of these patients in the vasoplegic population (10.7%, p= 0.02)
    - 0 deaths in methylene blue group
    - 6 deaths in placebo group (21.4%) p= 0.01
- Time from surgery to resolution of vasoplegia at 48 hours: p = 0.002



Levin, R. L. et al. Society of Thoracic Surgeons. 2004

ANALYSIS OF STUDY

Pros

- Randomized controlled trial
- Similar baseline characteristics

Cons

- No specific definition of vasopressor requirements
- Small sample size and published in 2004
- High mortality in non-vasoplegic group

Conclusions

- Methylene blue decreases duration of vasoplegia when compared to placebo

Levin, R. L. et al. Society of Thoracic Surgeons. 2004

3 EVIDENCE FOR HYDROXOCOBALAMIN

HYDROXOCOBALAMIN

Mechanism of Action

- Binds and directly inhibits nitric oxide synthase, and nitric oxide
- Binds hydrogen sulfide

Dosing

- 5 grams over 15-360 minutes
- Some recommend giving a 2nd dose if unresponsive

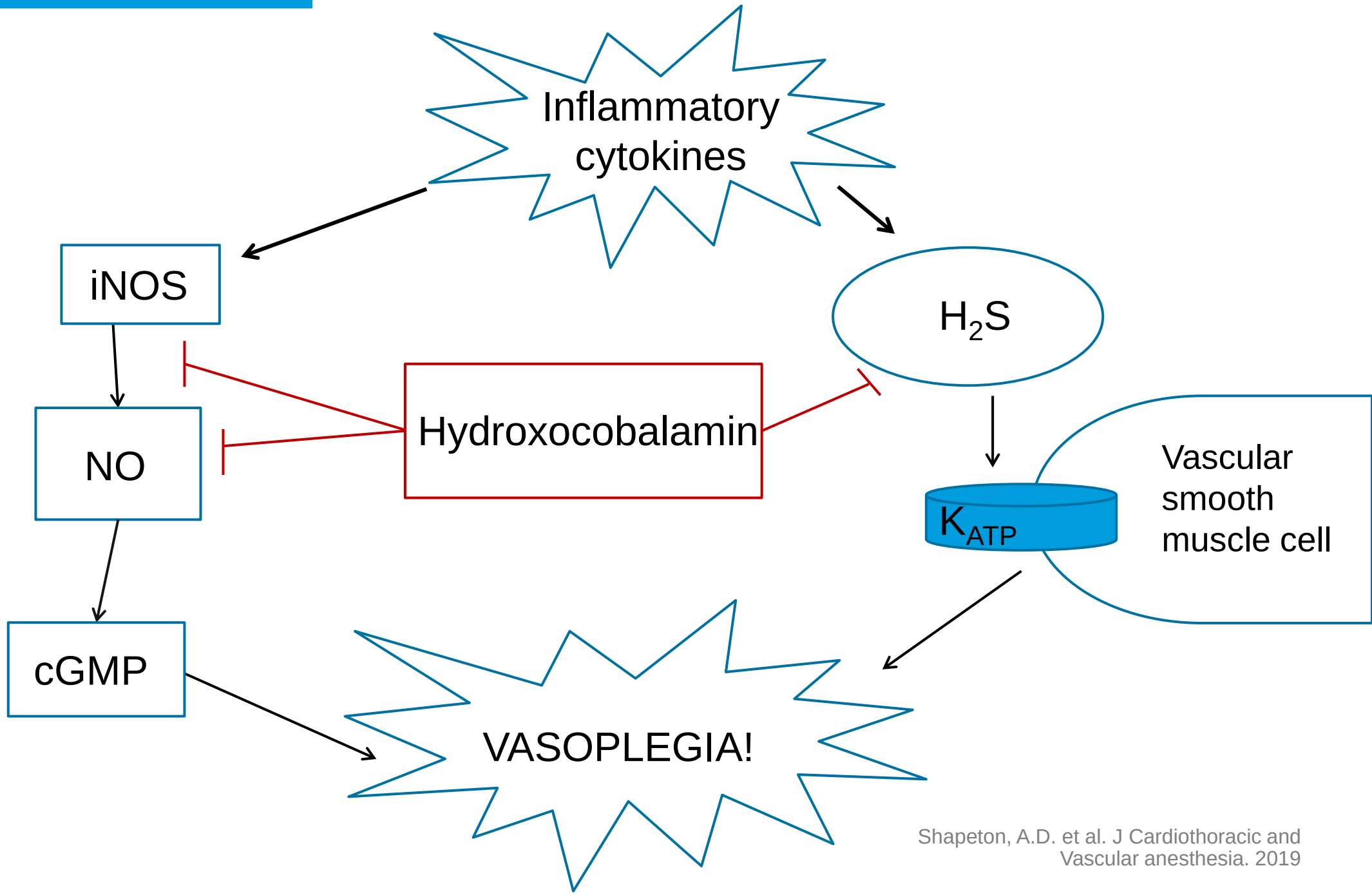
Side Effects

- Hypertension
- Headache
- Injection site reaction
- Anaphylaxis
- Red color of bodily fluids
- Cobalt toxicity
- False dialysis alarms

Lab Interactions

- Hemoglobin for 12-16 hours
- Creatinine, glucose, Alkaline phosphatase for 24 hours
- Bilirubin for up to 4 days
- aPTT, PT and INR for 1-2 days

Shapeton, A.D. et al. Journal of Cardiothoracic and Vascular Anesthesia. 2019



Shapeton, A.D. et al. J Cardiothoracic and Vascular anesthesia. 2019

CASE SERIES FOR HYDROXOCOBALAMIN

Patients Included (n=24)	
At least 2 of the following: • Vasopressin ≥ 0.04 units/min • Norepinephrine ≥ 0.1 mcg/kg/min • Epinephrine ≥ 0.1 mcg/kg/min	AND the following: • MAP ≤ 65 mmHg and/or • Systemic vascular resistance index (SVRI) ≤ 1600 dynes-s^1cm^5/m^2 and • Cardiac index ≥ 2.5 $L/min/m^2$

Armour, S. et al. Anesth Analg. 2019

CASE SERIES FOR HYDROXOCOBALAMIN RESULTS

Vasopressin: -0.01 (p= 0.0146)
Norepinephrine: -0.03 (p= 0.005)
Epinephrine: -0.00 (p= 0.581

MAP → mean difference of 9 (P= 0.0003)
SBP → mean difference of 14 (P= 0.0028)

At 210 minutes: MAP and SBP returned to pre-administration levels
Vasopressor requirements remained lower than prior to infusion

Armour, S. et al. Anesth Analg. 2019

ANALYSIS OF STUDY

Pros

- Shows an increase in MAP and SBP
- Analyzes time from infusion to back to baseline hemodynamics

Cons

- Case series
- Timing was up to the treating provider
- 54% also were given methylene blue

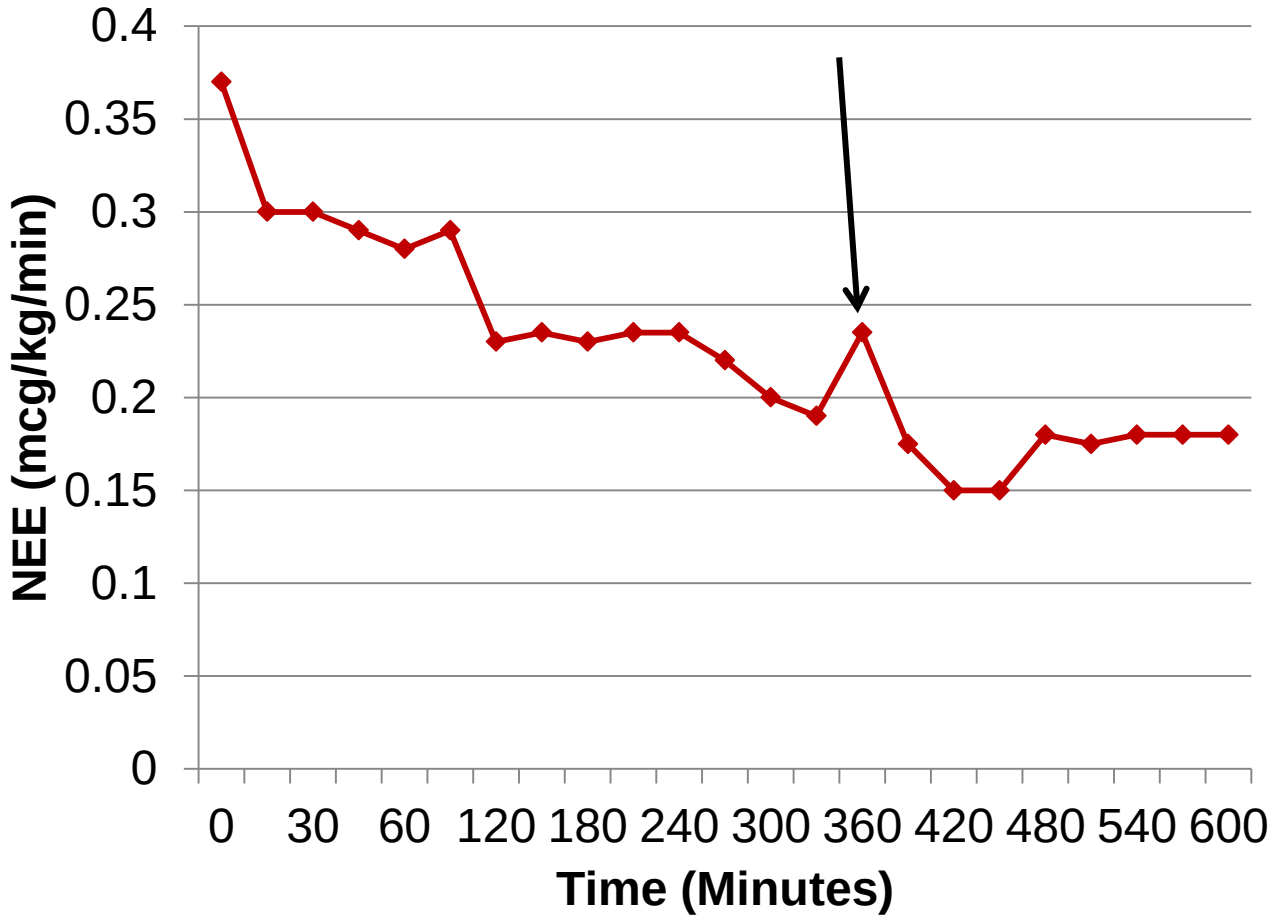
Conclusions

- Hydroxocobalamin may increase hemodynamics and can be used as a rescue agent

Armour, S. et al. Anesth Analg. 2019

EXTENDED INFUSION HYDROXOCOBALAMIN

- Patients (n=12)
  - Vasoplegic shock after cardiovascular surgery
  - Salvage therapy after all other agents are exhausted
- Dosing: 5 grams over median of 6 hours
- Results
  - Mean norepinephrine equivalents (NEE) was reduced over time (p=0.04)
  - Did not completely resolve vasoplegia
  - 6 of 12 patients died



Equal to norepinephrine 0.1 mcg/kg/min

- Epinephrine 0.1 mcg/kg/min
- Dopamine 15 mcg/kg/min
- Phenylephrine 1 mcg/kg/min
- Vasopressin 0.04 units/min

Seelhammer, T. G. et al. Heart & Lung. 2021

ANALYSIS OF EXTENDED INFUSION STUDY

Pros	• Analyzes dose and infusion time specifically for vasoplegic shock
Cons	• Case series • 50% mortality
Conclusions	• Hydroxocobalamin extended infusion over 6 hours may decrease norepinephrine equivalents but is not proven to affect clinical outcomes

Seelhammer, T. G. et al. Heart & Lung. 2021

4 EVIDENCE COMPARING METHYLENE BLUE AND HYDROXOCOBALAMIN

RETROSPECTIVE COHORT: METHYLENE BLUE VS. HYDROXOCOBALAMIN

Methods

- Retrospective
- Inclusion: received either agent in operating room or ICU for suspected vasoplegic shock
- Exclusion: received both agents or non-cardiac transplant

Patients (n=35)

- 16 patients: methylene blue
- 19 patients: hydroxocobalamin
- Methylene blue group more comorbidities
- Surgeries: aortic repair, CABG, cardiac transplantation

Dosing

- Average methylene blue: 1.6 mg/kg
  - Most commonly as a bolus
- Hydroxocobalamin 5 g over 15 minutes

Furnish, C. et al. J Cardiothoracic and Vascular Anesthesia. 2020

METHYLENE BLUE VS. HYDROXOCOBALAMIN RESULTS

- Norepinephrine equivalents (primary outcome)
  - Methylene blue: No difference at any time point after infusion
  - Hydroxocobalamin: 1 hour (p=0.03) and 4 hours (p=0.04)
  - No differences between the two agents

<u>Equal to norepinephrine 0.1 mcg/kg/min</u>

- Epinephrine 0.1 mcg/kg/min
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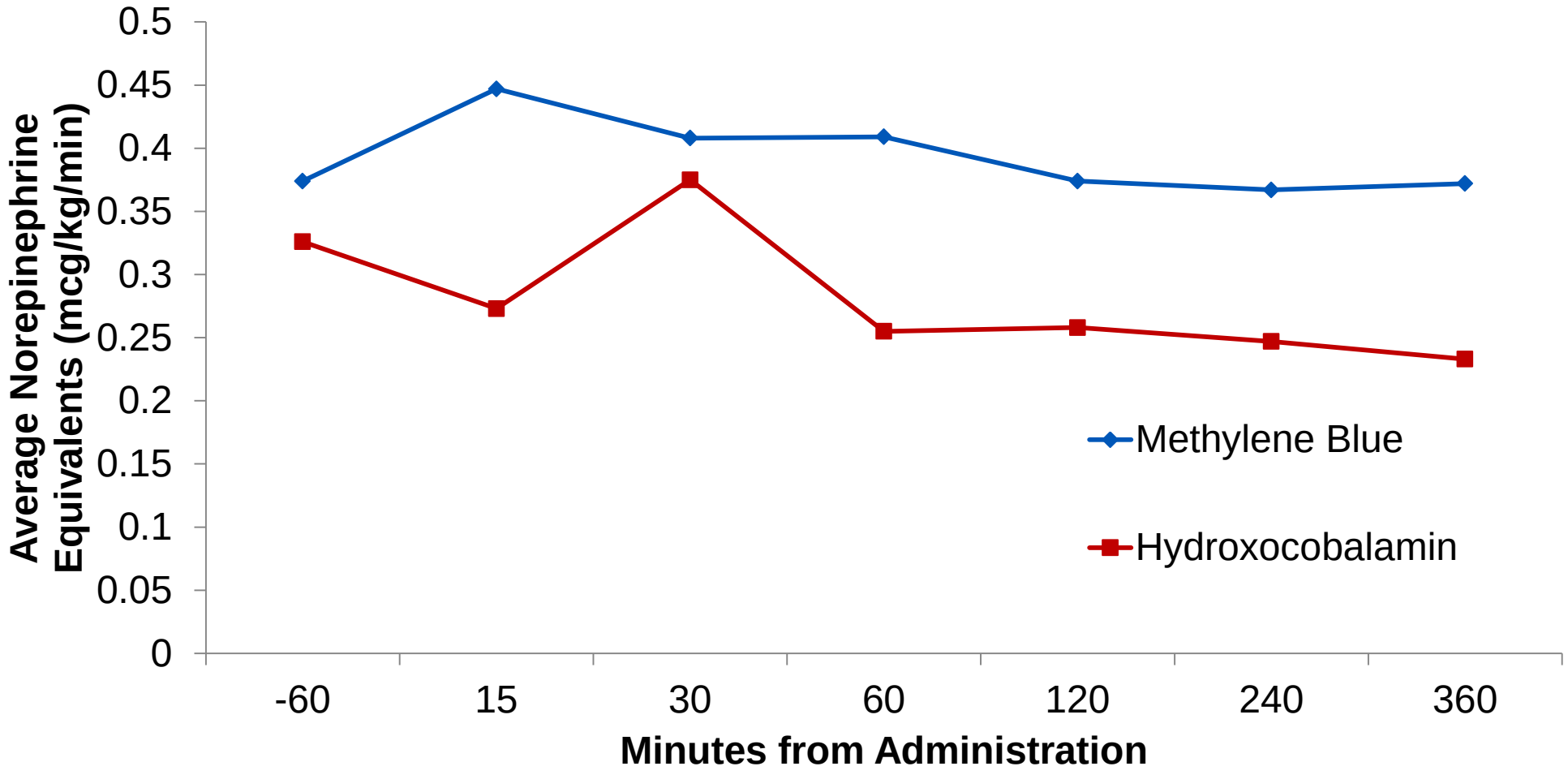

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  - Hydroxocobalamin: 1 hour (p=0.03) and 4 hours (p=0.04)
  - No differences between the two agents
- MAPs increased compared to baseline
  - Methylene blue: p<0.01 at all time points
  - Hydroxocobalamin: p<0.01 until 2 hours after

<u>Equal to norepinephrine 0.1 mcg/kg/min</u>

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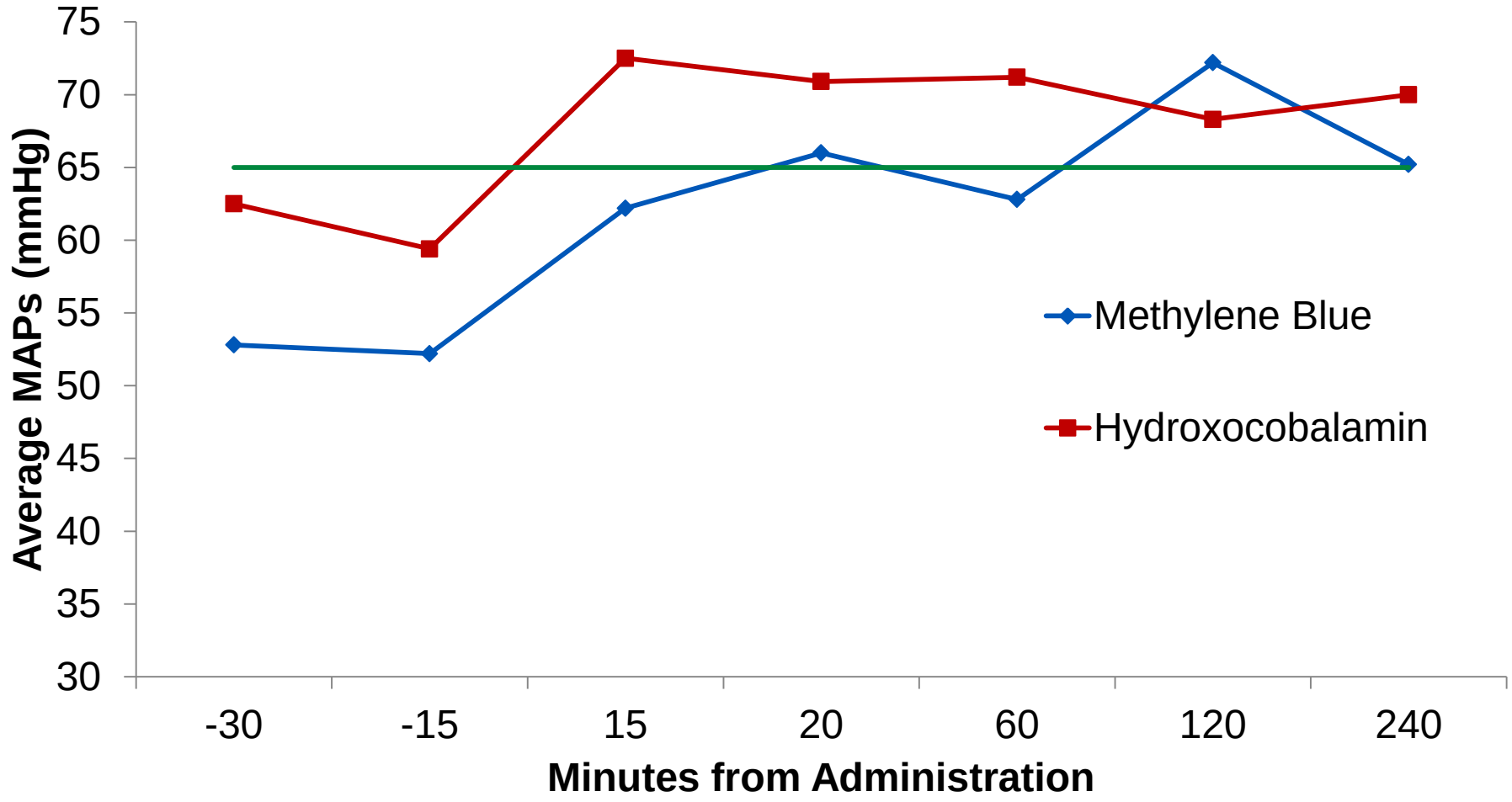
METHYLENE BLUE VS. HYDROXOCOBALAMIN RESULTS



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- MAPs increased compared to baseline
  - Methylene blue: p<0.01 at all time points
  - Hydroxocobalamin: p<0.01 until 2 hours after
- No differences:
  - Systemic vascular resistance (p=0.53)
  - Mortality (p=0.51)
  - ICU- free days (p=0.4)
  - Mechanical ventilation – free days (p=0.65)

Equal to norepinephrine 0.1 mcg/kg/min

- Epinephrine 0.1 mcg/kg/min
- Dopamine 15 mcg/kg/min
- Phenylephrine 1 mcg/kg/min
- Vasopressin 0.04 units/min

Furnish, C. et al. J Cardiothoracic and Vascular Anesthesia. 2020

METHYLENE BLUE VS. HYDROXOCOBALAMIN STUDY ANALYSIS

Pros	• First cohort to compare methylene blue with hydroxocobalamin as monotherapy
Cons	• Retrospective non-randomized cohort • Methylene blue group was more critically ill
Conclusions	• Hydroxocobalamin reduces norepinephrine equivalents at 1 hour and 4 hours post infusion • No clinical difference can be concluded between hydroxocobalamin and methylene blue

Furnish, C. et al. J Cardiothoracic and Vascular Anesthesia. 2020

RETROSPECTIVE COHORT: METHYLENE BLUE AND HYDROXOCOBALAMIN

Methods

- Retrospective
- Received methylene blue with or without hydroxocobalamin for refractory vasoplegic syndrome rescue therapy
- Exclusions: Cardiac index < 2.2 L/min/m^2 or temporary mechanical circulatory support

Patients (n=20)

- 14 patients: methylene blue only
- 6 patients: methylene blue + hydroxocobalamin
- No differences in baseline characteristics
- Surgeries: aortic repair, CABG, cardiac transplantation

Dosing

- Methylene blue 100 mg in monotherapy group
  - 50 mg in the combination group ($p<0.05$)
- Hydroxocobalamin 5 g over 15 minutes

Feih, J.T. et al. J Cardiothoracic and Vascular Anesthesia. 2018

RETROSPECTIVE COHORT: METHYLENE BLUE AND HYDROXOCOBALAMIN RESULTS

- Primary outcome: Maintaining MAP> 60 mmHg at 1 hour post-infusion
  - No difference 71% in methylene blue monotherapy and 82% in combination therapy (p=0.33)
- Maintaining MAP >60 mmHg at any time: no differences
- Vasopressor doses at any time: no differences
- Proportion of starting NEE
  - At one hour: 1.00 in monotherapy vs. 0.83 in combination group p=0.003
  - At 6 hours: 0.83 in monotherapy vs. 0.64 in combination group p=0.034
- Survival:
  - 7 of 14 patients in monotherapy group
  - 4 of 6 patients in combination group

Feih, J.T. et al. J Cardiothoracic and Vascular Anesthesia. 2018

METHYLENE BLUE WITH HYDROXOCOBALAMIN COMBINATION THERAPY STUDY ANALYSIS

Pros	• First cohort to compare methylene blue with hydroxocobalamin as combination therapy
Cons	• Small sample study • Retrospective cohort
Conclusions	• No difference in maintaining MAP goals • Combination therapy reduces vasopressor requirements

Feih, J.T. et al. J Cardiothoracic and Vascular Anesthesia. 2018

WHAT IS THE CONCLUSION FROM THE EVIDENCE AVAILABLE FOR METHYLENE BLUE AND HYDROXOCOBALAMIN IN PATIENTS WITH REFRACTORY VASOPLEGIC SHOCK?

A. Hydroxocobalamin reduces mortality

B. Methylene blue reduces mortality

C. Hydroxocobalamin reduces norepinephrine equivalents

D. Methylene blue reduces norepinephrine equivalents

5 DETERMINING TREATMENT

SUMMARY OF EVIDENCE

Methylene Blue

- Shown in a randomized controlled trial to improve hemodynamics and vascular tone
- Contraindicated in G6PD deficiency and patients taking serotonergic medications

Hydroxocobalamin

- Has been shown in case reports to reduce mean arterial pressure and systolic blood pressure
- Many interactions with lab values

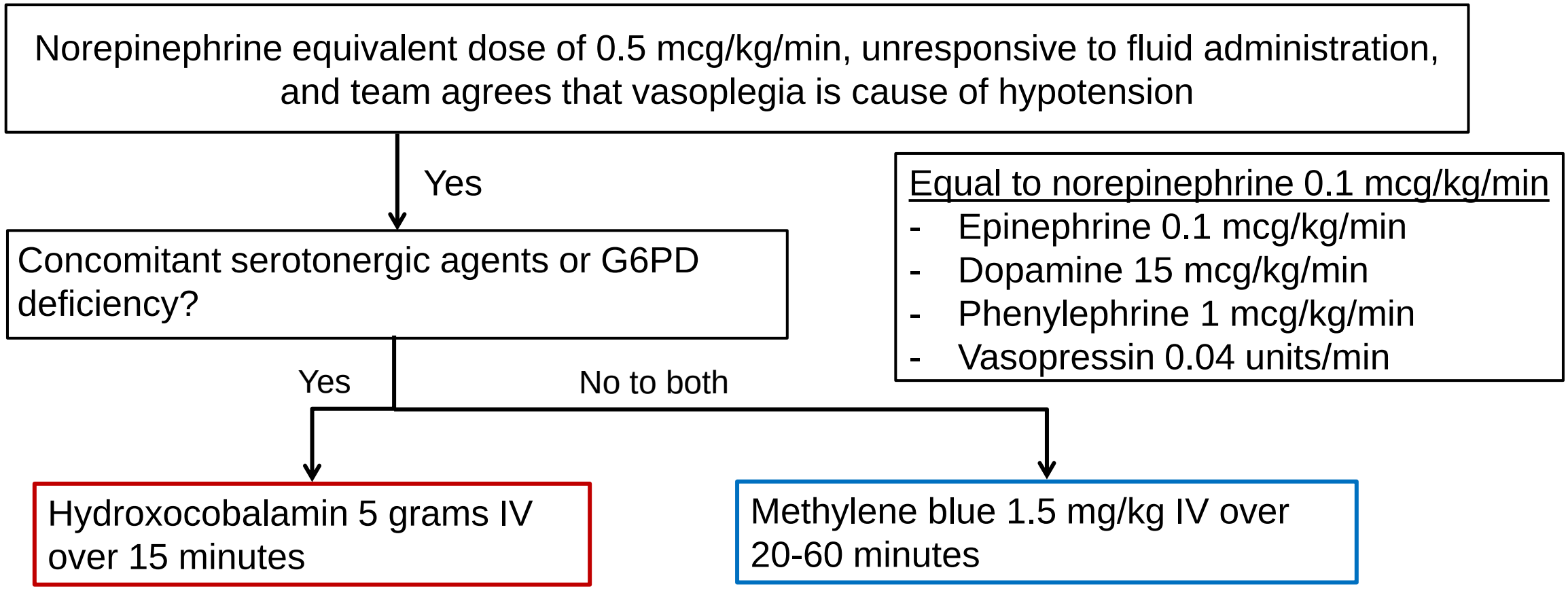
Both Medications

- Cohort comparing hydroxocobalamin and methylene blue showed no difference between agents in reducing NEE, improving hemodynamics, or clinical outcomes
- Combination therapy shows reduction in norepinephrine equivalents

CB presents to the cardiac intensive care unit after cardiopulmonary bypass surgery on norepinephrine equivalents of 0.5 mcg/kg/min. CB meets criteria for vasoplegic shock and has been taking linezolid for osteomyelitis for 1 month. What agent would you use and at what dose?

A. Hydroxocobalamin 5 grams over 15 minutes
B. Hydroxocobalamin 5 grams over 6 hours
C. Methylene blue 1.5 mg/kg x1
D. Methylene blue 1.5 mg/kg followed by 0.25 mg/kg/hr for 6 hours

CONCLUSIONS



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QUESTIONS