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Overloadipine – Emerging Therapies to Treat Refractory Shock

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INTRODUCTION

- Refractory vasodilatory shock develops from uncontrolled vasodilation and hyporesponsiveness to vasopressors.
- Management of calcium channel blockers (CCB) toxicity can be difficult because it can result in refractory vasodilatory shock making it often fatal despite standard treatment.

CASE PRESENTATION

- 21-year-old male with history of depression and prior suicide attempts presented after intentional ingestion of amlodipine (300 mg) and metformin (150 tablets of 1000 mg).
- Presented with slightly altered mentation and hypotension, then quickly deteriorated and required intubation and high vasopressor requirements.
- Transferred to PSVMC for consideration of venoarterial extracorporeal membrane oxygenation (VA-ECMO). Since he was hyperdynamic on echocardiogram, our team did not feel he would benefit from VA-ECMO.
- His vasopressor requirements surpassed the normal recommended doses

	Patient	Normal
Norepinephrine	200 mcg/min	30 mcg/min
Epinephrine	100 mcg/min	5-20 mcg/min
Phenylephrine	360 mcg/min	5-200 mcg min
Vasopressin	0.04 U/min	0.01-0.04 U/min

- Due to no improvement, methylene blue and hydroxycobalamine (vitamin B12) were initiated for his refractory shock.
- He responded favorably to this therapy. Norepinephrine dose was halved and Epinephrine down to 10 mcg/min almost immediately.
- It took several days to wean him off the vasopressors and he was able to transfer to the medical floor in stable condition.

• References upon request

FIGURES

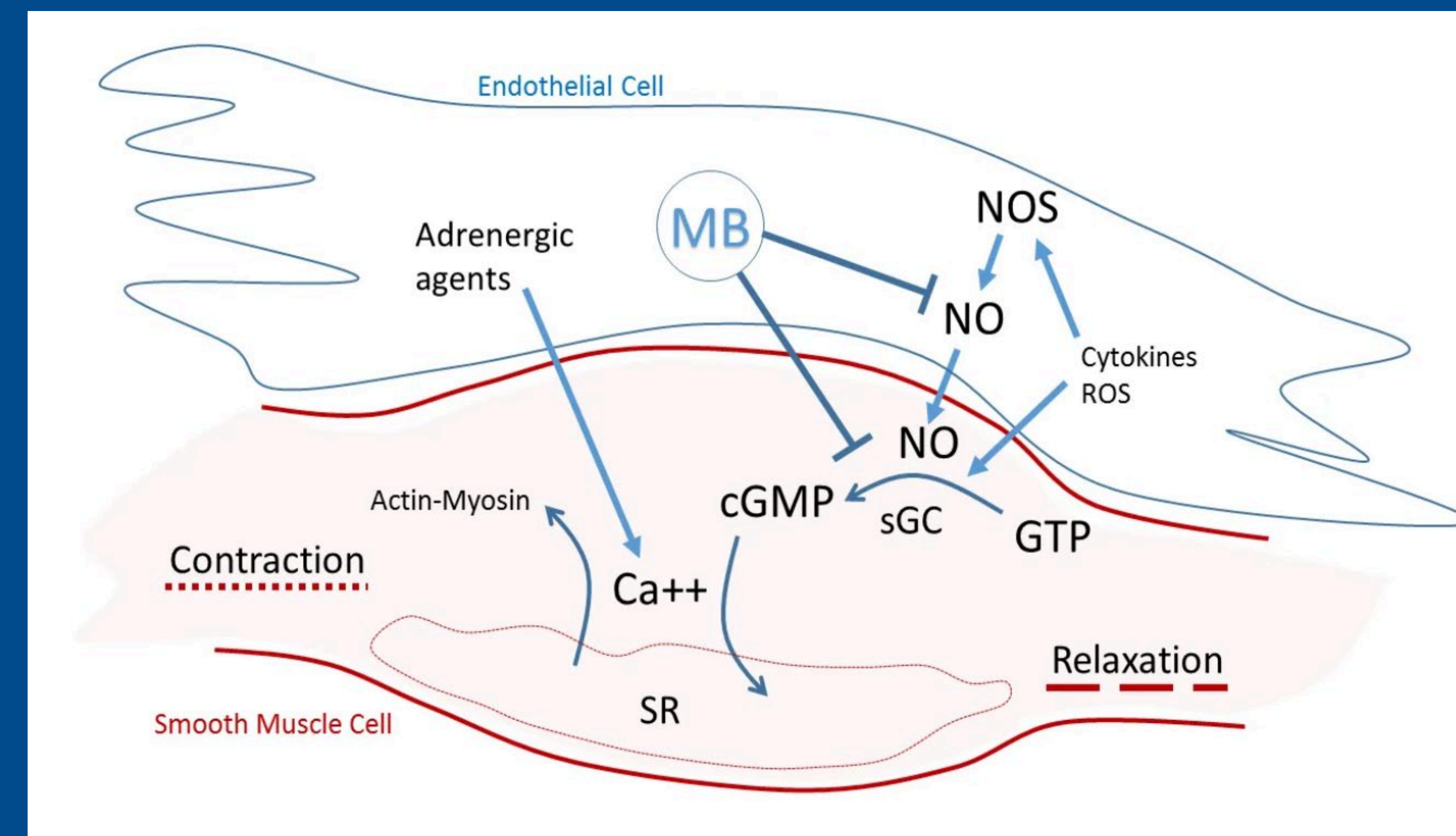


Figure 1: Mechanism of methylene blue: Cytokines and ROS upregulate nitric oxide synthase and stimulates soluble guanylate cyclase (sGC), both of which generate cGMP. cGMP shifts calcium into the sarcoplasmic reticulum (SR) therefore lowering intracellular calcium concentration and decreasing contraction. Methylene blue inhibits both NO synthesis and cGMP synthesis



Figure 2 & 3: Methylene blue turns urine green blue and vitamin B12 turns urine red

DISCUSSION

- Higher doses of vasopressors are typically required for CCB toxicity and co-ingestions can also alter the pharmacokinetics in unpredictable ways.
- Emerging therapies, such as methylene blue and vitamin B12, were tried. These have previously been used in cardiac patients who experienced vasoplegia postoperatively.
- Methylene blue and vitamin B12 are thought to increase systemic vascular resistance by decreasing nitric oxide synthesis thereby preventing smooth muscle relaxation allowing vasoconstriction in response to catecholamines (Figure 1).
- Both therapies have been used only in case-series and case-reports; there has yet to be randomized trials to validate their use.
- Interesting side effect of methylene blue and vitamin B12 depicted in Figure 2 & 3. This resulted in his urine turning purple. The CRRT sensor needed to be changed so that the machine did not think his urine was blood.
- This case highlights the importance of considering alternative therapies such as methylene blue and vitamin B12 in cases of refractory shock unresponsive to standard therapies.

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