A new vasopressor: Angiotensin II (LJPC-501)

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Overview

- Why a new vasopressor?
- What is it?
- Clinical trial results
- Compassionate use at VUMC

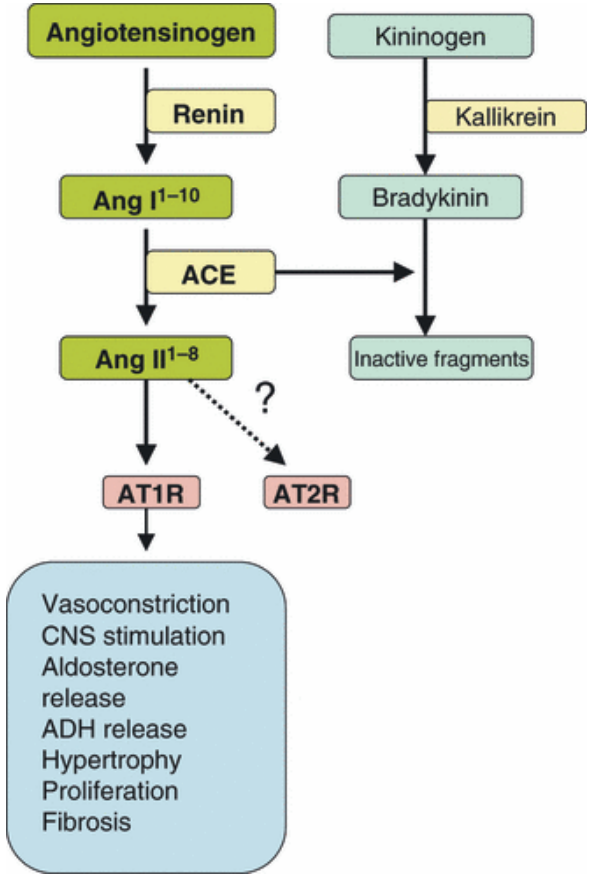
Why a new vasopressor?

- Patients with shock refractory to vasopressors have worse outcomes, including higher mortality (60-98%)
- High doses of catecholamines are associated with detrimental effects
  - Cardiotoxicity, tachyarrhythmias, necrosis, stimulation of bacterial growth, inhibition of immune cells, insulin resistance

Chest. 2013 Mar; 143(3): 664–671.
Lancet. 2007 Aug 25;370(9588):636-7.
J Intensive Care Med. 2009 Sep-Oct;24(5):293-316.
Ann Intensive Care. 2017; 7: 43.

Angiotensin II in sepsis

- Renin-angiotensin-aldosterone-system (RAAS)
  - Regulates Na, H2O retention, vasoconstriction, and blood pressure
- In sepsis, renin and angiotensin are increased but angiotensin receptor expression is decreased
- Equivalent cardiac and blood pressure response compared to norepinephrine in pigs



Crit Care. 2015; 19(1): 98.
J Intern Med. 2008 Sep;264(3):224-36

Angiotensin II for the Treatment of Vasodilatory Shock (ATHOS-3)

- Randomized, double blind, placebo controlled clinical trial phase 3 trial (75 ICUs, 9 countries)
- Inclusion criteria:
  - ≥ 18 years old
  - Vasodilatory shock despite ≥25 ml/kg over previous 24 hrs
  - High dose vasopressors (>0.2 mcg/kg/min or equivalent) for 6-48 hrs
  - Bladder and arterial catheters
- Exclusion:
  - Burns >20% BSA, ACS, bronchospasm, liver failure, mesenteric ischemia, active bleeding, abdominal aortic aneurysm, ANC<1000, VA ECMO, high dose steroids

N Engl J Med. 2017 Aug 3;377(5):419-430.

Angiotensin II for the Treatment of Vasodilatory Shock (ATHOS-3)

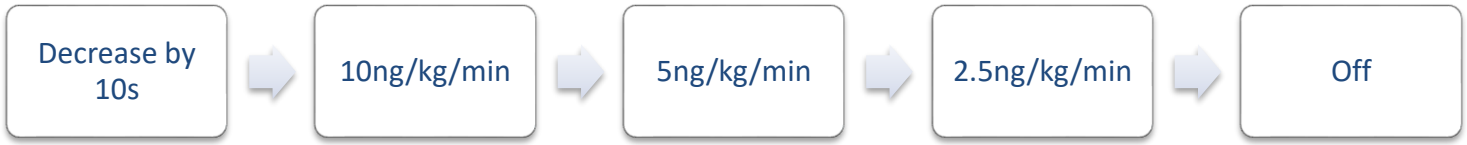
- Intervention
  - Angiotensin II infusion vs placebo
- Study Procedure
  - Angiotensin 20ng/kg/min titrated to MAP ≥ 75 during first 3 hrs (max 200ng/kg/min)
  - Other vasopressors held constant during adjustment period
  - 3-15hrs: all vasopressors adjusted for MAP 65-75
- Primary Endpoint
  - MAP ≥75 or increase of at least 10mmHg at 3 hrs

Angiotensin II for the Treatment of Vasodilatory Shock (ATHOS-3) - Results

- Greater achievement of MAP goal at 3hr with Ang II
  - 69.9% vs 23.4% ($p<0.001$)
- Greater increase in MAP with Ang II
  - 12.5 mmHg vs 2.9 mmHg ($p<0.001$)
- Lower cardiovascular SOFA scores with Ang II
- Lower doses of other vasopressors required after 3 hrs
- No difference in mortality at day 7 or 28
  - 29 vs 35% ($p=0.22$); 46 vs 54% ($p=0.12$)

Using Angiotensin-II at VUMC

- Who:
  - Patients in shock requiring > 0.2mcg/kg/min norepinephrine equivalent for ≥2 hrs
- Dosing:
  - Titrating up: Initiate at 5ng/kg/min. Titrate by 10ng/kg/min
  - Once at MAP goal: *decrease vasopressin first* followed by norepinephrine
  - Titrating down: titrate over 15 mins



Vasopressor Equivalent Doses

Drug	Dose	NE Equivalent
Norepinephrine	0.1 mcg/kg/min	0.1 mcg/kg/min
Vasopressin	0.04 units/min	0.1 mcg/kg/min
Epinephrine	0.1 mcg/kg/min	0.1 mcg/kg/min
Phenylephrine	0.1 mcg/kg/min	0.1 mcg/kg/min
Dopamine	15 mcg/kg/min	0.1 mcg/kg/min

Conclusions

- Angiotensin II is effective at increasing MAP when added to high-dose vasopressors
- Angiotensin II may allow for down-titration of other vasopressors
- Any mortality benefit is still yet to be determined
- Angiotensin is available at VUMC for a limited time with specific approval under a compassionate use protocol

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