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Catecholamine-Sparing Strategies

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Disclosures

- La Jolla Pharmaceutical Company
  - Advisory Board meeting attendance

Objectives

- Discuss the utilization of angiotensin II in refractory vasodilatory shock
- Examine the evolving evidence for novel V1a receptor agonist therapies in refractory septic shock

Overview

- Introduction
  - Review catecholamine vasopressors
  - Rationale for catecholamine-sparing strategies
- Angiotensin II
- V1a Receptor Agonists
- Conclusions

Vasopressors

- First isolated ~ 1900
- Catecholamines
  - Norepinephrine
  - Epinephrine
  - Dopamine
- Non-catecholamines
  - Phenylephrine
  - Vasopressin/terlipressin
  - Angiotensin II (AT2)

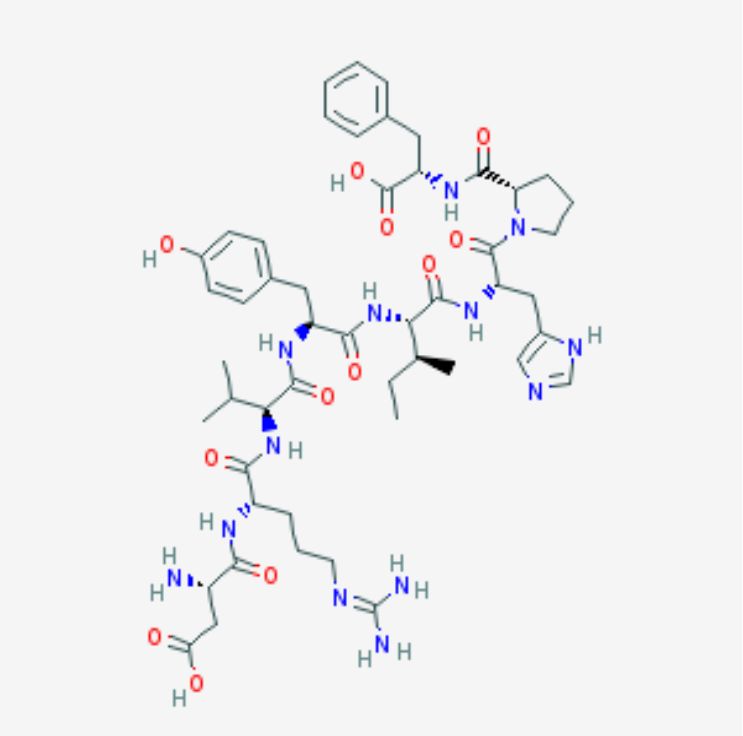
Zarychanski, R, et al. Historical Perspectives in Critical Care Medicine: Blood Transfusion, Intravenous Fluids, Inotropes/Vasopressors, and Antibiotics. Crit Care Clin 2009; 25:201-220.

Adverse Effects of Catecholamines

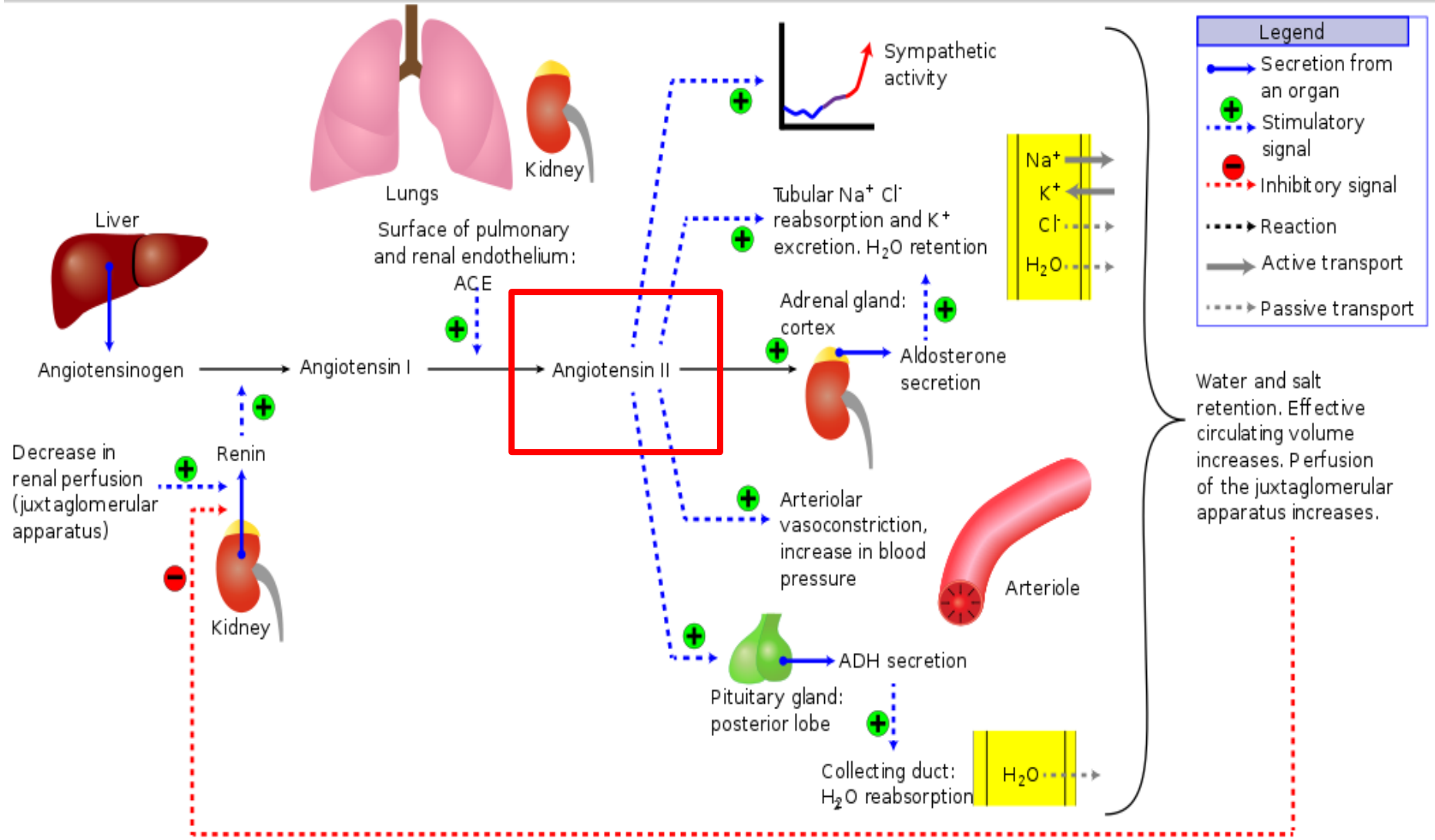
- Arrhythmias
- Ischemia
- Increased myocardial O2 demand
- Hyperglycemia
- Decreased cardiac output
- Inflammation
- Immunosuppression
- Increased mortality??

Levy, B, et al. Vasoplegia treatments: the past, the present, and the future. Critical Care (2018) 22:52
Andreis, DT, Singer, M. Catecholamines for inflammatory shock: a Jekyll-and-Hyde conundrum. Intensive Care Med (2016)42:1387-97
Stolk, RF, et al. Potentially Inadvertent Immunomodulation: Norepinephrine Use in Sepsis. AJRCCM 2016; 194(5): 550-58
McIntyre, WF, et al. Association of Vasopressin plus Catecholamine Vasopressors vs. Catecholamines Alone with Atrial Fibrillation in Patients with Distributive Shock: A Systematic Review and Meta-analysis. JAMA 2018; 319(18): 1889-1900

Angiotensin II



Renin-angiotensin-aldosterone system



Angiotensin II

- Has been used in humans since 1940s for a variety of disease states
- Recent review of ~1100 studies in > 31,000 patients
  - 34 studies demonstrated dose-response relationship on BP (only 2 studies in hypotensive patients)
  - Cirrhosis w/ ascites→less sensitive to pressor effects; natriuresis and diuresis
  - Pregnancy→progressive resistance to pressor effects
- Safety
  - Potential to exacerbate LV failure in acute CHF
  - Potential to cause asthma exacerbation

BP = blood pressure; LV = left ventricular; CHF = congestive heart failure

Busse, LW, et al. Clinical Experience with IV Angiotensin II Administration: A Systematic Review of Safety. Crit Care Med; 45(8); 1285-94.

ATHOS-3

- Phase III trial evaluating AT2 for severe vasodilatory shock
  - Randomized, double-blind, multicenter, placebo-controlled; May 2015-January 2017
  - N = 321
  - Purpose: to determine effectiveness of AT2 for vasodilatory shock resistant to high-dose vasopressors
  - Primary Outcome: MAP response 3 hours after start of infusion

MAP = mean arterial pressure

Khanna, A, et al. Angiotensin II for the Treatment of Vasodilatory Shock. NEJM. 2017 May 21.

ATHOS-3 Results

Outcome	AT2 *N=163 (%)*	Placebo *N=158 (%)*	P-value
MAP response at hour 3	114* (70)	37 (23)	< 0.001
Mean change in SOFA score	1.05±5.5	1.04±5.34	0.49
7-day all cause mortality	47 (29)	55 (35)	0.22
28-day all cause mortality	75 (46)	85 (54)	0.12
Any serious adverse event	99 (61)	106 (67)	-

*79/114 (69%) were “super-responders”

Khanna, A, et al. Angiotensin II for the Treatment of Vasodilatory Shock. NEJM. 2017 May 21.
McCurdy, MT, et al. Association of Angiotensin II Dose with All-Cause Mortality in Patients with Vasodilatory Shock.. https//isicem.esn.eu/posters_listing/see_poster/312/2018/jury

Subgroup Analyses

Population *(AT2 = 163; placebo = 158)*	**N** *(AT2 vs. placebo)*	**Day 28 Mortality (%)** *(AT2 vs. placebo)*	**P-value**
"Super-responders"	79 vs. 84 N/A (placebo)	32.9 vs. 58.6 53.9	0.0007
APACHE II > 30	58 vs. 65	51.8 vs. 70.8	0.037
AKI on RRT	45 vs. 60	53 vs. 30	0.012
MAP < 65	52 vs. 50	54.2 vs. 70.4	0.10
ARDS*	122 vs. 121	48 vs. 57	NS
AT1/AT2 $\geq$ 1.63** *(AT2 = 142; placebo = 139)*	68 vs. 72	HR 0.64	0.047

*Defined by baseline PaO2/FiO2 < 300
**Signifies relatively low AT2 state

McCurdy, MT, et al. Association of Angiotensin II Dose with All-Cause Mortality in Patients with Vasodilatory Shock.. https//isicem.esn.eu/posters_listing/see_poster/312/2018/jury
Szerlip, H, et al. Effect on Disease Severity on Survival in Patients Receiving Angiotensin II for Vasosdilatory Shock. Crit Care Med; 46(1)S
Busse, LW, et al. Outcomes in Patients with Acute Respiratory Distress Syndrome Receiving Angiotensin II for Vasodilatory Shock. https//isicem.esn.eu/posters_listing/see_poster/65/2018/jury
Tumlin, JA, et al. Outcomes in Patients with Vasodilatory Shock and Renal Replacement Therapy Treated with Intravenous Angiotensin II. Crit Care Med; 46 (6): 949-57.
Wunderink, RG, et al. Baseline angiotensin levels and ACE effects in patients with vasodilatory shock treated with angiotensin II. Intensive Care Medicine Experimental 2017, 5(Suppl 2): 0703

Adverse Reactions

Adverse Event	AT2 *(N=163)*	Placebo *(N=158)*
Any	142	145
Any leading to discontinuation	23	34
Atrial fibrillation	5	5
Peripheral ischemia	7	4
Thrombotic events	21	8
Fungal infection	10	2
Delirium	9	1
Acidosis	9	1

Bauer, SB, et al. Safe Use of Vasopressin and Angiotensin II for Patients with Circulatory Shock. Pharmacotherapy 2018;38(8):851-61.
Khanna, A, et al. Angiotensin II for the Treatment of Vasodilatory Shock. NEJM. 2017 May 21.

ATHOS-3 Critiques

- Manufacturer involved in all aspects of trial
- Dosing protocol
- No details provided regarding other care provided (~90% septic shock)
- Inclusion criteria
  - 25 mL/kg fluid resuscitation
  - ScvO2 & CVP or CI used to define high-output shock
- Goal MAP 75 mmHg
- No clinically meaningful short-term outcomes reported
  - Lactate clearance, urine output

SCVO2 = central venous oxygen saturation; CVP = central venous pressure; CI = cardiac index
Khanna, A, et al. Angiotensin II for the Treatment of Vasodilatory Shock. NEJM. 2017 May 21.

AT2—The Good, The Bad, and The Ugly

- Good
  - Effective vasopressor
  - Catecholamine-sparing
  - May provide benefit in certain populations
- Bad
  - Very limited published data in septic shock
  - Concerning ADEs
- Ugly
  - AWP $1800 per vial

ADE = adverse drug event; AWP = average wholesale price

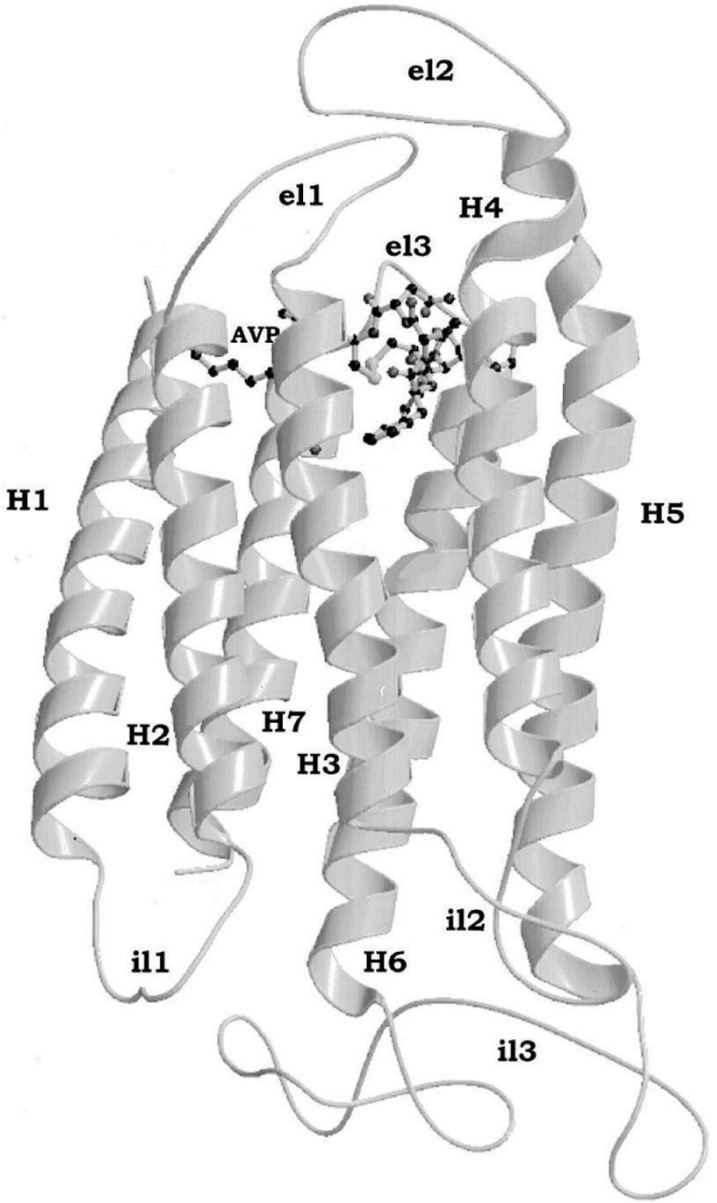
Unanswered Questions

- Is the catecholamine-sparing effect enough?
- What is the effect on short-term outcomes?
- Are there long-term adverse effects?
- Who are the ideal patients?
- What is the ideal starting dose?

Conclusions

- AT2 is a potentially beneficial addition to the treatment of septic shock
- More data is needed on short-term clinical outcomes and long-term adverse effects

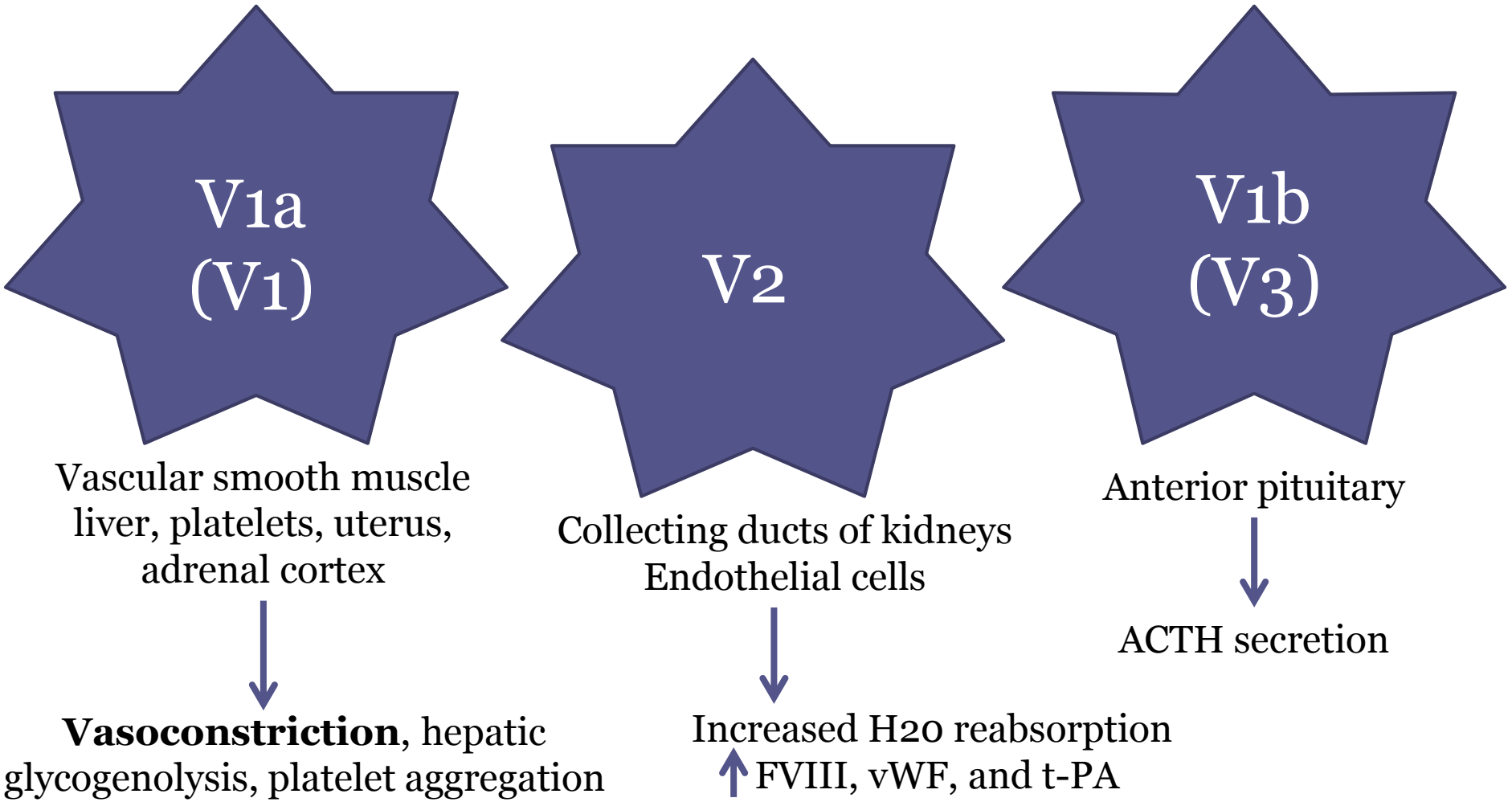
V1a Receptor Agonists



http://ccforum.com/content/15/4/226

Critical Care

Vasopressin Receptors



vWF = von Willebrand factor; t-PA = tissue plasminogen activator

Petersen, MB. The Effect of Vasopressin and Related Compounds at V1a and V2 Receptors in Animal Models Relevant to Human Disease. Basic & Clinical Pharmacology & Toxicology 2006, 99, 96-103.

Vasopressin in Septic Shock

- Initial spike followed by rapid decline of vasopressin levels
- Increases cortisol levels
- Coronary/pulmonary vasodilation via NO production
- Infusion effects: decreased norepinephrine doses, increased urine output/CrCl, and decreased cardiac output

NO = nitric oxide; CrCl = creatinine clearance

Holmes, CL, et al. Physiology of Vasopressin Relevant to Management of Septic Shock. CHEST 2001; 120:989-1002.
Russell, JA. Bench-to-bedside review: Vasopressin in the management of Septic Shock. Critical Care 2011, 15:226 (http://ccforum.com/content/15/4/226)

VASST

- Evaluated vasopressin (AVP) versus norepinephrine (NE) effect on 28 day mortality in septic shock
  - Multicenter, randomized, double-blind; N = 778
  - Stratified by baseline NE dose
  - No difference in primary outcome (35.4% vs. 39.3%)
    - Secondary outcomes: No difference in 90 day mortality, any organ dysfunction subgroup, or LOS
    - No difference in adverse effects
- Conclusions
  - AVP significantly decreased NE doses at day 4 ($p < 0.001$)
  - AVP MAY improve mortality in patients with less severe shock

LOS=length of stay

Russell, JA, et al. Vasopressin versus Norepinephrine Infusion in Patients with Septic Shock. NEJM 2008; 358(9):877-87.
Russell, JA. Bench-to-bedside review: Vasopressin in the management of Septic Shock. Critical Care 2011, 15:226 (http://ccforum.com/content/15/4/226

Terlipressin

- Synthetic analogue of lysine vasopressin
- 2x higher affinity for V1a receptor vs. V2 receptor
- Longer half-life (50 min vs. 6 min)
- Bolus and continuous infusion studied
- Meta-analyses show conflicting effects on mortality
- Therapeutic and adverse effects similar to vasopressin
- Not available in US

Lange, M. et al. Vasopressin vs. terlipressin in the treatment of cardiovascular failure in sepsis. Intensive Care Med 2008; 34(5):821-32.

Terlipressin vs. NE for Septic Shock

- Multicenter, randomized, double-blind trial in 21 Chinese ICUs
  - Terlipressin 20-160 mcg/hr vs. NE 4-30 mcg/min
  - Target enrollment: 1100
  - Trial stopped after 50% enrollment due to futility
  - No difference in 28 day mortality (40% vs. 38%)
  - More adverse effects in terlipressin group (30% vs. 12%)
    - Primarily digital ischemia

Liu, Z, et al. Terlipressin versus norepinephrine as infusion in patients with septic shock: a multicentre, randomised, double-blinded trial. Intensive Care Med (https://doi.org/10.1007/s00134-018-5267-9)

Selepressin

- Selective V1a agonist
- Animal data demonstrates superiority over AVP and NE
  - Improved hemodynamic stability
  - Reduced lung edema and cumulative fluid balance
  - Preserved renal function
  - Attenuated coagulation disorders
  - Decreased systemic inflammation
  - May decrease vascular leakage
  - Improved survival

He, X, et al. A Selective V1a Receptor Agonist, Selepressin, Is Superior to Arginine Vasopressin an d to Norepinephrine in Ovine Septic Shock. Crit Care Med 2016; 44:23-31.

Selepressin in Early Septic Shock

- Phase II dose-finding study
  - Multicenter, randomized, double-blind, placebo-controlled; N=52
  - Patients with early septic shock randomized to 1 of 3 doses of selepressin or placebo
    - 3.75 ng/kg/min arm stopped due to safety concerns→N=50 patients in final analysis
  - Open-label NE to maintain MAP $\geq$ 60
- Primary endpoints: stabilization of MAP and cumulative NE doses

Russell, JA, et al. Selepressin, a novel selective vasopressin V1a agonist, is an effective substitute for norepinephrine in a phase IIa randomized, placebo-controlled trial in septic shock patients. Critical Care (2017) 21:213

Results

	Selepressin 2.5 ng/kg/min (N=19)	Selepressin 1.25 ng/kg/min (N=10)	Placebo (N=21)
NE-free at Hour 12	50%	0%	0%
NE-free at Hour 24	70%	10%	20%
NE-free at Hour 48	70%	60%	40%
Cumulative NE dose at day 7 (mcg/kg)	249	659	761
Alive and free of mechanical ventilation at day 7	54%	31%	23%

- Selepressin 2.5 ng/kg/min resulted in faster shock reversal and lower cumulative NE doses
- No difference in ICU or hospital LOS or 28 day mortality
- Adverse effects similar

Russell, JA, et al. Selepressin, a novel selective vasopressin V1a agonist, is an effective substitute for norepinephrine in a phase IIa randomized, placebo-controlled trial in septic shock patients. Critical Care (2017) 21:213

SEPSIS-ACT

- Adaptive Phase IIb/III clinical trial of selepressin for septic shock
- Multicenter, randomized, blinded, placebo-controlled
- Evaluating up to 4 dosing strategies (1.7-5 ng/kg/min)
- Primary outcome: Pressor and ventilator-free days
- Target enrollment: 1800 patients
- **Study terminated after 868 patients enrolled due to futility**

ClinicalTrials.gov: https://clinicaltrials.gov/ct2/show/NCT02508649?term=selepressin&rank=1. Accessed 10/8/18.

Unanswered Questions

- Could alternate dosing strategies of terlipressin be beneficial?
- Results of SEPSIS-ACT?

Summary

- Vasopressin and its analogs (VA) are effective vasopressors and are catecholamine-sparing
- Low-dose vasopressin appears to have fewer ADEs than other agents
- VA may decrease the incidence of AKI in septic shock
- Selective V1a agonism may provide additional benefit but more data is needed

AKI = acute kidney injury

Nedel, WL, et al. Renal Outcomes of Vasopressin and Its Analogs in Distributive Shock: A Systematic Review and Meta-Analysis of Randomized Trials. Crit Care Med 2018. DOI: 10.1097/CCM.0000000000003471.

Conclusions

- Available evidence suggests strategies to decrease catecholamine exposure are necessary
- Many unanswered questions remain
  - What is the ideal vasopressor “cocktail”?
  - Does timing of vasopressor initiation matter?
  - Should vasopressor studies use more clinically meaningful endpoints?
    - Days alive and free vs. 28 day mortality

Russell, JA, et al. Days alive and free as an alternative to a mortality outcome in pivotal vasopressor and septic shock trials. Journal of Critical Care 47 (2018) 333-337.

Learning Assessment Questions

- 1. Clinical evidence supports the use of angiotensin II for the following:
  - A. Decreasing mortality in patients with septic shock
  - B. Increasing blood pressure in patients with vasodilatory shock
  - C. Increasing blood pressure in patients with cardiogenic shock
  - D. Improving organ dysfunction (i.e. decreasing SOFA score) in patients with septic shock

- 1. Clinical evidence supports the use of angiotensin II for the following:
  - A. Decreasing mortality in patients with septic shock
  - B. Increasing blood pressure in patients with vasodilatory shock
  - C. Increasing blood pressure in patients with cardiogenic shock
  - D. Improving organ dysfunction (i.e. decreasing SOFA score) in patients with septic shock

  - Answer B is correct. The ATHOS-3 trial demonstrated a statistically significant increase in mean arterial pressure (MAP) within 3 hours in patients with vasodilatory shock.

- 2. Which of the following are potential advantages for the use of selepressin in patients with septic shock?
  - A. Decrease in cumulative fluid balance
  - B. Decreased time to resolution of shock
  - C. Avoidance of procoagulant effects of V2 receptor agonism
  - D. Decreased time on mechanical ventilation
  - E. All of the above

- 2. Which of the following are potential advantages for the use of selepressin in patients with septic shock?
  - A. Decrease in cumulative fluid balance
  - B. Decreased time to resolution of shock
  - C. Avoidance of pro-coagulant effects of V2 receptor agonism
  - D. Decreased time on mechanical ventilation
  - E. All of the above

  - Answer E is correct. Preliminary animal and human studies of selepressin have demonstrated all of the above effects. Larger studies are needed to confirm these effects.

Thank you!