Blockage of Arginine Vasopressin Receptor 2 Reduces Increase in Pulmonary Vascular Resistance in Ovine Sepsis Model

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Background

- Sepsis is a major public health problem in the U.S. affecting more than 700,000 people every year.

(Angus DC. J Am Med Assoc, 2010; Dellinger RP. Intens Care Med, 2013; Lagu *et al.*, Crit Care Med, 2012)

- The overall mortality of sepsis is around 30 %.

(Strehlow *et al.*, Ann Emerg Med, 2006; Lagu *et al.*, Crit Care Med, 2012)

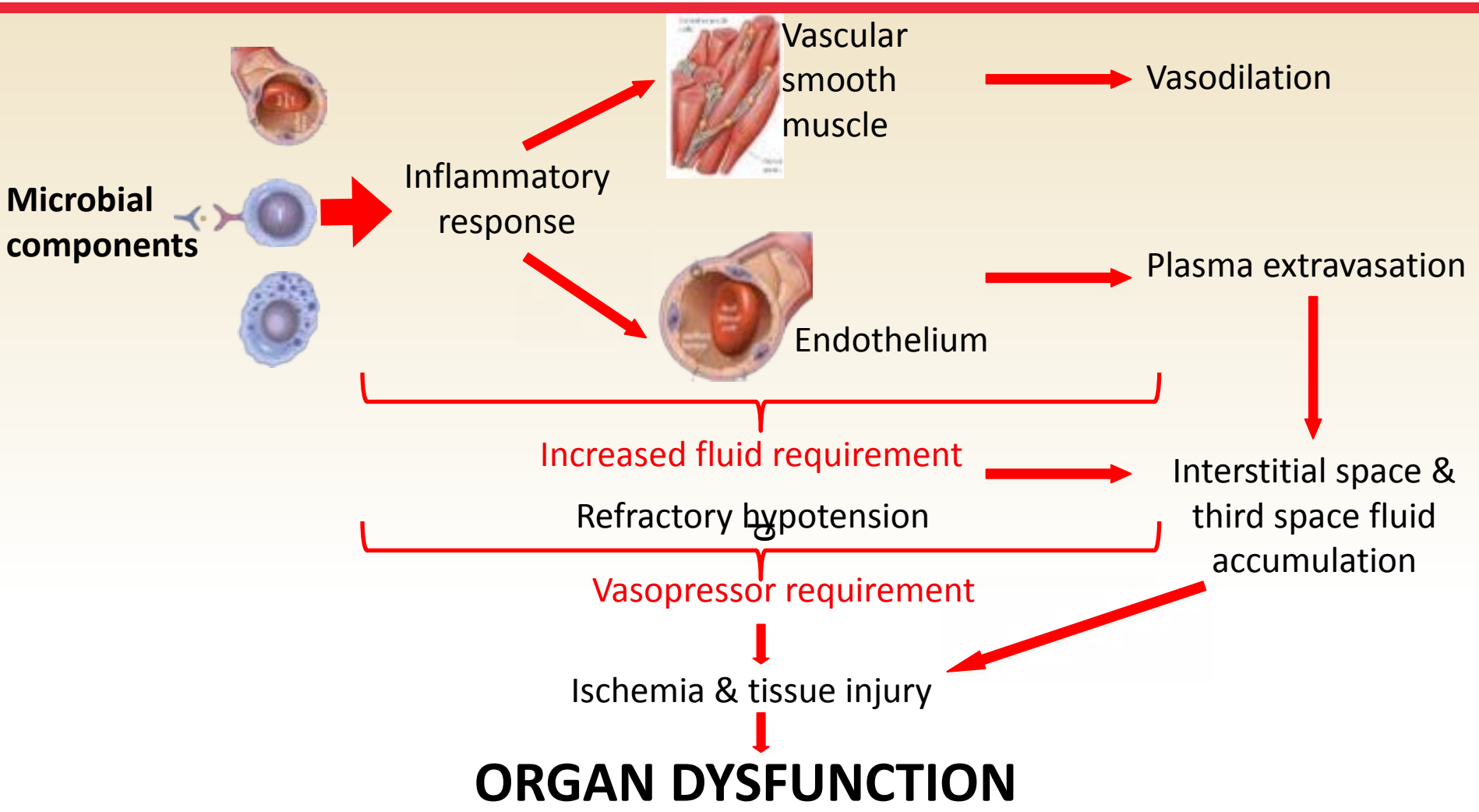
- The mortality rate has not decreased in the past two decades, despite the major advances have been made in the management of sepsis.

(Esteban *et al.*, Crit Care Med, 2007; Alberti *et al.*, Intens Care Med, 2002)

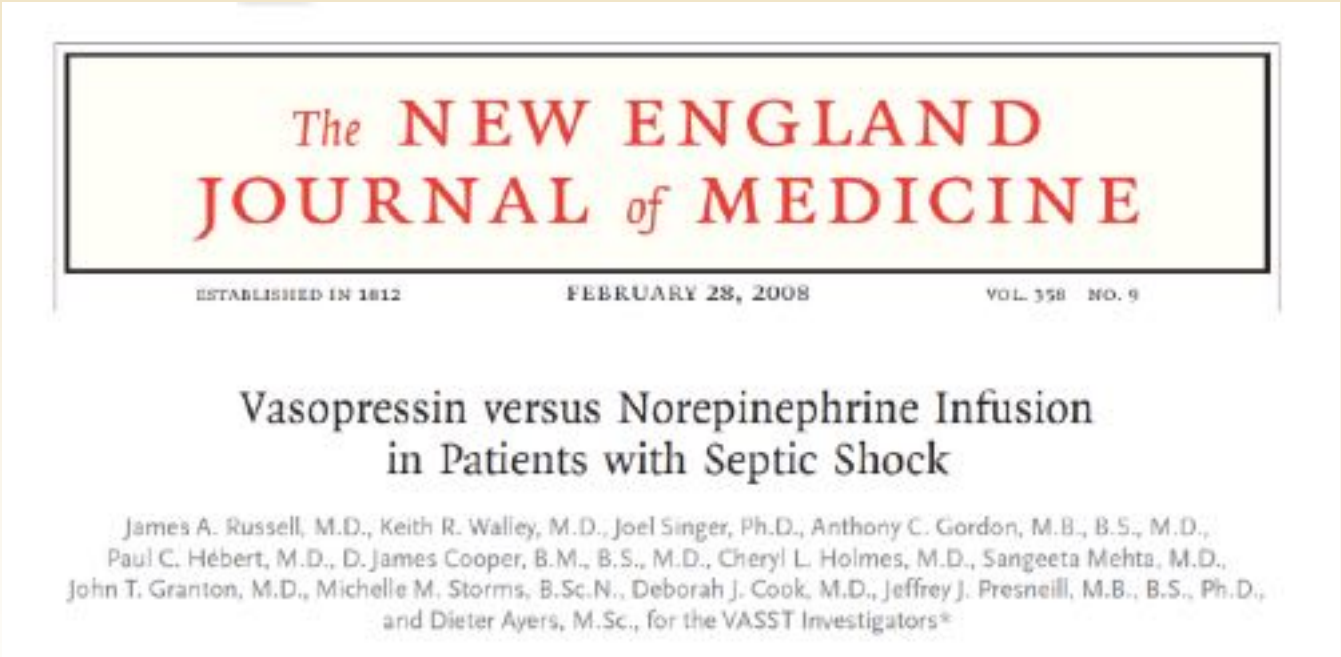
- In sepsis, vascular leakage and pulmonary vascular resistance are associated with poor prognosis and no treatment is available to date.

(Farand *et al.*, Can J Anest, 2006; Cinel & Dellinger. Curr Opin Infect Dis, 2007)

Sepsis and Vascular Leakage: Pathophysiology and Management



Arginine Vasopressin (AVP) as Treatment for Sepsis



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Vasopressin versus Norepinephrine Infusion in Patients with Septic Shock

James A. Russell, M.D., Keith R. Walley, M.D., Joel Singer, Ph.D., Anthony C. Gordon, M.B., B.S., M.D., Paul C. Hébert, M.D., D. James Cooper, B.M., B.S., M.D., Cheryl L. Holmes, M.D., Sangeeta Mehta, M.D., John T. Granton, M.D., Michelle M. Storms, B.Sc.N., Deborah J. Cook, M.D., Jeffrey J. Presneill, M.B., B.S., Ph.D., and Dieter Ayers, M.Sc., for the VASST Investigators*

- In **2008,** a large clinical trial was performed to compare the therapeutic effect of AVP vs. norepinephrine.
- AVP failed to decrease the mortality of septic patients compared to norepinephrine.
- However, an improvement in survival rate was obtained in patients that received a lower dose of AVP.

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(Russell *et al.,* N Eng J Med, 2008; Vincent *et al.,* Clin Anaes, 2008)

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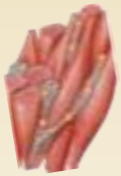
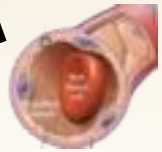
AVP Receptors

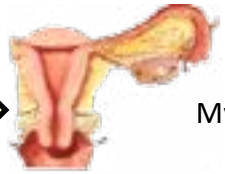
AVP

V_1R →  Vascular smooth muscle cells → Vasoconstriction

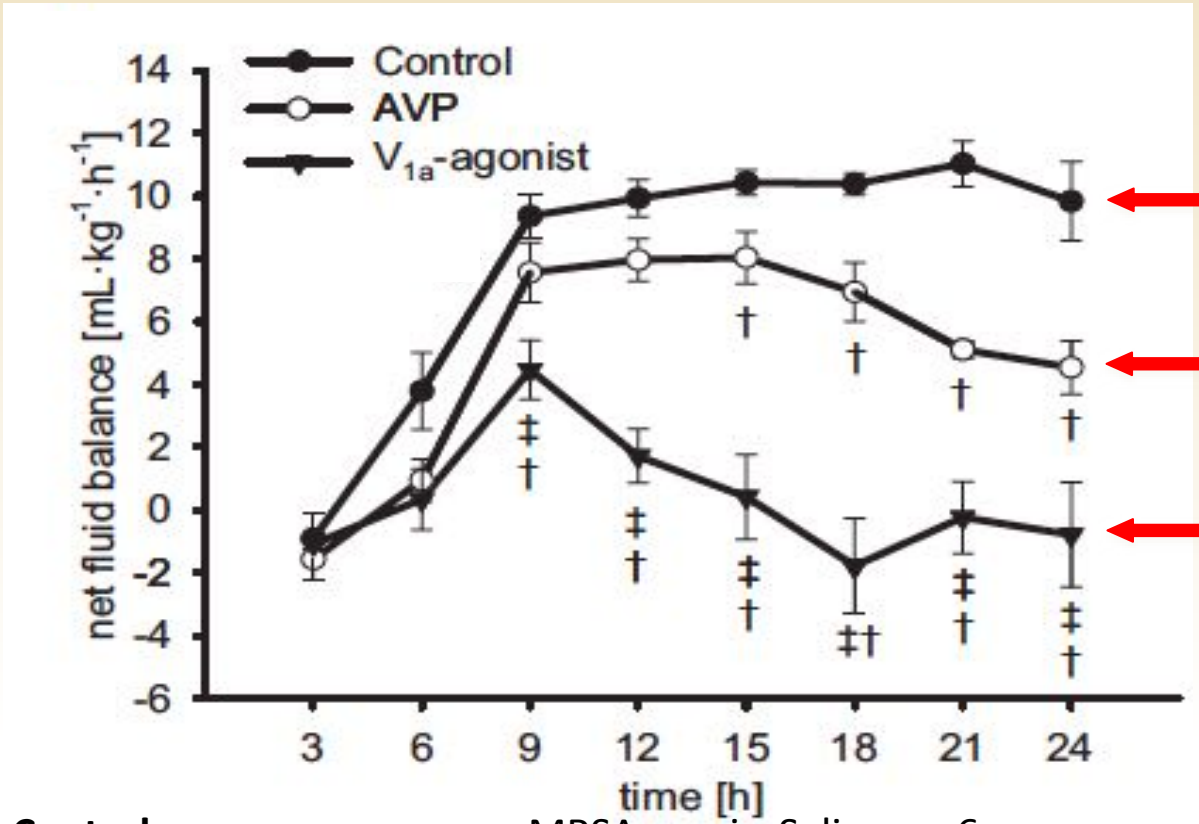
V_2R →  Renal collecting duct cells → Increase water reabsorption

V_2R →  Endothelial cells → Release of von Willebrand factor (vWF)

V_3R →  Anterior pituitary gland → Release of adrenocorticotropic hormone (ACTH)

Oxytocin receptor →  Myometrium → Uterine contractions

Septic Sheep Treated with V_1R Agonist Accumulated Less Fluid Than Sheep Treated with V_1R/V_2R Agonist (AVP)



Control (placebo)

Vasopressin (AVP)

V_1R agonist (long acting)

Control MRSA sepsis, Saline, n=6

V_1R/V_2R agonist MRSA sepsis, AVP 0.01 U/min, n=6

V_1R agonist MRSA sepsis, Phe2-Orn8-Vasotocin (POV), 0.01 U/min, n=6

**P* <0.05 vs. BL

†*P*<0.05 vs. Control

‡*P*<0.05 vs. AVP

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(Rehberg *et al.*, AJP-Heart Circ Physiol, 2012)

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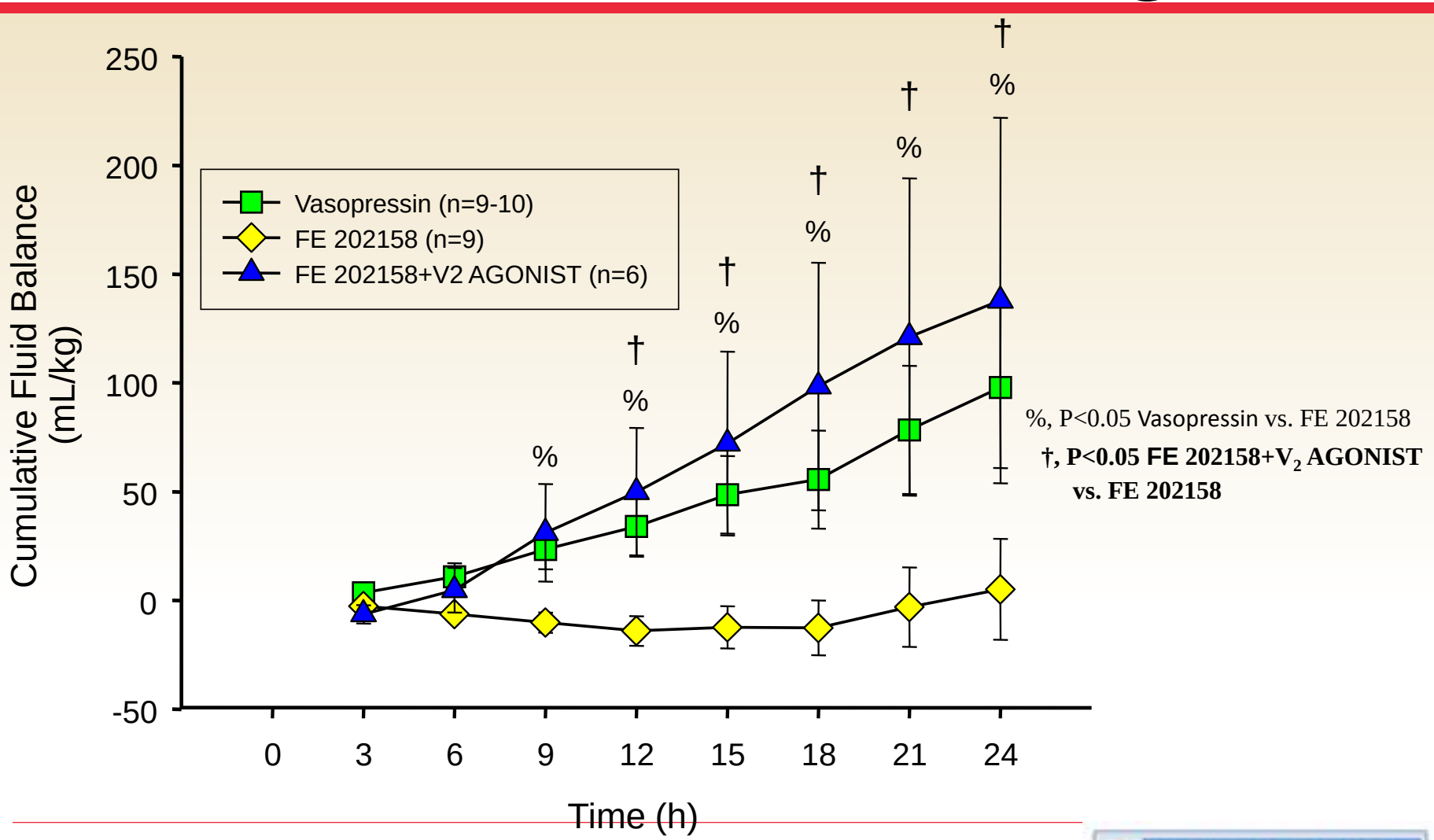
V_2R Agonist Abolishes $V_{1a}R$ Agonist's Effect on Vascular Leakage



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Overall Goal and Hypothesis

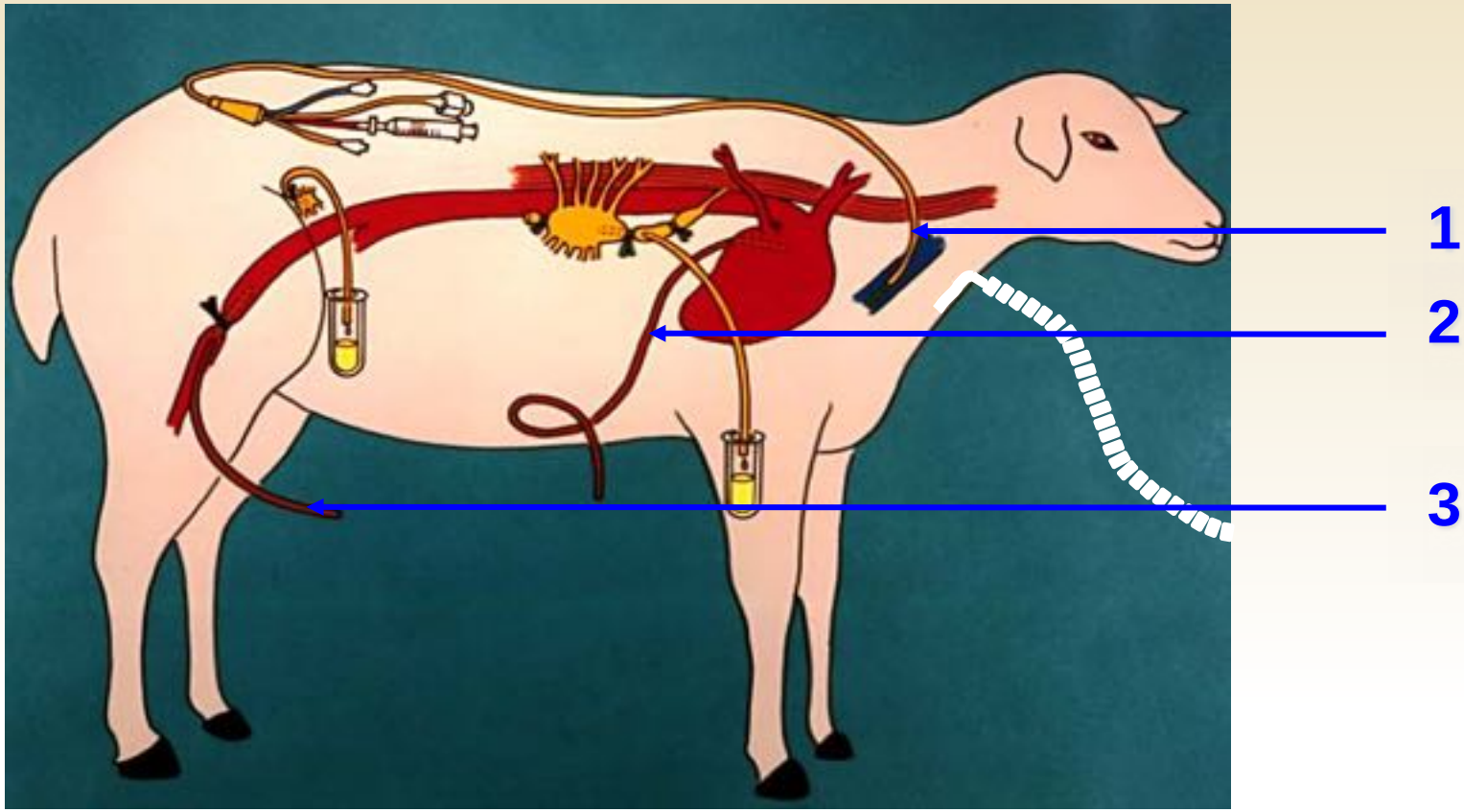
Goal:

To elucidate the role of V_2R receptor during methicillin-resistant *Staphylococcus aureus* (MRSA) sepsis and to test the safety and efficacy of the V_2R antagonist, tolvaptan (TLVP) as a potential treatment for septic patients.

Hypothesis:

Blockage of V_2R activation attenuates pulmonary and systemic vascular hyperpermeability and pulmonary vascular resistance during MRSA sepsis.

Materials & Methods: Conscious Ovine MRSA Sepsis Model

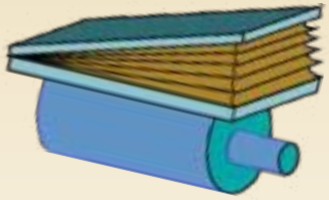


Female sheep weighing ~35kg were surgically prepared for chronic study at least 5-7 days before the experiment: pulmonary artery (Swan Ganz) (1), left atrium (2), and femoral artery (3) catheters were inserted for continuous monitoring of hemodynamics and intermittent blood sampling.

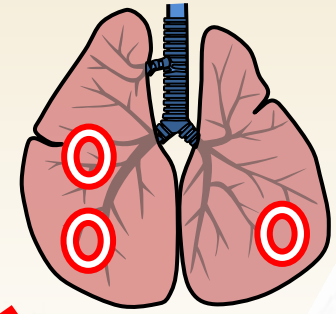
(Enkhbaatar *et al.*, Shock, 2008)

Materials & Methods: Conscious Ovine MRSA Sepsis Model

Female sheep
30 - 40 kg

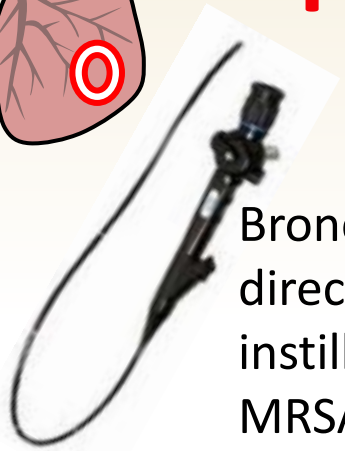


Smoke inhalation injury



+

24 hrs of monitoring under mechanical ventilation



Bronchoscope directed instillation of MRSA

~2.5X10^{11}CFU

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(Enkhbaatar *et al.*, Shock, 2008)

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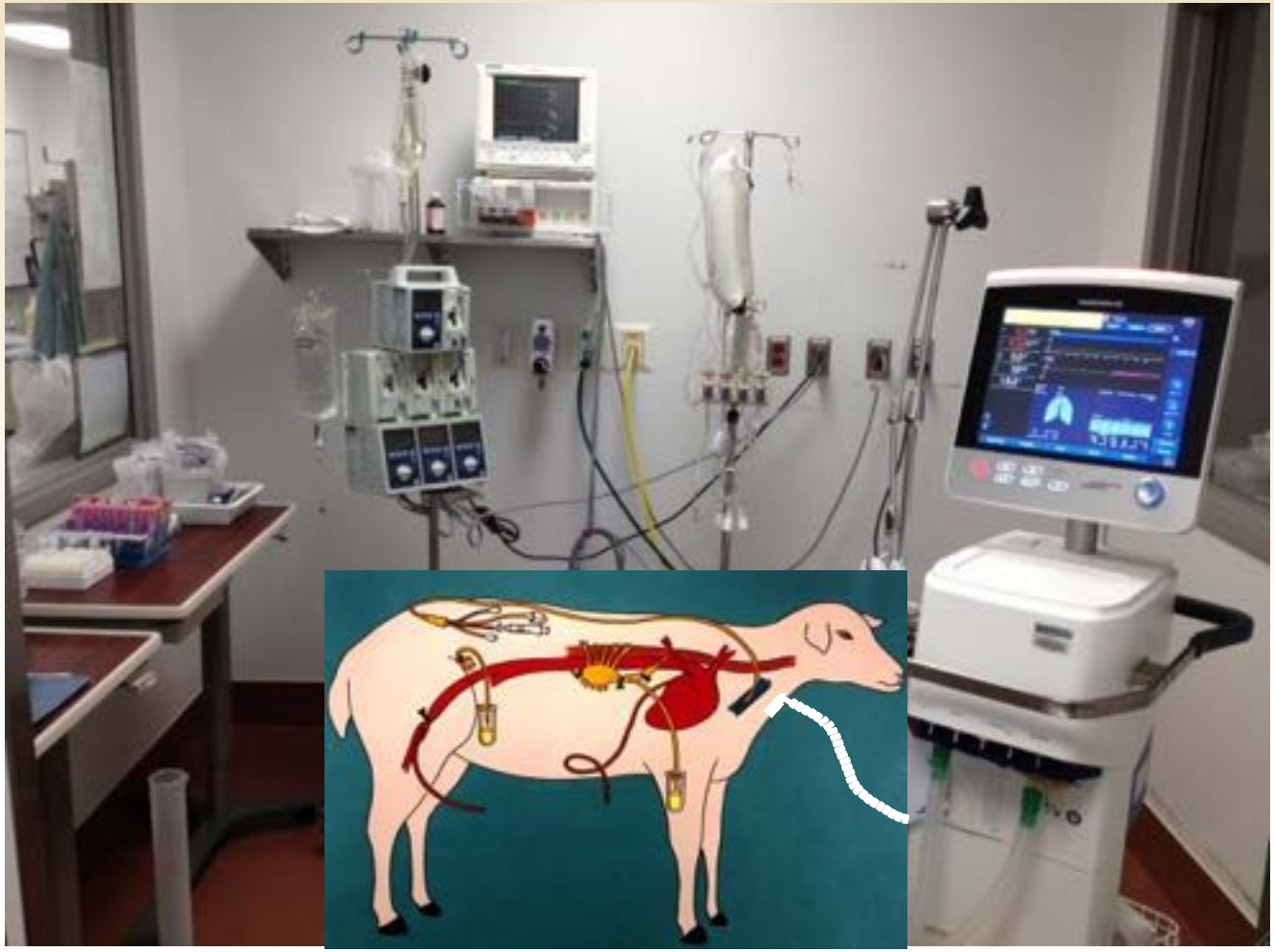
Materials & Methods: Conscious Ovine MRSA Sepsis Model



(Enkhbaatar *et al.*, Shock, 2008)

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Materials & Methods:
Conscious Ovine MRSA Sepsis Model

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(Enkhbaatar *et al.*, Shock, 2008)

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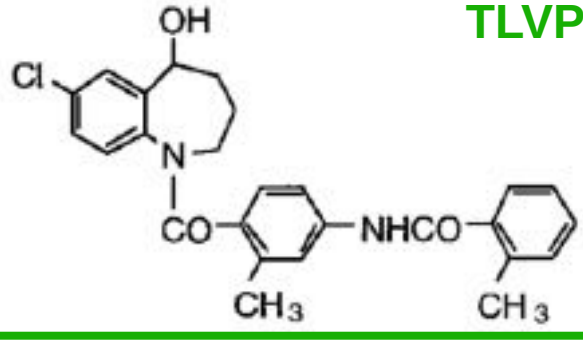
Animal Groups and Treatments

- **Sham, n = 6, No injury + saline**
- **Control, n = 7, Injury + saline**
- **DDAVP (V_2R agonist, desmopressin), n = 6, Injury + DDAVP 38 ng/kg/h. 23 hrs infusion**
- **TLVP (V_2R antagonist, tolvaptan), n = 6, Injury + TLVP 417 mcg/kg/h. 23 hrs infusion**

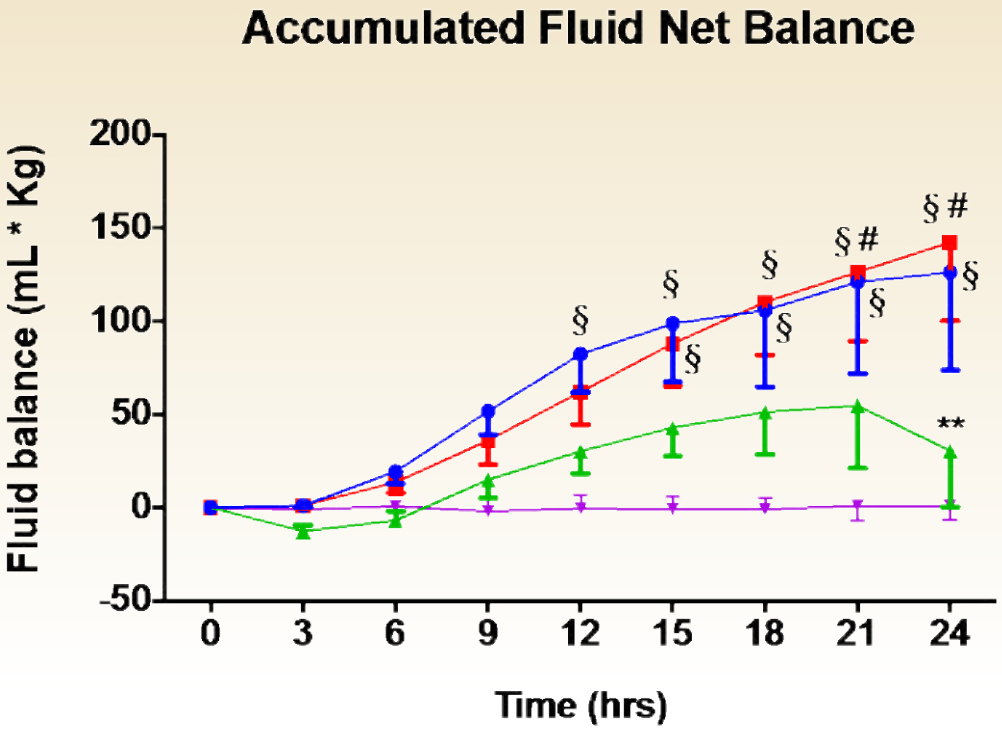
DDAVP

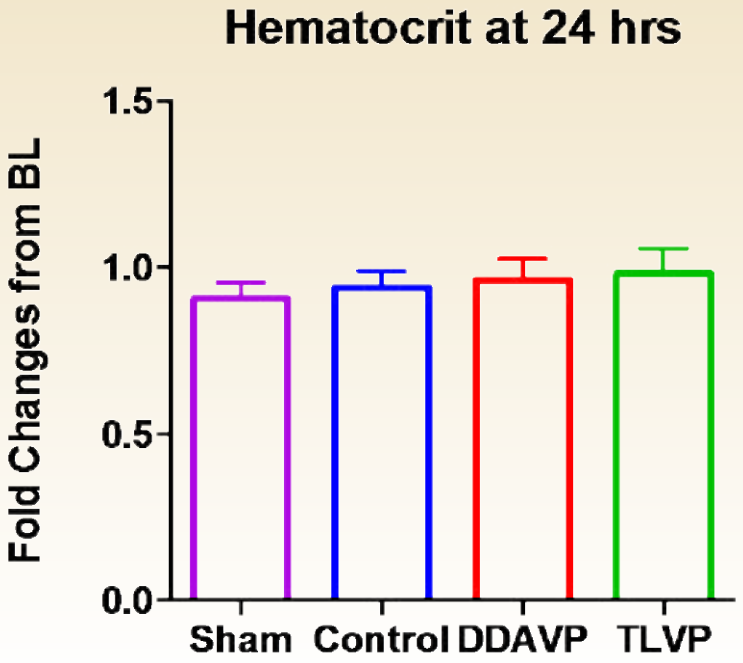
TLVP



- A total of 25 sheep were randomized into four groups.
- Continuous i.v. infusion, as a treatment, was given one hour after the injury.
- Fluid resuscitation was adjusted to maintain hematocrit ± 3% from baseline (BL).

TLVP Treatment Prevented the Systemic Accumulation of Fluid





▼ Sham, n=6
● Control, n=7
■ DDAVP (V_2R agonist), n=6
▲ TLVP (V_2R antagonist), n=6

Two-way ANOVA
**, $p < 0.01$ vs. Control
§ , $p < 0.05$ vs. Sham
#, $p < 0.05$ TLVP vs. DDAVP

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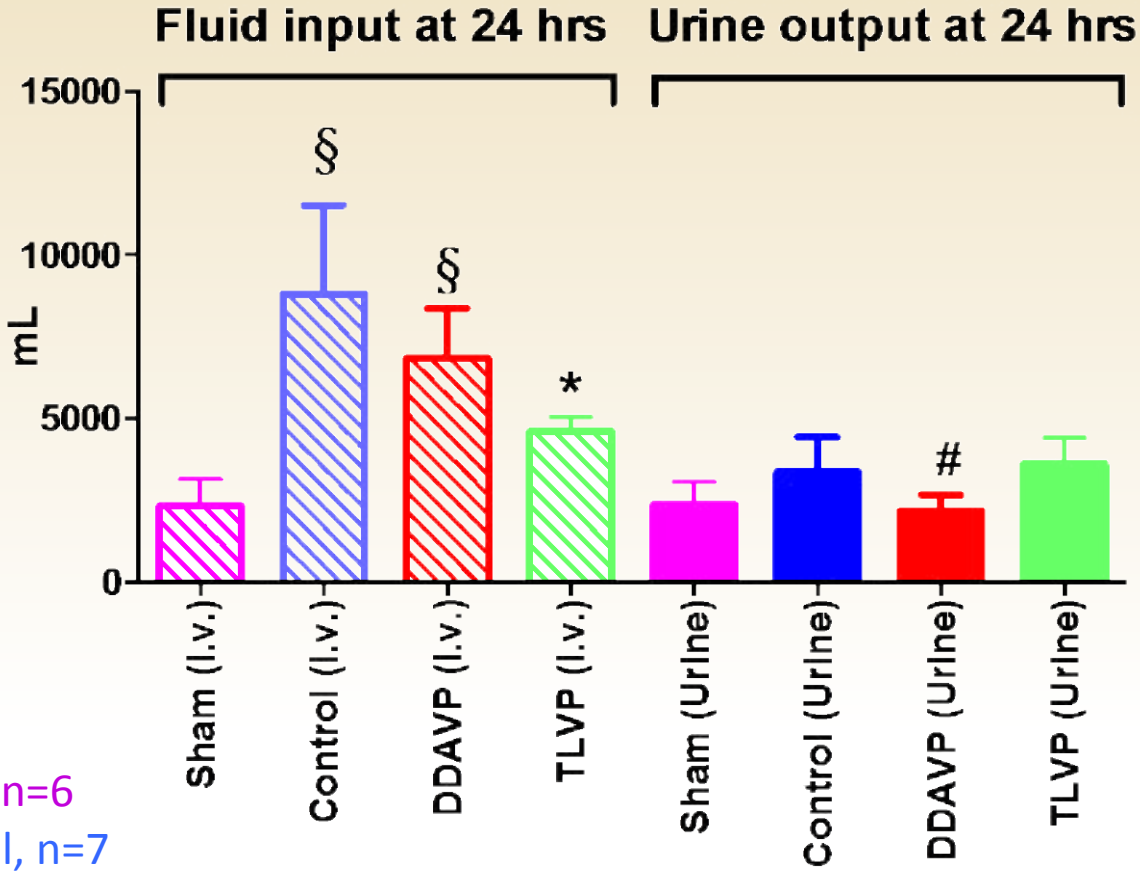
TLVP Treatment Reduced the Fluid Requirements



▼ Sham, n=6
● Control, n=7
■ DDAVP (V_2R agonist), n=6
▲ TLVP (V_2R antagonist), n=6

Two-way ANOVA
*, $p < 0.05$ vs. Control
§ , $p < 0.05$ vs. Sham
#, $p < 0.05$ TLVP vs. DDAVP

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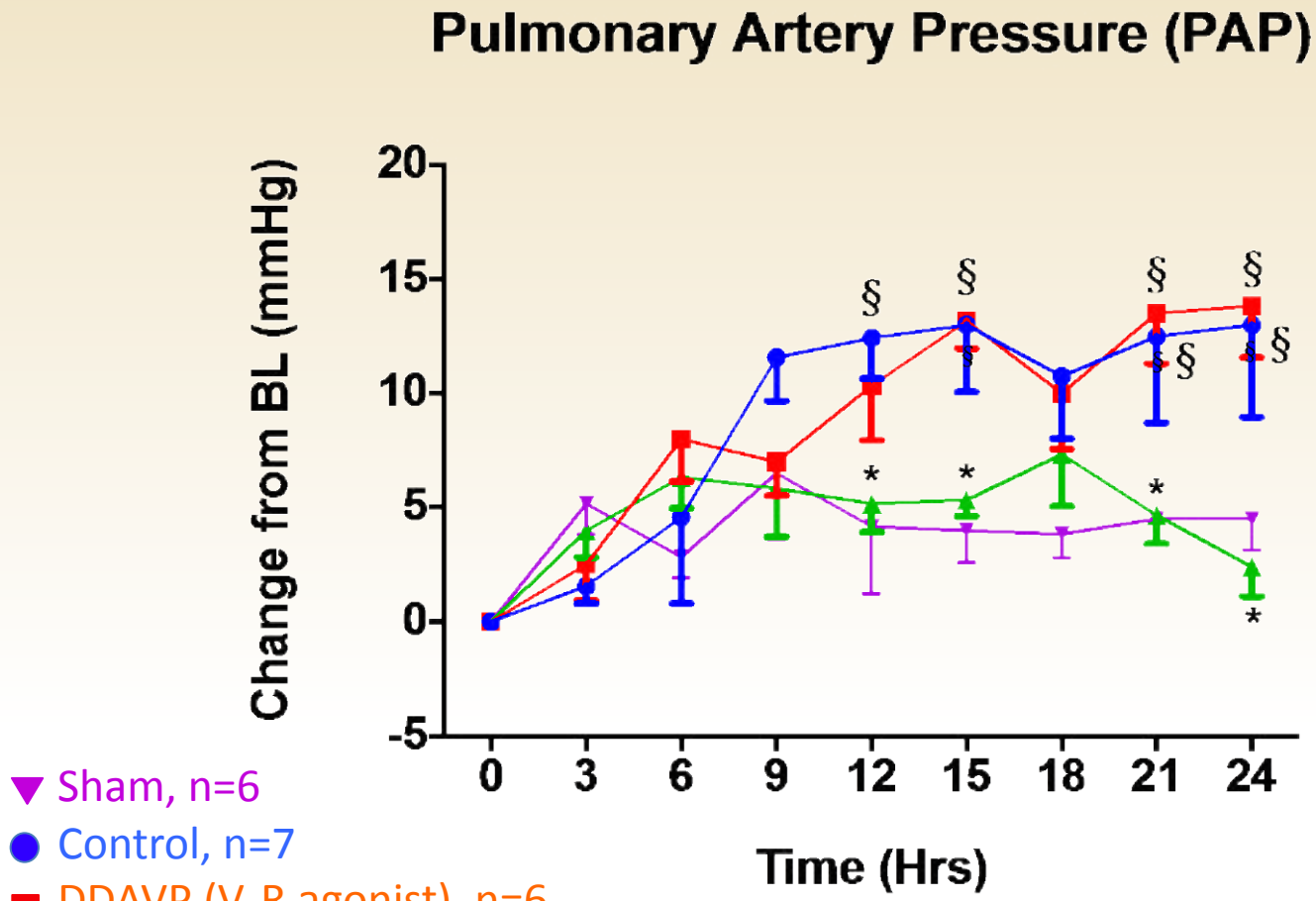
TLVP Treatment Decreased the Pulmonary Artery Pressure (PAP)



▼ Sham, n=6
● Control, n=7
■ DDAVP (V_2R agonist), n=6
▲ TLVP (V_2R antagonist), n=6

Two-way ANOVA
*, $p < 0.01$ vs. Control
§ , $p < 0.05$ vs. Sham

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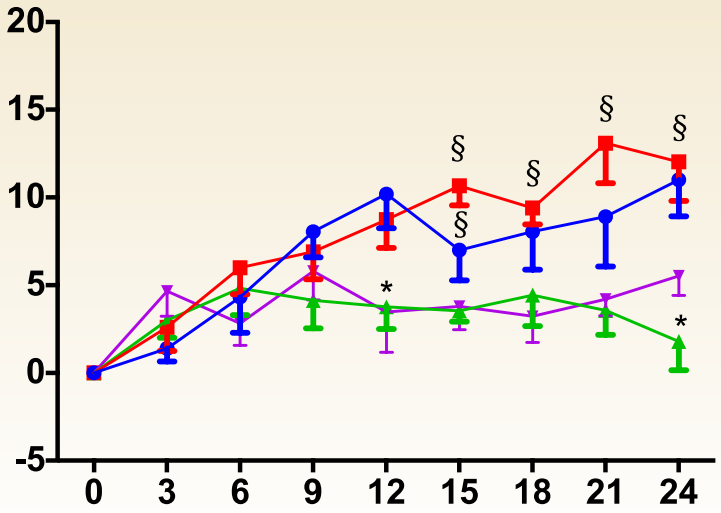
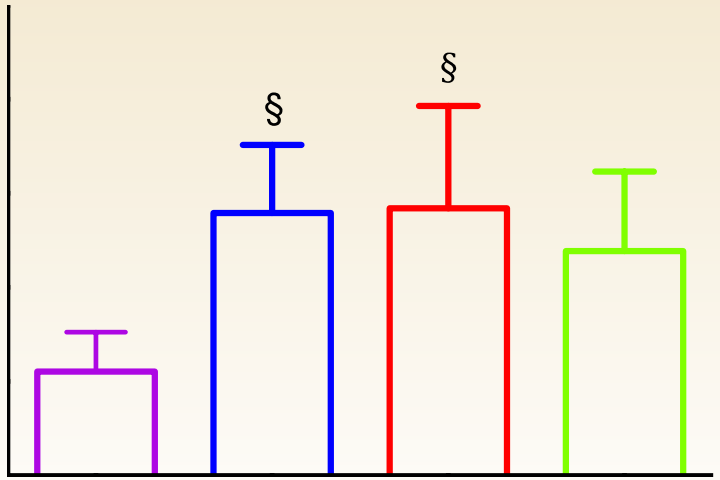
Pulmonary Microvascular Capillary Pressure (Pc) and Water Content Were Decreased





▼ Sham, n=6
● Control, n=7
■ DDAVP (V_2R agonist), n=6
▲ TLVP (V_2R antagonist), n=6

Two-way ANOVA
*, $p < 0.05$ vs. Control
§ , $p < 0.05$ vs. Sham
Pc = 0.6 PCWP + 0.4 PAP

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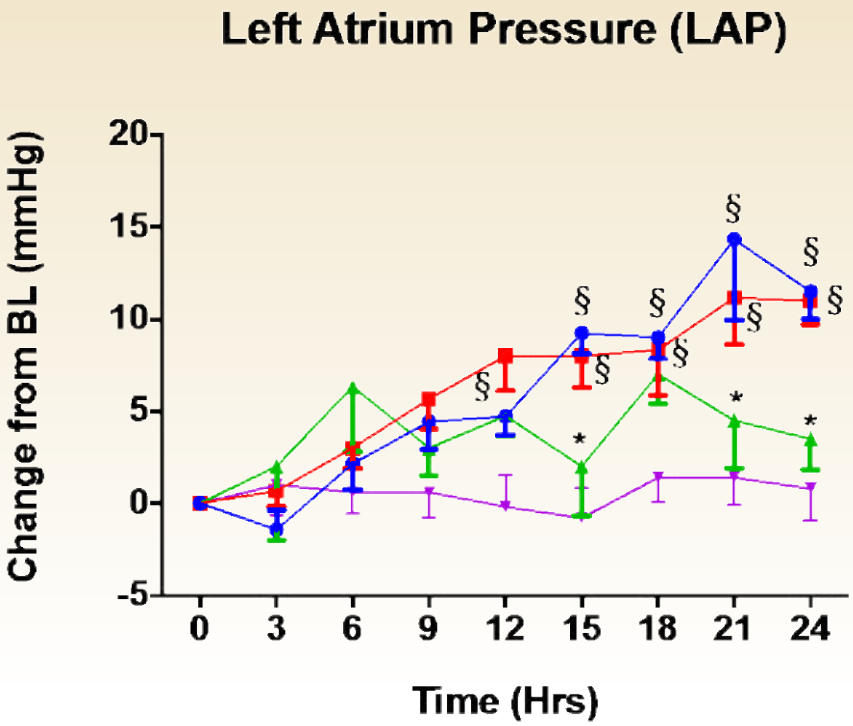
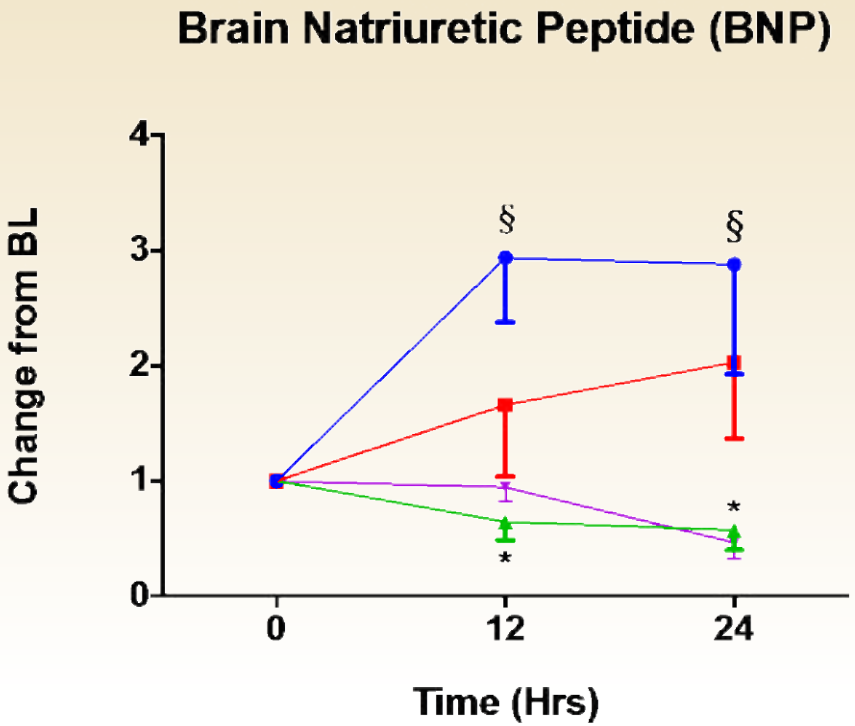
TLVP Treatment Prevented the Increase of Left Atrium Pressure (LAP) and Brain Natriuretic Peptide (BNP)





▼ Sham, n=6
● Control, n=7
■ DDAVP (V_2R agonist), n=6
▲ TLVP (V_2R antagonist), n=6

Two-way ANOVA
*, $p < 0.05$ vs. Control
§ , $p < 0.05$ vs. Sham

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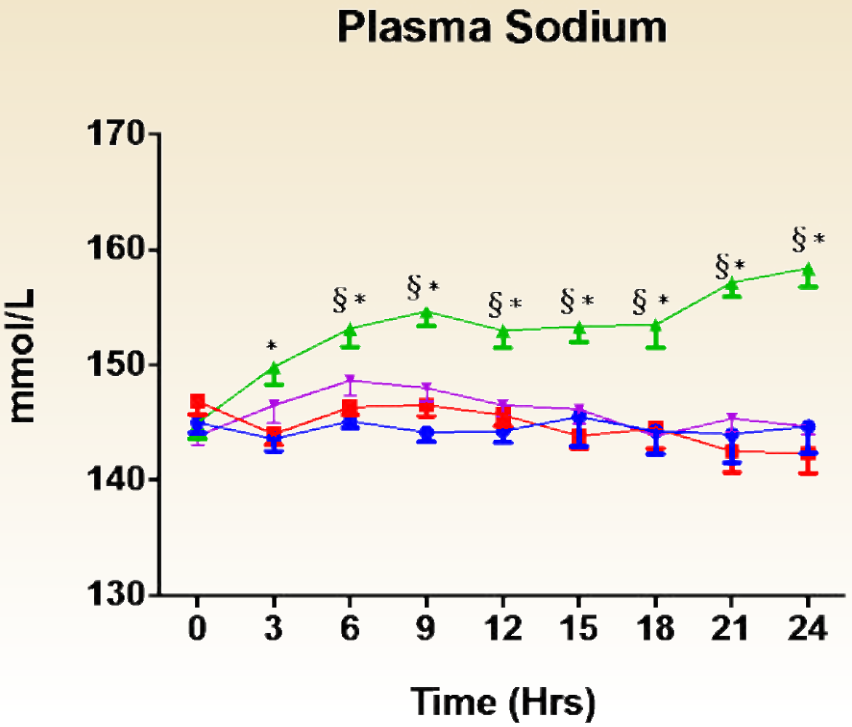
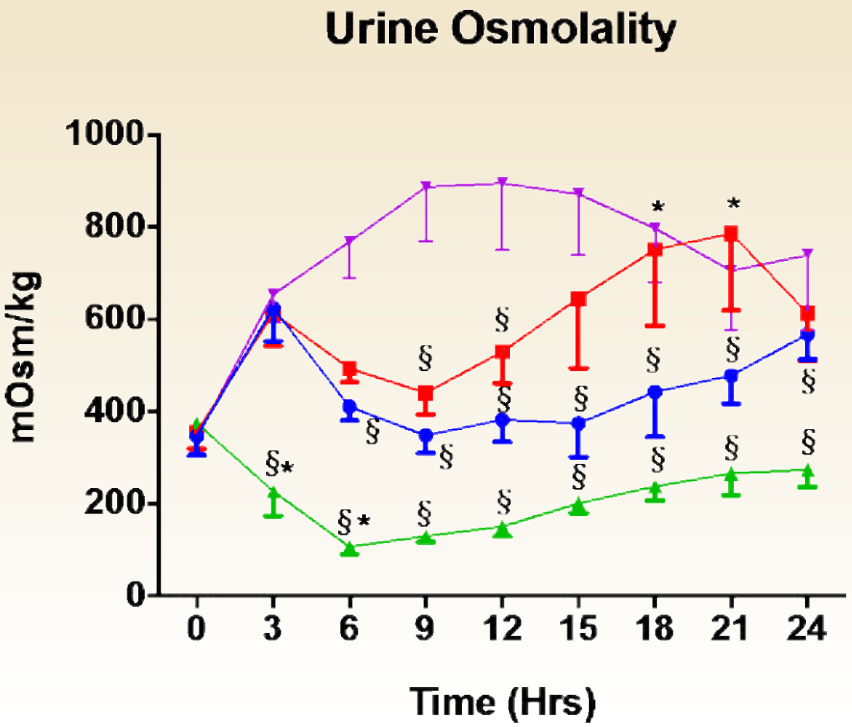
TLVP Treatment at 10 mg/kg/day Increased the Sodium Retention





▼ Sham, n=6
● Control, n=7
■ DDAVP (V_2R agonist), n=6
▲ TLVP (V_2R antagonist), n=6

Two-way ANOVA
*, $p < 0.05$ vs. Control
§ , $p < 0.05$ vs. Sham

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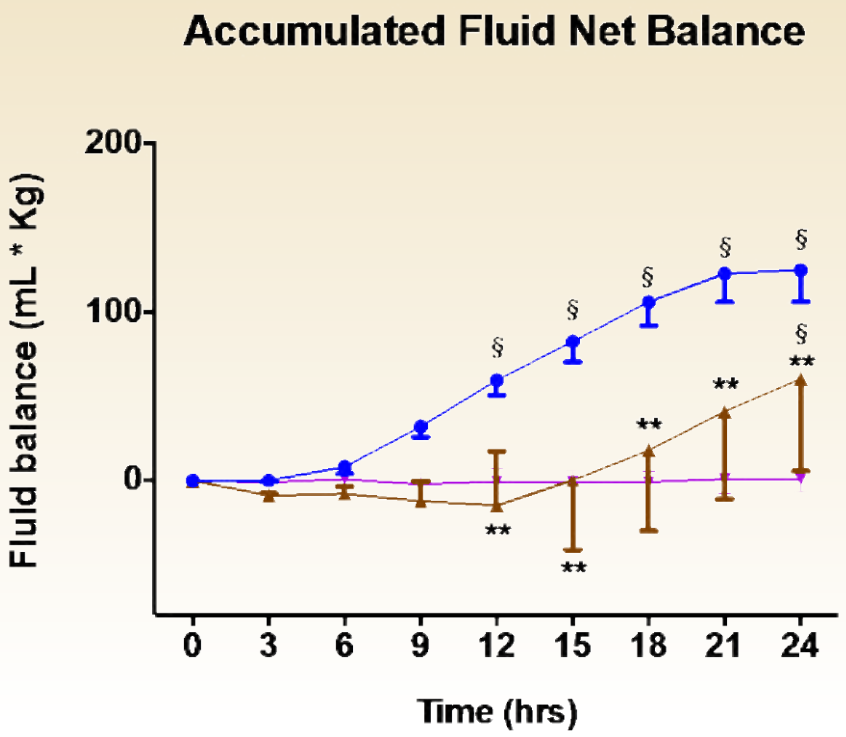
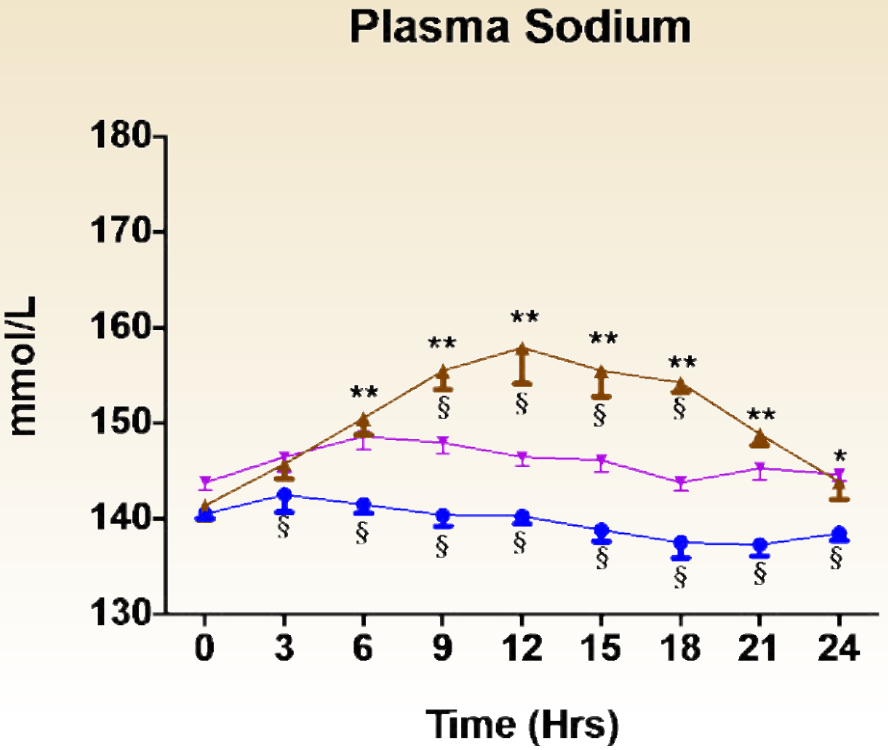
Lower Dose of TLVP Prevented the Accumulation of Fluids with Less Sodium Retention





▼ Sham, n=6

● Control, n=5

▲ TLVP (400 mcg/kg/h. 8 hrs infusion), n=3

Two-way ANOVA

*, $p < 0.05$ vs. Control

**, $p < 0.01$ vs. Control

§ , $p < 0.05$ vs. Sham

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Summary

1) Blockage of V_2R with TLVP (10 mg/kg/day):

- Reduced fluid requirement
- Reduced fluid retention
- Reduced lung water content
- Attenuated heart muscle overstretch
- Improved heart performance
- Decreased pulmonary vascular resistance

2) V_2R agonist DDAVP did not affect the above variables

3) TLVP caused moderate and transient increase in plasma sodium

Conclusion

- The data indicate that the activation of arginine vasopressin V_2 receptor plays a critical role in the pathophysiology of vascular hyper-permeability and cardiopulmonary hemodynamic changes during sepsis.

- V_2R antagonist TLVP should be considered as a therapeutic tool in septic patients, particularly those with severe fluid retention and tissue edema.

Future Directions

- Investigate the V_2R mediated downstream mechanisms with *in vitro* cell-based assays.
- Find the optimal therapeutic dose of TLVP.
- Test the combination of TLVP with V_1R agonist in our model.

Acknowledgments & Support

Translational Intensive Care Unit Team

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