DO VASOACTIVE DRUGS AND FLUIDS IMPROVE RENAL PERFUSION?

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Erasme University Hospital
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• In circulatory failure, the body tries to preserve the perfusion of vital organs such as brain/heart.

• Splanchnic, renal, muscular and cutaneous circulations may be compromised.
Different vascular beds have different vascular resistances.
• In circulatory failure, the body tries to preserve the perfusion of vital organs such as brain/heart.

• Splanchnic, renal, muscular and cutaneous circulations may be compromised.

• In sepsis, endothelial dysfunction contributes to a loss of regulation that may further alter distribution of perfusion, among but also inside the organs.
MAP, mmHg

Renal BF, mL/min

CTRL

ENDO

Bellomo et al
AJRCCM 59:86;1999
Renal hypoperfusion in sepsis?

Renal PO2 decreases despite maintenance of renal blood flow

Johannes T et al
Crit Care 10:R88;2006
Vasopressor agents
Renal BF, mL/min

MAP, mmHg

CTRL
+ NE

CTRL

Bellomo et al
AJRCCM 59:86;1999

Dogs
Dogs

Renal BF, mL/min

MAP, mmHg

CTRL

ENDO

CTRL + NE

ENDO + NE

Bellomo et al
AJRCCM 59:86;1999
Correction of hypotension improves urine output and renal function in septic patients

MAP 50 => 78 mmHg

Patients with septic shock (n=14)
Table 3. Indices of systemic oxygen metabolism as mean arterial pressure (MAP) is increased from 65 mm Hg to 85 mm Hg

<table>
<thead>
<tr>
<th></th>
<th>MAP</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>65 mm Hg</td>
</tr>
<tr>
<td>$\dot{D}_O_2$ (mL/min/m$^2$)</td>
<td>620 ± 59</td>
</tr>
<tr>
<td>$\dot{V}_O_2$ (mL/min/m$^2$)</td>
<td>119 ± 12</td>
</tr>
<tr>
<td>S$\bar{V}_O_2$ (%)</td>
<td>76 ± 3</td>
</tr>
<tr>
<td>Lactate (mEq/L)</td>
<td>3.1 ± 0.9</td>
</tr>
</tbody>
</table>

F, $p$ value for repeated-measures ANOVA as MAP is increased from 65 mm Hg to 85 mm Hg; LT, $p$ value for extension of ANOVA for linear trend; $\dot{D}_O_2$, oxygen delivery; $\dot{O}_O_2$, oxygen consumption; S$\bar{V}_O_2$, venous oxygen saturation.

Data are presented as mean ± SE.
Table 4. Indices of regional perfusion as MAP is increased from 65 mm Hg to 85 mm Hg

<table>
<thead>
<tr>
<th></th>
<th>MAP</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>65 mm Hg</td>
</tr>
<tr>
<td>Urinary output (mL)</td>
<td>49 ± 18</td>
</tr>
<tr>
<td>Capillary blood flow (mL/min/100 g)</td>
<td>6.0 ± 1.6</td>
</tr>
<tr>
<td>Red cell velocity (au)</td>
<td>0.42 ± 0.06</td>
</tr>
<tr>
<td>Pico₂ (mm Hg)</td>
<td>41 ± 2</td>
</tr>
<tr>
<td>Pa-Pico₂ (mm Hg)</td>
<td>13 ± 3</td>
</tr>
</tbody>
</table>

F, p value for repeated-measures analysis of variance (ANOVA) as MAP is increased from 65 mm Hg to 85 mm Hg; LT, p value for extension of ANOVA for linear trend; au, arbitrary units; Pico₂, gastric intramucosal PCO₂; Pa-Pico₂, arterial-gastric intramucosal CO₂ gradient.

Data are presented as mean ± SE.
PRESSURE GOAL?

28 pts with septic shock

Bourgouin et al
CCM 33:790;2005
<table>
<thead>
<tr>
<th></th>
<th>65 mmHg</th>
<th>75 mmHg</th>
<th>85 mmHg</th>
<th>$p^a$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate (bpm)</td>
<td>103 ± 23</td>
<td>103 ± 27</td>
<td>102 ± 29</td>
<td>NS</td>
</tr>
<tr>
<td>Cardiac index (l min$^{-1}$ m$^{-2}$)</td>
<td>3.4 ± 0.8</td>
<td>3.6 ± 0.9*</td>
<td>3.7 ± 0.9</td>
<td>0.002</td>
</tr>
<tr>
<td>Norepinephrine (µg kg$^{-1}$ min$^{-1}$)</td>
<td>0.3 ± 0.2</td>
<td>0.5 ± 0.3*</td>
<td>0.7 ± 0.5</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Blood Lactate (meq .l$^{-1}$)</td>
<td>2.8 ± 1.9</td>
<td>2.9 ± 2.1</td>
<td>2.9 ± 2.4</td>
<td>NS</td>
</tr>
<tr>
<td>Urinary output (ml h$^{-1}$)</td>
<td>76 ± 64</td>
<td>93 ± 68*</td>
<td>96 ± 73</td>
<td>0.02</td>
</tr>
<tr>
<td>Serum creatinine (µmol 1$^{-1}$)</td>
<td>232 ± 123</td>
<td>234 ± 136</td>
<td>234 ± 141</td>
<td>NS</td>
</tr>
<tr>
<td>Creatinine clearance (ml min$^{-1}$)</td>
<td>42 ± 31</td>
<td>42 ± 31</td>
<td>43 ± 32</td>
<td>NS</td>
</tr>
<tr>
<td>Resistance index</td>
<td>0.75 ± 0.07</td>
<td>0.71 ± 0.06*</td>
<td>0.71 ± 0.05</td>
<td>0.003</td>
</tr>
</tbody>
</table>

* $p < 0.05$ 65 vs. 75 mmHg (Wilcoxon post-hoc test); $^a$ Friedman test

11 pts septic shock
High variability in response to increase in MAP

11 pts septic shock

Deruddre et al
ICM 33:1557;2007
Impact of nature of vasopressor agents?
Dopamine vs norepinephrine?

De Backer et al
NEJM 362: 779; 2010

1679 pts
Vasopressin improves renal function?
Vasopressin improves renal function?
Creatinine clearance
mL/min

VASOPRESSIN IN PATIENTS WITH SEPTIC SHOCK

P<0.01

Patel et al
Anesthesiol
96:576;2002

DDB USI
### VASOPRESSIN IN PATIENTS WITH SEPTIC SHOCK

Russell JA et al  
NEJM 358:877;2008

<table>
<thead>
<tr>
<th>Variable</th>
<th>Norepinephrine Group (N = 382)</th>
<th>Vasopressin Group (N = 396)</th>
<th>P Value†</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>no./total no. (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Free of organ dysfunction</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>17 (0–24)</td>
<td>19 (0–24)</td>
<td>0.58</td>
</tr>
<tr>
<td>Vasopressor use**</td>
<td>17 (0–24)</td>
<td>19 (0–24)</td>
<td>0.61</td>
</tr>
<tr>
<td>Respiratory</td>
<td>2 (0–14)</td>
<td>3.5 (0–16)</td>
<td>0.15</td>
</tr>
<tr>
<td>Ventilation††</td>
<td>6 (0–20)</td>
<td>8.5 (0–20)</td>
<td>0.24</td>
</tr>
<tr>
<td>Renal</td>
<td>18.5 (3–28)</td>
<td>21.5 (4–28)</td>
<td>0.54</td>
</tr>
<tr>
<td>Renal-replacement therapy</td>
<td>23 (5–28)</td>
<td>25 (6–28)</td>
<td>0.64</td>
</tr>
</tbody>
</table>
Gordon AC et al
ICM 36:83;2010

VASST

Non AKI

Injury

Risk

Failure

P<0.01

Serum Creatinine (µmol/L)

Days

AVP n= 154
NE n= 160

AVP n= 68
NE n= 62

AVP n= 53
NE n= 53

AVP n= 97
NE n= 82

0 5 10 15 20

120 100 80 60 40 20 0

133 26 19 15

139 42 26 16

26 19

48 9 4 4

52 13 7 4

AVP n= 154
NE n= 160

AVP n= 68
NE n= 62

AVP n= 53
NE n= 53

AVP n= 97
NE n= 82

0 5 10 15 20

250 200 150 100 50 0

200 150 100 50

133 26 19 15

139 42 26 16

26 19

48 9 4 4

52 13 7 4

26 19

48 9 4 4

52 13 7 4
### VASOPRESSIN IN PATIENTS WITH SEPTIC SHOCK

**Potential beneficial effect in some subgroups**

Gordon AC et al  
*ICM* 36:83;2010

#### Need for RRT during 28-days study period

<table>
<thead>
<tr>
<th></th>
<th>Total</th>
<th>NE</th>
<th>AVP</th>
<th>p value*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Non AKI</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>315 (40.4)</td>
<td>160</td>
<td>155</td>
<td></td>
</tr>
<tr>
<td>Risk</td>
<td>36 (11.4)</td>
<td>20 (12.5)</td>
<td>16 (10.3)</td>
<td>0.54</td>
</tr>
<tr>
<td>Injury</td>
<td>106 (13.6)</td>
<td>53</td>
<td>53</td>
<td></td>
</tr>
<tr>
<td>Non AKI Risk</td>
<td>29 (27.4)</td>
<td>20 (37.7)</td>
<td>9 (17.0)</td>
<td>0.02</td>
</tr>
<tr>
<td>Injury</td>
<td>130 (16.7)</td>
<td>62</td>
<td>68</td>
<td></td>
</tr>
<tr>
<td>Failure</td>
<td>47 (36.4)</td>
<td>23 (37.7)</td>
<td>24 (35.3)</td>
<td>0.78</td>
</tr>
<tr>
<td>Non AKI Injury</td>
<td>179 (23.0)</td>
<td>82</td>
<td>97</td>
<td></td>
</tr>
<tr>
<td>Injury</td>
<td>135 (75.4)</td>
<td>60 (73.2)</td>
<td>75 (77.3)</td>
<td>0.52</td>
</tr>
</tbody>
</table>
Fluids
Because we expect that fluid administration will result in an improved tissue perfusion
STARLING RELATIONSHIP

Why do we give fluids?

Stroke volume

Preload
EFFECTS OF FLUID LOADING IN SEPSIS

Cholley et al.
AJP 269:H375;1995
Impact of fluid resuscitation on survival

Zhong et al
Shock 2:203;1994

Pigs
Fluid resuscitation is essential!

Hollenberg et al
AJRCCM ;1991

Rats CLP
Fluid resuscitation is essential!

Zanotti S et al
ICM 2009

Mice CLP
Why do we give fluids in AKI?

Fluid administration

↑ Cardiac output

↑ Renal perfusion

↑ Urine output
Effects of fluids on renal perfusion

T0 base, T1 lps, T2 lps + fluids
NR = not resuscitated

Johannes T et al
Crit Care 10:R88;2006
Effects of fluids on creatinine clearance

Johannes T et al
Crit Care 10:R88;2006

T0 base, T1 lps, T2 lps + fluids
NR = not resuscitated
Effects of fluids on renal perfusion

Legrand et al
ICM 2011
Changes in renal Doppler predict changes in urine output after fluid challenge

Moussa M et al
SCCM 2012

44 oliguric pts receiving fluid expansion
Changes in renal Doppler predict changes in urine output after fluid challenge

<table>
<thead>
<tr>
<th>Metric</th>
<th>Resp</th>
<th>Non Resp</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>SOFA</td>
<td>6(3.5-8.5)</td>
<td>10.5 (7.8-13.3)</td>
<td>0.00</td>
</tr>
<tr>
<td>AGE</td>
<td>66 (48-79)</td>
<td>62 (48-75.5)</td>
<td>0.00</td>
</tr>
<tr>
<td>RIFLE</td>
<td>1 (0-2)</td>
<td>2.5 (1.3-3)</td>
<td>0.00</td>
</tr>
<tr>
<td>Resistivity Index</td>
<td>0.71 (0.62-0.79)</td>
<td>0.78 (0.72-0.81)</td>
<td>0.03</td>
</tr>
<tr>
<td>Pulsatility Index</td>
<td>1.1 (0.9-1.3)</td>
<td>1.3 (1.1-1.4)</td>
<td>0.94</td>
</tr>
<tr>
<td>VS (cm/s)</td>
<td>41.8 (33.7-45.9)</td>
<td>39 (25.4-61.3)</td>
<td>0.21</td>
</tr>
<tr>
<td>VD (cm/s)</td>
<td>11.1 (7.4-18.5)</td>
<td>8.8 (6.8-12.7)</td>
<td>0.73</td>
</tr>
<tr>
<td>Vm (cm/s)</td>
<td>26 (19.7-32.8)</td>
<td>24.5 (15.7-39.6)</td>
<td>0.25</td>
</tr>
<tr>
<td>HR (bpm)</td>
<td>98 (88-118)</td>
<td>90 (75-117)</td>
<td>0.00</td>
</tr>
<tr>
<td>MAP (mmHg)</td>
<td>81.7 (66-93.7)</td>
<td>67 (61-75)</td>
<td>0.72</td>
</tr>
<tr>
<td>CVP (mmHg)</td>
<td>7 (4.3-12)</td>
<td>11 (8-12.8)</td>
<td>0.23</td>
</tr>
<tr>
<td>CO</td>
<td>8.60</td>
<td>5.10</td>
<td>0.90</td>
</tr>
<tr>
<td>LACTATE (mmol/l)</td>
<td>2.1 (1.2-4.6)</td>
<td>1.5 (1.1-2.85)</td>
<td>0.12</td>
</tr>
</tbody>
</table>

44 oliguric pts receiving fluid expansion

Moussa M et al SCCM 2012
Changes in renal Doppler predict changes in urine output after fluid challenge

Moussa M et al
SCCM 2012

Changes in resistivity index predict changes in urine output with an AUC 0.75 (P=0.002)

44 oliguric pts receiving fluid expansion
Response to fluids?

• All patients do not respond to fluids
STARLING RELATIONSHIP

Stroke volume

Preload
STARLING RELATIONSHIP

Stroke volume vs Preload
STARLING RELATIONSHIP

Stroke volume

Preload

DDB  USI
Response to fluids?

• All patients do not respond to fluids
• All patients do not tolerate fluids

=> It is relevant to identify the patients who are likely to respond to fluid or not

=> It is relevant to evaluate how patients respond to fluids
FLUID CHALLENGE

• 500 mL of colloid or 1000 mL of crystalloid solution over 30 min

• Hemodynamic measurements before and during FC

• Safety rules for stopping FC (increase in PAOP, CVP…)

• Evaluation of effectiveness
  • Positive test: increase in CO of at least 10-15%
  • Negative test: absence of change in CO despite increase in PAOP/CVP/volumes…
  • Non definite: no change in CO and in PAOP/….
Response to fluids?

- Edema may have deleterious effects
  - Lung edema
  - Increased abdominal pressure
- A positive fluid balance is associated with poor outcome

=> Fluids restriction?
A positive fluid balance is associated with a poor outcome in sepsis

Vincent et al
CCM 34:344;2006

<table>
<thead>
<tr>
<th></th>
<th>OR (95% CI)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>SAPS II score (per point increase)</td>
<td>1.0 (1.0–1.1)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td><strong>Cumulative fluid balance</strong> (per liter increase)</td>
<td>1.1 (1.0–1.1)</td>
<td>.001</td>
</tr>
<tr>
<td>Age (per year increase)</td>
<td>1.0 (1.0–1.0)</td>
<td>.001</td>
</tr>
<tr>
<td>Initial SOFA score (per point increase)</td>
<td>1.1 (1.0–1.1)</td>
<td>.002</td>
</tr>
<tr>
<td>Blood stream infection</td>
<td>1.7 (1.2–2.4)</td>
<td>.004</td>
</tr>
<tr>
<td>Cirrhosis</td>
<td>2.4 (1.3–4.5)</td>
<td>.008</td>
</tr>
<tr>
<td>Pseudomonas infection</td>
<td>1.6 (1.1–2.4)</td>
<td>.017</td>
</tr>
<tr>
<td>Medical admission</td>
<td>1.4 (1.0–1.8)</td>
<td>.049</td>
</tr>
<tr>
<td>Female gender</td>
<td>1.4 (1.0–1.8)</td>
<td>.044</td>
</tr>
</tbody>
</table>

1177 septic pts
A positive fluid balance is common in critically ill patients with acute renal failure

Payen D et al
Crit Care 12;R34; 2008

3147 pts
Liberal followed by restrictive fluid strategy in septic ARDS?

Murphy C et al
Chest 136:102;2009

212 pts with septic shock
Liberal followed by restrictive fluid strategy in septic ARDS?

Murphy C et al
Chest 136:102;2009

212 pts with septic shock

<table>
<thead>
<tr>
<th>Variables</th>
<th>Adjusted OR</th>
<th>95% CI</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>APACHE II score, 1-point increments</td>
<td>1.07</td>
<td>1.01–1.14</td>
<td>0.030</td>
</tr>
<tr>
<td>Charlson comorbidity score, 1-point increments</td>
<td>1.11</td>
<td>1.01–1.23</td>
<td>0.040</td>
</tr>
<tr>
<td>Renal replacement therapy</td>
<td>3.15</td>
<td>1.51–4.79</td>
<td>0.020</td>
</tr>
<tr>
<td>Colloid administration</td>
<td>2.94</td>
<td>1.41–4.47</td>
<td>0.011</td>
</tr>
<tr>
<td>AIFR not achieved</td>
<td>4.94</td>
<td>2.07–11.79</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Duration of vasopressors, 1-day increments</td>
<td>1.24</td>
<td>1.04–1.47</td>
<td>0.017</td>
</tr>
<tr>
<td>CLFM not achieved</td>
<td>6.13</td>
<td>2.77–13.57</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>
Fluids and AKI: A delicate balance

Hypovolemia

Overload

Hypoperfusion

Edema
Inotropic agents