VASOPRESSOR AGENTS IN SEPTIC SHOCK

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Professor of Intensive Care, Université Libre de Bruxelles
President European Society of Intensive Care Medicine
Even non sustained (<60min) hypotension is associated with a poor outcome and should not be neglected.

Marchick et al
ICM 35:1261;2009

700 pts with sepsis at ED

OR 2.7 (1.2-5.8)
Time spent with hypotension is associated with a poor outcome

Dunser M et al
ICM 35:1225;2009

274 pts with sepsis in ICU
High doses of vasopressors used to reach a given pressure levels are deleterious

290 pts with septic shock
VP for MAP > 70 mmHg

MAP quartiles:
I 70-74.3
II 74.3-77.8
III 77.8-82.1
IV 92.1-99.7
• Both severity and duration of hypotension are associated with poor outcome.

• It sounds thus reasonable to try to correct hypotension without delay.

• Which blood pressure target?
  • Which agent should be used?
Does correction of hypotension with vasopressors affect tissue perfusion?
Correction of hypotension improves urine output and renal function in septic patients

MAP 50 => 78 mmHg

Patients with septic shock (n=14)
Correction of hypotension improves microvascular reactivity (NIRS)

Georger et al
ICM 36:1882;2010

MAP 54 => 77 mmHg
Which blood pressure target?
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>$49 \pm 18$</td>
</tr>
<tr>
<td>Capillary blood flow (mL/min/100 g)</td>
<td>$6.0 \pm 1.6$</td>
</tr>
<tr>
<td>Red cell velocity (au)</td>
<td>$0.42 \pm 0.06$</td>
</tr>
<tr>
<td>Pico$_2$ (mm Hg)</td>
<td>$41 \pm 2$</td>
</tr>
<tr>
<td>Pa-Pico$_2$ (mm Hg)</td>
<td>$13 \pm 3$</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; Pico$_2$, gastric intramucosal Pco$_2$; Pa-Pico$_2$, arterial-gastric intramucosal CO$_2$ gradient.

Data are presented as mean ± se.
High vs Low MAP?

65-70 vs 80-85 mmHg

- But lower incidence of AKI with high MAP in previously hypertensive patients
- Higher rate of arrhythmias and AMI in high MAP

798 pts septic shock
High vs Low MAP?

73-75
65-70 VS 80-85 mmHg

Target
65-70

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

Renal Doppler

11 pts septic shock

Deruddre et al
ICM 33:1557;2007
Impact of MAP/NE on microvascular perfusion

Dubin et al
Crit Care 2009

N=20

Capillary microvascular flow index

Mean arterial blood pressure

65 mm Hg  75 mm Hg  85 mm Hg
Vasopressor Support

Adrenergic agents:
- Dopamine
- Norepinephrine
- Epinephrine
- Phenylephrine
# Adrenergic Agents

<table>
<thead>
<tr>
<th></th>
<th>Alpha</th>
<th>Beta</th>
<th>Dopa</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dopamine</td>
<td>++</td>
<td>+(+  )</td>
<td>+</td>
</tr>
<tr>
<td>Noradrenaline</td>
<td>+++++</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Epinephrine</td>
<td>+++++</td>
<td>+++++</td>
<td>-</td>
</tr>
<tr>
<td>Phenylephrine</td>
<td>+++++</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>
ADRENERGIC AGENTS

Alpha
+ vasopressor effect
- increase in afterload, decrease in regional blood flows

Beta
+ inotropic effect, increase in regional blood flows
- arrhythmias, immunodepression, metabolic effects

Dopa
+ increase in renal and splanchnic blood flow (?)
- alteration hypothalamo-pituitary axis
Hemodynamic effects of vasopressors

CO

MAP

DOPA

NOREPINEPHRINE

EPINEPHRINE

PHENYLEPHRINE
Rats
CLP

Ducrocq N et al
Anesthesiology
116:1083;2012
DOPAMINE vs NOREPINEPHRINE

Effects on regional blood flow?
Correction of hypotension improves urine output and renal function in septic patients

MAP 50 => 78 mmHg

Patients with septic shock (n=14)
Effects of dopamine, norepinephrine and epinephrine in patients with septic shock
<table>
<thead>
<tr>
<th>Influence on</th>
<th>Effect</th>
<th>Mechanism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pituitary hormones</td>
<td>Suppression</td>
<td>Indirectly via nNOS, D₂ receptor</td>
</tr>
<tr>
<td>Prolactin</td>
<td>Suppression</td>
<td>D₂ receptor</td>
</tr>
<tr>
<td>Thyroid hormones</td>
<td>Suppression</td>
<td>D₂ receptor</td>
</tr>
<tr>
<td>Growth hormones</td>
<td>Suppression</td>
<td>D₂ receptor</td>
</tr>
<tr>
<td>Glucocorticoid</td>
<td>Induction</td>
<td>α₂ receptor, D₂ receptor</td>
</tr>
<tr>
<td>Cytokines</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IL-10</td>
<td>Induction</td>
<td>β receptor, ROS</td>
</tr>
<tr>
<td>TNF-α (monocytes, HUVECs)</td>
<td>Suppression</td>
<td>β receptor, ROS</td>
</tr>
<tr>
<td>TNF-α (neutrophils)</td>
<td>Suppression</td>
<td>D₁ receptor</td>
</tr>
<tr>
<td>IL-1</td>
<td>Suppression</td>
<td>β receptor, ROS</td>
</tr>
<tr>
<td>IL-6 (monocytes, HUVECs)</td>
<td>Suppression</td>
<td>β receptor, ROS</td>
</tr>
<tr>
<td>IL-6 (glomerulosa cells)</td>
<td>Induction</td>
<td>D₂ receptor</td>
</tr>
<tr>
<td>IL-12 p40</td>
<td>Suppression</td>
<td>β receptor</td>
</tr>
<tr>
<td>Chemokines</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IL-8 (HUVEC)</td>
<td>Induction</td>
<td>ROS</td>
</tr>
<tr>
<td>IL-8 (PTEC)</td>
<td>Suppression</td>
<td>ROS</td>
</tr>
<tr>
<td>Gro-α</td>
<td>Suppression</td>
<td>ROS</td>
</tr>
<tr>
<td>ENA-78</td>
<td>Suppression</td>
<td>ROS</td>
</tr>
<tr>
<td>Adhesion molecules</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CD11b/CD18</td>
<td>Suppression</td>
<td>ROS</td>
</tr>
<tr>
<td>E-selectin</td>
<td>Suppression</td>
<td>ROS?</td>
</tr>
<tr>
<td>ICAM-1</td>
<td>Suppression</td>
<td>ROS?</td>
</tr>
<tr>
<td>Nitric oxide</td>
<td></td>
<td></td>
</tr>
<tr>
<td>In HUVECs</td>
<td>Suppression</td>
<td>ROS</td>
</tr>
<tr>
<td>In monocytes</td>
<td>Induction</td>
<td>β receptor</td>
</tr>
<tr>
<td>Apoptosis</td>
<td>Induction</td>
<td>D₁ and β receptor, ROS</td>
</tr>
<tr>
<td>In neutrophils</td>
<td>Induction</td>
<td>D₁ and β receptor, ROS</td>
</tr>
<tr>
<td>In lymphocytes</td>
<td>Induction</td>
<td>D₁ and β receptor, ROS</td>
</tr>
<tr>
<td>PLA₂ metabolites</td>
<td>Suppression</td>
<td>?</td>
</tr>
<tr>
<td>Respiratory burst</td>
<td>Suppression</td>
<td>D₁ receptor</td>
</tr>
</tbody>
</table>

But these agents are not only correcting blood pressure.
NOREPINEPHRINE vs EPINEPHRINE

Background
Dose dependent stimulation of beta adrenergic receptor with EPI

VO2

CO

Dose
Metabolic effects of epinephrine


Lactate mm/L

Epinephrine
Norepinephrine + dobutamine

Hours

0 1 6 12
MAP

pH

Lactate

330 pts septic shock

Annane et al
Lancet 370:676;2007
Levy B et al
CCM 2011

30 pts cardiogenic shock

Norepi + dobu
VS
Epi
EPI vs NOREPI (+-DOBU)

330 pts septic shock
DOPAMINE vs NOREPINEPHRINE
DOPAMINE vs NOREpinephrine

SOAP study

1058 pts in shock
(any cause)

Log Rank = 4.6; p = 0.032

No dopamine
n=683

Dopamine
n=375

Sakr et al
CCM 34:589;2006
**DOPAMINE vs NOREPINEPHRINE**

**SOAP study**

1058 pts in shock

Multivariate logistic regression

<table>
<thead>
<tr>
<th></th>
<th>Coefficient</th>
<th>Mean, SE</th>
<th>Odds ratio (95% CI)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean SOFA score</td>
<td>0.424</td>
<td>0.031</td>
<td>1.528 (1.437-1.624)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Mean fluid balance</td>
<td>0.348</td>
<td>0.059</td>
<td>1.416 (1.261-1.591)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Medical admission</td>
<td>0.857</td>
<td>0.167</td>
<td>2.356 (1.697-3.271)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Age</td>
<td>0.018</td>
<td>0.005</td>
<td>1.018 (1.007-1.029)</td>
<td>0.001</td>
</tr>
<tr>
<td>Dopamine administration</td>
<td>0.514</td>
<td>0.172</td>
<td>1.673 (1.193-2.345)</td>
<td>0.003</td>
</tr>
<tr>
<td>Cancer</td>
<td>0.716</td>
<td>0.243</td>
<td>2.046 (1.270-3.297)</td>
<td>0.003</td>
</tr>
</tbody>
</table>

Sakr et al

CCM 34:589;2006
SACiUCI study

DOPAMINE vs NOREPINEPHRINE

Povoa et al
CCM 37:410;2009

458 patients
septic shock

Log rank = 22.13
p < .001
Comparison of Dopamine and Norepinephrine in the Treatment of Shock

Daniel De Backer, M.D., Ph.D., Patrick Biston, M.D., Jacques Devriendt, M.D., Christian Madl, M.D., Didier Choched, M.D., Cesar Aldecoa, M.D., Alexandre Brasseur, M.D., Pierre Defrance, M.D., Philippe Gottignies, M.D., and Jean-Louis Vincent, M.D., Ph.D., for the SOAP II Investigators*

- Prospective
- Randomized
- Double blind
- Multicenter
Administration of vasoactive drugs:

Open label NE

Study drug (DOPA vs NE)

Dose increments (study drug)*:
• 2 mcg/kg.min for DOPA
• 0.04 mcg/kg.min for NE

Maximal dose (study drug)*:
• 20 mcg/kg.min for DOPA
• 0.19 mcg/kg.min for NE

* Calculated after
Marik et al JAMA 272:1354;1994
De Backer et al CCM 31:1659;2003
2011 Patients were assessed for eligibility

332 Were excluded
- 94 Had arrhythmia
- 79 Had shock lasting >4 hr
- 73 Were not enrolled by their physician
- 38 Had major therapeutic limitation
- 20 Had been included in the study previously
- 16 Were <18 yr of age
- 12 Were brain-dead

1679 Underwent randomization

858 Were assigned to receive dopamine
- 858 Were included in intention-to-treat analysis

821 Were assigned to receive norepinephrine
- 821 Were included in intention-to-treat analysis
Comparison of dopamine and norepinephrine as the first vasoactive agent in the management of shock

De Backer et al
NEJM 362: 779; 2010

<table>
<thead>
<tr>
<th>Type of shock</th>
<th>DOPA</th>
<th>NOREPI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Septic</td>
<td>542 (63)</td>
<td>502 (61)</td>
</tr>
<tr>
<td>Cardiogenic</td>
<td>135 (16)</td>
<td>145 (18)</td>
</tr>
<tr>
<td>Hypovolemic</td>
<td>138 (16)</td>
<td>125 (15)</td>
</tr>
<tr>
<td>other</td>
<td>48 (6)</td>
<td>44 (5)</td>
</tr>
</tbody>
</table>

\[ p = 0.707 \]
Norepinephrine vs Dopamine in shock (SOAP investigators)

De Backer et al
NEJM 362: 779; 2010
Comparison of dopamine and norepinephrine as the first vasoactive agent in the management of shock

De Backer et al
NEJM 362: 779; 2010

* p<0.05
Cardiac index

De Backer et al
NEJM 362: 779; 2010
Lactate

De Backer et al
NEJM 362: 779; 2010
Norepinephrine vs Dopamine in shock (SOAP investigators)

De Backer et al
NEJM 362: 779; 2010

P = 0.07 by log-rank test

No. at Risk
Norepinephrine  821  617  553  504  467  432  412  394
Dopamine       858  611  546  494  452  426  407  386
Comparison of dopamine and norepinephrine as the first vasoactive agent in the management of shock

De Backer et al
NEJM 362: 779; 2010

Hazard Ratio (95% CI)

Type of shock
- Hypovolemic
- Cardiogenic
- Septic
- All patients

Norepinephrine Better
Dopamine Better

Septic (1044) / Cardiogenic (280) / hypovolemic (263)
Comparison of dopamine and norepinephrine as the first vasoactive agent in the management of shock

De Backer et al
NEJM 362: 779; 2010

Arrhythmias
N=200

P < 0.001

DOPA
NOREPI

Atr fib
Ventr tachyc
Ventr fib
Other trials ??
Septic shock n=252 / Single centre

Patel et al
Shock 33: 375; 2010
Arrhythmias
N= 40

DOPA
NOREPI

Patel et al
Shock 33: 375; 2010

P < 0.001

Septic shock n=252 / Single centre
## Dopamine vs norepinephrine in septic shock
### A meta-analysis

<table>
<thead>
<tr>
<th>Study</th>
<th>Norepinephrine</th>
<th>Dopamine</th>
<th>RR [95%CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Event  Total</td>
<td>Event  Total</td>
<td></td>
</tr>
<tr>
<td>Martin et al.</td>
<td>7 16</td>
<td>10 16</td>
<td>1.43 [0.73-2.80]</td>
</tr>
<tr>
<td>Marik et al.</td>
<td>5 10</td>
<td>6 10</td>
<td>1.20 [0.54-2.67]</td>
</tr>
<tr>
<td>Ruokonen et al.</td>
<td>4 5</td>
<td>3 5</td>
<td>0.75 [0.32-1.74]</td>
</tr>
<tr>
<td>Mathur et al.</td>
<td>14 25</td>
<td>19 25</td>
<td>1.36 [0.90-2.05]</td>
</tr>
<tr>
<td>De Backer et al.</td>
<td>249 502</td>
<td>291 542</td>
<td>1.08 [0.98-1.19]</td>
</tr>
<tr>
<td>Patel et al.</td>
<td>51 118</td>
<td>67 134</td>
<td>1.16 [0.89-1.51]</td>
</tr>
<tr>
<td><strong>Overall</strong></td>
<td>330 676</td>
<td>396 732</td>
<td>1.12 [1.01-1.20]</td>
</tr>
</tbody>
</table>

**RR**

- **Dopa/norepi**

**Norepi better**
Adrenergic agents:
- Dopamine
- Norepinephrine
- Epinephrine

Non-Adrenergic agents:
- Vasopressin
- (NO inhibition)
Vasopressin deficiency in septic shock

Landry et al
Circ 95:1122;1997
VASOPRESSIN IN PATIENTS WITH SEPTIC SHOCK

Vasopressin 0.03-0.05 u/min in 5 patients with septic shock

Mean arterial Pressure
mmHg

P<0.01

Landry et al
CCM 25:1279;1997
The pro side
- increases blood pressure
- spares vasopressors
- improves renal function (?)
- less arrhythmias

The con side
- high doses are detrimental
- decreases cardiac output
- promotes gut ischemia (?)
- impairs liver function (?)
- Impact on platelets (?)
802 septic shock pts

VASST
Russell et al
NEJM 358:877;2008
Mortality (%) according to severity at baseline

More severe n= 400 (NE > 15 mcg/min)  

Less severe n= 378 (NE < 15 mcg/min)
Vasopressin vs Noradrenaline as Initial therapy in Septic Shock (VANISH): a randomised controlled trial.

A double-blind parallel group factorial (2x2) randomised controlled trial of vasopressin (up to 0.06 u/min) vs noradrenaline, and hydrocortisone vs placebo in septic shock.

Gordon A et al

400 pts

To be presented at ESICM LIVES 2015
LNNMA IN PATIENTS WITH SEPTIC SHOCK

Lopez et al
CCM 32:21;2004

Placebo

Log-Rank Test p<.001
Wilcoxon Test p<.001

Survival Distribution Function

Day of Study

LNNMA
• Correction of hypotension (MAP ~65 mmHg)

• MAP higher than 65-70 mmHg do not seem to further improve tissue perfusion

• Adrenergic agents as first line agent, with norepinephrine as the 1st choice agent

• Vasopressin appears to be promising in septic shock
Thank you