Evaluating need for fluids

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The goals

- Adequate tissue perfusion that results in adequate delivery of oxygen (and other nutrients) and removal of waste products in order to preserve organ function

  - What determines blood flow?
    - Venous Return - Cardiac Output
    - Blood pressure
    - Tone of the pre-capillary sphincters
    - CVP - Resistance to VR

Fluids are NOT a therapy but sometimes an effective way to increase global/regional blood flow
Approach

• What is the clinical problem?

• Would the problem be solved by improving perfusion pressure, improving cardiac output (or it’s distribution) or both?
  • is the improvement in perfusion pressure best achieved by increasing MAP with vasopressor or by increasing CO (fluids) or decreasing post capillary pressure (CVP) or combinations?
  • is the improvement in cardiac output best achieved by fluids or by improving myocardial performance (increase inotropy, decrease RV or LV after load optimizing heart rate, increasing diastolic dilatation, decreasing ejection force etc)?

• did the intervention have the expected effect and did the clinical problem partly/completely resolve?
Hi Glenn,

First – RELIEF is a milestone in post-operative therapy!

The findings are clear: A fluid liberal regimen that delivers about 6 L in the first 24 hours of surgery (from incision to 24 hr later) is superior.

A restrictive fluid regimen that delivers on 3.7 L (about 2.5 L less) leads to

1. More oliguria
2. More vasopressor use
3. More AKI
4. More RRT
5. More surgical site infection

Epidemiology Based Fluid Resuscitation
## Table 2. Blood Loss and Administered Intravenous-Fluid Volumes.*

<table>
<thead>
<tr>
<th>Variable</th>
<th>Restrictive Fluid (N = 1490)</th>
<th>Liberal Fluid (N = 1493)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>At 24 hr after surgery</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median cumulative total for intravenous fluids (IQR) — ml</td>
<td>3671</td>
<td>6146</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

*Results were largely unchanged after multiple imputation.
Conclusions

In conclusion, our study shows that **it is safe to allow peri-operative urine output to drop to 0.2 mL/kg.h**, rather than pursuing the standard target of 0.5 mL/kg/h, in the majority of patients undergoing abdominal surgery who do not have significant risk factors for AKI. Importantly, this simple change in perioperative practice spares significant amounts of intravenous fluids.
Conservative fluid management or deresuscitation for patients with sepsis or acute respiratory distress syndrome following the resuscitation phase of critical illness


**Conclusions:** In adults and children with ARDS, sepsis or SIRS, a conservative or deresuscitative fluid strategy results in an increased number of ventilator-free days and a decreased length of ICU stay compared with a liberal strategy or standard care. The effect on mortality remains uncertain.

**Large randomized trials are needed to determine optimal fluid strategies in critical illness.**
Why fluids in shock?

To increase Venous Return with the specific goal to improve tissue perfusion in order to restore/improve tissue oxygen delivery so that cellular respiration and viability is preserved to sustain organ function.
Understanding venous return

Baseline
Venous return 5 L·min⁻¹

Effect of a Fluid Bolus
Venous return 6 L·min⁻¹
Changes in the mean systemic filling pressure during a fluid challenge in postsurgical intensive care patients

The effect of fluid resuscitation on the effective circulating volume in patients undergoing liver surgery: a post-hoc analysis of a randomized controlled trial

JJ Vos, AF Kalmar, HGD Hendriks, J Bakker, TWL Scheeren

J Clin Monit Comput 2018;32(1):73-80

- 30 patients following major hepatic resection
  - ✓ 500 ml fluid in 30 minutes
  - ✓ age 57± 13
  - ✓ 14 male
  - ✓ BMI 26±3.9 ~ BSA 1.96±0.18
  - ✓ NE at baseline: 0.15 (0.01-0.74)
The effect of fluid resuscitation on the effective circulating volume in patients undergoing liver surgery: a post-hoc analysis of a randomized controlled trial

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J Clin Monit Comput 2018;32(1):73-80

\[ r^2 = 0.75 \]
\[ p < 0.0001 \]
The effect of fluid resuscitation on the effective circulating volume in patients undergoing liver surgery: a post-hoc analysis of a randomized controlled trial

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Discussion

In this study, we evaluated the effects of fluid administration on the effective circulating blood volume using a cardiovascular model. Firstly, the model-derived variables closely followed theoretically predicted volume-induced changes and allow a more detailed differentiation between fluid responders and non-responders. Pmsa increased in both groups following fluid administration. Yet, in responders, CVP did not change and as such, Pvr (Pmsa–CVP) increased which led to an increase in CI. In other words, the heart was able to generate more output from the increase in venous return. In non-responders, CVP increased to a similar extent as Pmsa and the increase in CVP helps reducing venous return. Importantly, EH, decreased as the heart was unable to handle the increase in venous return, while in responders EH remained stable, i.e. the efficiency of the heart in handling an increase in venous return was maintained.

Secondly, the observation that PPV, SVV and Pvr predict FR equivalently, might suggest that Pvr can be used alternatively for the prediction of FR in case the former variables cannot be used.

4.1 Physiologic differentiation between fluid responders and non-responders

CO is determined by the effective circulating blood volume (ECBV), the resistance to venous return and the pressure within the right atrium \[25\]. Pmsa, as a surrogate of ECBV, is determined both by vascular filling and tone and provides a pressure variable for the determination of flow, i.e. venous return. Subsequently, Pvr functions as the driving pressure for generating venous return and hence, CO. The current data support this theory because, according to our definition of FR (i.e. an increase in CI > 20%), Pvr increased in responders but remained unchanged in non-responders—a finding that was previously also observed in post-cardiac surgery patients receiving even a more "subtle" fluid challenge (250 ml) in comparison with our study \[13\]. In physiologic terms, these observations suggest that in fluid responders, the heart is able to handle the increase in Pmsa by generating more output, numerically reflected by an increase in Pvr. In non-responders, the increase in Pmsa cannot be handled by the heart. CVP increases passively, as a consequence of both increased venous return and Pvr (mmHg)

\[\Delta Pvr (\text{mmHg})\]

\[\Delta CI (\text{L min}^{-1} \text{m}^{-2})\]

\(R^2 = 0.93\)

(closed circle responders, open circle non-responders)
Septic vs Obstructive shock


- **Cardiac Index**
  - BL
  - T1
  - T2
  - T3

- **CVP**
  - BL
  - T1
  - T2
  - T3

- **Fluids**
  - BL
  - T1
  - T2
  - T3

- **UO**
  - BL
  - T1
  - T2
  - T3

**Legend:**
- **Sepsis**
- **Tamponade**

**Key Points:**
- **T1** induction of shock by decreasing CO to 50% of BL
- **T2** initial resuscitation to restore BL CO
- **T3** fluid resuscitation to fluid unresponsiveness (dCO<10%)

* sepsis vs tamponade
Critical medicine investigations

Regional perfusion can be attributed to the increase in cardiac output. Nevertheless, the time frame of our model might have been too short for the development of profound tissue edema, which is a very common problem in patients and as such might hamper the translation of our results to clinical practice.

Third, SDF imaging is a valuable technique, but it is based on semiquantitative analyses. Therefore, data reliability may be affected by technical expertise and interobserver bias despite the use of standardized analysis software. Finally, we recognize that the sample size was limited for a multivariate analysis between the two groups. However, the sample size was adequate to address the specific aims of this study. Definitive determinations of the relationship between microcirculatory and systemic variables in sepsis require a more robust sample of longitudinal data.

CONCLUSIONS

Resuscitation of cardiac output to preshock levels produced a full recovery of the peripheral circulation in obstructive but not in endotoxemic shock. Apparently, the relationship between the systemic circulation and different microvascular and different peripheral perfusion variables is dependent on the underlying cause of circulatory shock. Our data show that different microvascular and peripheral perfusion variables can be used to assess the adequacy of hemodynamic resuscitation during different types of shock. Supranormal optimization of cardiac output is needed to restore these different variables in sepsis but might still not lead to full recovery of tissue oxygenation. Further research is required to assess the reproducibility of our findings in a clinical setting and further elucidate the relationship between systemic and different peripheral circulation and oxygenation variables as targets for systemic therapeutic interventions during the early phase of septic shock.

ACKNOWLEDGMENT

We thank P. Specht for her technical assistance in the experimental setup.

# Septic vs Obstructive shock


<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>T1</th>
<th>T2</th>
<th>T3</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Lactate</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>S</td>
<td>1.1(0.6)</td>
<td>5.5(1.6)</td>
<td>4.0(2.1)</td>
<td>3.6(1.6)</td>
</tr>
<tr>
<td>T</td>
<td>0.7(0.1)</td>
<td>5.1(1.5)</td>
<td>4.2(1.2)</td>
<td>2.1(0.8)</td>
</tr>
<tr>
<td><strong>DO$_2$</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>S</td>
<td>502(145)</td>
<td>33(101)</td>
<td>513(125)</td>
<td>732(184)</td>
</tr>
<tr>
<td>T</td>
<td>522(48)</td>
<td>212(25)</td>
<td>547(76)</td>
<td>506(87)</td>
</tr>
<tr>
<td><strong>VO$_2$</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>S</td>
<td>174(78)</td>
<td>178(20)</td>
<td>231(128)</td>
<td>267(102)</td>
</tr>
<tr>
<td>T</td>
<td>195(48)</td>
<td>180(28)</td>
<td>218(34)</td>
<td>183(54)</td>
</tr>
</tbody>
</table>
Urine output in experimental hemorrhagic shock
Rat

Urine output in mL/h:
- **HES-RA**
- Hemorrhagic shock

Kidney cortical microPO$_2$:

Time (min):
- BL
- Shock
- R-30
- R-60

Microcirculatory PO$_2$ (mmHg):
Hemodynamics

LPS shock: fluids - NE

MAP (mm Hg)

Time Point

Arterial Blood Flow

Time Point

Legend:
- LPS
- LPS-RA
- LPS-RN
Kidney microcirculatory PO$_2$

LPS shock: fluids - NE
Unintended consequences; fluid resuscitation worsens shock in an ovine model of endotoxemia

Byrne et al Am J Respir Crit Care Med 2018 (in press)

**Figure 1: experimental timeline**

Schematic representation of the experimental protocol. Anesthesia and surgical instrumentation were followed by a 1 hour stabilization period during which no interventions were performed. Endotoxemic shock was induced with a 4 hour escalating dose endotoxin infusion. Resuscitation occurred in the last hour of the endotoxin infusion with animals either receiving a 40ml/kg bolus of 0.9% saline or commencing protocolized haemodynamic support. After resuscitation all animals were monitored for a further 12 hours during which both groups received protocolized haemodynamic and respiratory support. Blood gases were taken hourly during the 16 hours of the experiment and analyzed immediately on an ABL800 Flex (Radiometer, Copenhagen, Denmark). During the monitoring period hourly microdialysis samples were recovered and analyzed for lactate and pyruvate on an ISCUS clinical microdialysis analyzer (Hammarby Fabriksväg, Stockholm, Sweden). The bottom scale indicates the blood sampling timepoints throughout the experiment. * Indicates timepoints at which blood was taken for serum cytokines (IL-1β, IL-6, IL-8, IL-10 and TNFα), troponin, ANP, BNP, hyaluronan and creatinine. ‡ Indicates timepoints at which blood was taken to measure hyaluronan only. ** Indicates timepoints at which blood was taken to measure serum cytokines and hyaluronan. ‡‡ Indicates timepoints blood was taken to measure serum cytokines.

Cytokine measurements were performed using an in house ELISA for interleukin 1-beta (IL-1β), interleukin 6 (IL-6), interleukin 8 (IL-8), interleukin 10 (IL-10) and tumour necrosis factor alpha (TNFα). The methodology of the cytokine analysis has been published previously. Cardiac troponin I was measured using Beckman Coulter Unicel DxI AccuTnI+3 immunoassay (Beckman Coulter, Brea, CA, USA). Hyaluronan was measured using a hyaluronan quantikine ELISA Kit (R&D systems, Minneapolis, USA). Serum ANP and BNP were measured using custom ovine radioimmunoassay (Endolab, Christchurch Heart Institute, Christchurch, New Zealand). Creatinine was measured using a COBAS Integra 400 blood chemistry analyzer (Roche Diagnostics, Australia).
Unintended consequences; fluid resuscitation worsens shock in an ovine model of endotoxemia

Byrne et al Am J Respir Crit Care Med 2018 (in press)
Unintended consequences; fluid resuscitation worsens shock in an ovine model of endotoxemia

Byrne et al Am J Respir Crit Care Med 2018 (in press)
Elevated central venous pressure is associated with impairment of microcirculatory blood flow in sepsis: a hypothesis generating post hoc analysis

Vellinga et al. BMC Anesthesiology 2013, 13:17
Pilot study (6 hours) in 30 patients randomised to
- SV optimisation guided FR (control)
- PP only patients with abnormal PP received FR unless CI<2.5 L/min.M²
  - 3 out of CRT - Perfusion Index - Fore arm-Finger temp - StO₂
No differences in baseline data
Abdominal sepsis most prominent (18 patients)
All patients on vasopressors
### Early peripheral perfusion guided fluid therapy in patients with septic shock


<table>
<thead>
<tr>
<th></th>
<th>CONTROL</th>
<th>PROTOCOL</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fluid Balance 0-6h</td>
<td>6069 (1715)</td>
<td>4227 (1081)</td>
<td>0.65</td>
</tr>
<tr>
<td>(treatment)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fluid Balance 6-72h</td>
<td>10028 (941)</td>
<td>7565 (982)</td>
<td>0.08</td>
</tr>
<tr>
<td>(observation)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MV (h)</td>
<td>74 (24-129)</td>
<td>63 (3-144)</td>
<td>0.68</td>
</tr>
<tr>
<td>Hospital Stay (d)</td>
<td>34 (8)</td>
<td>16 (3)</td>
<td>0.05</td>
</tr>
</tbody>
</table>
## Early peripheral perfusion guided fluid therapy in patients with septic shock


<table>
<thead>
<tr>
<th></th>
<th>CONTROL</th>
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</tr>
</thead>
<tbody>
<tr>
<td>SOFA (0-72)</td>
<td>11.0 (5.3-15.3)</td>
<td>8.3 (5.5-13.1)</td>
</tr>
<tr>
<td>Mean difference (mixed linear model)</td>
<td><strong>-2.23 (-4.98–0.51)</strong></td>
<td></td>
</tr>
</tbody>
</table>
Early start of vasopressor limiting fluid resuscitation volume

Gustavo Ospina (not published)

Fluid Resuscitation volume before start VP

VP within 1h: **0.0** [0.0-8.8 mL/kg]
VP later 1h: **22.5** [12.5-35.8 mL/kg]**

**P<0.001**
Are you afraid to start vasopressors early in septic shock?
The results of FENICE should be a wake-up call to all of us. We need to acknowledge that we hardly understand the basics of this complex area. We need to define or redefine fluid resuscitation, fluid challenge, fluid expansion, fluid bolus, fluid responsiveness and fluid therapy.

We propose that the intensive care societies and existing research networks and trial groups place fluid resuscitation at the top of the research agenda and promote collaborative efforts covering all aspects, including physiology, experimental medicine, clinical research, implementation sciences and industry. Different organizational frameworks will likely be needed to ensure the buy-in from all of the aforementioned; we trust the academic leadership of intensive care medicine to do what is right.
Conclusions

- Fluids should be used to deal with a clinical problem that is likely to be solved by an increase in cardiac output (and it’s possible effect on MAP)
- Fluids should be given to increase MSFP without a significant rise in CVP
- Fluids should NOT be given to increase CVP
- Fluids should NOT be administered in a predefined total volume
  - ✓ Unless you have to drive blinded
- Fluids should be administered in single volumes (250-500mL) and the (side)effect should be assessed after each infusion
- Fluid restriction can be used in many cases
Reasons to die in space

- Not following the rules exactly as written
- Following the rules exactly as written