Vasoactive agents in liver transplant anesthesia: hemodynamic optimization tactics

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Liver transplantation stats

- Approx. **25,000** liver transplants were conducted globally in 2013
- More than **5,500** liver transplants are performed each year in Europe
- Cirrhosis is the leading cause of adult liver transplants.
- Based on data from the European Liver Transplant Registry, **118,441** liver transplants performed in 28 countries between 1968 and 2014
- 1-year survival: more than 9 out of 10
- 5-year survival: 8 out of 10
- Many recipients living for up to 20 years
Where we are, who we are, what we do

- Level 2 solid organ transplantation program
- UNOS area 6, collecting donor organs from 6 states of USA: WA, OR, ID, MO, AK, HI

- Single organ transplants, per year:
  - heart
  - lungs
  - liver – about 90-100
  - kidney – about 150-170

- Combine organ transplants:
  - liver & kidney – about 10
  - kidney & pancreas about 10-15
  - liver & intestine – 1-2
  - heart & liver – 1
  - lungs & liver – 1
Disclosure

Regretfully, I have nothing to disclose:
- no financial/vested interests
- no conflict of interests

I have interest in research and practice improvement only
Presentation outline

- Hemodynamic regulation in the End-Stage Liver Disease patient
- Factors contributing to the hemodynamic profile
- Hemodynamic optimization: what, when, and how to correct
- Vaso-active agents use
Anesthesia setup I

**Monitoring:**

Routine: ECG, Non-invasive BP, Pulse oxymetry; arterial line (1 or 2)

PA (Swan-Ganz) catheter: CO, CI, SVR, SvO₂

TEE

Bi-spherical Index (BIS)

Thrombo-elastography: PT/PPT, INR, PLT and more
Anesthesia setup II

Vascular access and volume management

Large-bore triple-lumen catheter/PA introducer in IJ

Belmont® rapid infusion pump

Maintenance

Isoflurane

Fentanyl continuous infusion, 3-5 mcg/kg/h

Cis-Atracurium infusion, 0.8-1 mcg/kg/min
Hemodynamic goals

- MAP: 75-85 mmHg
- HR: <100/min
- CVP: < 20 mmHg
- MPAP: < 25 mmHg
- CO/Cl: >4 L/min / >2 L/min*m²
- SVR: > 500 dynes / sec / cm⁻⁵
- Mixed Venous SvO2: >75%
Vasomotor tone regulation in ESLD: vasoplegia

- Cardiovascular response to catecholamines is substantially attenuated in ESLD patients
- Sensitivity of β-adrenoreceptors is relatively decreased
- Plasma free norepinephrine and epinephrine levels are significantly higher
- Fraction of epinephrine contributing to total catecholamines increased up to 50% (normal: about 17%)
- Dopamine concentration is unchanged
- As a result, **systemic vasoplegia** due to low SVR is typical for ESLD
Hepatic Blood Flow: Impact of Anesthesia-related factors

**Increase:**
- Dopamine, (3mcg/kg/min)
- Hypercapnia
- Acidosis
- Hypoxemia (+/-)

**Decrease:**
- PPV (+PEEP)
- β - blockers, α - agonists, H₂ blockers
- Hypocapnia
- Alkalosis
- Hyperglycemia

- All anesthetic techniques in the absence of surgical stimulation decrease HBF by 30%.
- Isoflurane, Sevoflurane and Desflurane maintain HBF
- Fentanyl has no effect on HBF
Dissection phase

- Drop of intra-abdominal pressure
- Laparotomy ascites evacuation
- Rapid splanchnic volume increase (mesenteric blood pooling)
- Decrease of venous return
- Blood loss, fluid shift, acidosis
- CO/CI and MABP decrease
Anhepatic phase: Portal and Caval cross-clamp

- Portal clamp: drop of venous return is variable (loss of 20-30% of baseline venous return)
- With developed porto-caval collaterals (long-standing portal hypertension) – loss of 15 to 20% of pre-clamp venous return
- IVC complete clamp: approximately 50% decrease of venous return
- IVC partial clamp: variable, 25 - 50% decrease of venous return
Veno-venous bypass (VVB)

- VVB provides flow rates ranged from 1.5 to 3.6 L/min
- VVB is advocated in cases:
  - total IVC clamp
  - 30% drop in MABP
  - 50% decrease in CI during 5 min test- IVC cross-clamping period
Veno-venous bypass: pro’ and contra’

**Pros:**
- Preserving the CO/CI, maintaining hemodynamic stability
- Maintaining CBF, especially in FHF cases
- Maintaining the RBF and kidney function (?)
- Longer anhepatic phase
- Blood loss reduction (?)
- Improving the clinical outcome (?)
- Lower lactate

**Cons:**
- Pulmonary air emboli, thrombosis
- No evidence of maintaining normal perfusion of abdominal organs and preserving renal function
- Longer operative and warm ischemia time
- Higher rate of post-reperfusion syndrome
- Increasing bleeding
- No evidence for improving the clinical outcome
- Higher procedure cost
Liver graft reperfusion

Myocardial injury: arrhythmias, asystolic arrest

Vasoplegia

Decrease of CO/CI, SVR and MABP

Temperature drop

Decreased sensitivity to catecholamines / vasoactive agents

lactic acidosis

Hemodilution

Blood loss

Anemia, hypovolemia

RV overload; PAP and CVP increase

Factors deficit + consumption, Hemodilution

Fibrinolysis
Post-reperfusion syndrome

- PRS is defined as a:
  - > 30% of MABP decrease from that in the anhepatic stage,
  - for longer than for 1 min, during the first 5 min after reperfusion of the liver graft.
Lactic Acidosis in ESLD may be beneficial!

- Decreased synthesis of hepatic pyruvate dehydrogenase, hence impaired lactate – to – bicarbonate conversion
- Acidosis itself decreases lactate clearance
- Severe LA (lactate > 5 mEq/l) is associated with mortality rates 50-56%
- Short duration acidosis prevents anoxic cell death, and reoxygenation at low pH prevents cell toxicity
- Reperfusion at low pH blocks increase of mitochondrial membrane permeability, which allows mitochondrial re-polarization and prevents cell death

However,
Lactate during liver transplant

Vitin A. et al., 2010
## Porto-pulmonary syndrome

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>MPAP</td>
<td>&gt;25 mmHg at rest</td>
</tr>
<tr>
<td></td>
<td>&gt;30 mmHg with exercise/stress</td>
</tr>
<tr>
<td>PCWP</td>
<td>&lt;15 mmHg</td>
</tr>
<tr>
<td>PVR</td>
<td>&gt;120 dynes/sec/cm(^5)</td>
</tr>
<tr>
<td>Trans-pulmonary gradient</td>
<td>&gt; 10 mmHg</td>
</tr>
</tbody>
</table>
Intra-operative Pulm HTN management

- Fluid restriction (especially crystalloids)
- Diuretics (Furosemide, not Mannitol)
- Nitroglycerine infusion, 1-1.5 mcg/kg/min
- Epoprostenol, 2-12 mcg/kg/min
- CVVH / hemodialysis
- Nitric Oxide inhalation 20-25 ppm
- **Vasopressin** decreases PAP while maintaining systemic MABP
Blood loss: predisposing factors

1. MELD score >25
2. Portal hypertension
3. Pre-existing + ongoing consumption & dilution coagulopathy
4. Long, traumatic liver dissection
5. “Hostile abdomen” – s/p laparotomy
6. Re-do OLT
7. Long ischemia times
8. Aged/marginal quality donor organ
9. Donor-recipient organ size discrepancy
Hemotransfusion during OLT

• Different surgical techniques, anesthesia protocols, transfusion triggers and institutional practices

• RBCs use: 10 y. ago – 20 units, currently: 1-5 to 0 (average)

• Modern trends: restriction of RBCs and other blood products use to absolutely necessary minimum; use of Cell Saver

• Massive RBCs, FFP and PLT transfusions are independent predictors of negative impact on recipient and graft survival
Ways of blood loss reduction

1. Piggy-back technique with IVC preservation – partial IVC clamp
2. Maintaining the low CVP (controversial)
3. Minimum hemodilution: limit crystalloids infusion
4. Vasoactive agents use
“Low CVP” paradigm I

To maintain CVP around 5-7 mmHg:

- crystalloid, colloid and blood products volume restrictions,
- diuretics,
- Nitroglycerine
- Anti-Trendelenburg position
“Low CVP” paradigm II

Pro:

• potential for blood loss decrease
• lowered transfusion requirements
• oxygen delivery improvement to the liver graft by creating a greater MABP/CVP gradient

Contra:

• Increased post-op renal failure
• Increased 30-days mortality
• increased dosage of vasopressors - > peripheral vasoconstriction
• promoting metabolic acidosis

“CVP decrease should be avoided in liver transplant patients” (Ozier Y et al., 2008)
Vasoactive agents use

- **Routine use** (doses in mcg/kg/min):
  - Phenylephrine, 0.01 – 1.5
  - Norepinephrine, 0.01-0.5

- **Optional**:
  - Epinephrine, 0.01 – 0.05
  - Dopamine, 3
  - Vasopressin, 0.04 U/min
Can we do five treatments at a time and speed up this process?

I was just passing by looking for mice.
Vasopressin

- Increases SVR, decreases MPAP, normalizes CO/CI, and, potentially, CVP.
- Maintains mean BP
- Decreases portal pressure, HBF and SBF
- Improves impaired renal function, enhances diuresis, thus improves Na balance and lactate elimination
- Enhances platelet aggregation and increases levels of Pro- factor VIII and von Willebrand factor
- Does not promote lactic acidosis
- *Seems to be able to decrease blood loss during pre- and anhepatic phases of OLT*
Vasoactive agents timing/dosage during OLT

Phenylephrine
- 0.2-0.4

Epinephrine
- 0.1-0.2

Norepinephrine
- 0.6-1

Epinephrine
- 0.01-0.03

Dopamine 3

Vasopressin
- 0.04 U

Norepinephrine
- 0.01-0.5

Epinephrine
- 1-1.5

Vasopressin
- 1-2 U

Nitroglycerin
- 1-1.5

CaCl₂ 1-2g;
Phenylephrine 100-500ug
Ephedrine 10-15 mg
Epinephrine 0.1-1mg
Vasopressin 1-2 U
Methylene blue 1-1.5 mcg/kg
Sodium bicarbonate
Circulatory pathophysiology and options in hemodynamic management during adult liver transplantation.

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Hemodynamic effects of low-dose vasopressin vs phenylephrine

Vasopressin vs phenylephrine & epinephrine effect on blood loss

- The EBL before liver graft reperfusion 50.2% lower ($p=0.0094$) and TBL 38.8% lower ($p=0.0548$), than in control (Phenyl/Epinephrine) group (Vitin A et al., 2010)
Conclusions

- Phenylephrine may be a first choice
- Vasopressin may be used during dissection and anhepatic stages; use after reperfusion remains controversial.
- Epinephrine may be used throughout, but should be discontinued ASAP
- Albeit efficient, Norepinephrine appears to be the less suitable drug
- Nitroglycerine may be effective for post-reperfusion PAP surge correction
Questions?

Thanks for attention!
Welcome to Seattle!