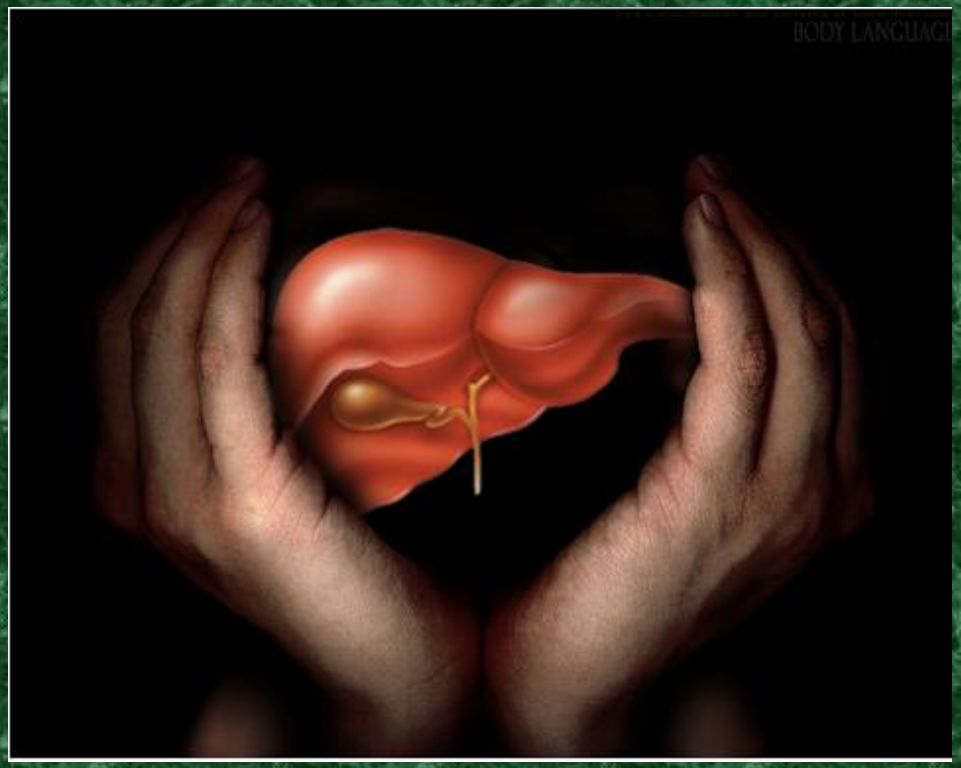

Vasoactive agents in liver transplant anesthesia: hemodynamic optimization tactics

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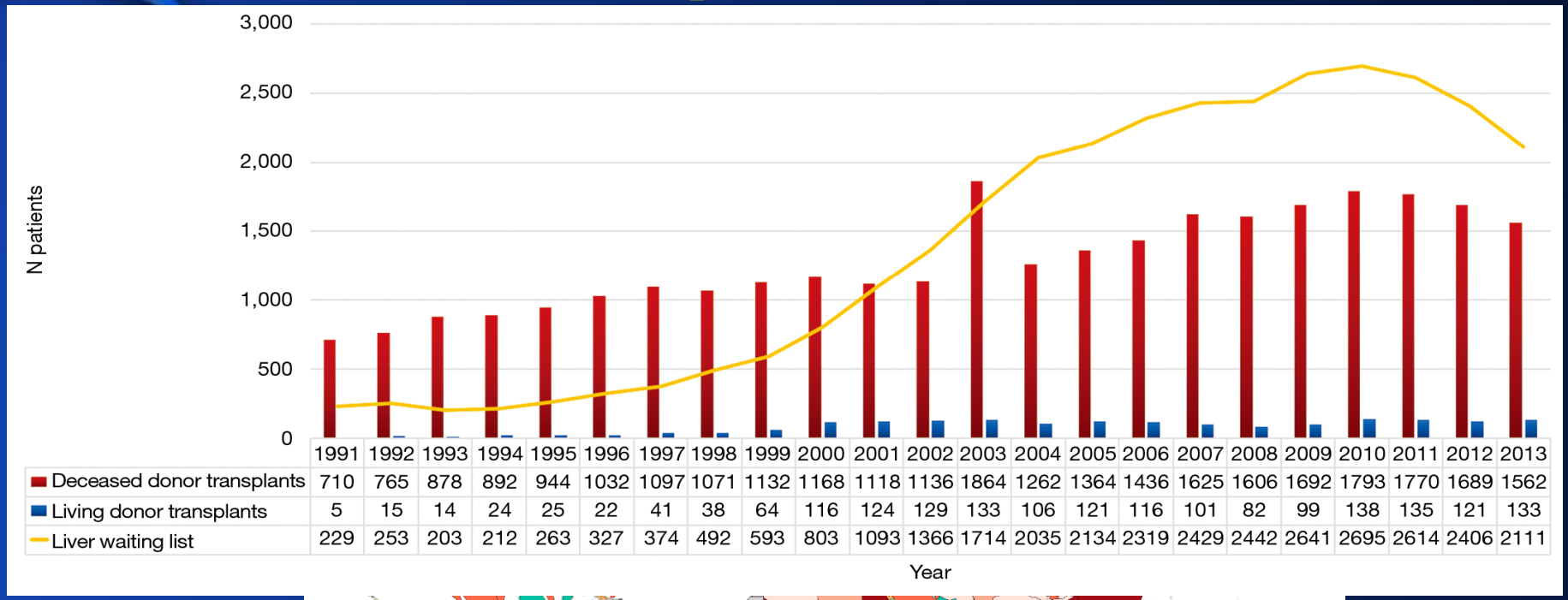
University of Washington Medical Center, Seattle, WA, USA

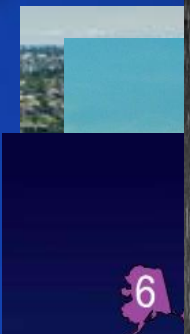
Liver transplantation stats

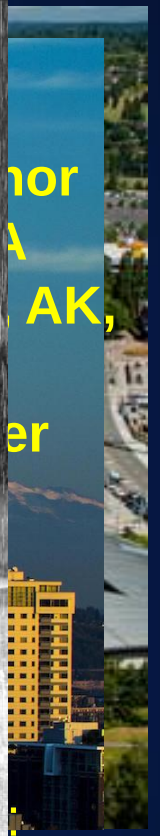


	1991	1992	1993	1994	1995	1996	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013
Deceased donor transplants	710	765	878	892	944	1032	1097	1071	1132	1168	1118	1136	1864	1262	1364	1436	1625	1606	1692	1793	1770	1689	1562
Living donor transplants	5	15	14	24	25	22	41	38	64	116	124	129	133	106	121	116	101	82	99	138	135	121	133
Liver waiting list	229	253	203	212	263	327	374	492	593	803	1093	1366	1714	2035	2134	2319	2429	2442	2641	2695	2614	2406	2111

- 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: about 8 out of 10
- Many recipients living for up to 20 years

Where we are, who we are, what we do





Disclosure

Regretfully, I have nothing to disclose:

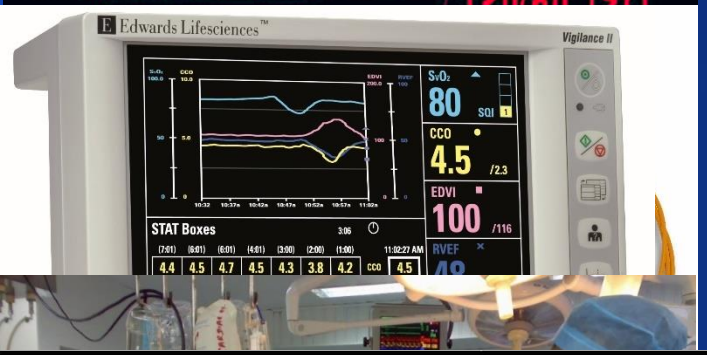
- no financial/vested interests
- no conflict of interests

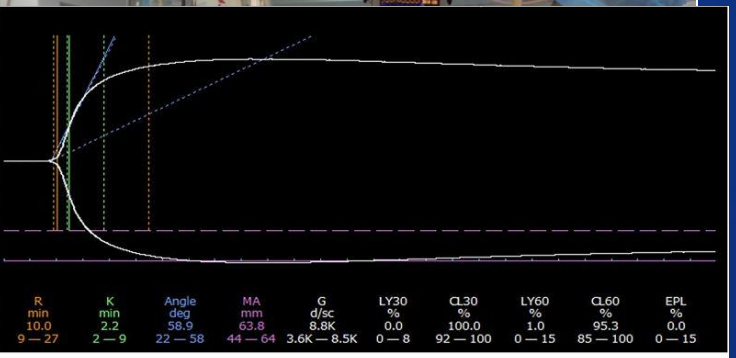
I have interest in research and practice improvement ***only***

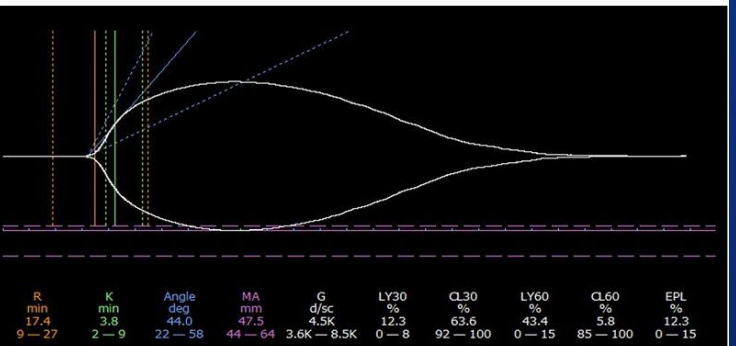
Presentation outline

- 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)

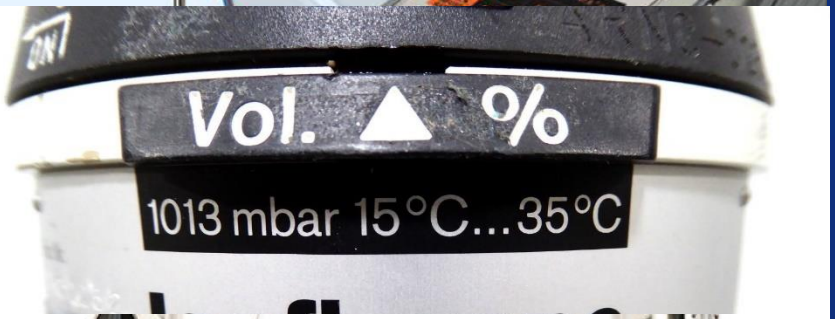
PA (Swan-Ganz) catheter: CO, CI, SVR, SvO_2

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

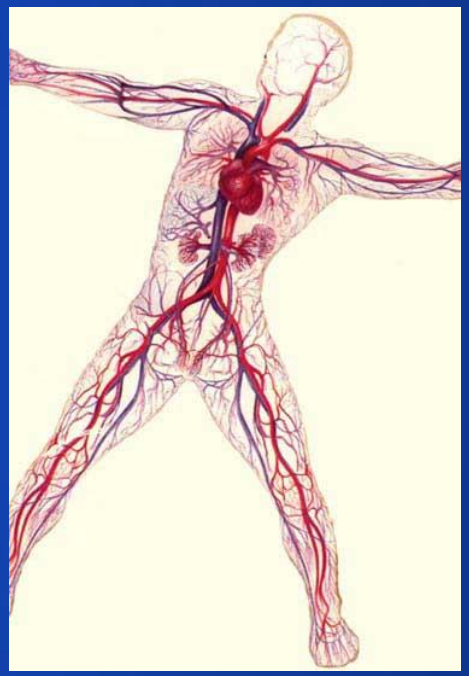
Fentanyl continuous infusion, 3-5 mcg/kg/h

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/CI: >4 L/min / >2 L/min*m^2
- SVR: > 500 dynes / sec / cm^{-5}
- Mixed Venous SvO2: >75%

Vasomotor tone regulation in ESLD: vasoplegia

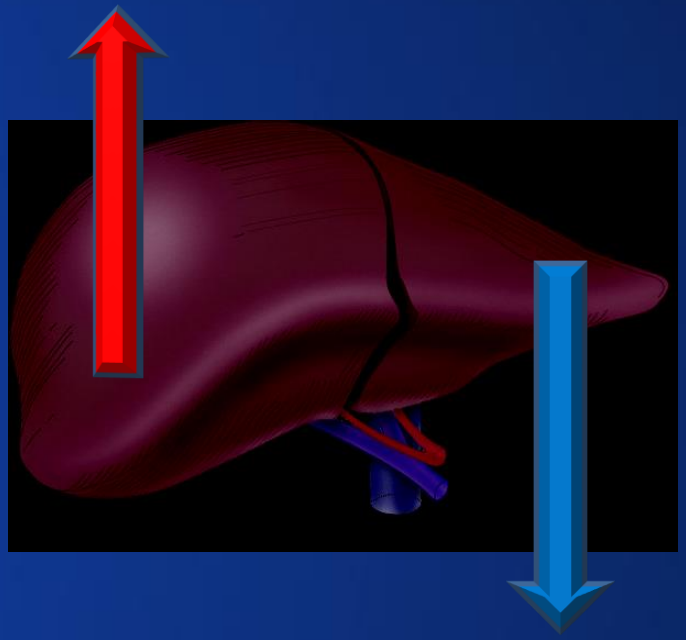


- Cardiovascular response to catecholamines is substantially attenuated in ESLD patients
- Sensitivity of β-adrenorecpetors is relatively decreased
- Plasma free norepinephrine and epinephrine levels are significantly higher
- Fraction of epinephrine contributing to total catecholamines increased up 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, H_2 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

Laparotomy ascites evacuation

Drop of intra-abdominal pressure

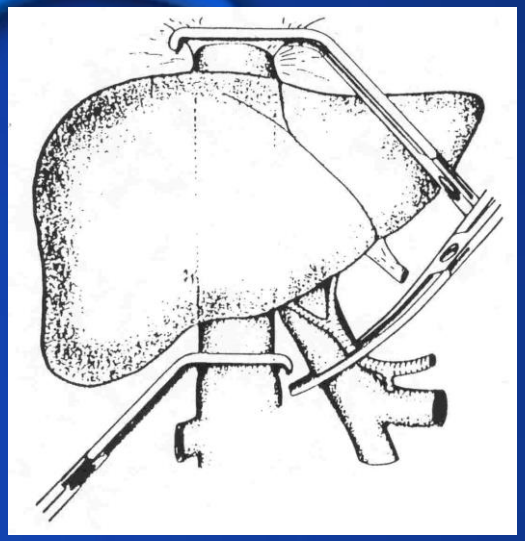
Rapid splanchnic volume increase (mesenteric blood pooling)

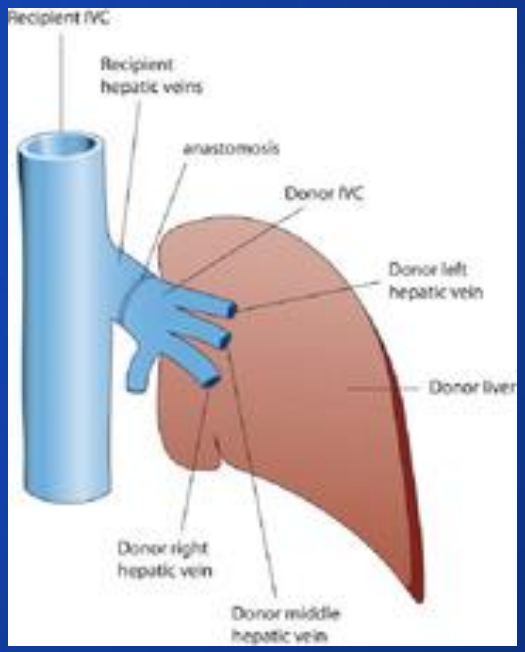
Decrease of venous return

Blood loss, fluid shift, acidosis

CO/CI and MABP decrease

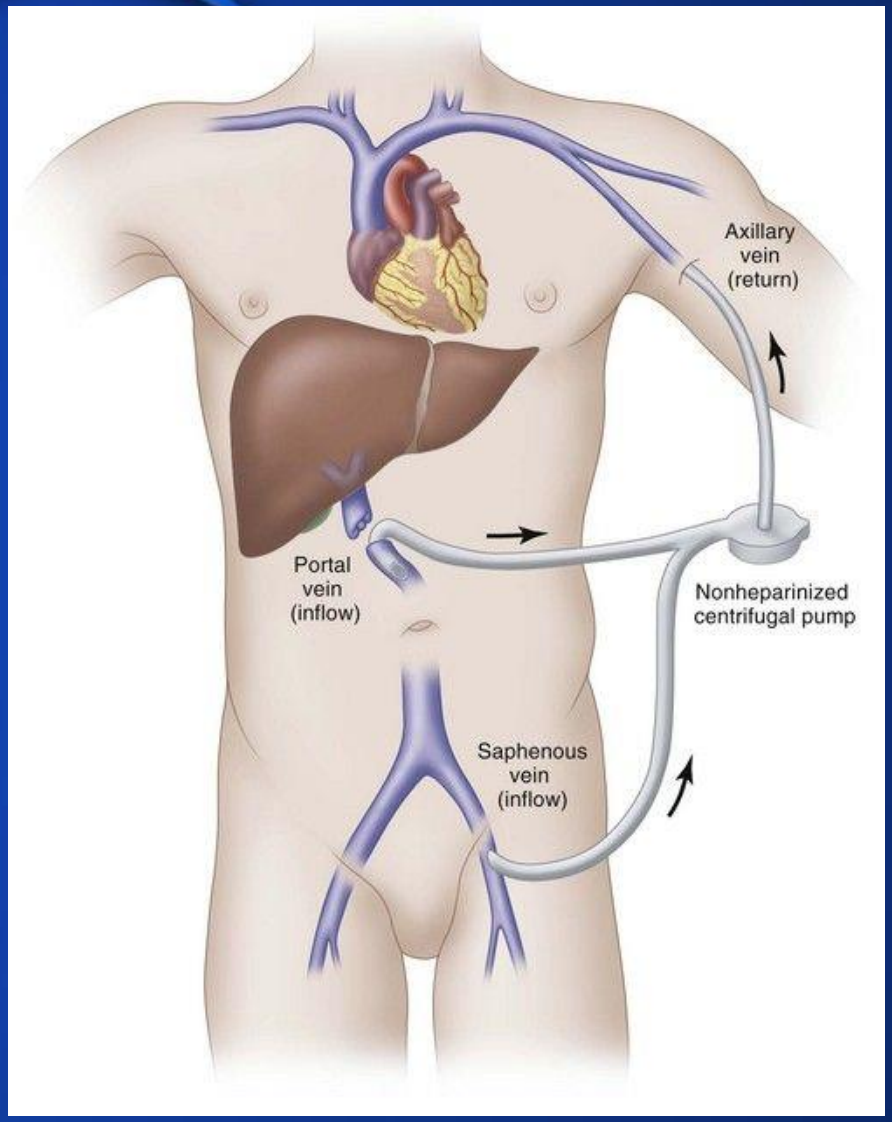
Anhepatic phase: Portal and Caval cross-clamp





- 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

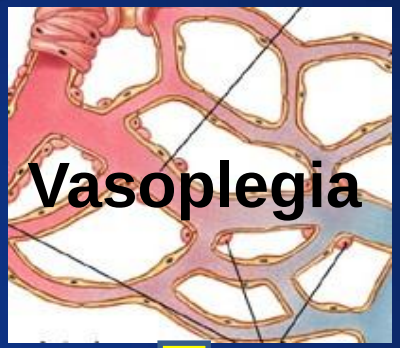
Veno-venous bypass: pro' and contra'

- 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

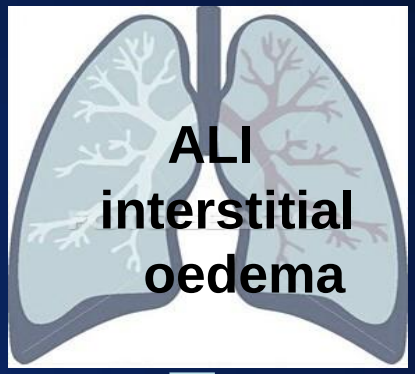
- Pulmonary air emboli, thrombosis
- No evidence of maintaining normal perfusion of abdominal organs and preserving renal function
- Longer operative and warm ischemia time
- Higher rate of post-reperfusion syndrome
- Increasing bleeding
- No evidence for improving the clinical outcome
- Higher procedure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

Liver graft reperfusion

Myocardial injury: arrythmias, asystolic arrest

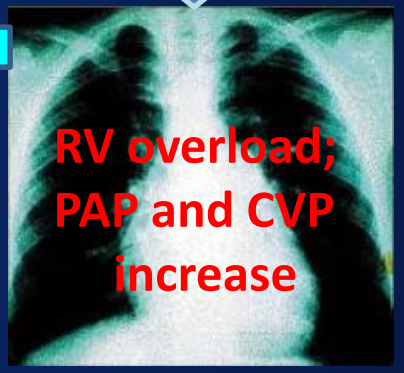


Vasoplegia



ALI interstitial oedema

Decrease of CO/CI, SVR and MABP



RV overload; PAP and CVP increase

Temperature drop

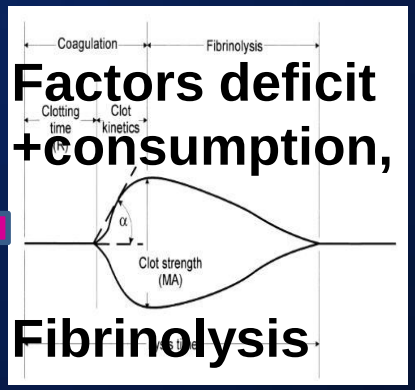
Decreased sensitivity to catecholamines /vasoactive agents

lactic acidosis

Hemodilution

Blood loss

Anemia, hypovolemia

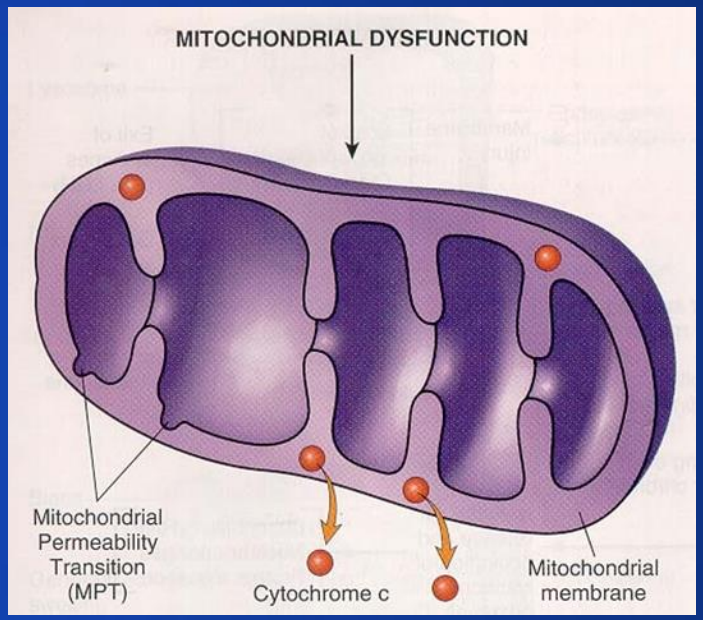


Factors deficit +consumption, Fibrinolysis

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!

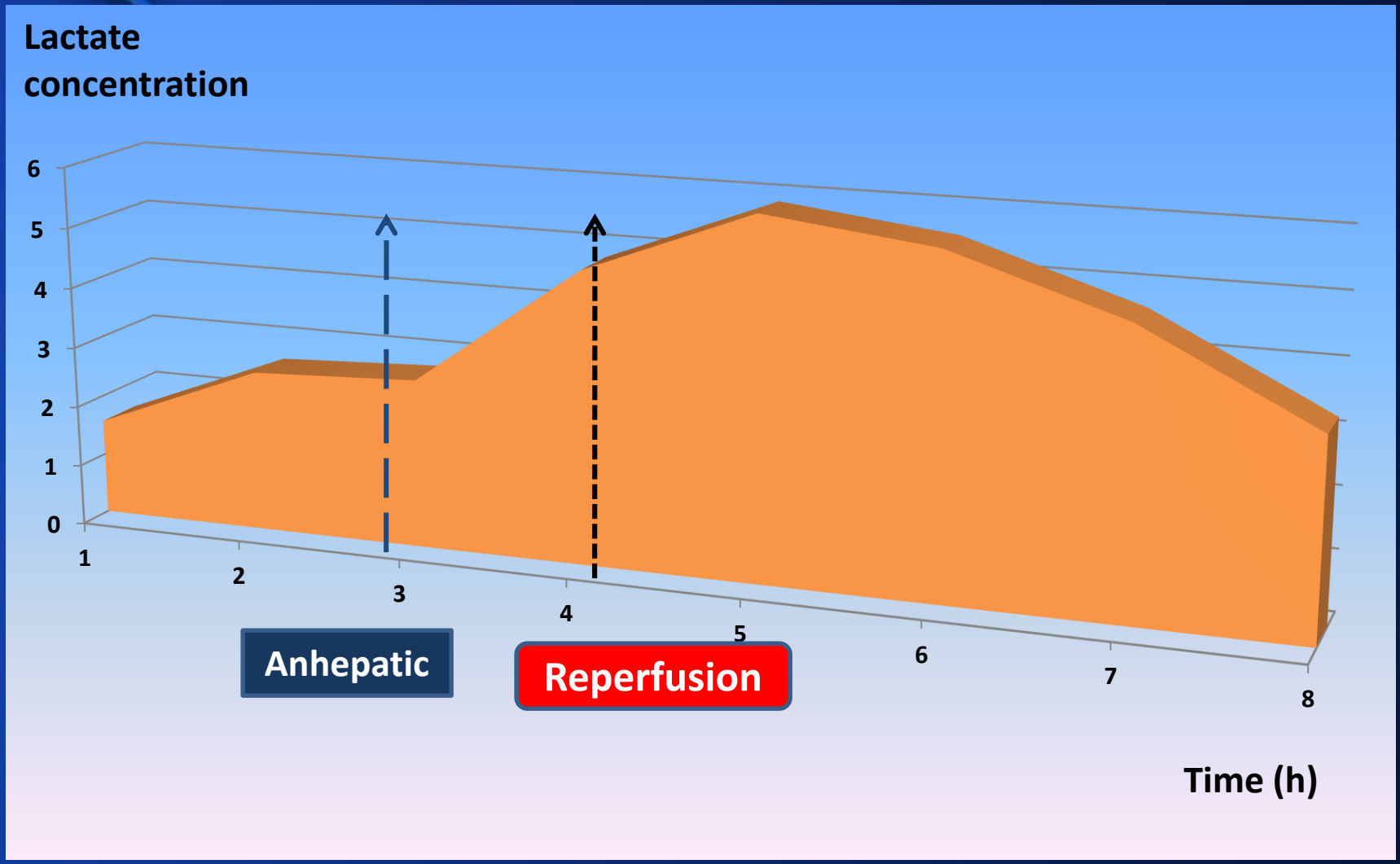


- Decreased synthesis of hepatic pyruvate dehydrogenase, hence impaired lactate – to – bicarbonate conversion
- Acidosis itself decreases lactate clearance
- Severe LA (lactate > 5 mEq/l) is associated with mortality rates 50-56%

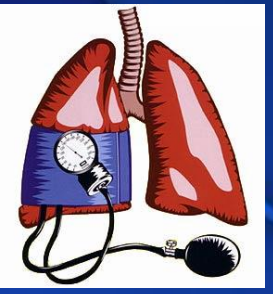
However,

- 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

Lactate during liver transplant



(Vitin A. et al., 2010)

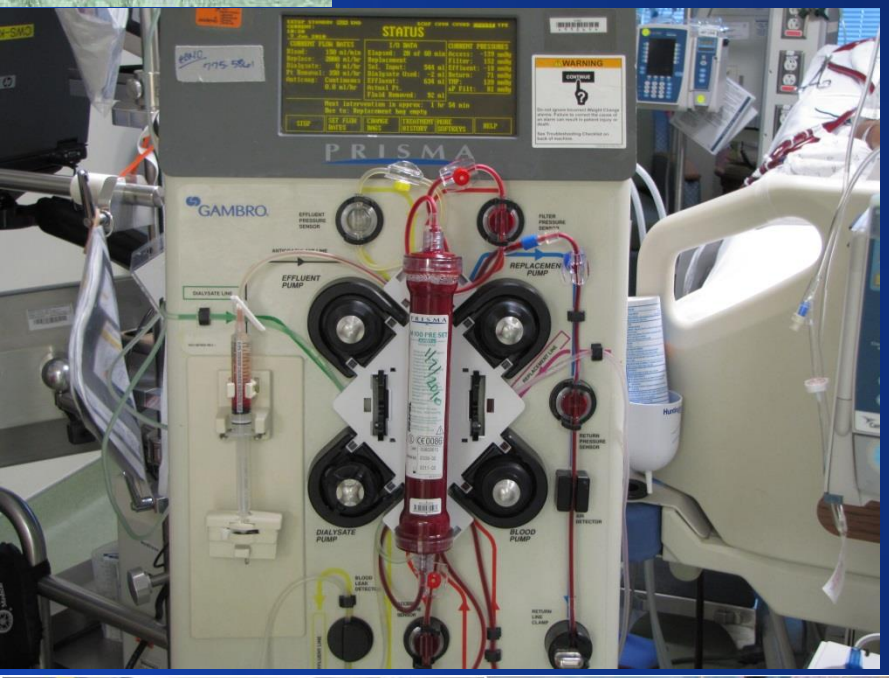


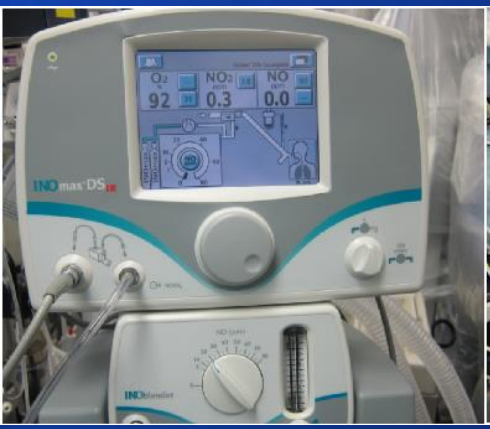
Porto-pulmonary syndrome

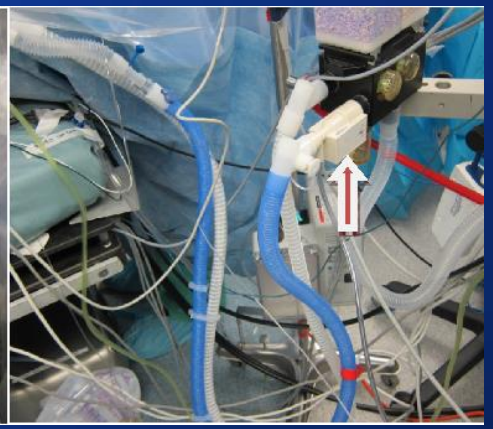
Parameters	Value
MPAP	>25 mmHg at rest >30 mmHg with exercise/stress
PCWP	<15 mmHg
PVR	>120 dynes/sec/cm^5
Trans-pulmonary gradient	> 10 mmHg

	Normal	Mild	Moderate	Severe
NYHA class	–	I, II	II, III	III, IV
Mean pulmonary arterial pressure (mm Hg)	15–24	25–34	35–44	>45
Cardiac index (L min^{-1} m^{-2})	2·5–4·0	>2·5	>2·5	<2·0
Pulmonary vascular resistance (dyne s^{-1} cm^{-5})	<240*	240–500	500–800	>800
Right arterial pressure (mm Hg)	0–5	0–5	5–8	>8
Prognosis	–	Favourable	Questionable	Poor
Specific treatment required†	–	No	Questionable	Yes
Reversibility after liver transplantation	–	Yes	Questionable	No

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

Changing trends in transfusion practice in liver transplantation
Yves Ozier[a] and Mei-Yung Tsou[b]

Predictors of Blood Product Use in Orthotopic Liver Transplantation Using the Piggyback Hepatectomy Technique

R.S. Mangus, S.B. Kinsella, M.M. Nobari, J.A. Fridell, R.M. Vianna, E.S. Ward, R. Nobari, and A.J. Tector

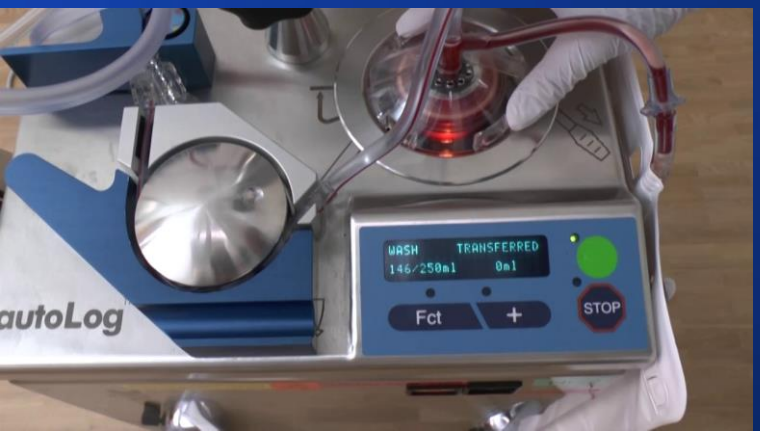
Intraoperative Massive Transfusion Decreases Survival After Liver Transplantation

I.F.S.F. Boin, M.I. Leonardi, A.C.M. Luzo, A.R. Cardoso, C.A. Caruy, and L.S. Leonardi

10. Surgeon-related factors…

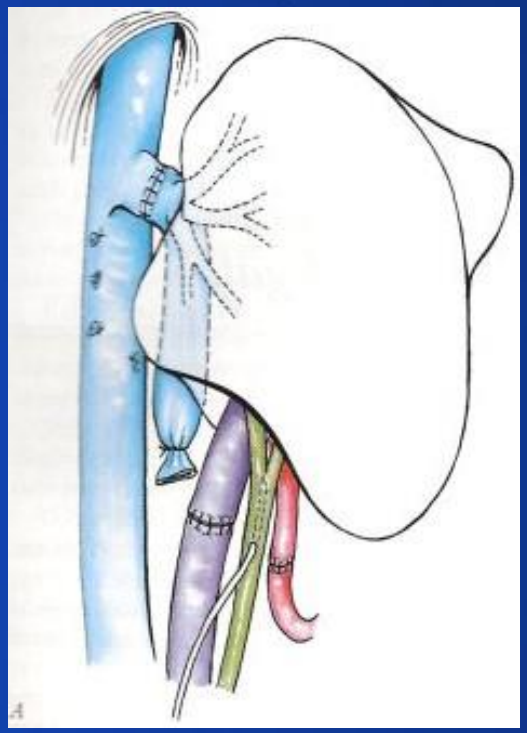
1. MELD score >25
2. Portal hypertension
3. Pre-existing + ongoing consumption & dilution coagulopathy
4. Long, traumatic liver dissection
5. "Hostile abdomen" – s/p laparotomy
6. Re-do OLT
7. Long ischemia times
8. Aged/marginal quality donor organ
9. Donor-recipient organ size discrepancy

Hemotransfusion during OLT



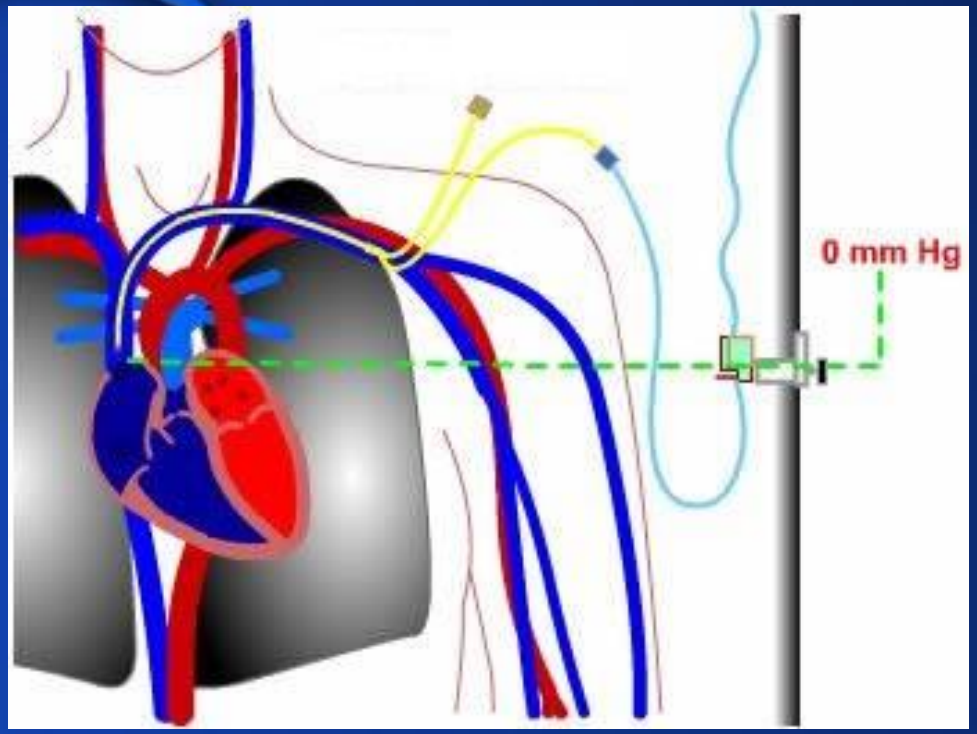
- Different surgical techniques, anesthesia protocols, transfusion triggers and institutional practices
- RBCs use: 10 y. ago – **20** units, currently: **1-5 to 0** (average)
- Modern trends: restriction of RBCs and other blood products use to ***absolutely necessary minimum; use of Cell Saver***
- 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

LIVER TRANSPLANTATION 12:117–123, 2006

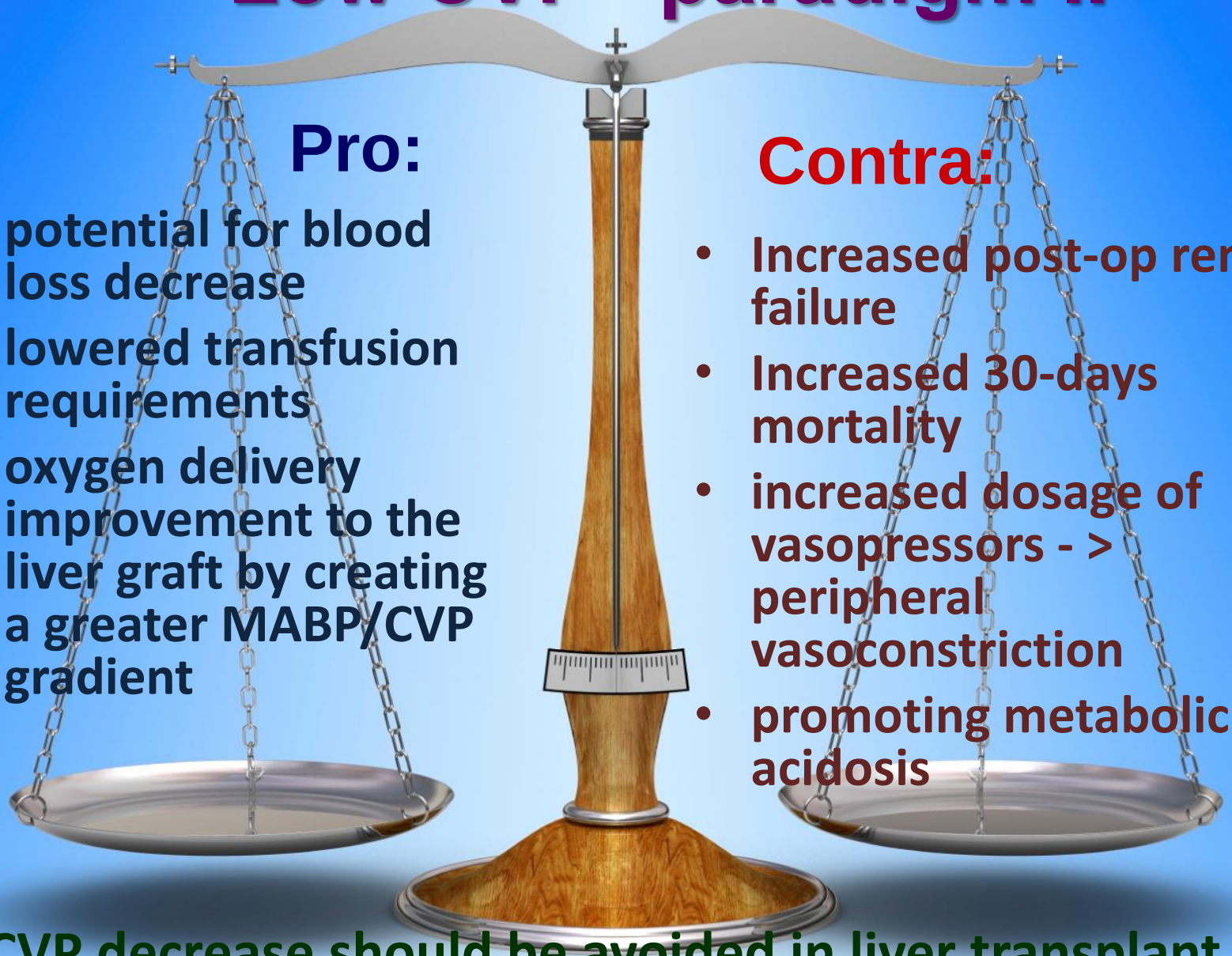
ORIGINAL ARTICLE

Effect of Low Central Venous Pressure and Phlebotomy on Blood Product Transfusion Requirements During Liver Transplantations

Luc Massicotte,[1] Serge Lenis,[1] Lynda Thibeault,[1] Marie-Pascale Sassine,[1] Robert F. Seal,[2] and André Roy[3]

[1]Department of the Centre Hospitalier de l'Université de Montréal (CHUM); [2]Department of Anesthesiology and Pain Medicine of the University Alberta; and [3]Department Of Surgery, Hepato-biliary Service, of the CHUM

“Low CVP” paradigm II



Pro:

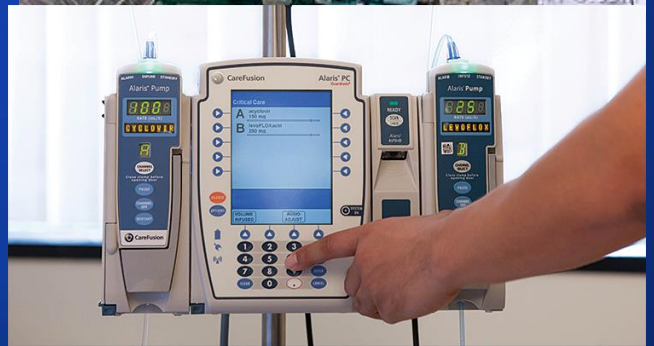
- potential for blood loss decrease
- lowered transfusion requirements
- oxygen delivery improvement to the liver graft by creating a greater MABP/CVP gradient

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



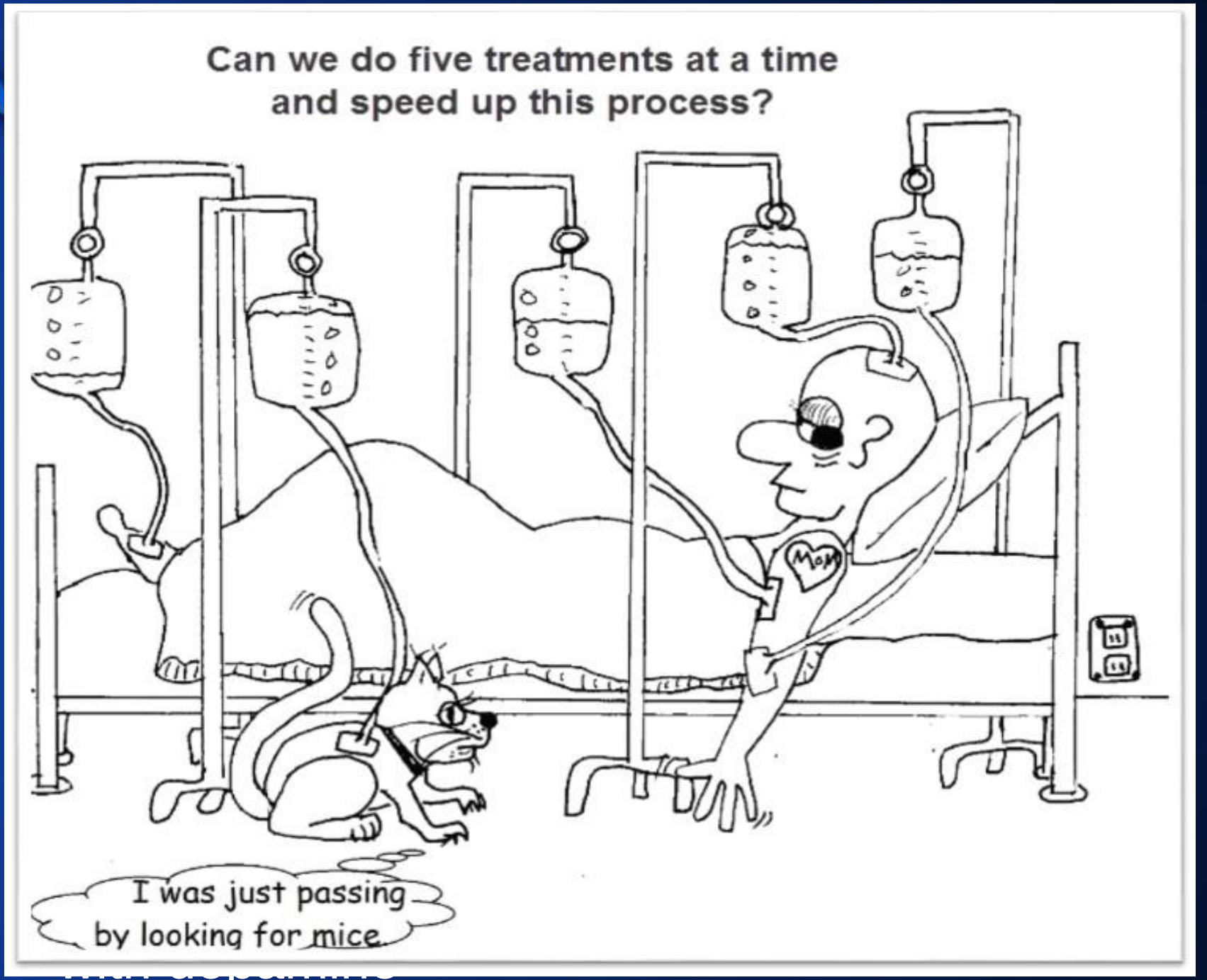
- **Routine use** (doses in mcg/kg/min):
- Phenylephrine, 0.01 – 1.5
- Norepinephrine , 0.01-0.5
- **Optional**:
- Epinephrine, 0.01 – 0.05
- Dopamine, 3
- Vasopressin, 0.04 U/min


Phenylephrine
HCl Injection USP
50 mg/5 mL
SANDOZ


NOREPINEPHRINE
BITARTRATE INJECTION USP
FOR IV INFUSION ONLY
4 mg/4 mL
1 mg/mL
Rx ONLY


Epinephrine
Injection, USP

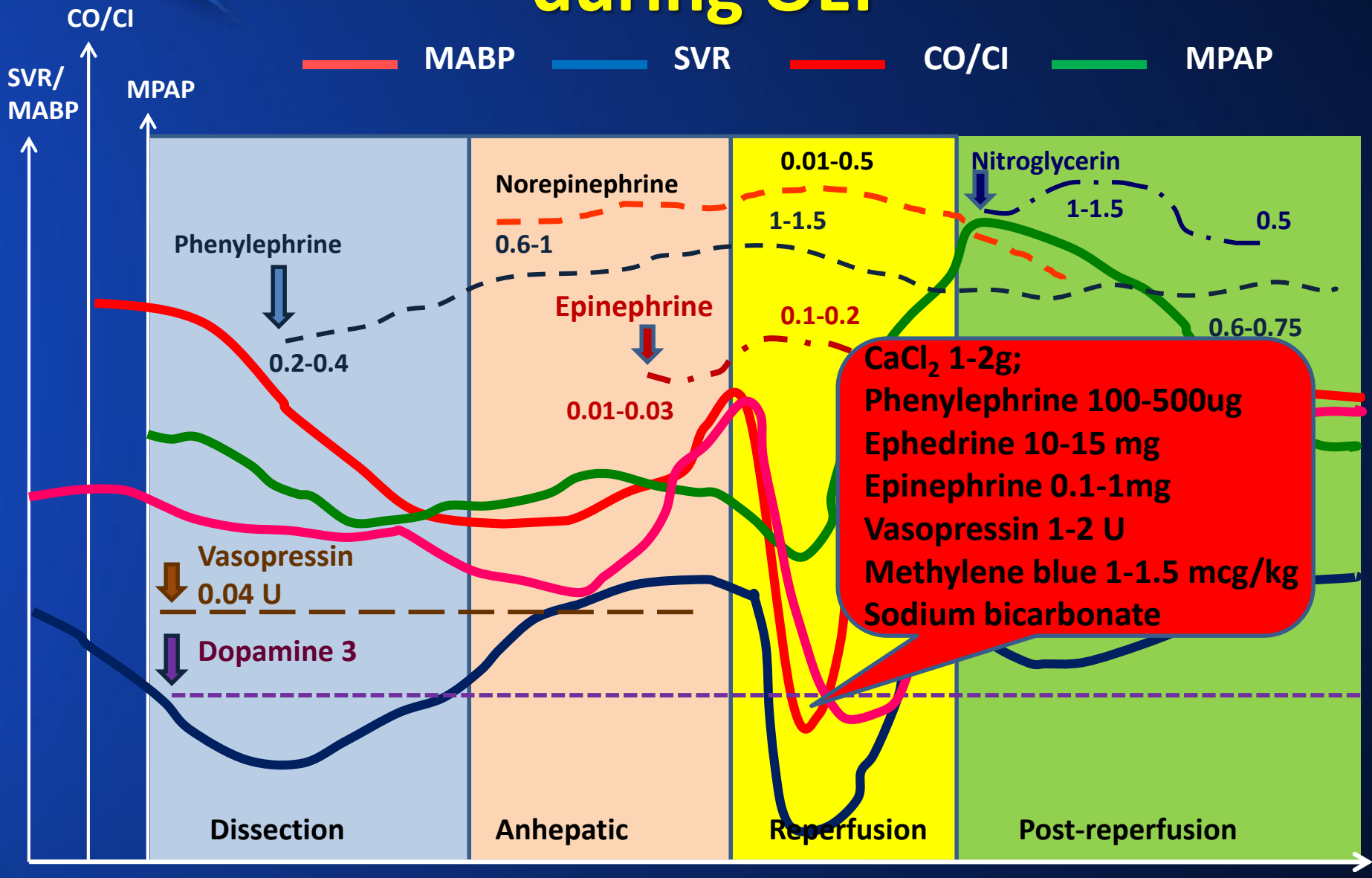

Hospira
250 mL
Dopamine
Hydrochloride
in 5% Dextrose
400 mg/250 mL
1600 mcg/mL


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



Vasopressin in OLT

Liver Transpl Surg. 1997 Jul;3(4):379-87.

Circulatory pathophysiology and options in hemodynamic management during adult liver transplantation.

Mandell MS, Katz JJ, Wachs M, Gill E, Kam I.
Department of Anesthesiology, University of Colorado, Health Science Center, Denver 80262, USA.

The Use of Vasopressin Bolus to Treat Refractory Hypotension Secondary to Reperfusion During Orthotopic Liver Transplantation

Jonathan V. Roth, MD
Department of Anesthesiology

LIVER TRANSPLANTATION 14:1664-1670, 2008

ORIGINAL ARTICLE

Vasopressin Decreases Portal Vein Pressure and Flow in the Native Liver During Liver Transplantation

Gebhard Wagener,[1] Gina Gubitosa,[1] John Renz,[2] Milan Kinkhabwala,[2] Tricia Brentjens,[1] James V. Guarrera,[2] Jean Emond,[2] H. Thomas Lee,[1] and Donald Landry[3]
Departments of [1]Anesthesiology, [2]Surgery, and [3]Medicine, College of Physicians and Surgeons, Columbia University, New York, NY

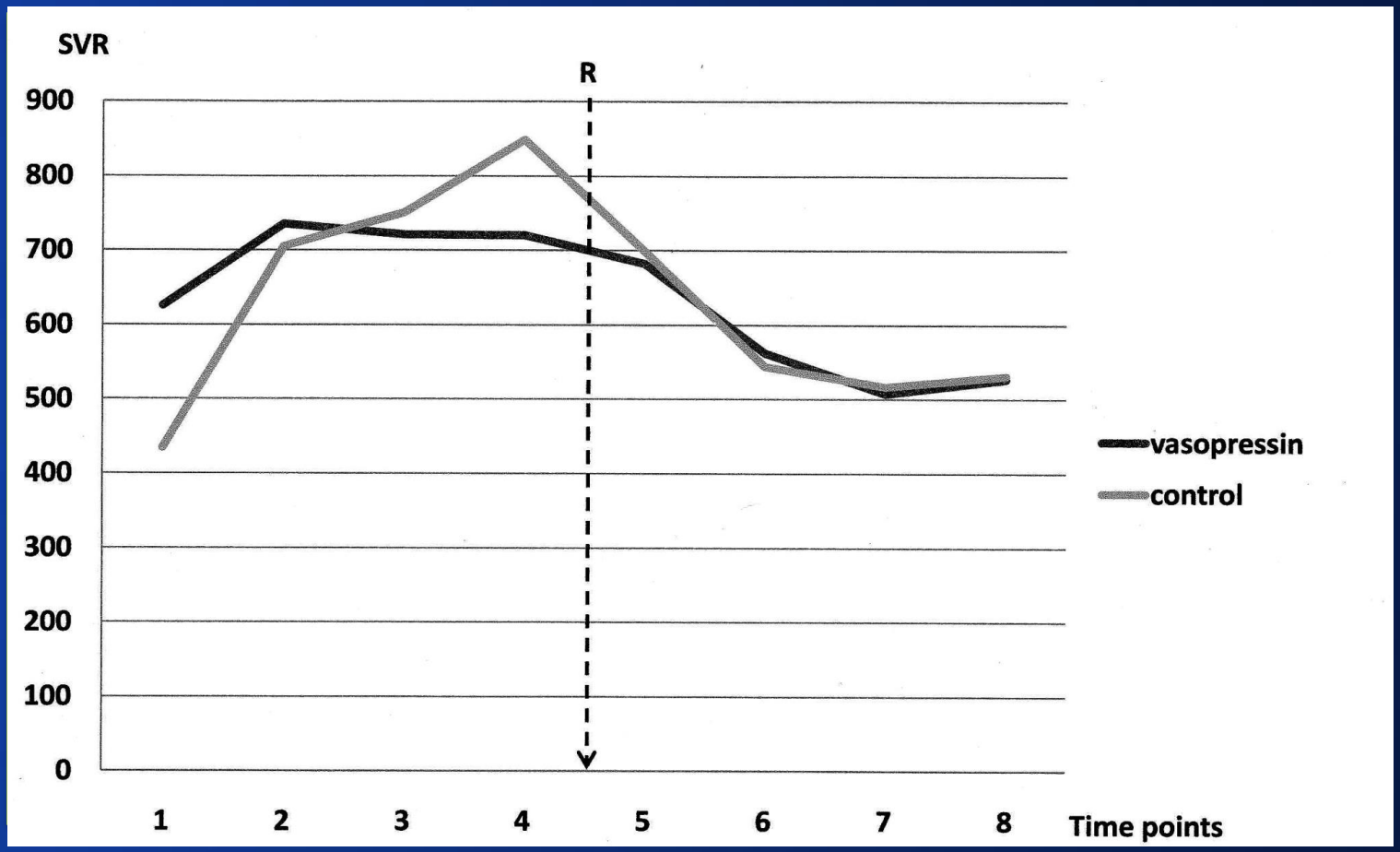
The Development of Perioperative Practices for Liver Transplantation: Advances and Current Trends

Merceds Susan Mandell[1], Mei-Yung Tsou[2]*
[1]Department of Anesthesiology, University of Colorado Health Sciences Center, Aurora, Colorado, U.S.A., and [2]Department of Anesthesiology, Taipei Veterans General Hospital and National Yang-Ming University School of Medicine, Taipei, Taiwan, R.O.C.

injury. Anesthesiologists found that they could use vasoconstrictors to increase systemic vascular resistance during surgery, which in turn improved blood pressure and organ perfusion.[22] Anesthesiologists also borrowed techniques from the field of hepatology that specifically controlled splanchnic blood flow.[23] Anesthesiologists discovered that intra-abdominal blood loss would be reduced by limiting splanchnic blood flow during surgery.[20] Drugs used to control variceal bleeding such as vasopressin are now commonly used during surgery to selectively limit blood flow to the gut in order to reduce surgical bleeding.[24] Control of the circulatory system made the use of venovenous bypass optional.[25] This reduced the anhepatic time, along with the cold ischemic and total surgical time—factors that are strongly correlated with outcome.[26] These

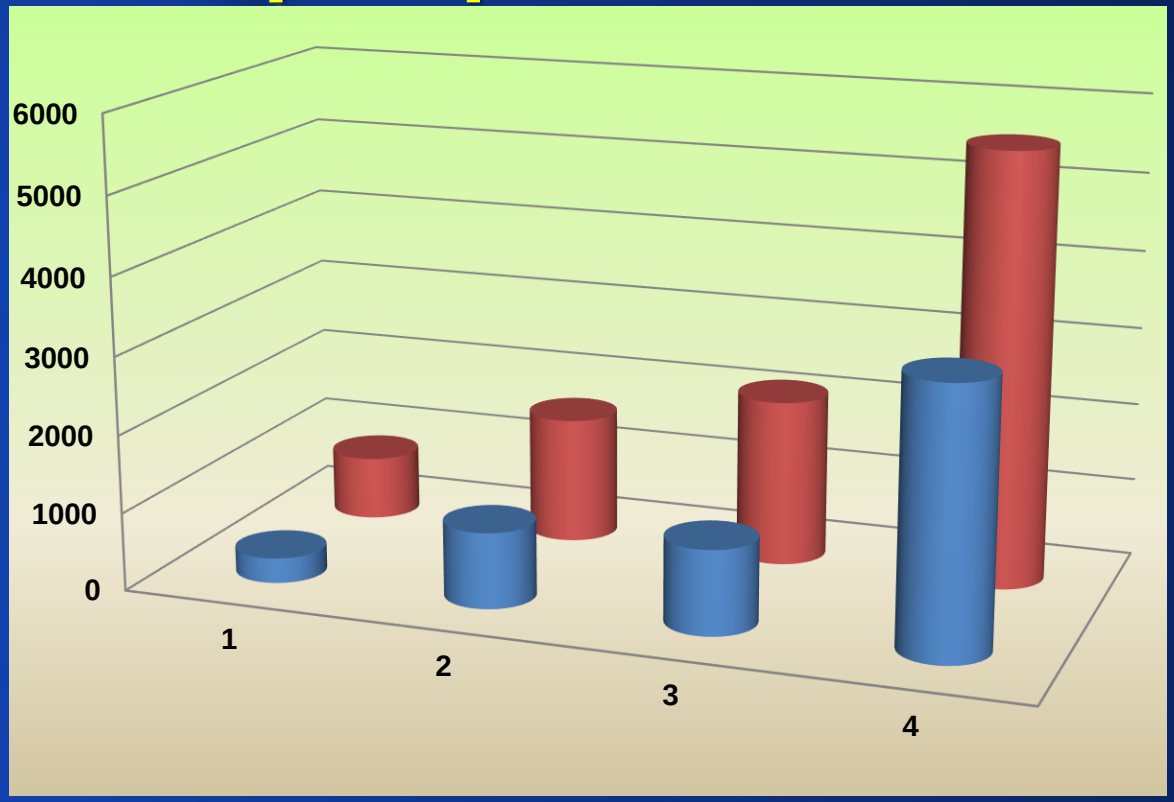
J Chin Med Assoc • September 2008 • Vol 71 • No 9

Hemodynamic effects of low-dose vasopressin *vs* phenylephrine



Vitin AA, Martay K, Vater Y, Dembo G, Maziarz M (2010) Effects of Vasoactive Agents on Blood Loss and Transfusion Requirements During Pre-Reperfusion Stages of the Orthotopic Liver Transplantation. J Anesthe Clinic Res 1:104 doi:10.4172/2155-6148.1000104

Vasopressin vs phenylephrine & epinephrine effect on blood loss



1. Cell-saver return before reperfusion
2. Cell-saver total returned volume
3. EBL before reperfusion
4. EBL total

vasopressin

Phenylephrine & epinephrine

- 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!