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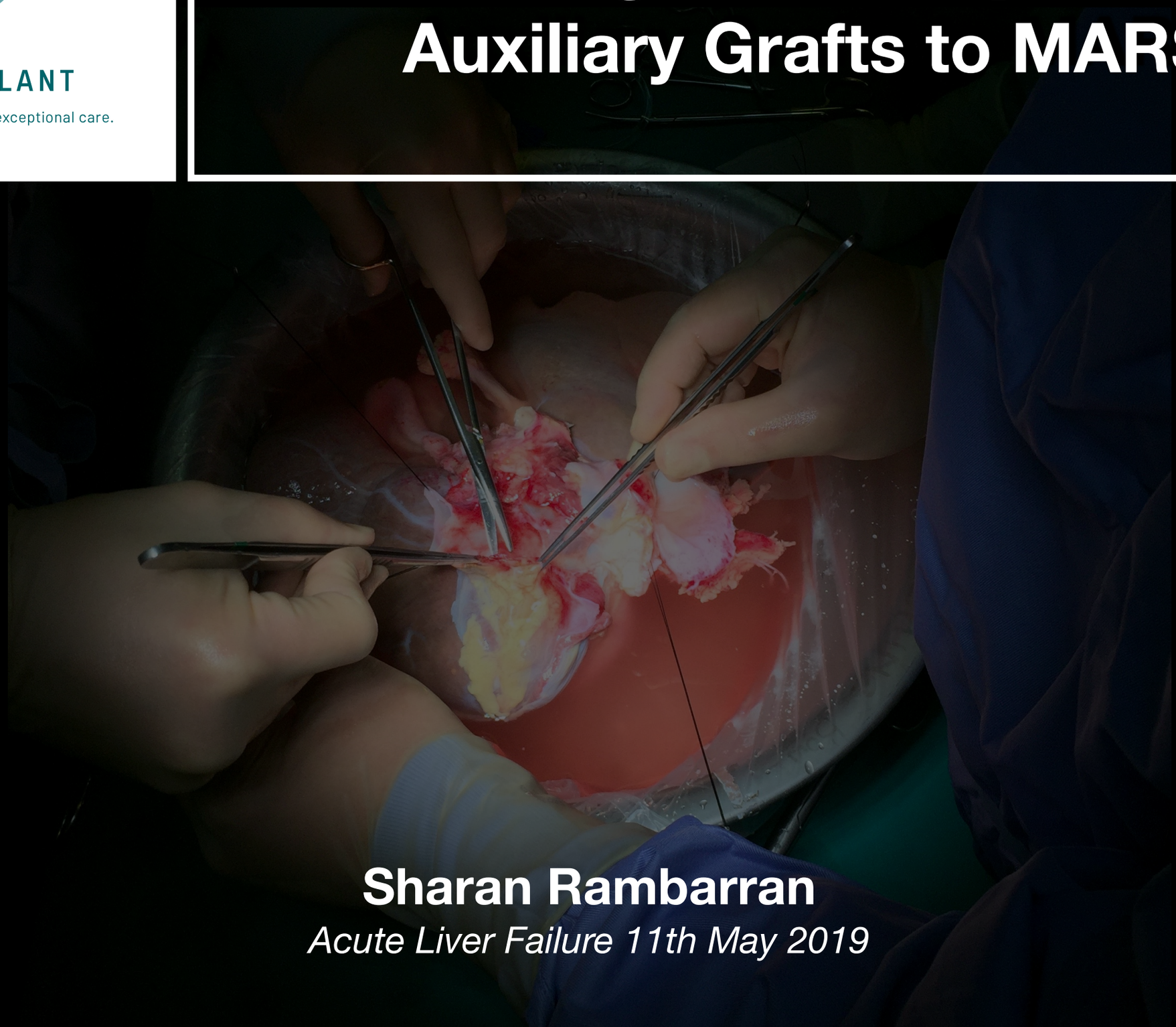
Bridge therapies:
Auxiliary Grafts to MARS



Sharan Rambarran

Acute Liver Failure 11th May 2019

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Concept

Bridge to transplant

Vs

Bridge to recovery

Hepatic encephalopathy

Imminent herniation

Inflammatory mediators /cytokines / toxins / SIRS

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Time is running out…

Clinical Practice Guidelines

Table 11. (A) Acute Liver Failure Poor Prognosis Criteria in use for selection of candidates for Liver Transplantation. (B) Criteria for emergency liver transplantation.

A

Factor	Clichy [323]	Kings College [321]	Japanese [6]
Age†	+	+	+
Aetiology	–	+	–
Encephalopathy†	+	+	+
Bilrubin*	–	±	+
Coagulopathy†	+	+	+

B

King's College criteria

ALF due to paracetamol

- Arterial pH <7.3 after resuscitation and >24 h since ingestion
- Lactate >3 mmol/L or
- The 3 following criteria:
  - Hepatic encephalopathy >grade 3
  - Serum creatinine >300 µmol/L
  - INR >6.5

ALF not due to paracetamol

- INR >6.5 or
- 3 out of 5 following criteria:
  - Aetiology: indeterminate aetiology hepatitis, drug-induced hepatitis
  - Age <10 years or >40 years
  - Interval jaundice-encephalopathy >7 days
  - Bilirubin >300 µmol/L
  - INR >3.5

Beaujon-Paul Brousse criteria (Clichy)

- Confusion or coma (hepatic encephalopathy stage 3 or 4)
- Factor V <20% of normal if age <30 year
  or
- Factor V <30% if age >30 year

† Factors common to all prognostic models.
* Bilirubin not included in paracetamol criteria.

Cadaveric
Whole
Split
Reduced

Living donor
Adult to child
Adult to adult
Right vs left

ABO Incompatible

Extended Criteria donor

Orthotopic liver transplant

Ventilation
Dialysis
ICP monitors
Antibiotics
Cardiac

ICU support

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Hypothermic
Normothermic
Organ metra

Machine pe ion devices

Total Hepatectomy

Acute liver failure

Bridge to recovery

Bridge to transplant

Xenografts

Porcine ex vivo
In vivo

Auxiliary grafts

HALT
APOLT
Left
Right

Liver assist

MARS
Prometheus
SPAD

Tissue Engineering and Regenerative medicine

BioArtificial Liver
Hepatocyte transplantation

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Auxiliary grafts

- Surprisingly long history - since ***1990***
- Organ shortage - partial grafts
- High acute liver failure waitlist death
- Borne out of necessity due to lack of current immunosuppression
- Ability to STOP immunosuppression once native liver recovers
- Toxic liver and risk of handling vs ICP

Belghiti J **et al** ***HPB 2004*** **vol 6 number 2**

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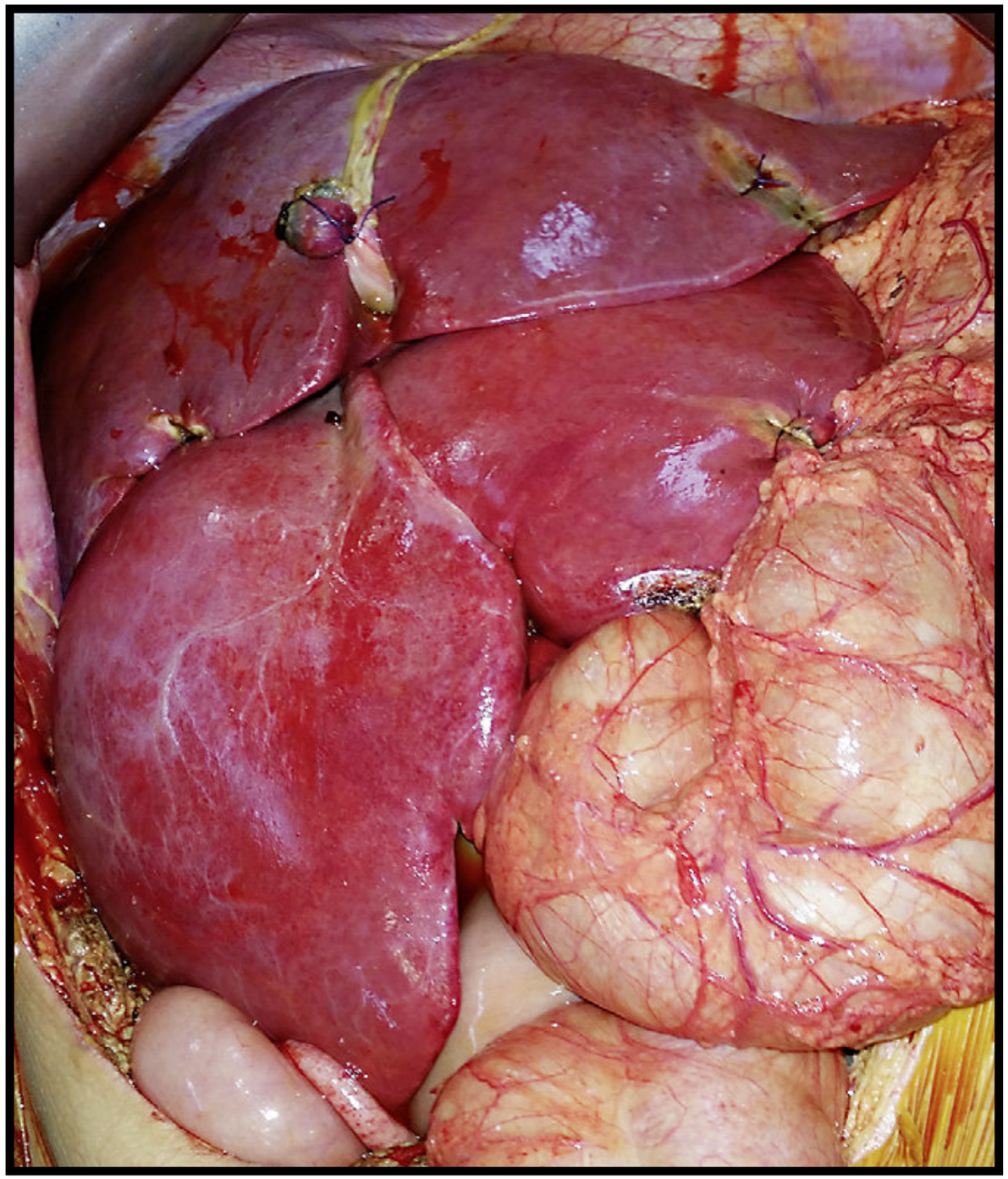
Heterotopic Auxiliary Liver Transplant



Stamfl DA et al reported the first HALT in acute liver failure

15 year female with fulminant Wilson's disease

Elevation of intracranial pressures prevented any manipulation of the native liver

Right lobe used

Needed ABOI orthotopic transplant 27 days later

But.. showed that the procedure could be lifesaving and was feasible

Stamfl DA et al Gastroenterology 1990

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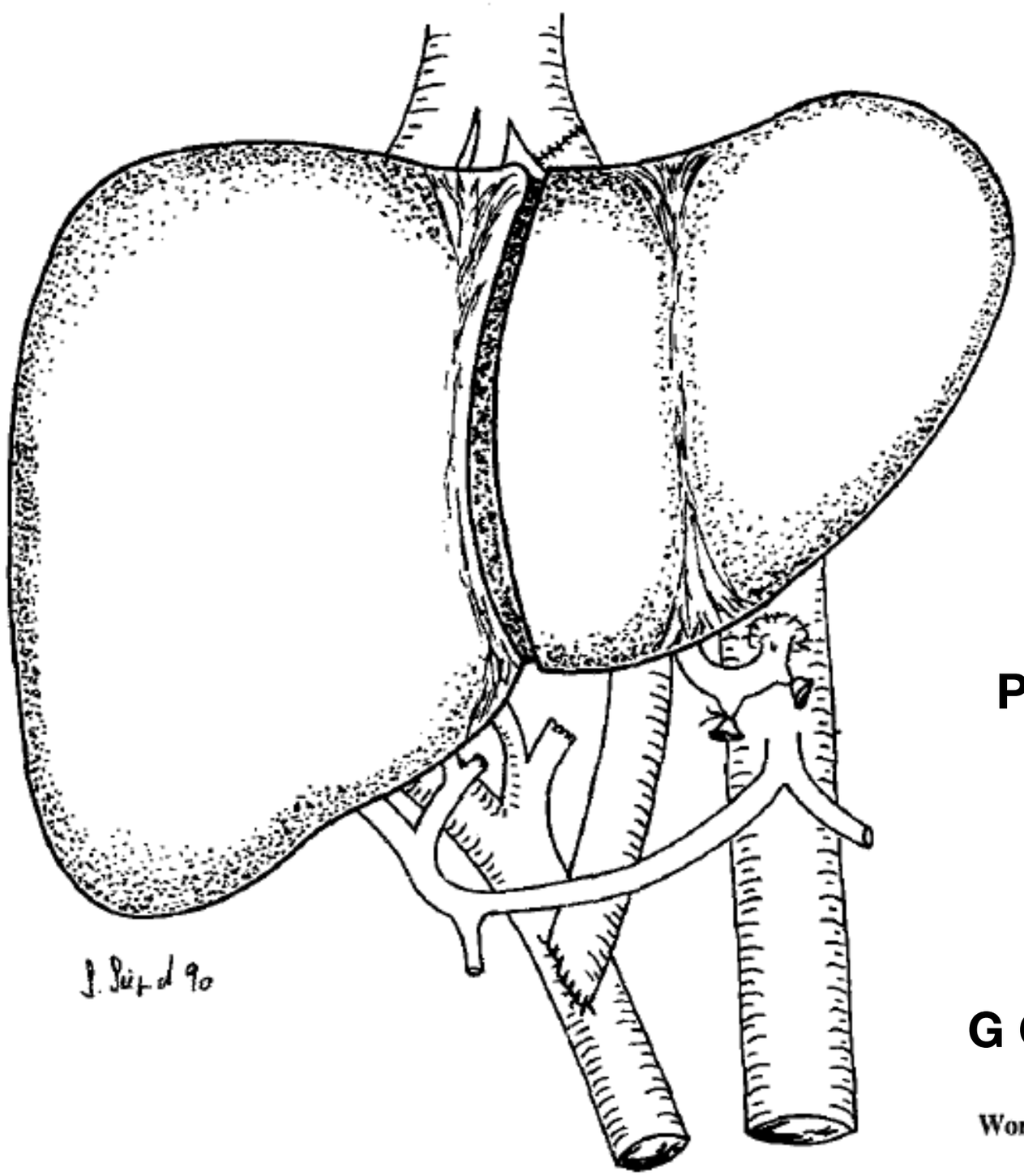
Auxiliary partial orthotopic liver transplant



Issues with HALT:
Space
Competing venous flow
PGN

APOLT:
2 cut surfaces!
Space
Preserves enough liver to regenerate
Technically tricky

G Gubernatis et al

World J. Surg. 15, 660–666, 1991

World Journal of Surgery

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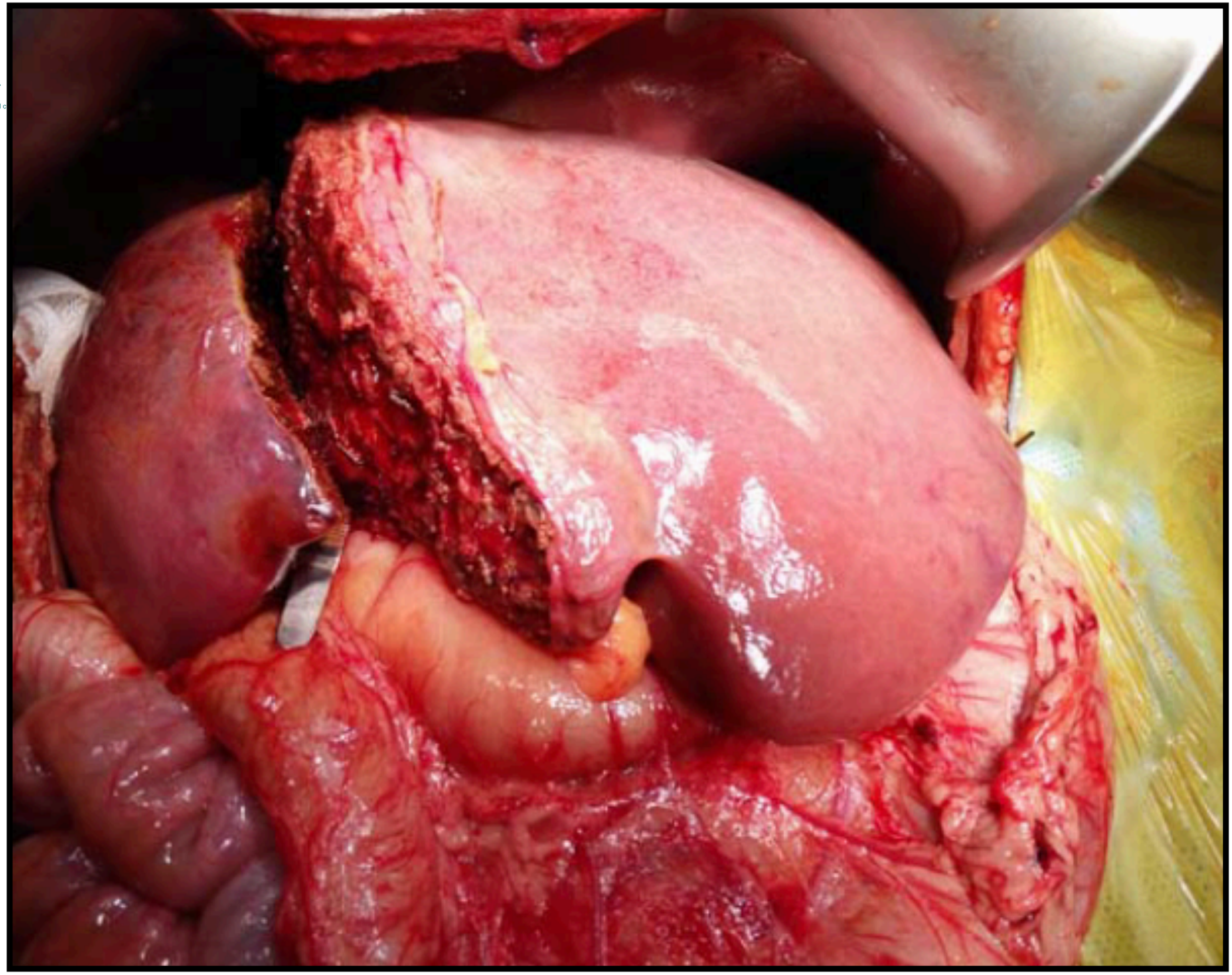

LLS APOLT in 2 year old with acute Hep A

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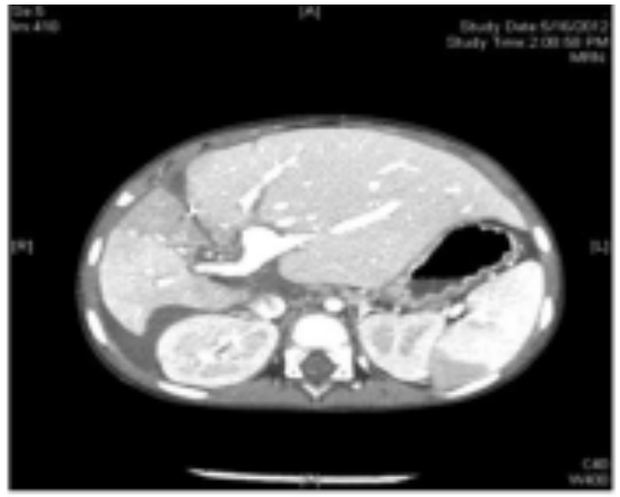
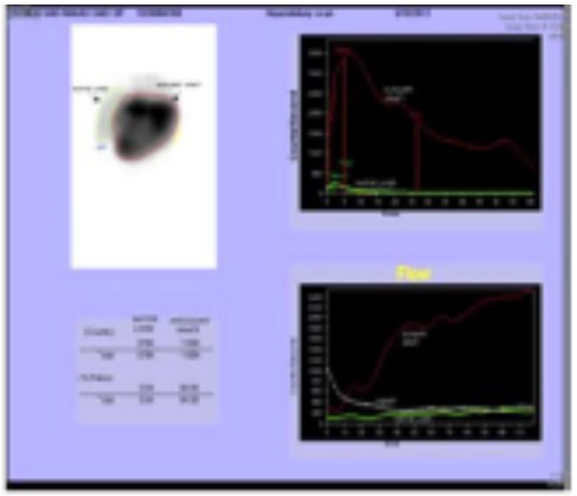
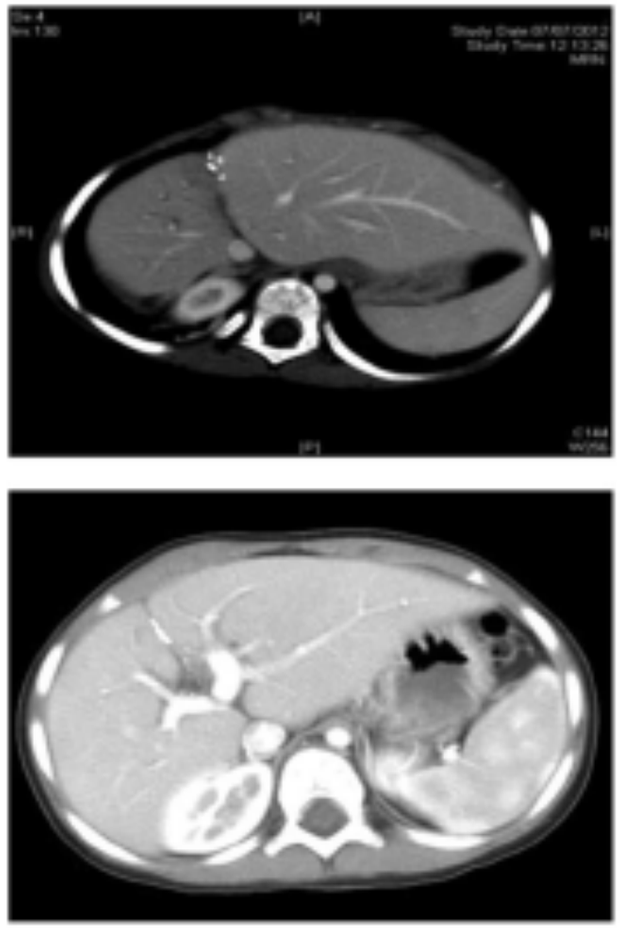
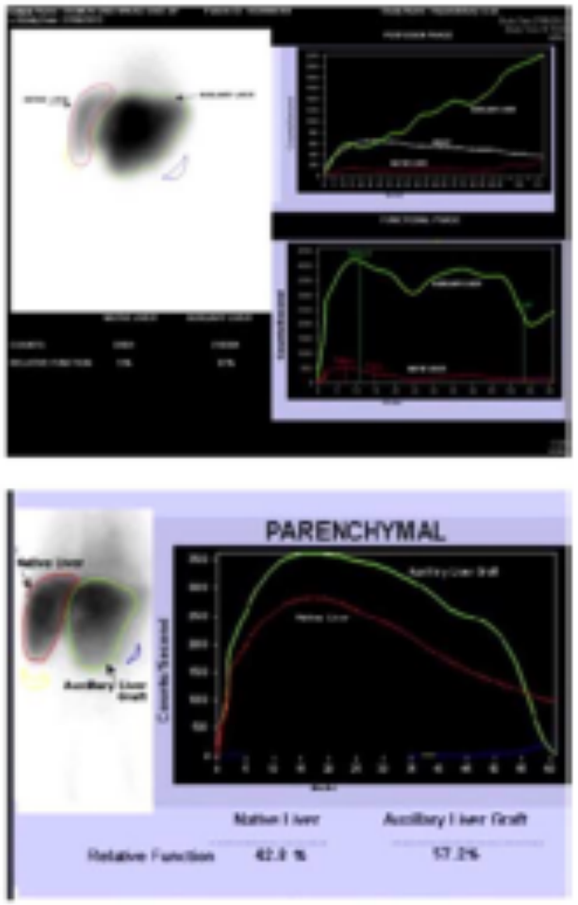
Recovery

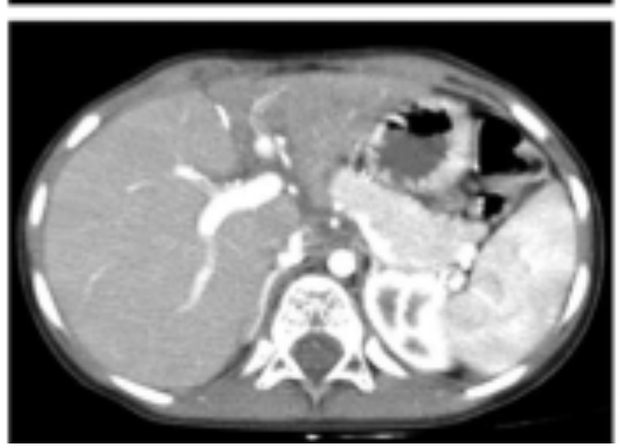
- Native liver remnant
- Immunosuppression for at least 6 months
- Confirm native hepatic recovery and growth
- HIDA scan and serial CT imaging
- Slow withdrawal of immunosuppression
- Induced rejection and atrophy of graft
- Graft hepatectomy if needed

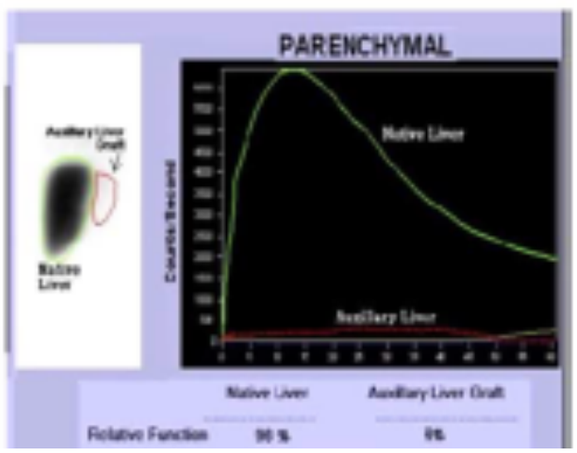












Liver Transplantation 22 1265-1274 2016 AASLD.

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Pick your patient…

- Young adults and children higher regenerative ability
- Preserved hepatic scaffold / pure hepatocyte lost
- Pathologic processes most suitable:
  - Hepatitis A and E viral infection
  - Paracetamol overdose
  - Mushroom poisoning

Liver Transplantation 22 1265-1274 2016 AASLD.

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Ideal artificial liver

- 1. Detoxification
- 2. Biosynthesis
- 3. Regulation

- *Allow bridge to recovery or transplant*
- *Purification vs detoxification*

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Extended criteria donor

Definition of extended criteria donors

Advanced age

Macrovesicular steatosis

DCD

Organ dysfunction at procurement
- ICU stay greater than 7 days
- Hypernatremia greater than 165
- Bilirubin greater than 3
- Elevated aspartate aminotransferase/alanine aminotransferase
- Vasopressor use

Cause of death: anoxia, cerebrovascular accident

Disease transmission
- HBcAb+
- HBsAg+
- Hepatitis C virus
- CDC high-risk donors
- HIV positive
- Extrahepatic malignancy

CIT greater than 12 hours

I Vokin A Kuo
Clin Liver Dis 21 (2017) 289–301

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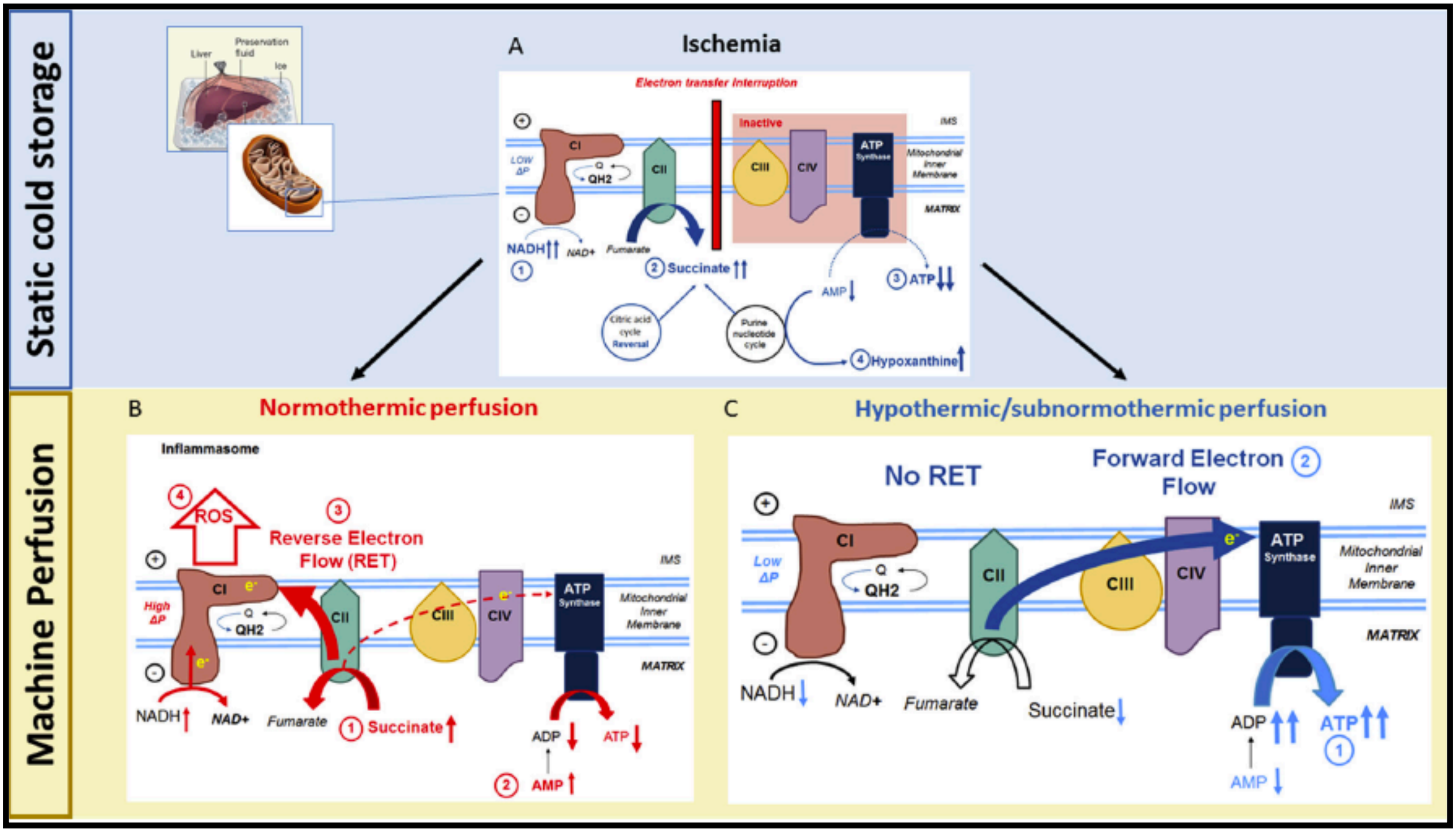
Static storage vs Machine Perfusion



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Ischaemic-Reperfusion-Injury

Ischaemic injury

- Glycogen consumption
- Adenosine triphosphate (ATP) depletion
- Lack of oxygen
- Parenchymal cell death, release of reactive oxygen species (ROS), proteases and damage-associated molecular patterns (DAMPs)

Reperfusion injury

- Reactive oxygen species (ROS) production
- Activation of the inflammatory immune innate response
- Release of inflammatory mediators (cytokines, chemokines, adhesion molecules, reactive oxygen species (ROS) and proteases)

Reperfusing-modalities of machine perfusion shorten the ischaemic period, whereas they inevitably trigger the detrimental pathways associated with reperfusion. Pharmacological and non-pharmacological interventions may mitigate the injury associated with reperfusion

Or

Non-reperfusing-modalities of machine perfusion optimise the mitochondrial oxidative function and replenish cellular energy stores

Or

Ischaemia-free organ transplantation may prevent completely ischaemia-reperfusion injury

World J Transplantation 2019 January 16; 9(1): 14-20

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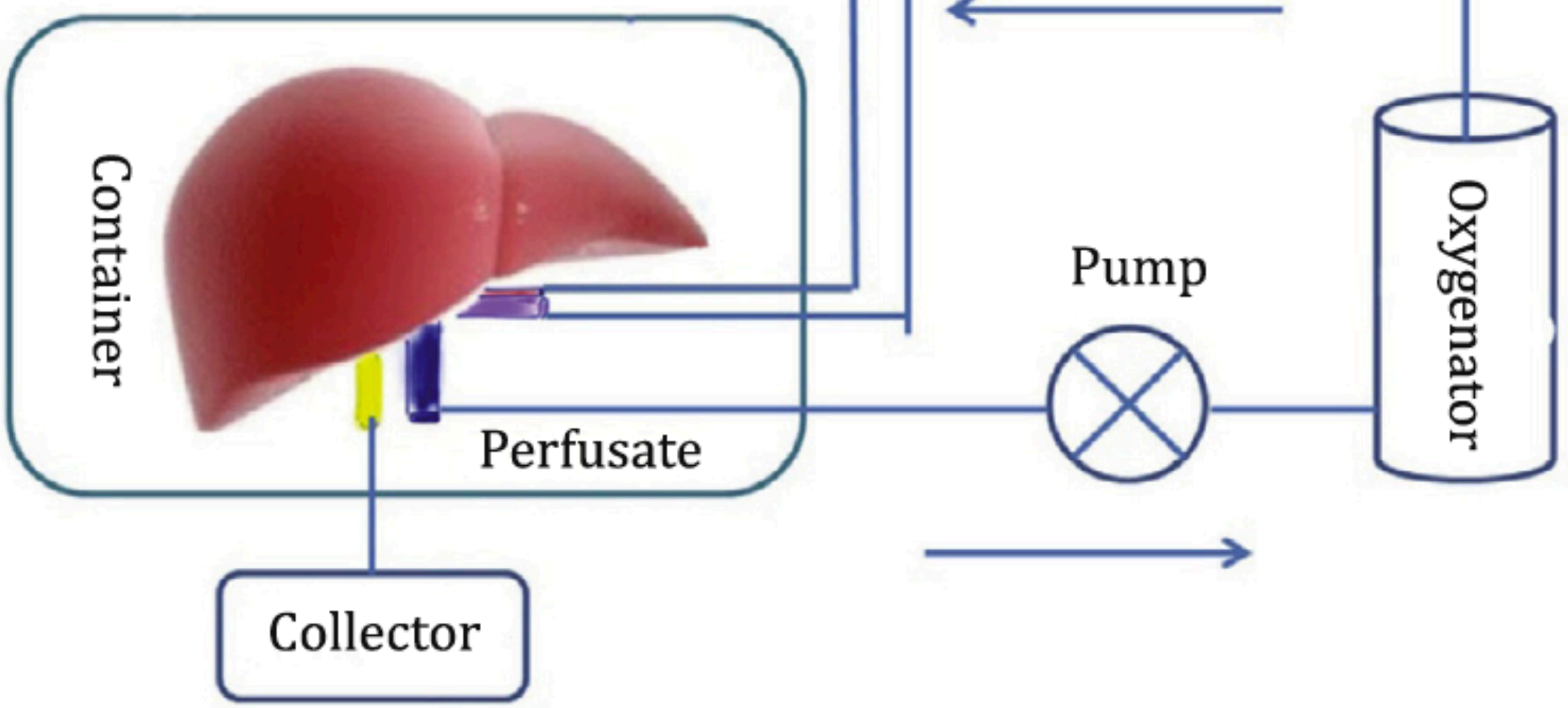
Machine Perfusion systems



J.-J. Jia et al./Hepatobiliary & Pancreatic Diseases International 17 (2018) 387–391

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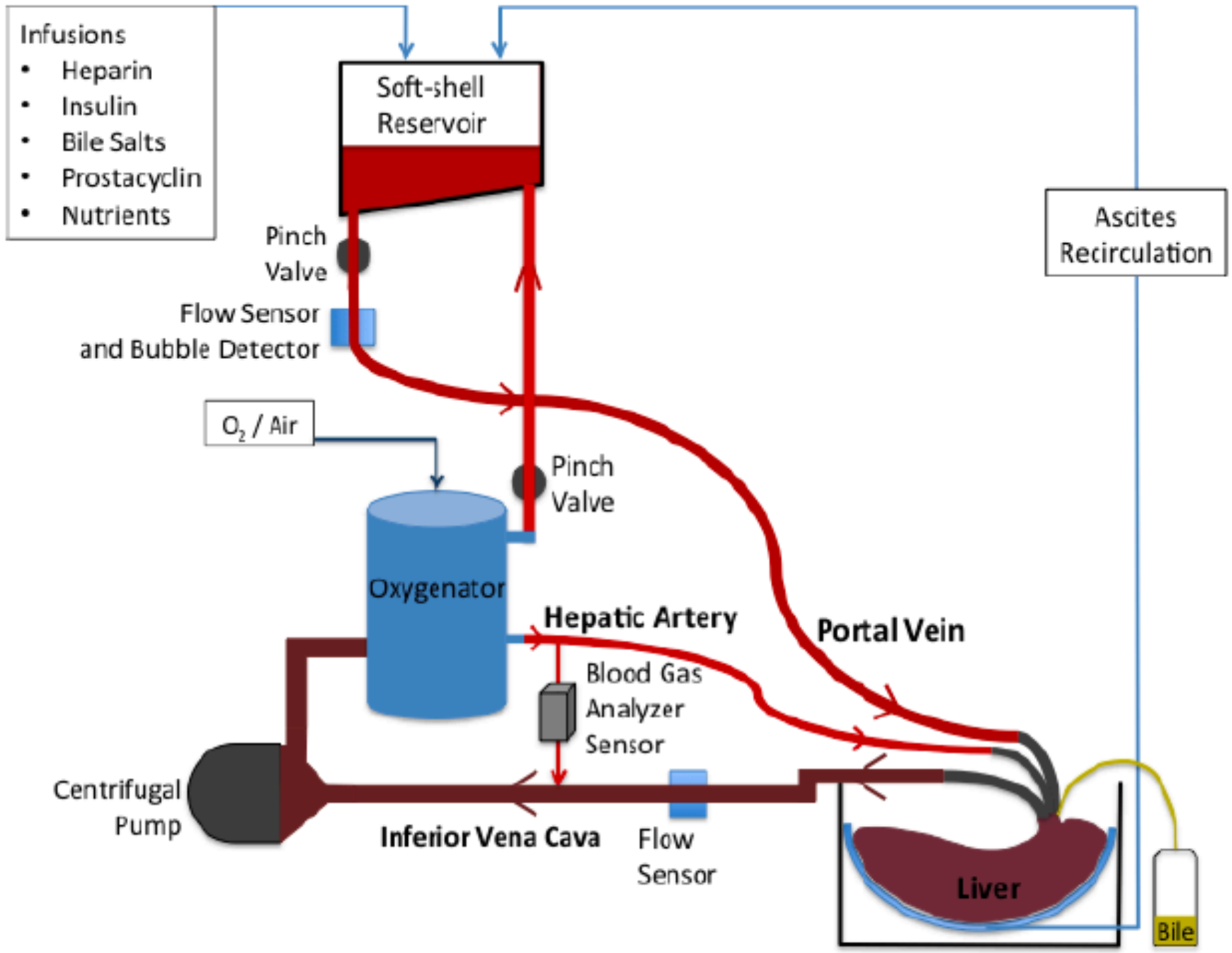
Liver Transplantation After *Ex Vivo* Normothermic Machine Preservation: A Phase 1 (First-in-Man) Clinical Trial



OrganOx metra

American Journal of Transplantation 2016; 16: 1779–1787

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Machine perfusion devices

JOURNAL OF **HEPATOLOGY**

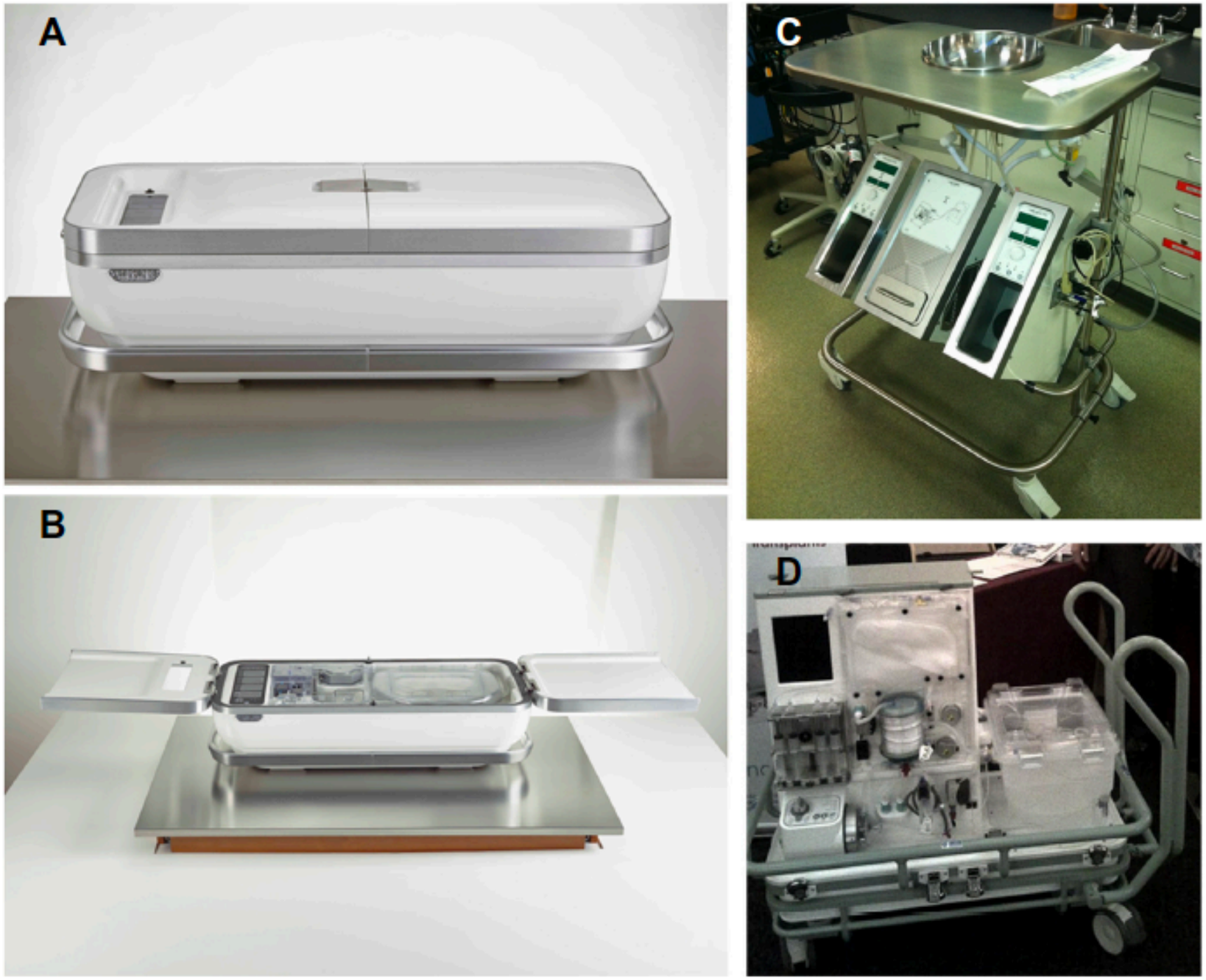

Fig. 3. Machine perfusion devices. (A, B) Photograph of Organ Recovery Systems Inc. LifePort® Liver Transporter prototype. (C) ECOPS device (Organ Assist®). (D) The OrganOx® *metra*™ device.

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Machine Perfusion Options and trials on the go…

Details of the MP strategy.

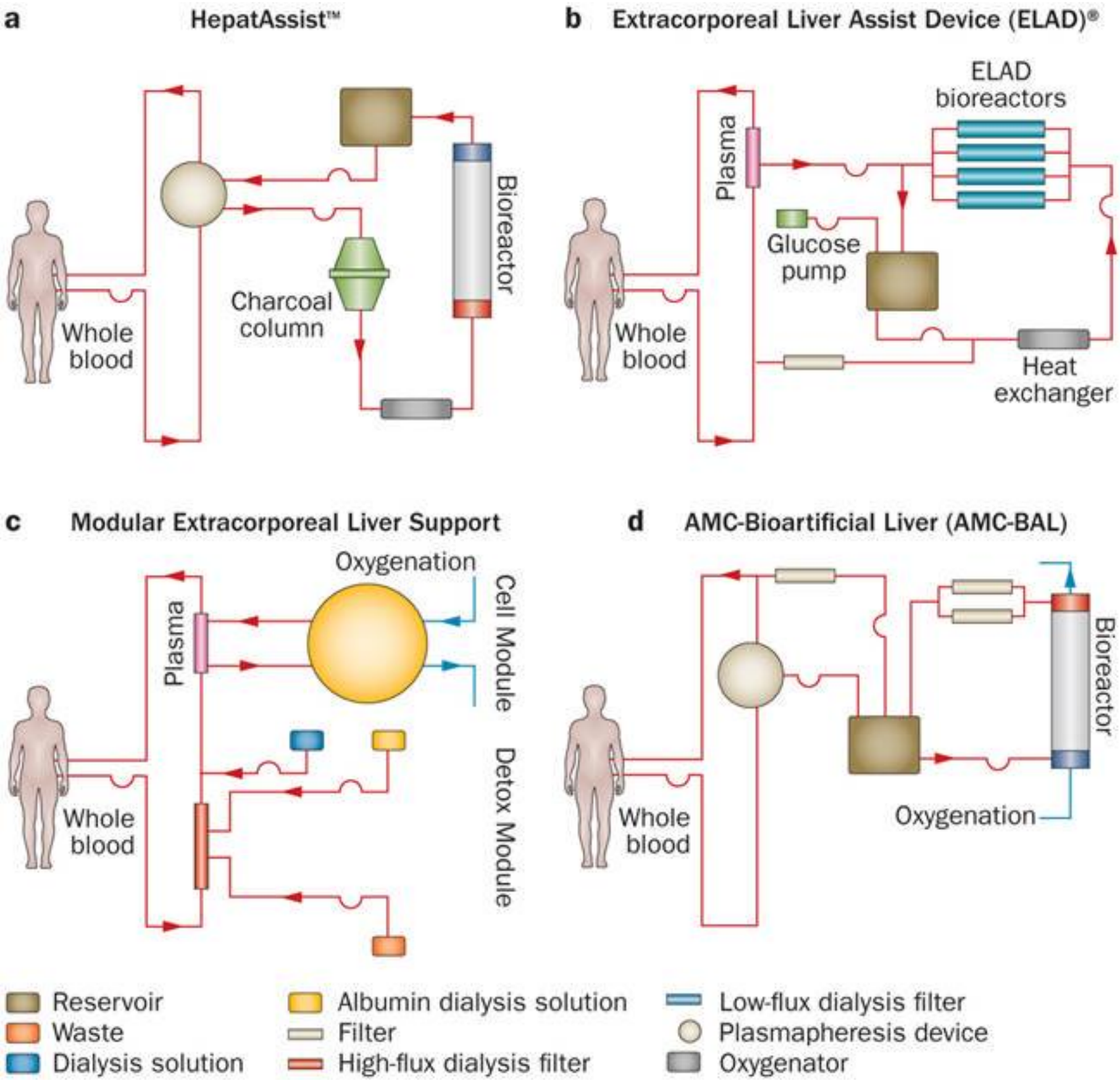
Variables	HMP	HOPE	EHOPE	DHOPE	SMP	COR	NMP
Temperature (°C)	0–12	0–12	0–12	0–12	25–34	25–34	35–38
Oxygen	No	Yes	Yes	Yes	Yes	Yes	Yes
Perfusion route	PV	PV	PV + HA	PV + HA	PV/PV + HA	PV/PV + HA	PV/PV + HA
Perfusate	Solution	Solution	Solution	Solution	Oxygen carrier	Oxygen carrier	Oxygen carrier
Bile production	No	No	No	No	Yes	Yes	Yes
Metabolism	Low	Low	Low	Low	Decreased	Increased	Normal
Intervention site	Recipients site	Recipients site	Recipients site	Recipients site	Recipients site	Recipients site	From donor to recipients site
Main mechanism	Metabolism delay, decreased oxygen need	Metabolism delay, energy recovery	Metabolism delay, energy recovery	Metabolism delay, energy recovery	Graft reconditioning, energy recovery	Graft reconditioning, energy recovery	Mimic physiology, energy charge, initiate repair process

MP: machine perfusion; HMP: hypothermic machine perfusion; HOPE: hypothermic oxygenation machine perfusion; EHOPE: end ischemia HOPE; DHOPE: dual HOPE; SMP: subnormothermic machine perfusion; COR: controlled oxygenated rewarming; NMP: normothermic machine perfusion; PV: portal vein; HA: hepatic artery.

Recent clinical trials of NMP.

Author (year)	Experimental groups	MP Time	Observation parameters	Device, perfusate, route and oxygen
Ravikumar (2016) [16]	NMP ($n = 20$) vs SCS ($n = 40$)	3.5–18.5 h	30-d graft survival, ALT/AST	OrganOx, blood based solution, HA (60–75 mmHg) and PV, oxygen (maintain normal pH and PO_2)
Mergental (2016) [17]	NMP ($n = 5$)	255–564 min	Lactate, bile production, hospital stay, 6-mon survival	Liver Assist and OrganOx, blood based solution, PV and HA, oxygen (no details)
Selzner (2016) [18]	NMP ($n = 10$) vs SCS ($n = 30$)	340–580 min	Lactate, bile production, ALT/AST, ICU stay, hospital stay, complications	OrganOx, Steen solution, PV and HA, oxygen (no details)
Watson (2017) [19]	NMP ($n = 12$)	122–530 min	Post-reperfusion syndrome, vasoplegia, PNF, oxygen tension	Liver Assist, blood based solution, PV (660–1130 mL/min) and HA (208–390 mL/min), oxygen (621–671 mmHg or 153–187 mmHg)
Bral (2017) [20]	NMP ($n = 10$) vs SCS ($n = 30$)	3.3–22.5 h	ALT/AST, lactate, 1-mon graft survival, ICU and hospital stays	OrganOx, blood based solution, PV (500 mL/min) and HA (150 mL/min), oxygen (no details)

OrganOx system: OrganOx Ltd., Oxford, UK. MP: machine perfusion; NMP: normothermic machine perfusion; SCS: static cold storage; HA: hepatic artery; PV: portal vein; ALT: alanine transaminase; AST: aspartate aminotransferase; ICU: intensive care unit; PNF: primary non-function.



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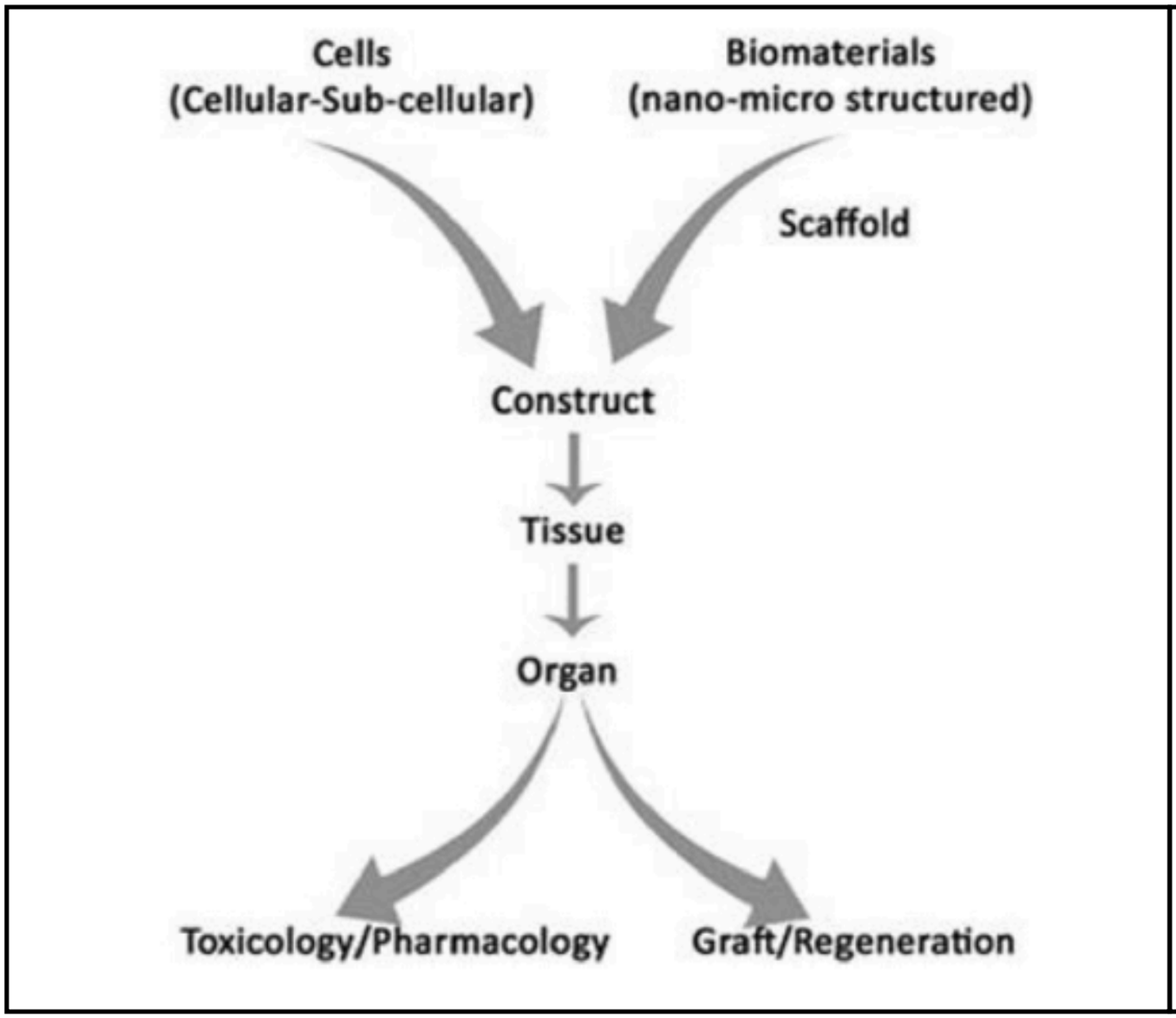
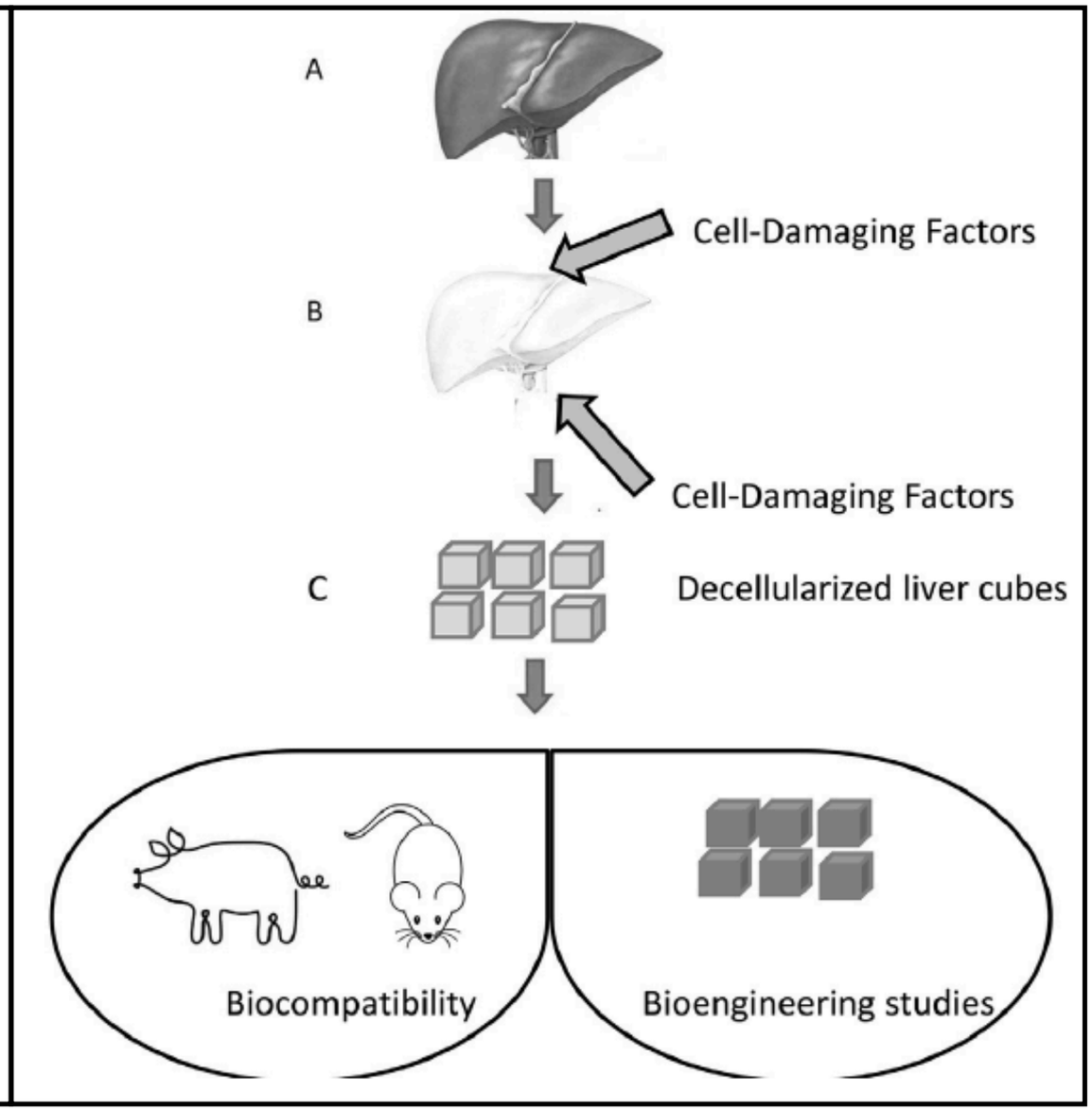
Tissue Engineering and Regenerative Medicine

- 3 decades of research - proper studies rare
- Compared to orthotropic liver transplant benefits minimal
- Tissue revascularisation and integration into host circulation
- Safe metabolically active source of cells
- Hepatocyte transplantation and tissue engineering methods
- Hepatocyte transplantation for metabolic disorders maybe acute liver failure

Liver support strategies: cutting-edge technologies
B. Struecker, N. Raschzok & I Sauer *Nature Reviews Gastroenterology & Hepatology*
03/2014

Tissue Engineering and Regenerative Medicine





M. Cesaretti et al. / Transplantation Reviews 33 (2019) 72–76

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Current status of Xenotransplantation

- Pioneered in the 1960's
- Until 2012 longest recorded survival 9 days
- Pig to Non-human Primate (baboon)
- XenoTX immunosuppression protocol developed
- Survival >900 days possible
- Interspecies immune modulated thrombosis and coagulopathy

B. Ekser et al. / International Journal of Surgery 23 (2015) 240–246

Albumin Dialysis

- Plasma exchange
- M
  -
  -
  -
  -
- S
  -
  -
- Fractionated plasma separation and adsorption **Prometheus**

Recommendations

- Liver support systems (biological or adsorbent) should only be used in the context of RCT (**evidence level II-1, grade of recommendation 1**).
- Plasma exchange in RCT, has been shown to improve transplant-free survival in patients with ALF, and to modulate immune dysfunction (**evidence level I, grade of recommendation 1**).
- Plasma exchange may be of greater benefit in patients who are treated early and who will not ultimately undergo LTx (**evidence level I, grade of recommendation 2**).

Journal of Hepatology **2017** vol. 66 | 1047–1081

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Conclusion

Liver transplant for fulminant failure

Many options when organs few and far between

Most still outside the realms of current clinical practice

Guidelines govern current practice

The arsenal of the liver transplant team continues to grow

Development of skills and understanding should be concentrated

Refer your patient early

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