



INFLUENCIA DEL AUMENTO DEL FLUJO PORTAL EN LA RECUPERACIÓN FUNCIONAL DEL INJERTO “SMALL-FOR SIZE”

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“Small-for-size” syndrome (SFSS)

- Occurs in the context of extensive hepatectomy or partial liver transplant (LDLT, split)
- Defined by clinical signs:
 - Prolonged cholestasis
 - Coagulopathy
 - Refractory ascites
 - Mild-to-moderate AST elevation
 - Encephalopathy



SFSS pathogenesis

- Multifactorial and poorly understood
- Associated with
 - Graft $<0.8\%$ of recipient body weight
 - Excessive portal venous inflow
 - Obstructed hepatic venous outflow
 - Recipient's metabolic and physical state
 - Graft steatosis



Reduced intrahepatic vascular bed



Higher portal flow per gram of liver



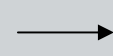
Increased portal pressure



SINUSOIDAL SHEAR STRESS



Sinusoidal endothelial cell injury



Sinusoidal narrowing



Kupffer cell activation



Release of inflammatory cytokines



INJURY & CELL DEATH



Increased portal resistance

“Small-for-size” Syndrome



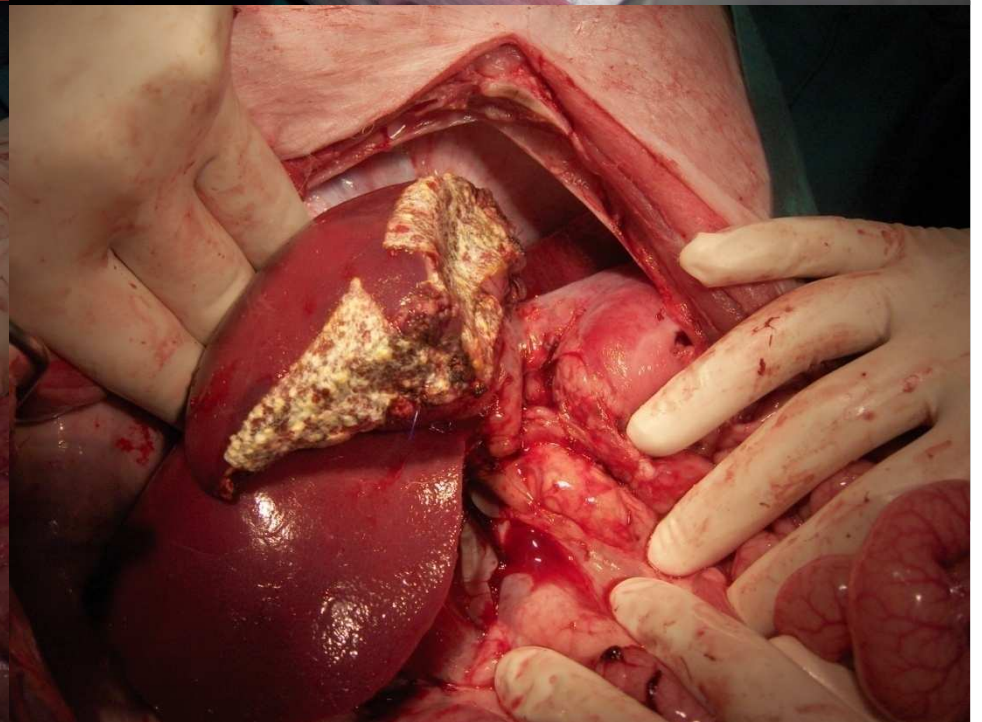
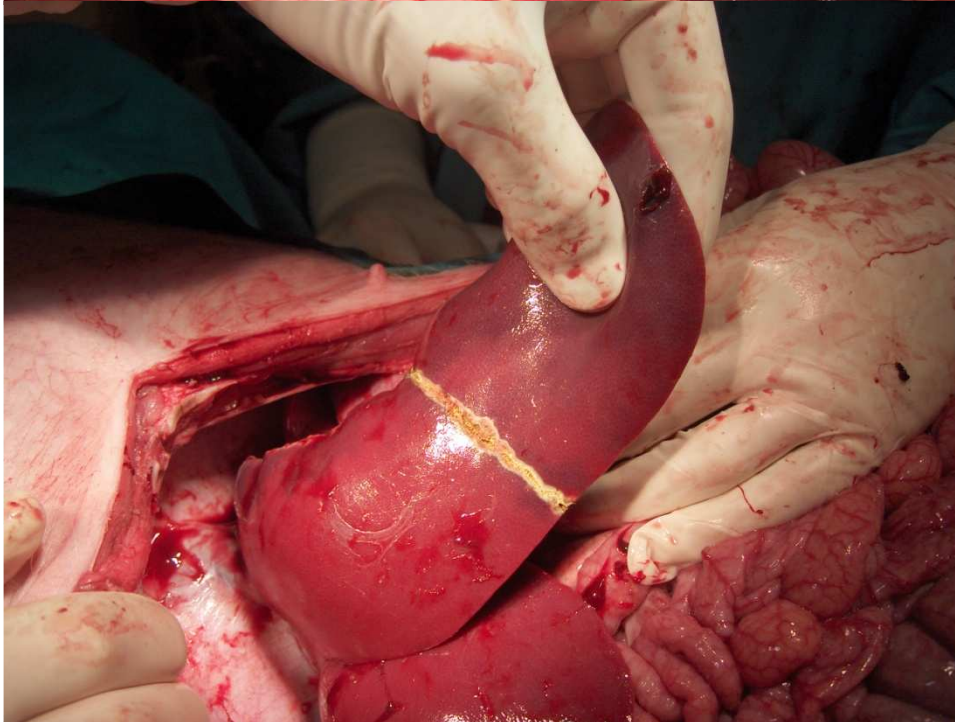
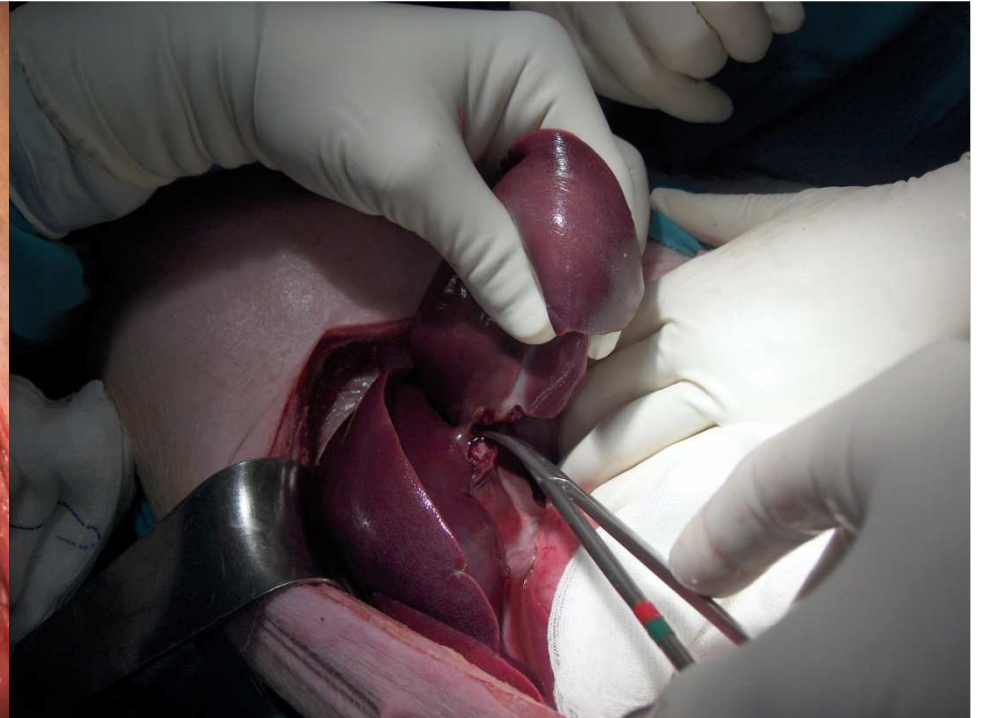
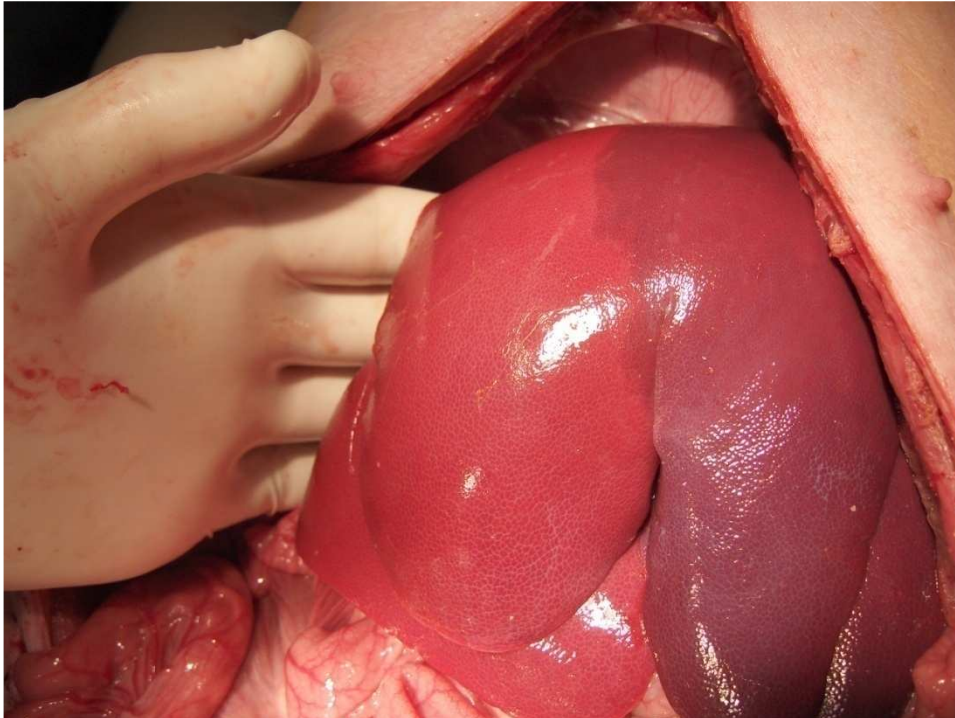
Porcine SFS model

Study the pathophysiology of and hemodynamic alterations associated with the SFS syndrome and graft failure



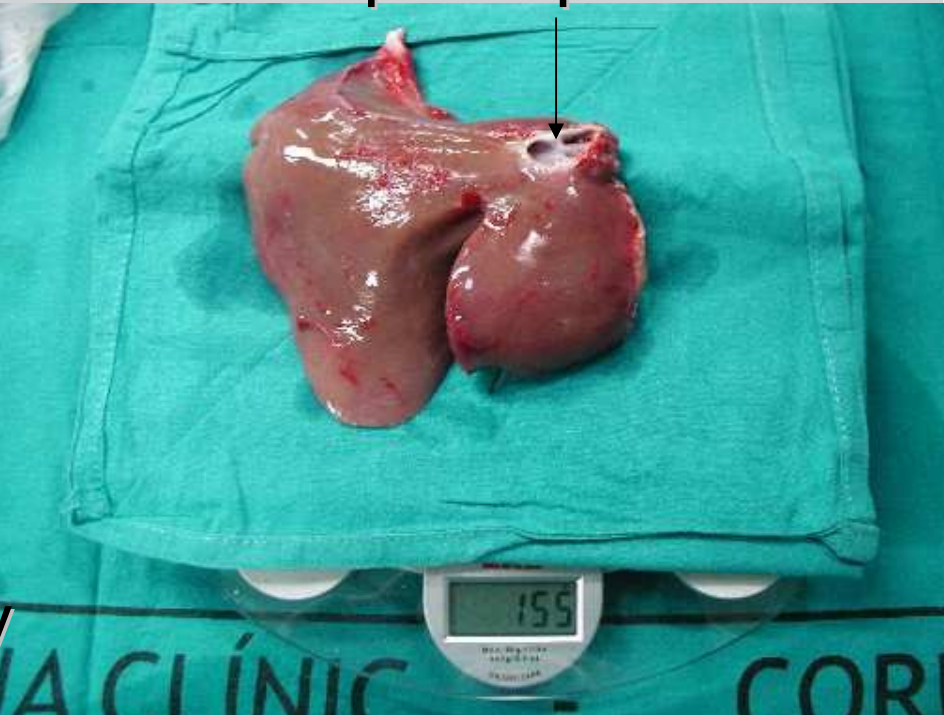
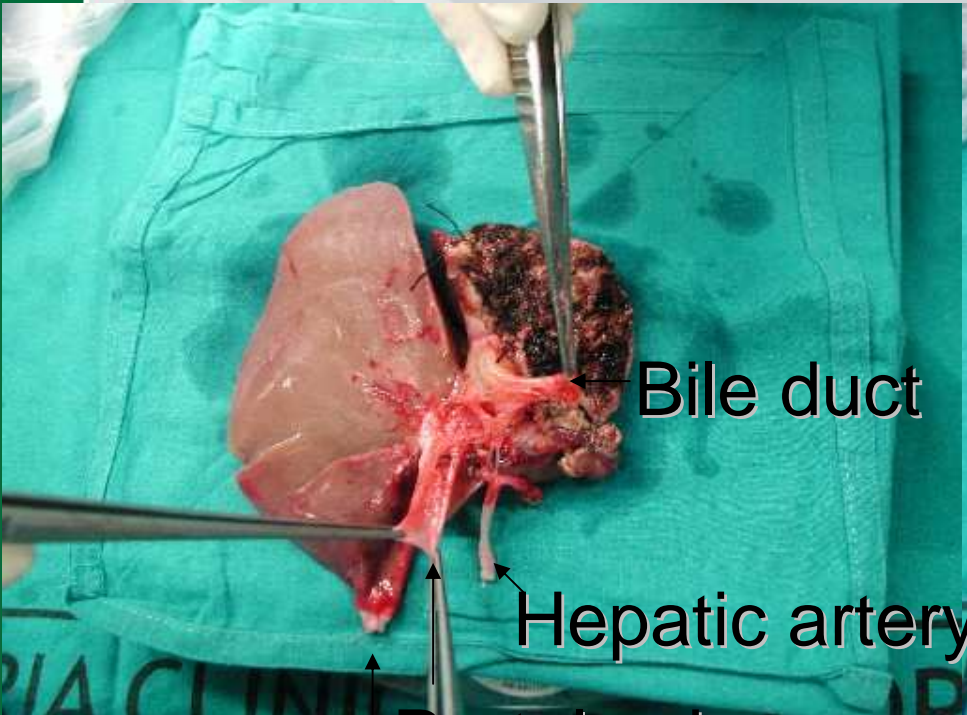
Donor procedure

- Male, body weight **15-20 kg**
- 70% hepatectomy
 - Removal of segments II, III, IV, V, and half of VIII
 - Kelly forceps to crush-clamp parenchyma
 - Electrocautery, haemostatic sutures to treat cut surface
- Graft perfused with 4°C UW, removed, weighed, and cold-stored for 5h





Suprahepatic IVC



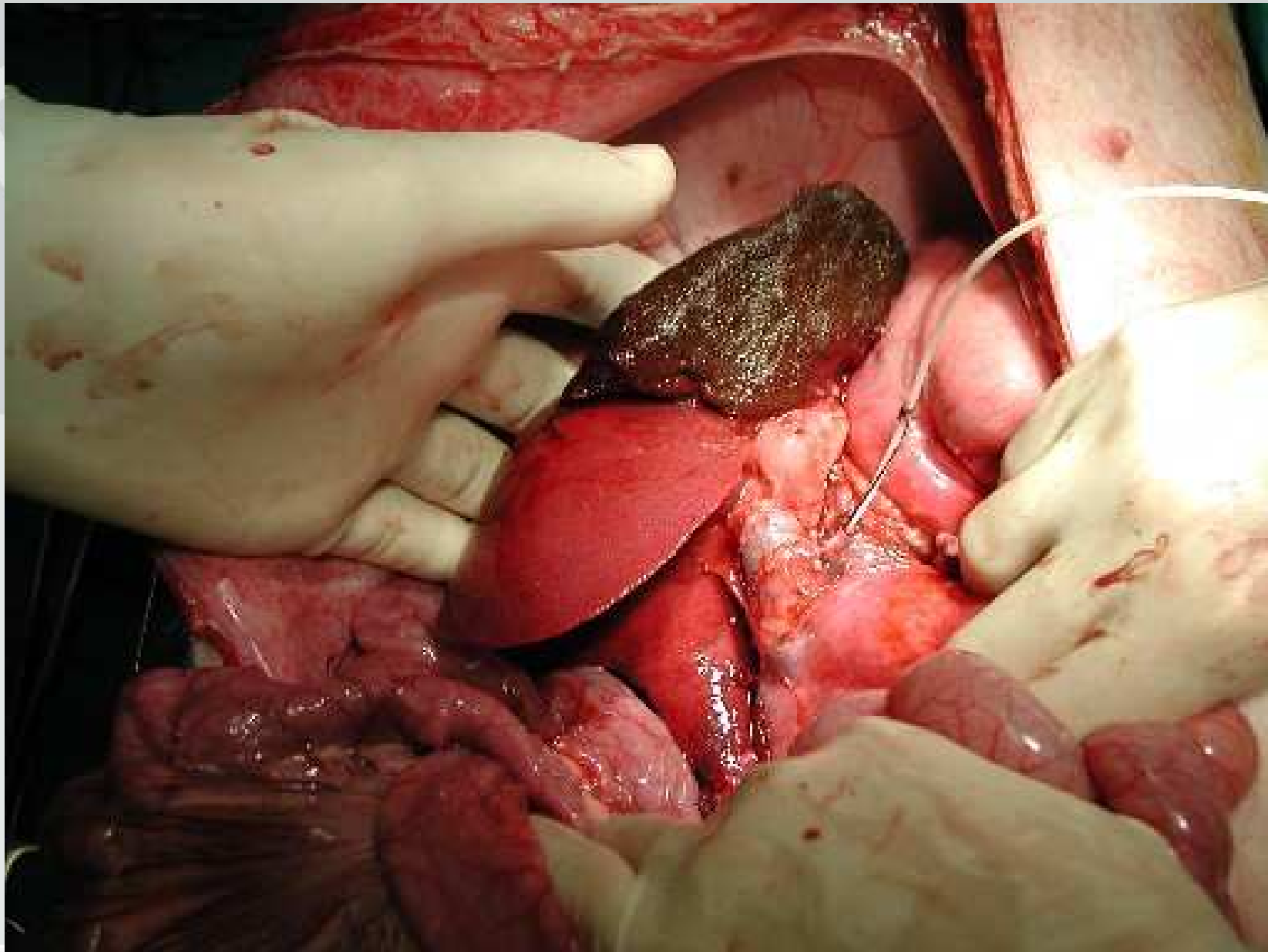
Infrahepatic IVC

Infrahepatic IVC



Recipient procedure

- Implant of graft into larger recipient → **20% SLV**
- Male, body weight **30-35 kg**
- Total hepatectomy and subsequent implant of partial graft
- No veno-venous bypass (anhepatic time < 20min)
- Native liver weighed





Hemodynamic monitoring

- Portal venous pressure and flow, hepatic arterial flow, and hepatic venous pressure measured
 - At baseline in donor
 - After portal and arterial reperfusion
- Cardiac output, central venous pressure, heart rate, mean arterial pressure, and systemic vascular resistance measured continuously



Design

- Recipient animals were followed for up to five postoperative days, in order to determine their survival and the evolution of blood-based parameters reflecting the function and viability of the partial liver graft.
- Intensive pig supervision protocol post-OLT



Study end

- Under general anesthesia on the 5th postoperative day,
 - Reevaluation of hemodynamic parameters
 - Complete extirpation of the graft for weighing and tissue sampling
 - Administration of phenobarbital and KCl
- *Non-survivors were autopsied.*



Portal Hyperperfusion: Mechanism of Injury and Stimulus for Regeneration in Porcine Small-for-Size Transplantation

TABLE 1. Donor, Recipient, Graft, and Transplant Characteristics

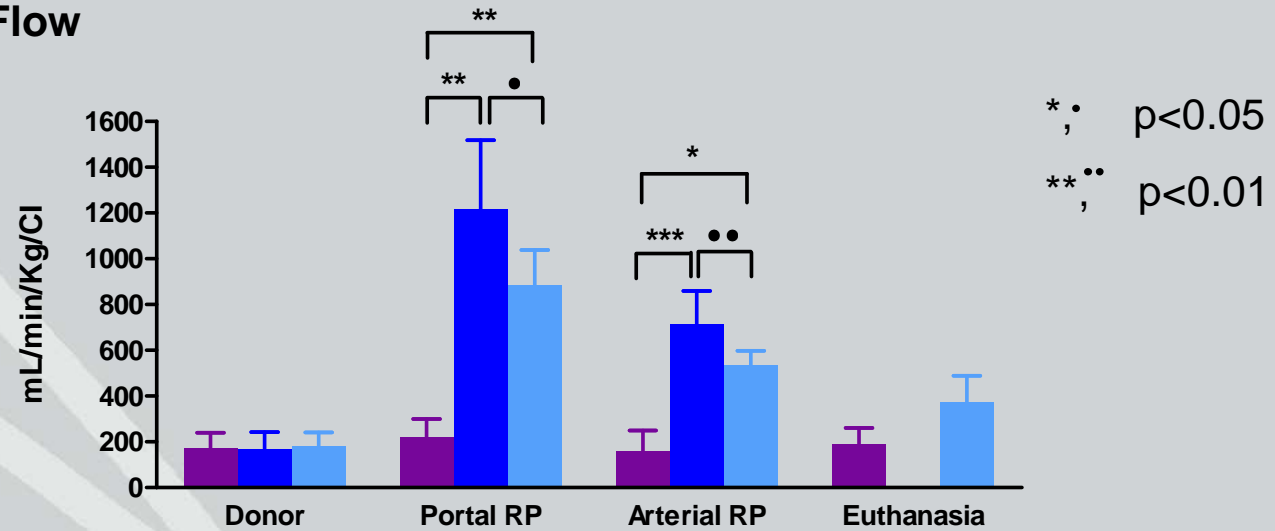
	SFS Group (n = 17)	Whole Liver Group (n = 6)	P
Donor weight (kg)	15.9 (14.6-16.7)	30.9 (29.2-33.0)	0.002*
AST _{D,0} (IU/L)	32.4 (27.5-43.1)	28.5 (23-41.5)	0.355
Bilirubin _{D,0} (mg/dL)	0.4 (0.2-0.5)	0.2 (0.1-0.4)	0.444
QPT _{D,0} (%)	100	100	1
Recipient weight (kg)	30.3 (30.0-34.0)	33.8 (31.3-36.0)	0.178
AST _{R,0} (IU/L)	32 (27-34)	29 (21-32.5)	0.395
Bilirubin _{R,0} (mg/dL)	0.3 (0.2-0.4)	0.1 (0.1-0.2)	0.122
QPT _{R,0} (%)	100	100	1
Partial graft (g)	178 (165-205)	653 (640-686)	0.002*
SLV (%)	23.2 (19.3-25.3)	93.4 (89.4-96.8)	0.002*
CIT (minutes)	334 (313-340)	344 (316-384)	0.958
WIT (minutes)	21 (20-25)	20 (19-22)	0.278

NOTE: The subscript "D,0" refers to the donor at baseline, and the subscript "R,0" refers to the recipient at baseline.

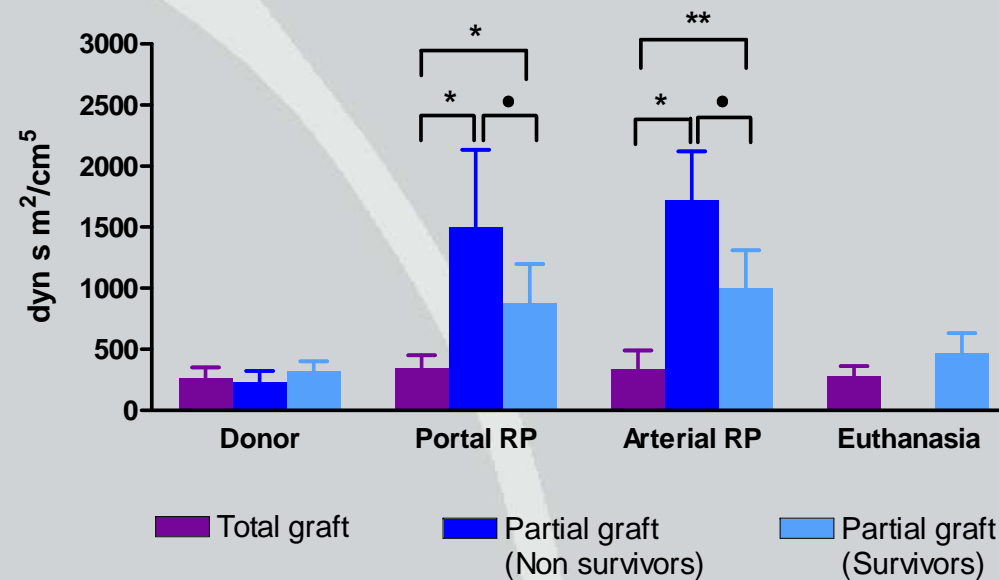
*Statistically significant.

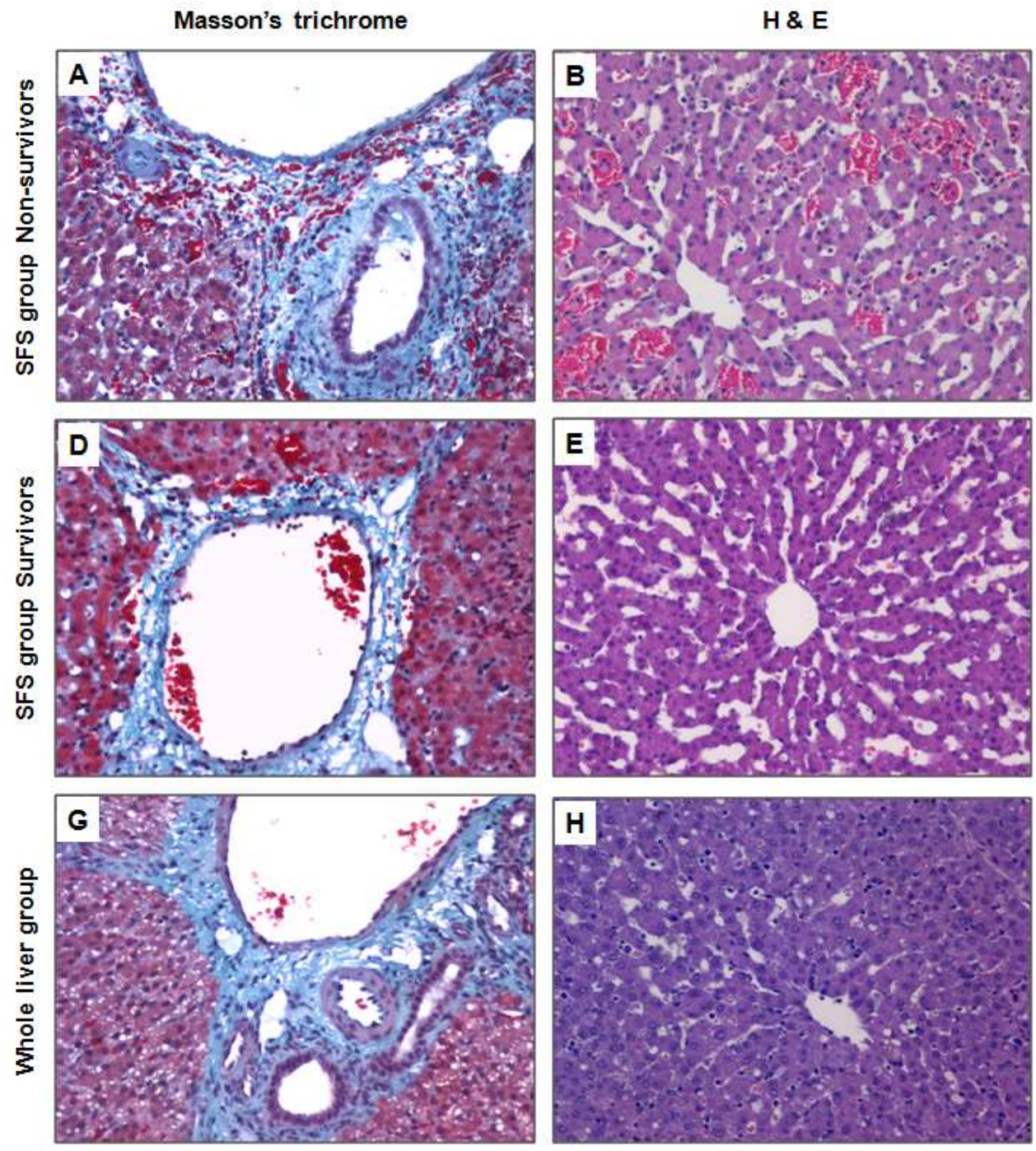


Portal Vein Flow



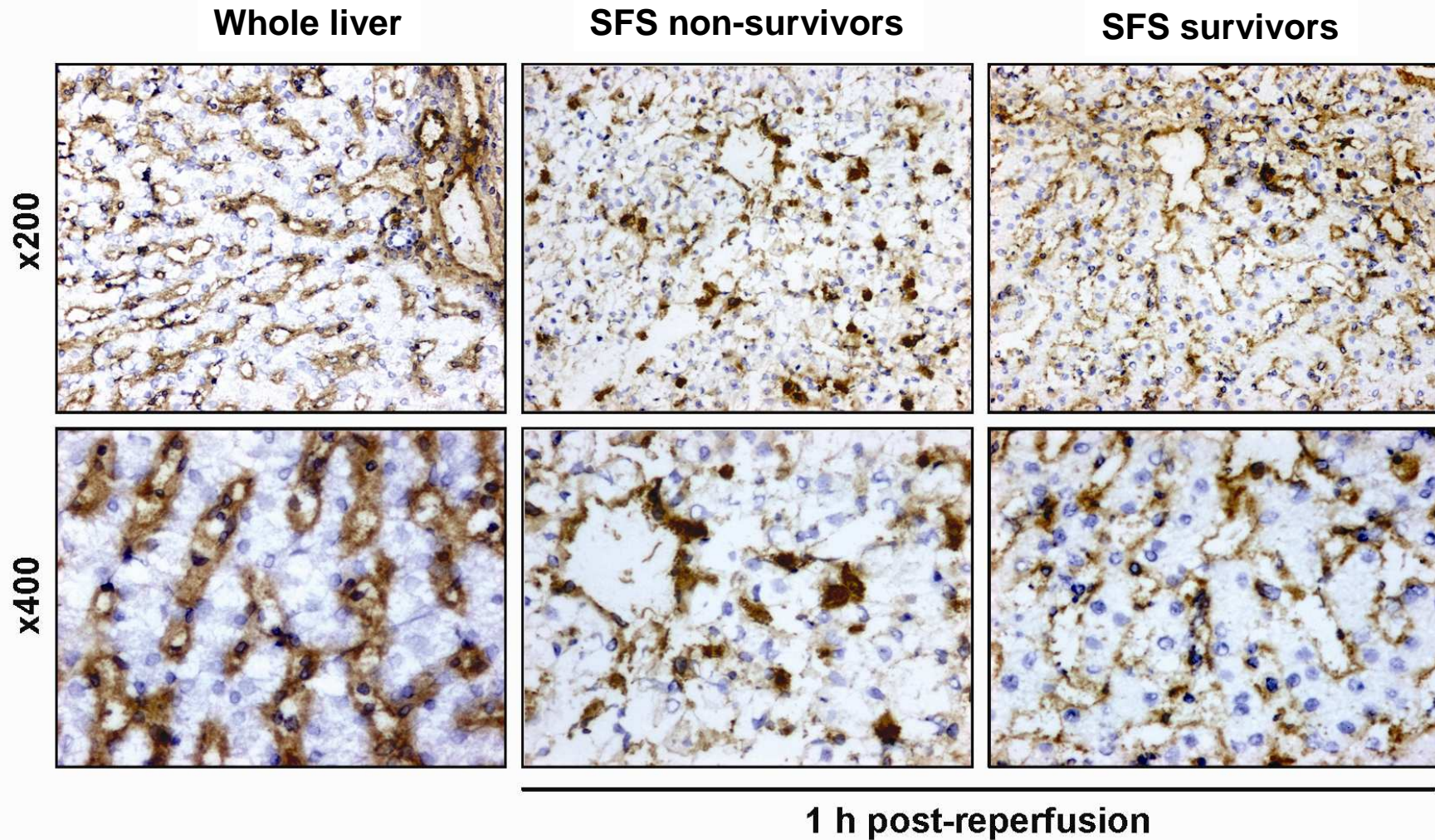
Portal Resistance







Immunostaining anti CD31





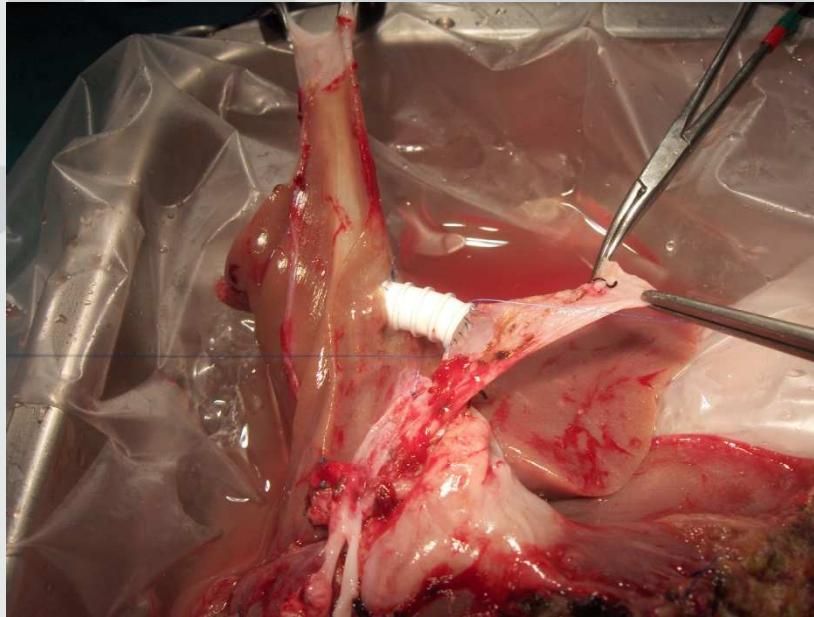
Objective

Decompress prophylactically the portal bed with a calibrated portocaval shunt (PCS), in order to prevent the deleterious consequences of superfluous inflow



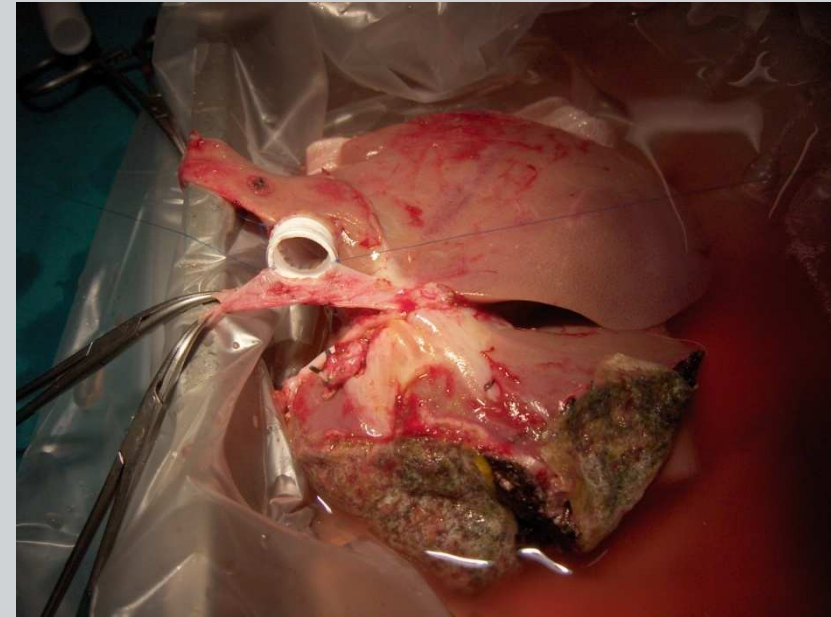
Methods

Group CG: no porto-caval shunt (PCS)



Group S6

6-mm GoreTex® shunt
between PV and IVC



Group S12

12-mm GoreTex® shunt
between PV and ICV

Hessheimer AJ, Ann Surg (in press)



Results

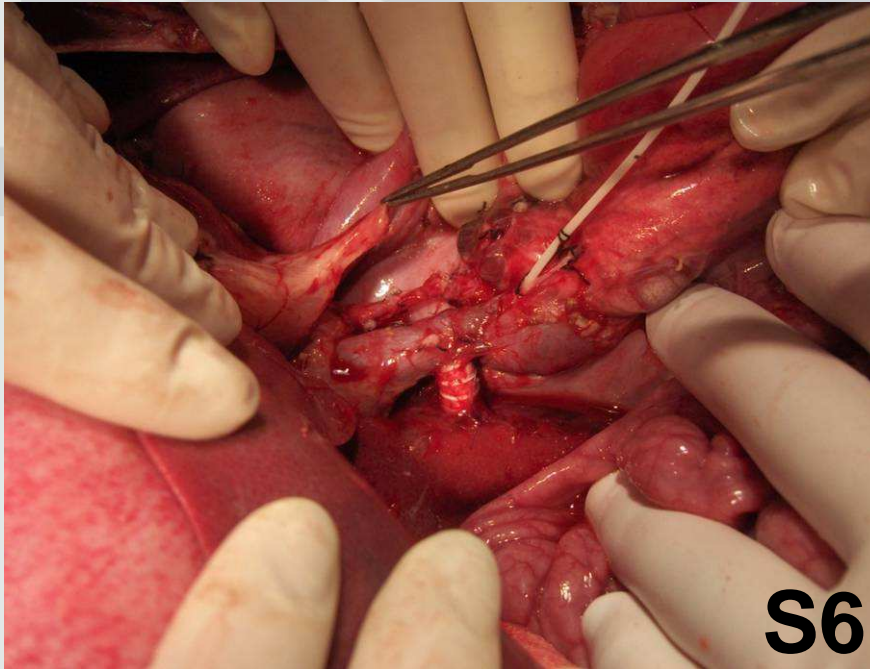
	Group CG (n=17)	Group S6 (n=6)	Group S12 (n=6)	<i>p</i>
AST_{r/0} (IU/L)	40±14	33±8	30±24	ns
Bil_{r/0} (mg/dL)	0.3±0.2	0.3± 0.3	0.2±0.2	ns
PT_{r/0} (%)	98±1	97±5	95±3	ns
Partial graft (g)	195±41	203± 55	196±54	ns
GWBWR (%)	0.60±0.15	0.70± 0.16	0.65± 0.20	ns
SLV (%)	24±9	22±6	23±10	ns
CIT (min)	296±30	305±37	309±35	ns
WIT (min)	23±7	24±7	27±6	ns
PART (min)	49±10	43±6	41±9	ns

AST₀, baseline aspartate aminotransferase; **Bil₀**, baseline bilirubin; **PT₀**, baseline prothrombin time; **GWBWR**, Graft-weight-to-body-weight ratio; **SLV**, standard liver volume; **CI**, cold ischemia; **WI**, warm ischemia; **PART**, portal-to-arterial reperfusion time.

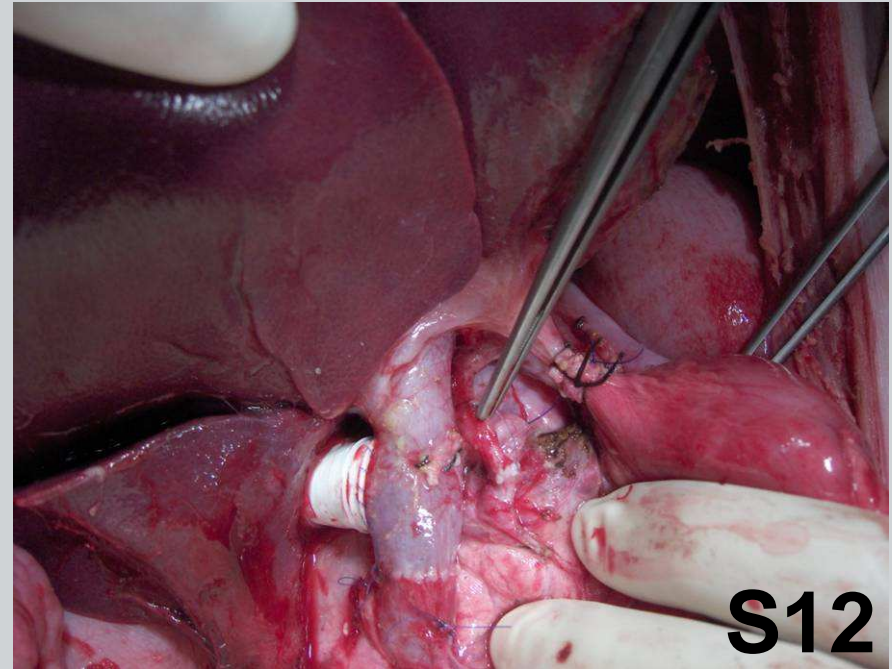
*Groups compared: CG & S6, CG & S12, S6 & S12; *p*<0.05 considered significant.



Gore-Tex[®] porto-caval shunt after reperfusion



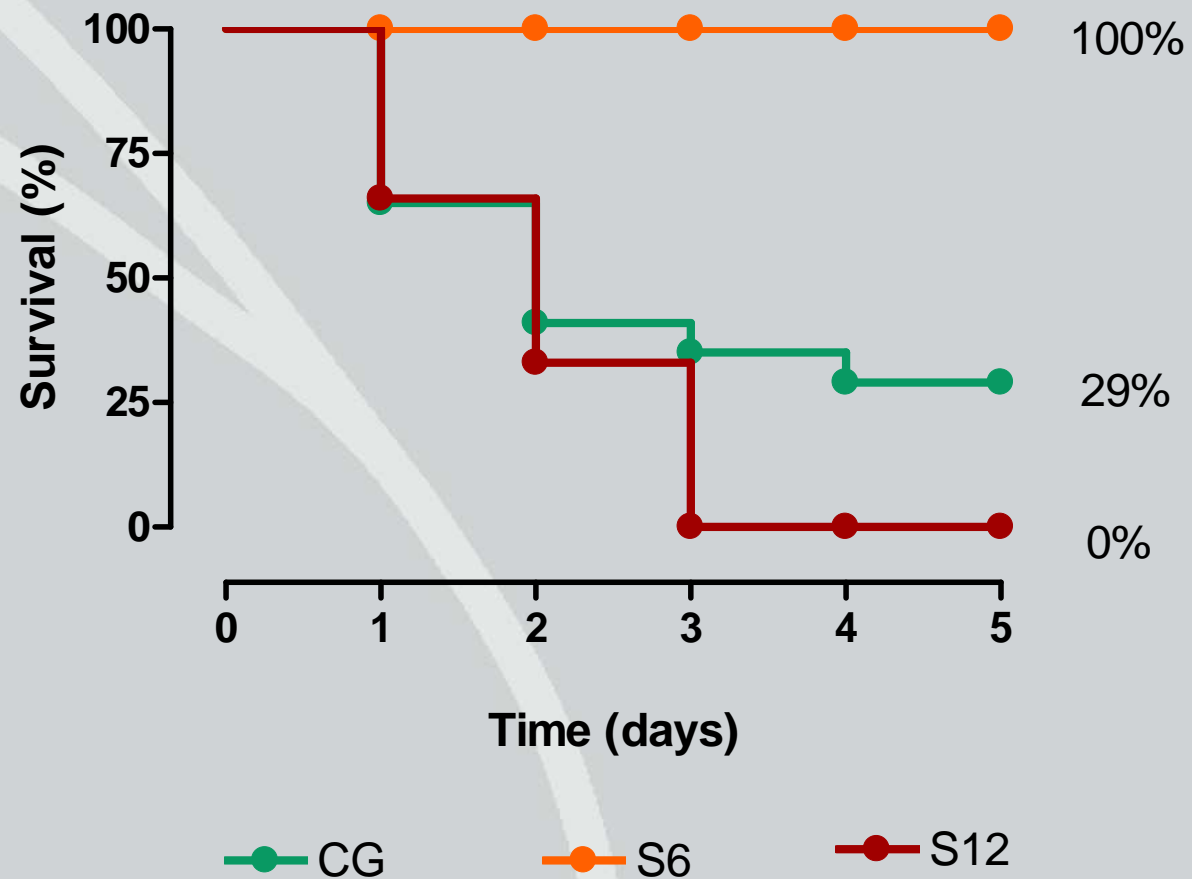
Portal flow reduction
43 ± 9 %



Portal flow reduction
79 ± 3 %

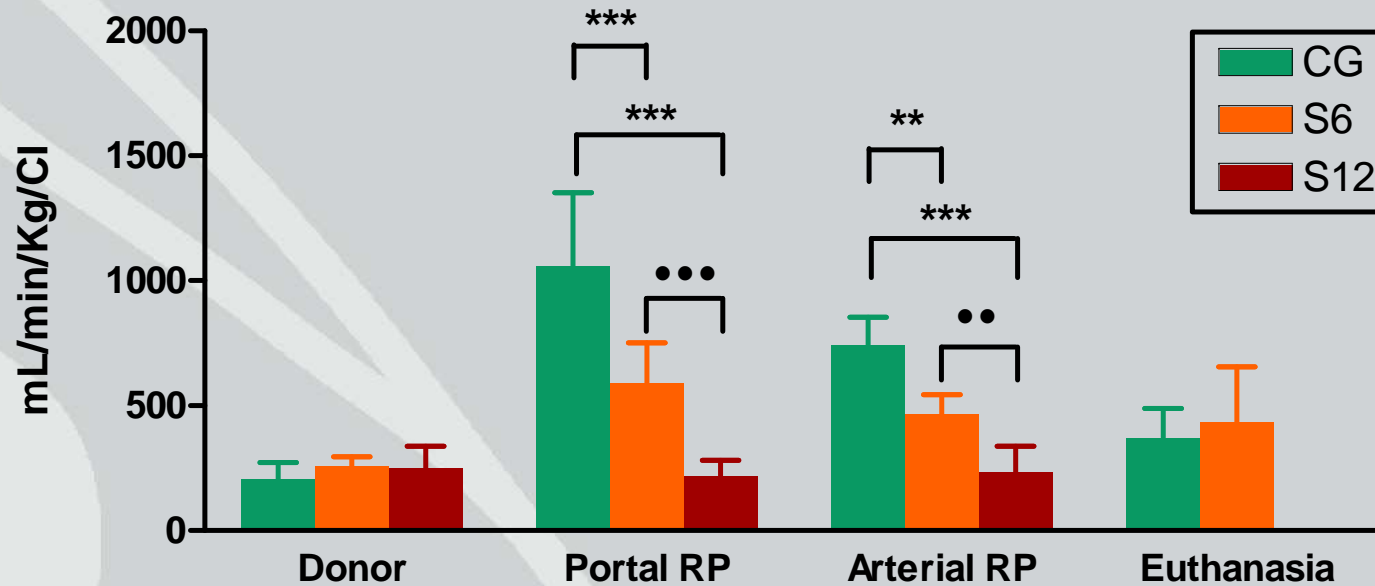


Survival after SFS liver transplantation





Portal Vein Flow

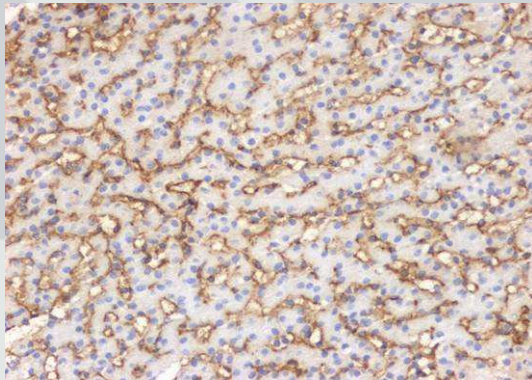


	Basal	Portal RP	Variation
CG	205±67	1061±291	517%
S6	258±38	591±159	229%
S12	250±88	218±62	87%

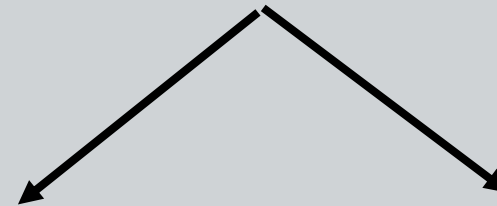


Immunostaining anti CD31

DONOR

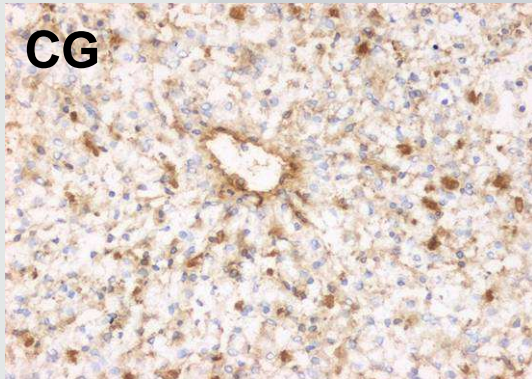


Integrity of sinusoidal endothelium
after portal reperfusion

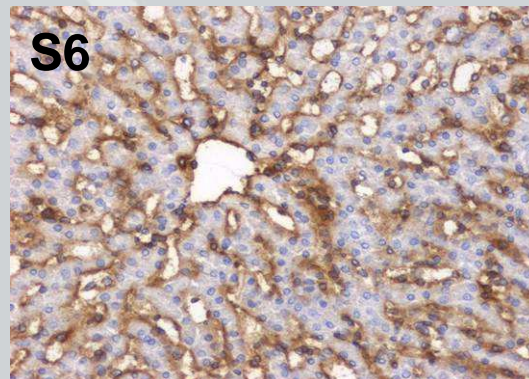


1h REPERFUSION

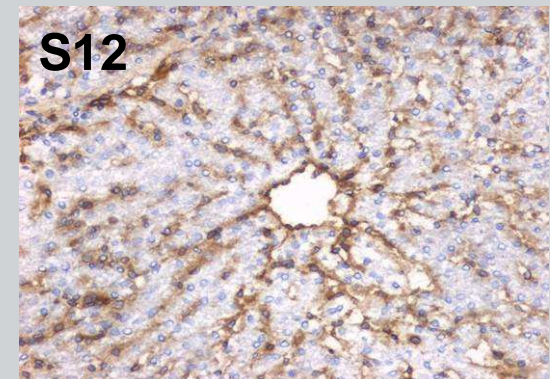
CG



S6

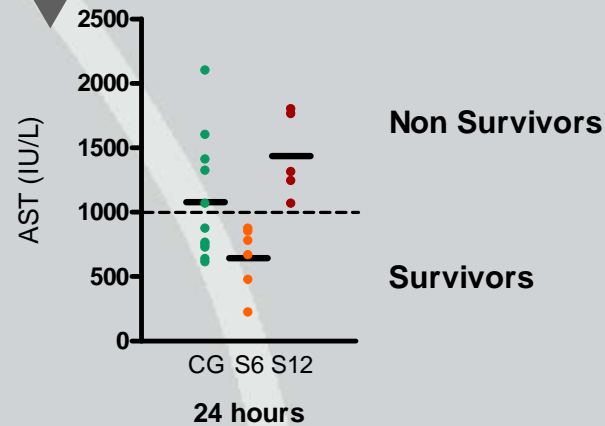
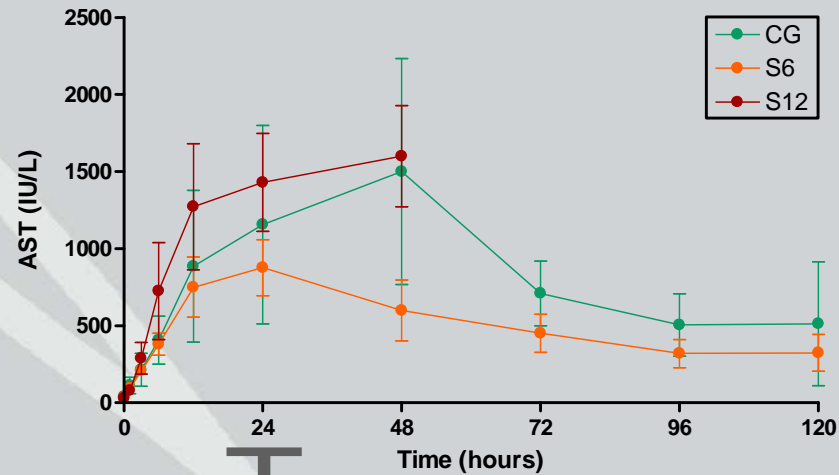


S12





Evolution of biochemical parameters

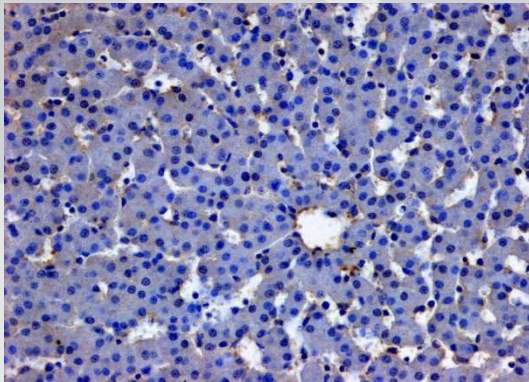


Survivors after 48h in CG n=5 (29%)

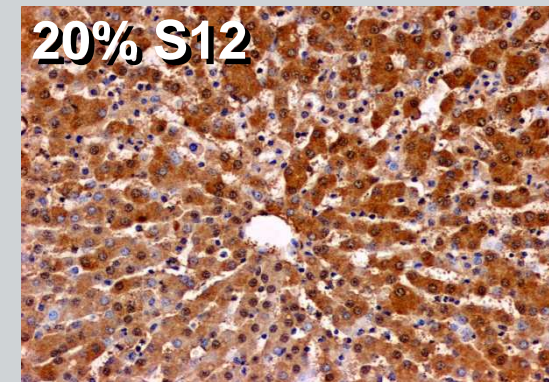
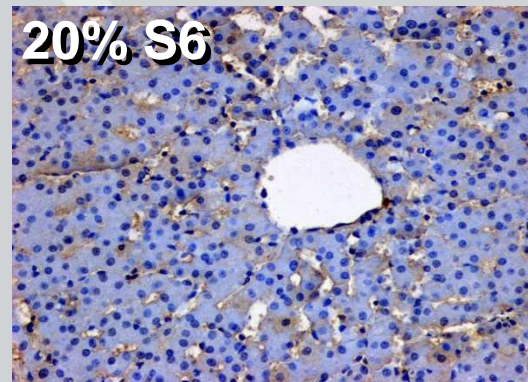
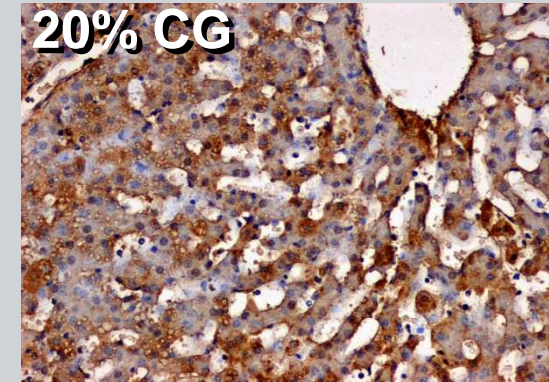
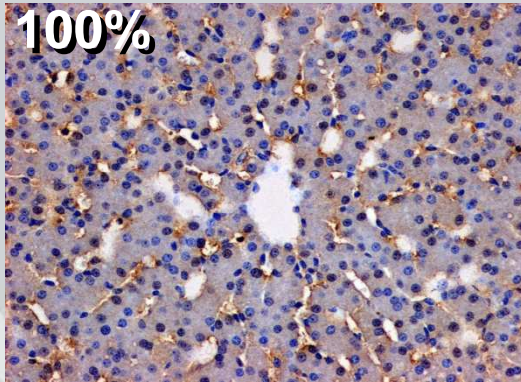


Immunostaining anti ET-1

Donor



1 hour postreperfusion



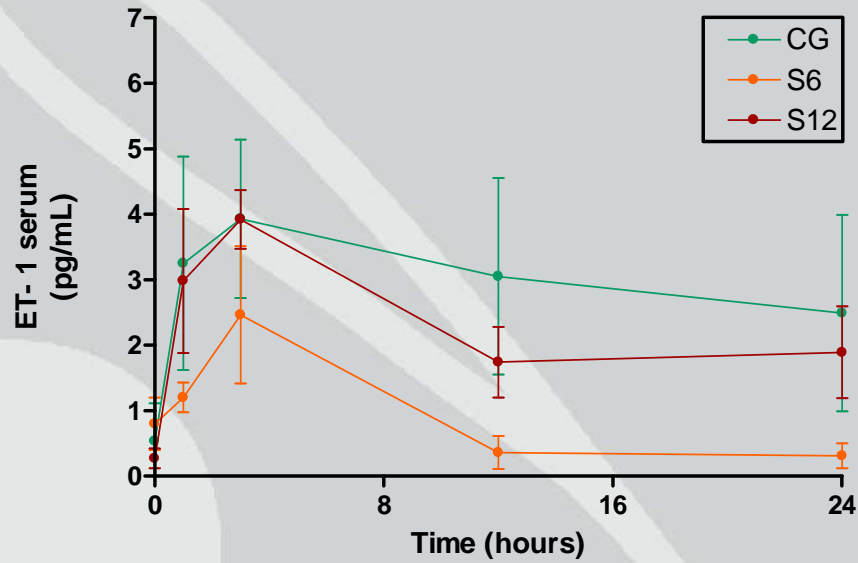
SLV

100% - total graft

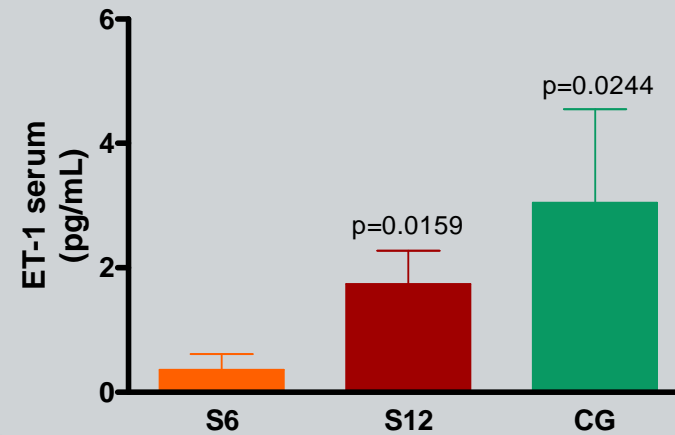
20% - partial graft



Posttransplant Serum ET-1

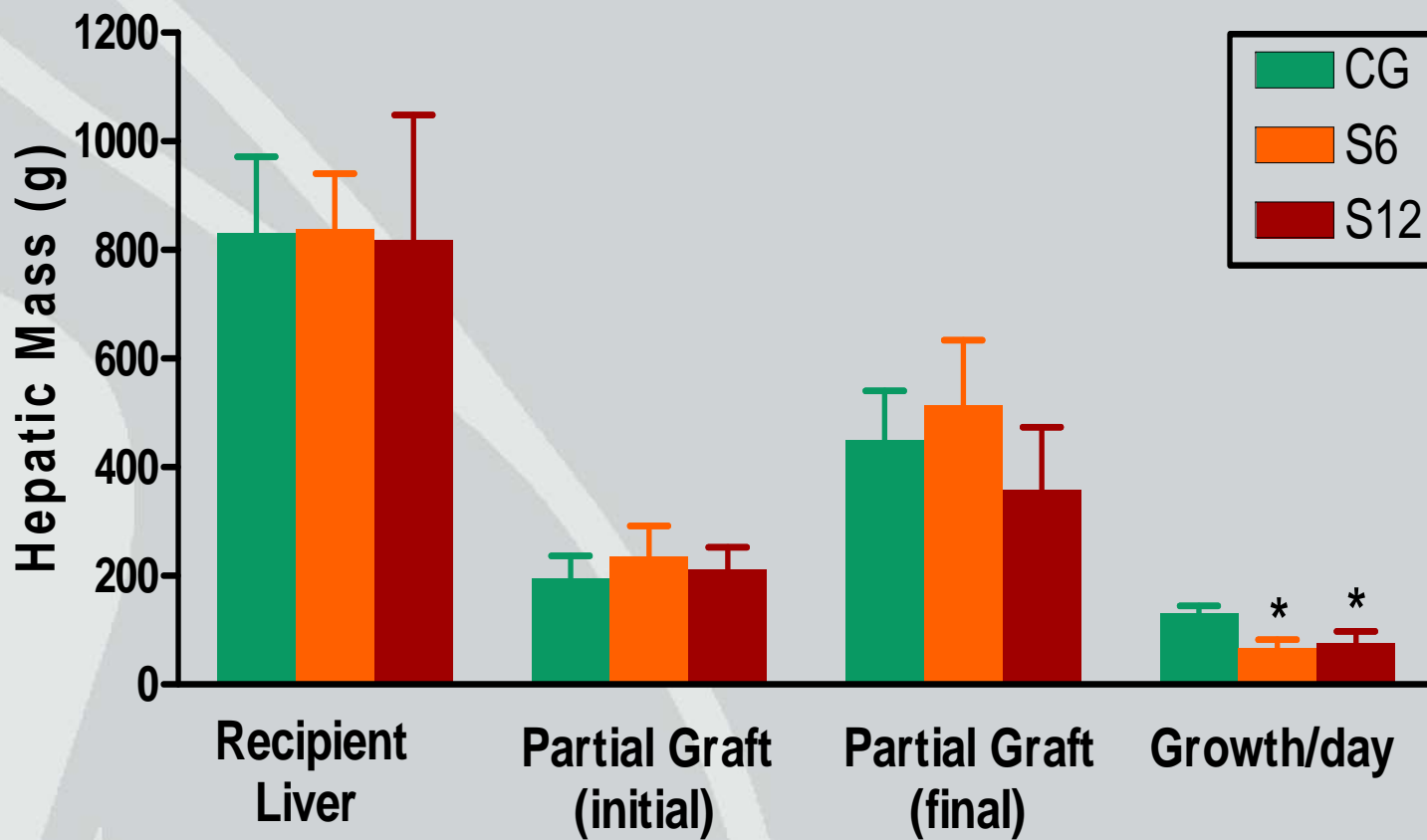


Levels at 12 hours



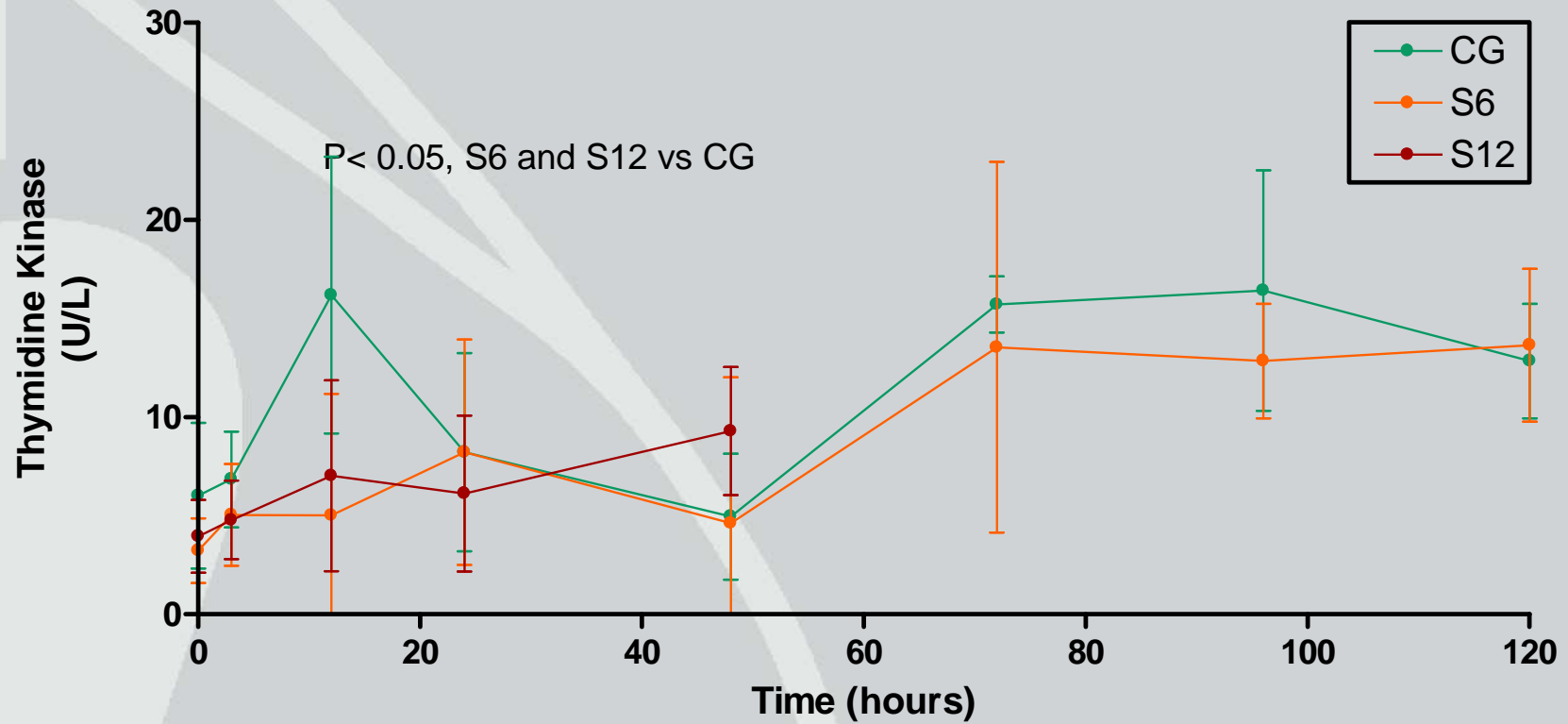


Regeneration of hepatic mass





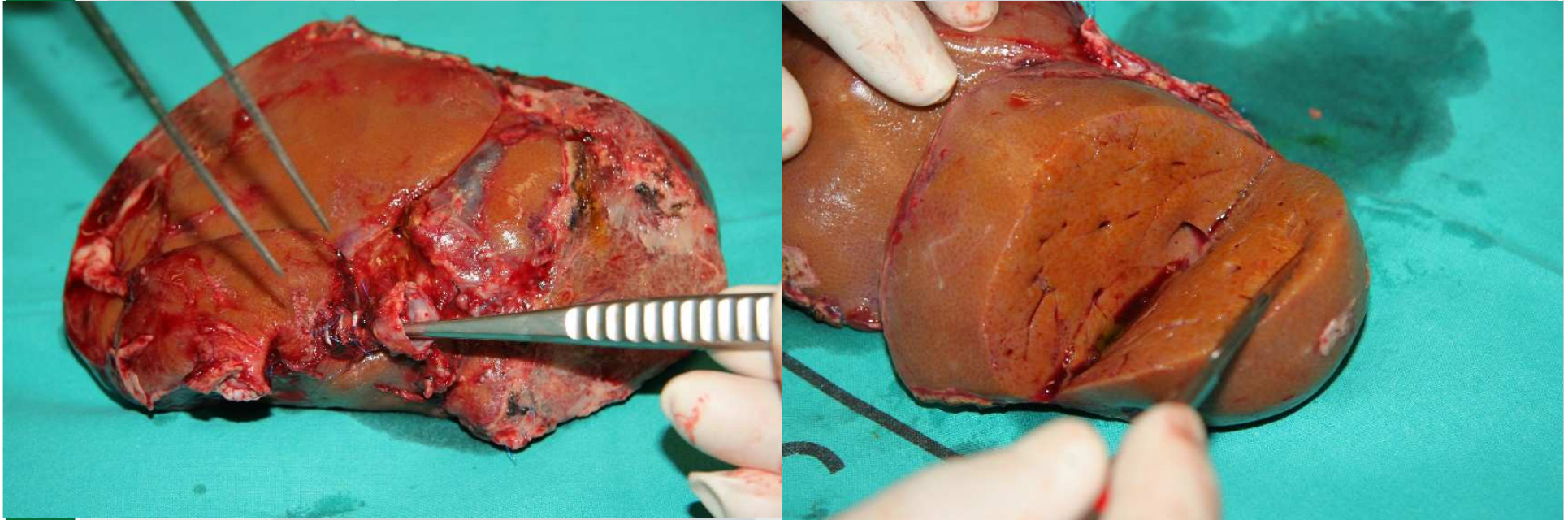
Evolution of serum TK activity



Survivors after 48h in CG n=5 (29%)



Regeneration of hepatic mass

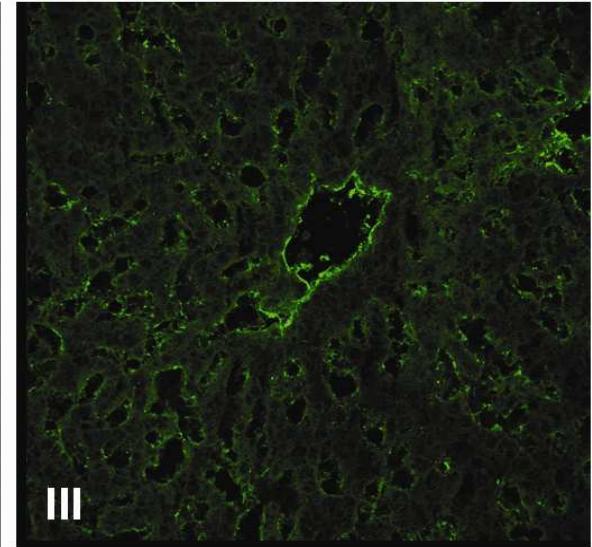
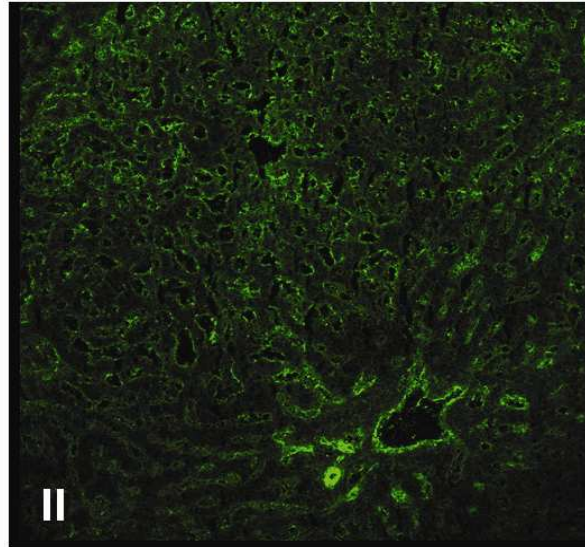
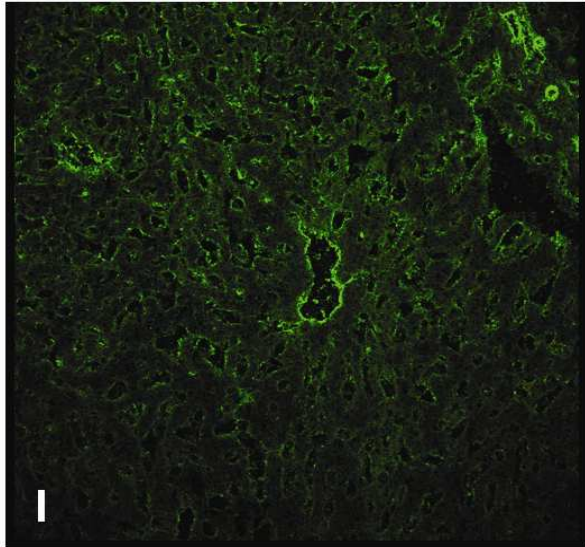


S6 graft at euthanasia (5th postoperative day)

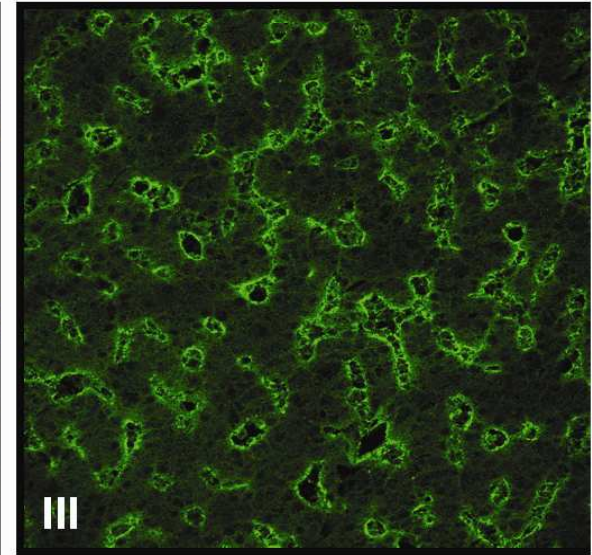
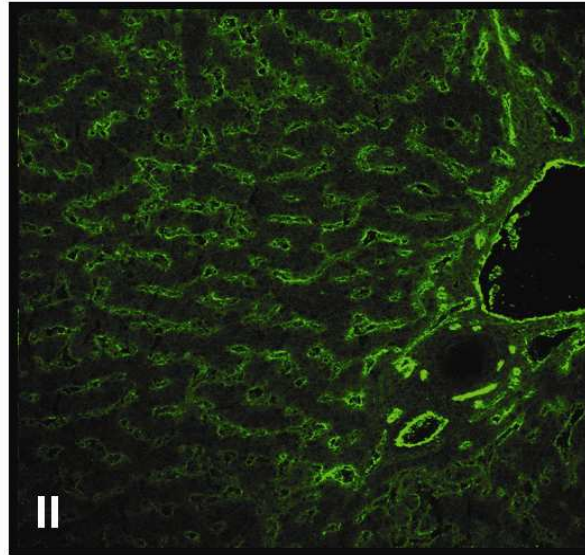
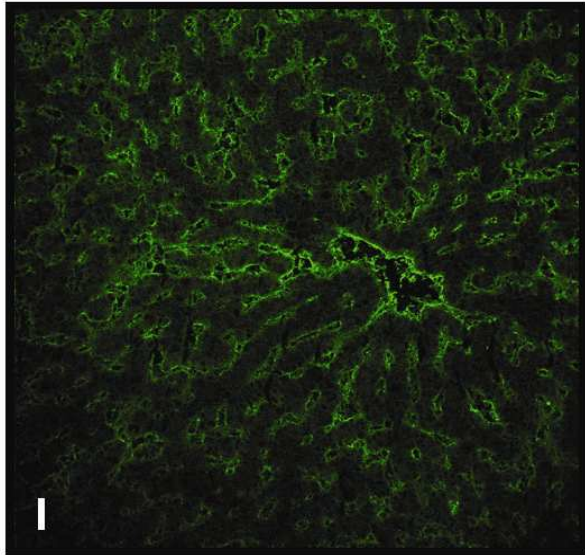


Immunofluorescence of the sinusoidal endothelium

Donor



Euthanasia



x200

x200

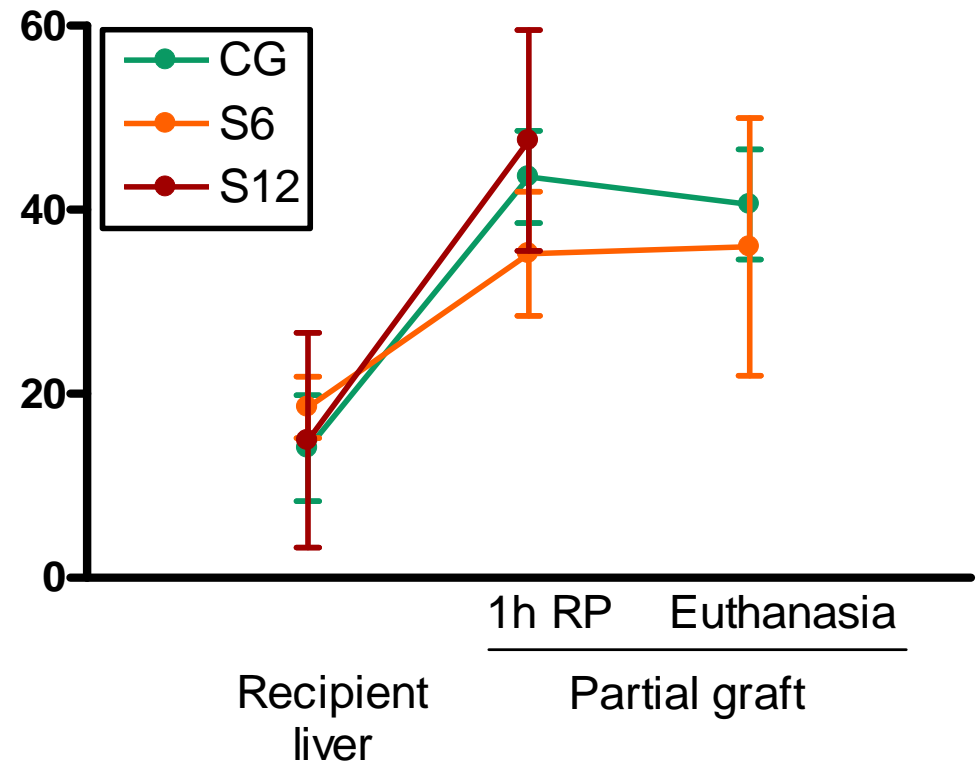
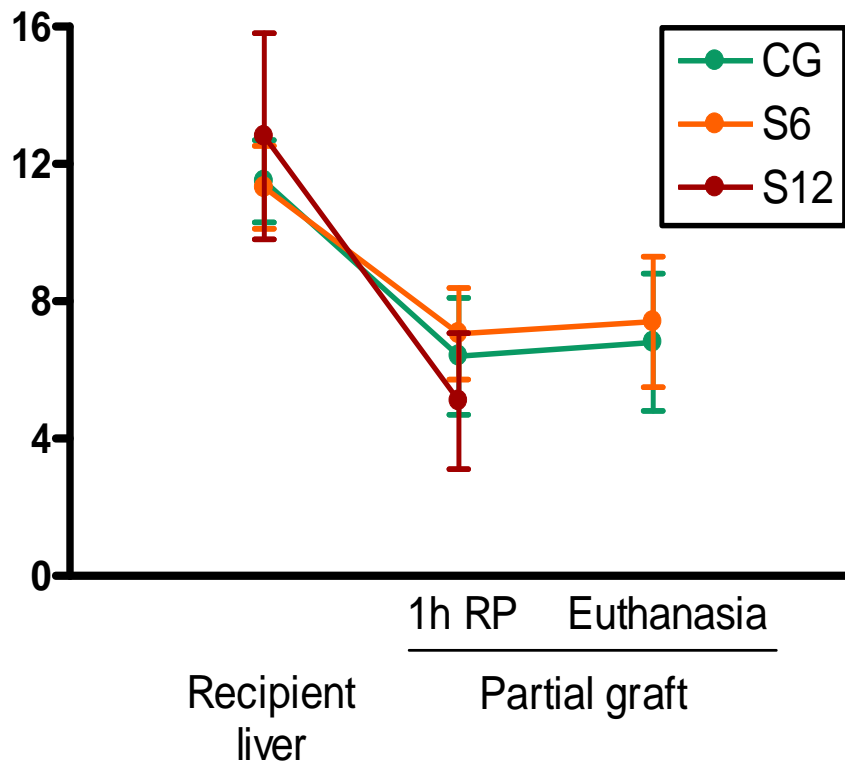
x400

Hepatic function (ICG clearance)

0000000000075						07.08	16:40	5.6	
HORA	E	PDR	R15	CB	BU	PDR	5.6		
16:40	0	5.6	43.2	****	****	R15	43.2		

Plasma Dissapareance Rate (PDR)

Retention Rate 15 min (R15)





Conclusions

- Excessive portal venous flow, pressure gradient and resistance are key factors that are associated with the development of SFS graft failure.
- Hepatic endothelial cell injury occurred very early after reperfusion and to a greater extent in recipients that develop SFS graft failure.



Conclusions

- A calibrated porto-caval shunt (PCS) that maintained postreperfusion PVF around twice its baseline value consistently produced a favorable outcome after SFS liver transplantation.
- Regenerated liver mass is structurally intact but metabolically ineffective.