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TOPIC HIGHLIGHT

2016 Liver Transplantation: Global view

Post reperfusion syndrome during liver transplantation: From pathophysiology to therapy and preventive strategies

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Abstract

This review aims at evaluating the existing evidence regarding post reperfusion syndrome, providing a description of the pathophysiologic mechanisms involved and possible management and preventive strategies. A PubMed search was conducted using the MeSH database, "Reperfusion" AND "liver transplantation" were the combined MeSH headings; EMBASE and the Cochrane library were also searched using the same terms. 52 relevant studies and one ongoing trial were found. The concept of post reperfusion syndrome has evolved through years to a multisystemic disorder. The implications of the main organ, recipient and procedure related factors in the genesis of this complex syndrome are discussed in the text as the novel pharmacologic and technical approaches to reduce its incidence. However the available evidence about risk factors, physiopathology and preventive measures is still confusing, the presence of two main definitions and the numerosity of possible confounding factors greatly complicates the interpretation of the studies.

Key words: Liver transplantation; Reperfusion; Ischemia-reperfusion injury; Hemodynamics; Drug therapy

Core tip: Post reperfusion syndrome (PRS) is a serious intraoperative complication of liver transplantation that can influence recipient's morbidity and mortality. This review provides a description of the evolution throughout the years of the concept of PRS, and gathers the existing evidence regarding the pathophysiologic mechanisms involved and the possible management and preventive strategies.

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INTRODUCTION

Liver transplantation is a major surgical procedure involving important fluid shifts, and which is often performed on patients with hemodynamic alterations related to the underlying liver pathology.

Post reperfusion syndrome is a serious intraoperative complication that typically appears after portal vein declamping, and involves dramatic cardiovascular and metabolic derangements that can influence recipient's morbidity and mortality.

The definition of post reperfusion syndrome (PRS) has evolved throughout the years and its pathophysiology, risk factors and management are still debated.

This review intends to gather the existing evidence regarding PRS, provide a description of the pathophysiologic mechanisms involved and possible management and prevention.

LITERATURE RESEARCH

A PubMed search was conducted using the MeSH database. "Reperfusion" AND "liver transplantation" were the combined MeSH headings.

EMBASE, Cochrane library ClinicalTrials.gov and clinicaltrialsregister.eu were also searched using the same terms.

The abstracts were reviewed by three independent researchers and those not relevant to the search were excluded, only English language articles were taken into consideration.

The quality of the studies was assessed using the Jadad Scale.

The search in PubMed, EMBASE and Cochrane library produced a total of 359 results. Based on the review of the abstracts 307 were found not to be relevant and excluded. The full papers of the remaining 52 articles were independently reviewed by 3 researchers.

The Clinicaltrials.gov search produced a total of 48 studies, only 3 of these were relevant to our review, 2 of them were already published and the complete articles had already been obtained. None of the trials found in clinicalregister.eu were relevant to the search terms (Figure 1).

DEFINITION AND INCIDENCE OF PRS

Post reperfusion syndrome was first defined by Aggarwal *et al*[1] as a decrease in mean arterial pressure (MAP) greater than 30% below the baseline value, lasting for at least 1 min, occurring during the first 5 min after reperfusion of the liver graft (unclamping of hepatic hilum).

Hilmi *et al*[2] later expanded this definition introducing a classification of PRS in mild and severe: (1) mild PRS, defined by a decrease of MAP and/or heart rate (HR) not reaching 30% of baseline value, lasting for less than 5 min, and responsive to an intravenous bolus dose of Calcium Chloride (1 g) and/or epinephrine ($\leqslant$ 100 mcg) without the need to start a continuous infusion of vasopressors; and (2) significant PRS, defined by greater hemodynamic instability, a drop in MAP/HR exceeding 30% of baseline, asystole or hemodynamically significant arrhythmias; or the need to start the infusion of vasopressors during the intraoperative period and to continue throughout the postoperative period. Other presentations of significant PRS include a prolonged (defined as lasting more than 30 min) or recurrent (defined as reappearing within 30 min after resolution) fibrinolysis that requires treatment with antifibrinolytic agents.

Recently, Fukazawa *et al*[3], considering a large study population, gave a temporal description of the phenomenon, dividing post reperfusion hemodynamic recovery into three phases:

Phase 1 - from portal vein reperfusion to 5 min after portal vein reperfusion.

Phase 2 - from 5 min after portal vein reperfusion to hepatic artery reperfusion.

Phase 3 - from hepatic artery reperfusion to 240 min after portal vein reperfusion.

During phase 1, an abrupt hypotension is observed, vasopressors and volume loading are often used to manage hemodynamics in this phase.

Phase 2 is characterized by a progressive decline of MAP until the hepatic artery reperfusion is completed. Finally during Phase 3 a sustained hemodynamic recovery is seen.

Patients with PRS had a significantly higher fall in arterial blood pressure (ABP) in phase 1, and maintained a lower MAP in phase 2, but in phase 3, hemodynamic recovery restored parameters comparable to baseline values. In this study the Aggarwal *et al*[1] definition of PRS was used.

PRS incidence varies largely among the considered studies, ranging from 12%[4,5] to 77%[6]. This variability could be the result of differences in the patient population, and standard pretreatment in each single transplant center. Also the PRS definition used has a role, in fact Hilmi *et al*[2] considered a broader time frame, and added fibrinolysis to their definition of PRS, making it wider than the Aggarwal definition.

RISK FACTORS FOR PRS AND CLINICAL IMPLICATIONS

Several authors have attempted to list possible risk factors for PRS in order to promote better management

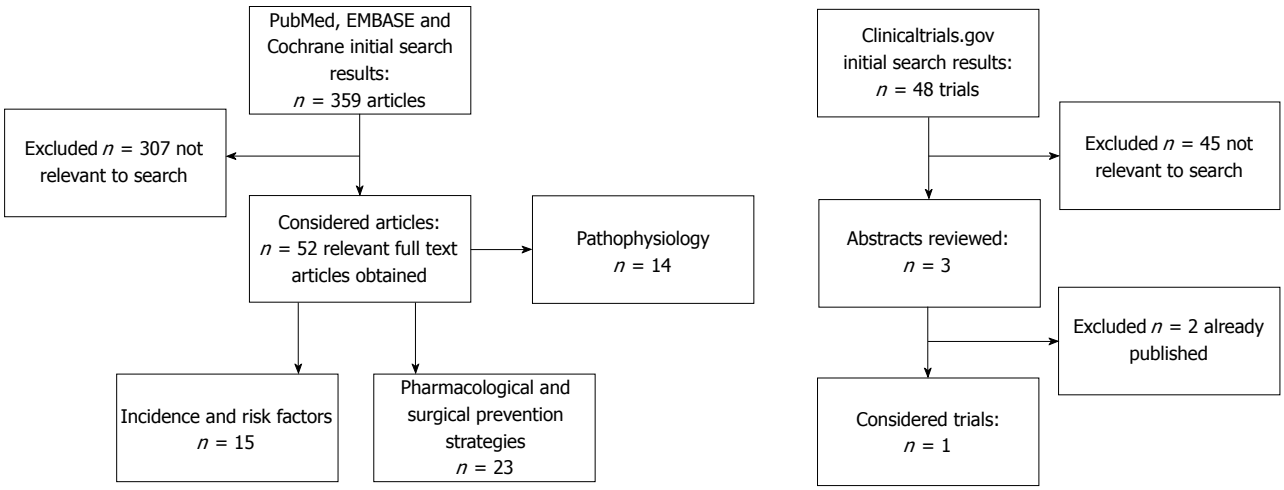

Figure 1 Flow chart showing selection of studies.

and possibly preventive strategies. The data emerging from the literature however is not univocal. A simple schematization of the current knowledge on this matter can be made, by dividing the risk factors in three categories: donor/organ related, recipient related and procedure related.

Literature studies investigating PRS risk factors and clinical implications are synthesized in Table 1.

The main risk factors related to the donor and the liver graft which emerged from the literature review were the age of the donor[3,7,8], the cold ischemia time (CIT)[5,9,10] and, in more recent reports, the Donor Risk Index[3]. The presence of macrovescicular steatosis was also reported by Chung *et al*[11] as a risk factor. Finally the mismatch in size between the recipient and the grafted organ, described by the Body Surface Area Index, represents a risk factor for the incidence and severity of PRS[7]; in fact the syndrome is more severe and frequent in patients transplanted with large organs for their size.

Most of the risk factors emerging from the literature review are related to the recipient of the liver graft. These include the recipient age[2], the model for end-stage liver disease (MELD) score[11,12], a high creatinine level[11,12], a high potassium level[5], a low calcium level[13], and a low hemoglobin level[11]. Only one study has associated the occurrence of PRS with the presence of left ventricular diastolic dysfunction preoperatively[9], whilst others have correlated it with an elevated heart rate (HR)[4,11,13] and reduced central venous pressure (CVP)[3,13]. One study has pointed out a correlation between fulminant hepatic failure and an increased incidence of PRS[12]. The hemodynamic response to clamping of the inferior vena cava (IVC) is also correlated with the development of PRS and has been proposed as an intraoperative "test" for the syndrome. In particular PRS occurs more frequently in those patients who do not react with a substantial increase in systemic vascular resistance index (SVRI) after the clamping of the IVC, showing weaker cardiovascular reflexes[14].

Finally some aspects of the surgical technique have been positively associated with the occurrence of PRS, in particular a prolonged warm ischemia time (WIT)[2], the curtailment of the anhepatic phase of the procedure[13], and the use of classical technique with veno-venous bypass (VVB)[4].

A rapid and homogeneous graft reperfusion visually evaluated by the attending surgeon and an impaired sympathetic activity, were also correlated with the incidence of PRS[15,16].

Most of the studies reviewed were retrospective and involving single transplant centers using different anesthesia protocols, hence it is hard to draw a decisive picture of the most important risk factors for PRS.

PRS increases perioperative mortality[9,10,12], intraoperative need for blood derivatives transfusions[2,4,17], intensive care unit (ICU) and hospital length of stay[2,17] and postoperative kidney injury[9,10].

MECHANISMS OF PRS

PRS genesis involves multiple systems, in this section the main hemodynamic aspects of this syndrome and the implications of the above described risk factors in its occurrence, are described.

Table 2 synthesizes the considered literature studies investigating the mechanisms of PRS.

Hemodynamics

PRS is frequently characterized by a rapid fall of ABP, a reduction of HR and SVRI associated to an increase or, sometimes, a reduction in cardiac index (CI). Pulmonary capillary wedge pressure (PCWP) can decrease or increase, stroke volume index decreases (SVI) while there is usually an increase of both pulmonary vascular resistance index (PVRI) and pulmonary arterial pressure (PAP)[18,19].

It is clear that both the cardiac and vascular func-

Table 1 Incidence, risk factors and graft effects

Ref.	Title	Type of study	No. subjects	Definition of PRS	PRS pretreatment	Incidence	Risk factors	Graft and recipient effects	Jadad score
Garutti Martinez *et al*[14]	Response to clamping of the inferior vena cava as a factor for predicting postreperfusion syndrome during liver transplantation	Retrospective	94	30% drop in MAP within 5' lasting for 1'	Fluid challenge to achieve PCWP at least 12 mmHg before clamping the IVC	28.7%	A low increase in SVRI after clamping of IVC is predictive of PRS, this could be correlated to the sensitivity of baroreflexes and hence a more responsive cardiovascular system in those patients who did not develop PRS	N/A	1
Chui *et al*[5]	Postreperfusion syndrome in orthotopic liver transplantation	Retrospective	321	MAP < 60 mmHg together with classical hemodynamic disturbance (?)	?	12.8%	↑ CIT, ↑ potassium and ↓ bT after reperfusion	-	1
Nanashima *et al*[8]	Analysis of postrevascularization syndrome after orthotopic liver transplantation: the experience of an Australian liver transplantation center	Retrospective	100	30% drop in MAP within 5' lasting for 1'	?	29%	older donor age	↑ post reperfusion lactate and transaminase; ↑ creatinine on POD 7	1
Ayanoglu *et al*[13]	Causes of postreperfusion syndrome in living or cadaveric donor liver transplantations	Retrospective	145	30% drop in MAP within 5' lasting for 1'	20% mannitol + Ca gluconate 1-2 g + 30-50 mEq $NaHCO_3$	48.9%	Shorter duration of anhepatic phase, ↑ calcium requirements, ↑ HR pre-post reperfusion, ↓ CVP during the dissection period	-	1
Hilmi *et al*[2]	The impact of postreperfusion syndrome on short-term patient and liver allograft outcome in patients undergoing orthotopic liver transplantation	Retrospective	338	Hilmi definition	?	55% (significant PRS)	↑ WIT, older recipient age	↑ days on ventilator, ICU stay, hospital stay, need for retransplantation, RBC, FFP, CRYO tansfusions and fibrynolisis, no differences in recipient survival	1
Paugam-Burtz *et al*[10]	Postreperfusion syndrome during liver transplantation for cirrhosis: outcome and predictors	Prospective	75	30% drop in MAP within 5' lasting for 1'	Colloids, 500 mL	25%	↑ CIT, absence of porto-caval shunt	↑ severe acute renal failure, ↑ 15 d mortality	1
Cordoví de Armas *et al*[15]	Rapid and homogeneous reperfusion as a risk factor for postreperfusion syndrome during orthotopic liver transplantation	Prospective	94	30% drop in MAP within 5' lasting for 1'	None	32.90%	SQR (reperfusion's speed-quality) can be considered an unambiguous predictor of PRS	N/A	1
Siniscalchi *et al*[12]	Hyperdinamic circulation in acute liver failure: reperfusion syndrome and outcome following liver transplantation	Retrospective	58	30% drop in MAP within 5' lasting for 1'	N/A	41%	↑ MELD, creatinine, FHF	↑ hospital mortality, ↓ survival rates at 3, 6, 12 mo	0
Khosravi *et al*[17]	Postreperfusion syndrome and outcome variables after orthotopic liver transplantation	Retrospective	184	Hilmi definition	?	17.4% (significant PRS)	-	↑ post reperfusion blood loss and need for RBC, FFP, PLT. ↑ hospital stay	1
Bukowicka *et al*[4]	The occurrence of postreperfusion syndrome in orthotopic liver transplantation and its significance in terms of complications and short-term survival	Retrospective	340	30% drop in MAP within 5' lasting for 1'	?	12.10%	↑ CIT, classical technique with VVB, higher HR at the beginning of operation, no correlation with donor' age, and recipient' age or sex	↑ intraoperative RBC and FFP requirements, ↑ early postoperative complications	1

Fukazawa *et al*[7]	Body surface area index predicts outcome in orthotopic liver transplantation	Retrospective	1228 (3 groups: small for size; controls; large for size)	30% drop in MAP within 5' lasting for 1'	N/A	49% control group, 51% large for size	Lower BSAi is associated with ↓ incidence in PRS, while older donor age ↑ PRS. Note: lower BSAi group had significantly lower age and significantly higher CIT. Low BSAi significantly ↑ arterial hepatic artery thrombosis risk; both low and high BSAi ↓ graft survival	N/A	0
Chung *et al*[11]	Incidence and predictors of postreperfusion syndrome in living donor liver transplantation	Retrospective	152	30% drop in MAP within 5' lasting for 1'	None	34.2%	Macrovescicular graft steatosis, ↑ recipient MELD score, ↑ preoperative HR, INR, bilirubin and creatinine; lower preoperative haemoglobin, ↑ prereperfusion RBC requirements, lower prereperfusion urine output	↑ Bilirubin peak in the first five POD	0
Xu *et al*[9]	Postreperfusion syndrome during orthotopic liver transplantation: a single-center experience	Retrospective	330	30% drop in MAP within 5' lasting for 1'	100 mcg phenylephrine, or 10 mcg epinephrine if SBP < 90 mmHg, graft flushed with 500 mL of 5% albumin before reperfusion	17%	Preoperative LVDD, ↑ CIT	↑ Intraoperative mortality, postoperative renal failure, hospital mortality	1
Kim *et al*[16]	Sympathetic withdrawal is associated with hypotension after hepatic reperfusion	Retrospective	218	30% drop in MAP within 5' lasting for 1'	-	35% (77 PRS *vs* 141 No-PRS)	Low LF/HF and SBP measured before hepatic graft reperfusion were significantly correlated with subsequent PRS occurrence, suggesting that sympathovagal imbalance and depressed SBP may be key factors predisposing to reperfusion-related severe hypotension in liver transplant recipients	N/A	1
Fukazawa *et al*[3]	Hemodynamic recovery following postreperfusion syndrome in liver transplantation	Retrospective	715	30% drop in MAP within 5' lasting for 1'	?	31.6%	↑ donor age, DRI, CVP before reperfusion	No effects on graft survival or early graft dysfunction	1

PRS: Post reperfusion syndrome; MAP: Mean arterial pressure; PCWP: Pulmonary capillary wedge pressure; IVC: Inferior vena cava; SVRI: Systemic vascular resistance index; CIT: Cold ischemia time; bT: Body temperature; POD: Post operative day; HR: Heart rate; CVP: Central venous press; FFP: Fresh frozen plasma; CRYO: Cryoprecipitate; SQR: Reperfusion speed-quality; MELD: Model For end-stage liver disease; FHF: Fulminant hepatic failure; PLT: Platelets; VVB: Veno-venous bypass; BSAi: Body surface Area index; SBP: Systolic arterial blood pressure; LVDD: Left ventricular diastolic disease; LF: Low frequency power; HF: High frequency power; DRI: Donor risk index.

tion are involved in the genesis of the syndrome.

Global hemodynamic aspects: At the time of reperfusion, the recipient's heart has to handle a sudden load of cold, acidotic, diselectrolitemic blood, coming from the liver graft, which can impair its functional reserve. This produces a ventriculo-arterial decoupling which has a multifactorial etiology, involving the composition of the blood load, and also the inflammatory mediators deriving from the liver graft. These mediators have a differential effect on right and left ventricular circulations. In particular,

Table 2 Pathophysiology

Year	Ref.	Title	Type of study	No. subjects	Findings	Jadad score
1993	De Wolf *et al*[22]	Right ventricular function during orthotopic liver transplantation	Prospective	20	RVEF maintained throughout the OLT procedure	1
1994	Ronholm *et al*[36]	Complement system activation during orthotopic liver transplantation in man	Prospective	16	The complement cascade activation demonstrated during OLT is located in the gut and triggered by hypoperfusion of the gut due to clamping of the portal and caval veins. There was a significant correlation between activation of complement with high concentration of C3a anaphylatoxin and development of PRS	1
1995	Blanot *et al*[41]	Circulating endotoxins and postreperfusion syndrome during orthotopic liver transplantation	Prospective	15	No correlation between plasma endotoxins detectable with the LAL (limulus amoebocyte lysate) test and PRS. However the endotoxenemia is still an important risk factor	1
1995	Scholz *et al*[38]	Activation of the plasma contact system and hemodynamic changes after graft revascularization in liver transplantation	Prospective	17 (19 OLT procedures)	Liver graft reperfusion was associated with a significant increase in Kallikrein activity with a concomitant drop in antiprotease activity and high molecular weight kininogen. Hemodynamic changes correlated with the plasmatic concentrations	0
1997	Bellamy *et al*[33]	Changes in inflammatory mediators during orthotopic liver transplantation	Prospective	10	After reperfusion SVRI decreased and CI increased; these were accompanied by increases in TNF-α , TNF-α-R, IL-1β, IL-1 receptor antagonist, IL-6, IL-8; no changes in PAF and Thromboxane B2; Leukotriene C4, D4, E4 decreased	1
1999	Acosta *et al*[21]	Effect of reperfusion on right ventriculoarterial coupling in liver transplantation	Prospective	52	Similar ↑ in CI, RVEDVI, RVSWI in both PRS and non PRS patients, better ventriculo-arterial coupling in non PRS patients due to a decrease in pulmonary vascular elastance	1
1999	Acosta *et al*[31]	Changes in serum potassium during reperfusion in liver transplantation	Retrospective	106	No correlation between changes in serum potassium and PRS	1
2004	Bellamy *et al*[37]	Complement membrane attack complex and hemodynamic changes during human orthotopic liver transplantation	Prospective	40	The formation of MAC complex and degradation of C3,C4 increased markedly at the time of liver graft reperfusion. Concomitantly SVRI decreased and CI increased, with changes correlated to the activation of the MAC	1
2008	Ripoll *et al*[25]	Cardiac dysfunction during liver transplantation: incidence and preoperative predictors	Retrospective	209	22.5% abnormal cardiac response to reperfusion, predictive factors: hyponatremia, lower PAP and lower CVP and PCWP, at the beginning of the intervention. Preoperative echocardiography couldn't predict abnormal response	1
2011	Bezinover *et al*[34]	Release of cytokines and hemodynamic instability during the reperfusion of a liver graft	Prospective	17	The concentration of TNF-α correlated directly with the amount of catecholamines used to treat hemodynamic instability. No correlation between any cytokine levels and the duration of CIT, the surgical technique, and the quality of the liver graft	1
2012	Xu *et al*[23]	Evaluation of the right ventricular ejection fraction during classic orthotopic liver transplantation without venovenous bypass	Prospective	30	RV function is impaired during the anhepatic and early reperfusion stages, particularly in the high MELD score patients	1
2013	Siniscalchi *et al*[18]	Hyperdynamic circulation in cirrhosis: predictive factors and outcome following liver transplantation	Retrospective	242	Hyperdynamic circulation is associated to ↓ MAP, SVI and ↑ PCWP and PVRI 10 min after reperfusion	1
2013	Escobar *et al*[26]	Stroke volume response to liver graft reperfusion stress in cirrhotic patients	Prospective	271	Non-responder patients (35.7%) had higher MELD score, left atrial diameter and low SVRI at the beginning of the intervention. These patients experienced more early cardiovascular events and ICU stay	1
2014	Tsai *et al*[35]	Ischemic reperfusion injury-induced oxidative stress and pro-inflammatory mediators in liver transplantation recipients	Prospective	14	Malondialdehyde (MDA) is one of the intermediate metabolites from lipid peroxidation and representing a indirectly measure of oxidative stress-induced liver injury. Recipients with higher values of preoperative bilirubin, AST, ALT, MELD score, INR, and blood loss tended to have significantly higher levels of MDA and may suffer more injury from this insult	1

RVEF: Right ventricular ejection fraction; OLT: Orthotopic liver transplantation; C3a: Complement anaphylatoxin 3a; PRS: Post reperfusion syndrome; SVRI: Systemic vascular resistance index; CI: Cardiac index; TNF: Tumor necrosis factor; IL: Interleukin; PAF: Platelet activating factor; RVEDVI: Right Ventricular end-diastolic volume index; RVSWI: Right ventricular stroke work index; MAC: Complement membrane attack; PAP: Pulmonary arterial pressure; CVP: Central venous pressure; PCWP: Pulmonary capillary wedge pressure; CIT: Cold ischemia time; RV: Right ventricular; MELD: Model for end-stage liver disease; MAP: Mean arterial pressure; SVI: Stroke volume index; PVRI: Pulmonary vascular resistance index; SVRI: Systemic vascular resistance index; ICU: Intensive care unit.

many inflammatory mediators have a vasoconstricting effect on pulmonary arterioles, and are implicated in the sudden increase of PVRI and PAP[20] in PRS. At the same time the global effect on the systemic circulation is a reduction of the indexed vascular resistance.

Arrhythmias are frequent during reperfusion and can further contribute to the hemodynamic deterioration.

Right cardiac function and pulmonary circulation: The contribution of right cardiac function and pulmonary circulation to PRS are still a matter of debate.

Acosta *et al*[21] studied a population of cirrhotic patients undergoing OLT in order to evaluate the right ventricular (RV) function in PRS. Their findings show that both non-PRS and PRS patients have a similar increase in CI, right ventricular end diastolic volume index (RVEDVI) and right ventricular systolic work index (RVSWI). On the other hand, patients who did not develop PRS had a greater decrease in the elastance of the pulmonary arterial bed, entailing a better ventriculo-arterial coupling. These results suggest that RV function is not strictly implicated in PRS, but it is the alterations in the pulmonary arterial response to reperfusion that alters ventriculo-arterial coupling, leading to the hemodynamic manifestations of the syndrome.

The stability of RV function throughout OLT, had already been described by De Wolf *et al*[22].

More recently, Xu *et al*[23] evaluated right ventricular ejection fraction (RVEF) in a series of 30 patients undergoing classic OLT without VVB, finding that baseline RVEF was lower than the expected normal value, decreased significantly throughout the procedure until 5 min post reperfusion. After 5 min post reperfusion RVEF started to increase, reaching levels higher than baseline value at 48 h post operatively. In this study RVEF correlated significantly with intraoperative SVI alterations and PRS incidence. Moreover, higher MELD patients had lower baseline RVEF. These findings are in contrast with the ones of previous studies, and this divergence was attributed to the different surgical techniques adopted. In fact, the surgical technique adopted greatly influences RV preload during the anhepatic and reperfusion phases, and notably RVEF is highly preload dependent.

Cirrhotic cardiomyopathy: Cirrhotic cardiomyopathy was initially described as a complication of alcoholic cirrhosis, and has been recently recognized as an independent entity. To date, there are no definite diagnostic criteria for this condition.

It is characterized by an increased stiffness of the cardiac fibers associated with hypertrophy, fibrosis and subendothelial edema. This configures a systolic and/or diastolic dysfunction, electrophysiological abnormalities with a prolonged QT interval and chronotropic incompetence[24].

This condition induces a non-proportional increase in CI or left ventricular (LV) ejection fraction in response to an increase in end-diastolic ventricular pressure. This indicates an inadequate ventricular reserve, and an impairment of ventricular relaxation with reduction of ventricular filling. This could have an important role in liver transplantation considering the extreme fluid shifts and preload variations that characterize this surgical procedure.

The role of cirrhotic cardiomyopathy in relation to PRS in unknown and the literature review did not find any study considering this specific aspect. However Xu *et al*[9] found that a left ventricular diastolic dysfunction, diagnosed at the preoperative echocardiogram, was associated with the development of PRS intraoperatively.

Ripoll *et al*[25] defined an abnormal cardiac response as a reduction in preload-recruitable stroke work, evaluated 10 min after reperfusion. They did not find an association between preoperative echocardiographic variables and this intraoperative abnormal cardiac response. However they did find an association of this abnormal cardiac response with hyponatremia and a lower CVP, PAP and PCWP at the beginning of the intervention.

Escobar *et al*[26] used a different definition of myocardial dysfunction as less than 10% increase of SVI after graft reperfusion (non-responder) and found a correlation between non-responders and high preoperative MELD score, left atrial diameter and low preoperative SVRI.

Hyperdynamic circulation: Hyperdynamic circulation[27] is a typical feature of advanced cirrhosis, and its severity is often reflected by the MELD and Child scores.

The pathogenesis of this condition is not completely understood, however it is characterized by a splanchnic arteriolar vasodilatation, mainly responsible for a reduction in SVRI. This is also associated with sodium retention, and a compensatory increase in CI and HR. Nitric oxide (NO) production induced by various cytokines seems to play a role in the development of this condition, since augmented levels of NO are found in advanced cirrhotic patients[28].

In a study from our group[18], patients with hyperdynamic circulation presented a higher blunt in ABP and higher PVRI, PCWP and lower SVI at 10 min after reperfusion, underlying also a possible concurrent cardiac dysfunction.

Bezinover *et al*[29] found a correlation between the preoperative plasmatic cyclic guanosine monophosphate (cGMP) levels and hemodynamic instability after reperfusion; cGMP is produced by soluble guanylate cyclase that is activated by NO. NO is also responsible for oxidant species production by reacting with the superoxide anion radical, producing peroxynitrite and hydroxyl radical that are powerful oxidants. Patients with advanced cirrhosis present also reduced concentrations of antioxidant species such as glutathione[30].

Considering the supra cited involvement of NO in hyperdynamic circulation, this could be a molecular base for the more pronounced hemodynamic instability clinically observed at reperfusion, and could be an interesting target for eventual pharmacotherapies.

Electrolytes and PRS: After reperfusion, an increase in serum potassium and a reduction in serum Calcium are usually observed, evidence in this field is conflicting, Acosta *et al*[31] did not find a direct relation between post reperfusion potassium increase and PRS, whilst Chui *et al*[5] found an increased incidence of PRS in patients with higher post reperfusion potassium levels.

Severity of cirrhosis in the recipient: Preoperative MELD score is indicated as a risk factor in some of the considered studies[11,12]. A more compromised liver function correlates with hyperdynamic circulation, cirrhotic cardiomyopathy, renal dysfunction with alterations in serum electrolytes and impaired coagulation with a higher need for blood products transfusions, these conditions and their role in PRS pathophysiology were already described above.

Ischemia-reperfusion injury to the liver graft and organ-related factors

The ischemic injury starts developing during the storage period of the liver graft, and it is characterized by the activation of xanthine oxidase, NADPH oxidase and various lytic enzymes by the cytoplasmic increase in calcium levels within liver cells, together with the production of reactive oxygen species (ROS) and inflammation. After reperfusion, cellular swelling is observed due to an altered Na^+/K^+/ATPase function and the release and delivery of ROS in the local and the systemic circulation, inducing Kupffer cells to produce cytokines. There is also a local imbalance between endothelin-1 and NO production, which induces a vasoconstriction of sinusoids that fosters the entrapment of platelets and neutrophils[32].

These numerous processes produce a wide array of consequences on the grafted organ and most importantly on the recipient's organism, contributing greatly to the pathophysiology of PRS.

Bellamy *et al*[33] demonstrated a post reperfusion increase in tumor necrosis factor (TNF)-α, TNF-α receptor 1, interleukin (IL)-1β, IL-1 receptor antagonist, IL-6 and IL-8 along with the reduction in SVRI and the increase in CI.

More recently, Bezinover *et al*[34] demonstrated a significant correlation between the concentration of TNF-α obtained from the flushed blood at the end of the irrigation of the liver graft, and the need for vasopressors to treat hemodynamic instability after reperfusion; this correlation was not confirmed for IL-1β, IL-2 and IL-8.

Interestingly, cold ischemia time did not correlate with the quantity of cytokines released and with the need for vasopressors. The other aspect underlined by the authors is that the excess of cytokines is not completely removed by the flushing technique used, so that other flushing techniques or alternative pharmacologic strategies need to be investigated.

The baseline pro/antioxidant equilibrium of the recipient could also play a role in the hemodynamic response to liver reperfusion. This aspect, in particular the possible implication of NO, has been partially discussed in the paragraph dedicated to hyperdynamic circulation.

Tsai *et al*[35] studied the plasmatic levels of malondialdehyde, one of the intermediate metabolites of lipid peroxidation, during OLT, and found significantly higher levels of malondialdehyde at 5 min after reperfusion in higher MELD recipients, confirming that more advanced cirrhosis sensitizes recipients to oxidative damage.

The complement system also plays a major role in immune and inflammatory response, and is therefore involved in the reactions to graft reperfusion. Rønholm *et al*[36] investigated the activation of the complement system by dosing the levels of C3, C5 and their degradation products and the formation of the MAC complex during OLT and around the reperfusion period. Their results show a correlation of the severity of the hemodynamic derangement with the levels of C3a, and a stronger activation of the complement system in the portal blood and the intestines. It is speculated that this stronger activation is triggered by the hypoperfusion of the gut during portal and caval clamping. Bellamy *et al*[37] demonstrated a significant activation of the complement cascade after graft reperfusion. Their results show an increase in the formation of the Membrane Attack Complex and concentration of C3 degradation product, with a concomitant drop in C3 and C4 plasma concentrations. The activation of the complement system was significantly correlated with the hemodynamic derangements of the post reperfusion period, but did not influence postoperative liver function tests.

The plasmatic contact system has also been demonstrated to take part in the development of PRS. Scholz *et al*[38] evaluated the levels of Kallikrein, prekallikrein, High Molecular weight Kininogen and some circulating inhibitors such as α2Macroglobulin and Kallikrein inhibitor. Their results show a progressive reduction of the plasmatic levels of the evaluated proteins throughout the anhepatic phase of OLT, followed by a great increase in the activity of Kallikrein in the post reperfusion period, associated with a continued drop in the concentrations of other proteins. This indicates an activation of the plasmatic contact system, most likely caused by the endothelial damage of the grafted organ, which exposes negatively charged subendothelial surfaces. The activation of Kallikrein leads to the production of Bradikinin, a very potent vasodilator, which can mediate some of the

phenomena observed in PRS.

Activated Protein C (APC) and Protein C are largely involved in both the regulation of fibrinolysis during OLT and the modulation of the immune response to reperfusion.

As Ilmakunnas *et al*[39] showed in their study, a large amount of Protein C and APC is sequestered within the liver graft at the time of reperfusion. This is related to the activation of Kupffer cells as part of ischemia reperfusion injury, and has a role in modulating the immune response triggered by it, by reducing the amounts of TNF-α and IL-8 released by the graft after reperfusion, in part responsible for the hemodynamic response of the recipient.

The extremely wide array of processes described give a picture of the physiopathological response to ischemia-reperfusion injury, and the extreme complexity of PRS. However if on the one hand side the syndrome is produced by a large number of factors, all these mechanisms and plasmatic cascades also constitute potential therapeutic and preventive targets of the syndrome.

Intestinal ischemia-reperfusion injury: During the hepatectomy phase of OLT the intestines can be badly perfused due to venous congestion and surgical manipulation. After the hepatectomy is completed and without a VVB in place this condition can be further worsened, leading to a degree of failure of the intestinal barrier to contain bacterial products in the lumen. At the same time hepatic Kupffer cells are not in place to detoxify these products from the blood. For these reasons some investigators have suggested that intestinal bacterial products could be involved in the pathophysiology of PRS. Blanot *et al*[40,41] collected blood samples from 15 patients undergoing OLT to assess the presence of measurable endotoxemia at the end of the anhepatic phase and after graft reperfusion. Their study found no correlation between the presence of detectable endotoxemia and the occurrence of PRS. However it must be noted that the number of patients considered in this study was very small, hence these results do not categorically exclude a possible involvement of lipopolysaccharide (LPS) and its multiple effects in the pathophysiology of PRS. Tsoulfas *et al*[42] in an animal model investigated the activation of the whole LPS signalling cascade, including CD14, LPS-binding protein, and toll-like receptor expression, induced by different CIT of the liver grafts being transplanted. They found a significant induction of the components of the LPS signalling cascade, which was directly and proportionally correlated to a longer CIT of the grafts. However their study did not address the precise clinical role of this signalling activation and its consequences. To our knowledge to this date no other studies involving the possible role of LPS or other bacterial derived substances in PRS have been carried out.

Marginal grafts: Some studies[2,3] found that recipients receiving marginal grafts were more susceptible to developing PRS. The two aspects more frequently involved were graft steatosis and donor age.

Graft steatosis is associated with micro or macrovesicular intracellular lipid deposits, which increase cellular volume and may result in partial or complete obstruction of the sinusoidal space. Moreover, steatotic livers are more susceptible to ischemia-reperfusion damage because of a reduction in energy stores, a decreased capacity to restore ATP levels after reperfusion, a dysfunction of Kupffer cells, an increased leukocyte adhesion and a more vigorous lipid oxidation.

These aspects could explain the more pronounced hemodynamic derangement observed in patients transplanted with fatty livers.

Donor age is a quite non-specific factor, liver ageing implies an increased level of steatosis, higher susceptibility to endothelial injury and decreased synthetic function[43].

Ischemia time: CIT of the liver graft is the most frequently appointed risk factor in the reviewed studies[4,5,9,10]. At a microscopic level, a prolonged CIT is associated with marked alterations of sinusoidal endothelial cells followed by hepatocyte apoptosis, the activation of nuclear factor kappa B (NF-κB) seems to have a role in liver injury and inflammatory response after reperfusion.

In an animal study, Gu *et al*[44] found a significant correlation between the length of CIT and the production of various transcription factors and cytokines such as NF-κB and TNF-α. Neutrophil activity was also interested with an increase in cellular adhesion molecules such as intracellular adhesion molecule (ICAM)-1 and myeloperoxidase.

Interestingly, as mentioned above, Bezinover *et al*[34] did not find a correlation between CIT and the amount of cytokines detected in the blood flushed from the transplanted liver in humans, however we have to say that the temporal frame of CIT evaluated in this study was more restricted (6-10 h) than the one experimentally induced by Gu *et al*[44] (6-24 h). Moreover, differences in graft resistance to ischemia-reperfusion injury could have an effect in modifying these results.

WIT, especially if prolonged, could deteriorate the cellular metabolic deficit because of the toxic metabolites present in venous blood. Only one study[2] indicated WIT as a possible risk factor for PRS.

Procedure related factors

The three most important procedure related aspects highlighted by the studies considered, concern the preservation solutions, the transplantation technique and the washout technique used before reperfusion.

Table 3 describes the considered studies involving

procedure related factors.

Preservation solutions: Preservation solutions are designed to blunt the repercussions of hypothermia and hypoxemia during storage on tissues and cells. The most important repercussions are cell swelling and cytoskeletal alterations, expansion of the interstitial space, intracellular acidosis and generation of oxygen derived species. The main components of a preservation solution are electrolytes, oncotic agents and additives.

On the basis of the main electrolyte concentration, preservation solutions can be divided in Intracellular and Extracellular. Intracellular compositions (Euro-Collins solution, University of Wisconsin solution) present high potassium concentrations, whilst Extracellular compositions (Celsior solution, Histidine-Tryptophan-Ketoglutarate solution, Institute Georges Lopez solution and Tissue and Organ Conservation Solution) have low potassium concentrations.

Oncotic agents are added in order to reduce cell swelling and are represented by hydroxyethyl starch or polyethylene-glycol.

Additives are substances that have various functions mainly related to the reduction of ischemia-reperfusion injury, such as trimetazidine, hormones, proteasome inhibitors, carbonic anhydrase and statins[45].

The different preservation solutions could influence the incidence of PRS by exerting an effect on the liver graft and/or the recipient.

The effects on the graft are related to the rapidity of tissue cooling and the capacity to wash out during flushing before reperfusion. The effects on recipients are due to the possible hemodynamic effects of the specific components of the solution.

We found three literature studies comparing preservation solutions in relation to PRS.

Ko *et al*[46] compared University of Wisconsin solution (UW) with histidine-tryptophan-ketoglutarate solution (HTK), finding a significantly higher incidence of PRS in the HTK group. The incidence of PRS was reduced and not significantly different to UW in the subgroup where the HTK solution was flushed before reperfusion. This effect can be explained by the higher potassium levels found in UW group, and the high Histidine concentration in HTK solution, which can be easily converted into Histamine, resulting in a longer transient vasodilatation in the HTK group. These results were confirmed in another study by Ghafaripour *et al*[47].

García-Gil *et al*[48] compared Celsior solution (CS) with UW, finding a reduced incidence of PRS, lower potassium, magnesium and glucose levels in CS group. They ascribed this hemodynamic effect to the different electrolytes concentrations between the two solutions.

Transplantation technique: The use of VVB during OLT has been extensively discussed in the past, and its role has progressively changed with the advances in the surgical technique.

VVB offers some advantages, such as a restoration of the intestinal and renal venous drainage, that allow for a longer anhepatic phase, increased cardiac filling pressures and improved hemodynamic stability. This is balanced with an increased risk of venous thrombosis and embolism.

Because of the improved hemodynamic stability it offers, the VVB technique has been thought to prevent the development of PRS. To the contrary, various studies have demonstrated that VVB has no protective effect or, in some reports, worsens the hemodynamic response to reperfusion[4,49,50].

However, it is difficult to ascribe a clear causative effect to VVB because of the important biases of the studies evaluated. In fact, the VVB technique nowadays is mainly utilized in a limited number of cases with specific indications, such as re-transplantation or when technical difficulties can be anticipated. These can increase the length of the surgical intervention and possibly CIT and WIT, which also have a role in causing PRS.

Washout technique: The delivery into the systemic circulation of all the mediators produced by the graft subject to ischemia-reperfusion injury is a fundamental step in the pathogenesis of PRS. Graft washout technique has been shown to influence the incidence of hemodynamic alterations after reperfusion.

Fukazawa *et al*[51] studied the effects of a backwards reperfusion from the supra-hepatic Vena Cava after a crystalloid portal flush, against the classical portal blood flush with forward unclamping; they found a significant reduction in intraoperative cardiac arrests, total intraoperative epinephrine dose, post-reperfusion transfusions of RBC and FFP and a nearly significant (P = 0.074) reduction in PRS. The more gradual rewarming of the liver graft, associated to a reduction in blood loss and an improved recipient volemic status granted from the crystalloid flush with backward unclamping, may all have concurred to the improved hemodynamic stability, as observed by the authors.

Ducerf *et al*[52] found a lower reduction in SVRI and MAP 15 min after liver reperfusion in patients where arterial reperfusion anticipated portal reperfusion, *vs* patients where portal reperfusion was performed first. However, the amount of drugs used to treat established PRS did not differ between the two groups. They hypothesized that the gradual release of mesenteric venous pressure in the arterial reperfusion group could be the basis for the improved stability observed.

These data were not confirmed by Moreno *et al*[53], who found a higher increase in CI, PAP, and MAP in the group receiving portal reperfusion first. Gastric and arterial pH decrease was more accentuated in the group receiving the arterial reperfusion first. The incidence of PRS and the use of inotropes were not

Table 3 Surgical prevention/treatment strategies

Year	Ref.	Title	Type of study	Rationale	No. subjects	Definition of PRS	Effects	Jadad score
1992	Jugan *et al*[50]	The failure of venovenous bypass to prevent graft liver postreperfusion syndrome	Prospective interventional	VVBP should grant a better hemodynamic stability during reperfusion	58 (29 VVBP *vs* 29 NBP)	30% drop in MAP within 5' lasting for 1'	No differences in PRS incidence	1
1997	Millis *et al*[54]	Randomized controlled trial to evaluate flush and reperfusion techniques in liver transplantation	Randomized Controlled Trial	The techniques used to flush and reperfuse the graft could have an impact on PRS	88 (4 groups: hepatic arterial or portal vein flush with or without vena caval venting)	Three criteria: MAP < 60 mmHg at 1'; MAP < 60 mmHg at 5'; and a decrease of 30% or more for the MAP percent area under the curve (%AUC) during the first 5'	↓ PRS incidence in patients transplanted with a portal vein flush without vena caval venting versus arterial flush with/without vena caval venting	5
1999	Acosta *et al*[49]	Influence of surgical technique on postreperfusion syndrome during liver transplantation	Prospective interventional	The stability granted by the piggy-back (PGB) technique during the anhepatic phase without the need for VVBP could be extended to the initial minutes of reperfusion	71 (8 VVBP *vs* 43 NBP *vs* 20 PGB)	30% drop in MAP within 5' lasting for 1'	The greatest percent decrease in SVRI, and incidence of PRS, occurred in the VVBP group	1
2000	Durcef *et al*[52]	Hemodynamic profiles during piggyback liver grafts using arterial or portal revascularization	Prospective, randomized	The techniques used to flush and reperfuse the graft could have an impact on PRS	59 (29 HA *vs* 30 PV)	20% drop in MAP within the first 10' lasting for 5'	Initial arterial revascularization of the liver graft leads to a more stable hemodynamic profile. The time lag between arterial revascularization and the following portal anastomosis allows venous mesenteric pressure release	3
2006	Moreno *et al*[53]	Hemodynamic profile and tissular oxygenation in orthotopic liver transplantation: Influence of hepatic artery or portal vein revascularization of the graft	Randomized Controlled Trial	Simultaneous arterial and portal anastomosisis feasible due to the hemodynamic improvement offered by the piggy-back technique with temporary portacaval shunt	60 (30 IAR *vs* 30 IPR)	30% drop in MAP within 5' lasting for 1'	IPR leads to ↑ values of preload parameters, ↑ CO and MAP values than IAR. This increase in pulmonary pressure was lower in the artery group so that IAR of the graft may be indicated in case of poor pulmonary and cardiac reserve	3
2006	Gruttadauria *et al*[55]	Comparison of two different techniques of reperfusion in adult orthotopic liver transplantation	Retrospective	Better hemodynamic stability of caval venting than flushing with cold Ringer Lactate solution	50 (25 portal vein flush, no caval venting *vs* 25 caval venting, no portal vein flush)	30% drop in MAP within 5' lasting for 1'	↑ hemodynamic and metabolic stability in the group with portal vein flush	1
2008	Ko *et al*[46]	Greater hemodynamic instability with histidine-tryptophan-ketoglutarate solution than University of Wisconsin solution during the reperfusion period in living donor liver transplantation	Retrospective	Different vasoactive substances concentration in the two solutions	87 (28 UW *vs* 59 HTK)	30% drop in MAP within 5' lasting for at least 1' and up to more than 1 h	↑ PRS incidence in non flushed HTK group, flushing the solution ↓ PRS incidence similar to UW	1
2010	Ghafaripour *et al*[47]	Hypotension after reperfusion in liver transplantation: histidine-tryptophan-ketoglutarate versus University of Wisconsin solution	Randomized Controlled Trial	Different vasoactive substances concentration in the two solutions	89	30% drop in MAP within 5' lasting for at least 1' and up to more than 1 h	↑ PRS incidence in both flushed and non flushed HTK groups, flushing the solution ↓ PRS incidence	3
2011	Garcìa-Gil *et al*[48]	Celsior versus University of Wisconsin preserving solutions for liver transplantation: postreperfusion syndrome and outcome of a 5-year prospective randomized controlled study	Randomized Controlled Trial	Different potassium concentrations in the two solutions may imply different PRS outcomes as the outcome is closely related to hyperkalemia	102 (51 CS *vs* 51 UW)	30% drop in MAP within 5' lasting for 1'	Significant ↓ of PRS incidence in CS group; greater control over magnesium, potassium and glucose levels, no differences in long term outcomes	4

2012	Hong *et al*[56]	Regulated hepatic reperfusion mitigates ischemia-reperfusion injury and improves survival after prolonged liver warm ischemia: a pilot study on a novel concept of organ resuscitation in a large animal model	A pilot study in a animal model	The modification of reperfusion perfusate and cellular environment after warm ischemia would reverse the metabolic deficit and facilitate recovery of organ function	12 (6 RHR *vs* 6 control)	30% drop in MAP within 5' lasting for 1'	Regulated hepatic reperfusion (RHR) by using an energetic substrate-enriched, oxygen-saturated, and leukocyte-depleted perfusate delivered under regulated reperfusion pressure, temperature, and pH mitigates ischemia-reperfusio injury, facilitates liver function recovery, and improves survival after prolonged WI	1
2013	Fukazawa *et al*[51]	Crystalloid flush with backward unclamping may decrease postreperfusion cardiac arrest and improve short-term graft function when compared to portal blood flush with forward unclamping during liver transplantation	Retrospective	CB flush grants a lower blood loss during reperfusion, a gradual rewarming wich could foster systemic hemodynamics and graft survival	478 (313 CB *vs* 165 PF)	30% drop in MAP within 5' lasting for 1'	No differences in PRS incidence, ↓ PNF and cardiac arrest incidence; ↑ 30-d graft survival in CB group	1

PRS: Post reperfusion syndrome; VVBP: Veno-venous bypass; NBP: Without veno-venous bypass; MAP: Mean arterial pressure; PGB: Piggy-back; SVRI: Systemic vascular resistance index; HA: Hepatic artery revascularization; PV: Portal vein revascularization; IAR: Initial arterial revascularization; IPR: Initial portal revascularization; CO: Cardiac output; UW: University of wisconsin solution; HTK: Histidine-tryptophan-ketoglutarate solution; CS: Celsior solution; RHR: Regulated hepatic reperfusion; WI: Warm ischemia; CB: Crystalloid flush with backward unclamping; PF: Portal blood flush with forward unclamping; PNF: Primary non function.

different between the two groups.

Millis *et al*[54] found a lower incidence of PRS in patients transplanted with a portal vein flush without venting of the vena cava, *vs* arterial flush with or without venting of the vena cava or portal flush with venting of the vena cava, VVB was used in all the patients of this series.

The superiority of portal vein flush without venting of the vena cava against portal flush with venting of the vena cava, in terms of hemodynamic stability, was confirmed in a later study by Gruttadauria *et al*[55] in a series of patients transplanted with a classical technique without VVB.

A recent animal study by Hong *et al*[56] evaluated the effects of a regulated hepatic reperfusion with a substrate-enriched, oxygen-saturated and leukocyte-depleted perfusate, under regulated reperfusion pressure, temperature, and pH. The study was conducted using a model of experimentally induced warm ischemia of the liver, and found a significant reduction in PRS incidence in the regulated hepatic reperfusion group.

PREVENTION AND MANAGEMENT OF PRS

PRS involves a severe multisystemic alteration of homeostasis and may negatively affect patient and allograft outcomes. To this date the treatment of established PRS by the anesthesiologist is supportive, involving, amongst other strategies, vasoactive drugs (phenylephrine, epinephrine and norepinephrine), calcium chloride repletion and volume loading. However, the severity of the syndrome can vary greatly and so the efficacy of its treatment.

A number of strategies to prevent the occurrence of the syndrome or reduce its hemodynamic and systemic effects have been proposed, and could improve outcomes, yet to this date none of these are strongly supported by evidence.

Table 4 synthesizes the considered literature studies involving pharmacological interventions to reduce PRS incidence.

Antioxidant therapies

The use of antioxidant therapies during liver transplantation has been advocated as a possible preventive strategy for PRS.

Acetylcysteine has been widely investigated in liver pathology, mainly in relation to acetaminophen, or amanita phalloides poisoning. This drug acts as an antioxidant by restoring intracellular glutathione stores and could reduce oxidative stress and the release of oxygen radicals and cytokines from the reperfused liver graft.

Bromley *et al*[57] in a randomized controlled trial tested the effects of Acetylcysteine during OLT. Their results show a significant improvement in oxygen delivery

Table 4 Pharmacological prevention/treatment strategies

Year	Authors	Title	Type of study	Rationale	No. subjects	Definition of PRS	Effects	Jadad score
1995	Bromley *et al*[57]	Effects of intraoperative N-acetylcysteine in orthotopic liver transplantation	Prospective	NAC could be beneficial in blunting the reperfusion effects of OLT	50 (25 NAC *vs* 25 glucose)	-	NAC ↑ DO2 and CI; ↓ MAP and SVRI, no difference in reperfusion events or postoperative outcome	3
1995	Milroy SJ *et al*[61]	Improved haemodynamic stability with administration of aprotinin during orthotopic liver transplantation	Randomized Controlled Trial	Aprotinin ↓ fibrinolysis and inflammatory response	55 (3 drop outs, 26 placebo, 26 aprotinin)	-	Aprotinin ↑ SVRI and ↓ CI in aprotinin group, no differences in vasopressors need	5
1999	Acosta *et al*[66]	Atropine prophylaxis of the postreperfusion syndrome in liver transplantation	Prospective	Pretreatment with atropine could partially prevent the developing of PRS	41 (11 PRS *vs* 30 NPRS)	30% drop in MAP within 5' lasting for at least 1' and up to more than 1 h	No significant changes in HR occurred, bradycardia was prevented. No change in MAP was recorded	1
2001	Molenaar *et al*[19]	Reduced need for vasopressors in patients receiving aprotinin during orthotopic liver transplantation	Randomized Controlled Trial	Aprotinin ↓ fibrinolysis and inflammatory response	67 (24 high-dose aprotinin *vs* 21 regular-dose aprotinin *vs* 22 placebo)	Syndrome characterized by a decrease in MAP and SVRI and an increase in CI and mean pulmonary artery pressure	Aprotinin ↓ need for vasopressors during OLT, especially during the early postreperfusion period	3
2002	Koelzow *et al*[58]	The effect of methylene blue on the hemodynamic changes during ischemia reperfusion injury in orthotopic liver transplantation	Randomized Controlled Trial	Methylene blue (MB) is an inhibitor of inducible NO synthase and an NO scavenger	36 (18 MB 1.5 mg/kg *vs* 18 placebo)	30% drop in MAP within 5' lasting for at least 1' and up to more than 1 h	MB ↑ MAP and CI, ↓ epinephrine requirement, SVR did not change significantly, ↓ lactate levels	1
2003	Findlay *et al*[62]	Aprotinin reduces vasoactive medication use during adult liver transplantation	Data obtained from patients enrolled in a previously completed, prospective, randomized, double-blind study	Aprotinin ↓ fibrinolysis and inflammatory response	63 (33 aprotinin *vs* 30 placebo)	-	↓ use of vasoactive infusions in the aprotinin group	3
2011	Fukazawa *et al*[59]	The effect of methylene blue during orthotopic liver transplantation on post reperfusion syndrome and postoperative graft function	Retrospective	Methylene blue (MB) is an inhibitor of inducible NO synthase and an NO scavenger	715 (105 MB bolus dose *vs* 610 control)	30% drop in MAP within 5' lasting for at least 1' and up to more than 1 h	No differences in PRS incidence, post reperfusion MAP, need for vasopressors or transfusions and secondary outcomes	1
2011	Ryu *et al*[63]	Nafamostat Mesylate attenuates post reperfusion syndrome	Randomized Controlled Trial	Aprotinin has been proven effective in preventing PRS but it has been withdrawn from the market, Nafamostat is a protease inhibitor that acts similarly and could prove useful	61 (31 treated *vs* 31 placebo, 42 excluded)	30% drop in MAP within 5' lasting for at least 1' and up to more than 1 h	Nafamostat ↓ PRS incidence, hastened post reperfusion MAP recovery to normal values and ↓ need for early and late postreperfusion vasopressors	5
2012	Ryu *et al*[6]	Epinephrine and phenylephrine pretreatments for preventing postreperfusion syndrome during adult liver transplantation	Randomized Controlled Trial	Pretreatment with a vasopressor should reduce PRS incidence and need for continous vasopressor support in late postreperfusion period	96 (32 normal saline *vs* 33 epinephrine *vs* 31 phenylephrine)	30% drop in MAP within 5' lasting for 1'	↓ PRS incidence and ↓ need for vasopressors in late postreperfusion period in both pretreatment groups. Overshoot MAP in 6% of patients in both pretreatment groups. No differences in perioperative laboratory data and mortality	5

2013	Kong *et al*[64]	Epsilon-aminocaproic acid improves postrecirculation hemodynamics by reducing intraliver activated protein C consumption in orthotopic liver transplantation	Randomized Controlled Trial	APC has a role in coagulation and inflammation and could influence the levels of cytokines involved in the developement of PRS after reperfusion	59 (31 EACA *vs* 28 controls)	30% drop in MAP within 5' lasting for at least 1' and up to more than 1 h	↓ PRS incidence, ↑ MAP, ↓ need for vasopressors, blood transfusion and FFP in EACA group	5
2013	Chung *et al*[68]	Effects of magnesium pretreatment on the levels of T helper cytokines and on the severity of reperfusion syndrome in patients undergoing living donor liver transplantation	Randomized Controlled Trial	Magnesium has a protective role over ischemia-reperfusion injury	40 (20 mg pretreatment *vs* 20 controls)	30% drop in MAP within 5' lasting for at least 1' and up to more than 1 h	↓ PRS incidence	5
2014	Fayed *et al*[67]	Goal directed preemptive ephedrine attenuates the reperfusion syndrome during adult living donor liver transplantation	Randomized Controlled Trial	Preemptive ephedrine administration prereperfusion targeting a rational level of MAP may reduce the incidence of PRS	100 (50 control *vs* 50 ephedrine)	30% drop in MAP within 5' lasting for 1'	↓ PRS incidence, need for postreperfusion vasoconstrictor support without over shooting of hemodynamic indices. ↓ need for postoperative mechanical ventilation	5

PRS: Post reperfusion syndrome; NAC: N-acetylcysteine; OLT: Orthotopic liver transplantation; DO2: Oxygen delivery; CI: Cardiac index; MAP: Mean arterial pressure; SVRI: Systemic vascular resistance index; NPRS: Without post reperfusion syndrome; HR: Heart rate; MB: Methylene blue; NO: Nitric oxide; SVR: Systemic vascular resistance; CIT: Cold ischemia time; APC: Activated protein C; EACA: Epsilon-aminocaproic acid; FFP: Fresh frozen plasma.

and CI, associated with a decrease in MAP and SVRI; base deficit did not significantly differ between groups. Based on these results Acetylcysteine acted as a mild vasodilator and had no significant effects on reperfusion events and OLT outcomes.

Methylene blue (MB) is a dye used in several settings in medicine. It acts as a specific inhibitor of soluble guanylate-cyclase and Inducible NO synthase (iNOS). Due to this unusual mechanism of action, MB has been studied as an adjunct to vasopressor therapies in several settings including septic shock and post bypass hypotension in cardiovascular surgery. The drug produces a contraction in vascular muscle, increasing the SVR, MAP and cardiac contractility. Moreover MB, as a modulator of the production of NO, could be expected to improve graft function by reducing ischemia-reperfusion injury.

The use of MB in OLT was first investigated by Koelzow *et al*[58] in a randomized controlled trial. Their results showed a significant increase in MAP and CI with no improvement in SVRI. Lactate levels one hour after reperfusion were lower in the treatment group possibly indicating a positive effect on graft function of MB. Interestingly this study showed that the predominant mechanism of action of MB on OLT hemodynamics was the increase, or preservation, of cardiac contractility, whilst in other scenarios such as sepsis its action had been more pronounced on the peripheral vasculature and SVR.

More recently Fukazawa *et al*[59] retrospectively analyzed a large cohort of patients undergoing OLT and the effects of MB administration on post reperfusion events and post-operative outcomes. Their results did not show any statistically significant effect of a single dose of MB on PRS and intraoperative hemodynamics, nor any detrimental or positive effect on graft function. However it must be noted that the incidence of Primary Non Function and retransplantation after 60 d were lower in the MB treated group, as was the graft survival, even if these results were not statistically significant. The role of MB in OLT is therefore still not supported by evidence and a large randomized trial would be needed to shed light on its real potential as an additional therapy during OLT.

Protease inhibitors

Fibrinolysis has a major role in the pathophysiology of PRS. The use of serine protease inhibitors such as aprotinin, mainly investigated to reduce the need for blood products transfusion during OLT[60], has been proposed and used to blunt the hemodynamic effects of PRS. Aprotinin was marketed to improve surgical hemostasis by inhibiting plasmin and therefore fibrinolysis; the drug, especially at higher doses also has an effect on other serine proteases such as Kallikrein. It is the drug's effect on the Kallikrein-Kinin system that is most likely involved in aprotinin effects on PRS and hemodynamic stability during OLT.

Milroy *et al*[61] were the first ones to investigate a possible role of aprotinin in the hemodynamic management of OLT patients, especially during the early post reperfusion period, their work showed a significant improve in SVRI, but no significant difference in vasopressor requirements.

Later Molenaar *et al*[19] in a randomised controlled trial showed a reduction in vasopressor requirements during OLT, which was particularly pronounced in the early post reperfusion period. This reduction in vasopressor requirements was not caused by a reduction in surgical bleeding, but mainly correlated to an improved hemodynamic stability and vascular tone. Their protocol for the use of aprotinin entailed a bolus dose at induction of anaesthesia and a subsequent continuous infusion.

Findlay *et al*[62] later reproduced the same results by using a lower dosing protocol of aprotinin, suggesting that the effect of the drug on serine proteases other than plasmin is different in liver transplant patients compared to other populations. Aprotinin is no longer available for clinical use in several settings after a number of trials have questioned the drugs safety.

More recently Ryu *et al*[63] have used Nafamostat Mesylate, also a synthetic serine protease inhibitor mainly used for anticoagulation in CRRT or in the treatment of pancreatitis, to reproduce the same effects previously obtained with aprotinin in other studies. The administration of Nafamostat reduced the incidence and the severity of PRS, and patients treated with the drug had shorter ICU length of stay. These interesting results were achieved with only a bolus dose of Nafamostat before reperfusion.

Kong *et al*[64] have investigated epsilon-aminocaproic acid (EACA) as an antifibrinolytic agent, and its effect on PRS and the levels of APC. The results of their study show a significant reduction in blood products requirements in the EACA group, associated with a lower incidence of PRS and reduced need for vasopressors. The measured levels of APC show that, EACA treated patients, had less intrahepatic consumption of the protein after reperfusion of the graft, indicating a generally less pro-inflammatory state. This could explain the improved hemodynamic profile of the patients treated with EACA. The use of EACA in OLT as an antifibrinolytic agent has been less widespread compared to Tranexamic Acid. This is mainly related to the fact that Dalmau *et al*[65] have compared the two antifibrinolytic agents in OLT finding that Tranexamic Acid reduced transfusion requirements more than EACA.

Vasopressor pretreatment

A more practical approach to pharmacological pretreatment of PRS is the preemptive administration of vasoactive drugs. The first study to address this matter was conducted by Acosta *et al*[66] who used Atropine pretreatment before reperfusion to prevent the triggering of the Bezold-Jarisch reflex by the preload challenge to the right ventricle at reperfusion. Their results showed no occurrence of bradycardia after reperfusion, but no effect on MAP and hypotension in patients developing PRS.

Later Ryu *et al*[6] in a randomized controlled trial tested the preemptive use of phenylephrine (100 mcg) or Epinephrine (10 mcg) at reperfusion on the occurrence of PRS and its severity. Their result show a significant reduction in the occurrence of PRS in both treatment groups, associated with a reduced need for vasopressors in the post reperfusion period. Few episodes of blood pressure overshooting occurred, and no effects on perioperative laboratory variables or mortality rates and hospital length of stay were recorded.

Fayed *et al*[67] replicated similar results using a goal directed administration of ephedrine starting 5 min before reperfusion and aiming at a MAP level of 85 to 100 mmHg. Their results show a reduction of the incidence of PRS, no occurrence of hemodynamic overshooting episodes and a reduction in the duration of postoperative mechanical ventilation.

Magnesium sulphate

Magnesium sulphate has been shown to have protective effects in a number of conditions involving ischemia-reperfusion injury. The supplementation of magnesium stabilizes the transmembrane electrophysiologic potential, reducing the intraplasmatic Calcium influx, which is responsible for many of the mechanisms involved in ischemia-reperfusion injury.

A recent study by Chung *et al*[68] investigated the effects of $MgSO_4$ pretreatment on PRS and the immune response to graft reperfusion. Patients were given 35 mg/kg of $MgSO_4$ intraoperatively before reperfusion. The results showed a significant reduction in the incidence and duration of PRS, and a variation in the expression of cytokines, indicating a modulation of the immune response. The administration of magnesium produced a reduction of IFN-γ, and an increase in IL-4 and IL-10. This indicates a shift in T cell activity towards Th2 lymphocytes, which provided a more favorable cytokine balance and fewer hemodynamic events.

Ischemic preconditioning

Ischemic preconditioning (IPC) is a surgical strategy, which aims at protecting tissues from ischemia-reperfusion injury. It has been described first in the heart muscle[69], and has been later successfully applied to several other tissues including the liver. The technique consists in applying brief periods of ischemia and reperfusion to the tissue before a more prolonged ischemic period. In Liver surgery IPC has been widely applied to warm ischemia in liver resections[70], whilst the data regarding its use in OLT are more conflicting. A number of clinical trials and a Cochrane review have investigated the application of

IPC in donor liver retrievals[71-75] demonstrating positive effects on ischemia reperfusion injury but not certain improvements in the clinical outcomes. Considering the pathophysiology of PRS the possibility of blunting the ischemia-reperfusion injury to the liver graft could theoretically be beneficial to the patients. However to this date the application of an ischemic preconditioning technique to the liver graft is still debated and to our knowledge no clinical trial has addressed the effects of the application of this technique to the incidence and severity of PRS. Finally newer approaches to ischemic preconditioning are being investigated in animal models such as remote ischemic preconditioning, indicating the beneficial effect on ischemia-reperfusion injury provided by intermittent conditioning of a tissue other than the one subject to ischemia[76-78]. These newer techniques and their investigation could allow for a more deep understanding of the mechanisms of ischemia-reperfusion injury and preconditioning, and could represent a potentially useful technique to be applied to liver transplant.

ONGOING CLINICAL TRIALS

Our search found only one ongoing clinical trial related to PRS (NCT01886664), which compares Sevoflurane to Desflurane in relation to PRS incidence.

CONCLUSION

Since its first definition, PRS has evolved greatly, firstly described as an isolated fall in arterial pressure it is now a complex entity involving several aspects of physiology. This evolution has happened in parallel to the deepening of the knowledge of the interactions between the liver graft and the recipient and the mechanisms of ischemia-reperfusion injury.

To date PRS has been widely investigated in both its physiopathology and risk factors, but the level of evidence that can be drawn from the analysis of the existing literature is poor. The presence of two main definitions of PRS complicates the interpretation of the results of the studies considered. Moreover the surgical technique has dramatically evolved over time, in particular with the development and widespread use of the piggy-back technique, greatly affecting the incidence and characteristics of the syndrome. The quality of the studies considered is globally low. The studies investigating risk factors for PRS are numerous but often show conflicting results and fail to reproduce results. They are mostly retrospective and contemplate small samples in relation to the number of variables considered and the factors inducing possible biases. The risk factors investigated are plenty and their precise role in PRS is still not clear.

Studies evaluating treatment strategies present the same problems so far described, even though their overall quality is higher and, especially the more recent ones, are well designed and contemplate larger samples. Overall it appears clear that the number of possible confounding factors influencing the results is extremely high, involving both the surgical procedure technique, the organ graft and the patient conditions. For these reasons it is also difficult to design rigorous future studies evaluating therapeutic and preventive strategies for PRS, as the number of variables that should be controlled and standardized is very high.

Given these premises, there is a need to establish a single consensus definition of PRS.

Since the complexity of the phenomenon is high, future studies evaluating risk factors and therapeutic strategies should pay much attention in granting the better homogeneity possible in confounding factors and an adequate numerosity.

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