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ORIGINAL ARTICLE

Reperfusion of liver graft during transplantation: techniques used in transplant centres within Eurotransplant and meta-analysis of the literature

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Summary

It remains unclear which liver graft reperfusion technique leads to the best outcome following transplantation. An online survey was sent to all transplant centres ($n = 37$) within Eurotransplant (ET) to collect information on their technique used for reperfusion of liver grafts. Furthermore, a systematic review of all literature was performed and a meta-analysis was conducted based on patients' mortality, number of retransplantations and incidence of biliary complications,

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depending on the technique used. Of the 28 evaluated centres, 11 (39%) reported performing simultaneous reperfusion (SIMR), 13 (46%) perform initial portal vein reperfusion (IPR), 1 (4%) performs an initial hepatic artery reperfusion (IAR) and 3 (11%) perform retrograde reperfusion (RETR). In 21 centres (75%), one reperfusion technique is used as a standard, but in only one centre is this decision based on available literature. Twenty centres (71%) said they would agree to participate in randomized controlled trials (RCT) if required. For meta-analysis, IAR vs. IPR, SIMR vs. IPR and RETR vs. IPR were compared. There was no difference between any of the techniques compared. There is no consensus on a preferable reperfusion technique. Available evidence does not help in the decision-making process. There is thus an urgent need for multicentric RCTs.

Introduction

Anterograde reperfusion of liver grafts can be done either simultaneously or sequentially. In the latter, reperfusion of the portal vein followed by the hepatic artery (initial portal reperfusion; IPR) or vice versa (initial artery reperfusion; IAR) is performed. In simultaneous reperfusion (SIMR), hepatic artery and portal vein are reperfused simultaneously. The rarely used retrograde reperfusion (RETR) is performed through the caval vein first, followed by anterograde portal venous reperfusion.

Initial portal reperfusion is the most widely used reperfusion technique. The reason for following this sequence is to ensure that the recipient liver receives blood in the shortest possible time, as portal vein anastomosis is easier, technically, than hepatic artery anastomosis [1]. In addition, endotoxin translocation is reduced, because of intestinal outflow obstruction [2]. The disadvantage of IPR is an increased risk of warm ischaemic damage to the bile ducts (ischaemic type biliary lesion, ITBL), where the blood supply depends solely on the hepatic artery [3]. Similar to IAR, the motivation for SIMR is to reduce the incidence of biliary complications [4,5]. An additional advantage of SIMR is that anastomosis can be repaired without completely interrupting blood flow to the graft, in case there are problems with one of the anastomoses. The disadvantage of this technique is a prolongation of warm ischaemia and the anhepatic phase, which can be detrimental to postoperative graft function, survival and morbidity [6,7]. In the retrograde reperfusion technique, the vascular clamp on the inferior vena cava is removed immediately after completion of IVC anastomosis, allowing retrograde reperfusion during construction of portal vein anastomosis [8,9]. The advantage is that it shortens the warm ischaemia time, efficiently removes perfusion fluid from the graft before anterograde blood flow is re-established and results in reduced partial clamping time of the vena cava with a haemodynamic more stable patient, however, this technique is associated with a higher rate of biliary complications [3,10].

It is still unclear from available literature which method of revascularization of the liver graft is the best in terms of development of complications and quality of liver graft. The level of evidence in most of the studies is very low [11]. We aimed to investigate which reperfusion technique of the liver graft in deceased donor liver transplantation is the most widely used in transplant centres within ET, and performed a review and meta-analysis of available literature on the topic to analyse which reperfusion technique is the best in terms of patients' survival, number of retransplantations and amount of biliary complications.

Materials and methods

Online survey

An online questionnaire was sent to all transplant centres ($n = 37$) within ET. Each centre was asked about the reperfusion technique used, whether the procedure is standardized (based on personal/institutional experience or based on literature) or not (individual decision of the surgeon/other), the need for RCT in this field and whether the centre would be interested in participating in a multicentre RCT.

Systematic literature search

The literature search followed standardized methods of the Cochrane Collaboration [12]. We systematically searched Medline with the following key words: Technique of reperfusion of the transplanted liver graft, anterograde reperfusion, retrograde reperfusion, IPR and IAR. The last search was carried out on May 2012.

Study selection and data extraction

All papers dealing with the surgical reperfusion technique of the transplanted liver graft at all levels of the pyramid of

evidence were eligible for inclusion. Animal studies and studies providing insufficient data on our predefined outcome variables (mortality, number of retransplantation, incidence of biliary complications) as well as a double publication and a study which was published only in abstract form were excluded [13–15]. Search findings were screened for potentially relevant studies by two independent authors (GM and MK), who separately evaluated these articles and extracted their data. Any disagreement during study selection and data extraction was resolved by discussion with a third author (PS). The methodological quality of included trials was assessed in a standardized way by means of the CLEAR NPT checklist [16].

Predefined outcome variables

Predefined outcome variables of the meta-analysis were chosen according to their clinical relevance and availability in the majority of studies included. These were patient survival, retransplantation rate and the total incidence of biliary complications. Because time-to-event data were not available, analysis of patient survival is based on an odds ratio (OR) for the 3-month mortality rates reported in the individual studies. If these rates were not available, ORs for the comparison of the 6-month mortality rates were used instead. Retransplantations and reports of biliary complications were treated in a similar manner. It was not possible to discriminate between anastomotic and nonanastomotic biliary strictures because of the small amount of studies containing this information.

Meta-analysis

The following study types were considered for meta-analysis: Retrospective studies, prospective nonrandomized studies and randomized controlled studies. Reviews were excluded. Studies without a control group (e.g., case series) were excluded because a comparison of case series for different treatment arms is prone to selection bias (e.g., different inclusion criteria in the different studies). A total of 11 studies met the inclusion criteria, with the following comparisons IAR vs. IPR, SIMR vs. IPR, SIMR vs. RET, IPR vs. SIMR. Endpoints were binary in nature (including mortality, for which only rates to a given time point were available), hence the performance of a meta-analysis of OR. Study-specific effect measures were pooled via the conventional Mantel-Haenszel random effects meta-analysis technique [17] and are reported as an OR with a 95% confidence interval (CI). Heterogeneity of the study-specific results is quantified by the descriptive I^2 inconsistency measure.

A substantial amount of the trials included in this meta-analysis were not randomized and observational in nature; the present meta-analysis should be considered hypothesis-generating instead of decisive. In line with this, CIs and *P*-values are reported without multiplicity correction.

Results

Online survey

The survey was submitted to all transplant centres within ET on 18 October 2011, and the online platform was accessible until 31 May 2012. The centres responded within 2–196 days (mean 56 days ± 46.2 days; median 58 days, range 2–196 days).

By the end of May 2012, 30 of the 37 transplant centres (81%) had responded to our online survey. However, owing to incomplete survey records, only 28 of the 30 responses have been included in this study (Table 1). The results were as follows: 11 centres (39%) perform SIMR; 13 centres (46%) perform IPR, 1 centre (4%) performs IAR and 3 centres (11%) perform RETR. In 21 of the 28 (75%) centres, the technique and order of reperfusion is standardized. In 20 (95%) of these centres, this standard is based on personal/institutional experience; only in one single centre is the choice of the technique based on available literature in animal models [18]. In the remaining 7 (25%) centres, the technique is not standardized and is left to the discretion of the surgeon performing the procedure.

Twenty centres (71%) agree on the need for randomized controlled trials (RCT) in this field and would participate in a multicentric RCT.

Results of the literature search and meta-analysis

The online search was carried out on May 2012. We searched MEDLINE (Pubmed) using the following key words: technique of reperfusion of the transplanted liver graft, anterograde reperfusion, retrograde reperfusion, IPR, IAR. A total of 23 manuscripts dealing with the reperfusion technique of the transplanted liver graft were considered for inclusion in this review. Studies on children were not available. Animal studies were excluded [18–22].

As detailed in materials and methods, a total of 15 studies were identified for inclusion in the present review (five randomized clinical studies, two prospective nonrandom-

Table 1. Results of the survey on reperfusion techniques used to transplant liver graft in 28 European transplantation centres.

Reperfusion technique	*N*	%
Simultaneous reperfusion	11	39
Initial portal reperfusion	13	46
Initial arterial reperfusion	1	4
Retrograde reperfusion	3	11

ized studies, four retrospective studies and two case series, two reviews). The reviews [3,11] and case series [8,9] were excluded from the meta-analysis. In total, 11 studies could be included. Table 2 summarizes the principal characteristics of the 11 studies included in the meta-analysis, with reperfusion technique, group size, endpoints and level of evidence. The following comparisons were admitted: IPR vs. IAR, SIMR vs. IPR, RETR vs. SIMR. Predefined outcome variables were as follows: mortality, number of retransplantation and amount of biliary complications.

Based on those variables, our meta-analysis led to the following results (Table 2):

Initial artery reperfusion versus initial portal reperfusion
Six studies were included in this comparison: three randomized [1,23,4], two prospective nonrandomized [25,26] and one retrospective study [27]. Meta-analysis of the four included studies did not reveal evidence in favour of a specific reperfusion technique. The ORs for biliary complications, retransplantation and mortality were statistically insignificant and numerically pointed to opposite directions [biliary complications: OR = 0.86, 95% CI = (0.29, 2.53); retransplantation: OR = 2.73, CI = (0.76, 9.82); mortality: OR = 0.55, CI = (0.16, 1.96)].

Simultaneous reperfusion versus initial portal reperfusion
Four studies were included in this comparison: one randomized study [28] and three retrospective studies [4,5,29]. Although no differences were observed for mortality and rate of retransplantation within the studies, significant differences are reported for biliary complications and are therefore presented in detail: biliary complications occurred in four patients in the SIMR group and in nine in the IPR group ($P = 0.05$) in the study performed by Adani *et al.* [28]. In particular, anastomotic stenoses were observed in 15% vs. 19% ($P = 0.78$) and intrahepatic nonanastomotic biliary strictures in 26% vs. 0% ($P = 0.01$) for IPR vs. SIMR respectively. Sankary *et al.* studied a total of 128 patients, 45 SIMR vs. 83 IPR [4]. Biliary complications occurred in one patient after SIMR and in seven patients after IPR. All observed complication were nonanastomotic biliary lesions ($P = 0.03$). Massarollo *et al.* [5] included a total of 76 patients (50 SIMR vs. 26 IPR). Biliary complications occurred in only one patient after SIMR

Table 2. Summary of the principal characteristic of the 11 studies included in the meta-analysis, with group size, procedure, endpoints and level of evidence.

Author	Study design	Reperfusion technique and group size	Mortality 3-months (or 1-month or 1-year)	Number of retransplantation	Total biliary complications	Level of evidence*
Noun *et al.* 1997	Prospective nonrandomized study	IAR ($n = 15$) vs. IPR ($n = 14$)	1 vs. 0 (7% vs. 0%)	0 vs. 1	1 vs. 1	4
Ducerf *et al.* 2000	Randomized clinical study	IAR ($n = 29$) vs. IPR ($n = 30$)	2 vs. 2 (7% vs. 7%)	1 vs. 3	2 vs. 2	2b
Sadler *et al.* 2001	Retrospective study	IAR ($n = 26$) vs. IPR ($n = 26$)	4 vs. 1 (15% vs. 4%)	n.a.	n.a.	3b
Walsh *et al.* 2002	Prospective nonrandomized study	IAR ($n = 10$) vs. IPR ($n = 10$)	1 vs. 0 (10% vs. 0%)	0 vs. 0	n.a.	4
Moreno *et al.* 2006	Randomized clinical study	IAR ($n = 30$) vs. IPR ($n = 30$)	1 vs. 1 (3% vs. 3%)	0 vs. 0	5 vs. 4	2b
Sabatè *et al.* 2010	Randomized clinical study	IAR ($n = 14$) vs. IPR ($n = 16$)	n.a.	0 vs.2	n.a.	2b
Sankary *et al.* 1995	Retrospective study	SIMR ($n = 45$) vs. IPR ($n = 83$)	n.a.	n.a.	1 vs. 7	3b
Massarollo *et al.* 1998	Retrospective study	SIMR ($n = 50$) vs. IPR ($n = 26$)	7 vs. 7 (14% vs. 27%)	n.a.	1 vs. 9	3b
Polak *et al.* 2005	Retrospective study	SIMR ($n = 31$) vs. IPR ($n = 71$)	6 vs. 10 (19% vs. 14%)	2 vs. 6	7 vs. 6	3b
Adani *et al.* 2011	Randomized clinical study	SIMR ($n = 21$) vs. IPR ($n = 19$)	1 vs. 2 (5% vs. 11%)	0 vs. 1	4 vs. 9	2b
Heidenhain *et al.* 2006	Randomized clinical study	SIMR ($n = 66$) vs. RETR ($n = 65$)	3 vs. 4 (5% vs. 6%)	6 vs. 3	2 vs. 8	2b

SIMR, simultaneous reperfusion; IPR, initial portal reperfusion; IAR, initial arterial reperfusion; RETR, retrograde reperfusion.
*According to the Oxford Centre for Evidence-Based Medicine 2005 (www.cebm.net).

(anastomotic stricture). In contrast, nine complications were observed after IPR (eight anastomotic and one nonanastomotic, $P < 0.001$). Polak *et al.* [29] observed a total of 102 patients (31 SIMR vs. 71 IPR). Biliary complications occurred in seven patients after SIMR and in six after IPR ($P = 0.06$). In particular, anastomotic stenoses were observed in four patients after SIMR and in two after IPR ($P = 0.06$), intrahepatic nonanastomotic biliary strictures were observed in three patients after SIMR and in four after IPR (P = n.s.). SIMR might result in less biliary complications when compared with IPR, but this was not statistically significant in the meta-analysis [OR = 0.34, CI = (0.05, 2.28)], despite the differences reported by Adani, Sankary and Massarollo. Qualitatively similar results were obtained for the retransplantation rate [OR = 0.61, CI = (0.14, 2.69)] and for mortality [OR = 0.62, CI = (0.28, 1.41)].

Simultaneous reperfusion versus retrograde reperfusion (RETR)

Only one study, which was a randomized controlled trial, was available [10]. In this study by Heidenhain *et al.* [10], a total of 131 patients were included (66 SIMR vs. 65 RETR). One year after transplantation, 63 patients were still alive after SIMR as opposed to 61 after RETR. A retransplantation was necessary in six patients after SIMR (one case of portal thrombosis and five initial nonfunction) and in three after RETR (one case of ITBL and two hepatic artery thrombosis) ($P = 0.115$). Biliary complications occurred in two patients after SIMR and in eight after RETR ($P = 0.053$). All the complications were ITBLs.

Retrograde reperfusion (RETR)

Two case series from the same surgical department and author were available [8,9]. In one of these studies, a total of 39 patients were included [8]. One year after transplantation, 34 patients were alive. Retransplantation was necessary in three patients because of hepatic artery thrombosis. In the other study, a total of 53 patients were included [9]. One year after transplantation, 45 patients were alive. Retransplantation was necessary in three patients because of hepatic artery thrombosis.

Reviews

One review and one systematic review were available [3,11]. In the review of Polak *et al.* [3], each study at various levels of the pyramid of evidence was included, including animal studies. No meta-analysis was performed. The author concluded that sequential revascularization allows a short warm ischaemia time, which is an important determinant of outcome and initial hepatocellular function. RETR seemed to correlate with a low incidence of initial graft dysfunction. RETR and IPR seemed to be associated with higher risk of ITBL. The prolongation of warm ischaemia time and the anhepatic phase with SIMR may impair the graft function [3]. In the systematic review of Gurusamy *et al.* [11], only five randomized controlled trial were included [1,10,23,24,28]. The comparisons performed included IAR vs. IPR, SIMR vs. IPR and RETR vs. SIMR. There were no significant differences in mortality, graft survival or severe morbidity rates in any of the comparisons.

Taken together, similar to Gurusamy KS *et al.* [11], we did not find any statistically significant difference in the outcome of the different reperfusion techniques (Fig. 1). However, we found weak evidence in favour of SIMR in all pairwise meta-analytical comparisons with IPR, with qualitatively similar ORs in favour of SIMR in all three endpoints considered.

Discussion

Based on the results of our online survey, IPR is the most frequently used reperfusion technique in transplant centres within ET. Almost all centres base their decision solely on personal/institutional experience. Only one centre performing SIMR (4%) bases the decision on a study in which 24 pigs were randomized into three different reperfusion groups: IPR, IAR and SIMR [18]. Liver enzymes were significantly impaired in IAR, and histological analysis revealed the highest degree of necrosis, haemorrhage and inflammation compared to the other groups. SIMR resulted in significantly higher bile production when compared with IAR and IPR. These authors believe that SIMR could provide some potential advantages: the liver receives a larger total blood volume during the initial and critical phase of reperfusion, warm ischaemia time for the biliary tract is reduced and the arterial anastomosis can be performed under technically easier conditions (no retrograde bleeding, no swelling of the graft) [18]. This is in contrast to the conclusion of the review of Polak *et al.* [3] in which the prolongation of warm ischaemia time and anhepatic phase associated with SIMR is thought to have an overall negative impact on postoperative graft function.

These few and heterogenous results indicate a substantial lack of evidence and therefore underline the need for RCTs (which most of the centres within ET would support) to determine the optimal reperfusion technique.

To achieve a conclusive answer from literature, we performed a meta-analysis. We could not find any significant difference for our predefined outcome variables mortality, number of retransplantations and incidence of biliary complications in any of the comparisons. Still, several single publications report significant differences, but with overall different results regarding our chosen predefined outcome variables, in particular regarding the development of biliary complications. Anastomotic biliary complications are most

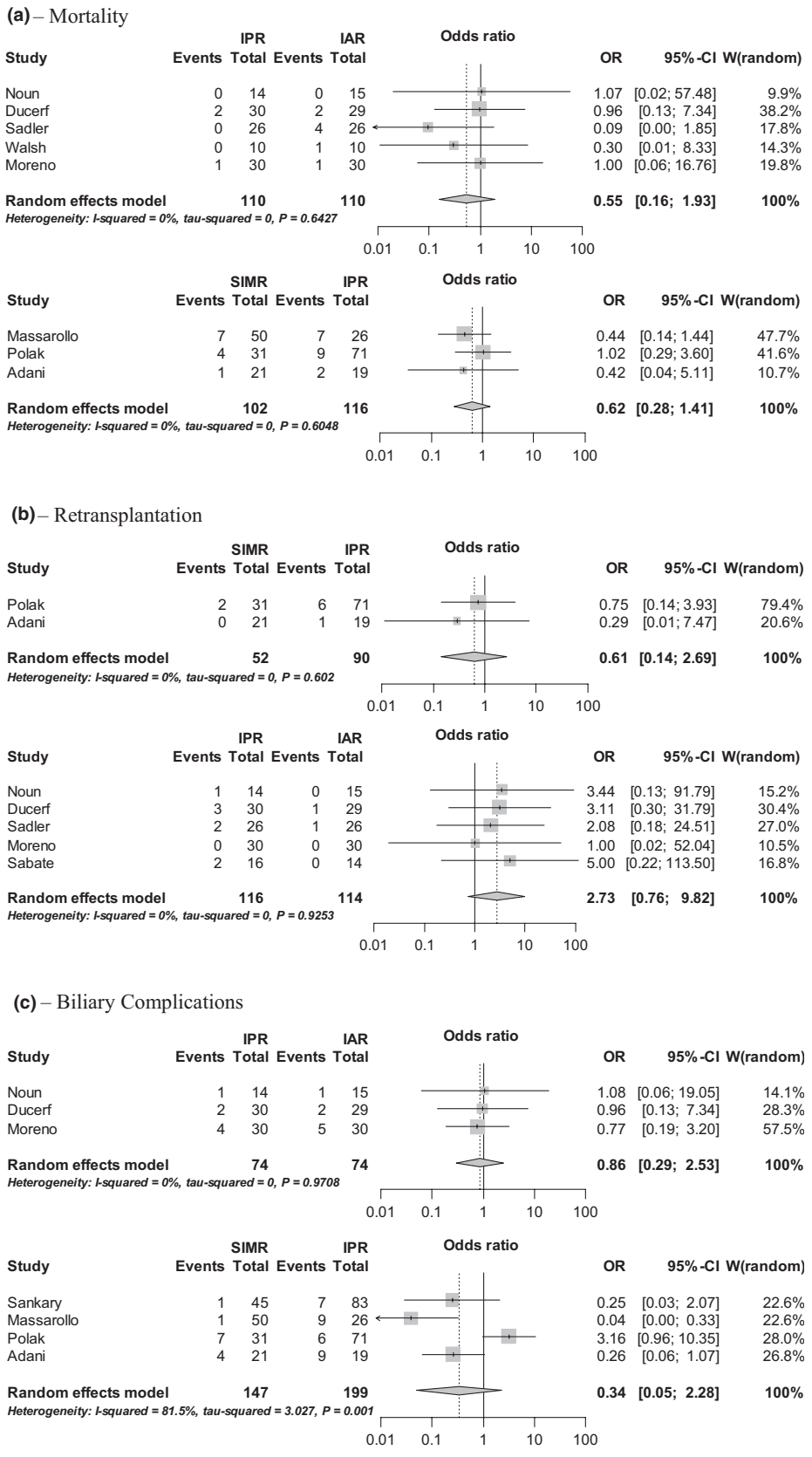

Figure 1 Results of the meta-analysis. (a) Mortality. (b) Retransplantation. (c) Biliary complications.

likely not connected to reperfusion injury or the method of reperfusion. Unfortunately, most studies in published literature do not differ between anastomotic and nonanastomotic biliary lesions. Therefore, in our meta-analysis, only biliary complications in general could be included.

Sankary *et al.* [4] compared SIMR with IPR. Biliary complications occurred in one patient after SIMR and in seven after IPR. All observed complications were nonanastomotic biliary lesions ($P = 0.03$). Massarollo *et al.* also compared SIMR vs. IPR [5]. Biliary complications occurred in one patient after SIMR (anastomotic stricture) and in nine (eight anastomotic and one nonanastomotic) after IPR ($P < 0.001$). In contrast, no advantage of either of the two reperfusion protocols (SIMR vs. IPR) was observed by Polak *et al.* [29], especially with respect to the incidence of nonanastomotic biliary lesions. However, in this study, cold ischaemia time was shorter than in [4] and [5] (8.7 h vs. 10.7 h and 13.3 h respectively). The conclusion drawn was that the order of revascularization does not influence the incidence of ITBL when the cold ischaemia time is kept short (<9 h). In the study of Adani *et al.* [28], SIMR was safe and feasible, reducing the incidence of intrahepatic biliary strictures by decreasing the duration of arterial ischaemia to the intrahepatic bile ducts. The study of Heidenhain *et al.* [10] is the only one that analysed the development of biliary complications when using RETR. Biliary complications occurred in two patients in the SIMR group and in eight in the RETR group ($P = 0.053$; please note that when we used standard chi-squared test without continuity correction on the paper's data, as described by the authors, the result was $P = 0.045$). Although the results in the original manuscript were not significantly different, the authors concluded that RETR seemed to be detrimental for the biliary epithelium. Upon performing the statistical analysis of the paper's data ourselves, we found statistically significant more biliary complications after RETR when compared to SIMR. Therefore, we agree with the opinion of Heidenhain *et al.* and suggest that RETR results in more biliary complications than SIMR.

On the other hand, SIMR results in prolongation of warm ischaemic time and the anhepatic phase when compared with other reperfusion techniques. No conclusive reports exist as to whether this prolongation might affect organs, especially marginal organs that are accepted for transplantation, according to the extended donor criteria, negatively. It is still unclear and diverging reports exist on whether marginal organs are associated with increased primary non- or dysfunction [30,31], or whether it solely depends on the condition of the recipient and transplantation. No studies exist with regard to this topic on used reperfusion technique.

After the introduction of cava-sparing techniques for the recipient's hepatectomy, the routine use of a temporary femoral-to-jugular veno-venous bypass (VVB) during liver transplantation is not recommended [32]. A survey carried out in 2006 among transplant centres in Germany showed that VVB is not used as a standard procedure in 86% of all centres [33]. Liver transplantation without VVB is safe with regard to potentially ensuing renal, neurological and gastrointestinal complications, as VVB itself resulted in a high rate of complications [32].

The potential benefit of using porto-caval shunt, however, is still under debate. Most of the studies included in this work use a porto-caval shunt, despite the piggy-back technique and only partially clamping the cava. Our centre does not apply the porto-caval shunt and no disadvantages have been observed. Venous congestion in the intestine could damage the epithelial lining of the intestine wall and lead to bacterial translocation [2] and sepsis, which might be reduced in IPR. Still, not one of our analysed studies focuses on that topic. Overall, no conclusive data in studies with high evidence exist. Most of the studies recently published show no benefit by using a porto-systemic shunt [34–37].

Taken together, we found no significant differences in used reperfusion technique with regard to mortality, rate of retransplantation and rate of biliary complications. However, even if not significant, we found evidence in favour of SIMR in all pairwise meta-analytical comparisons with IPR, with qualitatively similar ORs in favour of SIMR in all three endpoints considered (see Fig. 1). The difficulties encountered in our meta-analysis are generated by the lack of large randomized controlled studies on that topic. Aim of our meta-analysis could only be to identify the most promising technique that might result in better outcomes. Therefore, it was mandatory also to include studies with lesser level of evidence like not randomized trials. The trend of superiority using SIMR can only be evaluated in a proper RCT. Thus, based on evidence currently available and the limited number of studies on liver reperfusion, it is not possible to support or refute any reperfusion technique.

These results are in accordance with the systematic review and meta-analysis of Gurusamy *et al.* [11], where no significant differences in patient survival, graft survival or rate of serious adverse events between the groups in any of the comparisons was observed. There was furthermore no significant difference in the transfusion requirements between the groups in any of the comparisons [11]. In contrast to Gurusamy *et al.*, we did not only include RCTs. This decision was based primarily on the lack of randomized studies in the field. Still, we did not find unequivocal evidence in favour of a specific reperfusion technique.

Patient mortality, number of retransplantations and rate of biliary complications were chosen as outcome variables in our meta-analysis, as those were the only clinically relevant and contemporarily analysed parameters in the major-

ity of the selected studies. However, early graft function and the incidence of ITBLs would represent the best parameters for organ function that depend on the reperfusion technique. Unfortunately, none of the available studies gives a definition of early graft function. As surrogate parameters, primary nonfunction and postreperfusion syndrome could be analysed. Primary nonfunction was analysed only in 4 of the 11 studies and postreperfusion syndrome in only 2 of the 11 studies included in our meta-analysis. Therefore, those parameters could not be used for meta-analysis.

Together with the observation that European transplant centres use very heterogeneous reperfusion techniques (usually defined by the institution or the experience of the surgeon), the present results confirm the urgent need for large RCTs on reperfusion techniques, which is our next goal. We suggest first to run a monocentric screening trial in which IAR is compared to SIMR according to a drop-the-loser design. The purpose of this trial would be to identify the most successful reperfusion technique among the two candidates. Assuming 1-year graft survival rates of 80% and 90% in these two techniques, a sample size of 50 patients per group is necessary to identify the winner with 90% probability in a direct comparison of the observed graft survival rates. The winner of the screening trial is then compared to IPR, which is currently the most frequently used reperfusion technique in European transplantation centres, in a subsequent open, multicentre, randomized controlled trial. A RCT with the same inclusion criteria and homogenous and sensitive outcome parameters with the same standards in surgical and perioperative treatment is necessary to answer the question as to which is the best reperfusion technique. Graft survival (binary endpoint, with 1-year follow-up) might be the most sensitive marker to analyse outcome, depending on the reperfusion technique and might be a proper candidate as a primary endpoint. Secondary endpoints might include liver function, determined by coagulation parameters, hepatocellular death assessed by transaminases and injury of the biliary tract according to ITBLs with a follow-up period of 1 year.

As most of the transplant centres within ET would support and participate in an RCT in the field, our goal does not appear to be far stretched and can be performed within a reasonable amount of time.

Authorship

GM, MK: participated in research design, writing of the manuscript, performance of the research, data analysis. PH: participated in research design, performance of the research. MG: participated in writing of the manuscript, data analysis, contributed analytical tools. WOB, TB, GAB, HF, MG, WH, JNMI, JCK, EK, JK, JL, TL, HL, SN, BN, GO, AP JP, JP, JR, XR MKS, DS, NS, US, DLS, KT, DY: participated in the performance of the research. HB: participated in research design and data analysis. PS: participated in research design, writing of the manuscript, performance of the research, data analysis.

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