Utility of Basal Regional Oximetry as an Early Predictor of Graft Failure After Liver Transplant

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ABSTRACT

Introduction. Adequate perfusion and oxygenation to liver graft after transplantation is essential for its viability. Hepatic oximetry (hepatic tissue oxygenation [$LSrO_2$]) through near infrared spectroscopy (NIRS) can help by showing real time oxygen content of the graft.

Methods. In this prospective study, we enrolled 50 consecutive patients undergoing liver transplant surgery from deceased donors.
Liver NIRS ($LSrO_2$) was continuously measured for 24 hours then analyzed and correlated with other clinical data such as hemoglobin (Hb), mixed venous oxygen saturation, cardiac index (CI), central venous pressure, arterial gases, diuresis, blood lactate, liver biochemistry, and normalized index ratio (INR). Severity disease scales and cold-warm ischemia time were also measured, as well as Doppler ultrasound (DUS) at hour 24. A statistical analysis with IBM SPSS 22 using Pearson correlation was carried out.

Results. $LSrO_2$ could anticipate serious bleeding and hemodynamic events showing a decrease >10% from basal data.
We found a significant correlation between $LSrO_2$ with CI at 3 hours (P=.044), hemoglobin (Hb) at hour 3 and 24 (P = .004 and P = .002, respectively), and with Apache II (P=.041). A significant correlation was also detected between cold ischemia and INR at hour 24 (P=.016).
No correlation of $LSrO_2$ was found with lactate, liver biochemistry, and DUS data.

CHANGES in regional oxygen saturations (SrO_2) monitored by NIRS are recognized as sensitive indicators of perfusion-metabolism coupling [1–4]. The maintenance of adequate tissue perfusion and end organ oxygen delivery is one of the primary goals in the management of the critically ill patient. Accurate monitoring systems to detect changes in regional blood flow or an imbalance between oxygen delivery and utilization remain less than optimal [5,6].

One drawback of the NIRS method is that it does not measure tissue oxygenation pO_2 but provides information on vascular oxygenation (oxygen saturation), which results from the balance between oxygen delivery and oxygen consumption [7]. Nevertheless, SrO_2 provides an approach to general oxygenation and total blood flow to the tissue explored that, in the case of the liver, was already described by El-Desoky et al in 2 excellent experimental studies on animals in 1999 and 2001 [8,9].

Despite the remarkable progress in liver transplantation, graft and patient loss still occur as a result of posttransplant complications such as hepatic artery occlusion, portal vein thrombosis, primary nonfunction, and acute graft rejection [10,11]. Impairment of the liver graft microcirculation and tissue hypoxia are both common pathology in all these complications with eventual loss of the graft without early intervention [12]. Early detection of this impairment could reduce the overall morbidity and mortality of liver

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transplantation by allowing earlier treatment. Measurement of hepatic tissue oxygenation ($LSrO_2$) has been shown to correlate significantly with the microcirculatory impairment and liver dysfunction induced by ischemia and reperfusion injury [13,14].

The usefulness of NIRS for measurement of hepatic blood flow and oxygenation has been sufficiently demonstrated by the experimental studies of Tokuta et al [15] and El-Desoky [8,9], in which NIRS showed its value in detecting low flow and low oxygenation states of the liver during its clamping complex surgery.

Currently, liver transplant has evolved and is a common surgery technique but can also carry problematic situations during the posttransplant period, such as delayed function of the graft or vascular liver ischemia, that jeopardize the viability of the organ. Early detection of any malfunction of the graft may give rise to carrying out medical, surgical, or invasive solutions to give optimal solutions to optimize and preserve the hepatic graft.

OBJECTIVE

The aim of the study was to analyze the usefulness of $LSrO_2$ to determine any possible reduction in the hepatic graft flow and its oxygenation, due to vascular obstruction or bleeding, and to know the correlation of $LSrO_2$ with clinical parameters associated with ischemia, ischemia and reperfusion injury, or any malfunctioning of the graft. We also tried to analyze any correlation of $LSrO_2$ with clinical data, liver biochemistry profile, and DUS.

METHOD

We carried out a longitudinal, prospective, single-center, and noninterventional study, which was approved by the Ethics Committee of the University Hospital Infanta Cristina, Badajoz, Spain (tertiary hospital).

All patients were admitted to the intensive care unit (ICU) for the immediate postoperative period of at least 48 hours.

Fifty-seven consecutive adult patients undergoing primary elective liver transplantation were enrolled in the study. All patients received a liver allograft from deceased donors. Seven patients with a body mass index >29.9 were excluded as subcutaneous adipose tissue of more than 2 cm could limit the penetration depth of NIRS [16]. Consequently, a total of 50 patients (41 men, 9 women, with a mean age 57.3 and standard deviation (SD) of 8.37) were finally included in the study. None of the patients suffered from severe cardiac, pulmonary, or skin disease.

NIRS Technique and Clinical Data

NIRS is a noninvasive technique that allows continuous monitoring of regional oxygen saturation (SrO_2) of tissue sampled under the NIRS optode. Measurements in this study were performed with INVOS 5100 C (Somanetics, Medtronics, Minneapolis, Minn). NIRS optodes used in this study have a maximum penetration depth of approximately 2.5 cm. NIRS measurements were performed by the ICU nurse and recorded on each patient's electronic file.

In all patients undergoing liver transplantation with a body mass index <2.9, overlying tissue thickness was measured preoperatively with a surgical ruler by the surgeon. After wound closure, the location of the liver allograft was marked at the skin with a surgical skin marker.

Upon arrival at the ICU, 1 NIRS optode was attached to the level of the liver allograft. NIRS monitoring started immediately after arrival. All patients were measured while in the supine position.

$LSrO_2$ measurements were monitored and stored continuously for 24 hours. The routinely performed DUS was performed in the first 6 postoperative hours.

Vital parameters, such as blood pressure, heart frequency, oxygen saturation, blood gas analysis, blood lactate, mixed venous saturation (SvO_2), pulmonary capillary wedged pressure, cardiac index (CI), and diuresis were recorded online. Serum levels of hemoglobin, lactate and liver biochemistry profile as serum alanine aminotransferase (ALT), aspartate aminotransferase (AST), lactic dehydrogenase, gamma-glutamyl transferase (GGT), and alkaline phosphatase (FA) were obtained every 8 hours in the first postoperative day.

Severity index scales such as Sequential Organ Failure Assessment (SOFA) and Apache II were also calculated on ICU admission, and cold/warm ischemia time were registered.

DUS

DUS was performed on the first and fifth postoperative day according to protocol standards to assess blood flow in liver allografts. Measurements were performed with an iU22 system (Philips, Amsterdam, the Netherlands), with a C5-2 curved array transducer. Pulsatility index (PI) and resistive index (RI) were calculated. A PI cutoff value of ≥1.8 was used to confirm impaired blood flow. DUS was performed by experienced hepatologists that were blinded to NIRS results.

Statistical Analysis

Results are expressed as mean ± SD. After the study period, SrO_2 baselines of optodes were off-line normalized at 100% in each patient. Statistical analyses were performed in SPSS (version 22; SPSS, Chicago, Ill, United States). A calculation of correlation between mean $LSrO_2$ measurements with SOFA, Apache II, cold

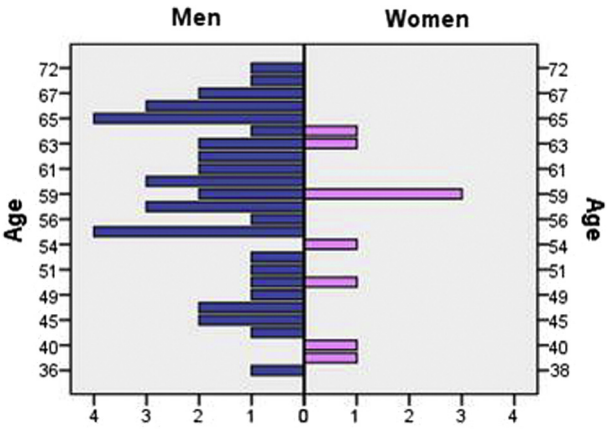

Fig 1. Demographic Data of the Population. N = 50 patients, 9 women and 41 men, age = 36–72; mean ($\bar{x}$) = 57.3; standard deviation (σ) = 8.37; median = 59.

Table 1. Adverse Events Observed in the Study. All Cases Were Detected Early On SrO_2

Adverse Events Directly or Not Related With Surgery			
Type	Details	No.	Observations
Bleeding/anemia	Transfusion >3 blood units (in first 12 h)	12	5 surgically revisited
Cardiac	Low cardiac output	2	1 cardiogenic shock (Takotsubo) 1 rapid atrial fibrillation
Sepsis	Septic shock MOD	1	Exitus
Respiratory	Bronchospasm	1	Reintubation
Total severe events		16	

Abbreviation: MOD, multiple organ dysfunction.

and warm ischemia time, Hb, SvO_2, CI, lactate, AST, ALT, FA, GGT, and normalized index ratio (INR) at 1, 2, or 3 different time periods (hour 3, hour 8, hour 24) was carried out. A Pearson correlation coefficient was used. $P < .05$ was defined as statistically significant.

RESULTS

Demographic data is displayed in Fig 1. We found several severe adverse events during the study, not clearly related with surgery, that are depicted in Table 1. Sixteen patients showed adverse events. No more than 1 event was observed on the same patient. All 16 patients and events were successfully alerted by a maintained decrease of more than 10% of the $LSrO_2$ basal data. Seven patients among the bleeding/anemia group were successfully treated with intravenous vitamin K and prothrombin complex, but 5 of them required a return to the operating theater; all of them with successfully reached hemostasis. No graft loss was observed in this bleeding/anemia group of patients.

An important adverse event was experienced by 1 patient with no previous cardiac medical history who developed an early cardiogenic shock due to Takotsubo syndrome demonstrated by transthoracic and transesophagic cardiac ultrasound exploration and further confirmed by a ventriculographic study. This patient responded optimally to dobutamine and levosimendan, but an intra-aortic counterpulsation balloon pump support was initially needed. Another patient developed a rapid atrial fibrillation that positively responded to cardiac electrical cardioversion.

One more patient with a medical background of bronchospasm crisis developed a new one that could not be solely managed with medication; reintubation plus mechanical ventilation support was required for 48 hours.

Finally, a refractory septic shock due to pulmonary origin and abdominal complicated peritonitis that led to multiple organ dysfunction was the cause of the only 1 patient's death during the study.

The mean value of $LSrO_2$ was 74 (SD 5.7) with a tendency of a slight progressively increment along the following hours, showing a mean value of 76 (SD 4.1) at hour 24.

When studying correlation of $LSrO_2$, relevant and significant findings at hour 3 (Fig 2) were found between this parameter and Hb ($P = .004$), as well as with CI ($P = .044$). It was also found with the Apache II scale ($P = .041$) but not with SOFA ($P = .069$) (Fig 3).

At hour 24, we also found significant correlation between $LSrO_2$ and Hb ($P = .002$) (Fig 2). No correlation was met with lactate at any moment of the study ($P = .113$; $P = .293$ and $P = .141$, respectively).

Importantly, neither at the beginning nor at the end of the study was a correlation observed between $LSrO_2$ and liver biochemistry (AST, ALT, GGT, and FA): AST at hour 3

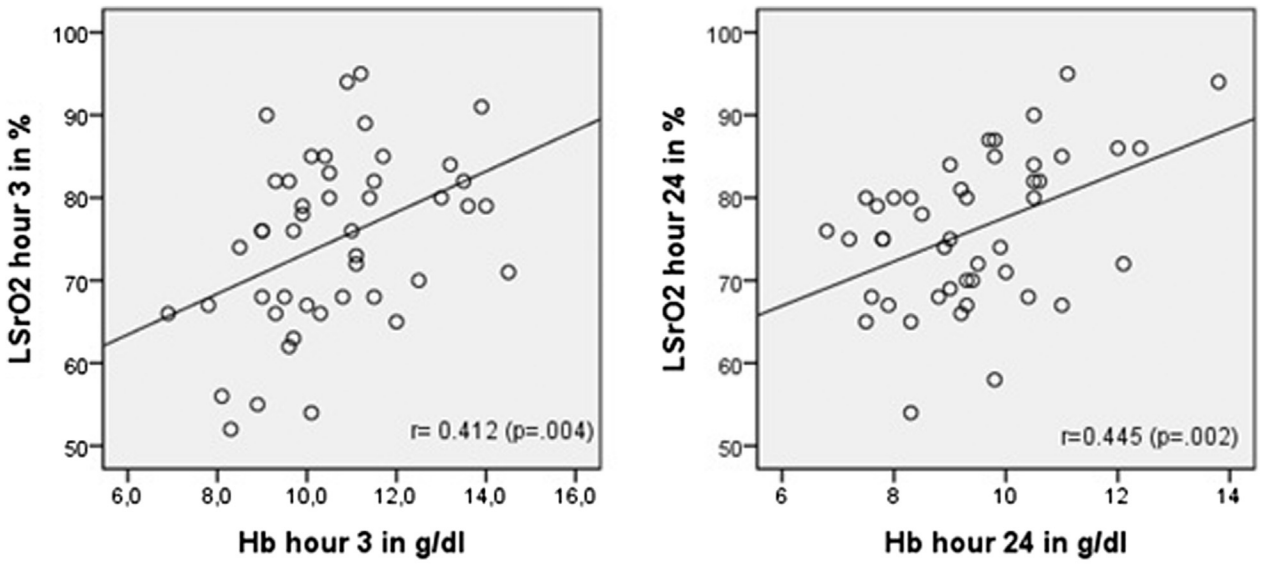

Fig 2. Scatter plot and linear regression of $LSrO_2$ versus Hb at hours 3 and 24. $LSrO_2$ expressed in percentage and Hb in g/dL.

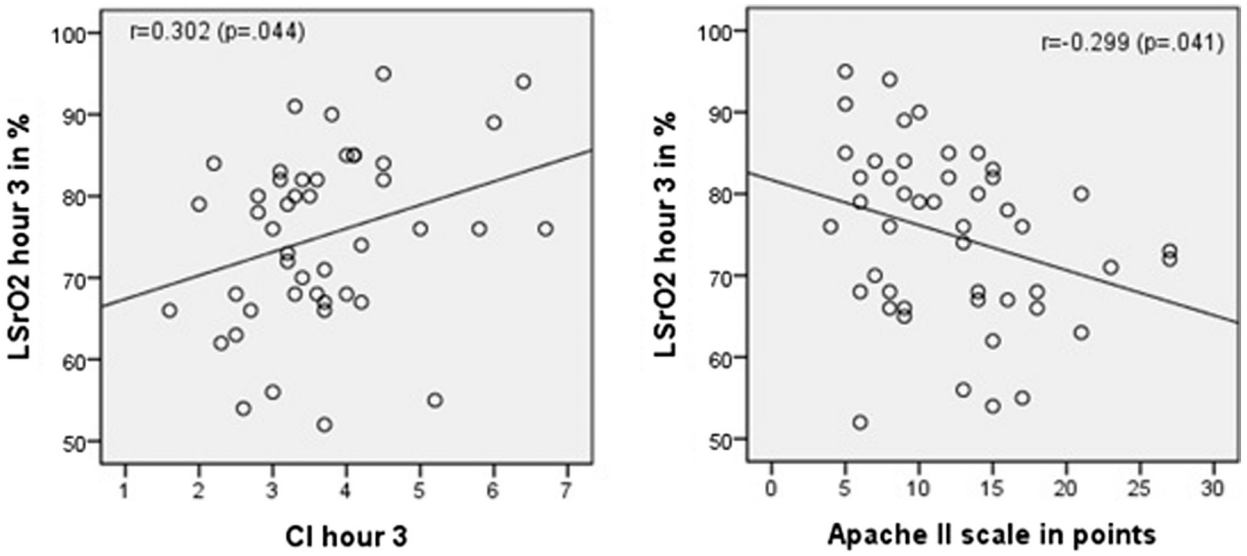

Fig 3. Scatter plot and linear regression of $LSrO_2$ versus CI at hour 3 and versus Apache II. $LSrO_2$ expressed in percentage and Apache II in scale points.

($P = .571$) and at hour 24 ($P = .365$); ALT at hour 3 ($P = .365$) and at hour 24 ($P = .454$); GGT at hour 3 ($P = .381$) and at hour 24 ($P = .652$); and FA at hour 3 ($P = .952$) and at hour 24 ($P = .417$).

Finally, among hemodynamic parameters, a correlation was encountered between $LSrO_2$ and CI at hour 3 ($P = .044$) but not at hours 8 and 24. No correlation could be found as well between $LSrO_2$ and SvO_2 ($P = .293$).

DUS data expressed as RI and PI did not correlate with $LSrO_2$ at hour 24 ($P = .738$ and $P = .799$, respectively). We could not also find any statistical connection between $LSrO_2$ and cold-warm ischemia time ($P = .780$ and $P = .951$).

In a more exhaustive survey focused on the subgroups, a significant correlation was found between cold ischemia and INR at the final period (hour 24) ($P = .016$) (Fig 4).

A significant statistical correlation also existed between INR at admission (hour 3) and all liver biochemistry parameters (hour 3 and hour 24) (Table 4).

A more detailed data analysis is depicted in Tables 2 and 3.

DISCUSSION

Any clinical situation or scenario that leads to low liver flow or low oxygen delivery to the liver will cause hepatic damage that will result in a metabolic impairment of the graft and possibly predispose a delay in graft functioning, rejection, and biliary or vascular complications [15].

The finding of a significant correlation between $LSrO_2$ with Apache II on admission can be explained by the influence of previous severity state on the outcome of illness [16,17].

The liver is an organ that actively interacts with all body systems, so the patient who receives a liver graft faces a huge set of physiological changes. During and in the immediate postoperative period, the liver is subjected to a wide variety of potentially damaging factors, including hypotension, hypoxia, ischemia, and hepatotoxic drugs; in addition, donor-related factors (hepatic steatosis, use of vasoactive drugs, hemodynamic changes), surgical-related aspects (intra- or postoperative hemorrhage, vascular or biliary complications), or immune responses (rejection) might lead to a very different outcome. In summary, the postoperative outcome of each patient varies greatly depending on the patient's

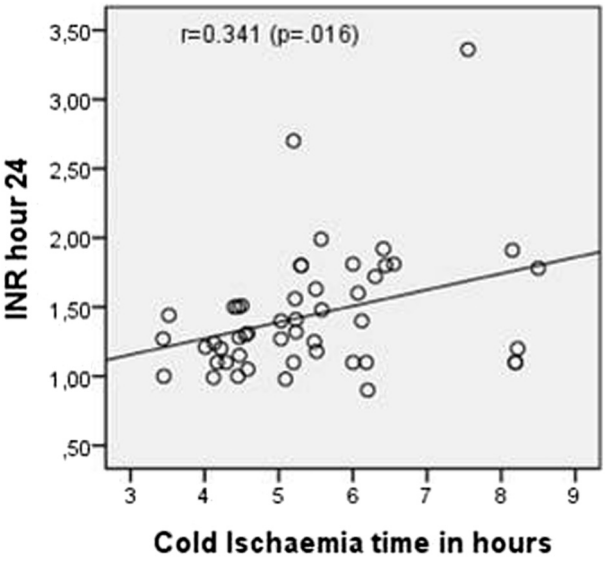

Fig 4. Scatter plot and linear regression of INR versus cold ischemia at hour 24. INR expressed in ratio, cold ischemia in hours.

Table 2. Correlation Between $LSrO_2$ With Different Variables, Clinical, Biochemistry, and DUS

	$LSrO_2$ 3 h	$LSrO_2$ 8 h	$LSrO_2$ 24 h
Lactate hour 3	$r = -0.229$ ($P = .134$)		
Cardiac index hour 3	$r = 0.302$ ($P = .044$)*		
AST hour 3	$r = -0.085$ ($P = .571$)		
ALT hour 3	$r = -0.145$ ($P = .365$)		
GGT hour 3	$r = 0.155$ ($P = .381$)		
FA hour 3	$r = 0.100$ ($P = .952$)		
Hb hour 3	$r = 0.412$ ($P = .004$)*		
SvO_2	$r = 0.157$ ($P = .293$)		
SOFA	$r = -0.267$ ($P = .069$)		
Apache II	$r = -0.299$ ($P = .041$)*		
Lactate hour 8		$r = -0.160$ ($P = .293$)	
Cardiac index hour 8		$r = 0.256$ ($P = .086$)	
Lactate hour 24			$r = -0.231$ ($P = .141$)
Cardiac index hour 24			$r = 0.163$ ($P = .278$)
AST hour 24			$r = -0.138$ ($P = .365$)
ALT hour 24			$r = -0.120$ ($P = .454$)
GGT hour 24			$r = -0.073$ ($P = .652$)
FA hour 24			$r = -0.136$ ($P = .417$)
Hb hour 24			$r = 0.445$ ($P = .002$)*
PI			$r = 0.051$ ($P = .738$)
RI			$r = -0.039$ ($P = .799$)
Cold ischemia time			$r = 0.042$ ($P = .780$)

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; DUS, Doppler ultrasound; FA, alkaline phosphatase; GGT, gamma-glutamyl transferase; Hb, hemoglobin; $LSrO_2$, hepatic tissue oxygenation; PI, pulsatility index; RI, resistive index; SOFA, Sequential Organ Failure Assessment; SvO_2, venous saturation.
*Statistically significant.

preoperative state, the quality of the donated organ, and the complexity of the surgery [17,18].

To our knowledge, this is one of the largest studies of $LSrO_2$ in adult liver transplant patients.

It is of utmost importance that $LSrO_2$ can detect problems early in the course of all patients with low blood flow states and low oxygenation, showing a clear decrease of at least 10% that was maintained until recovery.

Our study shows similar findings that were already described in experimental medical literature [8,13–15], where it was clearly demonstrated that $LSrO_2$ detects early significant liver decrease in flow or oxygenation, as happened in our study when low CI or bleeding with shock and with low Hb level occurred.

The lack of significant correlation between $LSrO_2$ and lactate levels in the case of liver transplantation has a reasonable explanation that relies on the clinical expression that severe liver illness is usually accompanied by higher levels of lactate, due to a malfunctioning metabolic state of the native liver that cannot properly use metabolic pathways to clear lactate.

Furthermore, as 5% of lactate is metabolized by the kidney, acute kidney injury in the setting of critical illness can worsen hyperlactatemia [19]. While the healthy liver has a huge functional reserve of metabolizing lactate [20], this lactate clearance is impaired in chronic liver diseases because of a decrease in the functional hepatocyte mass [21,22]. That is the reason for what elevation of lactate during early posttransplant surgery is, in many patients, not related to low perfusion or hypoxic states and that is the reason for the lack of correlation between $LSrO_2$ and lactate levels.

The observation of no correlation between $LSrO_2$ and liver biochemistry in the early postoperative period of liver transplant could be explained because, at the initial postoperative period, the level of hepatic biomarkers can be still confounding due to the mixture between the patient's previous transplant enzymatic level and the new situation

Table 3. Correlation Between Cold/Warm Ischemia With Different Variables, Biochemistry, and DUS

	Cold Ischemia Time	Warm Ischemia Time
PI	$r = 0.023$ ($P = .877$)	$r = -0.031$ ($P = .830$)
RI	$r = -0.106$ ($P = .468$)	$r = -0.035$ ($P = .811$)
INR hour 3	$r = 0.235$ ($P = .101$)	$r = -0.003$ ($P = .986$)
INR hour 24	$r = 0.341$ ($P = .016$)*	$r = -0.111$ ($P = .448$)
AST hour 3	$r = 0.120$ ($P = .405$)	$r = -0.056$ ($P = .702$)
ALT hour 24	$r = 0.218$ ($P = .136$)	$r = -0.053$ ($P = .718$)
ALT hour 3	$r = 0.084$ ($P = .587$)	$r = -0.057$ ($P = .712$)
ALT hour 24	$r = 0.130$ ($P = .401$)	$r = -0.060$ ($P = .699$)
GGT hour 3	$r = 0.340$ ($P = .040$)*	$r = -0.099$ ($P = .561$)
GGT hour 24	$r = 0.253$ ($P = .097$)	$r = -0.081$ ($P = .603$)
FA hour 3	$r = 0.146$ ($P = .351$)	$r = -0.030$ ($P = .849$)
FA hour 24	$r = -0.091$ ($P = .571$)	$r = -0.102$ ($P = .526$)

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; DUS, Doppler ultrasound; FA, alkaline phosphatase; GGT, gamma-glutamyl transferase; INR, internalized normalized ratio; PI, pulsatility index; RI, resistive index.
*Statistically significant.

Table 4. Correlation Between INR and Liver Biochemistry on Admission

	AST 3 h	AST 24 h	ALT 3 h	ALT 24 h	GGT 3 h
INR 3 h	$r = 0.393$ ($P = .005$)*	$r = 0.408$ ($P = .004$)*	$r = -0.396$ ($P = .008$)*	$r = 0.299$ ($P = .049$)*	$r = -0.458$ ($P = .004$)*

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; INR, normalized index ratio; GGT, gamma-glutamyl transferase.
*Statistically significant.

brought about by the graft after the ischemia/reperfusion state.

An explanation for the positive correlation at hour 24 between cold ischemia time and INR as well as with GGT could be found in the graft's damage due to preservation and clamping; a longer ischemia time brings about an alteration in the vitamin K dependent factors and damage in liver cells, where both actions expressed—in prolonged INR—an elevation of GGT.

The absence of any statistic correlation between $LSrO_2$ and DUS must be related with the very early implementation of the DUS study that perhaps cannot reflect main vascular problems that could appear later. Nevertheless, we must bear in mind that in our study no patient presented vein or arterial thrombosis, so the main severe vascular complications could not be captured.

Our study has several limitations in the number of patients and also in the absence of patients with serious arterial and venous complications that, although fortunately not usual, can really jeopardize graft viability and could have been explored with $LSrO_2$.

CONCLUSIONS

$LSrO_2$ is a new monitoring tool that brings valuable information about hepatic flow and oxygenation early after liver transplant. It can be easily practiced and interpreted, but more research on its use is still advisable.

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