Utility of Basal Regional Oximetry Saturation for the Diagnosis of Acute Tubular Necrosis in the Early Postoperative Period Following Kidney Transplantation

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ABSTRACT

Introduction. Adequate perfusion and oxygenation to a renal graft after transplantation are essential for its viability. Regional renal oximetry ($RSrO_2$) through near-infrared spectroscopy shows real-time oxygen content of the graft.

Methods. A prospective study was conducted. We enrolled consecutive patients undergoing renal transplant from deceased donors from January 2015 to February 2016. $RSrO_2$ was continuously measured for 24 hours, analyzed, and correlated with other clinical data such as hemoglobin, mixed central venous oxygen saturation ($ScvO_2$), blood pressure, central venous pressure, diuresis, and blood lactate. Severity disease scales, cold and warm ischemia times were also measured, as well as the pulsatility index (PI) and resistive index (RI) by Doppler-dúplex ultrasound (DUS) at 24 hours. A statistical analysis with IBM SPSS version 22 (IBM, Armonk, NY) using a Pearson correlation was carried out.

Results. $RSrO_2$ could anticipate serious arterial and bleeding events showing a maintained decrease >10% from basal data. A significant correlation was found between $RSrO_2$ with lactate at 8 and 24 hours ($P = .005$ and $P = .000$ respectively), as well as with initial diuresis at hour 3 ($P = .010$), initial $ScvO_2$ ($P = .010$), Sequential Organ Failure Assessment ($P = .015$), and warm ischemia ($P = .035$). A significant correlation was also detected between cold ischemia, RI, and diuresis ($P = .037$ and $P = .049$ respectively). No correlation was found between $RSrO_2$ and DUS data.

Conclusion. $RSrO_2$ is a useful tool for initial kidney transplant grafts monitoring and could give early warnings regarding bleeding and arterial thrombosis. $RSrO_2$ is found to have a correlation with initial diuresis, blood lactate, and $ScvO_2$. No matching data with Doppler was found.

CHANGES in regional oxygen saturations monitored by near-infrared spectroscopy (NIRS) are recognized as sensitive indicators of perfusion-metabolism coupling [1–4]. The maintenance of adequate tissue perfusion and organ oxygenation are some of the primary goals in managing critically ill patients. Accurate monitoring systems to detect changes in regional blood flow or an imbalance between oxygen delivery and its utilization remain sub-optimal [5,6].

Vascular complications in the early postoperative period following kidney transplantation occur approximately in 3%-8% of patients [7–10]. Thrombosis, bleeding, and kinking of either the renal artery or vein are typical vascular complications that cause impaired blood flow in renal grafts. To prevent graft loss, immediate surgical exploration is required [11].

Conventional monitoring of renal allografts is usually performed by means of urine output and creatinine serum

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0041-1345/19
https://doi.org/10.1016/j.transproceed.2018.12.011

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levels. However, both of these techniques are limited in detection of impaired blood flow [12]. Urine production might not be present in cases of delayed graft function, although blood flow in the graft can be adequate. Furthermore, in some patients undergoing transplantation, urine production by native kidneys continues, and thus urine production is not a source of information regarding graft function. With regard to creatinine serum levels, one limitation is that no changes can be detected immediately in patients with acute impaired blood flow because significant changes occur after a prolonged time. Moreover, determination of serum creatinine is a discontinuous measurement method.

Duplex ultrasound (DUS) specifically monitors blood flow in main renal arterial branches (arcuate and interlobar). It is the preferred first test to perform during immediate postoperative period to detect allograft dysfunction [13]. DUS has a sensitivity of 87%-94%, and a specificity of 86%-100% in diagnosing renal artery stenosis in allografts [14]. However, DUS is also a discontinuous diagnostic modality, providing only information concerning blood flow at one time point and depends on the expertise of the operator.

OBJECTIVE

The aim of the study was to analyze the usefulness of regional renal oximetry ($RSrO_2$) to determine early any possible reduction in graft flow and oxygenation due to arterial obstruction or bleeding and to know the correlation of $RSrO_2$ with clinical parameters associated with ischemia and postoperative acute tubular necrosis of the graft.

METHODS

We carried out a longitudinal, prospective, single-center, non-interventional study, approved by the Ethics Committee of the University Hospital Infanta Cristina, Badajoz, Spain. Sixty-six consecutive adult patients undergoing primary elective renal transplantation were candidates to be enrolled in the study, but 5 patients with body mass index >29.9 were excluded, as subcutaneous adipose tissue of more than 2 cm could limit the penetration depth of NIRS [15].

All patients received renal allografts from deceased donors. Consequently, a total of 61 white patients were finally included in the study. None of the patients suffered from severe cardiac, pulmonary, or skin disease. All patients were admitted to the intensive care unit (ICU) for the immediate postoperative period, at least 24 hours.

NIRS Technique and Clinical Data

NIRS is a noninvasive technique that allows continuous monitoring of regional oxygen saturation of tissue sampled under the NIRS optode. Measurements in this study were performed with INVOS 5100C (Medtronics, Minneapolis, Minn, United States). The NIRS optodes used in this study have a maximum penetration depth of approximately 2.5 cm. NIRS measurements were taken by the ICU nurse.

In all patients undergoing kidney transplantation with 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 renal allograft was marked on the skin with a surgical skin marker.

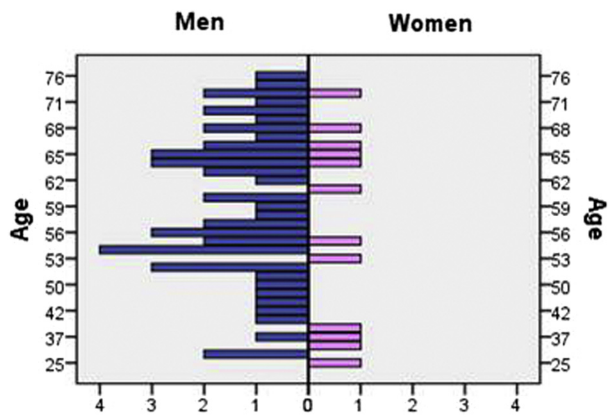

Fig 1. Demographic Data of the Population. N = 61 kidney transplant patients. Female 12, male 49. Age 25–76 years; mean ($\bar{x}$) = 58.7, SD (σ) = 10.7; median = 63.

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

$RSrO_2$ measurements were monitored and stored continuously until the routinely performed DUS on the first postoperative day. The duration of NIRS monitoring was 24 hours.

Vital parameters, such as blood pressure, heart frequency, oxygen saturation, blood lactate, central venous oxygen saturation ($ScvO_2$), central venous pressure, and diuresis, were recorded online in the ICU. Diuresis was recorded hourly. Serum levels of lactate, hemoglobin and creatinine were obtained every 8 hours in the first postoperative day.

Scores on the severity index scales Sequential Organ Failure Assessment (SOFA) and Apache II were also calculated on ICU admission and cold and warm ischemia times were registered.

Doppler-Dúplex Ultrasound

DUS was performed on the first and seventh postoperative days according to a protocol standard to assess blood flow in renal allografts. Measurements were performed with an iU22 system (Philips, Amsterdam, the Netherlands), with a C5-2 curved array transducer. The pulsatility index and resistive index (RI) were calculated. A PI cutoff value of ≥1.9 was used to confirm impaired blood flow and an RI cutoff >0.7 was used to diagnose acute tubular necrosis. DUS was performed by experienced radiologists, who were blinded to NIRS results.

Statistical Analysis

Results are expressed as mean ± standard deviation (SD) or median (and interquartile range, when appropriate). After the study period, the $RSrO_2$ baseline of optode was offline normalized at

Table 1. Total of Adverse Events Observed During the Study

Adverse Events Directly Related With Renal Graft Surgery		
Type	n	Observations
Bleeding (requiring surgery)	3	1 transplantectomy
Arterial thrombosis	1	Transplantectomy
Venous thrombosis	1	Surgical reparation
Total severe events	5	2 losses of grafts

Table 2. Different Correlation of $RSrO_2$ at Several Intervals and With Several Variables

	$RSrO_2$ hour 3	$RSrO_2$ hour 8	$RSrO_2$ hour 24
Lactate hour 3	$r = -0.004$ ($P = .078$)		
Lactate hour 8		$r = -0.419$ ($P = .005$)*	
Lactate hour 24			$r = -0.590$ ($P = .000$)*
Hb hour 3	$r = -0.168$ ($P = .243$)		
Hb hour 24			$r = 0.112$ ($P = .502$)
$ScvO_2$	$r = 0.424$ ($P = .010$)*		
Diuresis hour 3	$r = 0.348$ ($P = .017$)*		
SOFA	$r = -0.344$ ($P = .015$)*		
Apache II	$r = -0.002$ ($P = .988$)		
Pulsatility index			$r = 0.296$ ($P = .080$)
Resistive index			$r = -0.295$ ($P = .072$)
Cold ischemia time			$r = -0.167$ ($P = .278$)
Warm ischemia time			$r = -0.319$ ($P = .035$)*

Abbreviations: Hb, hemoglobin; $RSrO_2$, regional renal oximetry; $ScvO_2$, central venous oxygen saturation; SOFA, Sequential Organ Failure Assessment.
*Significant.

100% in each patient. Statistical analyses were performed with SPSS version 22 (IBM). The correlation between mean $RSrO_2$ measurements with SOFA, Apache II, cold and warm ischemia times, diuresis, hemoglobin, $ScvO_2$, lactate and mean urine output at hours 3, 8, and 24 were calculated. A Pearson correlation coefficient was used. $P < .05$ was defined as statistically significant.

RESULTS

Demographic details and characteristics of the 61 included patients are reported in Fig 1.

Median initial urine production was 90 (interquartile range, 20–200) cc/hour. None of the patients had an hourly urine production <20 cc. Although creatinine was measured every 12 hours, it was not taken into account for this study, for the aforementioned reasons.

Among major early adverse events, it must be highlighted that 1 patient suffered from acute arterial thrombosis of the allograft, which was indicated by a constant decrease of more than 10% of the basal $RSrO_2$; a transplantectomy was subsequently carried out. One patient suffered a venous thrombosis that was successfully surgically repaired but was not detected as early by $RSrO_2$ as arterial thrombosis. Three more patients presented serious bleeding events, which were detected early because of low $RSrO_2$ and later confirmed by low hemoglobin and clinical data. These patients needed surgical repair, and unfortunately one of them finally lost the graft (Table 1).

Mean cold and warm ischemia times were 15.5 hours (SD 5.17) and 66 minutes (SD 0.47), respectively.

Three patients required postoperative dialysis. DUS of the renal allograft revealed a PI of $\geq$2.5 in only 2 patients in the study.

The mean $RSrO_2$ value of optode at the start of $RSrO_2$ measurement was 81% $\pm$ 6%. End values of $RSrO_2$ were not significantly different ($P = .685$). The median variability of $RSrO_2$ data and curves over time was 5.8%. All results and the correlation study are depicted in Tables 2 and 3. A clear statistical significant negative correlation between $RSrO_2$ and serum lactate was observed all along the study (Fig 2). Diuresis was enhanced as $RSrO_2$ improved (Fig 3).

A clearly positive correlation was also observed between $ScvO_2$ and $RSrO_2$ during the first hours (Fig 3).

When correlating $RSrO_2$ with SOFA, a negative significant link was detected (Fig 4).

A statistical significant negative correlation between $RSrO_2$ and warm ischaemia was also found (Fig 4).

When observing DUS correlation and RI, it was found a positive correlation with cold ischaemia time and a negative one with diuresis (Fig 5).

DISCUSSION

This study showed that continuous $RSrO_2$ monitoring in patients undergoing kidney transplantation in the early postoperative period is safe and feasible. Performance of $RSrO_2$ measurements in all 61 patients succeeded and did not interfere with postoperative care. However, the added value of NIRS to monitor renal allograft oxygenation remains to be confirmed.

The $RSrO_2$ measurements obtained provide useful information concerning measurements in patients undergoing kidney transplantation securing and confirming adequate blood flow. A median variability of $RSrO_2$ curves over time of 5%-6% was observed and reflects normal $RSrO_2$ variability. In this study, a significant correlation was found between $RSrO_2$ measurements and serum levels of hemoglobin (Table 2).

Table 3. Different Correlation of Resistive Index and Pulsatility Index

	Resistive Index	Pulsatility Index
Warm ischemia time	$r = -0.140$ ($P = .343$)	$r = 0.114$ ($P = .460$)
Cold ischemia time	$r = 0.302$ ($P = .037$)*	$r = -0.037$ ($P = .813$)
Diuresis	$r = -0.292$ ($P = .049$)*	$r = -0.131$ ($P = .403$)

*Significant.

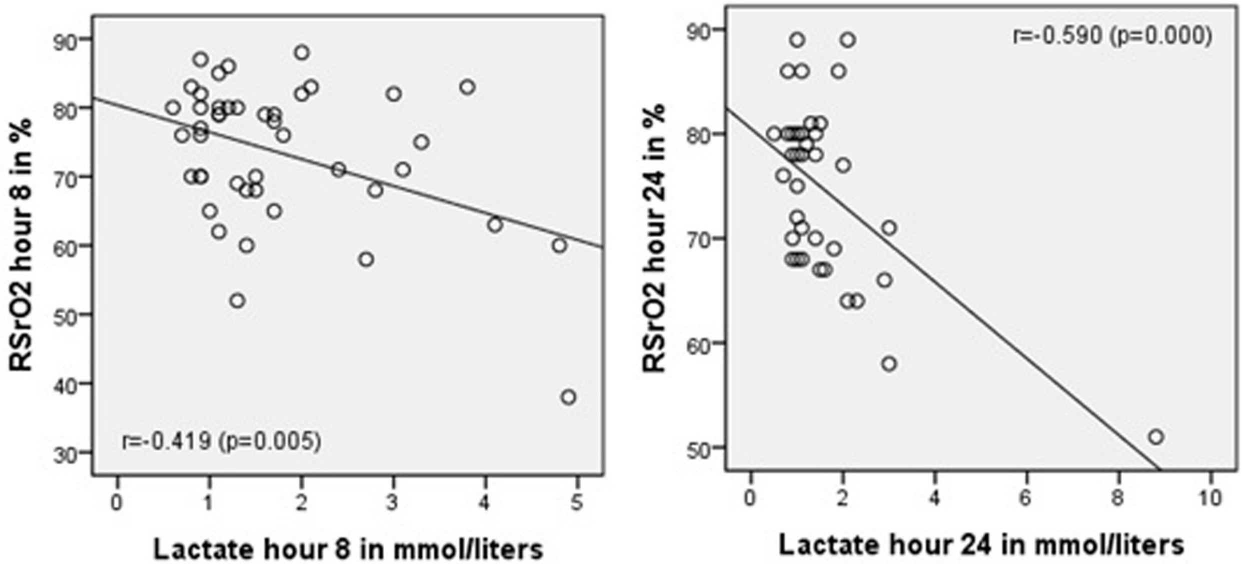

Fig 2. Scatter plot and linear regression of $RSrO_2$ vs lactate at hours 8 and 24.

A strong inverted correlation was found between $RSrO_2$ and lactate levels, almost from the initial postoperative period (Fig 2); this finding was expected, as it was already reported by Chakravarti et al [15] concerning a cohort of 23 infant patients undergoing cardiac surgery.

One of the main advantages of renal NIRS over most monitoring methods of renal allograft is that NIRS is a continuous measurement method. $RSrO_2$ can be used to achieve early detection of impaired blood flow in renal allograft, thereby highlighting the necessity of surgical exploration of vascular anastomoses and possibly increasing the success rates of salvage attempts. Another advantage of NIRS is its noninvasiveness. The $RSrO_2$ measurement is painless, harmless, and easy to manage. It is simple to apply to patients and theO_2 results are easily interpreted by doctors and nurses.

Although NIRS has promising features for renal allograft monitoring, the technique has several limitations for this specific application. A main disadvantage concerns the influence of the excess of overlying tissue thickness on the sensitivity of $RSrO_2$ curves to detect impaired blood flow in renal allografts. In patients with an overlying tissue

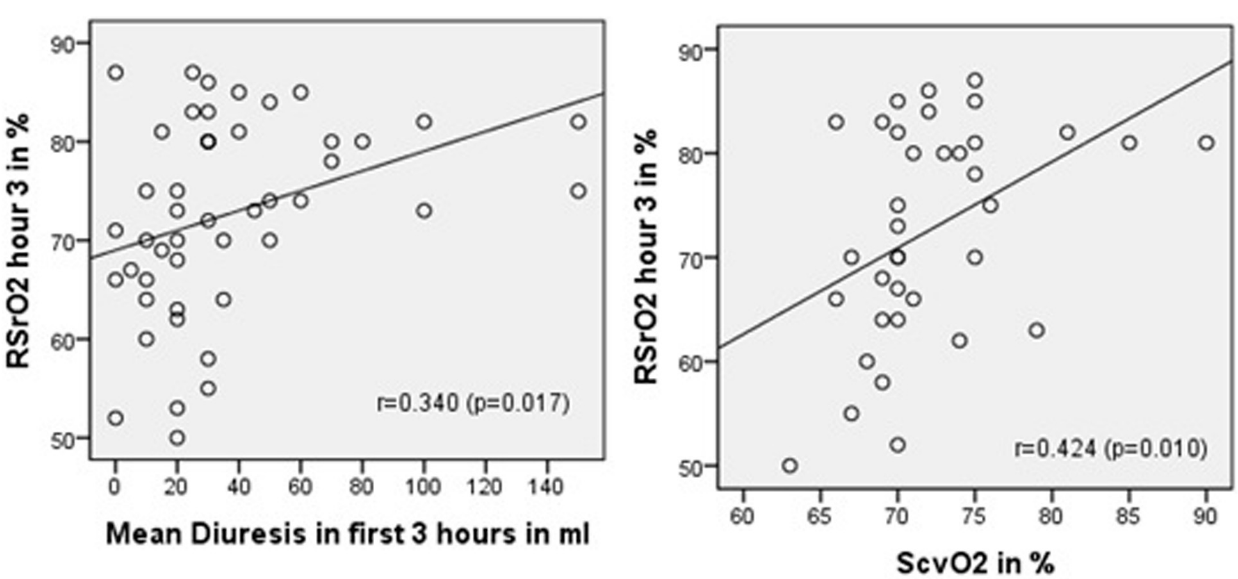

Fig 3. Scatter plot and linear regression of $RSrO_2$ vs $ScvO_2$ and mean diuresis at hour 3.

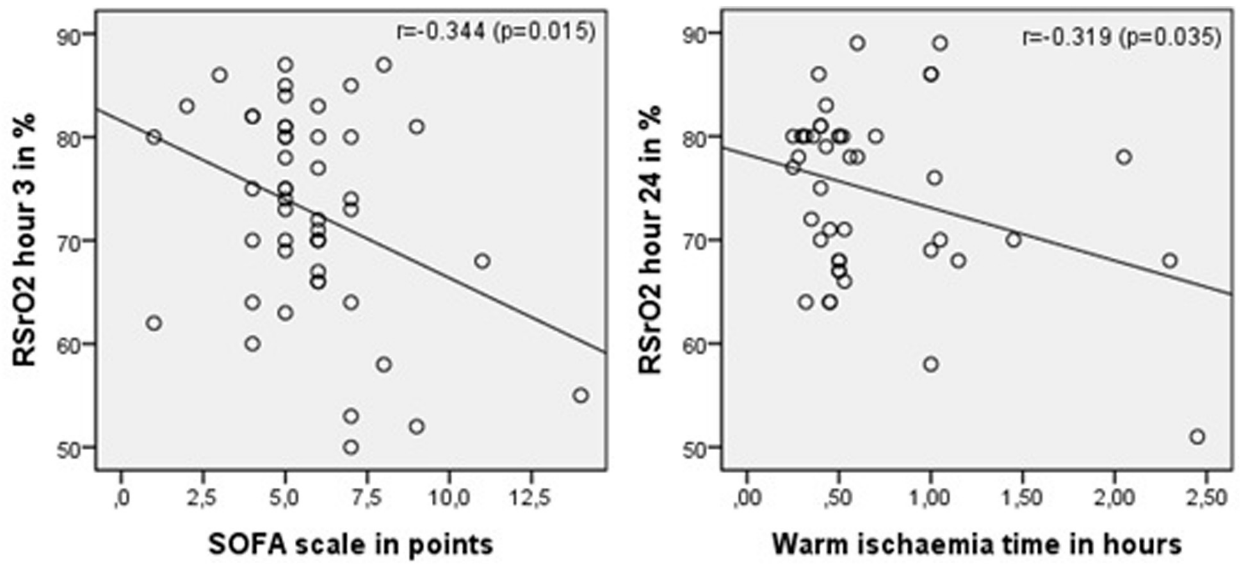

Fig 4. Scatter plot and linear regression of $RSrO_2$ at hour 3 vs SOFA and $RSrO_2$ at hour 24 vs warm ischemia time.

thickness of more than 1.5–2 cm located above the renal allograft, NIRS predominantly measures $RSrO_2$ of external graft tissue [16]. It is therefore necessary to apply strict exclusion criteria regarding overlying tissue thickness in NIRS measurements. $RSrO_2$ seems especially suitable in thin, young, and pediatric kidney transplantation patients because of a lower overlying tissue thickness.

Vidal et al successfully performed NIRS measurements in 24 pediatric patients in the early postoperative period after kidney transplantation and found that renal NIRS measurements significantly correlated with serum creatinine, estimated glomerular filtration rate, and urinary neutrophil gelatinase-associated lipocalin, although $RSrO_2$ measurements did not significantly correlate with diuresis [17].

In a cohort of 59 infants who underwent cardiac surgery and were continuously monitored for 24–48 hours with $RSrO_2$, Ruf et al [18] recently demonstrated that patients who developed acute kidney injury showed prolonged lower-than-normal $RSrO_2$. They concluded that $RSrO_2$ may be superior to conventional biochemical markers for prediction of postoperative acute kidney injury.

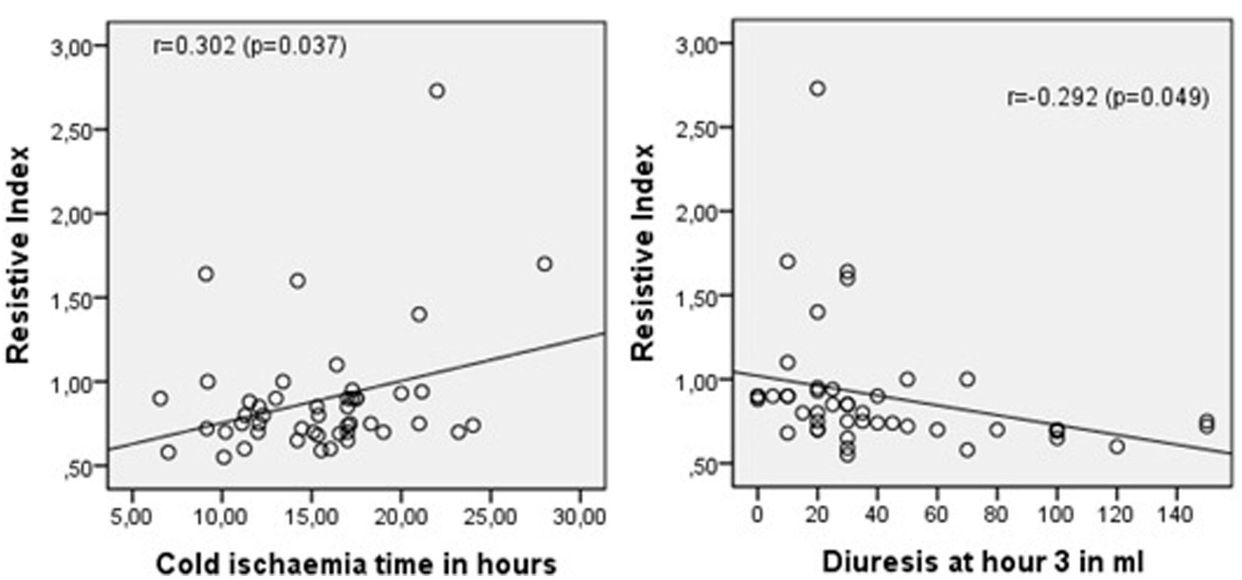

Fig 5. Scatter plot and linear regression of RI vs cold ischemia time and also between RI and diuresis at hour 3.

Our finding of statistic inverted correlation of $RSrO_2$ and warm ischemia time has a natural physiology explanation, as a graft under longer unprotected cold ischemia will suffer a more severe ischemia-reperfusion injury. Therefore, the specific contribution of the renal allograft oxygenation and the overlying tissue oxygenation to the $RSrO_2$ value could not be assessed and remains unknown. More evidence of the clinical applicability of $RSrO_2$ for monitoring renal grafts during the early postoperative period is needed, though its usefulness seems to be rapidly growing.

CONCLUSIONS

NIRS monitoring in patients in the early postoperative period after kidney transplantation is safe and feasible. The added value of NIRS to monitor renal allograft oxygenation remains to be determined, though it seems to be a promising helping tool.

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