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Research Article

Indicators for global tissue perfusion in patients undergoing orthotopic liver transplantation: A pilot study

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KEYWORDS

Mixed venous oxygen saturation;
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Abstract *Background:* Patients undergoing orthotopic liver transplantation are subjected to severe hemodynamic and metabolic derangements, close monitoring are always required. Mixed venous oxygen saturation (SVO_2) is often used to reflect supply/demand ration for oxygen in critically ill patients. Cardiac output (CO) and serum lactate levels are also sensitive markers for detecting early hemodynamic and metabolic changes. Patients with end-stage liver disease, possess hemodynamic and metabolic derangements that can render such tools insensitive. In the current trial we evaluated SVO_2, CO and serum lactate and since SVO_2 can sometimes be misleading especially in hyperdynamic status we assessed oxygen delivery (DO_2) and oxygen consumption (VO_2).
Patients and methods: Twenty patients with end-stage liver disease scheduled for live related liver transplantation were enrolled, CO, SVO_2, serum lactate levels, VO_2 and DO_2 were recorded during the following times; dissection phase (T1), an-hepatic phase (T2) and neo-hepatic phase (T3).
Results: All recorded parameters were comparable among the three phases of liver transplantation except for serum lactate levels that had increased significantly during T2 (7.10 ± 3.5 mmol/l, $P = 0.04$) and T3 (9.42 ± 4.65 mmol/l, $P = 0.001$) compared T1 (3.28 ± 2.7 mmol/l), however serum lactate levels and T2 and T3 were comparable. There was no evidence of any correlation among CO, SVO_2, serum lactate levels, VO_2 and DO_2.
Conclusion: Increase in serum lactate in this patient population is not necessarily due to increased production as a consequence of tissue hypoperfusion but rather may reflect improper lactate utilization since indicators of global tissue perfusion acted independently.

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1. Introduction

Patients with end-stage liver disease undergoing orthotopic liver transplantation are subjected to profound hemodynamic and metabolic changes. During the dissection phase bleeding and hypovolaemia are common [1], while in the an-hepatic phase there may be reduction in venous return, with subsequent reduction in left ventricular preload [2] and following declamping and starting of the neo-hepatic phase reperfusion

injury and metabolic derangement can be severe enough to lead to serious consequences [3]. In an attempt to minimize such effects, close, invasive and intense monitoring is usually required. The use of serum lactate levels had been introduced as a marker of unfavorable outcome in critically ill patients especially those with sepsis [4,5], as serum lactate had been widely used as an indicator of tissue hypoxia [6]. Moreover value of monitoring venous oxygen saturation among patients undergoing such procedure is beneficial [7], as venous oxygen saturation can detect early changes in hemodynamic and metabolic status of critically ill patients [8], there are increasing evidence describing patterns of mixed venous oxygen saturation (SVO_2) and central venous oxygen saturation ($ScVO_2$) [9,10] monitoring during surgery, in addition to evidence from septic patients [11] rendering estimation of venous saturation acts as a guide for therapeutic interventions. Recently, SVO_2 and $ScVO_2$ among patients undergoing liver transplantation had been assessed and proved to show marked agreement [7] provided that $ScVO_2$ was higher than SVO_2, however in healthy individuals, $ScvO_2$ is slightly less than SvO_2 [12] because the lower extraction ratio by the kidneys leaves a high oxygen content in the inferior vena cava. However, in low flow states or in shock, this gradient can be reversed by redistribution of blood flow associated with greater reduction in renal and splanchnic blood flow [13]. As various organs display physiological differences in oxygen delivery (DO_2) and consumption (VO_2), also DO_2 and VO_2 can change rapidly under pathophysiological conditions, yielding SVO_2 information on adequate tissue oxygenation unreliable specially when not continuously monitored (intermittent analysis). Furthermore, several diseases such as hepatic failure or severe sepsis with arterio–venous shunting limit the interpretation of absolute SVO_2 values as indicators of tissue oxygenation [14]. Thus intermittent venous saturations can be sometimes misleading regard to reflection of global tissue perfusion, since venous saturation reflects global tissue perfusion that relies on supply demand ratio for oxygen. So it is more logic to assess DO_2 and VO_2 directly, rather than SVO_2 especially if a pulmonary artery catheter (PAC) will be in place. In the current study we assessed changes in DO_2, VO_2 and SVO_2 to changes in cardiac output and serum lactate in patients undergoing orthotopic live donor liver transplantation. Our hypothesis is that DO_2, VO_2 and SVO_2 will not provide additional data that can aid in patient management.

2. Materials and methods

After approval of the local Ethics Committee and obtaining written informed consent, the study was designed to include 20 American Society of Anesthesiologist physical status (ASA) III or IV patients with end-stage liver disease, scheduled for orthotopic liver transplantation between 2007 and 2008. Induction of anesthesia was performed using propofol, fentanyl and atracurium. Anesthesia was maintained with sevoflurane adjusted between 1% and 2% in an air/oxygen mixture, fentanyl infusion at 1–2 $\mu g\,kg^{-1}\,h^{-1}$ and atracurium infusion at 0.5 $mg\,kg^{-1}\,h^{-1}$. Mechanical ventilation was provided using a tidal volume of 8–10 $ml\,kg^{-1}$ with the respiratory rate adjusted to maintain the $PaCO_2$ between 30 and 35 mmHg. All patients were monitored for temperature, noninvasive and invasive arterial blood pressure, five lead ECG, peripheral oxygen saturation, end-tidal carbon dioxide tension, hourly urinary output, and central venous pressure (CVP). A 7-Fr triple lumen CVP catheter (Arrow International Inc., Reading, PA, USA) was inserted into the right internal jugular vein. A pulmonary artery catheter (Abbott Laboratories, North Chicago, IL, USA) was also inserted into the right internal jugular vein. Intravascular electrocardiography was used to confirm the placement of the CVP catheter in the lower superior vena cava directly above the junction of superior vena cava with the right atrium. The pulmonary artery catheter (PAC) was positioned using wedge pressure and confirmed with fluoroscopy. Liver transplantation was performed with preservation of the retrohepatic caval vein (the piggyback technique). Blood samples were obtained simultaneously from the pulmonary artery catheter and from arterial line during dissection (T1, 60 min following skin incision), anhepatic (T2, immediately after removal of the diseased liver) and neo-hepatic phases (T3, following anastomosis of hepatic artery). All samples obtained from the pulmonary artery catheter were withdrawn over 30 s using a low-negative pressure technique and never with the balloon inflated; a standard volume of 1.5 ml of blood was obtained and analyzed for mixed venous oxygen saturation. Also 1.5 ml of blood was obtained from arterial line and sent for analysis using a co-oximeter (ABL 700; Radiometer, Copenhagen, Denmark) that allows measuring serum lactate levels and the device is calibrated daily. All samples were obtained after withdrawal of dead space and flushing fluid. Since no evidence supporting superiority of venous versus arterial serum lactate levels [15,16], in the current study we used serum lactate levels obtained from the arterial sample. Immediately after series of blood samples were drawn, cardiac output (CO) was recorded. CO was determined by the thermodilution technique using triplicate method, where three measurements were obtained and averaged using the PAC.

Arterial–venous oxygen content difference (CaO_2–CvO_2) was measured as

$$\begin{aligned} CaO_2\text{–}CvO_2 = [&Hb \times 1.36 \times (SaO_2/100) \\ &+ (0.0031 \times PaO_2) - Hb \times 1.36 \times (SVO_2/100) \\ &+ (0.0031 \times PVO_2)], \end{aligned}$$

VO_2 was calculated as CO (dl/min) $\times$ ($CaO_2 - CvO_2$), while DO_2 was calculated as $CaO_2 \times$ CO (dl/min). Serum hemoglobin was calculated using the venous sample, since venous samples offers better precision than arterial sample [17].

3. Statistical analysis

Data are expressed as mean ± SD, hemodynamic, metabolic and oxygenation parameters were analyzed using one way ANOVA where phases (T1–T3) were the independent variables, if statistical significance was reached a Tukey post hoc test was performed to identify level of significance. Pearson correlation was performed using individual changes in VO_2, DO_2, SVO_2, CO and serum lactate. $P < 0.05$ was considered as statistically significant. SPSS v.15.0 for windows was used for statistical analysis.

4. Results

Twenty patients with end-stage liver disease (Child C) were enrolled, 18 males and 2 females. Their mean age was 47.2

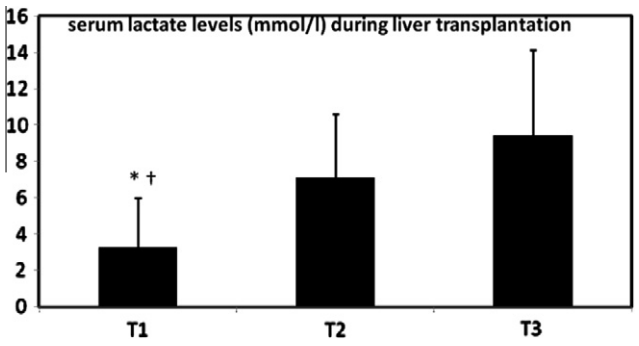

Figure 1 Demonstrates serum lactate levels (mmol/l) among various stages of orthotropic liver transplantation. T1 = dissection phase, T2 = an-hepatic phase and T3 = neo-hepatic phase. *Denotes significantly lower compared to T2 ($P = 0.04$). †Denotes significantly lower compared to T3 ($P = 0.001$).

(8.1) years and height 171 (14.2) cm. Fifteen patients were having transplantation due to hepatitis C virus, four patients due to hepatocellular carcinoma and one patient with autoimmune hepatitis. Serum lactate level recorded during dissection phase (T1) was significantly lower compared to those recorded at anhepatic and neo-hepatic phases (T2 and T3); however serum lactate values recorded during T2 and T3 were comparable (3.28 ± 2.7, 7.10 ± 3.5 and 9.42 ± 4.65 mmol/l, respectively) (Fig. 1). All other recorded parameters were comparable among different phases of liver transplantation (T1–T3) (Table 1).

Changes in serum lactate levels and cardiac output did not demonstrate correlation with any of the measured parameters. Also changes in SVO_2 did not demonstrate meaningful correlations with DO_2 and VO_2 (Figs. 2–4).

5. Discussion

The finding in the current study can be summarized as follows: (a) serum lactate among patients with end-stage liver disease had significantly increased during an-hepatic and neo-hepatic phases compared to those during dissection phase, despite comparable hemodynamic and oxygenation parameters; (b) parameters as serum lactate levels, cardiac output and mixed venous oxygen saturations that are commonly used to reflect global tissue perfusion do not possess a meaningful correlation not only between each other but also with oxygen delivery and consumption among patients undergoing live donor liver transplantation.

In general increased serum lactate levels are either due to increased lactate production or reduced lactate uptake and clearance. Increased lactate production is almost always attributed to cellular hypoxia and treatment should be directed to optimize DO_2, however in the current study we demonstrated high serum lactate levels despite adequate DO_2. Thus lactate increase in the current situation is independent of oxygen delivery, and such finding had been previously observed in septic patients [18]. Thus the possible mechanism for increased serum lactate levels in the current trial can be linked mainly to impaired lactate uptake and utilization by the liver. Nevertheless increased lactate production can still occur due to abnormal metabolic consequences including increased glycolysis or muscle catabolism [19]. Regardless of the mechanism responsible for increased lactate, it is obvious that anaerobic metabolism is not the key player, and monitoring of serum lactate in the current situation reflects more lactate utilization rather than lactate production. Levraut and colleagues [20] demonstrated in 34 hemodynamically stable septic patients that mild hyperlactatemia is primarily due to defect in lactate utilization rather than defects in cellular oxygenation. Also Hamamoto and colleagues [21] found that serum lactate levels had increased despite normal hemodynamic and mixed venous oxygen saturation in pediatric patients who underwent the Fontan procedure for congenital heart disease. Also in the current trial lack of correlation between changes in lactate (Δ lactate) versus changes in all other parameters (Fig. 3) denotes that changes in lactate levels is independent from changes in such parameters in this specific patient population.

Mixed venous oxygen saturation is a commonly used parameter to reflect balance between oxygen delivery and oxygen consumption, in the current study we demonstrated lack of correlation between changes in SVO_2 versus VO_2 and DO_2 (Fig. 4). Jugan and colleagues [22] monitored mixed venous oxygen saturation among 30 patients undergoing liver transplantation demonstrated lack of correlation between SVO_2 and VO_2, also demonstrated significant but Poor correlation with cardiac output. The results in the current study show great agreement with Jugan findings except for that the correlation of SVO_2 was not only poor but insignificant (Fig. 2). Also Inomata [23] showed lack of correlation among changes in SVO_2 and VO_2 in cardiac surgery. Although oxygen consumption is

Table 1 Demonstrates mean (SD) of all measured parameters during various stages of liver transplantation.

Variable	T1	T2	T3	*P*
pH	7.36 (0.06)	7.35 (0.04)	7.30 (0.07)	0.07
Hb (g/dl)	8.93 (1.74)	8.69 (1.61)	8.23 (1.08)	0.37
CO (l/min)	9.82 (3.16)	9.93 (4.24)	10.78 (4.04)	0.80
CaO_2 (ml/100 ml)	13.09 (2.66)	12.95 (2.35)	12.51 (1.61)	0.81
CvO_2 (ml/100 ml)	1.40 (0.42)	1.48 (0.66)	1.21 (0.26)	0.37
CaO_2–CvO_2 (ml/100 ml)	11.69 (2.25)	11.47 (2.03)	11.30 (1.36)	0.89
VO_2 (ml/min)	1138.2 (370.1)	1102.3 (370.4)	1186.0 (366.9)	0.86
DO_2 (ml/min)	1274.4 (419.9)	1251.6 (448.4)	1310.9 (402.4)	0.94
SVO_2 (%)	90.3 (3.5)	92.8 (3.2)	89.3 (4.1)	0.06

T1 = dissection phase, T2 = an-hepatic phase and T3 = neo-hepatic phase. Hb = serum hemoglobin concentration, CO = cardiac output, CaO_2 = arterial oxygen content, CvO_2 = venous oxygen content, CaO_2–CvO_2 = arterio–venous oxygen content difference, VO_2 = oxygen consumption, DO_2 = oxygen delivery and SVO_2 = mixed venous oxygen saturation.

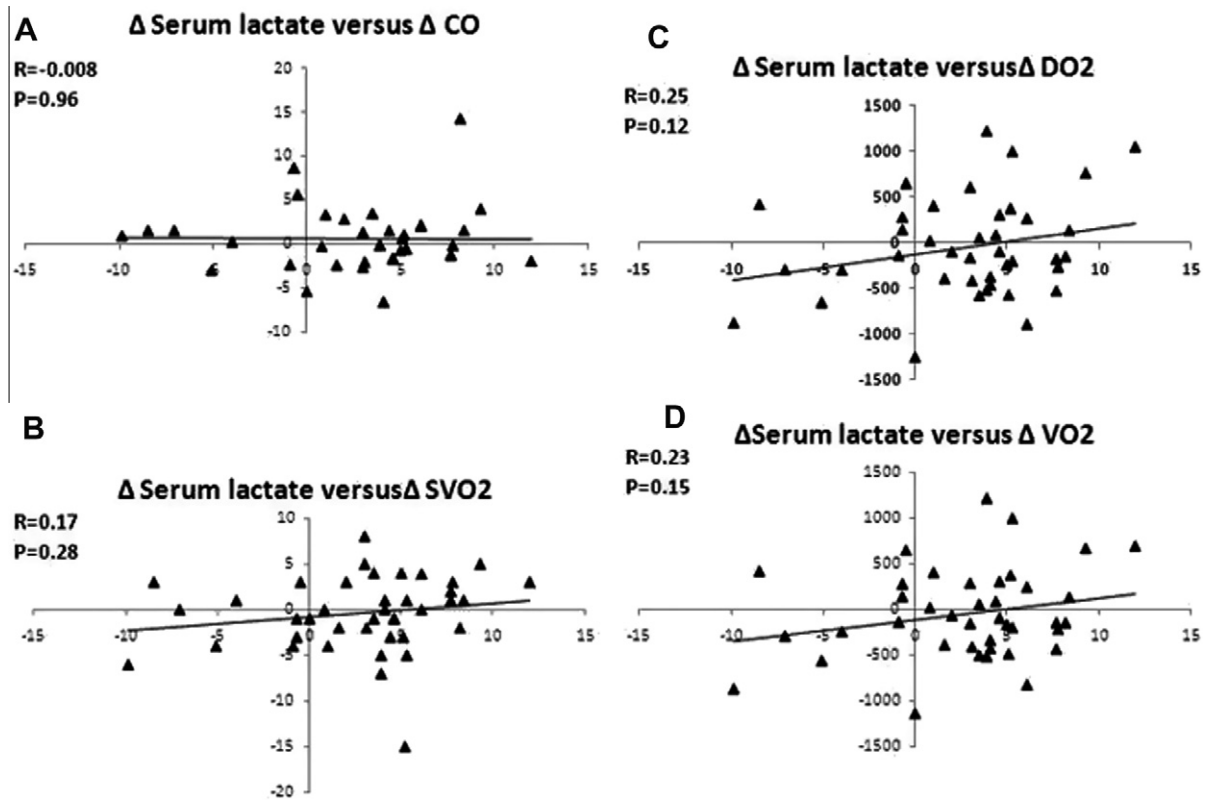

Figure 2 (A) Changes in serum lactate (mmol/l) versus changes in cardiac output (l/min); (B) changes in serum lactate (mmol/l) versus changes in mixed venous oxygen saturation (%); (C) changes in serum lactate (mmol/l) versus changes in oxygen delivery (ml/min) and (D) changes in serum lactate (mmol/l) versus changes in oxygen consumption (ml/min).

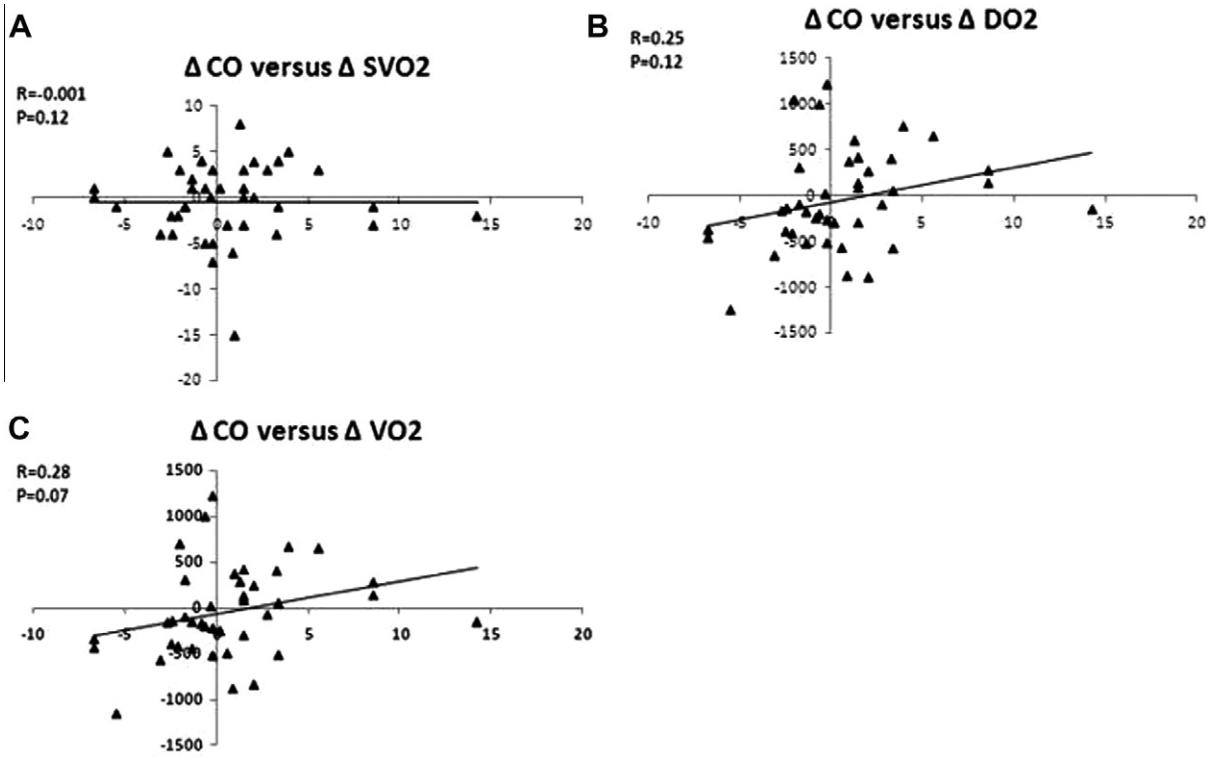

Figure 3 (A) Changes in cardiac output (ml/min) versus changes in mixed venous oxygen saturation (%); (B) changes in cardiac output (l/min) versus changes oxygen delivery (ml/min) and (C) changes in cardiac output (l/min) versus changes oxygen consumption (ml/min).

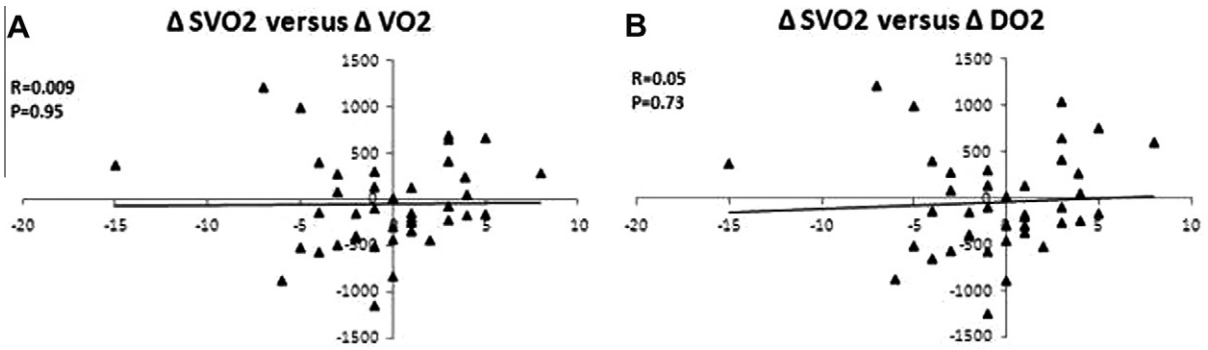

Figure 4 (A) Changes in mixed venous oxygen saturation (%) versus changes in oxygen consumption (ml/min) and (B) changes in mixed venous oxygen saturation (%) versus changes in delivery (ml/min).

approximately 250 ml/min under normal resting conditions, however we demonstrated very high values for VO_2 that was not paralleled by decrease in SVO_2. This phenomenon can be explained by the fact that oxygen delivery (DO_2) had increased significantly and thus the balance between DO_2 and VO_2 was maintained. Such increase in DO_2 can be primarily attributed to increase in cardiac output (Table 1). High cardiac output is primarily due to hyperdynamic circulation that is a persistent finding in patients with end-stage liver disease and characterized by both increase in heart rate and cardiac output with decreased systemic vascular resistance [24,25].

Also we demonstrated high SVO_2 values (Table 1) and lack of correlation between CO and SVO_2. Similar findings had been reported by El-Masry and colleagues [7] among similar patient population. Also in the current study we estimated actual VO_2 and DO_2 in an attempt to demonstrate a meaningful relationship instead of relying on SVO_2 that was consistently high and independent on cardiac output. However VO_2 and DO_2 relationship to CO did not differ from those with SVO_2 and CO rendering such patient population in a unique situation. Metabolic (high serum lactate levels), hemodynamic (hyperdynamic circulation) and oxygenation parameters (SVO_2, DO_2 and VO_2) in such patient population were independent from each other and no effective relationship could be identified, unlike many clinical conditions where CO, SVO_2 and serum lactate are considered the golden monitors for tissue perfusion and are usually used as goal oriented hemodynamic therapy [11,26,27]. In the current situation we agree with Crescenzi and colleagues, who encouraged comprehensive understanding of pathophysiology of hemodynamic changes prior to initiation of therapy [28].

Limitations included that all enrolled patients were hemodynamically stable and we cannot extrapolate such findings in patients with different hemodynamic conditions. The main stay behind this trial was that we observed marked increase in serum lactate in such patients despite acceptable hemodynamic and metabolic parameters. So we decided to study such phenomenon in an attempt to understand the reason for increased serum lactate thus we decided to study 20 patients as pilots but due to negative results we did not enroll further patients using proper power analysis.

6. Conclusion

Markers of global tissue perfusion in patients undergoing orthotopic liver transplantation with end-stage liver disease demonstrated a predictable pattern and the use of such tools in hemodynamically stable patients did not provide additional value and did not parallel metabolic derangements reflected by increased serum lactate levels.

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