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The effect of venovenous bypass on lactic acid levels during human liver transplantation (OLT)

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Abstract Lactate determinations did not contribute to the quantification of the systemic and regional tissue oxygenation during OLT. Venous stasis was not an important factor in the tissue imbalance between oxygen supply and oxygen demand.

Key words Liver transplantation
Lactic acid · Venovenous bypass

Introduction

It has been suggested that tissue oxygen uptake is often impaired in cirrhotic patients [8]. It is associated with a narrow arteriovenous oxygen content difference ($C_{a-v}O_2$), probably owing to a defective peripheral flow with decreased vasoactivity and arteriovenous shunting. Systemic oxygen consumption (VO_2) in this type of patient is maintained by an increased cardiac index [6]. During human liver transplantation (OLT), specifically in the anhepatic phase, the drop in cardiac index may alter oxygen delivery (DO_2) and consequently may change the cellular energy metabolism. Moreover, interstitial oedema owing to venous obstruction could be responsible for important changes in the oxygen diffusion barriers and could contribute to regional tissue hypoperfusion during the anhepatic stage. Lactate production has frequently been used as a marker of impaired aerobic metabolism [3]. Many authors [2] have found that systemic lactic acid levels progressively increase during OLT, but have failed to show any relationship with either immediate liver function or tissue oxygen changes.

The aim of this prospective randomized study was to evaluate the effect of venovenous bypass (BP) on regional tissue perfusion (hindlimbs and splanchnic territory) during OLT.

Patients and methods

A total of 40 OLTs were randomly allocated to receive either venovenous BP (BP group, $n = 20$) or a procedure without venovenous BP (no-BP, $n = 20$) stratified by diagnosis. BP started at the beginning of the operation following a previously described protocol [1]. Acute liver failure and retransplantations were excluded. All patients except five had a non-biliary cirrhosis.

The anaesthetic management of all patients followed our standard procedure [11]. Haemodynamic parameters were recorded and portal vein (PV) pressure (with a catheter placed through the superior mesenteric vein) and inferior vena cava (IVC) pressure were also recorded. Respiratory data comprising venous oxygen saturation (St_vO_2), carbon dioxide and oxygen venous partial pressure (P_vCO_2 and P_vO_2), pH, BE and lactate levels were obtained in the pulmonary artery, PV and IVC. Systemic oxygen delivery (DO_2), oxygen consumption (VO_2) and oxygen extraction ratio (VO_2/DO_2) were calculated using standard formulae. Oxygen content difference ($C_{a-v}O_2$) and CO_2 production ($C_{v-a}CO_2$) were also calculated as described by Kelman [4]. All parameters were determined at five different stages: at the beginning of the procedure (S1), at the end of hepatectomy (S2) and the anhepatic phase (S3), and 2 h after reperfusion (S4). Samples from the PV and IVC were only obtained at the end of the anhepatic phase (S3). Finally blood component requirements (packed red blood cells and fresh frozen plasma) and timing (anhepatic as well as total time) were considered.

Lactate levels were determined following the method of Kodak Ektachemslide assay [7]. Values < 9 mg/dl are considered normal in our laboratory. Hyperlactaemia was defined as venous lactate values > 18 mg/dl.

Analysis of variance (factorial or repeated measures) and linear regression tests were used. Differences were considered significant at $P < 0.05$. Data are presented as mean ± SE.

Results

Both groups were similar with respect to diagnosis, age, sex, duration of operation as well as blood loss (ml/kg) and blood component requirements (Table 1). Blood flow in BP patients was 2350 ± 680 ml/min, ranging from 1300 to 3700 ml/min. Mean duration of BP was 191 ± 45 min with a range from 110 to 300 min. IVC pressure rose during the BP (11 ± 3 vs 22 ± 8, $P = 0.0001$), but there were no signs of BP malfunction.

During the procedure the haemodynamic and gas transport variables behaved similarly in both groups (Table 2). During the anhepatic stage the no-BP patients had a lower CI ($P = 0.01$) and DO_2 ($P = 0.009$), but there were no differences in VO_2, both groups maintaining adequate levels. In no-BO patients there was a higher VO_2/DO_2 ratio ($P < 0.05$) and a higher $C_{a-v}O_2$ ($P = 0.007$). However, in both groups there was no pathological supply dependence (correlation) between VO_2 and DO_2 (BP group, $R^2 = 0.31$; no-BP group, $R^2 = 0.30$). Maintenance of oxygen consumption in the no-BP patients was by a significant increase in oxygen uptake, as suggested by the correlation between VO_2 and $C_{a-v}O_2$ ($R^2 = 0.62$, $P = 0.0001$), which was not found in BP patients ($R^2 = 0.11$, $P = 0.17$).

St_vO_2 values in the pulmonary vein during the anhepatic phase (Table 3) were significantly higher than in the IVC in both groups (BP group, $P < 0.005$; no-BP group,

Table 1 Clinical data

	Bypass group	No bypass group
Age (years)	59 ±7	49 ±9
Sex (m/f)	12/8	13/7
Child-Pugh	9.2±2.2	8.5±1.8
Blood loss	12127 ±1871	10194 ±880
Packed red cells	14.6±3.9	11.5±2.2
Fresh frozen plasma	5868 ±1168	5639 ±1048
Total time (min)	496 ±112	454 ±106
Anhepatic time (min)	94 ±24	96 ±28

Table 2 Haemodynamic and gas transport variables with and without venovenous bypass. Values are mean ±SE

		Baseline	Hepatectomy	Anhepatic phase	Reperfusion
C.I. (l/min per m^2)	BP	4.8±1.3	6.2±1.5**	4.6±1.1**	5.8±1.4*
	no-BP	4.6±1.5	4.9±1.4**[a]	3.1±0.8**[b]	5.4±1.2*
DO_2 (ml/min per m^2)	BP	705.3±42	766.5±60	592 ±57**[a]	709.6±46
	no-BP	620.3±45	683.3±50	424.5±19**[b]	616.2±51
VO_2 (ml/min per m^2)	BP	93 ±6	101.9±8.6	98.5±5	169.8±10
	no-BP	82.7±5	94.6±5.8	100.1±6	147.9±17
VO_2/DO_2 (%)	BP	13.5±0.7	13.5±0.7	19.1±1.5*	25.1±2
	no-BP	14.6±1	14.8±1	23.6±1.6*	24.3±2
$C_{a-v}O_2$ (ml/dl)	BP	2.1±0.1	1.8±0.1	2.5±0.1**	3.2±0.2
	no-BP	2 ±0.1[a]	1.9±0.2[a]	3.3±0.2**[a]	3.2±0.2
Lactate (mg/dl)	BP	8.7±0.9	33.1±4.3[a]	51.6±5[a]	63.9±6[a]
	no-BP	9.2±1	32 ±4.8[a]	50.2±2[a]	53.1±6[a]

* $P < 0.05$, ** $P < 0.01$ between groups at the same stage. [a] $P < 0.05$ and [b] $P < 0.01$ in the intragroup comparison with time period

Table 3 Cellular metabolic changes at the end of the anhepatic phase with and without venovenous bypass. Values are mean ±SE

		Anhepatic phase		
		Pulmonary artery	Portal vein	IVC
pH	BP	7.33±0.1	7.30±0.1	7.30±0.1
	no-BP	7.36±0.1	7.31±0.1[c]	7.28±0.1[a]
St_vO_2 (%)	BP	83.9 ±1.5	82.3 ±4	73.4 ±4*[b]
	no-BP	82.9 ±1.5	71.5 ±4[c]	58.8 ±5*[a]
$C_{v-a}CO_2$ (ml/dl)	BP	3.5 ±0.2	2.9 ±0.3*	5.7 ±0.6[c]
	no-BP	3.4 ±0.3	5 ±0.8*	7.7 ±0.9[b]
$C_{v-a}O_2$ (ml/dl)	BP	2.5 ±0.1**	2.2 ±0.3***	4.3 ±0.5**
	no-BP	3.3 ±0.2**	4.3 ±0.5***	7.2 ±0.9**
Lactate (mg/dl)	BP	51.6 ±5	50.8 ±5	51.5 ±5
	no-BP	50.2 ±2	52.6 ±9	47.5 ±5

* $P < 0.05$, ** $P < 0.01$, *** $P < 0.005$ between groups at the same stage. [a] $P < 0.001$, [b] $P < 0.005$, [c] $P < 0.01$ in the intragroup comparison with pulmonary arterial values

$P = 0.001$. Patients in the no-BP group had a higher CO_2 production in the IVC and PV those in the BP group ($P < 0.05$) which was directly correlated with an increase in the oxygen content difference ($P < 0.01$ and $P < 0.005$, respectively). pH values were similar in both groups. In no-BP patients, pH levels were lower in the PV ($P < 0.01$) and IVC ($P < 0.001$) than in mixed venous samples at the same stages.

Arterial lactate concentrations increased steadily during OLT. There were no differences in regional and arterial lactate levels between the groups compared at the same stages. The overall increases in lactate during the procedure were similar between groups (54 ± 25 mg/dl in the BP group vs 44 ± 23 mg/dl in the no-BP group, $P = 0.3$). Finally, lactate levels were directly correlated with the packed red cell requirement ($R^2 = 0.351$, $P = 0.0001$).

Discussion

Perioperative changes in tissue oxygenation parameters have been described during OLT in patients with veno-venous BP [10]. These studies suggest the need to increase CI in order to maintain an adequate DO_2. However, our randomized trial suggested that no-BP patients during the anhepatic stage have a significant decrease in CI (37%) and DO_2 (32%), but an adequate oxygen consumption for anaesthetized patients with muscle relaxation [9], and these values were similar in BP patients. This is due to a significant increase in oxygen extraction (VO_2DO_2, $P = 0.05$) as was indicated by the good correlation between $C_{a-v}O_2$ and VO_2 ($R = 0.62$, $P = 0.0001$).

Regional tissue perfusion in the IVC and splanchnic territory in the no-BP patients did not seem to be compromised. Although CO_2 production in the IVC was increased and pH decreased with respect to mixed venous samples, the lactate levels and base excess did not change. The pH changes may be accounted for by the increase in CO_2 production alone. This CO_2 production may indicate changes in regional cellular metabolism [12]. However, the increase in CO_2 production directly correlated with an increase in the $C_{a-v}O_2$ with an adequate regional respiratory quotient ($R = 1.04$). Surprisingly, this value was worse in the BP patients ($R = 1.32$). This is difficult to explain and deserves further study.

Arterial blood lactate concentration is a marker of tissue anaerobiosis and identifies systemic oxygen deficit. The development of lactic acidosis is thought to reflect an imbalance between the metabolic requirements and the oxygen supply [5]. The kinetics of lactate accumulation in blood are difficult to predict because blood concentration of any substance reflects not only its production but also its elimination and clearance, which in the case of lactate takes place primarily in the liver. In our study we did not find any correlation between lactic acidosis and gas transport variables.

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