

# Splanchnic Oxygen Consumption Is Impaired during Severe Acute Normovolemic Anemia in Anesthetized Humans

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**Background:** In conscious humans, reduction in hemoglobin concentration to 5 g/dl did not produce inadequate systemic oxygenation. However, systemic measures of inadequate oxygenation may not be sufficiently sensitive to detect inadequate oxygenation in individual organs such as splanchnic organs. The authors tested the hypothesis that acute normovolemic anemia to hemoglobin less than 6.0 g/dl in anesthetized humans reduces splanchnic oxygen consumption because of diminished whole body oxygen delivery.

**Methods:** Elective spine (n = 12) and abdominal (n = 7) surgery patients underwent acute normovolemic anemia to decrease the hemoglobin concentration close to 6.0 g/dl. The authors assessed the development of supply-dependent conditions in systemic and regional vascular beds by two primary measures before and after acute normovolemic anemia: oxygen consumption and surrogate biochemical markers of anaerobic metabolism, including plasma lactate, regional lactate kinetics, and ketone body ratio.

**Results:** When hemoglobin was reduced from  $13.6 \pm 1.2$  to  $5.9 \pm 0.3$  g/dl, oxygen supply dependency occurred in the splanchnic and preportal tissues but not at the systemic level. Regional supply dependency was accompanied by biochemical markers of anaerobic metabolism.

**Conclusions:** In anesthetized humans, a reduction in hemoglobin to 5.9 g/dl by acute normovolemic anemia diminished splanchnic and preportal whole body oxygen delivery and impaired splanchnic and preportal oxygen consumption. This was accompanied by increased plasma levels of regional lactate and an increased  $\beta$ -hydroxybutyrate-to-acetoacetate ratio. These findings suggest that the risk to the gastrointestinal tract during acute normovolemic anemia may be underestimated.

A RESTRICTIVE approach to administering blood products has evolved in recent years, motivated by pressure to conserve a limited blood supply and avoid adverse effects of transfusion.<sup>1,2</sup> This approach, combined with aggressive fluid resuscitation, often leads to acute normovolemic anemia (ANA) in the perioperative period.<sup>3</sup> The safety of ANA is based on the premise that, as arterial oxygen content decreases, tissues maintain oxy-

gen consumption by compensatory mechanisms that include increases in cardiac output, oxygen extraction ratio, and regional blood flow.<sup>4-6</sup> When whole body oxygen delivery ( $Do_2$ ) decreases below a critical point, compensatory mechanisms become insufficient. At that point, oxygen consumption becomes supply dependent and decreases as  $Do_2$  decreases.<sup>7</sup>

The critical point during ANA at which oxygen consumption becomes supply dependent can be expressed as a critical  $Do_2$  or critical hematocrit.<sup>7,8</sup> To date, systematic prospective efforts to determine the critical  $Do_2$  in conscious, healthy humans have failed, despite reducing hemoglobin concentration to 5 g/dl and further reducing cardiac output by infusion of  $\beta$ -adrenergic antagonists.<sup>9,10</sup> The data in anesthetized humans are limited to one case report.<sup>11</sup> However, studies that demonstrate preservation of systemic oxygen consumption during ANA have not examined regional supply dependency. Specifically, they have not examined the physiologic effects of ANA on splanchnic oxygen consumption and  $Do_2$ . Splanchnic oxygen consumption and  $Do_2$  may be influenced by various factors, such as redistribution of cardiac output to organs such as the heart and brain. If preservation of those organ systems occurs at the expense of the splanchnic vascular bed, splanchnic integrity could be compromised.<sup>12-15</sup> Heterogeneity of oxygen supply and demand exists between organs as well as within individual organs; this heterogeneity is further exacerbated during states of reduced oxygen delivery.<sup>13</sup> Furthermore, reduction in splanchnic perfusion associated with anesthesia, increases in splanchnic oxygen consumption associated with surgical trauma, and diminished perioperative oxygen extraction capabilities may also interfere with the ability of the splanchnic regions to adapt to reduced regional  $Do_2$  associated with ANA.<sup>15-17</sup>

Therefore, the risk to the gastrointestinal system may be underestimated during ANA. As a consequence, recommendations regarding hematocrit levels below which transfusion is indicated may be associated with inadequate regional  $Do_2$ . This implies that organ-specific regional measurements should be made to determine the sufficiency of oxygen in splanchnic organs. Knowledge of regional  $Do_2$  and oxygen consumption is important to anesthesiologists and surgeons because more than 50% of erythrocyte transfusions occur in the operating room.<sup>18</sup> To test the validity of our hypothesis that, dur-

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ing ANA and diminished  $\text{Do}_2$ , splanchnic and preportal oxygen consumption would be impaired despite preservation of systemic oxygen consumption, we produced ANA in patients undergoing anesthesia and surgery.

Our overall goal was to characterize systemic, splanchnic, preportal oxygen consumption and  $\text{Do}_2$  responses in anesthetized humans subjected to severe ANA. We accomplished this goal in anesthetized patients undergoing spine and abdominal surgery. To exclude the effects of surgical trauma on splanchnic oxygen consumption, we chose spine surgery patients in whom ANA was performed before surgery. In a group of patients undergoing abdominal surgery, we directly measured portal blood flow to study the effects of ANA on  $\text{Do}_2$  to splanchnic organs, excluding the liver. This group also facilitated quantification of the effects of superimposed surgical trauma on splanchnic oxygen consumption during ANA.

## Materials and Methods

The study was approved by the Institutional Review Board of the University of Texas Medical Branch in Galveston, Texas. Written informed consent was obtained from each patient. Twelve patients (10 men and 2 women) undergoing spine surgery and 7 patients (5 men and 2 women) undergoing abdominal surgery were included in the study. Preoperative diagnoses of patients undergoing abdominal surgery included nonmetastatic, medium- to well-differentiated gastric adenocarcinoma ( $n = 4$ ), and highly differentiated pancreatic neoplasm ( $n = 3$ ). Criteria for inclusion in the study were a baseline hemoglobin concentration of 12 g/dl or greater and absence of comorbid medical conditions, including coronary artery disease, congestive heart failure, unstable angina, hemodynamically significant valvular heart disease, diabetes mellitus, uncontrolled hypertension, hepatobiliary disease, and renal dysfunction. Hepatic failure was defined as total bilirubin concentration more than two times the upper normal range, and renal dysfunction was defined as serum creatinine concentration greater than 1.3 mg/dl.

Patients were premedicated with 0.5 mg lorazepam orally 1 h before arrival in the operating room. A 16-gauge intravenous catheter was placed for fluid infusion. Routine monitors, *i.e.*, blood pressure cuff, electrocardiogram (lead V5), and pulse oximeter probes, were applied in the operating room. General anesthesia was induced with sodium thiopental (3 mg/kg), with the trachea intubated after administration of cisatracurium (0.15 mg/kg). Patients were then mechanically ventilated (Servo 900C; Siemens AB, Solna, Sweden) with an inspired gas mixture of oxygen-nitrous oxide (50:50). The ventilator rate was adjusted to maintain normocapnia. Anesthesia was maintained with 0.5–1% (end-tidal)

isoflurane and intermittent fentanyl boluses (50–100  $\mu\text{g}$ ). The left radial artery was cannulated with a 20-gauge catheter to monitor blood pressure and obtain arterial blood samples. A pulmonary arterial catheter was inserted percutaneously *via* the left internal jugular vein after induction of anesthesia. The catheter was used for blood sampling and to monitor pulmonary arterial pressures, cardiac filling pressures, and cardiac output. The hepatic vein was cannulated *via* the right internal jugular vein, and a preformed side-vented catheter was positioned in the hepatic vein. The deep but nonwedged position of the catheter was verified by an interventional radiologist using fluoroscopy with a small amount of contrast dye. Hepatic vein blood samples were used to measure ketone bodies and splanchnic blood flow. Splanchnic blood flow was estimated by a primed (12 mg) and continuous (1 mg/min) intravenous infusion of indocyanine green (Cardiogreen; Becton-Dickinson, Franklin Lakes, NJ).<sup>19,20</sup> The blood samples were centrifuged, and indocyanine green extraction concentrations were determined spectrophotometrically using a wavelength of 805 nm. The blood concentrations were derived from a calibration curve; the coefficient of variation (SD/mean) of the indocyanine green extraction analysis was 0.7% ( $n = 12$ ). Splanchnic blood flow was then derived from the dye infusion rate and the arterial-hepatic venous dye concentration difference.<sup>20</sup> The mean ( $\pm$  SD) hepatic indocyanine green extraction ratio ([arterial indocyanine green concentration – hepatic venous indocyanine green concentration]/arterial indocyanine green concentration) was  $28 \pm 12\%$ .

We measured portal blood flow in seven patients undergoing abdominal surgery. After upper midline laparotomy, the portal vein distal to the gastroduodenal artery was isolated, and a dual-channel ultrasound transit-time flowmeter (Transonic Systems, Inc., Ithaca, NY) was connected to the portal venous (diameter 16–18 mm) probe to record blood flows continuously.

### *Induction of Acute Normovolemic Anemia*

After induction of anesthesia, blood was withdrawn from a peripheral vein and was simultaneously replaced with an equal volume of a 5% albumin solution to reach a target hemoglobin concentration of 6.0 g/dl or less and to maintain cardiac filling pressures. The amount of blood to be withdrawn was estimated from the relation proposed by Gross *et al.*<sup>21</sup> The method for producing ANA has been described previously.<sup>4,9</sup> Briefly, 500-ml aliquots of blood were removed through a large-bore peripheral intravenous cannula into CPDA-1 collection bags (Baxter Healthcare, Deerfield, IL). Removal of each 500 ml of blood required approximately 20 min. Isovolemia was maintained by holding pulmonary arterial occlusion pressure constant by intravenous infusion of 5% albumin solution or the subject's own platelet-rich plasma (after separation by centrifugation from the

erythrocytes of the removed blood) simultaneously with blood removal, in quantities slightly greater (by  $15 \pm 7\%$ , mean  $\pm$  SD) than that of the removed blood, to compensate for the extravascular distribution of albumin.<sup>22</sup>

### Measurements

All measurements were performed before surgery in the spine surgery group and during the initial phase of the operation in the abdominal surgery group. Thirty minutes after induction of anesthesia, baseline regional hemodynamic measurements were made with the patients receiving an inspired gas mixture containing oxygen-nitrous oxide (50:50) and 1% isoflurane. Lead V5 of the electrocardiogram was closely monitored for evidence of ischemia throughout the study period. Cardiac output was measured with thermodilution in triplicate, and the mean value was used for calculations. Hemoglobin concentration oxygen saturations were measured using a CO-Oximeter (IL 282; Instrumentation Laboratories, Lexington, MA). Arterial oxygen content was calculated as  $1.39 \cdot \text{hemoglobin concentration} \cdot \text{arterial oxygen saturation} + \text{dissolved oxygen}$ . Systemic  $\text{Do}_2$  was measured as the product of cardiac output or regional flow and arterial oxygen content. Systemic oxygen consumption was measured from inspired and expired gases by open circuit indirect calorimetry (DeltaTrac; Sensor Medics, Inc., Anaheim, CA). Splanchnic oxygen delivery ( $\text{ml} \cdot \text{min}^{-1} \cdot \text{m}^{-2}$ ) was calculated as the product of splanchnic blood flow and arterial oxygen content. Splanchnic oxygen consumption was calculated as splanchnic blood flow multiplied by the difference between arterial and hepatic venous oxygen content. Preportal oxygen delivery ( $\text{ml} \cdot \text{min}^{-1} \cdot \text{m}^{-2}$ ) was estimated as the product of portal venous oxygen content and blood flow. Preportal oxygen consumption ( $\text{ml} \cdot \text{min}^{-1} \cdot \text{m}^{-2}$ ) was calculated as portal blood flow multiplied by the difference between arterial and portal venous oxygen content.<sup>23</sup> Oxygen extraction was derived from oxygen consumption/ $\text{Do}_2$ . Lactate concentrations were measured enzymatically (YSI No 2700; Yellow Springs Instrument Company, Yellow Springs, OH).

### Regional Stable Isotope Analysis of Lactate Kinetics

A primed and continuous infusion (prime =  $8 \mu\text{mol/kg}$ ; infusion rate =  $0.56 \mu\text{mol} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ ) of lactate containing the stable isotope  $^{13}\text{C}$  was used to estimate exchange, production, and lactate oxidation.<sup>24</sup> This method is based on the measurement of pyruvate and lactate enrichment and concentrations in arterial and venous blood and the rate of blood flow through the splanchnic bed. The net balance of lactate across the splanchnic bed (NB) was calculated by multiplying the difference between arterial and venous lactate concentration by hepatic blood flow using the formula

$$\text{NB} = (\text{Ca} - \text{Cv}) \times \text{hBF},$$

where Ca and Cv are the arterial and venous lactate concentrations, respectively, and hBF is hepatic blood flow.<sup>24</sup>

The rate of uptake of lactate across the splanchnic bed (denoted Rd) was calculated by dividing the net uptake of tracer by the arterial lactate enrichment, using the formula

$$\text{Rd} = (\text{Ea} \times \text{Ca} - \text{Ev} \times \text{Cv}) \times \text{hBF/Ea},$$

where Ea and Ev are the values for arterial and hepatic venous lactate enrichment, respectively.

The rate of release of lactate from the splanchnic bed (Ra) was calculated from the difference between the rate of uptake and the net balance of unlabeled lactate across the splanchnic bed:

$$\text{Ra} = \text{Rd} - \text{NB}.$$

Clearance of lactate by the splanchnic bed was calculated by dividing Rd by the arterial concentration:

$$\text{Clearance} = \text{Rd/Ca}.$$

Stable isotopic enrichment of plasma glucose, pyruvate, lactate and alanine were determined by quadrupole chromatography-mass spectrometry (5985-B gas chromatograph-mass spectrometer; Hewlett Packard, Palo Alto, CA). Plasma concentrations of glucose and lactate were determined by an autoanalyzer (YSI Lactate and Glucose Analyzer; Yellow Springs Instruments, Columbus, OH).

### Statistical Analysis

Data obtained at the end of hemodilution were compared with data obtained at baseline. Patient characteristics data were described in terms of means and SDs. A Student *t* test was used to detect changes in splanchnic and preportal flow,  $\text{Do}_2$ , oxygen consumption and oxygen extraction ratio between baseline, and target hemoglobin concentration. These comparisons were conducted in the spine and abdominal surgery groups, respectively. To assure that the distributions of changes for each variable were normal, we used the Shapiro-Wilks normality test. All *P* values are two tailed, and statistical significance was accepted as  $P < 0.05$ . Results are presented as mean values  $\pm$  SDs.

## Results

Patient characteristics are listed in table 1. To reach the target hemoglobin level, the exchanged volume was  $2,375 \pm 155$  in both groups. Time to perform hemodilution was  $52 \pm 15$  min in the spine surgery group and  $48 \pm 10$  min in the abdominal surgery group. None of the patients in the spine surgery group required any vasopressors to maintain mean arterial pressure. How-

**Table 1. Patient Characteristics**

	Spine Surgery	Abdominal Surgery
Age, yr	41.8 ± 11	52 ± 8
Body surface area, m <sup>2</sup>	1.9 ± 0.2	1.8 ± 0.1
Male/female	10/2	5/2
Initial hemoglobin concentration, g/dl	13.9 ± 1.2	13.3 ± 0.5
Medications, No. of patients receiving β blockers, e.g., metoprolol	2	2

Data are expressed as mean ± SD.

ever, one patient in the abdominal surgery group required 5 mg ephedrine to maintain mean arterial pressure. The last dose of ephedrine was administered 50 min before the hemodynamic measurements after ANA had been induced. The total duration of the experiment was  $3.5 \pm 0.3$  h.

#### Systemic Responses to Acute Normovolemic Anemia

Decreases in hemoglobin concentration from  $13.6 \pm 1.2$  g/dl to  $5.9 \pm 0.3$  g/dl in the spine surgery group and from  $13.3 \pm 0.5$  g/dl to  $5.7 \pm 0.3$  g/dl in the abdominal surgery group increased the cardiac index without significantly changing heart rate (table 2). When the target hemoglobin concentration was reached, the increased cardiac index did not compensate for the decreased arterial oxygen content, *i.e.*, systemic  $\text{Do}_2$  significantly decreased ( $P < 0.05$  for spine surgery group and  $P < 0.05$  for abdominal surgery group; table 2). In contrast to decreased  $\text{Do}_2$ , systemic oxygen consumption and oxygen extraction increased at the target hemoglobin concentration ( $5.9 \pm 0.3$ ) in the spine surgery group ( $P < 0.05$  for oxygen consumption and  $P < 0.05$  for oxygen extraction) during ANA. Parallel changes in oxygen consumption and oxygen extraction were observed in abdominal surgery group ( $P < 0.05$  for oxygen consump-

tion and  $P < 0.05$  for oxygen extraction). Despite successfully reducing the hemoglobin concentration to 5.9 during ANA, systemic oxygenation was preserved as assessed by two primary measures: Oxygen consumption did not decrease, and there were only clinically insignificant increases in plasma lactate concentration (table 2).

#### Splanchnic and Preportal Measurements in Spine and Abdominal Surgery Patients

Compared with baseline, the level of splanchnic  $\text{Do}_2$  during ANA significantly decreased by  $65.2 \pm 3.6$  ml · min<sup>-1</sup> · m<sup>-2</sup> ( $P < 0.05$ ; table 3). Both splanchnic oxygen consumption and splanchnic flow during ANA decreased significantly compared with baseline levels. The mean decrease in oxygen consumption was  $20.9 \pm 5.7$  ml · min<sup>-1</sup> · m<sup>-2</sup> ( $P < 0.05$ ). The mean decrease for splanchnic flow was  $0.3 \pm 0.02$  l · min<sup>-1</sup> · m<sup>-2</sup> ( $P < 0.05$ ). The splanchnic oxygen extraction ratio increased compared with baseline by a mean of  $0.14 \pm 0.03$  ( $P < 0.05$ ; table 3).

Except for the preportal oxygen extraction level, which increased at target hemoglobin concentration compared with baseline levels, the other three variables decreased at the target hemoglobin concentration level (table 3).

#### Ketone Body Ratio and Lactate Kinetics in Spine Surgery Patients

At the target hemoglobin concentration, the mean ketone body ratio increased significantly from baseline by a mean of  $1.16 \pm 0.12$  ( $P < 0.05$ ; table 4). The net balance of unlabeled lactate decreased from a baseline value of  $557 \pm 27$  to  $347 \pm 37$  ( $P < 0.05$ ) during ANA.

Mean hepatic <sup>13</sup>C lactate uptake for patients at the target hemoglobin concentration increased significantly

**Table 2. Systemic Response of ANA in Spine (n = 12) and Abdominal (n = 7) Surgery Groups of Patients**

Variable	Spine Surgery Group		Abdominal Surgery Group	
	Baseline	ANA	Baseline	ANA
Core temperature	36.1 ± 0.2	35.8 ± 0.6	36.2 ± 0.3	35.7 ± 0.5
Hemoglobin, g/l	13.9 ± 1.2	5.9 ± 0.3	13.3 ± 0.5	5.7 ± 0.3
Heart rate, beats/min	73 ± 6	73 ± 5	82 ± 5	83 ± 7
MAP, mmHg	98 ± 12	92 ± 14	87 ± 12	75 ± 10
PAOP, mmHg	12.5 ± 3.0	14.5 ± 2	11.5 ± 3.3	13.5 ± 2.5
Cardiac index, ml · min <sup>-1</sup> · m <sup>-2</sup>	2.6 ± 0.3	3.4 ± 0.3*	2.6 ± 0.2	3.5 ± 0.3†
$\text{Do}_2$ , ml · min <sup>-1</sup> · m <sup>-2</sup>	494 ± 56.4	399 ± 61.2*	491 ± 43.1	382 ± 37.3†
$\text{VO}_2$ , ml · min <sup>-1</sup> · m <sup>-2</sup>	99 ± 10.1	113 ± 10.7*	101 ± 8.2	122 ± 5.2†
$\text{SaO}_2$ , %	97.6 ± 1.7	96.5 ± 1.5	96.7 ± 1.4	97.2 ± 1.2
$\text{SvO}_2$ , %	76.6 ± 2.8	70 ± 1.2	75 ± 1.8	72 ± 1.0
$\text{O}_2\text{ER}$ ( $\text{VO}_2/\text{Do}_2$ )	0.20 ± 0.02	0.29 ± 0.04*	0.20 ± 0.02	0.32 ± 0.04†
Plasma lactate, mm	0.88 ± 0.12	1.07 ± 0.13*	0.87 ± 0.10	1.02 ± 0.12†

Data are expressed as mean ± SD.

\*  $P < 0.05$  compared with baseline in spine surgery patients. †  $P < 0.05$  compared with baseline in abdominal surgery patients.

ANA = acute normovolemic anemia;  $\text{Do}_2$  = oxygen delivery; MAP = mean arterial pressure;  $\text{O}_2\text{ER}$  = oxygen extraction ratio; PAOP = pulmonary artery occlusion pressure;  $\text{SaO}_2$  = oxygen saturation;  $\text{SvO}_2$  = mixed venous oxygen saturation;  $\text{VO}_2$  = oxygen consumption.

**Table 3. Hepatosplanchnic and Preportal Flow, Do<sub>2</sub>, and O<sub>2</sub>ER in Patients Undergoing Spine and Abdominal Surgery**

Variable	Hepatosplanchnic (Spine Surgery)		Portal (Abdominal Surgery)	
	Baseline	ANA	Baseline	ANA
Flow, l · min <sup>-1</sup> · m <sup>-2</sup>	0.85 ± 0.06	0.56 ± 0.05*	0.59 ± 0.11	0.44 ± 0.43†
Do <sub>2</sub> , ml · min <sup>-1</sup> · m <sup>-2</sup>	109 ± 10.8	44 ± 10.1*	111 ± 10.8	35 ± 6.6†
VO <sub>2</sub> , ml · min <sup>-1</sup> · m <sup>-2</sup>	44 ± 3.8	23 ± 3.3*	16.1 ± 2.9	11.3 ± 2.4†
O <sub>2</sub> ER (VO <sub>2</sub> /Do <sub>2</sub> ),	0.40 ± 0.05	0.54 ± 0.13*	0.14 ± 0.02	0.33 ± 0.09†
Portal vein lactate, mm	—	—	0.4 ± 0.12	1.9 ± 0.14†

Data are expressed as mean ± SD.

P < 0.05: \* spine surgery compared with baseline, † abdominal surgery compared with baseline.

ANA = acute normovolemic anemia; Do<sub>2</sub> = oxygen delivery; O<sub>2</sub>ER = oxygen extraction ratio; VO<sub>2</sub> = oxygen consumption.

(216 ± 29.7 μmol/min) from baseline levels (P < 0.05) (table 4). The mean hepatic <sup>13</sup>C lactate release from the splanchnic bed at the target hemoglobin concentration during ANA was significantly increased by 140 ± 36.1 μmol/min from baseline (P < 0.05).

## Discussion

The most important finding of this study is that reducing hemoglobin concentration to 5.93 g/dl (hematocrit 17.79%) in anesthetized humans resulted in inadequate oxygenation in splanchnic organs as assessed by our two primary measures: (1) reduction in splanchnic and portal oxygen consumption and (2) regional (hepatic vein) increases in surrogate markers of anaerobic metabolism, *i.e.*, increased regional generation of lactate and an increased β-hydroxybutyrate-to-acetoacetate (βOHB/AcAc) ratio. Importantly, at the same level of ANA, systemic oxygen consumption was preserved.

Despite its critical importance, the response of splanchnic organs to ANA in humans has never been investigated. Therefore, we could compare our findings only to previous studies in pigs, which have similar cardiovascular and digestive systems to those in humans.<sup>25</sup> Experimental studies in anesthetized pigs demonstrated a two-phase response, consisting of preserved splanchnic oxygenation during mild ANA (hematocrit 14%) and progressive impairment during severe ANA (hematocrit 6%).<sup>26–29</sup>

Possible reasons for the apparently greater tolerance of pigs for ANA include interspecies differences, depth of anesthesia, and the beneficial redistribution of blood

flow, in favor of the mucosal layer, the dominant oxygen consuming part within the intestinal wall.<sup>28,29</sup> Moreover, in comparison to humans, pigs have a lower normal range of hemoglobin (8–9 g/dl), and the methodology used to measure regional blood flow could have also played a role in this differential response.<sup>27</sup> Anesthesia reduces splanchnic blood flow and increases splanchnic oxygen extraction.<sup>16,26</sup> One critical adaptive mechanism during ANA is the redistribution of cardiac output toward the heart and brain at the expense of organs perfused by the splanchnic vascular bed.<sup>12,14</sup> The reduction in splanchnic and portal blood flow during ANA influenced by preoperative medications must be entertained (*i.e.*, metoprolol).<sup>30,31</sup> Fortunately, it is unlikely that our results were modified by the β-blocker therapy, because it has been recently demonstrated that metoprolol in comparison with propranolol does not significantly reduce hepatic flow in patients with cirrhosis.<sup>32</sup> Therefore, the observed reductions in splanchnic and portal blood flow in the current study might be related to central sympathetic stimulation related to inadequate levels of anesthesia.

In experimental models, an oxygen supply-dependent state demonstrates decreased adenosine triphosphatase flux (oxygen consumption) in the liver. This was accompanied by increases in inorganic phosphate/adenosine triphosphatase (measured by nuclear magnetic resonance spectroscopy) and hepatic venous βOHB/AcAc.<sup>33,34</sup> In our patients, when the target level of hemoglobin concentration (5.9 g/dl) was reached during ANA, a reduction in splanchnic oxygen consumption was accompanied by increases in βOHB/AcAc, suggest-

**Table 4. Biochemical Markers of Anaerobic Metabolism in Hepatosplanchnic Vascular Bed Spine Surgery Patients (n = 12)**

Variable	Baseline	Acute Normovolemic Anemia
Ketone bodies ratio (βOHB/AcAc)	0.48 ± 0.04	1.64 ± 0.10*
Net balance of unlabeled lactate, μmol/min	557 ± 27	347 ± 37*
Hepatosplanchnic <sup>13</sup> C lactate uptake, μmol/min	434 ± 21.4	649 ± 38.6*
Hepatosplanchnic <sup>13</sup> C lactate release, μmol/min	358 ± 67.7	498 ± 90.7*

Data are expressed as mean ± SD.

\* P < 0.05 compared with baseline.

βOHB/AcAc = β-hydroxybutyrate-to-acetoacetate ratio.

ing regional dysoxia (oxygen consumption exceeds the ability of  $\text{Do}_2$  to provide oxygen consumption) and anaerobic metabolism.

Despite the occurrence of oxygen supply dependency in the splanchnic bed in our patients, the net balance of unlabeled lactate across the splanchnic region remained steady (positive) at baseline ( $557 \pm 27 \mu\text{mol}/\text{min}$ ) and during ANA ( $347 \pm 37 \mu\text{mol}/\text{min}$ ). Our data again reiterate the limitation of balance studies using (arterial-venous) difference of lactate across splanchnic organs.<sup>24,35</sup> Without knowing the total rate of lactate production by the entire body, lactate balance across a perfused bed or organ does not reveal the relative contribution of that bed or organ to lactate production. Also, the net balance of lactate does not allow separate estimation of lactate production and utilization. Finally, balance studies cannot determine whether the origin of the lactate is glycolysis or other nonglucose sources.<sup>36</sup> To overcome these limitations, we used the novel stable isotope tracer methodology to estimate exchange, production, and lactate oxidation. The calculated lactate kinetics across the total splanchnic circulation revealed a baseline splanchnic release of lactate  $358 \pm 67.7$  before ANA, which increased by 50% to  $498 \pm 90.7$  after ANA. This was accompanied by compensatory increase in hepatic uptake from  $434 \pm 21.4$  to  $649 \pm 38.6 \mu\text{mol}$  with maintained splanchnic uptake as evidenced by the post-ANA arterial lactate levels of  $1.07 \pm 0.13$  remaining within normal limits ( $< 2.2 \text{ mm}$ ). Although lactate may not always be a reliable indicator of limitations in oxygen availability, this rebalancing of lactate flux suggests that net anaerobic metabolism was occurring in the gut, and oxygen consumption supply dependency was occurring relatively early. However, the clinical importance of temporary splanchnic lactate production is unknown.

As in previous studies in conscious humans, in the current study, we did not define in anesthetized patients a critical level of systemic  $\text{Do}_2$  below which oxygen consumption declined, even though splanchnic and preportal oxygen consumption was impaired at the same level of ANA.<sup>9,10</sup> This suggests that systemic  $\text{Do}_2$  and oxygen consumption indices are not sufficiently sensitive to detect organ system dysfunction or regional dysoxia, especially in splanchnic organs.<sup>7,8,13,37</sup> Unlike in conscious humans, the levels of systemic  $\text{Do}_2$  and oxygen consumption were lower in our anesthetized subjects, which could be attributed to the effects of anesthetic drugs on the autonomic and cardiovascular system.<sup>38,39</sup> Anesthetic drugs, when combined with neuromuscular blockade and mechanical ventilation, reduce myocardial muscle and brain and whole body oxygen consumption in dose-dependent fashion.<sup>40,41</sup> This in turn might reduce critical  $\text{Do}_2$  (the value of oxygen delivery below which oxygen consumption becomes supply dependent). However, contrary to previous studies, in our anesthetized patients, we observed a signifi-

cant increase in systemic oxygen consumption and increased oxygen extraction. Our findings of increased systemic oxygen consumption and oxygen extraction could be attributable to light depth of anesthesia and sympathetic stimulation. Because anesthesia blunts the cardiac output response during ANA, higher critical hemoglobin levels have also been recently demonstrated at more profound anesthetic depths despite a progressive reduction in oxygen demand during anesthesia.<sup>42</sup> There are also experimental data that demonstrate an increase in critical  $\text{Do}_2$  during anesthesia, related to reduction in tissue oxygen extraction capabilities.<sup>17</sup> The systemic response associated with ANA in this study could have been influenced by preoperative medications, *i.e.*,  $\beta$  blockers. However, a study by Spahn *et al.*<sup>43</sup> demonstrate that chronic  $\beta$  blockade did not blunt the cardiac output and oxygen extraction responses to ANA in anesthetized patients.

This study does have some important strengths and limitations. Among the strengths are the ability to measure total splanchnic and portal blood flow and to estimate respective splanchnic and portal  $\text{Do}_2$  and oxygen consumption during ANA in anesthetized humans. None of these indices have been previously documented in humans during ANA. The novel aspect of this study is the inclusion of surrogate markers of anaerobic metabolism, *i.e.*, regional lactate synthesis and increased  $\beta\text{OHB}/\text{AcAc}$  ratio during supply dependency at the target levels of hemodilution.<sup>24,33,34</sup>

Foremost among the limitations is that we were not able to determine a critical  $\text{Do}_2$  for splanchnic organs in individual patients, as has been accomplished previously in animal models by using a linear regression technique to analyze the plot of oxygen consumption and  $\text{Do}_2$ .<sup>37</sup> However, such techniques are not feasible in clinical studies. We measured systemic oxygen consumption by indirect calorimetry, whereas splanchnic and preportal tissue oxygen consumption was estimated by using the Fick equation. This method has been criticized because of the potential problem of mathematical coupling.<sup>23,44</sup> However, it has been stated that the effects of coupled errors are limited by keeping the range of independent variables as large as possible (as in our study population).<sup>23</sup> We could also be criticized for producing such a profound hemodilution (6 g/dl hemoglobin) in view of the adverse effects of such a procedure on cognitive function.<sup>45</sup> To minimize such a risk, the patients were retransfused to return the hemoglobin to greater than 7 g/dl. In addition, anesthesia-induced reduction in brain oxygen consumption could have also protected the brain from such ill effects.<sup>46,47</sup> Finally, our results may not be applicable to patients with abnormal hemoglobin and patients with hypovolemia or shock.<sup>48</sup> Moreover, the high partial pressure of oxygen due to high inspired oxygen concentration could have also influenced our results.<sup>49</sup>

The indocyanine green infusion technique is limited by assessing only total splanchnic blood flow rather than the distribution of flow between the liver and gut.<sup>19,20</sup> In abdominal surgery group, only portal blood flow was measured during surgery. Therefore, we could not compare splanchnic vascular bed responses between abdominal surgery and spine groups during ANA. However  $\text{Do}_2$  and oxygen consumption responses during ANA were similar in both groups. Finally, the sample size of our abdominal surgery group (preportal group) was small. However, this reflects the relative inaccessibility of this vascular bed for hemodynamic studies. Nevertheless, this is the first study that provides quantitative data for splanchnic and preportal oxygen utilization during ANA.

In conclusion, acute reduction of hemoglobin concentration to  $5.9 \pm 0.3$  g/dl in anesthetized humans by ANA sufficiently diminished splanchnic and preportal  $\text{Do}_2$  such that oxygen consumption became impaired, although systemic oxygenation apparently remained adequate. Inadequate splanchnic oxygenation was also supported by the demonstration of increased regional lactate generation and increased plasma ratios of  $\beta\text{OHB}/\text{AcAc}$  sampled from the hepatic vein. Our findings demonstrate that the gastrointestinal tract has limited tolerance for ANA.

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