

Research

Intramucosal–arterial Pco_2 gap fails to reflect intestinal dysoxia in hypoxic hypoxia

Arnaldo Dubin¹, Gastón Murias², Elisa Estenssoro³, Héctor Canales⁴, Julio Badie⁵, Mario Pozo², Juan P Sottile⁴, Marcelo Barán⁶, Fernando Pálizas⁷ and Mercedes Laporte⁸

¹Principal Investigator, Cátedra de Farmacología, Facultad de Ciencias Médicas, Universidad Nacional de La Plata, Argentina

²Research Fellow, Cátedra de Farmacología, Facultad de Ciencias Médicas, Universidad Nacional de La Plata, Argentina

³Medical Director, Servicio de Terapia Intensiva, Hospital San Martín de La Plata, Argentina

⁴Staff physician, Servicio de Terapia Intensiva, Hospital San Martín de La Plata, Argentina

⁵Research Fellow, Cátedra de Farmacología, Facultad de Ciencias Médicas, Universidad Nacional de La Plata, Argentina

⁶Medical Director, Unidad de Transplante Renal, CRAI Sur, CUCAIBA, Argentina

⁷Medical Director, Servicio de Terapia Intensiva, Clínica Bazterrica de Buenos Aires, Argentina

⁸Director, Servicio de Laboratorio, Hospital San Martín de La Plata, Argentina

Correspondence: Arnaldo Dubin, adee@infovia.com.ar

Received: 1 May 2002

Revisions requested: 4 July 2002

Revisions received: 5 August 2002

Accepted: 6 August 2002

Published: 28 August 2002

Critical Care 2002, **6**:514-520 (DOI 10.1186/cc1813)

This article is online at <http://ccforum.com/content/6/6/514>

© 2002 Dubin *et al.*, licensee BioMed Central Ltd (Print ISSN 1364-8535; Online ISSN 1466-609X). This article is published in Open Access: verbatim copying and redistribution of this article are permitted in all media for any non-commercial purpose, provided this notice is preserved along with the article's original URL.

Abstract

Introduction An elevation in intramucosal–arterial PCO_2 gradient (ΔPCO_2) could be determined either by tissue hypoxia or by reduced blood flow. Our hypothesis was that in hypoxic hypoxia with preserved blood flow, ΔPCO_2 should not be altered.

Methods In 17 anesthetized and mechanically ventilated sheep, oxygen delivery was reduced by decreasing flow (ischemic hypoxia, IH) or arterial oxygen saturation (hypoxic hypoxia, HH), or no intervention was made (sham). In the IH group ($n=6$), blood flow was lowered by stepwise hemorrhage; in the HH group ($n=6$), hydrochloric acid was instilled intratracheally. We measured cardiac output, superior mesenteric blood flow, gases, hemoglobin, and oxygen saturations in arterial blood, mixed venous blood, and mesenteric venous blood, and ileal intramucosal PCO_2 by tonometry. Systemic and intestinal oxygen transport and consumption were calculated, as was ΔPCO_2 . After basal measurements, measurements were repeated at 30, 60, and 90 minutes.

Results Both progressive bleeding and hydrochloric acid aspiration provoked critical reductions in systemic and intestinal oxygen delivery and consumption. No changes occurred in the sham group. ΔPCO_2 increased in the IH group (12 ± 10 [mean \pm SD] versus 40 ± 13 mmHg; $P < 0.001$), but remained unchanged in HH and in the sham group (13 ± 6 versus 10 ± 13 mmHg and 8 ± 5 versus 9 ± 6 mmHg; not significant).

Discussion In this experimental model of hypoxic hypoxia with preserved blood flow, ΔPCO_2 was not modified during dependence of oxygen uptake on oxygen transport. These results suggest that ΔPCO_2 might be determined primarily by blood flow.

Keywords blood flow, carbon dioxide, hypoxia, oxygen consumption, tonometry

Introduction

Tonometry is one of the few clinical tools available for the monitoring of tissue oxygenation [1]. Decreases in gastro-

intestinal intramucosal pH (pH_i) have usually been considered as indicators of dysoxia [2–5]; that is, as heralds of insufficient O_2 to meet tissue demands. Recently, the intramucosal–

ANOVA = analysis of variance; CO = cardiac output; DO_2 = oxygen transport; ΔPCO_2 = intramucosal–arterial PCO_2 gradient; F_iO_2 = fraction of inspired oxygen; HH = hypoxic hypoxia; IH = ischemic hypoxia; pH_i = intramucosal pH; VO_2 = oxygen uptake.

arterial PCO_2 gradient (ΔPCO_2) has been claimed to be a better marker of gastrointestinal mucosal state of oxygenation [6]. PCO_2 can increase in intestinal lumen by two mechanisms [7]. One is by bicarbonate buffering of protons from the breakdown of high-energy phosphates and metabolic acids generated anaerobically, such as lactate, in which case increased PCO_2 would represent tissue dysoxia. Alternatively, in an aerobic state, it might be the result of hypoperfusion and decreased washout. In this latter case, oxygen metabolism could be preserved if the flow were adequate.

Grum *et al.* [2] found that pH_i and intestinal oxygen uptake (VO_2) were correlated in ischemia, in hypoxemia, and in a combination of both. However, in hypoxemic experiments, neither VO_2 nor pH_i fell. Hence, the value of tonometry in hypoxemia remains uncertain. If a rise in ΔPCO_2 reflected only a decrease in blood flow, this gradient might not be altered in hypoxemia, in which cardiac output (CO) is usually maintained and even increased. Our hypothesis was that ΔPCO_2 would not be modified in hypoxic hypoxia (HH) with preserved blood flow.

Methods

Surgical preparation

This study was approved by the local Animal Care Committee. Care of studied animals was in accordance with National Institutes of Health guidelines. Seventeen adult sheep (26.0 ± 9.1 kg [mean \pm SD]) were anesthetized with 30 mg/kg sodium pentobarbital, tracheostomized and then ventilated (Harvard Pump Ventilator; Harvard Apparatus, South Natick, Massachusetts, USA) with a tidal volume of 15 ml/kg, a respiratory rate of 12 per minute, and a positive end-expiratory pressure of 5 cmH_2O throughout the experiment. The starting fraction of inspired oxygen (F_iO_2) was 0.21. Additional pentobarbital was administered if necessary. Neuromuscular blockade was provided with a single dose of pancuronium (0.06 mg/kg). Catheters were placed into the femoral artery and vein and into the pulmonary artery (flow-directed thermodilution fiberoptic pulmonary artery catheter; Abbott Critical Care Systems, Mountain View, California, USA).

After performing a midline laparotomy, we performed splenectomy and a gastrotomy with drainage of gastric contents. We placed an electromagnetic blood flow transducer around the superior mesenteric artery. A catheter was advanced into the superior mesenteric vein, and a tonometer was inserted into the ileum.

Measurements and derived calculations

CO was measured in triplicate by the thermodilution technique, with 5 ml of iced saline (HP OmniCare Model 24 A 10; Hewlett Packard, Andover, Massachusetts, USA), and was referred to body weight. Superior mesenteric artery blood flow (intestinal blood flow) was measured by the electromagnetic method (Spectramed Blood Flowmeter model SP 2202 B; Spectramed Inc., Oxnard, California, USA) and indexed to intestinal weight.

Arterial mixed venous and mesenteric venous PO_2 , PCO_2 , and pH , and haemoglobin concentrations and saturations were measured with a blood gas analyzer and a co-oximeter, respectively (ABL 30 and OSM 3; Radiometer, Copenhagen, Denmark). Systemic and intestinal oxygen transport and uptake (DO_2 , VO_2 , intestinal DO_2 , and intestinal VO_2 respectively) were calculated with standard formulae.

Intramucosal PCO_2 was measured by saline tonometry (TRIP Sigmoid Catheter; Tonometrics, Inc., Worcester, Massachusetts, USA) [8]. After an equilibration period of 30 minutes, 1.0 ml was discarded. PCO_2 was measured in the remnant (ABL 30; Radiometer). pH_i and ΔPCO_2 were calculated with a correction factor for the equilibration time. Kolkman *et al.* [9] showed that the variability of intramucosal PCO_2 measurements is independent of dwell time. Assessments at short dwell times should therefore be reliable.

We calculated venoarterial and intramucosal-arterial CO_2 content differences to evaluate the changes in the CO_2 dissociation curve [10]. To compute intramucosal CO_2 content, intramucosal PCO_2 , pH , and mesenteric venous oxygen saturation were considered as representative of mucosal blood.

Experimental procedure

After a stabilization period of at least 30 minutes, we performed basal measurements (0 minutes). Sheep were then assigned to ischemic hypoxia (IH [$n=6$]), HH ($n=6$), or sham ($n=5$) groups. In the IH group, bleeding was performed in three steps of 10 ml/kg at intervals of 30 minutes. In the HH group, 2 ml/kg 0.1 M hydrochloric acid was instilled into the trachea, and F_iO_2 was raised to 0.50. Saline solution was infused to keep intestinal blood flow constant. Measurements were repeated at 30, 60, and 90 minutes. Body temperature was maintained stable with a heating lamp.

Finally, animals were killed with supplemental pentobarbital and a KCl bolus. Indian ink was infused through the superior mesenteric artery, and dyed intestinal segments were dissected and weighed.

Statistical analysis

Data are expressed as means \pm SD except where noted otherwise. Analysis within groups was performed with a repeated-measures analysis of variance (ANOVA) and a paired *t*-test with Bonferroni correction. One-way ANOVA and unpaired *t*-test with Bonferroni correction were used for one-time comparisons. In both cases, *t*-tests were used when ANOVA results were significant; $P < 0.05$ was considered significant.

Results

Hemoglobin concentration, and arterial, mixed venous, and mesenteric venous blood gases and oxygen saturations in basal conditions, and during IH and HH and in the sham group are shown in Table 1.

Table 1

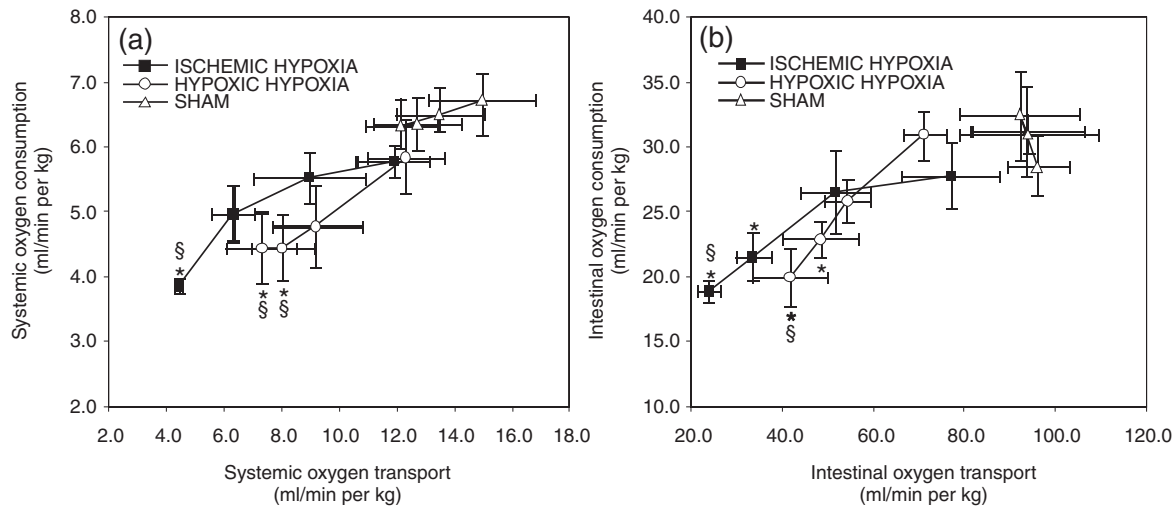
Hemoglobin concentration and arterial, mixed venous, and mesenteric venous blood gases and oxygen saturations in basal conditions and during ischemic hypoxia (IH) and hypoxic hypoxia (HH), and in the sham group

Parameter	Group	Basal	30 minutes	60 minutes	90 minutes
Hemoglobin (g%)	IH	9.1 ± 0.6	8.6 ± 0.6	7.9 ± 1.1*	7.4 ± 1.3*
	HH	10.2 ± 1.2	10.7 ± 1.0‡	11.2 ± 1.1‡	11.4 ± 1.2*‡
	SHAM	10.7 ± 1.6	11.0 ± 1.4‡	11.4 ± 1.3‡	11.2 ± 1.1‡
Arterial pH	IH	7.36 ± 0.10	7.35 ± 0.07	7.31 ± 0.10	7.25 ± 0.11*
	HH	7.41 ± 0.07	7.26 ± 0.10**	7.21 ± 0.12**	7.15 ± 0.13**
	SHAM	7.37 ± 0.09	7.39 ± 0.10	7.38 ± 0.10	7.36 ± 0.13
Arterial PCO ₂ (mmHg)	IH	33 ± 3	31 ± 4	28 ± 3**†	24 ± 4**††
	HH	29 ± 3	40 ± 8*	45 ± 11*	49 ± 13**
	SHAM	30 ± 4	28 ± 3†	28 ± 3†	28 ± 6†
Arterial PO ₂ (mmHg)	IH	79 ± 10	81 ± 12	82 ± 12†	91 ± 7††
	HH	91 ± 16	59 ± 23**	50 ± 13**	44 ± 7**
	SHAM	88 ± 12	86 ± 20	85 ± 20†	80 ± 17††
Arterial O ₂ saturation	IH	91.2 ± 2.9	90.7 ± 3.4	90.1 ± 3.0†	91.8 ± 2.8††
	HH	96.3 ± 3.0	69.9 ± 21.9*	60.0 ± 22.0*	52.3 ± 15.8**
	SHAM	96.1 ± 3.6	95.7 ± 3.2	94.9 ± 4.6†	93.0 ± 7.5††
Mixed venous pH	IH	7.31 ± 0.06	7.28 ± 0.08	7.19 ± 0.11*	7.09 ± 0.11**
	HH	7.36 ± 0.08	7.23 ± 0.10**	7.17 ± 0.13**	7.10 ± 0.13**
	SHAM	7.33 ± 0.09	7.33 ± 0.10	7.33 ± 0.10	7.34 ± 0.12§
Mixed venous PCO ₂ (mmHg)	IH	41 ± 3	43 ± 4	46 ± 4	49 ± 5*
	HH	36 ± 5	47 ± 9*	52 ± 12*	59 ± 15*
	SHAM	36 ± 5	35 ± 6	33 ± 4§§	32 ± 6§§
Mixed venous PO ₂ (mmHg)	IH	34 ± 4	27 ± 6**	20 ± 5**	18 ± 4**
	HH	38 ± 7	30 ± 11	28 ± 10**	24 ± 8**
	SHAM	40 ± 6	36 ± 8	42 ± 9§	43 ± 9§§
Mixed venous O ₂ saturation	IH	44.6 ± 11.0	28.4 ± 14.3*	16.4 ± 10.1**	11.2 ± 3.3**
	HH	52.9 ± 11.8	33.4 ± 21.5*	26.6 ± 18.6*	19.0 ± 12.0**
	SHAM	55.2 ± 12.1	53.3 ± 10.9‡	48.5 ± 16.5§§	48.8 ± 18.5§§
Mesenteric venous pH	IH	7.30 ± 0.09	7.28 ± 0.10	7.21 ± 0.12*	7.15 ± 0.14*
	HH	7.35 ± 0.10	7.21 ± 0.13**	7.16 ± 0.15**	7.10 ± 0.16**
	SHAM	7.35 ± 0.09	7.35 ± 0.09	7.33 ± 0.10	7.34 ± 0.10§
Mesenteric venous PCO ₂ (mmHg)	IH	42 ± 4	43 ± 4	44 ± 4	44 ± 5
	HH	39 ± 9	49 ± 14	54 ± 18	60 ± 21
	SHAM	36 ± 4	33 ± 4§	33 ± 4§	32 ± 6§
Mesenteric venous PO ₂ (mmHg)	IH	38 ± 8	32 ± 6*	25 ± 4*	25 ± 4*
	HH	38 ± 6	33 ± 10	29 ± 10*	26 ± 9*
	SHAM	43 ± 7	42 ± 10	42 ± 9‡	43 ± 9§
Mesenteric venous O ₂ saturation	IH	52.3 ± 16.8	41.6 ± 13.3**	30.2 ± 11.5**	20.3 ± 4.9**
	HH	57.5 ± 15.0	36.2 ± 23.1*	29.1 ± 23.2*	23.9 ± 17.5**
	SHAM	67.5 ± 10.5	63.3 ± 14.6	63.3 ± 14.6‡†	65.1 ± 16.4§§

* $P < 0.05$ versus basal; ** $P < 0.01$ versus basal; † $P < 0.05$ versus hypoxic hypoxia; †† $P < 0.01$ versus hypoxic hypoxia; ‡ $P < 0.05$ versus ischemic hypoxia; ‡‡ $P < 0.01$ versus ischemic hypoxia; § $P < 0.05$ versus ischemic and hypoxic hypoxia; §§ $P < 0.01$ versus ischemic and hypoxic hypoxia (paired or unpaired t -tests with Bonferroni correction, after analysis of variance < 0.05).

Systemic and intestinal supply dependence was induced in both the IH and HH groups. There were no significant changes in systemic and intestinal DO₂ and VO₂ in the sham group (Figure 1). In the IH group, supply dependence appeared with critical decreases in CO and superior mesen-

teric artery blood flow (0.104 ± 0.024 versus 0.048 ± 0.006 l/min per kg, and 0.664 ± 0.227 versus 0.258 ± 0.082 l/min per kg, respectively; $P < 0.0001$). In the HH group it was due to a progressive decrease in arterial oxygenation. CO and intestinal blood flow were maintained

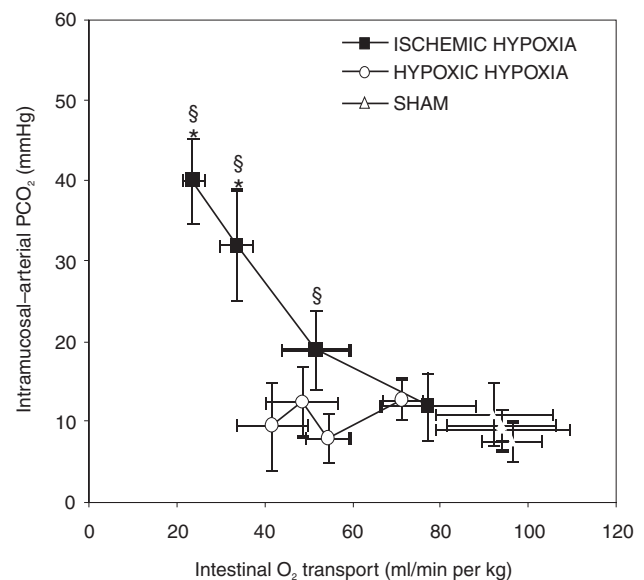
Figure 1

Systemic and intestinal oxygen supply dependence. **(a)** Relationship between systemic oxygen transport and consumption during ischemic and hypoxic hypoxia, and in the sham group. **(b)** Relationship between intestinal oxygen transport and consumption during ischemic and hypoxic hypoxia, and in the sham group. Data are expressed as means \pm SEM. * $P < 0.05$ versus basal oxygen consumption. § $P < 0.05$ versus sham group.

(0.446 ± 0.085 versus 0.431 ± 0.140 ml/min per kg, respectively; not significant), owing to the administration of normal saline (median 630 ml; range 20–1310 ml). Arterial and intramucosal pH fell significantly in the IH and HH groups. In the HH group it was primarily related to systemic respiratory and metabolic acidosis (Tables 1 and 2), because ΔPCO_2 did not increase. In addition, systemic and intestinal venoarterial PCO_2 gradients were not modified. CO_2 content differences also did not change (Table 2 and Figure 2). In contrast, in the IH group, ΔPCO_2 , systemic and intestinal venoarterial PCO_2 , and CO_2 content gradients increased significantly (Table 2 and Figure 2). In the sham group, CO_2 gradients and pH_i remained unchanged.

Discussion

Increased mucosal intestinal PCO_2 is used as a tool to detect tissue dysoxia, the condition in which O_2 delivery can no longer sustain O_2 uptake [11]. A great body of literature supports the role of intestinal PCO_2 as an early marker of dysoxia and regional hypoperfusion. Early studies considered pH_i as the reference parameter. Recently, some investigators have claimed that intramucosal PCO_2 , the variable actually measured by the tonometer, and ΔPCO_2 could more adequately reflect mucosal oxygenation [6,12]. pH_i is a calculated variable, from the Henderson–Hasselbach equation, with the assumption that arterial bicarbonate is representative of intramucosal bicarbonate. In a steady state, both values might be similar. However, in rapidly changing physiological situations, differences between arterial and mucosal CO_2 might arise owing to slow CO_2 equilibrium kinetics [13]. Therefore, pH_i values calculated from tonometry might differ from those

Figure 2

Relationship between intestinal oxygen transport and intramucosal-arterial PCO_2 difference during ischemic and hypoxic hypoxia, and in the sham group. Data are expressed as means \pm SEM. * $P < 0.05$ versus basal intramucosal-arterial PCO_2 difference. § $P < 0.05$ versus hypoxic hypoxia and sham group.

directly measured with tissue electrodes [14]. Moreover, acid-base states could influence pH_i in the absence of altered mucosal oxygenation. As a result, the acid-base

Table 2

CO₂ gradients and intramucosal pH during ischemic hypoxia (IH) and hypoxic hypoxia (HH), and in the sham group

Parameter	Group	Basal	30 minutes	60 minutes	90 minutes
Mixed venous–arterial PCO ₂ (mmHg)	IH	8 ± 2	12 ± 3*†	19 ± 5**††	25 ± 4**††
	HH	7 ± 2	7 ± 3	8 ± 3	9 ± 3
	SHAM	5 ± 2	7 ± 3†	6 ± 3‡	5 ± 3‡
Mixed venous–arterial CO ₂ content (vol%)	IH	4.3 ± 1.6	7.2 ± 4.8	10.9 ± 2.5**††	14.3 ± 3.6**††
	HH	4.6 ± 1.7	3.5 ± 1.4	3.4 ± 2.0	3.2 ± 1.0
	SHAM	4.0 ± 4.8	5.7 ± 3.1	6.9 ± 2.1	2.7 ± 1.8‡
Mesenteric venous–arterial PCO ₂ (mm Hg)	IH	9 ± 4	12 ± 3*††	16 ± 4**	19 ± 5††‡
	HH	9 ± 5	5 ± 3	20 ± 10	6 ± 2
	SHAM	6 ± 3	5 ± 2‡	6 ± 1‡	5 ± 2‡
Mesenteric venous–arterial CO ₂ content (vol%)	IH	4.7 ± 1.2	7.2 ± 3.2	8.2 ± 2.4**††	9.8 ± 2.2**††
	HH	6.6 ± 5.7	3.8 ± 2.6	3.4 ± 2.4	3.4 ± 2.3
	SHAM	3.0 ± 1.9	3.3 ± 1.1	5.4 ± 2.4	2.6 ± 1.8‡
Intramucosal–arterial PCO ₂ (mmHg)	IH	12 ± 10	19 ± 12*†	32 ± 17***††	40 ± 13***††¶
	HH	13 ± 6	8 ± 8	13 ± 11	10 ± 13
	SHAM	8 ± 5	11 ± 3‡	10 ± 4‡	9 ± 6‡
Intramucosal–arterial CO ₂ content (vol%)	IH	2.0 ± 0.4	2.4 ± 0.6††	2.8 ± 0.8**††	3.3 ± 0.8**††
	HH	2.0 ± 0.5	0.7 ± 0.8	0.9 ± 0.9	0.3 ± 1.2
	SHAM	1.7 ± 0.4	1.9 ± 0.7	2.1 ± 0.9	1.7 ± 0.5‡
Intramucosal pH	IH	7.24 ± 0.14	7.16 ± 0.16**	7.01 ± 0.22**	6.84 ± 0.21**
	HH	7.26 ± 0.14	7.19 ± 0.13**	7.10 ± 0.16**	7.07 ± 0.18**
	SHAM	7.28 ± 0.06	7.26 ± 0.09	7.17 ± 0.08	7.25 ± 0.10§§

* $P < 0.05$ versus basal; ** $P < 0.01$ versus basal; † $P < 0.05$ versus hypoxic hypoxia; †† $P < 0.01$ versus hypoxic hypoxia; ‡ $P < 0.05$ versus ischemic hypoxia; ‡‡ $P < 0.01$ versus ischemic hypoxia; § $P < 0.05$ versus ischemic and hypoxic hypoxia; §§ $P < 0.01$ versus ischemic and hypoxic hypoxia (paired or unpaired t -tests with Bonferroni correction, after analysis of variance < 0.05).

status of arterial blood will be reflected in both mucosal pH_i and PCO₂ [6,14]. In our experiments, pH_i fell progressively during hydrochloric acid-induced lung injury and decreased DO₂, reflecting ongoing systemic respiratory and metabolic acidosis. However, ΔPCO₂ remained unchanged.

Another issue that has been discussed extensively is the relative impact on mucosal PCO₂ of anaerobic production of CO₂ in comparison with decreased washout of aerobically generated CO₂ during low flow states. Many investigators [15–17] have ascribed increased PCO₂ found in shock states to continuing aerobic CO₂ production with decreased elimination; that is, to 'respiratory acidosis'. However, Schlichtig and Bowles [7] showed evidence supporting the role of intramucosal PCO₂ as a marker of dysoxia in extreme hypoperfusion, when VO₂ falls. In a dog model of cardiac tamponade, they demonstrated that mucosal PCO₂ could rise because of anaerobic CO₂ production below the critical DO₂. These conclusions were drawn by using the Dill nomogram, which can theoretically detect anaerobic CO₂ production from a comparison of the measured (%HbO_{2,v}) and calculated (%HbO_{2,v}^{Dill}) venous oxyhemoglobin, within a given venous PCO₂ value. Because venous PCO₂ is considered to be representative of tissue PCO₂, Schlichtig and Bowles made the calculation with its intestinal equivalent, intramucosal PCO₂. If

%HbO_{2,v}^{Dill} is lower than the measured %HbO_{2,v}, anaerobic production of CO₂ might be assumed. Similar values would represent aerobic CO₂ generation. Notwithstanding the original contribution of Schlichtig and Bowles [7] to the analysis of these topics, the use of low flow to produce critical oxygen delivery and falling VO₂ has been signaled as a potential confounding factor [18].

We studied these issues in a model of HH with preserved flow, because it allows a clear discrimination between hypoxia and hypoperfusion. There have been attempts to analyze pH_i behavior in HH, but critical intestinal DO₂ was not attained, and intestinal VO₂ and pH_i remained unchanged [2]. Our model consisted of an acute lung injury produced by endotracheal instillation of hydrochloric acid that rapidly generated severe hypoxemia, shown by the decrease in arterial PO₂ and pH. The acid also enhanced microvascular permeability [19–21], demonstrated by increased requirements of saline solution to maintain intestinal blood flow and by the increase in hemoglobin levels. However, other mechanisms could be acting to preserve blood flow, such as tachycardia and enhanced left ventricular contractility [22]. Deep arterial hypoxemia caused significant reductions in systemic and intestinal DO₂, but systemic and intestinal blood flow were preserved and hemoglobin concentration increased. Despite

the increase in systemic and intestinal oxygen extraction, systemic and intestinal VO_2 values decreased, and dependence of O_2 uptake on transport ensued. Dependence of oxygen consumption on transport during HH has been described by Cain *et al.* in a classical study [23], and it has been considered an indicator of anaerobic metabolism. Additional evidence of tissue dysoxia was the appearance of metabolic acidosis. Cain [24] also showed that there is a correlation between pH and lactate/pyruvate relationship in HH.

Another potential confounding factor that could affect arterial and intestinal PCO_2 and their differences is the shift of the CO_2 dissociation curve. As Jakob *et al.* [25] have shown, there can be a lack of correlation of CO_2 contents and PCO_2 , and, consequently, of their differences. Many determinants of the shifts of the CO_2 dissociation curve, such as changes in pH, in hemoglobin concentrations, and especially in oxygen saturations (the Haldane effect), were present. To discard a possible increase in venoarterial and intramucosal–arterial CO_2 contents without changes in PCO_2 differences in the HH group, we calculated CO_2 content differences. There were no increases in venoarterial and intramucosal–arterial CO_2 content differences during the period of supply dependence, as there were no changes in both PCO_2 differences. Shifts of the CO_2 dissociation curve therefore do not seem to influence our results.

Our model of HH is useful for discriminating the effects of hypoxia and low blood flow, because this last factor was kept constant throughout the experiment. ΔPCO_2 remained stable, although there were signs of anaerobic metabolism. Systemic and venoarterial PCO_2 differences also remained unchanged. Conversely, during supply dependence of VO_2 induced by hemorrhage, ΔPCO_2 and systemic and intestinal venoarterial PCO_2 differences widened, as well as the respective ΔPCO_2 content differences. Moreover, these parameters increased before any change in VO_2 , as we have described previously [26]. These results suggest that, at least in our experiments, tissue perfusion is a key determinant of increased ΔPCO_2 .

Nevière *et al.* [27] tested a similar hypothesis in pigs. They compared the effects of diminished blood flow with diminished inspired fraction of oxygen. In IH, ΔPCO_2 increased to 60 mmHg. In HH, ΔPCO_2 increased to 30 mmHg only in the last step of hypoxemia, although mucosal blood flow measured by laser Doppler flowmetry was preserved. The authors concluded that elevated intramucosal PCO_2 indicated local CO_2 generation. However, in the two previous stages of reduced FIO_2 there was supply dependence, and ΔPCO_2 remained unchanged. In our HH model, ΔPCO_2 was also stable. The differences between our data and those of Nevière *et al.* [27] could be ascribed to distinct microvascular features of the experimental subjects (pigs and sheep) or to different degrees of hypoxemia. In addition, as Nevière *et al.* pointed out, some degree of decrease in gut mucosal blood flow and heterogeneity might have been present, because

Key messages

- The intramucosal–arterial PCO_2 gradient fails to reflect intestinal oxygen supply dependence during hypoxic hypoxia
- Blood flow seems to be the main determinant of venoarterial and intramucosal–arterial PCO_2 gradients
- Tonometry seems to be a useful method for monitoring perfusion, with limited value in detecting anaerobic metabolism when flow is preserved

only global microvascular blood flow changes can be assessed by laser Doppler flowmetry. Nevertheless, both studies show that ΔPCO_2 could fail to reflect tissue dysoxia at some time during HH. In results similar to ours, Vallet *et al.* [28] showed that perfusion is a major determinant of venoarterial PCO_2 difference during critical IH or HH in isolated hindlimb. This gradient increases in ischemia and is preserved in hypoxia.

Venoarterial and intramucosal–arterial PCO_2 gradients are the result of interactions of changes in aerobic and anaerobic CO_2 production, the CO_2 dissociation curve, and blood flow to tissues. During oxygen supply dependence induced by hemorrhage, opposite changes in aerobic and anaerobic CO_2 production are present: aerobic CO_2 production decreases as a consequence of depressed aerobic metabolism, but anaerobic CO_2 production starts because of bicarbonate buffering of protons from fixed acids. Total CO_2 production might not increase, but O_2 consumption falls, so there is an increase in respiratory quotient [29,30]. This increase in VCO_2 relative to VO_2 might generate tissue and venous hypercarbia only in low flow states, in which there is diminished CO_2 removal. Other situations in which intramucosal acidosis could arise with preserved tissue perfusion are reperfusion injury [31] and cytopathic hypoxia generated by endotoxemia [32], with cellular damage and metabolic abnormalities as underlying mechanisms. However, impaired villous microcirculation has been advocated as the causal phenomenon in the latter [33].

Conclusions

To our knowledge, this is the first study showing that ΔPCO_2 fails to mirror intestinal tissue dysoxia. Our findings also suggest that blood flow might be the main determinant of ΔPCO_2 . Tonometry seems to be a useful method for monitoring perfusion, with rather limited value in detecting anaerobic metabolism when blood flow is preserved. Additional studies in other models of hypoxic and anemic hypoxia are needed to confirm our findings and to resolve discrepancies between studies.

Competing interests

None declared.

References

1. Third European Consensus Conference in Intensive Care Medicine: **Tissue hypoxia: how to detect, how to correct, how to prevent?** *Am J Respir Crit Care Med* 1996, **154**:1573-1578.
2. Grum CM, Fiddian-Green RG, Pittenger GL, Grant BJ, Rothman ED, Dantzker DR: **Adequacy of tissue oxygenation in intact dog intestine.** *J Appl Physiol* 1984, **56**:1065-1069.
3. Doglio GR, Pusajo JF, Egurola MA, Bonfigli GC, Parra C, Vetere L, Hernandez MS, Fernandez S, Palizas F, Gutierrez G: **Gastric mucosal pH as a prognostic index of mortality in critically ill patients.** *Crit Care Med* 1991, **19**:1037-1040.
4. Marik PE: **Gastric intramucosal pH. A better predictor of multi-organ dysfunction and death than oxygen-derived variables in patients with sepsis.** *Chest* 1993, **104**:225-229.
5. Maynard N, Bihari D, Beale R, Smithies M, Baldock G, Mason R, McColl I: **Assessment of splanchnic oxygenation by gastric tonometry in patients with acute circulatory failure.** *JAMA* 1993, **270**:1203-1210.
6. Schlichtig R, Metha N, Gayowski TJP: **Tissue-arterial PCO₂ difference is a better marker of ischemia than intramural pH (pHi) or arterial pH-pHi difference.** *J Crit Care* 1996, **11**:51-56.
7. Schlichtig R, Bowles SA: **Distinguishing between aerobic and anaerobic appearance of dissolved CO₂ in intestine during low flow.** *J Appl Physiol* 1994, **76**:2443-2451.
8. Taylor DE, Gutierrez G: **Tonometry. A review of clinical studies.** *Crit Care Clin* 1996, **12**:1007-1018.
9. Kolkman JJ, Steverink PJGM, Groeneveld ABJ, Meuwissen SGM: **Characteristics of time-dependent PCO₂ tonometry in the normal human stomach.** *Br J Anaesth* 1998, **81**:669-675.
10. Giovannini I, Chiarla C, Boldrini G, Castagneto M: **Calculation of venoarterial CO₂ concentration difference.** *J Appl Physiol* 1993, **74**:959-964.
11. Connett RJ, Honig CR, Gayeski TE, Brooks GA: **Defining hypoxia: a systems view of VO₂, glycolysis, energetics and intracellular PO₂.** *J Appl Physiol* 1990, **68**:833-842.
12. Vincent JL, Creteur J: **Gastric mucosal pH is definitely obsolete – please tell us more about gastric mucosal PCO₂.** *Crit Care Med* 1998, **26**:1479-1481.
13. Fiddian-Green RG: **Gastric intramucosal pH, tissue oxygenation and acid-base status.** *Br J Anaesth* 1995, **74**:591-606.
14. Puyana JC, Soller BR, Parikh B, Heard SO: **Directly measured tissue pH is an earlier indicator of splanchnic acidosis than tonometric parameters during hemorrhagic shock in swine.** *Crit Care Med* 2000, **28**:2557-2562.
15. Adroque HJ, Rashad MN, Gorin AB, Yacoub J, Madias NE: **Assessing acid-base status in circulatory failure. Differences between arterial and central venous blood.** *N Engl J Med* 1989, **320**:1312-1316.
16. Grundler W, Weil MH, Rackow EC: **Arteriovenous carbon dioxide and pH gradients during cardiac arrest.** *Circulation* 1986, **74**:1071-1074.
17. Dubin A, Silva C, Calvo G, Valli J, Fariña O, Estenssoro E, Mordujovich P: **End-tidal CO₂ pressure in the monitoring of cardiac output during canine hemorrhagic shock.** *J Crit Care* 1990, **5**: 42-46.
18. Vallet B, Tavernier V, Lund N: **Assessment of tissue oxygenation in the critically ill.** In *Yearbook of intensive care and emergency medicine*. Edited by Vincent JL. Berlin: Springer-Verlag; 2000:715-725.
19. Manny J, Manny N, Lelcuk S, Alexander F, Feingold H, Kobzik L, Valeri CR, Shepro D, Hechtman HB: **Pulmonary and systemic consequences of localized acid aspiration.** *Surg Gynecol Obstet* 1986, **162**:259-267.
20. St John RC, Mizer LA, Kindt GC, Weisbrode SE, Moore SA, Dorinsky PM: **Acid aspiration-induced acute lung injury causes leukocyte-dependent systemic organ injury.** *J Appl Physiol* 1993, **74**:1994-2003.
21. Crouser ED, Julian MW, Weisbrode SE, Dorinsky PM: **Acid aspiration results in ileal injury without altering ileal VO₂/DO₂ relationships.** *Am J Respir Crit Care Med* 1996, **153**:1965-1971.
22. Schertel ER, Pratt JW, Schaeffer SL, Valentine AK, McCreary MR, Myerowitz PD: **Effects of acid-induced lung injury on left ventricular function.** *Surgery* 1996, **119**:81-88.
23. Cain SM: **Oxygen delivery and uptake in dogs during anemic and hypoxic hypoxia.** *J Appl Physiol* 1977, **42**:228-234.
24. Cain SM: **pH effects on lactate and excess lactate in relation to O₂ deficit in hypoxic dogs.** *J Appl Physiol* 1977, **42**:44-49.
25. Jakob SM, Kosonen P, Ruokonen E, Parviainen I, Takala J: **The Haldane effect – an alternative explanation for increasing gastric mucosal PCO₂ gradients?** *Br J Anaesth* 1999, **83**:740-746.
26. Dubin A, Estenssoro E, Murias G, Canales H, Sottile P, Badie J, Barán M, Pálizas F, Laporte M, Rivas Diaz M: **Effects of hemorrhage on gastrointestinal oxygenation.** *Intensive Care Med* 2001, **27**:1931-1936.
27. Nevière R, Chagnon J-L, Teboul J-L, Vallet B, Wattel FB: **Small intestine intramucosal PCO₂ and microvascular blood flow during hypoxic and ischemic hypoxia.** *Crit Care Med* 2002, **30**: 379-384.
28. Vallet B, Teboul JL, Cain S, Curtis S: **Venoarterial CO₂ difference during regional ischemic or hypoxic hypoxia.** *J Appl Physiol* 2000, **89**:1317-1321.
29. Cohen IL, Sheik FM, Perkins RJ, Feustel PJ, Foster ED: **Effects of hemorrhagic shock and reperfusion on the respiratory quotient in swine.** *Crit Care Med* 1995, **23**:545-552.
30. Dubin A, Murias G, Estenssoro E, Canales H, Sottile P, Badie J, Barán M, Rossi S, Laporte M, Pálizas F, Giampieri J, Mediavilla D, Vacca E, Botta D: **End-tidal CO₂ pressure determinants during hemorrhagic shock.** *Intensive Care Med* 2000, **26**:1619-1623.
31. Nielsen VG, Tan S, Baird MS, McCammon AT, Parks DA: **Gastric intramucosal pH and multiple organ failure: impact of ischemia-reperfusion and xanthine-oxidase.** *Crit Care Med* 1996, **24**:1339-1344.
32. VanderMeer TJ, Wang H, Fink MP: **Endotoxemia causes ileal mucosal acidosis in the absence of mucosal hypoxia in a normodynamic porcine model of septic shock.** *Crit Care Med* 1995, **23**:1217-1226.
33. Tugtekin IF, Radermacher P, Theisen M, Matejovic M, Stehr A, Ploner F, Matura K, Ince C, Georgieff M, Trager K: **Increased ileal-mucosal-arterial PCO₂ gap is associated with impaired villus microcirculation in endotoxic pigs.** *Intensive Care Med* 2001, **27**:757-766.