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

Arnaldo Dubin[1], Gastón Murias[2], Elisa Estenssoro[3], Héctor Canales[4], Julio Badie[5], Mario Pozo[2], Juan P Sottile[4], Marcelo Barán[6], Fernando Pálizas[7] and Mercedes Laporte[8]

[1]Principal Investigator, Cátedra de Farmacologia, Facultad de Ciencias Médicas, Universidad Nacional de La Plata, Argentina
[2]Research Fellow, Cátedra de Farmacología, Facultad de Ciencias Médicas, Universidad Nacional de La Plata, Argentina
[3]Medical Director, Servicio de Terapia Intensiva, Hospital San Martín de La Plata, Argentina
[4]Staff physician, Servicio de Terapia Intensiva, Hospital San Martín de La Plata, Argentina
[5]Research Fellow, Cátedra de Farmacología, Facultad de Ciencias Médicas, Universidad Nacional de La Plata, Argentina
[6]Medical Director, Unidad de Transplante Renal, CRAI Sur, CUCAIBA, Argentina
[7]Medical Director, Servicio de Terapia Intensiva, Clínica Bazterrica de Buenos Aires, Argentina
[8]Director, Servicio de Laboratorio, Hospital San Martín de La Plata, Argentina

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

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Abstract

Introduction An elevation in intramucosal–arterial P_{CO_2} gradient (ΔP_{CO_2}) could be determined either by tissue hypoxia or by reduced blood flow. Our hypothesis was that in hypoxic hypoxia with preserved blood flow, ΔP_{CO_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 P_{CO_2} by tonometry. Systemic and intestinal oxygen transport and consumption were calculated, as was ΔP_{CO_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. ΔP_{CO_2} increased in the IH group (12 ± 10 [mean ± 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, ΔP_{CO_2} was not modified during dependence of oxygen uptake on oxygen transport. These results suggest that ΔP_{CO_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 gastrointestinal 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; D_{O_2} = oxygen transport; ΔP_{CO_2} = intramucosal–arterial P_{CO_2} gradient; F_iO_2 = fraction of inspired oxygen; HH = hypoxic hypoxia; IH = ischemic hypoxia; pH_i = intramucosal pH; V_{O_2} = oxygen uptake.

arterial P_{CO_2} gradient (ΔP_{CO_2}) has been claimed to be a better marker of gastrointestinal mucosal state of oxygenation [6]. P_{CO_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 P_{CO_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 (V_{O_2}) were correlated in ischemia, in hypoxemia, and in a combination of both. However, in hypoxemic experiments, neither V_{O_2} nor pH_i fell. Hence, the value of tonometry in hypoxemia remains uncertain. If a rise in ΔP_{CO_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 ΔP_{CO_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 ± 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 gastrostomy 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 P_{O_2}, P_{CO_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 (D_{O_2}, V_{O_2}, intestinal D_{O_2}, and intestinal V_{O_2} respectively) were calculated with standard formulae.

Intramucosal P_{CO_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. P_{CO_2} was measured in the remnant (ABL 30; Radiometer). pH_i and ΔP_{CO_2} were calculated with a correction factor for the equilibration time. Kolkman *et al.* [9] showed that the variability of intramucosal P_{CO_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 P_{CO_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 ± 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

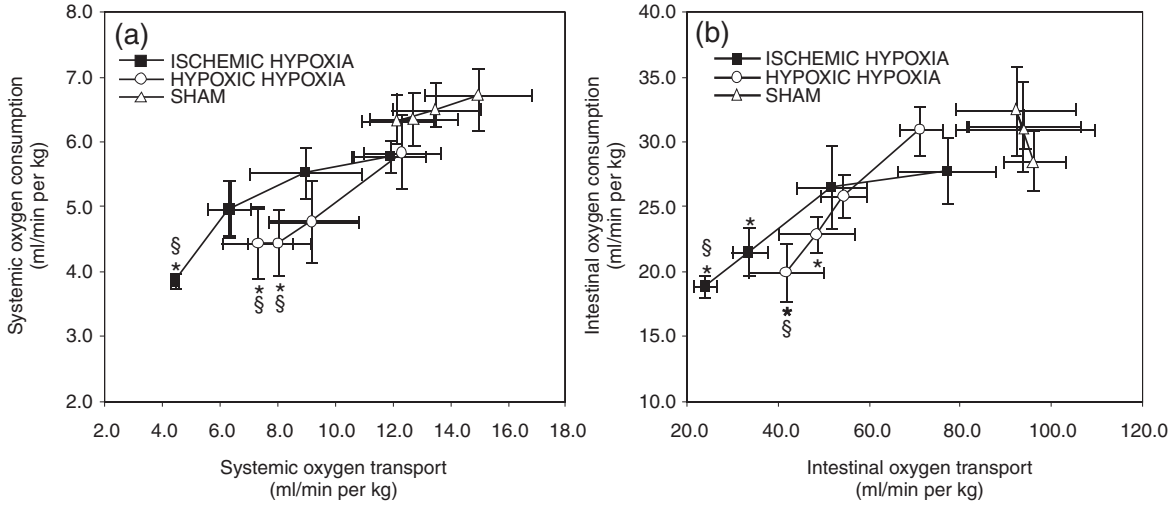
Hemoglobin concentration and arterial, mixed venous, and mesenteric venous blood gases and oxygen saturations in basal conditions and during ischemic hypoxia (HI) and hypoxic hypoxia (HH), and in the sham group

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 P_{CO_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 P_{O_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 P_{CO_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 P_{O_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 P_{CO_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 P_{O_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 D_{O_2} and V_{O_2} in the sham group (Figure 1). In the IH group, supply dependence appeared with critical decreases in CO and superior mesenteric 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



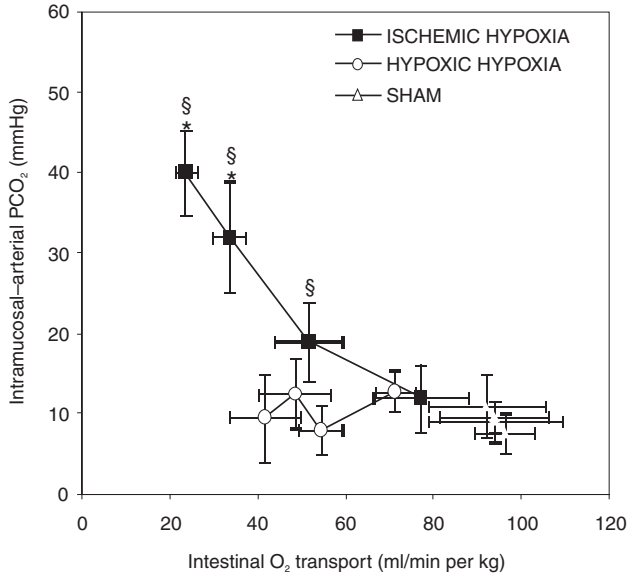
Systemic and intestinal oxygen supply dependence. **(a)** Relationship between systemic oxygen transport and consumption during ischemic and hypoxic hypoxia, and in the sham group. **(b)** Relationship between intestinal oxygen transport and consumption during ischemic and hypoxic hypoxia, and in the sham group. Data are expressed as means ± 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 ΔP_{CO_2} did not increase. In addition, systemic and intestinal venoarterial P_{CO_2} gradients were not modified. CO_2 content differences also did not change (Table 2 and Figure 2). In contrast, in the IH group, ΔP_{CO_2}, systemic and intestinal venoarterial P_{CO_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 P_{CO_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 P_{CO_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 P_{CO_2}, the variable actually measured by the tonometer, and ΔP_{CO_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 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

Figure 2



Relationship between intestinal oxygen transport and intramucosal–arterial P_{CO_2} difference during ischemic and hypoxic hypoxia, and in the sham group. Data are expressed as means ± SEM. * $P < 0.05$ versus basal intramucosal–arterial P_{CO_2} difference. § $P < 0.05$ versus hypoxic hypoxia and sham group.

Table 2

CO_2 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 P_{CO_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 P_{CO_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 P_{CO_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 P_{CO_2} [6,14]. In our experiments, pH_i fell progressively during hydrochloric acid-induced lung injury and decreased D_{O_2}, reflecting ongoing systemic respiratory and metabolic acidosis. However, ΔP_{CO_2} remained unchanged.

Another issue that has been discussed extensively is the relative impact on mucosal P_{CO_2} of anaerobic production of CO_2 in comparison with decreased washout of aerobically generated CO_2 during low flow states. Many investigators [15–17] have ascribed increased P_{CO_2} found in shock states to continuing aerobic CO_2 production with decreased elimination; that is, to 'respiratory acidosis'. However, Schlichtig and Bowles [7] showed evidence supporting the role of intramucosal P_{CO_2} as a marker of dysoxia in extreme hypoperfusion, when V_{O_2} falls. In a dog model of cardiac tamponade, they demonstrated that mucosal P_{CO_2} could rise because of anaerobic CO_2 production below the critical D_{O_2}. These conclusions were drawn by using the Dill nomogram, which can theoretically detect anaerobic CO_2 production from a comparison of the measured ($\%HbO_{2,v}$) and calculated ($\%HbO_{2,v}^{Dill}$) venous oxyhemoglobin, within a given venous P_{CO_2} value. Because venous P_{CO_2} is considered to be representative of tissue P_{CO_2}, Schlichtig and Bowles made the calculation with its intestinal equivalent, intramucosal P_{CO_2}. If $\%HbO_{2,v}^{Dill}$ is lower than the measured $\%HbO_{2,v}$, anaerobic production of CO_2 might be assumed. Similar values would represent aerobic CO_2 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 V_{O_2} 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 D_{O_2} was not attained, and intestinal V_{O_2} 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 P_{O_2} 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 D_{O_2}, but systemic and intestinal blood flow were preserved and hemoglobin concentration increased. Despite

the increase in systemic and intestinal oxygen extraction, systemic and intestinal V_{O_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 P_{CO_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 P_{CO_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 P_{CO_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 P_{CO_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. ΔP_{CO_2} remained stable, although there were signs of anaerobic metabolism. Systemic and venoarterial P_{CO_2} differences also remained unchanged. Conversely, during supply dependence of V_{O_2} induced by hemorrhage, ΔP_{CO_2} and systemic and intestinal venoarterial P_{CO_2} differences widened, as well as the respective ΔP_{CO_2} content differences. Moreover, these parameters increased before any change in V_{O_2}, as we have described previously [26]. These results suggest that, at least in our experiments, tissue perfusion is a key determinant of increased ΔP_{CO_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, ΔP_{CO_2} increased to 60 mmHg. In HH, ΔP_{CO_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 P_{CO_2} indicated local CO_2 generation. However, in the two previous stages of reduced F_{iO_2} there was supply dependence, and ΔP_{CO_2} remained unchanged. In our HH model, ΔP_{CO_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 only global microvascular blood flow changes can be assessed by laser Doppler flowmetry. Nevertheless, both studies show that ΔP_{CO_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 P_{CO_2} difference during critical IH or HH in isolated hindlimb. This gradient increases in ischemia and is preserved in hypoxia.

Key messages

- The intramucosal–arterial P_{CO_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 P_{CO_2} gradients
- Tonometry seems to be a useful method for monitoring perfusion, with limited value in detecting anaerobic metabolism when flow is preserved

Venoarterial and intramucosal–arterial P_{CO_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 V_{CO_2} relative to V_{O_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 ΔP_{CO_2} fails to mirror intestinal tissue dysoxia. Our findings also suggest that blood flow might be the main determinant of ΔP_{CO_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.

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