Intensive Care Med (2002) 28:609–615
DOI 10.1007/s00134-002-1259-9

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Effects of acid-base abnormalities on blood capacity of transporting CO_2: adverse effect of metabolic acidosis

Received: 16 January 2001
Accepted: 5 February 2002
Published online: 12 April 2002

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Abstract *Objective:* To investigate the effects of some acid-base abnormalities on blood capacity of transporting CO_2. *Design:* Prospective study. *Setting:* General and Cardiosurgical ICUs of a University hospital. *Patients:* Six groups of ten patients characterized by: metabolic alkalosis; respiratory alkalosis; absence of acid-base abnormalities; metabolic acidosis; uncompensated respiratory acidosis; and compensated respiratory acidosis.
Measurements and results: The CO_2 dissociation curve, Haldane effect, and the ratio Ra-v between Ca-vCO_2 and Pa-vCO_2 were calculated from arterial and mixed-venous blood gas analyses. The CO_2 dissociation curve was shifted upwards by metabolic alkalosis and compensated respiratory acidosis and downwards by metabolic acidosis. The slope of the curve was unaffected, but CO_2 transport not due to Haldane effect was significantly lower in respiratory acidosis since the slope was less steep at higher PCO_2 values. In comparison with controls, patients affected by metabolic acidosis showed lower Haldane effect values (0.18±0.15 vs 0.59±0.26 ml of CO_2 per ml of arterial-mixed venous O_2 content difference; P <.05) and Ra-v values (0.43±0.10 vs 0.84±0.17 ml of CO_2 transported by 100 ml of blood per Torr of arterial-mixed venous PCO_2 gradient; P <.05). *Conclusions:* Our findings suggest that acid-base abnormalities, particularly metabolic acidosis, markedly affect blood capacity of transporting CO_2 and may worsen tissue hypercarbia associated with hypoperfusion. However, because of possible errors due to small measurements and the assumptions of the method, in the future definitive clarification will require the construction of original CO_2 dissociation curves for each acid-base abnormality.

Keywords Acid-base abnormalities · Acidosis · Alkalosis · CO_2 · Carbon dioxide · Haldane effect

Introduction

In recent years tonometry has been largely employed for monitoring splanchnic perfusion in critically ill patients [1]. Since ischemic tissues are not only hypoxic, but also hypercapnic [2, 3], an increased gradient between local and arterial PCO_2 has been commonly regarded as an index of hypoperfusion of splanchnic organs (i.e., stomach, intestine, and tongue)[4, 5]. However, it has been recently recognized that changes of blood CO_2 transport capacity – for instance, by changes of Haldane effect [6] – can equally affect arterial-tissue PCO_2 gradients. If CO_2 transport is less effective, a higher arterial-venous PCO_2 difference becomes necessary to avoid CO_2 retention or supranormal perfusion. Consequently, when CO_2 transport is impaired, an abnormal arterial-tissue PCO_2

gradient could be misinterpreted as due to hypoperfusion.

Acid-base abnormalities are frequently observed in critically ill patients and can affect the CO_2 carrying power by influencing the rates at which CO_2 hydrates to bicarbonate and links haemoglobin to form carbaminocompounds [7]; the Haldane effect is also known to vary with changes of blood pH or bicarbonates [8, 9]. The effects of acid-base abnormalities on blood CO_2 carrying power could therefore be of value to explain PCO_2 gradients, but, conversely, have been poorly evaluated in critically ill patients up to the present.

The aim of this study was to investigate the effects of some acid-base abnormalities on blood capacity of transporting CO_2 in a group of critically ill patients.

Material and methods

Fifty consecutive patients admitted to the general and cardiosurgical Intensive Care Units of a University Hospital were enrolled according to the acid-base balance and divided into five subgroups of ten subjects each with metabolic alkalosis (group A), respiratory alkalosis (group B), metabolic acidosis (group D), uncompensated respiratory acidosis (group E), compensated respiratory acidosis (group F). Ten patients that did not show any acid-base abormality were also enrolled to make a control group C. An institutional ad hoc committee approved the protocol and the patients or their relatives gave their informed consent. Patient age, sex, main diagnosis, and criteria of inclusion are reported in Table 1. All the patients were mechanically-ventilated in the control mode and had a pulmonary artery catheter. Criteria of exclusion were: an axillary temperature over 37.5 °C or under 36 °C, bicarbonate or other alkalinizing drugs administered less than 6 h prior to the study, exogenous intoxications affecting acid-base status, and blood carboxyhaemoglobin or methaemoglobin levels higher than 1.5%.

Arterial and mixed venous blood samples were obtained from each patient. Blood was collected with pre-heparinized plastic syringes (Sarstedt, Germany), put in ice-cold water, and immediately analysed for pH, PCO_2, and PO_2 using a Stat Profile Ultra L Haemogasanalyzer at 37 °C (Nova Biomedical, USA) that was located in the Intensive Care Unit. Plasma bicarbonate was calculated by the blood gas analyzer. Blood haemoglobin concentration (Hb), haemoglobin saturation (SO_2), carboxyhaemoglobin, and methaemoglobin were evaluated by a Nova Oxymeter (Nova Biomedical, USA). Whole blood CO_2 content (CCO_2) expressed in millitres of CO_2 per 100 ml of whole blood was not measured, but calculated by Visser equation [10], modified by McHardy [11]:

$$CCO_2 = \left(1 - \frac{0.02924 \times Hb}{(2.244 - 0.422 \times SO_2)(8.74 - pH)}\right) \times 0.0301 \times PCO_2 \left(1 + 10^{pH-6.1}\right) \times 2.226 \quad (1)$$

Values calculated with this method do not significantly differ from values obtained manometrically, showing a regression line close to the identity [12]. The CO_2 dissociation curve equation ($CCO_2 = K * PCO_2^b$) and the Haldane effect (f_H) were calculated according to Loeppky and Coll [12]. Upwards or downwards shifts of the curve were evaluated by $CCO_2(40)$; this value is calculated by the CO_2 dissociation curve equation and corresponds to a PCO_2 value of 40 Torr [9]. The slope of the curve was determined at different PCO_2 values with the first derivate of CCO_2, $d(CCO_2)/d(PCO_2)$. CO_2 transport not due to Haldane effect ($Ca\text{-}vCO_2 - f_H$) was assessed with the CCO_2 difference between the points corresponding

Table 1 Age, sex, general (G-ICU) or cardiosurgical ICU (CS-ICU), and diagnosis of the patients enrolled in this study. Criteria of inclusion were applied on arterial blood

Patient no.	Age	Sex	ICU	Diagnosis
A – Metabolic alkalosis (pH >7.48, PCO_2 >35 Torr)				
1	77	F	G-ICU	Stroke
2	79	F	CS-ICU	Aortic valve replacement
3	71	M	CS-ICU	Aortic valve replacement
4	79	F	CS-ICU	Coronary revascularization
5	53	F	CS-ICU	Mitral vave replacement
6	67	M	G-ICU	Stroke
7	40	M	G-ICU	Measles, pneumonia
8	75	F	G-ICU	Acute respiratory failure
9	81	F	G-ICU	Stroke
10	77	M	G-ICU	Sepsis
B – Respiratory alkalosis (pH >7.48, $PaCO_2$ <32 Torr)				
11	77	F	G-ICU	Stroke
12	27	F	G-ICU	Head trauma
13	72	F	CS-ICU	Mitral valve replacement
14	59	M	G-ICU	Stroke
15	64	M	G-ICU	Cancer of lung, pneumonectomy
16	75	M	G-ICU	Abdominal aorta aneurism
17	69	F	G-ICU	Stroke
18	61	M	G-ICU	Abdominal aorta aneurism
19	63	M	G-ICU	Stroke
20	65	F	G-ICU	Stroke
C – Control group (pH 7.35 – 7.45, $PaCO_2$ 35–45 Torr)				
21	53	F	CS-ICU	Aortic and mitral valve replacement
22	69	M	CS-ICU	Coronary revascularization
23	60	M	CS-ICU	Coronary revascularization
24	63	F	CS-ICU	Coronary revascularization
25	71	M	CS-ICU	Aortic valve replacement
26	62	M	CS-ICU	Coronary revascularization
27	70	F	CS-ICU	Aortic valve replacement
28	56	M	CS-ICU	Coronary revascularization
29	75	M	CS-ICU	Aortic valve replacement
30	66	M	CS-ICU	Coronary revascularization
D – Metabolic acidosis (pH <7.3, PCO_2 <45 Torr)				
31	77	F	G-ICU	Cardiogenic shock
32	67	M	G-ICU	Arterial thrombosis, shock
33	27	F	G-ICU	Thrombocitopenia, septic shock
34	62	F	G-ICU	Stroke, renal failure
35	77	M	G-ICU	Pneumonia, septic shock
36	74	F	G-ICU	Acute leukemia, septic shock
37	79	F	G-ICU	Septic shock, renal failure
38	78	M	G-ICU	Colonic neoplasm, cardiac arrest
39	70	F	G-ICU	Cardiogenic shock
40	69	F	G-ICU	Stroke
E – Uncompensated respiratory acidosis (pH <7.3, $PaCO_2$ >60 Torr)				
41	89	F	G-ICU	Acute respiratory failure
42	27	F	G-ICU	Hodgkin disease, ARDS
43	72	M	G-ICU	Acute myocardial infarction
44	62	F	G-ICU	COPD
45	75	M	G-ICU	COPD
46	61	M	G-ICU	COPD
47	41	F	G-ICU	Peritonitis, septic shock
48	59	F	G-ICU	Oesophago-pleural fistula
49	62	M	G-ICU	COPD
50	61	M	G-ICU	Acute respiratory failure

Table 1 (continued)

Patient no.	Age	Sex	ICU	Diagnosis
F – Compensated respiratory acidosis (pH >7.3, $PaCO_2$ >60 Torr)				
51	70	F	G-ICU	COPD
52	75	M	G-ICU	COPD
53	62	F	G-ICU	COPD
54	75	M	G-ICU	COPD
55	60	M	G-ICU	COPD
56	76	M	G-ICU	COPD
57	42	M	G-ICU	Bulbar neoplasm, respiratory failure
58	64	F	G-ICU	COPD
59	68	M	G-ICU	COPD
60	56	M	G-ICU	COPD

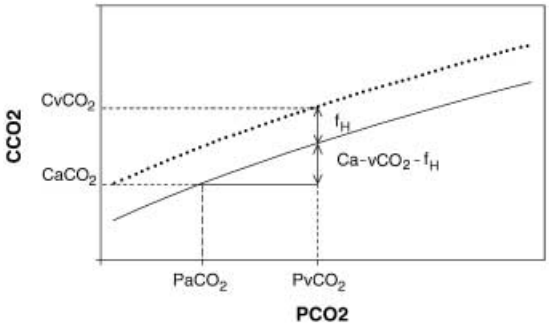

Fig. 1 Components of the arterial-venous CCO_2 difference (Ca-vCO_2). Arterial and venous (*dotted line*) CO_2 dissociation curves. The arterial-venous CCO_2 difference (Ca-vCO_2) is partly linked to Haldane effect (f_H) and partly to the arterial-venous PCO_2 difference (Ca-vCO_2 – f_H)

to $PaCO_2$ and $PvCO_2$ on the arterial CO_2 dissociation curve (Fig. 1). Finally the global blood capacity for transporting CO_2 was evaluated with the ratio Ra-v. This index [13] is the ratio between CCO_2 and PCO_2 arterial-mixed venous differences (Ca-vCO_2/Pa-vCO_2) and has been used to evaluate the amount of CO_2 transported by the blood in relation with the arterial-venous gradient of PCO_2.

All values are reported as mean (standard deviation). Two-way ANOVA (groups/arterial-venous sampling) for repeated measurements was employed for statistical analysis of parameters measured or calculated in arterial and venous blood; a one-way ANOVA for repeated measurements was employed for statistical analysis of arterial – mixed venous differences and f_H. Post hoc comparisons were performed with Student-Newman-Keuls (SNK) test. ANOVA and SNK test concerning pH were applied on correspondent hydrogen ion concentrations. *P* values <0.05 were considered as statistically significant.

Results

Table 2 shows data on Hb and arterial and mixed venous pH, PCO_2, CCO_2, bicarbonate, and SO_2. Differences among groups concerning pH, pCO_2, CCO_2, and bicarbonate were related to the admission criteria. Hb and

Table 2 Arterial and venous pH, PCO_2, CCO_2, SO_2, bicarbonate, and hemoglobin (Hb). Data are expressed as means (standard deviations). ANOVA and SNK test were not applied to pH, but were applied to hydrogen ion concentration. ANOVA among groups: **P* <0.001. Significant post hoc comparisons by SNK test (*P* <0.05) are also reported

	PH*		PCO_2 (Torr)*		CCO_2 (ml)*		SO_2 (%)		HCO_3^-(mM/l)*		Hb (g/l)
	Arterial	Venous	Arterial	Venous	Arterial	Venous	Arterial	Venous	Arterial	Venous	
Alkalosis											
A-metabolic	7.51 (.01)	7.48 (.02)	37.2 (2.1)	43.2 (1.9)	56.5 (3.7)	61.9 (3.4)	98.4 (2.5)	70.8 (9.2)	30.3 (1.6)	32.3 (1.0)	11.6 (2.2)
SNK test	A vs C D E F		A vs E F		A vs B C D F				A vs B C D F		
B-respiratory	7.52 (.03)	7.48 (.03)	28.4 (2.4)	32.7 (5.1)	44.6 (3.6)	47.8 (5.6)	98.1 (2.0)	70.4 (11.4)	23.6 (2.2)	24.7 (2.7)	10.7 (1.9)
SNK test	B vs C D E F		B vs E F		B vs A D E F				B vs A D E F		
Controls	7.42 (.03)	7.39 (.04)	38.8 (2.8)	45.2 (4.1)	48.6 (2.3)	53.9 (2.9)	98.2 (1.8)	67.6 (4.8)	25.1 (1.1)	27.4 (1.5)	11.9 (1.3)
SNK test	C vs A B D E		C vs E F		C vs A D E F				C vs A D E F		
Acidosis											
D-metabolic	7.18 (.09)	7.13 (.08)	39.2 (11.3)	47.0 (13.1)	29.4 (6.1)	32.7 (6.6)	96.9 (2.8)	74.3 (11.9)	14.8(3.0)	16.(3.2)	10.4 (2.6)
SNK test	D vs A B C E F		D vs E F		D vs A B C E F				D vs A B C E F		
E-resp.uncomp	7.20 (.07)	7.18 (.06)	81.6 (24.1)	86.6 (24.6)	63.6 (14.2)	65.7 (14.6)	91.6 (8.6)	64.1 (15.4)	31.(6.6)	31.(6.8)	11.6 (1.9
SNK test	E vs A B C D F		E vs A B C D		E vs B C D F				E vs B C D F		
F-resp comp	7.38 (.04)	7.35 (.04)	72.4 (10.0)	79.2 (12.0)	82.8 (7.0)	86.0 (8.6)	96.1 (3.1)	69.2 (14.5)	43.1 (2.9)	44.1 (3.6)	12.9 (3.1)
SNK test	F vs A B D E		F vs A B C D		F vs A B C D E				F vs A B C D E		

Table 3 Parameters describing CO_2 transport in the six groups of patients. Data are expressed as means (standard deviations). $CCO_2(40)$ is CCO_2 at PCO_2=40 Torr, calculated by the equation of the CO_2 dissociation curve; Ra-v is the ratio Ca-vCO_2/Pa-vCO_2; Ca-vCO_2 – f_H is the theoretical value of Ca-vCO_2 without the Haldane effect, calculated by arterial CO_2 dissociation curve and is also reported per Torr of Pa-vCO_2; finally, the Haldane effect is reported as millilitres of CO_2 per 100 ml of blood and millilitres of CO_2 per millilitre of arterial venous O_2 content difference. ANOVA among groups: * P <0.05; ** P <0.01; *** P <0.001 Comparison with controls by SNK test: **** P <0.05

	$CCO_2(40)$ ml (***)		Ra-v ml/Torr*	Pa-vCO_2 Torr	Ca-vCO_2 ml*	Ca-vCO_2 – f_H		Haldane factor (f_H)	
	Arterial	Venous				ml	ml/Torr*	ml% (**)	ml/Ca-vO_2**
A (n = 10) Metabolic alkalosis	59 (3) ****	61 (3) ****	.84 (.27)	6.2 (2.2)	5.5 (3.0)	2.6 (.9)	.41 (.04)	2.9 (2.2)	.71 (.42)
B (n = 10) Respir. alkalosis	50 (3)	50 (4)	.67 (.16)	4.6 (2.8)	3.3 (2.9)	2.2 (1.3)	.48 (.02)	1.1 (1.0)	.34 (.31)
C (n = 10) Controls	49 (2)	52 (2)	.84 (.17)	6.4 (2.0)	5.3 (1.6)	2.5 (.7)	.40 (.03)	2.8 (1.1)	.59 (.26)
D (n = 10) Metabolic acidosis	30 (3)****	30 (3)****	.43 (.10)****	7.9 (4.2)	3.3 (1.7)	3.0 (1.5)	.39 (.06)	.6 (.4)****	.18 (.15)****
E (n = 10) Uncomp. respir. acidosis	51 (9)	52 (10)	.46 (.21)	5.0 (1.9)	2.1 (1.0)****	1.3 (.6)	.27 (.06)****	.8 (.7)****	.22 (.19)
F (n = 10) Comp. respir. acidosis	72 (7)****	73 (8)****	.45 (.19)	6.8 (3.9)	3.3 (2.7)	1.7 (.8)	.27 (.04)****	1.6 (.3)	.38 (.31)

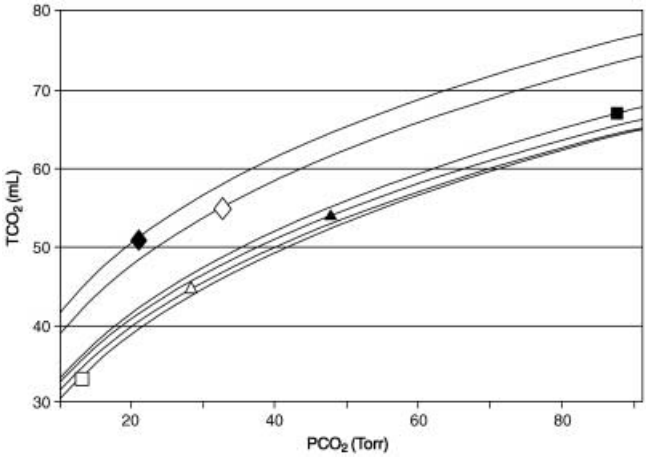

Fig. 2 CO_2 dissociation curves in *group A* – metabolic alkalosis (arterial ◇; venous ◆), *group B* – respiratory alkalosis (arterial △; venous ▲), and *group C* – controls (arterial □; venous ■)

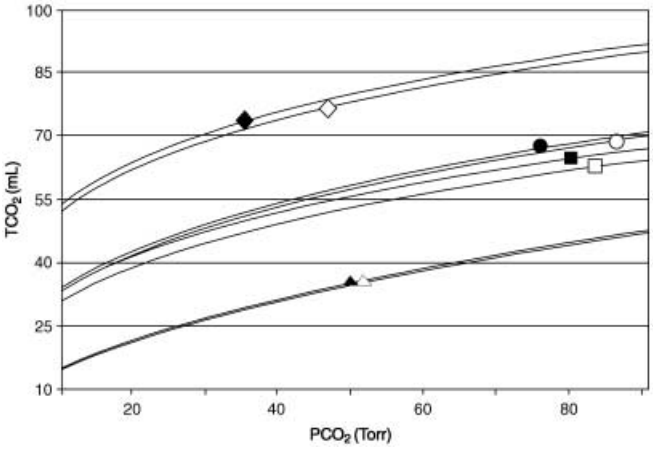

Fig. 3 CO_2 dissociation curves in *group C* – controls (arterial □; venous ■), *group D* – metabolic acidosis (arterial △; venous ▲), *group E* – uncompensated respiratory acidosis (arterial ○; venous ●), and *group F* – compensated respiratory acidosis (arterial ◇; venous ◆)

SO_2 did not differ among groups. In group D, metabolic acidosis was caused by gain of acid since anion gap (anion gap = Na – Cl – HCO_3^-) was 17.9±4.7 mEq/l in arterial blood due to renal failure and/or tissue hypoperfusion in all patients.

The parameters describing CO_2 transport are given in Table 3. In all the groups of patients affected by acid-base disturbances the mean value of Ra-v, a global index of blood capacity for transporting CO_2, was lower than in controls; the difference was more pronounced in patients affected by metabolic acidosis (group D) and by uncompensated and compensated respiratory acidosis (groups E and F); in these groups Ra-v mean values were about half of those observed in controls. The difference was statistically significant only in patients affected by metabolic acidosis.

Figures 2 and 3 show different conditions of the CO_2 dissociation curve; $CCO_2(40)$ values are given in Ta-

Table 4 First derivates of CCO_2, $d(CCO_2)/d(PCO_2)$, at different PCO_2 levels. The values represent the changes of CCO_2 (ml) per Torr of PCO_2 and describe the slope of the CO_2 dissociation curve. Data are shown as means (standard deviations). ANOVA did not demonstrate significant differences

PCO_2 (Torr)	20	30	40	50	60	70	80	90
A – Metabolic alkalosis	.68 (.04)	.51 (.04)	.41 (.03)	.35 (.03)	.31 (.03)	.28 (.03)	.25 (.03)	.23 (.03)
B – Respiratory alkalosis	.63 (.04)	.48 (.03)	.40 (.03)	.34 (.02)	.30 (.02)	.27 (.02)	.25 (.02)	.23 (.02)
C – Controls	.65 (.03)	.50 (.02)	.41 (.02)	.35 (.02)	.31 (.02)	.28 (.02)	.26 (.02)	.24 (.02)
D – Metabolic acidosis	.55 (.04)	.45 (.04)	.39 (.04)	.35 (.04)	.32 (.04)	.30 (.03)	.28 (.03)	.26 (.03)
E – Uncomp. respir. acidosis	.66 (.04)	.50 (.03)	.42 (.02)	.36 (.02)	.32 (.02)	.29 (.02)	.26 (.02)	.24 (.04)
F – Comp. respir. acidosis	.73 (.06)	.54 (.05)	.43 (.05)	.37 (.05)	.32 (.04)	.28 (.04)	.26 (.04)	.24 (.04)

ble 3. In comparison with group C, the curves of group D (metabolic acidosis) were significantly shifted downwards ($CCO_2(40)$ lower than in group C), while the curves of groups A (metabolic alkalosis) and F (compensated respiratory acidosis) were shifted upwards ($CCO_2(40)$ higher than in group C). By contrast, the slope of CO_2 dissociation curve was poorly affected by acid-base abnormalities since the first derivate $dCCO_2/dPCO_2$ at different values of PCO_2 (Table 4) was not significantly different among groups. CO_2 transport unrelated to Haldane effect ($Ca\text{-}vCO_2 - f_H$; Table 3) clearly depends on the slope of the portion of CO_2 dissociation curve on which patient blood moves. Therefore this form of CO_2 transport was less effective in groups E and F (uncompensated and compensated respiratory acidosis), which were characterized by the presence of hypercarbia.

The Haldane effect can be appreciated graphically in Figs. 2 and 3. The wider the interval between arterial and venous curves, the larger the effect. Values are given in Table 3. In all groups but A (metabolic alkalosis) mean values were lower than in controls. The ANOVA was highly significant and the SNK test demonstrated that the Haldane effect was significantly lower in groups D and E (metabolic and uncompensated respiratory acidosis) than in group C. However, when f_H – i.e., the Haldane factor expressed as milliltres of CO_2 per milliltres of arterial-venous O_2 content difference – was taken into account, only group D showed significantly lower values than group C.

Discussion

Although the relationship between acid-base status and Haldane effect has been known for a long time [8, 9], the influence of acid-base disorders on CO_2 transport has usually been poorly understood in critical care patient management, probably because of the lack of a global index of blood capacity of transporting CO_2. In order to evaluate CO_2 transport from tissues to alveoli, Bidani and Coll calculated the transfer capacity for CO_2, i.e., the ratio between CO_2 output and alveolar-mixed venous PCO_2 difference, and the transfer coefficient KCO_2, which represents the transfer capacity for CO_2 divided by cardiac output [14, 15]. However, these indices are not specific to blood capacity of transporting CO_2, since they also depend on respiratory and circulatory function. By contrast, Ra-v ratio is only indicative of blood capacity of transporting CO_2 and is easily computed from arterial and mixed venous haemogasanalysis data. Since Ra-v partly reflects the Haldane effect, it should be calculated on mixed venous blood values, although central venous blood could also probably be acceptable for clinical purposes. Indeed the processes involved in blood CO_2 and pH balance take very little time [15] and in most cases central venous haemoglobin saturation adequately reflects that of the mixed venous blood [16, 17]. However, 95% confidence intervals in predicting mixed venous SO_2 from central venous SO_2 values can be wide [18]. Ra-v calculated from central venous blood should therefore be evaluated together with the Haldane effect (expressed as milliltres of CO_2 per millilitres of arterial-venous O_2 content difference).

This study confirms that acid-base abnormalities can impair blood capacity of transporting CO_2. The highest mean value of Ra-v was observed in controls and in patients affected by metabolic alkalosis; all the other groups showed lower mean Ra-v values. Particularly, the blood of patients affected by metabolic or respiratory acidosis transported about half the amount of CO_2 transported by the blood of controls. The global capacity of transporting CO_2 reflected by Ra-v is affected by three major aspects: a) the shape of CO_2 dissociation curve; b) the PCO_2 values of arterial and mixed venous blood; and c) the magnitude of the Haldane effect.

The CO_2 dissociation curve represents the relationship between blood PCO_2 and CCO_2; $CCO_2(40)$ is the CCO_2 value at a PCO_2 of 40 Torr and has been used to point out differences among curves [9]. Our data clearly show that the CO_2 dissociation curve is shifted upwards by metabolic alkalosis and downwards by metabolic acidosis; in other words, at the same value of PCO_2, the blood of patients affected by metabolic alkalosis contains a far larger amount of CO_2 than the blood of patients affected by metabolic acidosis. This finding is explained by the infuence of hydrogen ion concentration on the dissociation of haemoglobin $HbNH_3^+$ and $HbNH_2$

groups; this affects both CO_2 hydration to bicarbonate and carbamino-bound CO_2 formation [19]. Very high CCO_2 values were observed in compensated respiratory acidosis. In this condition the increase of hydrogen ion concentration caused by hypercapnia was normalized by the increased renal excretion of hydrogen ions. These findings are consistent with the positive relationship between whole blood base excess and $TCO_2(40)$ described by Loeppky and Coll [9].

Upwards and downwards shifts of the CO_2 dissociation curve do not necessarily affect blood capacity of transporting CO_2. The CO_2 transport not linked to the Haldane effect depends on arterial-mixed venous PCO_2 gradient and on the slope of CO_2 dissociation curve rather than on the height of the curve; the steeper the curve, the larger the arterial-venous CO_2 content difference. Acid-base abnormalities did not affect the slope since CCO_2 derivates did not differ significantly among the groups. Differences in CO_2 transport not linked to the Haldane effect were mainly related to the presence of hypo- or hypercarbia. The CO_2 dissociation curve becomes less steep at higher PCO_2 levels. Related to this, low PCO_2 levels made CO_2 transport more effective in comparison with high PCO_2 levels.

The Haldane effect plays a major role in CO_2 transport. It originates from the increased buffer capacity of deoxyhaemoglobin in comparison with oxyhaemoglobin; as a consequence, venous blood carries a larger amount of CO_2 than arterial blood would at the same PCO_2 value. This explains the lack of coincidence of arterial and venous CO_2 dissociation curves. The influence of acid-base balance on Haldane effect is complex, partly because the magnitude of the effect can be actually expressed as the difference of CCO_2 (ΔCCO_2) or of pH (ΔpH) consequent to haemoglobin deoxygenation. An inverse relationship has been described between blood hydrogen ions and ΔCCO_2; in other words acidosis decreases the effect of haemoglobin deoxygenation on blood CO_2 content [19]. Conversely, a positive relationship exists between ΔpH and blood hydrogen ions [20]. In addition, PCO_2 affects the Haldane effect: hypercarbia increases ΔCCO_2 slightly [19] and decreases ΔpH [20]. The data collected in this study are consistent with these relationships. The Haldane effect was significantly decreased in the presence of metabolic acidosis. This may explain the Ra-v decrease observed in patients affected by metabolic acidosis. In patients affected by uncompensated respiratory acidosis the Haldane effect was less decreased, possibly because of the presence of hypercarbia.

It is well-known that derived values are characterized by a larger risk of error than measured values since they sum the errors from all the parameters employed for the calculation. In this study we used the methodology of Loeppky et al. [12] to calculate CCO_2 values, CO_2 dissociation curves, and f_H. This method enables obtaining these calculated values from simple parameters measured by arterial and venous haemogasanalysis and oximetry. However, apart from the potentially very large influence of small measurement or parameter errors in the equations employed, the application of the method to critically ill patients has important limits. First, the curves are standardized for only two specific populations (normal healthy men at rest and at exercise; patients with severe chronic disease). Second, 2,3 DPG is not measured. Third, there is a considerable range in confidence intervals for f_H. Therefore, our results need to be confirmed in the future for each of the acid-base disorders by the construction of original curves obtained through direct measurement of CCO_2 across a range of PCO_2 values.

In conclusion, our findings suggest that acid-base abnormalities, particularly metabolic acidosis, can markedly decrease blood capacity of transporting CO_2. Impaired blood CO_2 transport requires that either blood flow or arterial-mixed venous PCO_2 gradient increase in order to avoid CO_2 retention. In both cases increased cardiac or respiratory work could negatively affect the patient; alternatively tissue hypercapnia that characterizes respiratory failure and low output states [2, 3, 21, 22, 23] can worsen. Our data also suggest that an increased gradient between arterial and tissue PCO_2 can result from acid-base abnormalities even in the absence of hypoperfusion. In this case Ra-v calculation could possibly unveil impaired CO_2 transport and integrate data from gastric, intestinal, or tongue tonometry. Finally, in transferring our data to clinical practice, some limitations of this study concerning the assumptions of the method should be kept in mind; future, definitive validation of the effects of acid-base abnormalities on blood CO_2 transport will require the construction of original CO_2 dissociation curves for each acid-base abnormality.

Appendix

The equation of the CO_2 dissociation curve for arterial and mixed venous blood were as follows:

A. Metabolic alkalosis: a.b. $CaCO_2 = 20.26 \times PaCO_2^{.2879}$, m.v.b. $CvCO_2 = 22.34 \times PvCO_2^{.2747}$
B. Respiratory alkalosis: a.b. $CaCO_2 = 15.38 \times PaCO_2^{.3201}$, m.v.b. $CvCO_2 = 16.09 \times PvCO_2^{.3133}$
C. Controls: a.b. $CaCO_2 = 14.38 \times PaCO_2^{.3346}$, m.v.b. $CvCO_2 = 16.19 \times PvCO_2^{.3172}$
D. Metabolic acidosis: a.b. $CaCO_2 = 4.41 \times PaCO_2^{.5286}$, m.v.b. $CvCO_2 = 4.58 \times PvCO_2^{.5224}$
E. Uncompensated respiratory acidosis: a.b. $CaCO_2 = 15.33 \times PaCO_2^{.3388}$, m.v.b. $CvCO_2 = 15.85 \times PvCO_2^{.3342}$
F. Compensated respiratory acidosis: a.b. $CaCO_2 = 29.97 \times PaCO_2^{.2455}$, m.v.b. $CvCO_2 = 31.22 \times PvCO_2^{.2412}$

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