Understanding the carbon dioxide gaps

Thomas W.L. Scheeren[a], *Jannis N. Wicke*[a], *and Jean-Louis Teboul*[b,c]

Purpose of review
The current review attempts to demonstrate the value of several forms of carbon dioxide (CO_2) gaps in resuscitation of the critically ill patient as monitor for the adequacy of the circulation, as target for fluid resuscitation and also as predictor for outcome.

Recent findings
Fluid resuscitation is one of the key treatments in many intensive care patients. It remains a challenge in daily practice as both a shortage and an overload in intravascular volume are potentially harmful. Many different approaches have been developed for use as target of fluid resuscitation. CO_2 gaps can be used as surrogate for the adequacy of cardiac output (*CO*) and as marker for tissue perfusion and are therefore a potential target for resuscitation. CO_2 gaps are easily measured via point-of-care analysers. We shed light on its potential use as nowadays it is not widely used in clinical practice despite its potential. Many studies were conducted on partial CO_2 pressure differences or CO_2 content (cCO_2) differences either alone, or in combination with other markers for outcome or resuscitation adequacy. Furthermore, some studies deal with CO_2 gap to O_2 gap ratios as target for goal-directed fluid therapy or as marker for outcome.

Summary
CO_2 gap is a sensitive marker of tissue hypoperfusion, with added value over traditional markers of tissue hypoxia in situations in which an oxygen diffusion barrier exists such as in tissue oedema and impaired microcirculation. Venous-to-arterial cCO_2 or partial pressure gaps can be used to evaluate whether attempts to increase *CO* should be made. Considering the potential of the several forms of CO_2 measurements and its ease of use via point-of-care analysers, it is recommendable to implement CO_2 gaps in standard clinical practice.

Keywords
carbon dioxide gradients, cardiac output, central venous oxygen saturation, goal-directed therapy, lactate, septic shock

INTRODUCTION

One of the principles in the critically ill patient is to ensure adequate tissue perfusion of all organ systems. Critically ill patients are at greater risk for organ hypoperfusion than healthy individuals as they have a greater resting energy expenditure and oxygen consumption (VO_2) [1].

A key factor in resuscitation is detecting hypovolemia and treating it consequently. It is essential to guide fluid therapy without creating significant intravascular volume overload. Several approaches to resuscitation have been described to determine outcome in the critically ill. Nevertheless, no consensus is yet made on which approach could be seen as best indicator of the adequacy of the resuscitation. The described approaches include measuring the venous-to-arterial carbon dioxide partial pressure difference ($p_{v-a}CO_2$) or calculating the venous-to-arterial carbon dioxide content difference. These approaches are known as carbon dioxide (CO_2) gaps. This review aims to demonstrate the value of CO_2 gap measurements in daily practice as they can be obtained with point-of-care analysers in a considerable proportion of the intensive care population.

[a]Department of Anaesthesiology, University Medical Centre Groningen, University of Groningen, Groningen, The Netherlands, [b]Hôpitaux universitaires Paris-Sud, Hôpital de Bicêtre, Service de réanimation Médicale and [c]INSERM UMR S_999, Univ Paris-Sud, Paris, France

Correspondence to Thomas W.L. Scheeren, Department of Anaesthesiology, University Medical Centre Groningen, University of Groningen, Hanzeplein 1, PO Box 30 001, 9700 RB Groningen, The Netherlands. Tel: +31 50 361 6161; fax: +31 50 361 3763; e-mail: t.w.l.scheeren@umcg.nl

Curr Opin Crit Care 2018, 24:181–189
DOI:10.1097/MCC.0000000000000493

KEY POINTS

- Venous-to-arterial cCO_2 or partial pressure gaps are markers for the adequacy of *CO*.
- A normal CO_2 gap indicates that *CO* is high enough to wash out CO_2 from peripheral tissue and therefore could be used for further understanding the clinical state of critically ill patients.
- Either partial CO_2 pressure gap or the CO_2 gap to arterio-venous O_2 content difference ratio could be used to guide resuscitation therapy.
- All needed variables are easily measurable in daily practice via point-of-care blood gas analysers.

BASIC PRINCIPLES OF CARBON DIOXIDE GAPS

In the following section, we will describe the basics of CO_2 differences in venous and arterial blood (Tables 1 and 2).

Physiological basics

VO_2 is the difference between arterial and mixed venous oxygen content (cO_2) multiplied by the cardiac output (*CO*). Carbon dioxide production (VCO_2) is the difference between mixed venous and arterial CO_2 content multiplied by the *CO*. When rearranging the formulas of VO_2 and VCO_2, *CO* can be defined as VCO_2 divided by $p_{v-a}CO_2$. Assuming that the VCO_2 is constant and that the changes in CO_2 pressure and content are linearly related, *CO* would be inversely related to the CO_2 gap. This is basically a modification of the Fick principle [2,3]. The corresponding formulas can also be found in Table 2. These theoretical findings were validated in the clinical setting [4,5]. Under normal conditions, partial carbon dioxide pressure (pCO_2) gap ranges from 2 to 5 mmHg (0.3–0.7 kPa).

As CO_2 is approximately 20 times more soluble in blood plasma than oxygen [6], the diffusion from ischemic tissue into the venous effluent of CO_2 is much higher than that of oxygen in states of (relative) tissue hypoperfusion. Thus, the CO_2 gap can be used as a sensitive marker for occult tissue hypoperfusion [7]. Even in situations in which an oxygen diffusion barrier exists (e.g. occluded blood flow or oedema) which leads to a decreased oxygen extraction ratio and an increased oxygen debt, the problem is 'unveiled' due to the higher solubility of CO_2 and therefore an increased $p_{v-a}CO_2$ [8▪▪]. So, the CO_2 gap can be seen as marker of the adequacy of blood flow to remove CO_2 from the tissues rather than a marker of the adequacy of tissue oxygenation.

Table 1. Abbreviations

VO_2: oxygen consumption
VCO_2: carbon dioxide production
pCO_2: partial carbon dioxide pressure
pCO_2 gap: difference of partial pressures of CO_2 in venous and arterial blood gas samples
cCO_2: carbon dioxide content
cCO_2 gap: difference of the CO_2 contents in venous and arterial blood gas samples
cO_2: oxygen content
cO_2 gap: difference of the O_2 contents in arterial and venous blood gas samples
CO: cardiac output
CI: cardiac index
DO_2: oxygen delivery
SOFA: sequential organ failure assessment

Table 2. Calculations

$c_aO_2 = (1.34 \times S_aO_2 \times Hb) + (0.003 \times p_aO_2)$
$c_vO_2 = (1.34 \times S_vO_2 \times Hb) + (0.003 \times p_vO_2)$
$c_{a-v}O_2 = c_aO_2 - c_vO_2$
Plasma $cCO_2 = 2.226 \times S \times$ plasma $pCO_2 \times (1 + 10^{pH-pK'})$
$S = 0.0307 + [0.00057 \times (37 - T)] + [0.00002 \times (37 - T)^2]$
$pK' = 6.086 + 0.042 \times (7.4 - pH) + (38 - T) \times [0.00472 + 0.00139 \times (7.4 - pH)]$
Blood cCO_2 = plasma $cCO_2 \times [1 - 0.0289 \times Hb/(3.352 - 0.456 \times sO_2) \times (8.142 - pH)]$
$p_{v-a}CO_2 = p_vCO_2 - p_aCO_2$
$DO_2 = 10 \times CO \times c_aO_2$
$VO_2 = 10 \times CO \times c_{a-v}O_2$
$VCO_2 = 10 \times CO \times c_{v-a}CO_2$
$O_2ER = (c_aO_2 - c_vO_2)/c_aO_2$

$c_{a-v}O_2$, arteriovenous oxygen content difference; cCO_2, carbon dioxide content; *CO*, cardiac output; DO_2, oxygen delivery; Hb, haemoglobin; O_2ER, oxygen extraction rate; pCO_2, partial carbon dioxide pressure; $p_{v-a}CO_2$, arterial-to-venous carbon dioxide partial pressure difference; SO_2, saturation; VCO_2, carbon dioxide production; VO_2, oxygen consumption.

Haldane effect

Another particular relevant phenomenon in the context of CO_2 differences is related to the binding of CO_2 to haemoglobin (Hb), also known as the Haldane effect. It describes the binding capacity of CO_2 to Hb in relation to the bound oxygen and its release to the tissues. To appreciate its implications, it is necessary to understand the concept of CO_2 content (cCO_2), that is the sum of chemically bound and the physically dissolved CO_2 amounts in the blood. However, to calculate the cCO_2, the rather sophisticated Douglas formula is needed [9]. Looking at the curvilinear graph (Fig. 1), we

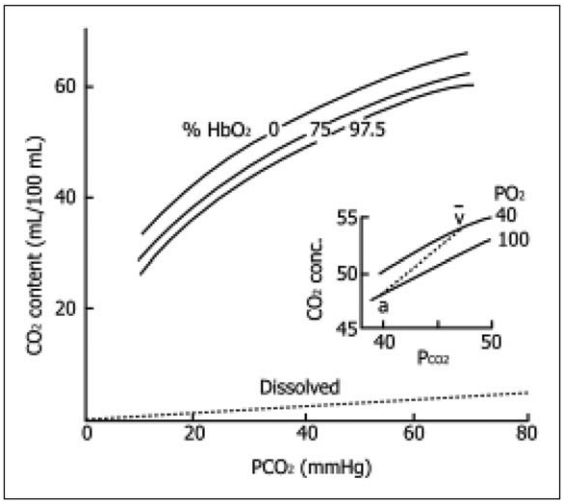

FIGURE 1. Carbon dioxide dissociation curve. Reproduced with permission [10▪▪].

can conclude that in a state of lower oxygen saturation (e.g. in venous blood, especially at high VO_2 or low flow), the CO_2 concentration is much higher than in well saturated blood (i.e. arterial blood) [10▪▪,11▪▪]. This implies that we should consider using $c_{v-a}CO_2$ instead of the commonly used $p_{v-a}CO_2$, particularly during severe hypoxemia or acidosis. Nevertheless, as mentioned above, this would mean elaborate calculations to conceive the clinical state. Therefore, even though it is slightly inferior to the $c_{v-a}CO_2$, the $p_{v-a}CO_2$ often is used in daily practice.

In addition, one should keep the effect of hyperoxia in mind which leads to an increase in unbound CO_2 – the pCO_2 – and therefore to an increase in the $p_{v-a}CO_2$ [12].

CLINICAL RELEVANCE OF CARBON DIOXIDE GAPS

In times of steadily increasing complexity of surgery and intensive care therapy, it is mandatory to develop strategies to adequately manage these situations. Herein we need tools to identify those patients at risk but also to effectively guide therapy. The following section summarizes the recent findings on the 'classic' CO_2 gaps as well as its modifications such as the sublingual-to-arterial CO_2 partial pressure difference. All of the studies included in the following can also be found in an overview table (Table 3).

Basic findings in ICU patients

Studies in critically ill patients showed an arithmetic correlation between cardiac index (*CI*) and the mixed venous-to-arterial CO_2 ($p_{mv-a}CO_2$) gap as mentioned above [2,3].

Traditionally, when talking about the $p_{v-a}CO_2$, the $p_{mv-a}CO_2$ is meant. However, its calculation requires a pulmonary artery catheter (PAC) to collect mixed venous blood samples. As the use of the PAC is decreasing over the last years, the gold standard CO_2 gap cannot be monitored in the majority of the intensive care populations nowadays. When considering the risks, it is not reasonable to insert a PAC only for this reason. Is it therefore an option to use central venous blood instead of mixed venous blood for calculating CO_2 gaps?

A study in 83 unselected intensive care patients showed that the $p_{v-a}CO_2$ and *CI* (measured by thermodilution via a PAC and transformed to natural logarithmic values) correlated negatively linearly for both mixed venous ($R^2 = 0.903$, $P < 0.0001$) and central venous ($R^2 = 0.892$, $P < 0.0001$) to arterial pCO_2 gap [13]. In accordance with that, mixed and central venous pCO_2 gaps were closely correlated [$r_s = 0.54$, 95% confidence interval (CI) 0.43–0.63, $P < 0.01$] in septic patients, and therefore, for the daily clinical routine, both can be used interchangeably to calculate the CO_2 gap [14]. As most ICU patients are equipped with a central venous catheter rather than a PAC, measuring $p_{cv-a}CO_2$ seems the best compromise.

Use of carbon dioxide gaps and outcome in patients with septic shock

The relation of CO_2 gaps and outcome was studied in several trials in critically ill patients; CO_2 gaps were used either as single variable or in combination with or in the context of other clinical variables. Septic shock represents a major group of the ICU patient population, so that many of the studies were conducted in those patients.

When prospectively and observationally classifying septic patients in four groups based on a predefined $p_{cv-a}CO_2$ (higher or lower than 6 mmHg) before the start of resuscitation and after 6 h, it was found that patients who were in the persistently high CO_2 gap group (>6 mmHg before start and after 6 h) had a significantly higher 28-day mortality and also a significantly higher Sequential Organ Failure Assessment score at day 3 [15]. A post-hoc analysis of earlier data of 53 patients with severe sepsis or septic shock demonstrated an increased in-hospital mortality in persistently high $p_{cv-a}CO_2$ of 0.8 kPa (about 6 mmHg; odds ratio 5.3, 95% CI 0.9–30.7, $P = 0.08$) at 24 h after the start of treatment [14].

In a retrospective analysis in 172 septic shock patients, it was found that the combination of central venous oxygen saturation ($S_{cv}O_2$), which classically is used as a variable for estimating the adequacy of resuscitation, along with the $p_{cv-a}CO_2$ (lower or higher than 6 mmHg) showed a better predictive

Table 3. Overview of the described studies

Population (number of patients)	Study type	Measurements	Cardiac output method	Commentary	Reference
Ventilated patients, $n=83$	Prospective	Correlation *CI* and $\Delta p_{mv}CO_2$: $R^2=0.903$; $P<0.0001$ Correlation *CI* and $\Delta p_{cv}CO_2$: $R^2=0.892$; $P<0.0001$	PAC	$\Delta p_{mv}CO_2$ and $\Delta p_{cv}CO_2$ interchangeable as surrogate for *CI*	[13]
Septic patients, $n=53$	Retrospective	Correlation $\Delta p_{mv}CO_2$ and $\Delta p_{cv}CO_2$: $R_s=0.54$; $P<0.01$ OR mortality and $\Delta p_{mv}CO_2$ (</≥0.8 kPA): 1.6; $P=0.53$	PAC	$\Delta p_{mv}CO_2$ and $\Delta p_{cv}CO_2$ are interchangeable as surrogate for *CI* No difference in mortality were seen	[14]
Septic patients, $n=85$	Prospective	28 days mortality and $\Delta p_{cv}CO_2$ (at 0 and 6 h, </≥6 mmHg): log-rank Mantel–Cox: 19.21; $P<0.001$ Correlation $\Delta p_{cv}CO_2$ and *CO*: $R^2=0.025$; $P<0.01$ 3 days SOFA score and persistently $\Delta p_{cv}CO_2 \geq 6$ at 6 h: $P<0.001$	PAC	Patient who $\Delta p_{cv}CO_2$ had not normalized after 6 h of resuscitation had a greater mortality risk	[15]
Septic shock, $n=172$	Retrospective	28 days mortality in $S_{cv}O_2$ (</≥70%) at 6 h: 50.0 vs. 29.5%; $P=0.009$ 28 days mortality in $S_{cv}O_2<70\%$ and $\Delta p_{cv}CO_2$ (</≥6 mmHg): 16.1 vs. 56.1%; $P<0.001$	PiCCO	A combination of $S_{cv}O_2$ and $\Delta p_{cv}CO_2$ better predictor for 28 days mortality than $S_{cv}O_2$ alone	[16]
Septic shock, $n=80$	Prospective	Correlation lactate and $\Delta p_{cv}CO_2$ at 0 h: $R=0.13$; $P=0.25$ Correlation lactate and $\Delta p_{cv}CO_2$ at 6 h: $R=0.42$; $P<0.0001$ Lactate and $\Delta p_{cv}CO_2$ (</≥0.8 kPa) at 6 h: 2.0 (1.2–3.5) vs. 3.6 (2.1–8.4) mmol/l; $P=0.002$ O_2ER and $\Delta p_{cv}CO_2$ (</≥0.8 kPa) at 6 h: 24% (21–28) vs. 31% (26–41); $P<0.0001$ *CI* and $\Delta p_{cv}CO_2$ (</≥0.8 kPa) at 6 h: 4.2 (3.2–5.0) vs. 3.2 (2.5–4.2) l/min/m^2; $P=0.004$ DO_2 and $\Delta p_{cv}CO_2$ (</≥0.8 kPa) at 6 h: 527 (427–702) vs. 470 (308–561) ml/min/m^2; $P=0.02$ $S_{cv}O_2$ and $\Delta p_{cv}CO_2$ (</≥0.8 kPa) at 6 h: 73% (70–76) vs. 63% (51–71); $P<0.0001$	PiCCO	$S_{cv}O_2$ in combination with $\Delta p_{cv}CO_2$ good predictor for decreasing lactate $\Delta p_{cv}CO_2$ useful tool for adequacy of tissue perfusion	[4]
Septic shock, $n=64$	Prospective	$\Delta p_{mv}CO_2$ (</≥6 mmHg) in survivors/nonsurvivors: 4.4 ± 2.3 vs. 5.9 ± 3.4 mmHg; $P<0.005$ *CI* in survivors/nonsurvivors: 3.8 ± 2.0 vs. 2.9 ± 1.3 l/min/m^2; $P<0.01$ Lactate in survivors/nonsurvivors: 4.5 ± 2.8 vs. 7.7 ± 5.3 mmol/l; $P<0.001$	PAC	Modest relationship of $\Delta p_{mv}CO_2$ and survival	[17]
Septic, $n=46$ vs. nonseptic ventilated patients, $n=15$	Prospective	Δp_cCO_2 septic/control: 14.8 ± 12.6 vs. 6 ± 2.7; $P<0.0001$ $\Delta p_{c-et}CO_{2:25}$ ± 16.3 vs. 9 ± 3.8 mmHg; $P<0.0001$ 28 days survivors/nonsurvivors and decreased Δp_cCO_2 at 36 h: 14.8 ± 12.6 vs. 9.8 ± 5.2 mmHg; $P<0.01$ Post-hoc cut-off Δp_cCO_2 for mortality: 9 mmHg; AUROC 0.94 (0.65–0.98)	PAC and/or Doppler TEE	Δp_cCO_2 surrogate for microperfusion $\Delta p_{cv}CO_2$ indicator of adverse outcome	[18]
Ventilated patients, $n=95$	Prospective	$\Delta p_{gm}CO_2$ in 28 days survivors/nonsurvivors at 0 h: 14 ± 11 vs. 19 ± 14 mmHg; NS $\Delta p_{gm}CO_2$ in 28 days survivors/nonsurvivors at 24 h: 15 ± 9 vs. 27 ± 14 mmHg; $P<0.01$ Lactate in 28 days survivors/nonsurvivors at 0 h: 2 ± 1.5 vs. 4.8 ± 4 mmol/l; $P<0.01$ Lactate in 28 days survivors/nonsurvivors at 24 h: 1.1 ± 0.6 vs. 3.9 ± 3 mmol/l; $P<0.01$	Not measured	$\Delta p_{gm}CO_2$ good indicator for survival	[19]
Ventilated, septic shock, $n=18$	Prospective, open label	Correlation $\Delta p_{sl}CO_2$ and $\Delta p_{cv}CO_2'$: $R^2=0.61$; $P<0.05$ $\Delta p_{sl}CO_2$ at 0-h and after 90-min dobutamine: 40 ± 15 vs. 17 ± 8 mmHg; $P<0.01$	PAC	$\Delta p_{sl}CO_2$ surrogate for microperfusion	[20]
Ventilated patients, $n=54$	Prospective	$\Delta p_{sl}CO_2$ in survivors/nonsurvivors: 19 ± 12.8 vs. 35.3 ± 18.3 mmHg; $P<0.0004$ $p_{sl}CO_2$: 53.2 ± 13.7 vs. 67.9 ± 21.0 mmHg; $P<0.004$ $s_{mv}O_2$ in survivors/nonsurvivors: 73 ± 10% vs. 69 ± 12%; $P=0.17$ Lactate in survivors/nonsurvivors: 3.4 ± 2.8 vs. 5.0 ± 5.1 mmol/l; $P=0.21$ Cut-off $\Delta p_{sl}CO_2$: 25 mmHg; AUROC 0.75	PAC	$\Delta p_{sl}CO_2$ and $p_{sl}CO_2$ better predictors for outcome than traditional markers	[21]
Sitting craniotomy, $n=51$	Prospective	Correlation *CI* and $\Delta p_{mv}CO_2$: $R^2=0.830$; $P<0.001$ Correlation *CI* and $\Delta p_{cv}CO_2$: $R^2=0.760$; $P<0.001$ Correlation *CI* and $S_{mv}O_2$: $R^2=0.324$; $P<0.001$ Correlation *CI* and $S_{cv}O_2$: $R^2=0.289$; $P<0.001$	PAC	$\Delta p_{mv}CO_2$ valid surrogate for *CI*	[22]
High risk surgery patients, $n=115$	Retrospective	$\Delta p_{cv}CO_2$ in complications/no complications: 8.7 ± 2.8 vs. 5.1 ± 2.6 mmHg; $P<0.001$ Lactate in complications/no complications: 1.54 (1.1–3.2) vs. 1.06 (0.8–1.8) mmol/l; $P=0.006$ $S_{cv}O_2$ in complications/no complications: 76.3 ± 6.3% vs. 78 ± 5.2%; $P=0.17$ Post-hoc cut-off $\Delta p_{cv}CO_2$ for complications/no complications: 5.8 mmHg; AUROC 0.86 (0.77–0.95)	Not measured	Increased $\Delta p_{cv}CO_2$ good indicator for postoperative complications	[23]

Table 3 (*Continued*)

Population (number of patients)	Study type	Measurements	Cardiac output method	Commentary	Reference
Cardiac surgery, $n=393$	Prospective	$\Delta p_{cv}CO_2$ in complications/no complications at 0 h: 10 (8.3–12) vs. 9.5 (7.9–11.3) mmHg; $P=0.066$ $\Delta p_{cv}CO_2$ in complications/no complications at 6 h: 8.5 (7–10) vs. 8.2 (6.3–9.8) mmHg; $P=0.250$ $S_{cv}O_2$ in complications/no complications at 0 h: 66 ± 10% vs. 67 ± 9%; $P=0.163$ $S_{cv}O_2$ in complications/no complications at 6 h: 66 ± 10% vs. 70 ± 8%; $P=0.003$ Lactate in complications/no complications at 0 h: 1.5 (0.5–3) vs. 1.3 (1–1.6) mmol/l; $P<0.0001$ Lactate in complications/no complications at 6 h: 1.9 (1.4–2.6) vs. 1.6 (1–2.2) mmol/l; $P<0.0001$	PAC and/or Doppler TEE	After cardiac surgery $\Delta p_{cv}CO_2$ cannot be used as predictor for adverse outcome	[24]
Postoperative after major abdominal surgery, $n=70$	Retrospective	$\Delta p_{cv}CO_2$ in complications/no complications at 0 h: $P=0.22$, data not stated Mean $\Delta p_{cv}CO_2$ during admission in complications/no complications: 7.8 ± 2 vs. 5.6 ± 2 mmHg; $P<10^{-6}$ Lactate in complications/no complications at 0 h: 1.4 ± 0.6 vs. 1.3 ± 0.5 mmol/l; $P=0.48$ *CI* at the end of surgery in complications/no complications: 3.2 ± 0.7 vs. 3.1 ± 0.6 l/min/m^2; $P=0.79$ Post-hoc cut-off $S_{cv}O_2$ for complications/no complications: 70.6%; AUROC 0.736 (0.61–0.86) Post-hoc cut-off $\Delta p_{cv}CO_2$ for complications/no complications: 6 mmHg; AUROC 0.758 (0.74–0.83)	Doppler TEE	$\Delta p_{cv}CO_2$ can serve as complementary target to identify inadequacy of fluid therapy	[25]
Septic shock with normal $S_{cv}O_2$ after early resuscitation, $n=50$	Prospective	Correlation *CI* and $\Delta p_{cv}CO_2$ at 0, 6 and 12 h; $r_0=0.57$, $r_6=0.58$, $r_{12}=0.58$; all $P<0.00001$ Lactate and $\Delta p_{cv}CO_2$ (</≥6 mmHg) at 0 h: 4.3 ± 1.6 vs. 2.7 ± 0.8 mmol/l; $P<0.0001$	PiCCO	An increased $\Delta p_{cv}CO_2$ in the presence of normal $S_{cv}O_2$ indicates inadequate resuscitation	[26]
Critically ill, $n=89$	Retrospective	$\Delta p_{cv}CO_2/c_{a-cv}O_2$ and lactate (</≥2 mmol/l): 1.1 ± 0.6 vs. 2.0 ± 0.9 mmHg/ml; $P<0.0001$ Correlation $\Delta p_{cv}CO_2/c_{a-cv}O_2$ and lactate: $r=0.57$; $P<0.0001$ Post-hoc cut-off $\Delta p_{cv}CO_2/c_{a-cv}O_2$ for hyperlactatemia: 1.4 mmHg/ml; AUROC 0.85 (0.79–0.91) 1 month survival and $\Delta p_{cv}CO_2/c_{a-cv}O_2$ (</≥1.4 mmHg/ml): 38 ± 10% vs. 20 ± 8%; $P<0.01$	PAC	$\Delta p_{cv}CO_2/c_{a-cv}O_2$ seems a reliable marker for global anaerobic metabolism	[30▪▪]
Septic shock, $n=35$	Prospective	Post-hoc cut-off $\Delta p_{cv}CO_2/c_{a-cv}O_2$ for lactate improvement (decrease of ≥10%): 1.4 mmHg/ml; AUROC 0.82 OR adequate lactate clearance and $\Delta p_{cv}CO_2/c_{a-cv}O_2$ (≥1.4 mmHg/ml): 0.1; $P<0.001$	Not measured	An increased $\Delta p_{cv}CO_2/c_{a-cv}O_2$ decreases the OR for adequate resuscitation in the presence of normal MAP and $S_{cv}O_2$	[31]
Postoperative after cardiac surgery, $n=72$	Retrospective	Post-hoc cut-off $\Delta p_{cv}CO_2/c_{a-cv}O_2$ to predict response to DO_2 challenge: 1.6 mmHg/ml; AUROC 0.77 ± 0.10; $P=0.032$	PiCCO	$\Delta p_{cv}CO_2/c_{a-cv}O_2$ appears to be a reliable marker for global anaerobic metabolism $\Delta p_{cv}CO_2/c_{a-cv}O_2$ can predict response to DO_2 challenge	[32]

ΔpCO_2, if not otherwise indicated partial CO_2 pressure gradient of a venous measurement indicated by the subscripted characters and respective arterial values; AUROC, area under the receiver operating curve; c, cutaneous; *CI*, cardiac index; cv, central venous; DO_2, oxygen delivery; gm, gastric mucosal; MAP, mean arterial pressure; mv, mixed venous; O_2ER, oxygen extraction rate; OR, odds ratio; PAC, pulmonary artery catheter; PiCCO, pulse contour cardiac output; $S_{cv}O_2$, central venous oxygen saturation; sl, sublingual; SO_2, oxygen saturation; SOFA, Sequential Organ Failure Assessment; TEE, transoesophageal echography.

value for 28-day mortality (16.1 vs. 56.1%, $P = 0.001$) than $S_{cv}O_2$ (lower or higher than 70%) alone (50.0 vs. 29.5%, $P = 0.009$) [16].

In addition, a moderate correlation of the CO_2 gap with lactate levels, which are commonly related to adverse outcome, was found after 6 h of treatment ($r = 0.42$, $P < 0.0001$) but not at the start of the treatment ($r = 0.13$, $P = 0.25$) in 80 patients with septic shock [4]. In patients with septic shock, a significantly higher $p_{mv-a}CO_2$ was found in nonsurvivors than in survivors (5.9 ± 3.4 vs. 4.4 ± 2.3 mmHg; $P < 0.05$). However, its prognostic value was found to be only modest [17].

Other forms of carbon dioxide gradients in the ICU

In addition to the commonly used $p_{cv-a}CO_2$ or the $p_{mv-a}CO_2$, many forms of CO_2 partial pressure differences (ear lobe, gastric mucosa and sublingual to arterial) have been studied with a spectrum of different objectives.

Cutaneous-to-arterial pCO_2 gap measured by an ear lobe device was found to be significantly higher at baseline in septic shock patients compared with stable ventilated patients in the ICU (14.8 ± 12.6 vs. 6 ± 2.7 mmHg, $P < 0.0001$). In addition, using a post-hoc analysis a cut-off level of 9 mmHg was identified to distinguish the septic shock group from the nonseptic (control) group. Herein a high sensitivity and a high specificity were found [86 and 93%, respectively, area under the receiver operating characteristic (ROC) curve of 0.94, 95% CI 0.85–0.98].

Furthermore, it was demonstrated that in 28-day survivors of the septic shock patients, the cutaneous-to-arterial pCO_2 gap decreased over the time until the end of the observations at 36 h (14.8 ± 12.6 to 9.8 ± 5.2 mmHg, $P < 0.01$) [18].

Also, when comparing gastric mucosal-to-arterial pCO_2 gap obtained via tonometry in ventilated patients on the ICU at admission, no significant difference was found in the 28-day survivors and nonsurvivors. However, when comparing the pCO_2 gap after 24 h of admission, it was found to have stabilized in survivors, whereas it had further increased in nonsurvivors. Of note, patients who had an increased gastric CO_2 of more than 20 mmHg after 24 h showed a mortality of more than 60% [19].

Further, it was demonstrated that sublingual and gastric mucosal pCO_2 correlated well ($r^2 = 0.61$, $P < 0.05$) in mechanically ventilated ICU patients [20]. In the same study, dobutamine decreased the sublingual-to-arterial pCO_2 gap, which was interpreted as improvement of the sublingual microcirculation. Another study on the sublingual CO_2 partial pressure ($p_{sl}CO_2$) in an unselected ICU group demonstrated that both the $p_{sl}CO_2$ and the $p_{sl-a}CO_2$ had a better predictive value for hospital mortality than classic variables such as lactate or mixed venous saturation at baseline (3.4 ± 2.8 vs. 5.0 ± 5.3 mmol/l, $P = 0.21$ and 73 ± 10 vs. $69 \pm 12\%$, $P = 0.17$, respectively) [21]. Although all these results derive from research settings, they could be seen as first step to use a CO_2 gap to guide resuscitation therapy in daily practice.

Use of carbon dioxide gaps in patients undergoing surgery

Comparable studies to those on the ICU were conducted in patients undergoing anaesthesia. In 51 patients who were scheduled for craniotomy in the sitting position, the relations of the $p_{mv-a}CO_2$, $p_{cv-a}CO_2$ and *CI* were inversely proportional in those who were worked up effectively beforehand and who were ranging at normal *CI* levels during surgery ($R^2 = 0.830$ and 0.760, respectively, both $P < 0.001$) [22].

In 115 patients who were undergoing high-risk (noncardiac) surgery, it was found that in those 78 who developed postoperative complications a significantly higher $p_{cv-a}CO_2$ was found at the time of ICU admission (8.7 ± 2.8 vs. 5.1 ± 2.6 mmHg, $P = 0.001$). Of those patients with complications, 54 developed organ failure. Herein *post hoc* an ideal cut-off value of the $p_{cv-a}CO_2$ of 5.8 mmHg for increased risk of postoperative complications was identified (area under the ROC 0.86, 95% CI 0.77–0.95) [23].

Such findings however could not be repeated for the postoperative period in 393 patients after cardiac surgery. A $p_{cv-a}CO_2$ higher or lower than 6 mmHg at admission on the ICU and 6 h later were not predictive for the development of major complications. Furthermore, no difference in mortality was found [24].

Use of carbon dioxide gap in goal-directed fluid therapy

In the context of the findings mentioned above, it is only logical that CO_2 gap was used as target for fluid resuscitation.

In a prospective, observational study of 80 septic shock patients a high baseline pCO_2 gap was associated with a lower *CI* (2.9 vs. 3.9 l/min/m^2) and a lower $S_{cv}O_2$ (61 vs. 73%). Patients who reached a normal $p_{cv-a}CO_2$ of less than 0.8 kPa (about 6 mmHg) after 6 h of resuscitation had decreased lactate levels (median [interquartile range]: 2.0 [1.2, 3.5] vs. 3.6 [2.1, 8.4] mmol/l, $P = 0.002$) and a decreased O_2 extraction rate (24% [21, 28] vs. 31% [26,41], $P < 0.0001$) in comparison with patients with a higher $p_{cv-a}CO_2$. At the same time *CI*, oxygen delivery (DO_2) and $S_{cv}O_2$ had increased in the patients with a normalized $p_{cv-a}CO_2$. So, for monitoring of

fluid resuscitation the $p_{cv-a}CO_2$ could be a useful tool to assess the adequacy of tissue perfusion [4].

In a retrospective analysis of complication rates after major abdominal surgery in 70 patients treated with a goal-directed fluid therapy algorithm, the value of $p_{cv-a}CO_2$ was demonstrated particularly in patients with a normal intraoperative $S_{cv}O_2$ of at least 71%; a high $p_{cv-a}CO_2$ could predict the development of postoperative complications (area under the ROC 0.785, 95% CI 0.74–0.83) with a discriminating cut-off $p_{cv-a}CO_2$ value of 5 mmHg. It was concluded that $p_{cv-a}CO_2$ can serve as complementary target to $S_{cv}O_2$ to identify inadequacy of fluid therapy [25].

In 50 septic shock patients with a normal or normalized $S_{cv}O_2$ after early resuscitation at the emergency department, it was also demonstrated that those with a persistently high $p_{cv-a}CO_2$ of more than 6 mmHg remained inadequately resuscitated as indicated by *CI* (2.7 ± 0.8 vs. 4.3 ± 1.6 l/min/m^2, $P < 0.0001$). Furthermore, $p_{cv-a}CO_2$ and *CI* were inversely correlated over time in these patients [26].

Based on all these findings, flow diagrams for a structured approach of management of shock have been developed. They put CO_2 gap in a central position, especially when $S_{cv}O_2$ is within the normal range due to alteration of oxygen extraction capacities (e.g. in case of sepsis) and thus, where interpretation of $S_{cv}O_2$ is uncertain. One of these flow diagrams is presented in Fig. 2 [8▪▪]. Other flow diagrams emphasize on the combination of lactate, $S_{cv}O_2$ and $p_{v-a}CO_2$ to help identify macrocirculatory and microcirculatory alterations (Fig. 3) [27▪]. Indeed, some authors have suggested that an increased $p_{v-a}CO_2$ could reflect microcirculation alterations not detected by other systemic haemodynamic variables [28▪▪]. It could be postulated that in poorly perfused areas, accumulation of CO_2 lead to increased venous pCO_2 due to the high diffusion of CO_2 through the tissues. Obviously, the hypothesis that increased $p_{v-a}CO_2$ reflects microcirculatory alterations rather than inadequate systemic blood flow remains to be confirmed but is not in contradiction with the general belief that in cases of increased CO_2 gap, therapeutic elevation of *CO* should be first considered with the goal of improving tissue oxygenation [29].

Use of the ratio of carbon dioxide gap to arteriovenous oxygen content difference in goal-directed fluid therapy

The use of the ratio of CO_2 gaps ($p_{v-a}CO_2$ or $c_{v-a}CO_2$) and the arteriovenous oxygen content difference

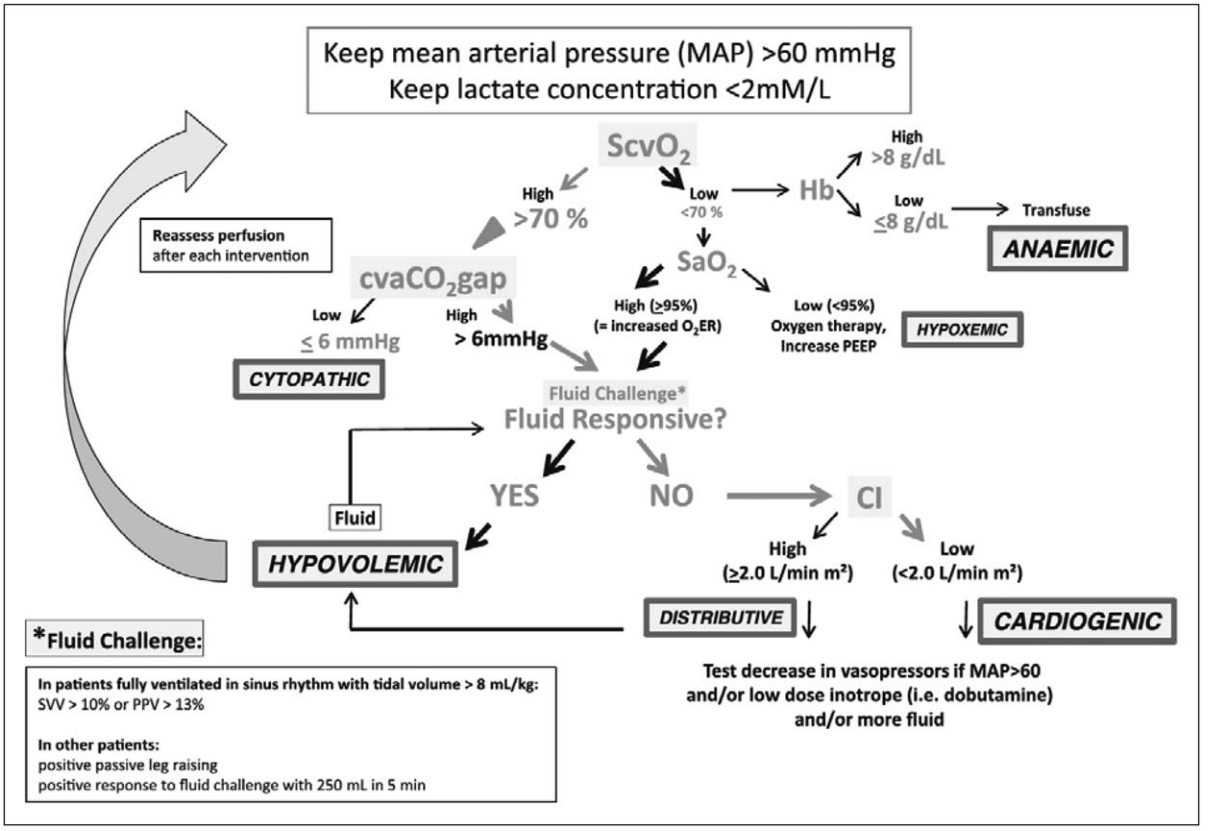

FIGURE 2. Flow-chart for analysing variables in tissue hypoxia according to Vallet *et al.* [8▪▪]. CI, cardiac index; $cvaCO_2$ gap, difference of partial pressures of CO_2 in venous and arterial blood; Hb, hemoglobin; PPV, pulse pressure variation; SaO_2, arterial oxygen saturation; $ScvO_2$, central venous oxygen saturation; SVV, stroke volume variation.

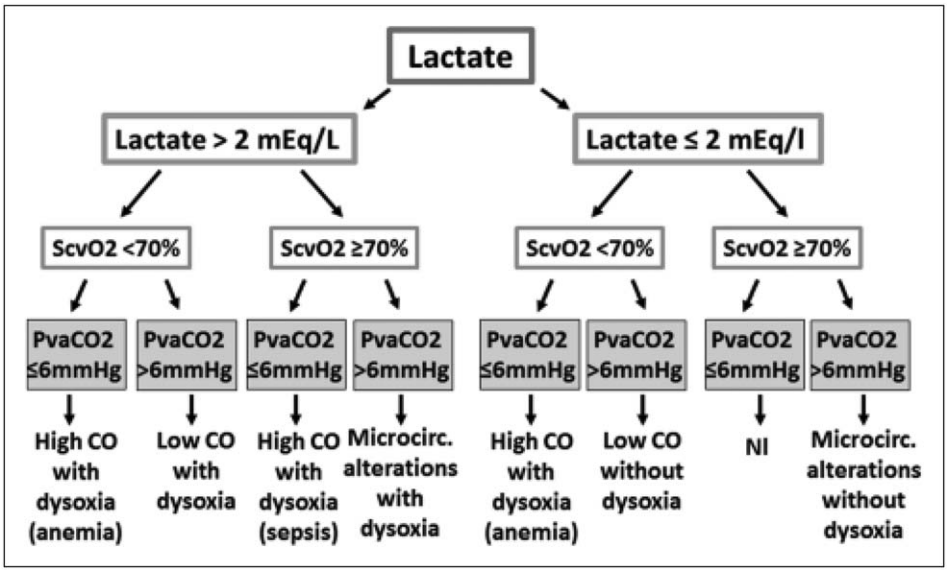

FIGURE 3. Integration of lactate, central venous oxygen saturation ($ScvO_2$) and arterial-to-venous carbon dioxide partial pressure difference ($PvaCO_2$) to identify alterations of the (micro)circulation according to De Backer. CO, cardioac output; NI, normal. Reproduced with permission [27▪].

($c_{a-v}O_2$) is a further step toward successful goal-directed fluid resuscitation. In tissue hypoxia aerobic VCO_2 is markedly decreased, whereas there is only a slight increase in anaerobic VCO_2. Simultaneously there is a significantly decreased VO_2, which exceeds the net decrease in VCO_2. As VCO_2 is the product of the cCO_2 and *CO* and VO_2 is the product of the cO_2 and *CO*, *CO* can be eliminated from the formula. This relation can also be expressed as the $p_{v-a}CO_2$ over the $c_{a-v}O_2$ ratio [28▪▪,30▪▪].

When post-hoc studying the $p_{mv-a}CO_2$ to $c_{a-v}O_2$ ratio in 89 critically ill patients, it was found that a ratio of 1.4 mmHg/ml was the optimal cut-off point to predict hyperlactatemia (higher or lower than 2 mmol/l) (area under ROC 0.85, 95% CI 0.79–0.91) [31]. At baseline, the $p_{mv-a}CO_2/c_{a-v}O_2$ ratio was significantly higher in the high lactate group (2.0 ± 0.9 vs. 1.1 ± 0.6 mmol/l), and there was a significant correlation between those two variables ($r = 0.57$) [31]. The same $p_{cv-a}CO_2/c_{a-v}O_2$ cut-off level of 1.4 mmHg/ml was found *post hoc* in 35 septic shock patients to predict an improved lactate clearance (decrease of $\geq$10%) after 24 h of resuscitation (area under the ROC 0.82, 95% CI 0.73–0.92) [32]. Also in this study, a significant correlation between lactate levels and $p_{cv-a}CO_2/c_{a-v}O_2$ was found ($r = 0.73$) [32]. Thus, both studies found that either central or mixed venous $p_{v-a}CO_2/c_{a-v}O_2$ was a reliable marker for anaerobic metabolism. Furthermore, in patients who were admitted to an ICU after cardiac surgery, $p_{cv-a}CO_2/c_{a-v}O_2$ was discriminating for more than 10% increase in VO_2 as respond to fluid therapy with a post-hoc cut-off value of 1.6 mmHg/ml. It could therefore serve as marker for global anaerobic metabolism and as predictor for the response to a DO_2 challenge. Accordingly, it was successfully used as target in fluid resuscitation therapy (area under ROC 0.77 ± 0.10, $P = 0.032$) [33].

CONCLUSION

In our review, we give an outline over the use of several CO_2 gaps for the haemodynamic assessment and the guidance of haemodynamic therapy in critically ill patients. All the components for the used formulas are in a gaining proportion measurable with point-of-care analysers. Those are increasingly available at bedside in the ICU.

Due to the Fick principle, it seems feasible to use the $p_{v-a}CO_2$ as a marker of the adequacy of *CO* to the global metabolic conditions [2,3]. Those theoretical findings have also been validated for critically ill patients [4] and for patients who are undergoing surgery [5,22].

Because of the higher solubility of CO_2 than that of O_2 in blood, the CO_2 effluent of hypoxic tissue is accordingly higher than that of O_2 in states of low flow. The $p_{v-a}CO_2$ can thus be used as a marker of tissue hypoperfusion rather than a tool to detect tissue hypoxia [6,7,8▪▪]. In theory, mixed venous blood samples obtained through a PAC are necessary for the gradient calculations. However, clinical studies [13,14] have shown that it is reasonable to use central venous blood samples in most patients not equipped with a PAC.

The CO_2 gaps are suggested to be used to guide resuscitation of shock states, especially when alteration of oxygen extraction prevents perfect

interpretation of $S_{cv}O_2$ [4,25,26]. Studies in critically ill patients further demonstrated that the $p_{cv-a}CO_2/c_{a-v}O_2$ ratio was closely correlated to lactate levels and lactate clearance, which are both classical markers of tissue hypoxia and often used as targets in goal-directed therapy algorithms [31,32].

Because of the ease of use and the range of possibilities of CO_2 gaps, it is recommendable to implement the use of CO_2 gaps and maybe also its ratio to $c_{a-cv}O_2$ in daily ICU practice.

Acknowledgements

None.

Financial support and sponsorship

T.W.L.S. received honoraria from Edwards Lifesciences and Masimo Inc. (both Irvine, CA, USA) for consulting and lecturing and Pulsion Medical Systems SE (Feldkirchen, Germany) for lecturing. J.N.W. declares not to receive any honoraria. J.-L.T. is a member of the medical advisory board of Pulsion Medical Systems (Feldkirchen, Germany).

Conflicts of interest

There are no conflicts of interest.

REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:

- ■ of special interest
- ■■ of outstanding interest

1. Moriyama S, Okamoto K, Tabira Y, *et al.* Evaluation of oxygen consumption and resting energy expenditure in critically ill patients with systemic inflammatory response syndrome. Crit Care Med 1999; 27:2133–2136.
2. Hall JE, Guyton AC. Guyton and Hall textbook of medical physiology. 13th ed. Philadelphia, PA: Elsevier, 2016. Chapter 20: Cardiac output, venous return, and their regulation; p. 245–258.
3. Physikalisch-medizinische Gesellschaft zu Würzburg. Sitzungsberichte der physikalisch-medicinischen Gesellschaft zu Würzburg. XIV. Sitzung am 9. Juli 1870. Fick: Ueber die Messung des Blutquantums in den Herzventrikeln. Würzburg: Verlag der Physik.-med. Gesellschaft; 1870. XVI–XVII.
4. Mallat J, Pepy F, Lemyze M, *et al.* Central venous-to-arterial carbon dioxide partial pressure difference in early resuscitation from septic shock: a prospective observational study. Eur J Anaesthesiol 2014; 31:371–380.
5. Mahutte CK, Jaffe MB, Sassoon CS, Wong DH. Cardiac output from carbon dioxide production and arterial and venous oximetry. Crit Care Med 1991; 19:1270–1277.
6. Pittman RN. The Regulation of Tissue Oxygenation. 2nd ed. San Rafael, CA: Morgan & Claypool Life Sciences, 2016. Chapter 4: Oxygen Transport; p. 23–36.
7. Silbert BI, Litton E, Ho KM. Central venous-to-arterial carbon dioxide gradient as a marker of occult tissue hypoperfusion after major surgery. Anaesth Intensive Care 2015; 43:628–634.
8. ■■ Vallet B, Pinsky MR, Cecconi M. Resuscitation of patients with septic shock: please 'mind the gap'! Intensive Care Med 2013; 39:1653–1655.

The brief review gives a clear overview of the available information over carbon dioxide (CO_2) gaps in the context of several types of shock.

9. Douglas AR, Jones NL, Reed JW. Calculation of whole blood CO_2 content. J Appl Physiol 1988; 65:473–477.
10. ■■ Mallat J, Lemyze M, Tronchon L, *et al.* Use of venous-to-arterial carbon dioxide tension difference to guide resuscitation therapy in septic shock. World J Crit Care Med 2016; 5:47–56.

This is very recommendable review on fluid resuscitation in septic shock. Herein amongst others the basics O_2 and CO_2 transport and usability of different measurements and gradients in daily practice are discussed in detail, especially the value of partial carbon dioxide pressure gradients.

11. ■■ Teboul JL, Scheeren T. Understanding the Haldane effect. Intensive Care Med 2017; 43:91–93.

In this brief review, the physiological background of the Haldane effect and its clinical implications are described.

12. Saludes P, Proença L, Gruartmoner G, *et al.* In response to: 'understanding elevated $P_{v-a}CO_2$ gap and $P_{v-a}CO_2/C_{a-v}O_2$ ratio in venous hyperoxia condition'. J Clin Monit Comput 2017; 31:1325–1327.
13. Cuschieri J, Rivers EP, Donnino MW, *et al.* Central venous–arterial carbon dioxide difference as an indicator of cardiac index. Intensive Care Med 2005; 31:818–822.
14. van Beest PA, Lont MC, Holman ND, *et al.* Central venous–arterial pCO_2 difference as a tool in resuscitation of septic patients. Intensive Care Med 2013; 39:1034–1039.
15. Ospina-Tascón GA, Bautista-Rincón DF, Umaña M, *et al.* Persistently high venous-to-arterial carbon dioxide differences during early resuscitation are associated with poor outcomes in septic shock. Crit Care 2013; 17:R294.
16. Du W, Liu DW, Wang XT, *et al.* Combining central venous-to-arterial partial pressure of carbon dioxide difference and central venous oxygen saturation to guide resuscitation in septic shock. J Crit Care 2013; 28:1110.e1–1110.e5.
17. Bakker J, Vincent JL, Gris P, *et al.* Veno-arterial carbon dioxide gradient in human septic shock. Chest 1992; 101:509–515.
18. Vallée F, Mateo J, Dubreuil G, *et al.* Cutaneous ear lobe PCO_2 at 37 °C to evaluate microperfusion in patients with septic shock. Chest 2010; 138:1062–1070.
19. Levy B, Gawalkiewicz P, Vallet B, *et al.* Gastric capnometry with air-automated tonometry predicts outcome in critically ill patients. Crit Care Med 2003; 31:474–480.
20. Creteur J, De Backer D, Sakr Y, *et al.* Sublingual capnometry tracks microcirculatory changes in septic patients. Intensive Care Med 2006; 32:516–523.
21. Marik PE, Bankov A. Sublingual capnometry versus traditional markers of tissue oxygenation in critically ill patients. Crit Care Med 2003; 31:818–822.
22. Tsaousi GG, Karakoulas KA, Amaniti EN, *et al.* Correlation of central venous–arterial and mixed venous–arterial carbon dioxide tension gradient with cardiac output during neurosurgical procedures in the sitting position. Eur J Anaesthesiol 2010; 27:882–889.
23. Robin E, Futier E, Pires O, *et al.* Central venous-to-arterial carbon dioxide difference as a prognostic tool in high-risk surgical patients. Crit Care 2015; 19:227.
24. Guinot P-G, Badoux L, Bernard E, *et al.* Central venous-to-arterial carbon dioxide partial pressure difference in patients undergoing cardiac surgery is not related to postoperative outcomes. J Cardiothorac Vasc Anesth 2017; 31:1190–1196.
25. Futier E, Robin E, Jabaudon M, *et al.* Central venous O_2 saturation and venous-to-arterial CO_2 difference as complementary tools for goal-directed therapy during high-risk surgery. Crit Care 2010; 14:R193.
26. Vallée F, Vallet B, Mathe O, *et al.* Central venous-to-arterial carbon dioxide difference: an additional target for goal-directed therapy in septic shock? Intensive Care Med 2008; 34:2218–2225.
27. ■ De Backer D. Detailing the cardiovascular profile in shock patients. Crit Care 2017; 21:311.

This is a recent review concerning the integration of different clinical variables to guide fluid therapy and to optimize tissue oxygenation in patients who are at a state of shock. It also describes the advantages and disadvantages of individual and protocolized fluid therapy.

28. ■■ Ospina-Tascón GA, Hernández G, Cecconi M. Understanding the venous–arterial CO_2 to arterial–venous O_2 content difference ratio. Intensive Care Med 2016; 42:1801–1804.

Another brief review on the ratios of the CO_2 to O_2 content gradients. It provides extra information about the processes which come along anaerobic metabolism at cellular level.

29. Teboul J-L, Saugel B, Cecconi M, *et al.* Less invasive hemodynamic monitoring in critically ill patients. Intensive Care Med 2016; 42:1350–1359.
30. ■■ Jakob SM, Groeneveld ABJ, Teboul J-L. Venous–arterial CO_2 to arterial–venous O_2 difference ratio as a resuscitation target in shock states? Intensive Care Med 2015; 41:936–938.

The brief review describes the basics of ratios of the CO_2 to O_2 content gradients and also gives a brief insight in the use of it in daily practise.

31. Mekontso-Dessap A, Castelain V, Anguel N, *et al.* Combination of venoarterial PCO_2 difference with arteriovenous O_2 content difference to detect anaerobic metabolism in patients. Intensive Care Med 2002; 28:272–277.
32. Mesquida J, Saludes P, Gruartmoner G, *et al.* Central venous-to-arterial carbon dioxide difference combined with arterial-to-venous oxygen content difference is associated with lactate evolution in the hemodynamic resuscitation process in early septic shock. Crit Care 2015; 19:126.
33. Du W, Long Y, Wang XT, Liu DW. The use of the ratio between the veno-arterial carbon dioxide difference and the arterial–venous oxygen difference to guide resuscitation in cardiac surgery patients with hyperlactatemia and normal central venous oxygen saturation. Chin Med J (Engl) 2015; 128:1306–1313.