Research Article

Bladder Mucosal CO$_2$ Compared with Gastric Mucosal CO$_2$ as a Marker for Low Perfusion States in Septic Shock

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1. Introduction

Tissue pressure of CO$_2$ is considered to be an indicative parameter of the microvascular perfusion, and this measure can be obtained from highly vascular areas such as sublingual, brain, conjunctiva, skin, or typically the intestinal area [1].

The most widespread indication is the estimation of tissue perfusion in sepsis and septic shock, although its use has been described in other types of shock (especially the hemorrhagic) [2], cardiovascular surgery, transplantation, or trauma and is associated with outcome [3].

Most commonly explored areas are the sublingual and intestinal areas [4, 5] but theoretically any sufficiently vascularized area would be suitable for measurement. We intend to study the value of bladder intramucosal CO$_2$ in an animal model of induced sepsis.

2. Material and Methods

2.1. Anesthetic Protocol. The anesthesiologists of this centre controlled the subjects. We studied six Beagle dogs between 12 and 15 Kg of weight that underwent the usual anesthetic procedure in this centre: anesthesia with sevoflurane, relaxation with atracurium, and mechanical ventilation aimed to obtain normal PaCO$_2$. 

2.2. Monitoring. All animals were monitored with a Picco catheter in the femoral artery, a central venous jugular vein catheter, and continuous end-tidal CO$_2$ measurement. In all subjects we registered every 60 minutes the mean arterial pressure (MAP), cardiac output (CO), and systolic volume variability (SVV). Arterial blood gases were measured before sepsis and then every 60 minutes for six hours. Survivors at this time were euthanized following the standard measured approved for this veterinary hospital.

Measurement of gastric mucosa CO$_2$ (CO$_2$-G) used for the calculation of the gap between PaCO$_2$ and CO$_2$-G ($\Delta$CO$_2$-G) was performed continuously with a Datex Ohmeda (GE Healthcare) monitor tonometry module and the probe for gastric tonometry TRIP Catheter (Intrumentarium Corp) that was positioned by gastroscopy after induction of anesthesia.
Measurement of CO₂ in bladder mucosa (CO₂-B) used for the calculation of the gap between PaCO₂ and CO₂-B (ΔCO₂-B) was performed in agreement with the technique described by Fiddian-Green [6] through a pulmonary artery catheter inserted into the bladder infusing 1 mL saline in the balloon and maintaining this for 60 minutes prior to its removal with subsequent immediate analysis to determine the pressure of CO₂.

2.3. Provocation of Sepsis [7]. With the subjects anesthetized, monitored in stable condition, we infused 1 mgr/Kg of body weight of ultra pure Escherichia Coli Lipopolisacharid (strain 0111 : B4, InvivoGen) diluted in 20 mL of saline solution and infused in 10 minutes.

2.4. Ethical Issues. This study was carried out in an experimental operating room of the Veterinary Hospital of the University of Córdoba, Spain. Survivors at the end of the follow-up were euthanized following the standard measures approved for this veterinary hospital. The Ethics and Clinical Research Committee at the Veterinary Hospital of the University of Córdoba have approved this protocol. This research was funded by a nonrestricted grant by Hospal with complete independence of the results of the study. None of the authors have any commercial relationship with the funding company.

2.5. Statistical Analysis. The analysis was carried out by the statistical package SPSS for Windows 11. Data are shown as mean ± standard deviation or proportions. For comparisons we used the Pearson correlation test and scatter plots, with a level of significance for all tests of 0.05.

3. Results

In all the subjects a state of severe shock was evident at the end of the induction. The subsequent evolution was marked by the maintenance of the low perfusion status until the end of the experiment (Table 1) and this effect was detected by changes in base deficit and CO₂-G but not so in CO₂-B (Figure 1).

In all measures, levels of CO₂-B were found to be significantly lower than CO₂-G, with a mean difference of 36.8 (P = 0.001) mmHg. Even though a correlation was found between both measurements (Figure 2), this was poor (r² = 0.29). In the same way, even when the correlation between CO₂-G and ΔCO₂-G was narrow (as it was expected), this was not the case for the relationship between CO₂-B and ΔCO₂-B (Figure 3). Finally, the correlation between CO₂-G and base deficit was good (r² = 0.45); this however was not the case for the CO₂-B correlation (r² = 0.03) (Figure 4).

4. Discussion

Determination of the mucosal CO₂ is one accepted method for assessment of perfusion states in shock patients. The possibility to measure this parameter in the bladder presents as an attractive alternative because this is a virtually universal access in patients in shock. However, according to our results, the usefulness of the bladder mucosal CO₂ as estimator of low perfusion is limited and cannot replace the accepted determination in gastric mucosa.

Sepsis is one of the major pathologies of intensive care (ICU) and one associated with high morbidity-mortality [8]. An early establishment of an appropriate antimicrobial treatment is the basis of current approaches to its management, but an appropriate resuscitation aimed to improve organs perfusion can have as positive an impact on survival as possible, according to the guidelines of Surviving Sepsis Initiative [9].

To provide an adequate treatment to the septic patient, it is also necessary to count with a proper monitoring protocol, and in this study we have tried to equate our measures to the regular monitoring of the critically ill patient.

The exploration of the perfusion status in the splanchnic area can be a key step in the evaluation of the septic patient if we consider that this is a compromised area (due to the initial compensatory mechanisms against shock) and also
a potential source for new inflammatory insults when oxygen
delivery is critical. Mucosal cells in the intestinal tract are
the most accessible source of information in the abdomen,
and evaluating their acid-base status can be a reflection of
the adequacy of splanchnic organs perfusion. In terms of
the monitoring strategies for the septic patient, the mucosal
CO₂ is an attractive possibility, for both its simplicity and
ease of interpretation and for many clinicians a funda-
mental monitoring device in critical patients in general
and in the septic patient in particular [10, 11], although
this debate remains inconclusive because its relationship
with the outcome is not unanimously recognized [12]. The
possible role of the bladder mucosa as another source for
measurement has theoretical benefits, because almost all
critically ill patients have a bladder catheter already inserted.

We observed, as expected, a decrease of tissue perfusion
gradually over hours, reflecting the increase in hepato-es-
planchic blood flow that occurs in sepsis, in concordance

| Minutes | Basal | 60 | 120 | 180 | 240 | 300 | 360 |
|---------|-------|----|-----|-----|-----|-----|-----|
| MAP* mmHg | 76 ± 12.6 | 41.2 ± 5.8 | 41.8 ± 7.6 | 39.4 ± 6.4 | 44.4 ± 12.1 | 47.1 ± 9.4 | 44.7 ± 9.4 |
| CO L/min | 1.4 ± 0.4 | 1.07 ± 0.5 | 1.02 ± 0.5 | 1.0 ± 0.5 | 1.06 ± 0.5 | 1.02 ± 0.5 | 0.99 ± 0.5 |
| SVV* % | 9.7 ± 2.6 | 18.2 ± 5.3 | 22.5 ± 5.2 | 25.5 ± 2.3 | 23 ± 6.6 | 21.8 ± 2.9 | 20.3 ± 4.9 |
| CO₂-Gastric* mmHg | 48.1 ± 12.1 | 67.1 ± 10.3 | 74.3 ± 14.9 | 81.1 ± 38.4 | 82.5 ± 48.6 | 81.9 ± 38.7 | 80.8 ± 28.3 |
| CO₂-Bladder mmHg | 29.1 ± 4.9 | 34.0 ± 10.4 | 31.7 ± 11.6 | 33.9 ± 9.8 | 38.6 ± 9.4 | 45.5 ± 14 | 50.0 ± 14.3 |
| Base Deficit | −7.7 ± 2.8 | −10 ± 2.3 | −10.5 ± 4.1 | −10.6 ± 4.4 | −9.9 ± 4.5 | −9.8 ± 5.5 | −12.0 ± 5.1 |

*: Statistically significant for P < 0.05. MAP: mean arterial pressure; CO: cardiac output; SVV: systolic volume variability. Data as mean ± standard deviation.

Figure 3: Correlation between mucosal CO₂ and Gap between mucosal and arterial CO₂.

Figure 4: Correlation between mucosal (gastric and bladder) CO₂ and base deficit in arterial blood.
with that observed in other studies [13, 14]. This was accompanied by a compatible hemodynamic pattern coincident with that found in other studies of E. Coli-induced sepsis in animal models [15].

All the monitoring data obtained in our study are close to those expected in an untreated septic shock. Therefore, our hypothesis was that these changes in low tissue perfusion would also be reflected by data obtained from the bladder tonometry, but this was not the case.

Measurements of CO2 obtained from the urinary bladder are not common in clinical practice, although it has been tested on models of ischemia-reperfusion [16] and hemorrhagic shock [17], exhibiting however in the latter case a worse correlation when compared with data provided by the CO2 obtained from the gut. These results have been also supported by a study on dogs where the gut PCO2 was found to be a more reliable measure when compared with samples measured in vitro [18].

While the pathogenesis of sepsis and septic shock is well recognized and it is accepted that the data provided by mucosal CO2 have unquestionable validity as a reflection of the severity of the shock, the search for new noninvasive and easy to perform monitoring strategies is constant in this field [19]. This is currently raising more expectation of the probing on the most proximal segments of gastrointestinal tract, especially the sublingual capnography [20].

Our data, in contrast to what might be expected, show that bladder PCO2 does not conform to the low perfusion state detected through the multiple monitoring we applied to the subjects of the study. One unavoidable bias in our study regards the use of different methods for gastric and bladder measurements, and this fact could explain in part the differences detected. Notwithstanding, the saline tonometry was the first described [6] and has been used as gold standard for the validation of the air tonometry in gastric mucosa [21]. Until now there have been no studies published with the air tonometry probe into the bladder environment, and its use would have introduced an even greater uncertainty in the results requiring in the first place a validation of the technique in this setting.

Another problem with our study is the small sample of subjects studied. Nevertheless, even with so low number of subjects the difference between the two measures was strikingly evident. Also, this being an experimental study developed in a rigidly controlled scenario, we must presume that under clinical conditions and subjected to more confounding variables, the lack of utility should be even more evident. In any case, a new study in a human clinical environment would definitely clarify this point.

The search for other reproducible and reliable means of measuring tissue CO2 should be maintained but, according to our data, measurement through bladder tonometry does not offer meaningful results and should not be used in the clinic as a guide to treatment.

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