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Comparison of 5% sodium bicarbonate and 10% sodium chloride as contrast agents for lung perfusion with electrical impedance tomography: a prospective clinical study

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Abstract

Introduction This study aimed to compare sodium bicarbonate ($NaHCO_3$) and sodium chloride (NaCl) as contrast agents for regional lung perfusion imaging with electrical impedance tomography in critically ill patients with respiratory failure.

Methods 15 mL 5% $NaHCO_3$ and 10 mL 10% NaCl were sequentially administered in all the enrolled patients with respiratory failure. EIT maps were divided into four cross-regions: upper right (UR), upper left (UL), lower right (LR), and lower left (LL).

Result A total of 20 pair bolus injections from 16 mechanically ventilated patients were obtained. Compared to $NaHCO_3$, NaCl caused a larger drop of maximum impedance amplitude after the bolus injection (1276 ± 329 vs. 509 ± 159 AU, $P < 0.001$). Regional perfusion distribution (%) of four cross-regions between two indicators were significantly correlated ($R^2 = 0.90$ for regional perfusion%, $p < 0.001$; $R^2 = 0.93$ for regional ventilation/perfusion matching, $p < 0.001$) in 80 pair measurements. The Bland–Altman analysis showed a strong overall agreement in regional perfusion distribution (%) [mean bias 0.09% (95% confidence interval, CI: -0.91%, 1.09%), lower limits of agreement (LOA) -8.03% (95% CI: -9.75%, -6.31%), upper LOA 8.21% (95% CI: 6.48%, 9.93%)] between indicators in 80 pair measurements.

Conclusion EIT with $NaHCO_3$ as a contrast agent yields a high agreement of regional lung perfusion compared to NaCl in critically ill patients with respiratory failure.

Keywords Contrast agent, Electrical impedance tomography, Regional lung perfusion

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Introduction

Electrical impedance tomography (EIT) is a non-invasive and radiation-free visualizing tool for the assessment of lung ventilation and perfusion. It has enabled the bedside monitoring of lung perfusion measurement through the indicator-based method for critically ill patients in the intensive care unit (ICU) [1, 2]. In recent years, the saline bolus-based EIT method for perfusion assessment has been widely investigated [3–5]. The reconstructed regional ventilation-perfusion (V/Q) images have many potentials in clinical. It has been suggested that lung V/Q profiles can help to identify massive pulmonary embolism at the bedside [1]. For patients with acute respiratory distress syndrome (ARDS), it can provide an indication of disease severity and prognosis [6, 7]. The EIT V/Q image also has the potential to guide the management of mechanical ventilation in postoperative cardiac surgery patients [8, 9].

However, concerns may be raised regarding the selection of the contrast agent. Currently, hypertonic sodium chloride (NaCl) is the most commonly used contrast agent. Clinical studies have shown that hyperchloremia resulting from saline-based fluid resuscitation may contribute to acute kidney injury and adverse outcomes [10, 11]. Therefore, the potential risks associated with the use of hypertonic NaCl as a contrast agent for EIT-based lung perfusion assessment should not be ignored. These risks prohibit the frequent use of hypertonic NaCl bolus within a short time period. It is, therefore, desirable to find an alternative contrast agent that enables repeated injections in a safer and less damaging way to meet the need for continuous monitoring of pulmonary blood flow in critically ill patients.

As a commonly used therapeutic fluid in shock resuscitation, sodium bicarbonate ($NaHCO_3$) has the potential for applications. Recently, two experimental studies indicated that $NaHCO_3$ might be an alternative option to hypertonic NaCl [12, 13]. $NaHCO_3$ has been found to be generally consistent with hypertonic NaCl as an indicator of lung perfusion in porcine models [13]. However, whether $NaHCO_3$ results in acceptable bias is unknown in critically ill patients. This clinical study aims to further investigate the correlation and agreement of lung perfusion and ventilation/perfusion (V/Q) matching between these two contrast indicators in critically ill patients with respiratory failure.

Method

Study design and population

This is a single-center, prospective, cross-over study (ClinicalTrials.gov, NCT06868810). The study was approved by the Institutional Research and Ethics Committee of the Peking Union Medical College Hospital (I-24PJ0505). Written informed consent was obtained from all participants or their next of kin. Mechanically ventilated patients in the intensive care unit with lung disease were screened. They were included if a central venous catheter was placed due to routine clinical treatments and if regional V/Q information was of interest. Exclusion criteria were: contraindications to the use of EIT (automatic implantable cardioverter defibrillator, chest wounds limiting electrode belt placement, implantable pumps, etc.), severe hyperchloremia (> 155 mmol/L), unable to tolerate breath-hold maneuver.

Study protocol

Each enrolled patient has received two separate bolus injections of 15 mL of 5% $NaHCO_3$ and 10 mL of 10% NaCl (except for one patient who received 5 pairs of injection). There was a 10-minute washout period between the two injections. The order of injections was determined randomly by flipping a coin. The procedure of bolus injection was performed based on our previous study [1]. Each injection was given via the central venous catheter during a breathing pause of at least 8 s at the end-expiratory hold. The patients' status remained unchanged throughout the study period.

EIT methods

EIT measurements were performed with PulmoVista 500 (Dräger Medical, Lübeck, Germany). A silicone EIT belt with 16 surface electrodes was placed around the patient's thorax at the 4th -5th intercostal space level in the supine position. Data were continuously recorded at 20 Hz. EIT data were analyzed offline using customized software programmed with MATLAB R2023 (MathWorks Inc., Natick, MA).

The functional ventilation map was reconstructed from an averaged period of tidal breathing [14]. The functional perfusion map was derived by calculating the slope of the impedance-time curve after contrast injection [15]. Regions of ventilation and perfusion were defined as pixels exceeding 20% of the maximum value of the functional ventilation and perfusion maps. Three types of regions were determined: the region that is mostly ventilated (R_V), the region that is mostly perfused (R_P), and the region with both ventilation and perfusion (R_{V+P}). Hence, regional V/Q match was calculated as follows:

V/Q match % = R_{V+P} / $(R_V+R_P+R_{V+P}) \times 100\%$ [16].

Outcome measurements

EIT images were divided into symmetrical, non-overlapping, four cross-regions: upper right (UR), upper left (UL), lower right (LR), and lower left (LL). The four regions of regional lung perfusion distribution (%) and regional V/Q match (%) were calculated [1]. Hence, 4 pairs of regional perfusion distribution and 4 pairs of V/Q matching were obtained in one EIT map.

Statistical analysis

The paired t-test was used to compare the change in impedance between the two indicators. Correlation and agreement between two contrast agents for regional lung perfusion and EIT-related parameters were performed by Pearson linear correlation and Bland–Altman analyses, respectively. Statistical analyses were conducted in R (Version 4.2.3) and the software package SPSS 25.0 (IBM Corp. Armonk, NY, USA). $P<0.05$ denotes statistical significance.

Results

15/16 patients only received one pair, including two fluid contrast bolus for lung perfusion, and 1/16 patient received five pairs of fluid bolus on different days. As a result, a total of 20 pairs of 15 ml 5% $NaHCO_3$ and 10 ml 10% NaCl fluid injections were recorded in the 16 patients. Moreover, one EIT image was divided into four regions. Hence, a total of 80 pairs (20 × 4) of regional perfusion and V/Q by the two solutions were obtained.

Patient characteristics

The baseline APACHE II score was 18 ± 5, and PaO_2/FiO_2 was 210 ± 79 mmHg. The etiology included pneumonia (9/16), extrapulmonary infection (5/16), pulmonary embolism (1/16), and alveolar hemorrhage (1/16). Patients' demographics and clinical characteristics are summarized in Table 1.

Table 1 Patients' demographics and clinical characteristics

Variable	
Patients' characteristics (*n* = 16)	
Age yr	57 ± 16
Sex (M/F)	13/3
BMI Kg/m^2	25 ± 4
Etiology n (%)	
Pneumonia	9 (56)
Extrapulmonary infection	5 (31)
Pulmonary embolism	1 (6)
Alveolar hemorrhage	1 (6)
Baseline parameters (*n* = 20)	
PH	7.4 ± 0.1
Na + mmol/L	142 ± 5
Cl- mmol/L	105 ± 7
HCO_3- mmol/L	22 ± 4
PaO_2/FiO_2 mmHg	210 ± 79
APACHE II Score	18 ± 5
VT ml	388 ± 56
PEEP cmH_2O	7 ± 2
FiO_2%	68 ± 28

Data are expressed as mean ± SD or number (%) as appropriate. BMI, body mass index; Na±, sodium ion; Cl-, chloride ion; HCO_3-, bicarbonate; APACHE, acute physiology, and chronic health evaluation; VT, tidal volume; PEEP, positive end-expiratory pressure.

Outcomes

Compared to 15 ml 5% $NaHCO_3$, 10 ml 10% NaCl caused a larger decrease in impedance after the bolus injection (1276 ± 329 vs. 509 ± 159 arbitrary unit, $P<0.001$). Figure 1 shows the impedance-time curves during tidal breathing and bolus injection periods from a single patient. Ventilation distribution, perfusion distribution, and regional V/Q match images were compared (Fig. 1A and B, **2**nd– 4th columns). A similar perfusion and V/Q match images were found between the two contrast agents.

Regional perfusion distribution (%) and V/Q match (%) in four cross-regions (UR, UL, LR, and LL) between two indicators were significantly correlated overall [$R^2=0.90$, regional perfusion%, $p<0.001$; $R^2=0.93$, regional V/Q matching, $p<0.001$] in 80 pairs of measurements (Fig. 2A and C). In the regional V/Q match, the LR and UL regions had a higher correlation of two indicators than the UR and LL regions. In perfusion distribution, LR region had the highest correlation. The Bland–Altman analysis showed a strong overall agreement in regional perfusion distribution(%) [mean bias 0.09% (95% confidence interval, CI: -0.91%, 1.09%), lower limits of agreement (LOA) -8.03% (95% CI: -9.75%, -6.31%), upper LOA 8.21% (95% CI: 6.48%, 9.93%)] and V/Q match (%) [mean bias − 0.04% (95% CI: -0.71%, 0.64%), lower LOA − 5.98% (95% CI: -7.14%, -4.82%), upper LOA 5.90% (95% CI: 4.75%, 7.06%)] between contrast agents in 160 pairs of measurements (Fig. 2B and D).

A case of repeated measurements

One patient received five pairs of contrast examinations on different days due to changes in his condition and the clinical need for lung perfusion assessment. A set of line graphs displaying changes in regional lung perfusion % and regional V/Q match % at different time points is presented in Fig. 3. In some regions, such as the lower right and upper right, the results from the two contrast agents are comparable. Whereas in certain regions, for example, the upper left and lower left, the regional lung perfusion % between $NaHCO_3$ and NaCl are more differentiated.

Discussion

To the best of our knowledge, this is the first clinical study to validate an alternative contrast agent for EIT-based regional lung perfusion assessment in clinical settings. In the present study, regional lung perfusion and the corresponding V/Q matching images were calculated using EIT with $NaHCO_3$ and with NaCl in 16 patients with respiratory failure. Although the decrease in impedance introduced by $NaHCO_3$ was lower than that by NaCl, the regional information provided by the two contrast agents was comparable. In a single patient who has received multiple examinations on different days, the EIT

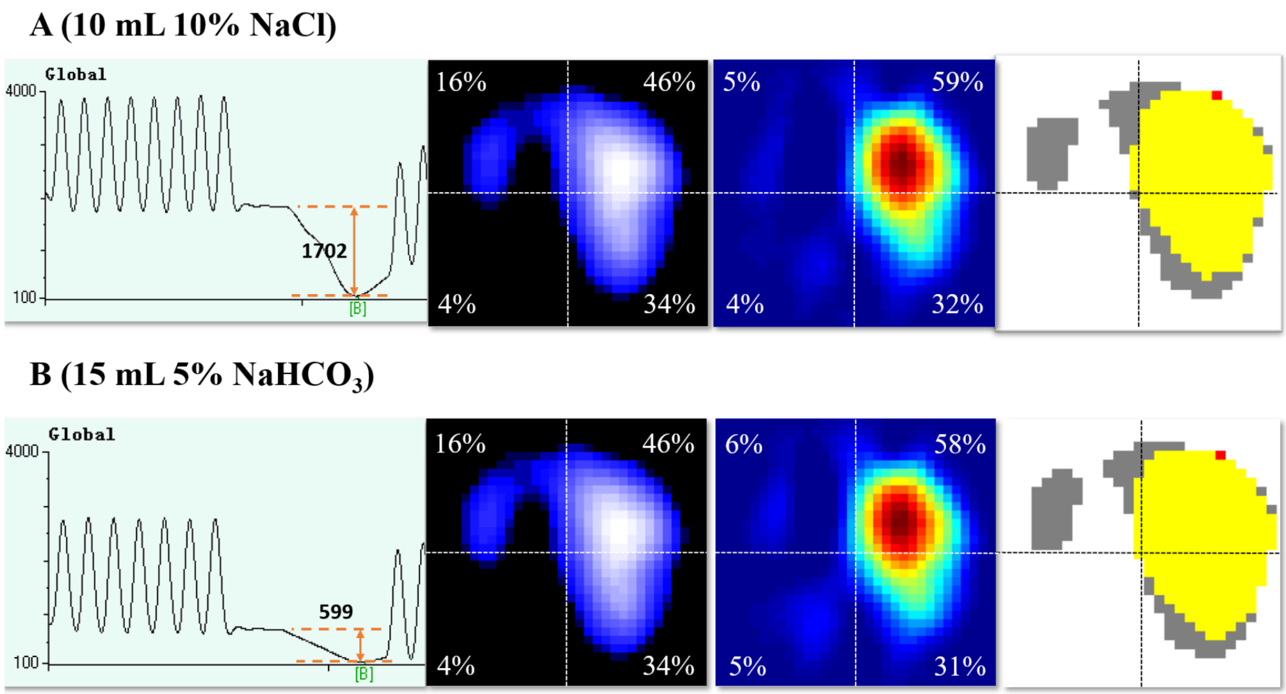

Fig. 1 An individual patient's data shows two contrasts agents for perfusion and regional V/Q estimation in electrical impedance tomography. 10 ml 10% NaCl caused a greater drop of impedance amplitude than 15 ml 5% $NaHCO_3$ during the breath hold period. A similar perfusion and V/Q match images were found between the two indicators. $NaHCO_3$, sodium bicarbonate; NaCl, sodium chloride

results generated by $NaHCO_3$ and NaCl are similar in some lung areas and different in others. More evidence with larger samples is required to validate the agreement between the two agents in monitoring dynamic changes in patients' pulmonary conditions in the future.

The EIT-based regional lung perfusion method is an emerging bedside tool for critically ill patients [17, 18]. It has been found to be a promising alternative to current lung perfusion imaging techniques such as single-photon emission computed tomography (SPECT), computed tomography (CT), or positron emission tomography (PET) [3, 4, 19]. The latter are often not applicable to ICU patients due to the risk of patient transportation. On the other hand, EIT enables timely and dynamic lung perfusion monitoring at the bedside, which provides valuable insights for clinicians. To date, hypertonic NaCl is the most frequently used contrast agent. The concentration of NaCl used by the researcher ranged from 3 to 20% (20% only presented in animal studies) [2]. Overall, 5-10% NaCl has been employed to assess lung perfusion and regional V/Q match in different clinical conditions at the bedside, such as ARDS, pulmonary embolism, COVID-19, etc [6, 16, 20–24]. The potential clinical applications of lung perfusion by EIT and advantages/disadvantages of 10% NaCl and 5% $NaHCO_3$ were summarized in Table 2.

The amount of fluid and chlorine contained in a bolus of hypertonic NaCl is small when compared to the whole internal environment. In general, the injected hypertonic NaCl is able to be equilibrated by the organism in a short period of time. However, in patients with severe illness in several conditions, the use of hypertonic NaCl is restricted. For example, in critically ill patients with hyperchloremia, which commonly occurs in septic shock, the addition of sodium chloride might deteriorate the situation and increase the risk of acute kidney injury [25]. Similarly, it is also prohibited in patients with severe electrolyte disorders, edematous diseases, and severe hypertension. Moreover, other side effects of hypertonic saline, such as global and regional hemodynamic effects [26], chloride overload, and impaired renal perfusion need to be considered. Therefore, it is warranted to validate another contrast agent without chloride in the critically ill patient with hyperchloremia.

$NaHCO_3$ is commonly used and accessible in hospitals and ICUs. It is the basic treatment for severe metabolic acidemia with the ability to balance the pH of the individual organism [27]. Recently, $NaHCO_3$ has been proposed as an alternative to hypertonic NaCl in two animal studies [12, 13]. Muders et al. investigated the ability of five different contrast agents in anesthetized pigs, including 5.85% NaCl, 8.4% $NaHCO_3$, 5% Glucose, isotonic balanced crystalloid solution, and Iomeprol 400 mg/ml. Among them, NaCl and $NaHCO_3$ showed the most satisfying results with the best signal and image quality. Gaulton et al. compared the proportion of lung

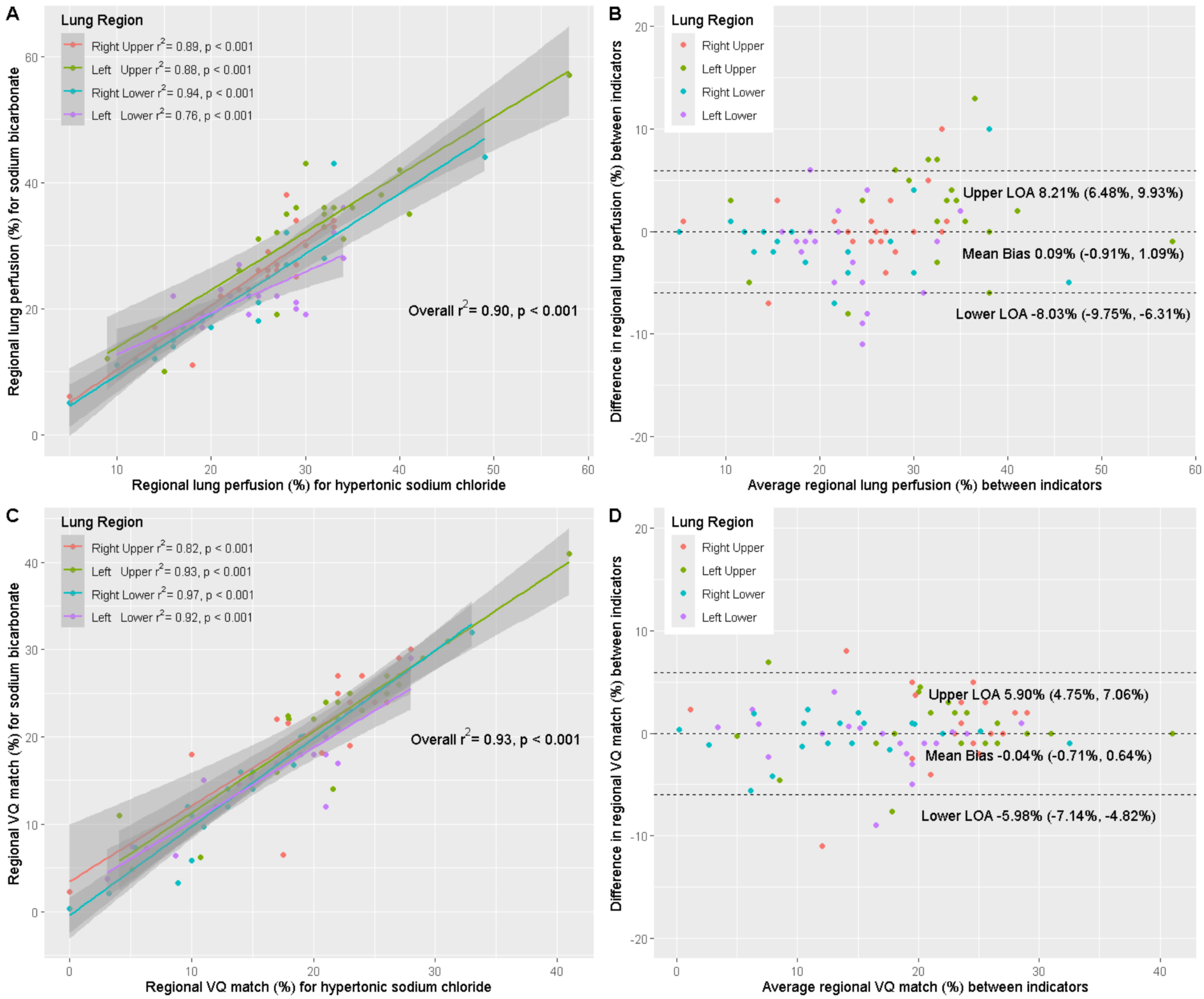

Fig. 2 Correlation and Bland-Altman agreement analysis of four cross-regional perfusion distributions and V/Q match between hypertonic sodium saline and sodium bicarbonate. **2A**, Scatter plot of regional lung perfusion (% of total perfusion) between indicators. Correlation defined by R^2 is shown overall and within each lung region. **2B**, Bland–Altman plot of regional lung perfusion (% of total perfusion) by lung region between indicators. **2C**, Scatter plot of regional V/Q match (%) between indicators. **2D**, Bland–Altman plot of r regional V/Q match (%) between indicators. LOA, limits of agreement

perfusion distribution in different lung regions by 12% NaCl and 8.4% $NaHCO_3$ in lung injury pig models. The results obtained with the two contrast agents were comparable. Thus, we conducted the first clinical research to further validate the potential of $NaHCO_3$ as an alternative contrast agent in the EIT-based lung perfusion technique under clinical conditions. In the present study, we adopted 15 mL of 5% $NaHCO_3$ rather than 10 mL of 8.4% $NaHCO_3$ (used in previous animal studies) because it is more accessible in the hospital and potentially less irritating to patients. The two solutions are comparable in conductivity for they contain similar amounts of sodium ions. However, the selection of doses and concentrations requires further investigation.

As a contrast agent, $NaHCO_3$ has several potential advantages: (1) $NaHCO_3$ has no chloride ions. The associated risk of kidney injury might, therefore, be low. It has the advantage in patients with hyperchloremia. (2) $NaHCO_3$ might have a lower impact on the internal environment, and multiple repeated bolus injections within a short period are relatively safe, especially in critically ill patients with shock. These patients have metabolic toxicity, and the administration of $NaHCO_3$ is required. (3) $NaHCO_3$ has a lower osmolality. It might cause less vascular irritation when performing peripheral bolus. Thus, NaHCO3 has the potential for peripheral venous injection, which might be able to eliminate the need for a central venous catheter.

There are several limitations in this study: (1) The sample size is small. (2) The change of plasmatic chloride, sodium levels, and pH were unavailable during different bolus solutions injections. The potential adverse effects

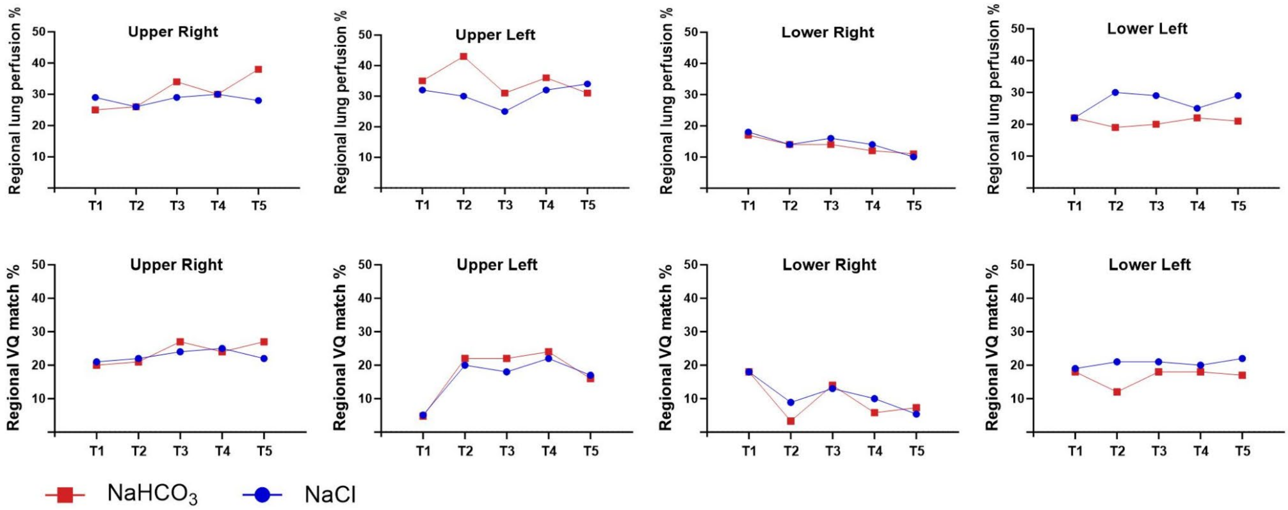

Fig. 3 Changes in regional lung perfusion % and regional V/Q match % by $NaHCO_3$ and NaCl on different days in a single patient. $NaHCO_3$, sodium bicarbonate; NaCl, sodium chloride

Table 2 Potential applications of EIT lung perfusion and advantages/disadvantages of 10% NaCl and 5% $NaHCO_3$

Potential applications	10 ml 10% NaCl	15 ml 5% $NaHCO_3$
• Identify etiologies of acute respiratory failure (pulmonary embolism-related disease, diffuse lung involvement disease, and focal lung involvement disease) • Monitor the effect of anticoagulation/thrombolytic therapy in pulmonary embolism. • Assess V/Q mismatch of ARDS • Assess the effect of prone position/high PEEP on lung perfusion and regional V/Q • Assess the effects of inhaled NO on lung perfusion	• Advantages: commonly used in many clinical trials • Potential disadvantages: hyperchloremia (risk of kidney injury), high risk of high osmolality for peripheral venous bolus	• Potential advantages: possible for peripheral venous bolus, potential benefit for shock patients with metabolic toxicity • Disadvantages: further study is required to validate 5% $NaHCO_3$ in different clinical conditions

V/Q, ventilation-perfusion; ARDS, acute respiratory distress syndrome; No, nitrogen monoxide.

(hyperchloremia, acidosis, and possible acute kidney injury) of a 10 ml bolus of 10% NaCl were speculated, and clear evidence was lacking. The included population was not sufficient to discern any differences following the injection of a single bolus per day. Hence, the potential benefits of 5% $NaHCO_3$ (vs. 10% NaCl) require further study. (3) Compared to NaCl, the impact of the novel contrast agent ($NaHCO_3$) on clinical decisions and outcomes was not evaluated. (4) We analyzed the agreement between the two contrast agents by dividing the lung into four regions, for it is most commonly used in clinical. A pixel-based analysis might be more accurate. (5) We did not use the cardiac output (CO) and minute ventilation (MV) for correction, which can also affect the analysis of V/Q. (6) End-expiratory and end-inspiratory holds were used during the saline bolus implementation for lung perfusion measurement. The end-expiratory hold was used in the present study, and the impaired circulation by breath hold was not found. The potential benefits of end-expiratory hold were the following: (a) little impact on venous return and circulation; (b) an obvious decrease of impedance could be easily caused at end-expiration with a lower impedance baseline. (7) The repeated measures were not preset in an individual patient. Actually, several lung perfusion assessments were required by the attending doctor on different days based on clinical conditions. We think an individual case with repeat measures might have interest in the dynamic assessment of agreement of the two solutions. (8) The measurement of lung perfusion by EIT is influenced not only by the contrast but also by the quality of injection (speed and consistency). For the saline bolus quality control, the investigator received the same standardized bolus training for the two contrast boluses. With the aim to reduce the variation of performers, the contrast bolus was done by the same investigator.

Conclusion

Our findings demonstrate that $NaHCO_3$ may be a comparable indicator to measure regional lung perfusion and V/Q by EIT in a cohort of critically ill patients. Further study is required to validate the impact of $NaHCO_3$ on clinical decisions and outcomes in clinical practice.

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Author contributions
HH and YC conceived the study protocol; HH, YC, YL, SY, and YG participated in the design and coordination of the study; YH, HH, YC, YG, SY, SW, and YL collected study data; YG, YC, YH, HH, YL, SY, SW, and ZZ participated in data interpretation; YG, YH, HH and YC drafted the manuscript; YL, SY and ZZ

revised the manuscript significantly. All authors read and approved the final version of the manuscript.

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Data availability
The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request. The datasets supporting the conclusions of this article are included within the article.

Declarations

Ethics approval and consent to participate
This study was conducted in accordance with the principles outlined in the Declaration of Helsinki. The study protocol was approved by the Institutional Research and Ethics Committee of the Peking Union Medical College Hospital (I-24PJ0505) and is registered at ClinicalTrials.gov (NCT06868810). Written informed consent was obtained from all participants or their next of kin.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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