


Correlation of End-Tidal Carbon Dioxide with Arterial Carbon Dioxide in Mechanically Ventilated Neonates: A Scoping Review

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Abstract

Monitoring CO₂ levels in intubated neonates is highly relevant in the face of complications associated with altered CO₂ levels. Thus, this review aims to present the scientific evidence in the literature regarding the correlation between arterial carbon dioxide measured by non-invasive methods in newborns submitted to invasive mechanical ventilation. The search was carried out from January 2020 to January 2021, in the Scopus, Medline, The Cochrane Library, Web of Science, CINAHL and Embase databases. Also, a manual search of the references of included studies was performed. The main descriptors used were: “capnography,” “premature infant,” “blood gas analysis,” and “mechanical ventilation.” As a result, 221 articles were identified, and 18 were included in this review. A total of 789 newborns were evaluated, with gestational age between 22.8 and 42.2 weeks and birth weight between 332 and 4790 g. Capnometry was the most widely used non-invasive method. In general, the correlation and agreement between the methods evaluated in the studies were strong/high. The birth weight did not influence the results. The gestational age of fewer than 37 weeks implied, in its majority, a moderate correlation and agreement. Therefore, we can conclude that there was a predominance of a strong correlation between arterial blood gases and non-invasive methods, although there are variations found in the literature. Even so, the results were promising and may provide valuable data for future studies, which are necessary to consolidate non-invasive methods as a reliable and viable alternative to arterial blood gasometry.

Keywords

capnography, transcutaneous blood gas monitoring, artificial respiration, newborn, blood gas analysis

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Introduction

Respiratory disorders are among the main factors responsible for the admission of newborns (NBs) to Neonatal Intensive Care Units (NICUs),¹ with an estimated frequency between 50.5% and 74.8% in Brazil.^{2,3} Arterial blood gas, widely used in NICUs, is considered the gold standard for blood gas analysis since it allows the assessment of possible respiratory, metabolic and circulatory disorders.⁴ However, it is an invasive exam, requiring arterial puncture, often difficult to perform,⁵ and can cause pain, infection, and harmful blood loss for hemodynamically unstable newborns.^{6,7} Besides, its result may be influenced by technical

issues such as the time between sample collection and sending it to the laboratory.

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Non-invasive assessment methods such as capnometry and transcutaneous carbon dioxide measurement are alternatives to arterial gasometry for monitoring newborns submitted to some ventilatory support, preventing frequent blood collections. Transcutaneous measurement of CO₂ (tcCO₂) is based on the diffusion of CO₂ through body tissues, which can be detected by a sensor positioned on the skin surface.⁸ Capnometry quantifies the level of CO₂ throughout the respiratory cycle by means of its concentration in exhaled air at the end of exhalation (PetCO₂). It is used for successful verification of orotracheal intubation, assessment of pulmonary circulation and respiratory status, and optimization of mechanical ventilation.⁹ The equipment used are capnometers, lateral flow (sidestream) or main flow (mainstream). In the mainstream, the sensor is connected directly to the endotracheal tube as part of the intubated patients' respiratory circuit. On the other hand, in the sidestream, the sensor is located in the equipment's central unit, where the gases are analyzed.^{10,11}

CO₂ is transported by hemoglobin to the lungs to be exhaled. The lungs have areas perfused by the bloodstream where gas exchange occurs, called alveolar ventilation, and areas that serve only for air conduction, called anatomical dead space. On the other hand, the physiological dead space refers to areas destined for gas exchange without effective function.¹¹ The balance between ventilation (V) and perfusion (Q) in the lung regions is essential for gas exchange. Some diseases can alter the V/Q ratio causing hypoxemia or hypercapnia. Thus, the comparison of the amount of CO₂ exhaled with the amount of CO₂ in arterial blood represents a good estimate of the V/Q ratio.¹¹ Numerous studies have shown a good correlation between PaCO₂ and PetCO₂, both in adults¹²⁻¹⁵ and children.^{16,17} However, in newborns and preterm infants, there are still few studies and reliable results. In this context, this review aims to present the scientific evidence in the literature regarding the correlation of arterial CO₂ with CO₂ measured with non-invasive methods in newborns undergoing invasive mechanical ventilation (IMV).

Material and Methods

This review was carried out according to the protocol recommended by the Joanna Briggs Institute.¹⁸ The included studies were listed based on the mnemonic strategy PCC—Population, Concept and Context, in which: P corresponds to newborns submitted to invasive mechanical ventilation; C is the correlation of arterial CO₂ with CO₂ from non-invasive methods; C means NICU. Therefore, based on this strategy, the guiding question was defined: "What is the existing scientific

evidence on arterial carbon dioxide measured by non-invasive methods in newborns submitted to IMV?

The search was carried out between January 2020 and January 2021, without delimitation of publication period in the following databases: Scopus, Medline, The Cochrane Library, Web of Science and CINAHL based on descriptors defined by consultation with Medical Subject Headings (MeSH) and synonyms in the English language. The following search strategy was used: (Capnography OR Capnometry OR "Transcutaneous carbon" OR "Carbon dioxide" OR "arterial carbon dioxide monitoring" OR "expired carbon dioxide") AND ("Premature babies" OR "premature babies" OR newborn OR "very low birth weight") AND ("Blood gas analysis") AND ("mechanical ventilation" OR "neonatal ventilation"). In the Embase database, the search for Embase Subject Headings (Emtree) and synonyms in English was performed: (Capnometry OR "Transcutaneous carbon" OR "Carbon dioxide" OR "arterial carbon dioxide monitoring" OR "expired carbon dioxide") AND (Prematurity OR "premature babies" OR newborns OR "very low birth weight babies") AND ("Blood gas analysis") AND ("artificial ventilation" OR "ventilation for newborns"). The research was limited to studies published in Portuguese, English, Spanish, and French. Complementary, a search was made from other sources, such as studies in progress in the Brazilian Clinical Trials Records (REBEC) and the US National Library of Medicine (NIH Clinical Trials). A manual search was performed in references of included studies.

From the initial search strategy, the selected articles were obtained by title and abstract by 2 authors independently (IPMM and AMN) to exclude duplicate articles and those that did not reach this review's goals. The inclusion criteria were observational studies and clinical trials that reported using blood gas analyses and non-invasive methods to predict CO₂ in newborns, with post-birth age up to six months, admitted to NICU to assess IMV. Studies carried out in children longer than six months or in adults, and in surgical environments, the emergency room and emergency care were excluded. Eventual disagreements between reviewers were resolved by consensus, and the agreement between them was measured by applying a Cohen¹⁹ Kappa statistic. The reference manager Mendeley was used to assist in the articles' screening.

In its turn, the screened articles in the previous step had their eligibility confirmed by reading in full, also carried out by a pair of reviewers independently (IPMM and AMN). Disagreement cases were assessed by a third reviewer (PKH). From the included articles, characteristics were extracted by a pair of reviewers independently

for narrative analysis. Then, the following data were extracted: authors, year of publication, sample, measurements, birth weight (in grams), gestational age (in weeks), main comorbidities, non-invasive method, reference standard, results, and conclusion. The presentation and discussion of the results were carried out descriptively.

Ethical Approval and Informed Consent

As this is a review, this study does not involve data collection in any form (tests, experiments, observation, interviews, questionnaires, evaluation of medical records) with human beings. Therefore, submission and approval by the institution's ethics committee does not apply.

Results

We identified 127 articles in the Scopus (98), Pubmed/Medline (10), Cochrane (10), Web of Science (1), CINAHL (4), and Embase (4) databases. In REBEC, 94 were identified, and none in the NIH clinical trials, totaling 221. After excluding 6 duplicate articles, we evaluated 215 by title and abstract, and after this 190 were excluded. The following reasons led to the exclusion: the titles and abstracts did not involve a comparative analysis among the methods of measuring CO₂ levels in an invasive and non-invasive; many studies were carried out in older children, adolescents, adults, and animals; and, finally, some of the publications did not correspond to articles but theses, monographs and books. After reading 25 articles in full and applying the eligibility criteria, 19 articles were excluded because the analysis of arterial blood gas was not performed, the newborns were submitted to non-invasive MV, environments outside the NICU and analysis of graphical waves of exhaled CO₂. Therefore, 6 articles were included. From the manual search in the references, 12 other articles were added at the end of the process, totaling 18 articles in the final sample. The *kappa* index showed an agreement of 0.889 between the reviewers, classified as almost perfect.²⁰ The search and selection process are presented in the flowchart (Figure 1), according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA).²¹

Population

A total of 789 NBs were evaluated in the 18 articles, and in only 760 NBs, arterial blood gases were used. The gestational age (GA) of newborns ranged from 22.8 to 42.2 weeks. In 8 studies, all newborns assessed were

premature with GA less than 37 weeks.²²⁻²⁹ Birth weight ranged from 332 to 4790 g, and in some studies, only newborns with extremely low birth weight,²⁵ very low birth weight²² and low birth weight were included.²⁴

The respiratory distress syndrome (RDS), meconium aspiration syndrome (SAM) and pneumonia were the main comorbidities associated with the newborns who had participated of the studies. The authors excluded neonates with congenital heart disease from most studies. The characteristics of the included studies population were classified according to the main author, year of publication, and type of study are shown in Table 1.

Non-Invasive Methods

Two articles used tcCO₂,^{23,34} and only 2 studies used both tcCO₂ and PetCO₂.^{27,36} The other articles evaluated the estimate of arterial CO₂ by capnometry, in which half of these used lateral flow capnometers and the others mainstream. The measurement performed in the non-invasive method occurred continuously (without pauses) in the majority of the studies.^{22,23,27,29,32,35} The measurement was recorded simultaneously with blood collection in most of the articles. In 2 studies it occurred before collection,^{28,34} 1 after the collection³⁰ and another before and after collection.³⁶ The umbilical artery was the primary arterial access used. The description of non-invasive methods evaluated in the studies is shown in Table 2.

Correlation and Agreement Between Non-Invasive and Arterial CO₂

Statistical tests verified the correlation and agreement analysis of the methods. The correlation coefficients and Bland-Altman analysis of agreement were most used. In general, the correlation of the methods was considered strong in 12 articles, moderate in 4 and weak in 1 article.

The Bland-Altman concordance analysis was applied in all studies that evaluated this parameter, having been considered high in 8 articles, moderate in 1 and low in 8.

For the articles that analyzed the influence of birth weight on the correlation and agreement between the methods, in 5 of them there was no influence, maintaining a strong correlation,^{22,26,28,33,38} high agreement,^{28,33,38} and low agreement.^{22,26} In 3 others, there was a decrease in correlation and agreement,³⁵ only in agreement³⁷ and only in correlation when weight was less than 1500 g.³¹

In studies that analyzed exclusively preterm infants, the correlation was strong^{22,25,26,28,29} and moderate.^{24,27} The agreement was high,^{25,28,30} moderate^{23,29} and low.^{22,24,35} One study compared the correlation

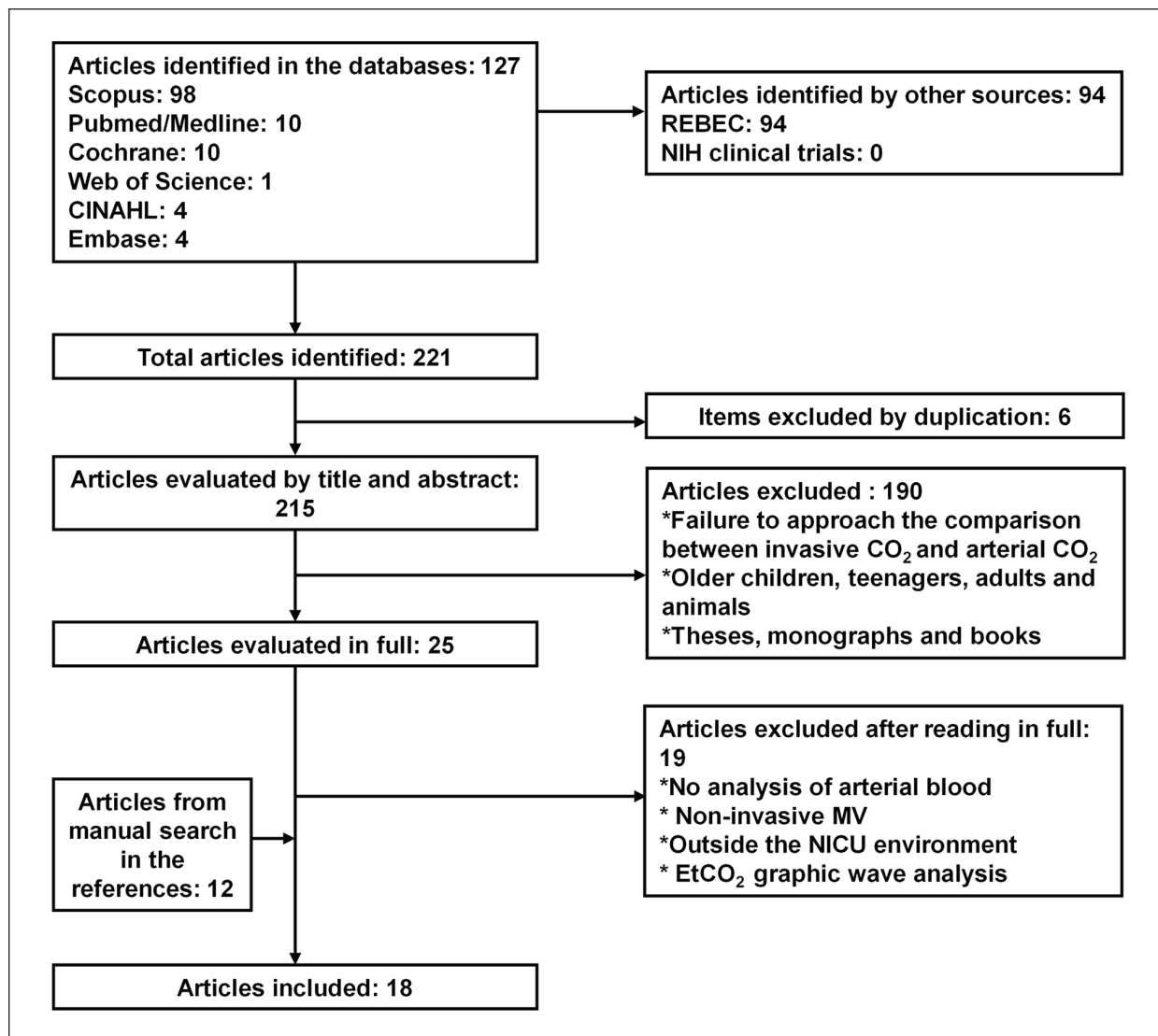


Figure 1. Flowchart of the stages of identification, screening and selection of articles.

and agreement between term and premature NBs, that both were high.³² Another study found only the correlation, which was strong in term and preterm NBs from 28 to 32 weeks and moderate in preterm infants from 32 to 37.³¹

About lung diseases, in 2 studies the correlation was greater in newborns with RDS using surfactant than in those who did not use it.^{6,24} In 2 studies, newborns with moderate and severe lung disease maintained a strong high correlation,^{29,37} and in only one, the correlation was moderate in the presence of SDR.³¹ Details about the statistical tests, the correlation and agreement values are shown in Table 3, and the conclusion of the results are shown in Table 4.

Discussion

The correlation and agreement between invasive and non-invasive methods for CO₂ analysis in newborns, especially in premature infants, is divergent in the literature. The newborns studied in this review had comorbidities, which can compromise the agreement of the methods. Despite the differences between the selected articles, such as GA, birth weight and comorbidities, many articles showed a strong correlation and agreement between the methods.

The non-invasive methods showed in this review were PetCO₂/EtCO₂ and tcCO₂. TcCO₂ were performed in few studies. It is a method that can be used in invasive and non-invasive ventilation and even in unventilated

Table 1. Characteristics of the Population Sample of the Articles Included.

Author	Sample (NB)	Measurements (method-PaCO ₂)	Gestational age (week)	Comorbidities
Meredith and Monaco ³⁰	16	132 PetCO ₂	22-40	RDS, sepsis, MAS, asphyxia
Nangia et al ³¹	152	152 ETcCO ₂	28-42	Asphyxia, MAS, RDS
Rozycki et al ²⁶	48	411 EtCO ₂	28.3 ± 4.7	Pulmonary disease
Wu et al ³²	61 (20 e 41 Premature Infants)	130 PetCO ₂	31.4 (22.8-42.2)	RDS, heart diseases
Aliwalas et al ²⁷	27 (Premature Infants)	81 PetCO ₂ e TcPCO ₂	Mean 26.3 (<28)	RDS
Singh and Singhal ²⁵	31 (ELBW <1000g)	754 EtCO ₂	23-27	RDS
Kugelman et al ³³	27	222 DETCO ₂ e 212 PETCO ₂	32.5 (24.8-40.8)	RDS, TEF
Bernet et al ³⁴	20	82 PtcCO ₂	38.25 (29-41)	DH, NEC, RDS
Bhat andAbhishek ⁶	32	133 EtCO ₂	27-40	RDS, MAS, sepsis, asphyxia
Kugelman et al ²⁸	16 (Premature Infants)	195 dCap	27.1 (24.7-34.7)	RDS
Trevisanuto et al ²²	45 (VLBW)	143 ETcCO ₂	23-33	RDS
Singh et al ^{35*}	48 AA: 29 (22 VLBW e 7 no-VLBW)	286 EtCO ₂ AA: 160 (119 VLBW 41 no-VLBW)	VLBW: 26.3 ± 2.3 No-VLBW: 36.2 ± 2.9	VLBW: RDS, IVH, ROP No-VLBW: GTC, RD
Tingay et al ³⁶	50	132 EtCO ₂ /TcCO ₂	Mean 37	IO, TEF
Mukhopadhyay et al ^{23**}	123 (52 após PtcCO ₂) AS:42	1338 PtcCO ₂ AS: 774	27.7 ± 3.9	RDS, MAS, PNPH, RD
Kugelman et al ³⁷	24	332 dCap	26.8 (23.6-38.6)	RDS, PH
Kugelman et al ³⁸	55 (25- OG; 30 - CG)	761 dETCO ₂	OG: 29.1 (24.5-39) CG: 28.2 (23.5-37.9)	OG: RDS, TTN, PH CG: RDS, TTN, PH
Lin et al ²⁴	34 (Premature Infants)	101 PetCO ₂ (53 VLBW e 48 no-VLBW)	VLBW: 28.3 ± 1.8 No-VLBW: 32.3 ± 1.9	BPD, PDA, RDS
Nakato et al ²⁹	51 (Premature Infants)	221 EtCO ₂	28.08 + 3.19	RDS, sepsis

Abbreviations: Newborn, newborn; ELBW, extremely low birth weight; VLBW, very low birth weight; AA, arterial samples; OG, open group; CG, closed group; ETcCO₂, end-tidal carbon dioxide; DETCO₂, distal end-tidal carbon dioxide; PETCO₂, proximal end-tidal carbon dioxide; PetCO₂, end-tidal carbon dioxide pressure; PtcCO₂ = TcPCO₂, transcutaneous carbon dioxide; dCap, distal capnography; RDS, respiratory distress syndrome; TEF, tracheoesophageal fistula; MAS, meconium aspiration syndrome; NEC, necrotizing enterocolitis; DH, diaphragmatic hernia; IVH, intraventricular hemorrhage; ROP, retinopathy of prematurity; RD, respiratory distress; IO, intestinal obstruction; GTC, gastroschisis; PH, pulmonary hypertension; TTN, transient tachypnea of the newborn; BPD, bronchopulmonary dysplasia; PDA, persistence of the ductus arteriosus; PNPH, persistent neonatal pulmonary hypertension.

*The values of gestational age, birth weight and comorbidities are for all patients, not discriminating against those who only received arterial blood collection.

**The values of gestational age and birth weight refer to all patients who were evaluated with PtcCO₂, without discrimination regarding arterial blood collections.

patients, while the expired CO₂ is used in IMV.⁸ One criteria of the review were to include the newborns submitted to IMV, which can have affected the smaller number of studies with a transcutaneous approach.

Among the studies that used tcCO₂, a moderate correlation and agreement was found and a low agreement. Although in other studies, they are strong in critically ill newborns³⁹ and very low birth weight newborns (VLBW).⁴⁰

The RDS, or hyaline membrane disease, was the comorbidity most associated with neonates in the studies included in this review. It is the leading cause of pulmonary involvement in newborns, especially in premature infants, with ventilatory management as one of the pillars of treatment, including the IMV.⁴¹ In general,

the correlation between EtCO₂ and PaCO₂ with lung disease was considered strong, although it has also been found weak in literature.⁴² In severe lung disease cases, the correlation and agreement were less reliable,³⁵ as demonstrated by another study.⁴³ The correlation was higher after the use of surfactant for RDS;²⁴ however, in another study, the correlation and agreement showed moderate after surfactant use.²⁷ A literature review that analyzed the prediction of PaCO₂ through EtCO₂ indicates that the correlation between the methods is stronger if no present lung disease.⁴⁴

In only one study,³² cardiopulmonary malformation appeared among the newborns' comorbidities, although it was a reason for exclusion in most articles. In situations of cyanotic congenital anomalies, PetCO₂ can be

Table 2. Characteristics of the Non-Invasive Methods Evaluated in the Studies and the Gold Standard.

Author	Non-invasive method: exhaled or transcutaneous CO ₂ (measurement)	Reference standard-arterial gasometry (sample)
Meredith and Monaco ³⁰	<i>Mainstream</i> -continuous, record after blood collection	Umbilical or peripheral artery
Nangia et al ³¹	<i>Sidestream</i> -continuous, record simultaneous with blood collection	Radial artery
Rozycki et al ²⁶	<i>Mainstream</i> -continuous, record simultaneous with blood collection	Arterial catheter
Wu et al ³²	<i>Mainstream</i> -no continuous, record simultaneous with blood collection	Umbilical or radial artery
Aliwalas et al ²⁷	<i>Sidestream microstream</i> and transcutaneous: no continuous, record simultaneous with blood collection	Umbilical artery
Singh and Singhal ²⁵	<i>Mainstream</i> -continuous	Umbilical or radial artery
Kugelman et al ³³	<i>Sidestream</i> (DET _{CO₂}), <i>mainstream</i> (PET _{CO₂})-continuous, record simultaneous with blood collection	Arterial catheter
Bernet et al ³⁴	Transcutaneous continuous-TOSCA: before blood collection; MicroGas: simultaneous with blood collection	Umbilical, radial or posterior tibial artery
Bhat and Abhishek ⁶	<i>Mainstream</i> -continuous, record simultaneous with blood collection	Arterial catheter
Kugelman et al ²⁸	<i>Sidestream microstream</i> -continuous, record simultaneous with blood collection	Arterial catheter
Trevisanuto et al ²²	<i>Mainstream</i> -no continuous, record simultaneous with blood collection	Umbilical artery
Singh et al ³⁵	<i>Sidestream microstream</i> -no continuous, record simultaneous with blood collection	Arterial (when available), capillary or venous
Tingay et al ³⁶	<i>Sidestream microstream</i> e transcutânea—continuous, record before and after blood collection	Arterial catheter
Mukhopadhyay et al ²³	transcutaneous no continuous, record simultaneous with blood collection	Arterial catheter
Kugelman et al ³⁷	<i>Sidestream microstream</i> -continuous, record simultaneous with blood collection	Arterial catheter
Kugelman et al ³⁸	<i>Sidestream microstream</i> -continuous, record simultaneous with blood collection	Arterial catheter
Lin et al ²⁴	<i>Mainstream</i> -continuous, record simultaneous with blood collection	Umbilical artery, collected 1h before the surfactant

Abbreviations: DET_{CO₂}, distal end-tidal carbon dioxide; PET_{CO₂}, proximal end-tidal carbon dioxide; Pet_{CO₂}, end-tidal carbon dioxide pressure; dCap, distal capnography.

accurate and, however, underestimate PaCO₂. In acyanotic anomalies, the correlation of PetCO₂ with PaCO₂ shows agreement.⁴⁵

There was variation for correlation and agreement between PetCO₂ and PaCO₂ associated to birth weight. In extremely low birth weight (ELBW) and very low birth weight (VLBW), the most correlations and concordances were strong/high. In Low birth, weight (LBW) showed moderate correlation and low agreement.²⁴ On the other hand, there is evidence that birth weight does not interfere with the agreement between PetCO₂ and PaCO₂.⁴⁶

About the gestational age, most studies ranged from preterm to post-term, and others exclusively preterm infants. The correlation in these cases was divided between strong and moderate, and the agreement was predominantly moderate. In the literature, a study⁴⁷ carried out with preterm infants found a linear correlation between TcPCO₂ and PaCO₂ and another⁴⁶ showed

that gestational age does not influence the agreement between PetCO₂ and PaCO₂.

This review did not include review studies and grey literature and delimitation of primary studies and language restriction. However, two reviewers extracted the articles independently, with subsequent consensus, showing excellent agreement.

This review showed some limitations, as most studies were cross-sectional, uncontrolled, and with small samples,^{25,27,28,33-35,37} selected for convenience and making it impossible to determine selection's fundamental criteria. There was variation in the measurements that occurred before and after the blood collection or simultaneously. Variations in the sample population were also identified in terms of age, birth weight, gestational age, and newborns' comorbidities. Therefore, the heterogeneity of the included studies does not allow a comparison between their results.

In general, the correlation and agreement between CO₂ from non-invasive methods with arterial blood

Table 3. Main Results of the Included Articles.

Author	Results
Meredith and Monaco ³⁰	PtcCO ₂ /PaCO ₂ : $r=0.79$, $P<.001$; AG: 0.86 ± 0.14 torr
Nangia et al ³¹	EtCO ₂ / PaCO ₂ : IG 28-32s: $r=0.73$, $P<.01$ /IG 32-37s: $r=0.61$, $P<.001$ /IG 37-41s: $r=0.81$, $P<.001$ / <1.5 kg: $r=0.62$, $P<.01$ / -1.5 - 2.5 kg: $r=0.92$, $P<.001$; >2.5 kg: $r=0.81$, $P<.001$ /MAS: $r=0.94$, $P<.001$ /Severe asphyxia: $r=0.76$, $P<.001$ /Recurrent apnea: $r=0.96$, $P<.001$ /RDS: $r=0.55$, $P<.01$ - 0.001
Rozycki et al ²⁶	EtCO ₂ /PaCO ₂ : $r=0.833$, $P<.001$; AG: -6.9 ± 6.9 mmHg (CI 95%: ± 11.5 mmHg)
Wu et al ³²	PtcCO ₂ /PaCO ₂ : $r=0.818$, $P<.001$; AG: 3.5 ± 7.1 mmHg (CI95%: 2.2a 4.7)
Aliwalas et al ²⁷	PtcCO ₂ /PaCO ₂ : 4hours: ICC=0.61; AG: -0.3 ± 2.2 mmHg/12hours: ICC=0.56; AG: 2.4 ± 1.4 mmHg/24hours: ICC=0.57; AG: 1.9 ± 1.8 mmHg TcPCO ₂ /PaCO ₂ : 4 hours: ICC=0.45; AG: 2.2 ± 2.3 mmHg /12 hours: ICC=0.73; AG: 4.4 ± 1.2 mmHg; 24 hours: ICC=0.53; AG: 2.6 ± 1.8 mmHg
Singh and Singhal ²⁵	EtCO ₂ /PaCO ₂ : $r=0.71$; ICC=0.81, $P<.0001$; AG: 5.6 ± 6.8 mmHg (CI 95% 5.11 a 6.09)
Kugelman et al ³³	Distal EtCO ₂ /PaCO ₂ : $r=0.72$, $P<.001$; AG: -1.5 ± 8.7 mmHg Proximal EtCO ₂ /PaCO ₂ : $r=0.21$, $P<.005$; AG: -10.2 ± 13.7 mmHg
Bernet et al ³⁴	PtcCO ₂ Tosca/PaCO ₂ : AG: 0.14 ± 1.45 kPa (CI 95%: -1.31 a 1.59) PtcCO ₂ /PaCO ₂ MicroGas (Conventional): AG: -0.08 ± 1.2 kPa (CI 95%: -1.28 a 1.12)
Bhat andAbhishek ⁶	EtCO ₂ /PaCO ₂ : $r=0.73$, $P<.001$; AG: -6.65 ± 7.54 mmHg (CI 95%: -7.9 a -5.35)
Kugelman et al ²⁸	dCap/PaCO ₂ : $r=0.68$, $P<.0001$; AG: -2 ± 10.7 mmHg
Trevisanuto et al ²²	EtCO ₂ /PaCO ₂ : $r=0.69$, $P<.0001$; AG: 13.5 ± 8.4 mmHg (CI 95%: -3 a 29.9)
Singh et al ³⁵	EtCO ₂ /PaCO ₂ : $r=0.68$; AG: 7.29 ± 10.2 mmHg (CI 95%: 27.12 a -12.55)
Tingay et al ³⁶	EtCO ₂ /PaCO ₂ : AG: 4.1 ± 9.0 mmHg TcCO ₂ /PaCO ₂ : AG: -0.8 ± 13.0 mmHg
Mukhopadhyay et al ²³	PtcCO ₂ /PaCO ₂ : AG: -7.2 ± 16 mmHg
Kugelman et al ³⁷	dCap/PaCO ₂ : $r=0.7$, $P<.001$; AG: -11.7 ± 10.3 mmHg
Kugelman et al ³⁸	dEtCO ₂ /PaCO ₂ : $r=0.73$, $P<.001$; AG: 3 ± 8.5 mmHg
Lin et al ²⁴	PtcCO ₂ /PaCO ₂ : $r=0.603$, $P<.01$; AG: 5.9 ± 7.6 mmHg
Nakato et al ²⁹	EtCO ₂ /PaCO ₂ : $r=0.853$, $P<.001$; AG: 0.352 ± 7.57 mmHg (CI 95%: 14.5-15.2)

Abbreviations: r, correlation coefficient; AG, agreement; ICC, intraclass correlation coefficient; EtCO₂, end-tidal carbon dioxide; dETCO₂, distal end-tidal carbon dioxide; PtcCO₂ = TcPCO₂, transcutaneous carbon dioxide; dCap, distal capnography; GA, gestational age; RDS, respiratory distress syndrome; SAM, meconium aspiration syndrome.

Table 4. Conclusion of the Included Articles.

Author	Conclusion
Meredith and Monaco ³⁰	Strong correlation and high agreement
Nangia et al ³¹	Strong correlation: birth weight between 1.5 e 2.5 kg, MAS, recurrent apnea, premature infants of 28-32 s, Term NBs, >2.5 kg and severe asphyxia; Moderate correlation : premature infants (32-37 s), birth weight <1.5 kg e RDS
Rozycki et al ²⁶	Strong correlation and low agreement
Wu et al ³²	Strong correlation and low agreement
Aliwalas et al ²⁷	Moderate correlation
Singh and Singhal ²⁵	Strong correlation and high agreement
Kugelman et al ³³	Strong correlation and high agreement for the distal method; Weak correlation and low agreement for the proximal method
Bernet et al ³⁴	Low agreement
Bhat andAbhishek ⁶	Strong correlation and high agreement
Kugelman et al ²⁸	Strong correlation and high agreement
Trevisanuto et al ²²	Strong correlation and low agreement
Singh et al ³⁵	Moderate correlation and low agreement
Tingay et al ³⁶	High concordance
Mukhopadhyay et al ²³	Moderate agreement
Kugelman et al ³⁷	Strong correlation and low agreement
Kugelman et al ³⁸	Strong correlation and high agreement
Lin et al ²⁴	Moderate correlation and low agreement
Nakato et al ²⁹	Strong correlation and high agreement

Abbreviations: RDS, respiratory distress syndrome; MAS, meconium aspiration syndrome.

gases showed to be strong/high in this review, although moderate and weak/low values were found. Non-invasive methods can help indicate considerable changes in PaCO₂ levels to avoid excessive blood sampling and reduce the exposure time to hypocapnia and hypercapnia. Furthermore, they can optimize professionals' clinical evaluation while blood collection from arterial blood gases is a complicated process compared to the non-invasive measure.

More studies and greater methodological rigor need to confirm that the CO₂ measurement by non-invasive methods and so permit the construction of specific protocols to guide the professionals who work in NICUs. The studies' results have shown promise that they can provide valuable data for future investigations, which are necessary to consolidate non-invasive methods as a viable and reliable alternative to arterial blood gases.

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Author Contributions

All authors conceptualized and designed the study. IPMM contributed on the acquisition, analysis, and interpretation of data, and drafted the manuscript. AMN and PKH contributed on conceptualization, methodology and drafted the manuscript. PKH, AMN, SOI, and PN contributed on data analysis and interpretation, reviewed, and approved the final draft of the manuscript.

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