A Mathematical Model for the Quantification of Pulmonary and Intrapulmonary Arteriovenous Anastomoses Blood Flow

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Research Article

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Abstract

Objectives: To develop a model for the calculation of pulmonary blood flow ($\dot{Q}p$) and blood flow through intrapulmonary arteriovenous anastomoses ($\dot{Q}_{IPAVA}$) under multiple physiological conditions.

Methods: A mathematical model was developed into which many experimental physiological parameters were input. Data were obtained simultaneously from arterial blood gases, metabolic measures, and noninvasive measures of cardiac output ($\dot{Q}_t$) in young and healthy men.

Results: It was possible to precisely calculate $\dot{Q}p$ and $\dot{Q}_{IPAVA}$ at rest and at moderate (50% of VO_{2max}) and heavy exercise (≥ 90% of VO_{2max}) in both normoxia (FIO_2 = 0.2093) and acute hypoxia (FIO_2 = 0.125).
In normoxia under heavy exercise, $\dot{Q}p$ decreased slightly (97.56% of $\dot{Q}_t$), and $\dot{Q}_{IPAVA}$ represented 2.44% of $\dot{Q}_t$.
Instead, in hypoxia at heavy exercise, $\dot{Q}p$ decreased significantly (85.25% of $\dot{Q}_t$), and $\dot{Q}_{IPAVA}$ increased significantly (14.75% of $\dot{Q}_t$), equal to $\dot{Q}_{IPAVA}$ of 3.48 L/min.
It was possible to demonstrate a negative contribution of $\dot{Q}_{IPAVA}$ directly to pulmonary gas exchange efficiency.
Furthermore, the model immediately identifies incorrect $\dot{Q}_t$ measurements.

Conclusions: This new mathematical model is precise in calculating $\dot{Q}p$ and $\dot{Q}_{IPAVA}$.
The required data are obtained through noninvasive instruments, which are easy to use and widespread in all hospitals. $\dot{Q}p$ differs significantly from $\dot{Q}_t$ under some physiological conditions. The application of this model in the medical field is expected to enable further advancements in scientific research and clinical practice.

1 Introduction

The pulmonary circulation supports the entire cardiac output ($\dot{Q}_t$) with high flow maintained at low intravascular pulmonary arterial pressure (1). Additionally, pulmonary vascular resistance (PVR) is low in healthy adult lungs, enabling delivery of full cardiac output by the thin-walled right heart with relatively low right ventricular pressure compared to left ventricular pressure generated by the thick-walled left heart that is required to overcome systemic pressures (2). This is because the lungs have an inherent protective mechanism against high PVR through the recruitment of capillaries and, to a lesser extent, the distension of the elastic vessels present in the circuit (2, 3). In fact, under conditions of rest, most of the capillary bed is not recruited (2, 4), and during exercise, in healthy subjects, when the cardiac output increases up to six times, the pulmonary artery pressure increases only moderately (2, 5).

However, the pulmonary vasculature is a dynamic system that responds rapidly to vasoactive mediators (2). For example, vasoconstriction due to smooth muscle contraction is caused by hypoxia (1, 6, 7, 8) and circulating vasoconstrictive mediators (2). Given this significant vasoreactivity, it is important to verify the distribution of pulmonary blood flow within the lung in particular environmental and physiological conditions. The measurement of cardiac output is currently carried out through various methods, such as indicator dilution techniques, the Fick method, arterial pulse contour analysis, ultrasound, and bioimpedance (9), and specifically during exercise, cardiac output can be measured by open-circuit acetylene uptake (10, 11). The most invasive and technically demanding measures (e.g., pulmonary artery catheterization and direct Fick method) are of course the most precise, while the less invasive measures (e.g., bioimpedance and ultrasound) are less precise. However, to understand how the pulmonary blood flow distribution behaves with respect to a given measured cardiac output, it is necessary to structure a mathematical model that allows the real quantification of pulmonary blood flow through the conventional pulmonary circulation that determines the real exchange of gases throughout the pulmonary epithelial tissue as well as larger diameter pulmonary arteriovenous malformations (PAVMs), which can act as right-to-left shunts in the lungs. "Physiologically, pulmonary arteriovenous shunting is commonly defined as the passage of blood through the lungs without taking part in gas exchange" (13 - Genovesi MG et al. 1976). Therefore, the cardiac and pulmonary blood flow that passes through either a patent foramen ovale and/or large diameter pulmonary arteriovenous malformations (PAVMs) and does not exchange gas within the lung are considered shunts.

Another possible route for pulmonary blood flow in healthy humans is through intrapulmonary arteriovenous anastomoses (IPAVA). The presence and existence of these blood flow pathways in healthy lungs is indisputable (25); however, their functional and physiological role is an area of important debate. In particular, in healthy subjects, IPAVA are typically closed or poorly perfused under resting conditions but can open during moderate to high intensity exercise in normoxia (14, 15, 25). In hypoxia, these pathways are perfused under resting conditions depending on the severity of hypoxemia (19, 20), and there is greater blood flow through these pathways with exercise and hypoxia (14, 15, 17, 20, 21, 22, 24, 25). Therefore, IPAVA are dynamic pulmonary pathways through which blood flows and that fraction of pulmonary blood flow is variably present depending on the conditions to which the subjects are exposed.

To elaborate the mathematical model, first, the physiological parameters of interest were identified. Then, the theory was interpreted by formulating nine equations. Next, experimental data available in the relevant literature (11) were input into the mathematical model. The human physiological data in this experiment (11) included blood gas data, metabolic data, and noninvasive measures of cardiac output.

2 Materials and Methods

2.1 Introductory note to the equations

The **measured** physiological parameters taken into consideration in this study that are involved in respiratory gas exchanges are HCO_3^-, PCO_2, (two blood parameters); VCO_2; and cardiac output ($\dot{Q}_t$).

It is necessary to consider the HCO_3^- concentration to quantify the total CO_2 content in blood as bicarbonate is transformed into CO_2 because of the reaction — $CO_2 + H_2O \leftrightarrow H^+ + HCO_3^-$ — catalyzed by carbonic anhydrase present in as many as 16 different isoforms (12) in various organ systems, including the lungs.

The formulation phase started with the use of Lavoisier's Law on Conservation of Mass. This law states that "nothing is created and nothing is destroyed, but everything is transformed"; thus, by this law, VCO_2 must represent the mass that is lost each minute in terms of PCO_2 and $[HCO_3^-]$ (the other form of CO_2) between venous and arterial blood through the lungs.

Because VCO_2 is expressed in L/min, PCO_2 is expressed in mmHg, $[HCO_3^-]$ is expressed in mmol/L, and $\dot{Q}_t$ in L/min, to perform the calculation, it is necessary to align all the dimensions and units of the physical quantities of all the parameters involved, thus ensuring, through dimensional analysis, the same dimensions (dimensional homogeneity) when an equality is established in the equations.

Therefore, new physiological parameters that were symbolized with the Greek letters Φ (uppercase phi) and ϕ (lowercase phi) were defined, and nine equations were formulated.

In particular, the letter Φ defines the total molar flow rate of CO_2, while ϕ better defines the partial flow components, which constitute the total molar flow rate of CO_2.

Specifically:

$\Phi CO_{2(e)}$ = total molar flow rate per minute of expired CO_2 (measured using a metabolic cart)

which is expressed in units of $\frac{\mathbf{mmol}}{\mathbf{min}}$ and calculated as follows:

$$\mathbf{\Phi CO_{2(e)}} = \frac{\mathbf{VCO_2}}{\mathbf{VmCO_2}} = \frac{\mathbf{VCO_2}}{\mathbf{22.26}},$$

where $VCO_2 = \frac{\text{mL } CO_2}{\text{min}}$ and $VmCO_2 = 22.26$ mL/mmol

$VmCO_2$*= molar volume at STP (volume occupied by a mole of CO_2 to Standard T° and P)

$VmCO_2^* = 22.26$ L/mol. If we refer to 1 millimole, it occupies 22.26 mL and its dimensions are mL/mmol

$\boldsymbol{\Phi CO_{2(\dot{Q}_t)}}$ = **total** molar flow rate per minute of $\mathbf{CO_2}$ **eliminated from blood** (measured with blood gas analyzer) between venous and arterial blood through the lungs, both **in the form of** $\mathbf{CO_2}$ and $\mathbf{HCO_3^-}$, calculated using the measure of **cardiac output** ($\dot{Q}_t$).

$\boldsymbol{\Phi CO_{2(\dot{Q}_t)}}$ is expressed in $\frac{\mathbf{mmol}}{\mathbf{min}}$ and consists of **two components, as given below:**

1. $\boldsymbol{\phi CO_{2(\dot{Q}_t)}}$= molar flow rate of only CO_2 eliminated from blood, between venous and arterial blood, through the lungs, calculated using $\dot{Q}_t$. It is expressed in $\frac{\mathbf{mmol}}{\mathbf{min}}$.
2. $\boldsymbol{\phi HCO_3^-{}_{(\dot{Q}_t)}}$= molar flow rate of only HCO_3^- eliminated from blood, between venous and arterial blood, through the lungs, calculated using $\dot{Q}_t$ and expressed in $\frac{\mathbf{mmol}}{\mathbf{min}}$.

2.2 FIRST EQUATION (Calculation of $\boldsymbol{\Phi CO_{2(\dot{Q}_t)}}$)

1st Equation

$$\boldsymbol{\Phi CO_{2(\dot{Q}_t)} = \left(\Delta[CO_2]_{(v-a)} + \Delta[HCO_3^-]_{(v-a)}\right) x\, \dot{Q}t}$$

Proof of the first equation.

From the law of conservation of mass (Antoine Lavoisier), **we must hypothesize** that the **CO_2 exhaled per minute** must be **exactly equal** to the **CO_2 content lost per minute** between venous and arterial blood, that is,

$$\Phi CO_{2(e)} = \Phi CO_{2(\dot{Q}_t)},$$

However, $\boldsymbol{\Phi CO_{2(\dot{Q}_t)} = \phi CO_{2(\dot{Q}_t)} + \phi HCO_{3(\dot{Q}_t)}^-}$.

To obtain $\boldsymbol{\phi CO_{2(\dot{Q}_t)}}$

$$\boldsymbol{\phi CO_{2(\dot{Q}_t)} = [(PCO_{2v} - PCO_{2a})\, K\,] \times \dot{Q}t}$$

PCO_{2v}= pressure of CO_2 in venous blood, expressed in mmHg,

PCO_{2a}= pressure of CO_2 in the arterial blood, expressed in mmHg,

K = solubility constant of CO_2. At 37 °C in plasma, with a value of 0.03 mmol/L • mmHg,

$\dot{Q}t$ = Cardiac output expressed in $\frac{\text{L}}{\text{min}}$.

The component relating to $\boldsymbol{[(PCO_{2v} - PCO_{2a})\, K] = \Delta[CO_2]_{(v-a)}}$ represents the concentration gradient of CO_2 eliminated through expiration between the venous and arterial blood (application of Henry's law). When the concentration gradient $\Delta[CO_2]_{(v-a)}$, expressed in $\frac{\text{mmol}}{\text{L}}$, is multiplied by $\dot{Q}t$ expressed in $\frac{\text{L}}{\text{min}}$, we obtain $\boldsymbol{\phi CO_{2(\dot{Q}_t)} = \frac{\text{mmol } CO_2}{\text{min}}}$.

This flow corresponds to the portion of CO_2 removed as such from the blood, between venous and arterial blood, during exhalation.

To obtain $\boldsymbol{\phi HCO_{3(\dot{Q}_t)}^-}$

$$\boldsymbol{\phi HCO_{3(\dot{Q}_t)}^-} = ([\mathbf{HCO_3^-}]_v - [\mathbf{HCO_3^-}]_a) \times \dot{Q}_t$$

$[HCO_3^-]_v$ = concentration of HCO_3^- in venous blood, expressed in $\frac{mmol}{L}$,

$[HCO_3^-]_a$ = concentration of HCO_3^- in the arterial blood, expressed in $\frac{mmol}{L}$,

The concentration gradient of bicarbonate between venous and arterial blood, $\Delta[\mathbf{HCO_3^-}]_{(v-a)}$, multiplied by $\dot{\mathbf{Q}}_t$, expressed in $\frac{L}{min}$, yields $\boldsymbol{\phi HCO_{3(\dot{Q}_t)}^-} = \frac{\mathbf{mmol\ HCO_3^-}}{\mathbf{min}}$.

This flow corresponds to the portion of HCO_3^- removed from the blood, between venous and arterial blood, during exhalation.

Therefore, the complete equation is:

$$\Phi CO_{2(\dot{Q}_t)} = \{[(PCO_{2v} - PCO_{2a})\ K] \times \dot{Q}_t\} + ([HCO_3^-]_v - [HCO_3^-]_a) \times \dot{Q}_t$$

that is, the 1st equation

$$\boldsymbol{\Phi CO_{2(\dot{Q}_t)} = (\Delta[CO_2]_{(v-a)} + \Delta[HCO_3^-]_{(v-a)})x\ \dot{Q}_t}$$

This first equation, according to Lavoisier's law, must be equal to $\Phi CO_{2(e)}$, but if the required experimental data (11) are entered into the first equation, we obtain

$$\boldsymbol{\Phi CO_{2(\dot{Q}_t)} > \Phi CO_{2(e)}}.$$

2.3 SECOND EQUATION (Calculation of Pulmonary flow of blood: first method)

2.3.1 Introductory note

By applying the first equation to Jonk's experimental data (11), we can realize that

$$\Phi CO_{2(\dot{Q}_t)} > \Phi CO_{2(e)}.$$

This is an impossible situation since these two flows, by Lavoisier's law on conservation of mass, **must be equal**. This is because the **cardiac output ($\dot{\mathbf{Q}}_t$) is greater than the actual pulmonary blood flow.** Therefore, a second equation was created, which models all the characteristics of a pulmonary flow of blood ($\dot{Q}p$), that is, the **actual flow of blood, expressed in liters, which passes through the lung every minute and allows the effective exchange of respiratory gases through the pulmonary epithelium.** To calculate the pulmonary flow of blood ($\dot{Q}p$), it is necessary to calculate whether there is a $\Delta\Phi CO_2$:

$$\Delta\Phi CO_2 = \Phi CO_{2(\dot{Q}_t)} - \Phi CO_{2(e)}.$$

If $\Delta\Phi CO_2 = 0$ then $\dot{Q}p = \dot{\mathbf{Q}}_t$.

If $\Delta\Phi CO_2 > 0$, then it is necessary to calculate the pulmonary blood flow ($\dot{Q}p$) with the following equation:

2nd Equation

$$\dot{Q}p = \dot{Q}t - \left(\dot{Q}t \times \frac{\Delta\Phi CO_2}{\Phi CO_{2(\dot{Q}t)}}\right)$$

The pulmonary flow of blood is expressed as follows:

$$\dot{Q}p = \frac{L}{min}.$$

2.4 THIRD EQUATION (The efficiency of $\dot{Q}p$ affects the efficiency of gas exchange)

2.4.1 Introductory note

If $\Delta\Phi CO_2 > 0$, then $\dot{Q}p < \dot{Q}t$, and consequently, their ratio, represented by $\frac{\dot{Q}p}{\dot{Q}t}$, is less than 1.

This dimensionless ratio represents the efficiency of pulmonary blood flow with respect to cardiac output and should be correlated to pulmonary vascular resistance.

The more $\dot{Q}p$ is less than $\dot{Q}t$, the greater the pulmonary arteriolar resistance and the lower the efficiency of pulmonary flow with respect to cardiac output.

The ratio $\frac{\dot{Q}p}{\dot{Q}t}$ should also determine the efficiency of the CO_2 excretion, which is given by the ratio $\frac{\Phi CO_{2(e)}}{\Phi CO_{2(\dot{Q}t)}}$. Therefore, it is necessary to verify whether the ratio $\frac{\Phi CO_{2(e)}}{\Phi CO_{2(\dot{Q}t)}}$ is equal to the ratio $\frac{\dot{Q}p}{\dot{Q}t}$ with the following equation:

3rd Equation

$$\frac{\Phi CO_{2(e)}}{\Phi CO_{2(\dot{Q}t)}} = \frac{\dot{Q}p}{\dot{Q}t}$$

2.5 FOURTH EQUATION (Calculation of $\dot{Q}p$: second method)

If there is an equality between the two expressions, namely, $\frac{\Phi CO_{2(e)}}{\Phi CO_{2(\dot{Q}t)}} = \frac{\dot{Q}p}{\dot{Q}t}$, then we could also calculate the pulmonary flow of blood as follows:

4rd Equation

$$\dot{Q}p = \left(\frac{\mathbf{\Phi CO_{2(e)}}}{\mathbf{\Phi CO_{2(\dot{Q}_t)}}}\right) \times \dot{Q}_t$$

2.6 FIFTH EQUATION (Identity between $\mathbf{\Phi CO_{2(\dot{Q}_p)}}$ and $\mathbf{\Phi CO_{2(e)}}$)

If we substitute the value of $\dot{Q}p$ in the first equation instead of the $\dot{Q}_t$ value, we obtain

$(\Delta[HCO_3^-]_{(v-a)} + \Delta[CO_2]_{(v-a)})$ x $\dot{Q}p = \phi HCO^-_{3(\dot{Q}p)} + \phi CO_{2(\dot{Q}p)} = \Phi CO_{2(\dot{Q}p)}$ where the two flows, $\Phi CO_{2(\dot{Q}p)}$ and $\Phi CO_{2(e)}$, are exactly identical, and therefore, we can obtain the 5th equation

5th Equation

$$(\Delta[\mathbf{HCO_3^-}]_{(v-a)} + \Delta[\mathbf{CO_2}]_{(v-a)}) \mathbf{x}\, \dot{Q}p = \mathbf{\Phi CO_{2(e)}}$$

2.7 SIXTH EQUATION (Proof of concept of the fifth equation)

6th Equation

$$\frac{\mathbf{\Phi CO_{2(e)}}}{\dot{Q}p} = \Delta[\mathbf{HCO_3^-}]_{(v-a)} + \Delta[\mathbf{CO_2}]_{(v-a)}$$

If the fifth equation is valid, entering the experimental data into the sixth equation, we must obtain an identity function.

2.8 SEVENTH EQUATION (Calculation of $\dot{Q}p$: third method)

In the absence of a cardiac output gauge or in the case of incorrect measurement of $\dot{Q}_t$ (when $\mathbf{\Phi CO_{2(\dot{Q}_t)}} < \mathbf{\Phi CO_{2(e)}}$), $\dot{Q}p$ can be derived from the previous equation by reworking it as follows:

7th Equation

$$\dot{Q}p = \frac{\Phi CO_{2(e)}}{\Delta[HCO_3^-]_{(v-a)} + \Delta[CO_2]_{(v-a)}}$$

Note: the second, fourth and seventh equations to calculate $\dot{Q}p$ always lead to the same result.

2.9 EIGHTH EQUATION (Calculation of $\dot{Q}_{IPAVA}$)

8th Equation

$$\dot{Q}_{IPAVA} = \dot{Q}t - \dot{Q}p$$

Proof of the eighth equation

Pulmonary perfusion ($\dot{\mathbf{Q}}$) is the blood flow, expressed in L/min, through the pulmonary circulation and corresponds to the blood flow of cardiac output ($\dot{Q}_t$), that is,

$$\dot{\mathbf{Q}}_t = \dot{\mathbf{Q}}$$

However, not always all pulmonary perfusion, determined by cardiac output, exchanges gas with the outside, and therefore pulmonary perfusion, $\dot{\mathbf{Q}}$, consists of two flows:

- The pulmonary blood flow that exchanges gas with the outside, namely, $\dot{Q}p$
- The pulmonary blood flow that does not take part in gas exchange, that is, $\dot{Q}_{IPAVA}$.

Therefore,

$$\dot{Q}_t = \dot{Q}p + \dot{Q}_{IPAVA}$$

To calculate the blood flow in $\dot{Q}_{IPAVA}$, the following operation will need to be performed:

$$\dot{Q}_{IPAVA} = \dot{Q}_t - \dot{Q}p$$

$\dot{Q}_{IPAVA}$ is expressed in L/min.

2.10 NINTH EQUATION (Evidence that $\dot{Q}_{IPAVA}$ negatively affects gas exchange efficiency)

9th Equation

$$\frac{\dot{Q}_{IPAVA}}{\dot{Q}_t} = 1 - \frac{\Phi CO_{2(e)}}{\Phi CO_{2(\dot{Q}_t)}}$$

Proof of the ninth equation

Dividing both sides of the 8th equation, namely, $\dot{Q}_{IPAVA} = \dot{Q}_t - \dot{Q}_p$, by $\dot{Q}_t$, we obtain

$$\frac{\dot{Q}_{IPAVA}}{\dot{Q}_t} = 1 - \frac{\dot{Q}_p}{\dot{Q}_t}$$

If $\frac{\Phi CO_{2(e)}}{\Phi CO_{2(\dot{Q}_t)}} = \frac{\dot{Q}_p}{\dot{Q}_t}$, by substituting for a $\frac{\dot{Q}_p}{\dot{Q}_t}$ the ratio $\frac{\Phi CO_{2(e)}}{\Phi CO_{2(\dot{Q}_t)}}$, we obtain the 9th equation

$$\frac{\dot{Q}_{IPAVA}}{\dot{Q}_t} = 1 - \frac{\Phi CO_{2(e)}}{\Phi CO_{2(\dot{Q}_t)}}$$

This ninth equation represents the direct evidence that $\dot{Q}_{IPAVA}$ affects the pulmonary gas exchange efficiency with its negative contribution.

If we multiply the $\frac{\dot{Q}_{IPAVA}}{\dot{Q}_t}$ ratio by 100 (expressing it as a percentage), we obtain the percentage of IPAVA blood flow ($\dot{Q}_{IPAVA}$) with respect to cardiac output ($\dot{Q}_t$)

$$\frac{\dot{Q}_{IPAVA}}{\dot{Q}_t} \text{ x } 100 = \%\ \dot{Q}_{IPAVA} \text{ with respect to cardiac output } (\dot{Q}_t)$$

Please note that the eighth and ninth equations are valid for healthy subjects, since in the presence of cardiopulmonary pathologies such as intracardiac shunt (atrial septal defect or PFO -patent foramen ovale) and large diameter pulmonary arteriovenous malformations, the blood flow, which does not exchange with the external environment, can take different routes than IPAVA.

However, since IPAVA are dynamic pathways whose opening is inducible by hypoxemia, several clinical conditions that cause embolic insults in subjects with diseases associated with concomitant arterial hypoxemic conditions can be explained through the opening of IPAVA at rest (20, 25). Therefore, the eighth and ninth equations are also valid for these subjects in these particular clinical conditions.

2.11 Application of Experimental Data on Equations

Some experimental data presented in a prior work (11) were input into the equations because the parameters required by the equations in this experiment had the characteristic of having been detected simultaneously (namely, venous and arterial PCO_2, venous and arterial bicarbonate concentration, $\dot{Q}_t$ and VCO_2).

In fact, this experimental model faithfully reproduces the structure of the equations that represent what is lost between venous and arterial blood and, at the same time, what is found in exhaled VCO_2.

The experimental data refer to the following physiological parameters: VCO_2, $\dot{Q}_t$, $[HCO_3^-]_v$, $[HCO_3^-]_a$, PCO_{2v}, PCO_{2a}, in different physiological conditions to which the subjects were subjected: **normoxia – placebo, **hypoxia – placebo, and in conditions of rest, moderate exercise (50% of VO_{2max}) and heavy exercise (≥ 90% of VO_{2max}).

Note: in Jonk's experiment (11), placebo refers to the experimental condition without acetazolamide.

** normoxia $FIO_2 = 0.2093$

** hypoxia $FIO_2 = 0.125$

2.12 Instruments and methods of measurement in Jonk's experiment (11)

$\dot{Q}_t$ was measured at rest and, during steady state, at 50% and ≥ 90% of VO_{2max} **using the noninvasive open-circuit acetylene uptake method** (10, 11).

Venous blood was drawn through two catheters placed one in a superficial vein of the dominant arm and the other in the left femoral vein pointing distally. Arterial blood was drawn through a catheter placed in the radial artery of the non-dominant arm.

Blood gas was analyzed by a Blood Gas Analyzer (IL Synthesis 45 analyzer). VCO_2 was measured with a TrueOne 2400 Parvo Medics Metabolic Cart.

3 Results

The application of the mathematical model started from the input of some experimental data (11) into the first equation. The input data were related to six parameters (VCO_2 $\dot{Q}_t$, $[HCO_3^-]_v$, $[HCO_3^-]_a$, PCO_{2v}, and PCO_{2a}) measured in subjects subjected to three different physiological conditions (at rest, moderate exercise and heavy exercise) in normoxia-placebo and hypoxia-placebo conditions.

The results are shown in Table 1, where the two flows, $\Phi CO_{2(e)}$ and $\Phi CO_{2(\dot{Q}_t)}$, are observed to be quite similar, but not identical, as indicated by Lavoisier's law on mass conservation. This is because the cardiac output ($\dot{Q}_t$) is an excessive multiplication factor of the two blood concentrations of CO_2 and HCO_3^-, for obtaining a flow identical to the expired CO_2 ($\Phi CO_{2(e)}$). Therefore, $\Phi CO_{2(\dot{Q}_t)}$ is always greater than $\Phi CO_{2(e)}$, except in two cases (normoxia-placebo/rest and hypoxia-placebo/moderate) in which $\Phi CO_{2(\dot{Q}_t)}$ is less than its respective $\Phi CO_{2(e)}$. This is an impossible situation because of the underestimated cardiac output ($\dot{Q}_t$) value during the measurement.

Tab. 1

$\Phi CO_{2(e)}$ = mmol/min $\Phi CO_{2(\dot{Q}t)}$ = mmol/min

NORMOXIA - PLACEBO

REST	MODERATE	HEAVY
$\Phi CO_{2(e)} = 14.82$	$\Phi CO_{2(e)} = 104.22$	$\Phi CO_{2(e)} = 207.55$
$\Phi CO_{2(\dot{Q}t)} = 12.48$	$\Phi CO_{2(\dot{Q}t)} = 105.91$	$\Phi CO_{2(\dot{Q}t)} = 212.80$

HYPOXIA - PLACEBO

REST	MODERATE	HEAVY
$\Phi CO_{2(e)} = 19.766$	$\Phi CO_{2(e)} = 87.15$	$\Phi CO_{2(e)} = 141.5$
$\Phi CO_{2(\dot{Q}t)} = 21.14$	$\Phi CO_{2(\dot{Q}t)} = 84.00$	$\Phi CO_{2(\dot{Q}t)} = 166.00$

Table 1
$\Phi CO_{2(e)}$ and $\Phi CO_{2(\dot{Q}t)}$ are quite similar, but $\Phi CO_{2(\dot{Q}t)}$ is always greater than $\Phi CO_{2(e)}$. Only in normoxia-placebo/rest and hypoxia-placebo/moderate was $\Phi CO_{2(\dot{Q}t)}$ less than $\Phi CO_{2(e)}$ because the $\dot{Q}t$ measurement was underestimated.

3.1 Calculation of pulmonary flow of blood ($\dot{Q}p$)

Analyzing the data presented in Table 1, for the two flows to make equal respect to Lavoisier's law, $\dot{Q}p$ must be calculated. In fact, as $\Delta\Phi CO_2 > 0$, $\dot{Q}p$ was calculated with one of the three equations to obtain it for each physiological condition (rest, moderate exercise, heavy exercise) both in normoxia and in hypoxia states. Then, by entering the calculated values of $\dot{Q}p$ into the fifth equation, instead of the measured $\dot{Q}t$ values as required by the first equation, we obtain the values of $\Phi CO_{2(\dot{Q}p)}$ that **coincide** with the values of $\Phi CO_{2(e)}$. By mathematically relating the two total flows, $\Phi CO_{2(\dot{Q}p)}$ and $\Phi CO_{2(e)}$, we obtain an identity function ($n = 6$, $y = x$, $R^2 = 1$), as shown in Figure 1. This demonstrates the validity of the fifth equation.

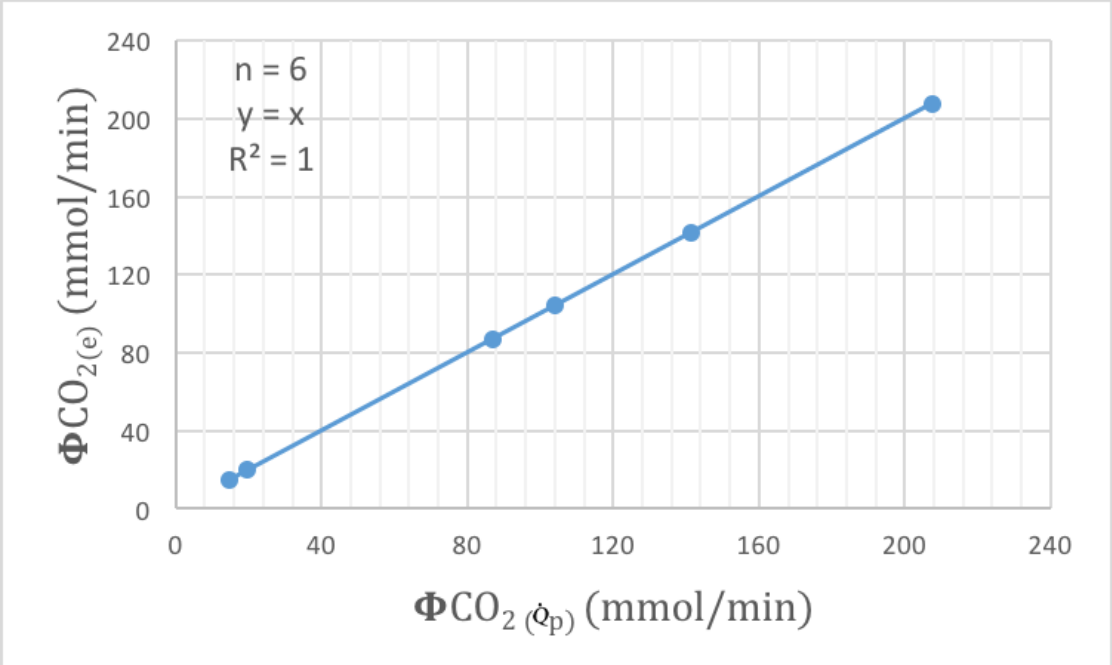

Figure 1

$\Phi CO_{2(e)}$ in relation to $\Phi CO_{2(\dot{Q}p)}$, calculated with $\dot{Q}p$ values, is an identity function.

3.2 Cardiac output ($\dot{Q}t$) compared to pulmonary blood flow ($\dot{Q}p$)

Figure 2 shows the behavior of $\dot{Q}p$, calculated with one of the three equations to calculate it, with respect to its own measured $\dot{Q}t$, under the various conditions (normoxia-placebo and hypoxia-placebo) and physiological states (rest, moderate and heavy exercise) examined. We can notice that $\dot{Q}t$ was always greater than $\dot{Q}p$, except in two conditions because of the underestimated $\dot{Q}t$ and marked with the red arrow.

Although $\dot{Q}p$ is less than its own $\dot{Q}t$, it is only minimally reduced under normoxia-placebo, whereas the reductions are very evident, especially under hypoxia-placebo, at heavy exercise.

In fact, in Figure 2A (normoxia-placebo), we can see that $\dot{Q}p$ decreased slightly, reaching its maximum decrease during normoxia under heavy exercise (97.56% of $\dot{Q}t$).

In contrast, in Figure 2B (hypoxia-placebo), we can see that during heavy exercise, $\dot{Q}p$ was considerably reduced (85.25% of $\dot{Q}t$), while at rest-hypoxia, the reduction in $\dot{Q}p$ was limited (93.51% of $\dot{Q}t$).

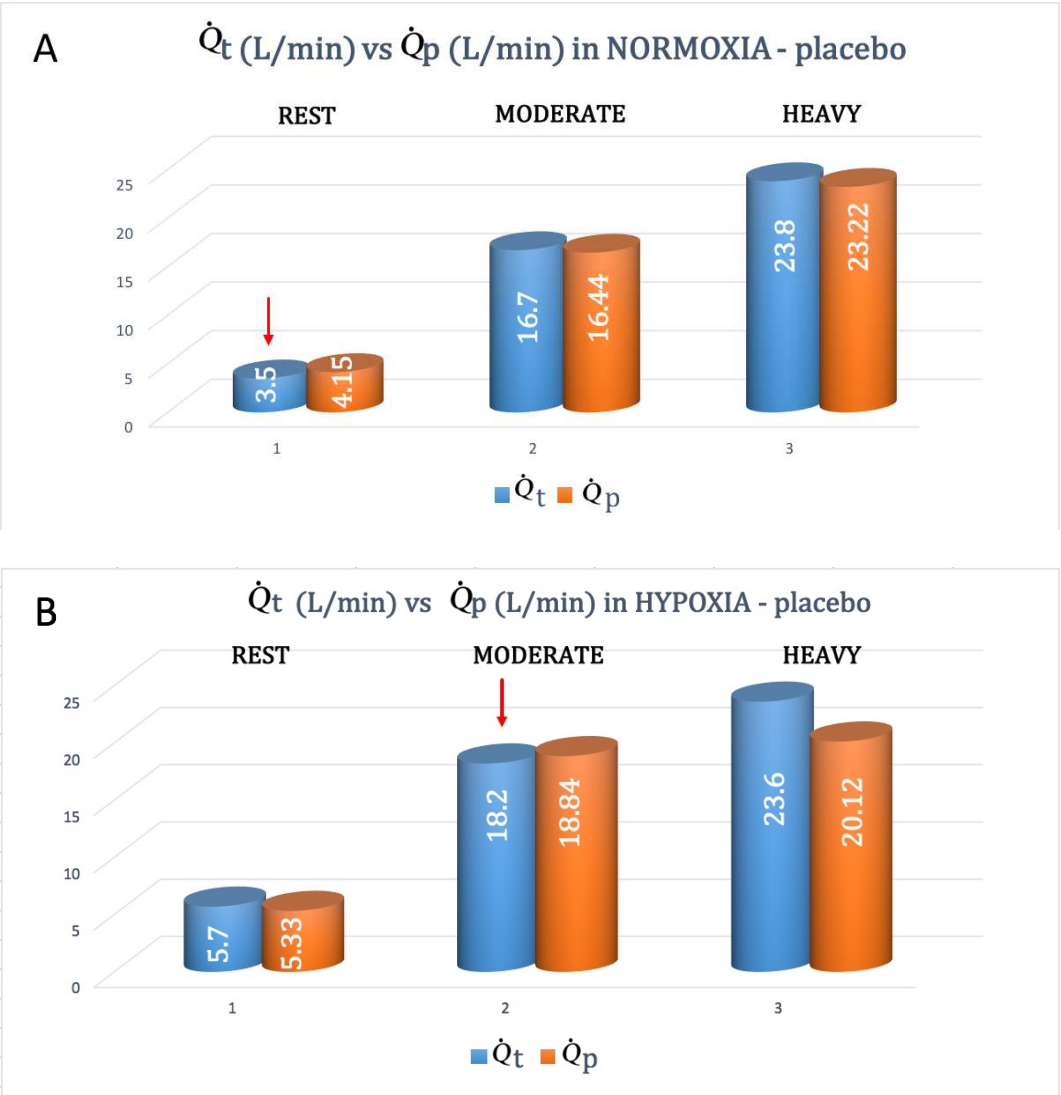

Figure 2

Cardiac output ($\dot{Q}_t$) compared to calculated pulmonary blood flow ($\dot{Q}p$) in **normoxia-placebo** (A) and **hypoxia-placebo** (B) under different physiological conditions (rest, moderate and heavy exercise).

(A) In **normoxia,** $\dot{Q}_t > \dot{Q}p$ under all physiological conditions, except in the rest-placebo (reported with the arrow) because of the underestimated $\dot{Q}_t$.

(B) In **hypoxia** $\dot{Q}_t > \dot{Q}p$ in all the physiological conditions, except in moderate-placebo (reported with the arrow) because of the underestimated $\dot{Q}_t$, but at high intensity of exercise $\dot{Q}_t \gg \dot{Q}p$.

3.3 Relationship between $\frac{\dot{Q}_p}{\dot{Q}_t}$ and $\frac{\Phi CO_{2(e)}}{\Phi CO_{2(\dot{Q}_t)}}$

If we calculate the $\frac{\Phi CO_{2(e)}}{\Phi CO_{2(\dot{Q}_t)}}$ ratio and $\frac{\dot{Q}_p}{\dot{Q}_t}$ ratio, we note that they are identical. By relating them, we obtain the graph of Figure 3, which is an identity function ($n = 6$, $y = x$, $R^2 = 1$). This demonstrates the validity of the third equation.

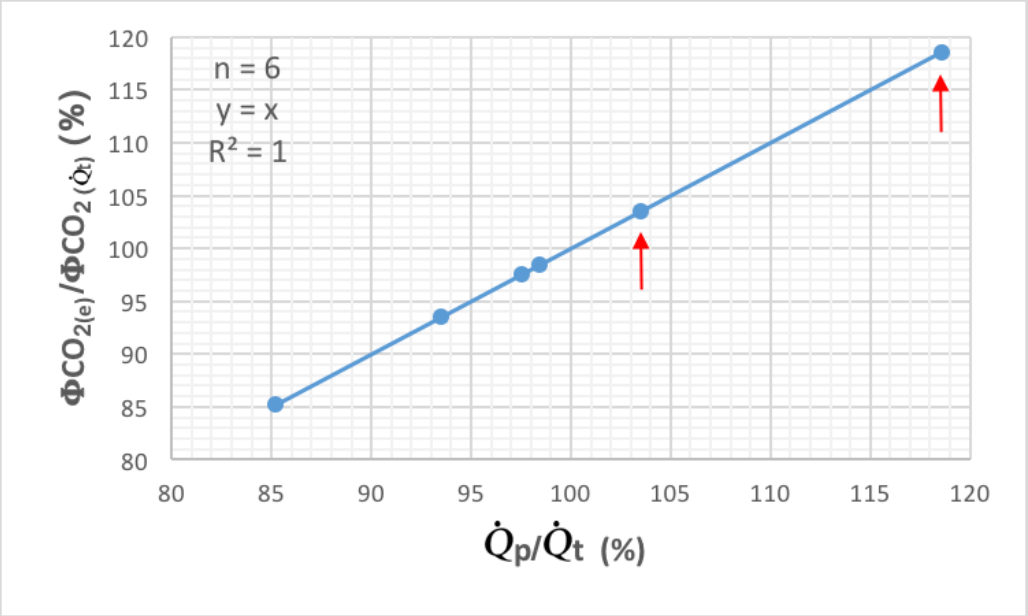

Figure 3

The relation between $\frac{\Phi CO_{2(e)}}{\Phi CO_{2(Qt)}}$ and $\frac{\dot{Q}p}{\dot{Q}t}$ (expressed as a percentage) is an identity function ($n = 6$, $y = x$, $R^2 = 1$). The two arrows indicate the two physiological states (normoxia-placebo/rest and hypoxia-placebo/moderate) in which $\dot{Q}t$ were underestimated, and therefore, $\dot{Q}p$ is inevitably greater than $\dot{Q}t$. As a result, the $\frac{\dot{Q}p}{\dot{Q}t}$ and $\frac{\Phi CO_{2(e)}}{\Phi CO_{2(Qt)}}$ ratios exceed 100% (impossible situation).

In other words, the equality of the two ratios has shown that the efficiency of pulmonary flow with respect to the flow of cardiac output affects the gas exchange efficiency of the alveolar epithelium in the same measure. Therefore, we have the same result obtained by the ratio between the two blood flows, $\frac{\dot{Q}p}{\dot{Q}t}$ expressed in L/min, and the result of the ratio between the millimoles of CO_2 effectively exhaled per minute (mmol/min) that we measure with the metabolic cart, compared to the mmol/min of CO_2 that would have been exhaled if all the flow of cardiac output had been exploited.

Since the untapped flow share of cardiac output refers to the $\dot{Q}_{IPAVA}$, this is the indirect demonstration that the shunt flow affects its negative contribution to pulmonary gas exchange efficiency.

Furthermore, given that the third equation is valid, the pulmonary blood flow ($\dot{Q}p$) can also be calculated with the fourth equation.

3.4 Relationship between $\frac{\dot{Q}_{IPAVA}}{\dot{Q}t}$ and $1 - \frac{\Phi CO_{2(e)}}{\Phi CO_{2(\dot{Q}t)}}$

Applying the ninth equation $1 - \frac{\Phi CO_{2(e)}}{\Phi CO_{2(\dot{Q}t)}} = \frac{\dot{Q}_{IPAVA}}{\dot{Q}t}$ to the experimental data, we noticed that it is an identity function. Unfortunately, we excluded two physiological conditions (normoxia-placebo/rest

and hypoxia-placebo/moderate) from the data processing, as the measured value of $\dot{Q}_t$ was underestimated. This identity relationship is the direct demonstration that the percentage of $\dot{Q}_{IPAVA}$ affects pulmonary gas exchange efficiency with its negative contribution (see Figure 4).

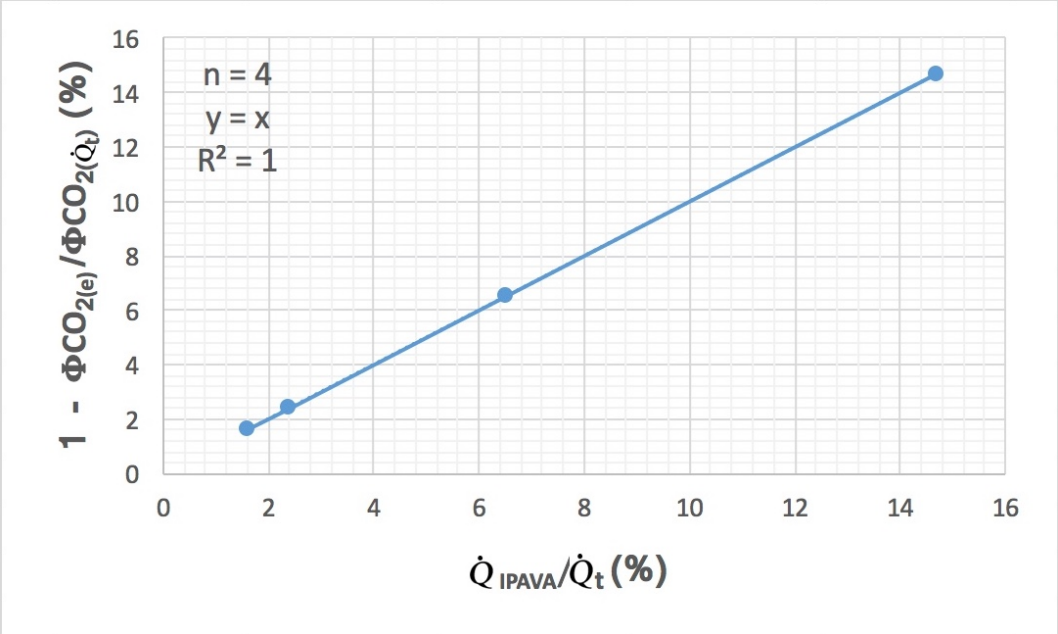

Figure 4

The relation between $1-\frac{\Phi CO_{2(e)}}{\Phi CO_{2(\dot{Q}_t)}}$ and $\frac{\dot{Q}_{IPAVA}}{\dot{Q}_t}$ (expressed as a percentage) is an identity function ($n = 4$, $y = x$, $R^2 = 1$). We excluded from the elaboration the two physiological states (normoxia-placebo/rest and hypoxia-placebo/moderate) in which their $\dot{Q}_t$ were underestimated. This relationship is the direct demonstration that the percentage of $\dot{Q}_{IPAVA}$ affects its negative contribution to pulmonary gas exchange efficiency.

3.5 Cardiac Output ($\dot{Q}_t$), Pulmonary Blood Flow ($\dot{Q}p$) and $\dot{Q}_{IPAVA}$ during Heavy Exercise in Normoxia and Hypoxia

Figure 5 shows, in placebo, the effect of hypoxia on $\dot{Q}_t$, $\dot{Q}p$ and $\dot{Q}_{IPAVA}$ compared to normoxia. A single physiological condition was examined, namely, that of heavy exercise (≥ 90% of VO_{2max}), because at rest (in normoxia) and at moderate exercise (in hypoxia), the two values of $\dot{Q}_t$, being underestimated, did not allow an investigation.

The results showed that under heavy exercise, hypoxia considerably reduced $\dot{Q}p$ (85.25%) compared to its own $\dot{Q}_t$, and $\dot{Q}_{IPAVA}$ increased up 14.75% of $\dot{Q}_t$, equal to 3.48 L/min, while in normoxia $\dot{Q}p$, it decreased only slightly (97.56% of $\dot{Q}_t$), and $\dot{Q}_{IPAVA}$ represented 2.44% of $\dot{Q}_t$, equal to 0.58 L/min.

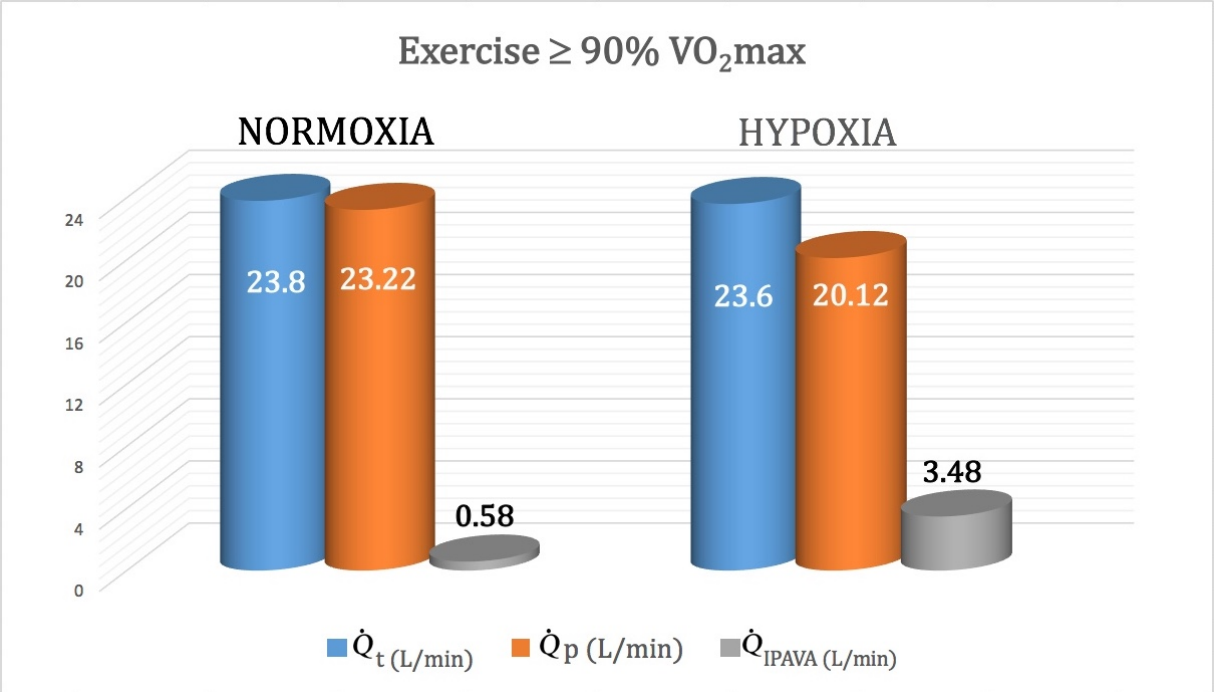

Figure 5

During heavy exercise (≥ 90% of VO_{2max}) in placebo. In normoxia, $\dot{Q}p$ represents 97.56% of $\dot{Q}_t$, and $\dot{Q}_{IPAVA}$ represents 2.44% of $\dot{Q}_t$, while in hypoxia, $\dot{Q}p$ represents 85.25% of $\dot{Q}_t$, and $\dot{Q}_{IPAVA}$ represents 14.75% of $\dot{Q}_t$, equal to 3.48 L/min.

3.6 Proof of concept of fifth equation

If we apply the sixth equation to experimental data, by relating the sums of the deltas of the HCO_3^- and CO_2 concentrations detected in venous and arterial blood with a blood gas analyzer with the $\Phi CO_{2(e)}$ (measured with the metabolic cart) divided by the pulmonary flow of blood ($\dot{Q}p$), we obtain Figure 6, in which the values coincide; that is, an identity function is evident (n = 6, y = x, $R^2 = 1$). This demonstrates the validity of the fifth equation.

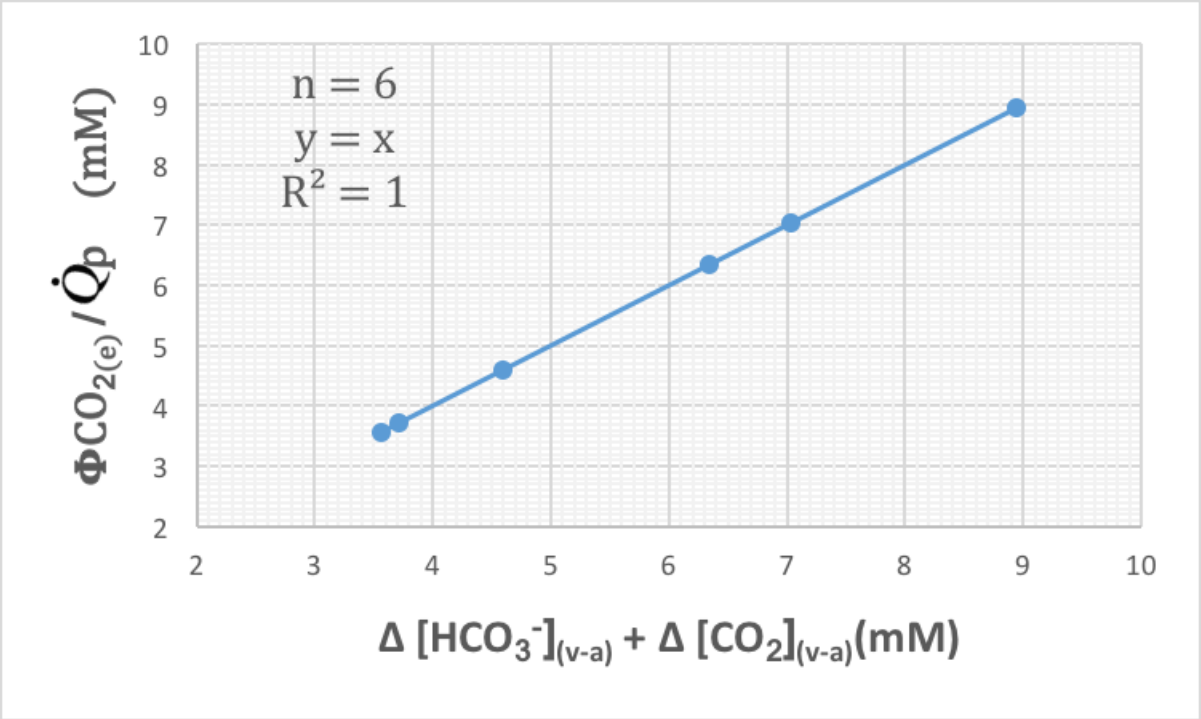

Figure 6

$\frac{\Phi CO_{2(e)}}{\dot{Q}p}$ in relation to $\Delta[HCO_3^-]_{(v-a)} + \Delta[CO_2]_{(v-a)}$ is an identity function (n = 6, y = x, $R^2 = 1$).

If we enter the $\dot{Q}t$ value instead of $\dot{Q}p$, $\Phi CO_{2(e)}$ per liter of blood ejected from the heart per minute (cardiac output) does not coincide with the sum of the deltas of HCO_3^- and CO_2 concentrations,
Note: the dimensional analysis of the physical quantities of the sixth equation shows dimensional homogeneity, and on both sides of the equation, we have the concentration expressed in mM (mmol/L).

4 Validation of the mathematical model

4.1 Validation of the model on a mathematical level

This mathematical model, aimed at identifying the pulmonary flow of blood ($\dot{Q}p$) and $\dot{Q}_{IPAVA}$, is based on literal equations (equality between two expressions) in which an unknown appears. Solving an equation that contains an unknown consists of determining the numerical value that, substituted for the unknown, makes the equality true and therefore valid.
The unknown is solved with a single number, and only this number verifies the equation.
In our case, the number, once the equation is solved, refers to our unknown $\dot{Q}p$.
The fifth equation, for example, can be rewritten as follows:

$$\mathbf{(a + b)\ x = c.}$$

To know the value of the unknown x, we need to solve the abovementioned equation as given below:

$$\mathbf{x} = \frac{\mathbf{c}}{\mathbf{a} + \mathbf{b}}$$

if we replace to:

a = $\Delta[HCO_3^-]_{(v-a)}$ known numerical value

b = $\Delta[CO_2]_{(v-a)}$ known numerical value

c = $\Phi CO_{2(e)}$ known numerical value

x = **unknown**, which represents $\dot{Q}p$ (pulmonary flow of blood)

we return to the fifth equation with the real physiological parameters

$$(\Delta[\mathbf{HCO_3^-}]_{(\mathbf{v-a})} + \Delta[\mathbf{CO_2}]_{(\mathbf{v-a})})\ \mathbf{x}\ \dot{Q}p = \mathbf{\Phi CO_{2(e)}}.$$

Therefore, $\dot{Q}p$ is determined by parameters detected and measured on each individual.

All physics formulas are literal equations, designed similarly to the formulas in this mathematical model. It is a particularly important algebraic model precisely because it allows the representation and solving of many real problems.

The quantification of $\dot{Q}p$ is precise, rigorous and repeatable, as long as the instruments used to measure the various parameters present in the equation are accurate.

4.2 Validation of the model on a chemical level

On the chemical level, we equalized the two expressions to obey Lavoisier's law, which, applied in particular to the excretion of CO_2, obliges us to affirm that all the CO_2 released between venous and arterial blood per minute (left-hand side of the equation) must be present in the CO_2 exhaled per minute (right-hand side of the equation).

The study started with the use of cardiac output by identifying it in pulmonary blood flow. Therefore, we multiplied $(\Delta[\mathbf{HCO_3^-}]_{(\mathbf{v-a})} + \Delta[\mathbf{CO_2}]_{(\mathbf{v-a})})$ x $\dot{Q}t$ and verified whether this left-hand side of the equation was equal to $\Phi CO_{2(e)}$, but the left-hand side of the equation was always greater than the right-hand side of the equation, that is,

$$(\Delta[\mathbf{HCO_3^-}]_{(\mathbf{v-a})} + \Delta[\mathbf{CO_2}]_{(\mathbf{v-a})})\ \mathbf{x}\ \dot{Q}\mathbf{t} > \mathbf{\Phi CO_{2(e)}}$$

Therefore, we realized that $\dot{Q}t$ is an excessive multiplication factor, and it is not possible to establish the equality. However, this approach allowed us to determine that $\dot{Q}t$ and $\dot{Q}p$ differ significantly from each other under some physiological conditions and that there is a part of the cardiac output that does not exchange CO_2 with the outside. Therefore, this procedure has allowed us to identify that even in healthy and athletic subjects, a particularly consistent shunt occurs, especially during high-intensity exercise in hypoxia.

4.3 Validation of the model at the biochemical and physiological levels

As stated in the introductory note to the equations of Materials and Methods, protons bind to bicarbonate to form carbon dioxide because of the reaction — $H^+ + HCO_3^- \leftrightarrow CO_2 + H_2O$ — catalyzed by carbonic anhydrase. We may wonder why blood $[HCO_3^-]$ should be considered to quantify total blood $[CO_2]$ in addition to PCO_2. In other words, we may wonder why the loss in HCO_3^- should not be already reflected in the change in PCO_2.

The CO_2 lost during exhalation and measured with the metabolic cart must represent all the CO_2 lost through the lungs between venous and arterial blood and measured with the blood gas analyzer (Lavoisier's law). If, reductio ad absurdum, we wanted to identify the exhaled CO_2 only with the delta PCO_2, we must equal only the delta PCO_2 (multiplied by 0.03 to have $\Delta[CO_2]_{(v-a)}$), lost between venous and arterial blood, multiplied by the pulmonary blood flow ($\dot{Q}p$), with the exhaled $VCO_2/22.26$. Then, the equation is as follows:

$$\Delta[\mathbf{CO_2}]_{\mathbf{(v-a)}} \mathbf{x}\, \dot{Q}p = \mathbf{\Phi CO_{2(e)}}$$

where

$$\dot{Q}p = \frac{\mathbf{\Phi CO_{2(e)}}}{\Delta[\mathbf{CO_2}]_{\mathbf{(v-a)}}}$$

Mathematical terms rewrite the equation as follows:

$$\mathbf{bx = c}$$

where

$$\mathbf{x = \frac{c}{b}}$$

A calculation example, using only PCO_2, in NORMOXIA-PLACEBO at rest is given below:

$\Phi CO_{2(e)}$ = 14.82 mmol/min
PCO_{2v}= 46.9 mmHg
PCO_{2a}= 38 mmHg
$\Delta PCO_2(v-a)$ = 46.9 - 38 = 8.9
$\Delta PCO_2(v-a)$ x K = $\Delta[CO_2]_{(v-a)}$ (Henry's Law)
where K = solubility constant of CO_2. At 37 °C in plasma, its value is 0.03 mmol/L • mmHg,
$\Delta[CO_2]_{(v-a)}$= 8.9 x 0.03 = 0.267 mmol/L
$\Delta [CO_2](v-a)$ x $\dot{Q}p$ must be equal to $\Phi CO_{2(e)}$ for Lavoisier's law.
Therefore, we calculate the value of $\dot{Q}p$ (our unknown):

$$\dot{Q}p = \frac{\mathbf{\Phi CO_{2(e)}}}{\Delta[\mathbf{CO_2}]_{\mathbf{(v-a)}}} = \frac{\mathbf{14.82}}{\mathbf{0.267}} = \mathbf{55.5\ L/min}$$

To exhale that quantity of CO_2 per minute (14.82 mmol/min), **at rest**, a pulmonary blood flow ($\dot{Q}p$) of **55.5 L/min** would be required if only PCO_2 was used to obtain the exhaled CO_2. Considering that the $\dot{Q}_t$ value at rest in normoxia is approximately **5 L/min**, $\dot{Q}p$ would be **eleven-fold greater** than $\dot{Q}_t$. This is an impossible physiological condition.

If we instead add delta bicarbonate concentration to delta PCO_2, we obtain a pulmonary flow ($\dot{Q}p$) of **4.15 L/min** (expected value).
Therefore, it is only the sum of the two deltas, $[CO_2]$ and $[HCO_3^-]$, multiplied by pulmonary blood flow, leading to the total exhaled CO_2.

5 Discussion

In healthy humans, pulmonary blood flow ($\dot{Q}p$) is currently thought to support the entire cardiac output ($\dot{Q}_t$), and both are considered identical; when $\dot{Q}_t$ is measured, this measure is also referred to as $\dot{Q}p$. According to the results of this study, instead, it is necessary to identify cardiac output only with pulmonary perfusion ($\dot{\boldsymbol{Q}}$) and not with $\dot{Q}p$.
In fact, from the results obtained by applying the first equation to experimental data (11), in which $\dot{Q}_t$ is used as a multiplicative factor to calculate $\phi CO_{2(\dot{Q}_t)}$ and $\phi HCO_{3\,(\dot{Q}_t)}^-$, their sum, represented by $\Phi CO_{2(\dot{Q}_t)}$, is always greater than $\Phi CO_{2(e)}$, which is the real flow of CO_2 from the lungs (table 1). This result is because of the $\dot{Q}_t$ value, which is greater than the actual $\dot{Q}p$ (Figure 2).
However, this is an impossible situation because, according to Lavoisier's law, the two flows must be identical. Therefore, we can deduce that if we use the measure of $\dot{Q}_t$ as a parameter to assess $\dot{Q}p$, we carry out a relatively high overestimation of it.
In contrast, if we calculate $\dot{Q}p$ with one of the three equations presented herein and enter its value into the fifth equation, instead of the value of $\dot{Q}_t$, we obtain $\Phi CO_{2(\dot{Q}p)}$ as identical to $\Phi CO_{2(e)}$ (Figure 1). Therefore, only using $\dot{Q}p$, Lavoisier's law on the conservation of mass can be satisfied for the excretion of CO_2 from human lungs, and all the CO_2 content that is lost between venous and arterial blood in terms of HCO_3^- and CO_2, multiplied by $\dot{Q}p$, can be found in the expired VCO_2.
Therefore, the expired CO_2 represents all the HCO_3^- and CO_2 lost between venous and arterial blood through the lungs. More precisely, as confirmed by applying the experimental data to the sixth equation (Figure 6), we can affirm that the number of millimoles of CO_2 exhaled for each liter of pulmonary blood that exchanges with the outside ($\dot{Q}p$) is equal to the sum of the deltas of the concentrations of HCO_3^- and CO_2 detected in the venous and arterial blood using a blood gas analyzer.
Furthermore, the three equations for calculating $\dot{Q}p$ made it possible to immediately identify errors in the measurement of cardiac output, and this aspect is relevant, as the noninvasive measurements of $\dot{Q}_t$ are sometimes incorrect, but there is no awareness of it.

5.1 Pulmonary flow ($\dot{Q}p$) of blood and its efficiency

From this study, we can define pulmonary flow of blood ($\dot{Q}p$) as the actual blood flow, expressed in liters, which passes through the pulmonary microcirculatory area each minute and allows the effective exchange of respiratory gases through the pulmonary epithelium. Therefore, it cannot be quantified with the same cardiac output value because, although minimal, there is a quantitative difference between cardiac output and pulmonary blood flow ($\dot{Q}p$).
The cardiac output ($\dot{Q}_t$) is exactly identical to the pulmonary blood flow ($\dot{Q}p$) only when all the blood flow starting from the right ventricle of the heart passes through the pulmonary microcirculation area,

and consequently, the CO_2 flow leaving the venous blood consisting of bicarbonate and CO_2 flows, that is, $\Phi CO_{2(\dot{Q}t)}$, is identical to the CO_2 flow eliminated outside, that is, $\Phi CO_{2(e)}$, measured externally with the metabolic cart. This can happen in healthy subjects when IPAVA are closed, at rest and when there are no malformations, such as patent foramen ovale and/or large diameter pulmonary arteriovenous malformations (PAVMs).

Consequently, with the three equations that calculate $\dot{Q}p$, we can evaluate the pulmonary blood flow, which represents the pulmonary perfusion ($\dot{Q}$) net of $\dot{Q}_{IPAVA}$. In fact, the part of pulmonary perfusion, represented by $\dot{Q}_{IPAVA}$, is not able to eliminate CO_2 towards the external environment; therefore, this component of CO_2 is not present in the VCO_2 measured with the metabolic cart.

The $\frac{\dot{Q}_p}{\dot{Q}_t}$ ratio represents the efficiency of pulmonary blood flow with respect to cardiac output and should be correlated with pulmonary arteriolar resistance. The more $\dot{Q}p$ is less than $\dot{Q}_t$, the greater the resistance offered by the vessels through which the pulmonary blood flow of $\dot{Q}p$ flows and the lower the efficiency of pulmonary flow with respect to cardiac output. From the results (Figure 3), the $\frac{\dot{Q}_p}{\dot{Q}_t}$ ratio is identical to $\frac{\Phi CO_{2(e)}}{\Phi CO_{2(\dot{Q}t)}}$, which represents the efficiency of the CO_2 excretion compared to CO_2, which would be eliminated if all cardiac output were used, but it should be emphasized that the pulmonary blood flow efficiency determines the efficiency of CO_2 excretion and, in general, the gas exchange efficiency. Therefore, the use of the measure of $\dot{Q}t$ to quantify $\dot{Q}p$, besides being inaccurate, does not allow the real evaluation of loss of efficiency of pulmonary blood flow and the consequent loss of efficiency in the excretion of CO_2, especially when the subjects are in different physiological states and/or changed environmental conditions (e.g., at rest, in exercise, in normoxia, in hypoxia) or in the presence of vasoconstrictor drugs or respiratory diseases.

5.2 Pulmonary flow of blood ($\dot{Q}p$) and its vasoreactivity

$\dot{Q}p$ is extremely variable because the pulmonary vasculature is a dynamic system that responds rapidly to vasoactive mediators (2). In this study, it varies compared to its $\dot{Q}t$ (see Figure 2) according to the physiological state in which the subjects are (rest, moderate or heavy exercise) and the conditions to which they are subjected (normoxia, hypoxia), but to ascertain whether there is a reduction (a loss of efficiency) in pulmonary flow with respect to cardiac output, it is necessary to refer to the $\frac{\dot{Q}_p}{\dot{Q}_t}$ ratio and express it as a percentage.

Particularly, if the subjects were in normoxia-placebo, $\dot{Q}p$ decreased slightly compared to its $\dot{Q}t$ (Figure 2A) in the different physiological states, reaching the maximum reduction with heavy exercise (97.56%). Therefore, in healthy subjects under normal conditions (normoxia), we verified that the value of $\dot{Q}p$ was very close to that of $\dot{Q}t$. Consequently, only in these subjects under normal conditions $\dot{Q}_t$ can be approximately quantified by obtaining it from the calculation of $\dot{Q}p$ increased by 1-2%, without resorting to cardiac output measurement. The physiological mechanisms underlying these results are well described by various authors (3, 2, 5) when they state that the lungs react to the increase in cardiac output during exercise, with an in-built protective mechanism against the increase

in pulmonary vascular resistance through the recruitment of capillaries and the distension of the elastic vessels present in the circuit.
In contrast, the effect of hypoxia alone significantly reduced $\dot{Q}p$ (85.25% under heavy exercise) compared to its own $\dot{Q}_t$ (Figure 2B, Figure 5). This is caused by hypoxic pulmonary vasoconstriction, which intervenes in hypoxia, as already observed by several authors (1, 6, 7, 8). Pulmonary vasoconstriction increases the resistance of the pulmonary arterioles, and consequently, we observed a decrease in $\dot{Q}p$.

5.3 IPAVA blood flow ($\dot{Q}_{IPAVA}$)

"Physiologically, pulmonary arteriovenous shunting is commonly defined as the passage of blood through the lungs without taking part in gas exchange" - Genovesi, et.al. (1976). Therefore, the part of pulmonary perfusion that does not exchange gas with the outside and, in particular, the CO_2 that is not present in the metabolic cart constitutes the shunt.
There are two types of shunts, namely, extrapulmonary and intrapulmonary shunts. They are normally present in cardiorespiratory diseases.

The presence of IPAVA (intrapulmonary arteriovenous anastomoses) in healthy humans, have been known to exist in human lungs for over 60 years (25), but there is an ongoing dispute over their functional role and relevance. In particular, approximately 30% of healthy, young and asymptomatic subjects have IPAVA that are open at rest in normoxia but breathing 100% O_2, and assuming an upright body position reduces blood flow through IPAVA in these 30% (26). IPAVA open in almost all healthy subjects, in normoxia during moderate- and high-intensity exercise (14, 15), and in hypoxia are already perfused at rest (19) and have even greater perfusion with exercise (15).
The transient patency of these IPAVA (18, 20) seem to safeguard the small capillaries when there are high flows and pressures in the pulmonary artery, especially at high exercise intensity and in hypoxia (14, 15). Conversely, during exercise in hyperoxia (100% O_2), IPAVA close (17, 18), and yet, there does not appear to be a substantial increase in pulmonary pressure or resulting pulmonary capillary damage. IPAVA, in healthy subjects, are large in diameter, that is, > 50 μm, (16), and as already pointed out, they have a dynamic regulation. They may bypass the pulmonary capillary circulation, and the flow of blood flowing into them goes directly to the left side of the heart. IPAVA have been detected in vivo, during exercise, with echocardiographic methods (transthoracic saline contrast echocardiography - TTSCE) (14, 15, 17, 25) and with technetium-99m labeled macroaggregated albumin (99mTc-MAA) (21, 22, 23, 25). However, both techniques have limitations (24):

- TTSCE is a simple, noninvasive technique for detecting the opening and closing of IPAVA under a variety of conditions. However, it is unable to quantify the percentage of cardiac output flowing through IPAVA (24) but only to verify that the flow increases or decreases according to the number of bubbles visible in the left ventricle (14, 15,17).
- 99mTc-MAA allows the calculation of the percentage of shunts with respect to the cardiac output, which flows in IPAVA but presents technical difficulties (preliminary selection of the MAA size) and possible errors in the subjective determination of the lung region of interest (ROI). Furthermore, another source of error in quantifying $\dot{Q}_{IPAVA}$ is the time, since any delay

between injection of labeled MAA and scanning will increase the possibility of overestimating IPAVA (24, 25).

However, both techniques made it possible to detect blood flow through IPAVA in healthy humans in normoxia during exercise (14, 20) and, at rest and during exercise, in hypoxia (19, 15). Furthermore, the simultaneous use of the two techniques, TTSCE and 99mTc-MAA, led to consistent data (24).

With the eighth equation, it was possible to quantify $\dot{Q}_{IPAVA}$ with a simple, precise method and easy to perform, since the **pulmonary flow, as presented in this model, represents the only portion that exchanges with the external environment.** Therefore, in healthy humans, when cardiac output is greater than pulmonary flow, the part of the flow that does not exchange CO_2 with the external environment, namely, $\dot{Q}_{IPAVA}$, is that one which flows through the vessels referable to intrapulmonary arteriovenous anastomoses (IPAVA).

Furthermore, we have shown, with the ninth equation, that the portion of the untapped cardiac output, which refers to the percentage of $\dot{Q}_{IPAVA}$, directly affects with its negative contribution to pulmonary gas exchange efficiency (Figure 4).

Therefore, as verified by various authors through the TTSCE and 99mTc-MAA techniques mentioned above (14, 15, 17,19, 20, 21, 22, 24, 25), in this study, the presence of $\dot{Q}_{IPAVA}$ was confirmed in healthy humans in conditions of both normoxia (during exercise) and hypoxia (at rest and during exercise). Unfortunately, as already pointed out, in normoxia at rest, the $\dot{Q}_t$ measure was underestimated; therefore, it was not possible to verify, in this study, if $\dot{Q}_{IPAVA}$ are open during this condition, although it should be emphasized that various authors (19, 20) have verified that in healthy humans, in normoxia at rest, $\dot{Q}_{IPAVA}$ are closed, but only in the vast majority of cases and not in all subjects (26). In normoxia, during exercise at 50% VO_2max, instead, we could see a $\dot{Q}_{IPAVA}$ of 1.56% of $\dot{Q}_t$, while at high intensity ≥ 90% of VO_2max, we quantified a $\dot{Q}_{IPAVA}$ of 2.44% of $\dot{Q}_t$, equal to $\dot{Q}_{IPAVA}$ of 0.58 L/min.
Under normoxia, during exercise, $\dot{Q}_{IPAVA}$was rather limited; under hypoxia, especially during heavy exercise, the $\dot{Q}_{IPAVA}$ was very high.
In fact, we calculated an $\dot{Q}_{IPAVA}$ of 3.48 L/min equal to a $\dot{Q}_{IPAVA}$ 14.75% of $\dot{Q}_t$.
At rest-hypoxia, instead, $\dot{Q}_{IPAVA}$ increased up to 6.49% of $\dot{Q}_t$, equal to $\dot{Q}_{IPAVA}$ of 0.37 L/min, and these data are congruent with what has been verified by other authors (19, 20) with the abovementioned methods.

5.4 What the mathematical model allows and does not allow to discriminate
The model allows us to understand the path taken by the pulmonary blood flow ($\dot{Q}p$), which exchanges CO_2 with the outside, that is, the pulmonary microcirculatory area, and to quantify it with precision in L/min and/or in % of cardiac output.

Regarding the pulmonary blood flow that runs through the shunt and therefore does not exchange CO_2 with the outside, it cannot discriminate whether the flow is going through intrapulmonary and/or extrapulmonary shunts but only succeeds in precisely quantifying the shunt in L/min and/or in % of cardiac output.
In this work, we refer only to IPAVA because they are present in healthy subjects, and the experimental data entered in this model refer to these subjects.
To discriminate the pathways traveled by the blood in any cardiopulmonary malformation, this diagnostic method should be integrated with other diagnostic methods (e.g., TTSCE).

In summary, this mathematical model allowed us to precisely quantify pulmonary blood flow ($\dot{Q}p$) for the first time and distinguish it from cardiac output ($\dot{Q}_t$) using noninvasive and easy-to-use measuring instruments. The model also made it possible to verify the vasoreactivity of pulmonary circulation when healthy subjects were subjected to variations in FIO_2 at rest and during exercise. Furthermore, it allowed us to detect the presence of $\dot{Q}_{IPAVA}$ in healthy humans and to accurately quantify the blood flow that flows in these arteriovenous vessels, in normoxia during exercise, and in hypoxia both at rest and during exercise. In addition, for the first time, we have shown that $\dot{Q}_{IPAVA}$ directly and negatively affect gas exchanges. This new mathematical model also immediately identified erroneous $\dot{Q}_t$ measurements of the experimental data.

6 Future prospects

The limitation of this study is that the new mathematical model was applied only to data from healthy and young men, whereas the presence of respiratory and metabolic pathologies, for example, should cause a specific variation of $\dot{Q}p$ and $\dot{Q}_{IPAVA}$, strictly depending on the type of pathology. Therefore, the use of this model, which uses noninvasive measuring instruments that are easy to use and widespread in all hospitals, could allow a precise, accurate, and early detection of pathology in action or formation phases, enabling related therapeutic approaches to be more targeted and more effective, thus minimizing any iatrogenic errors.
Therefore, the application of this mathematical model in medical research and in clinical and diagnostic practice is expected to enable a general advancement of the scientific understanding of this critical biological function.

Authors' contributions

The corresponding author was responsible for elaboration of the mathematical model, conceptualization, design, dataset search, and writing.

Conflict of Interest

The author declares no conflicts of interest, financial or otherwise.

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