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A New Objective Diagnostic Method for Chronic Heart Failure

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Abstract

Algebraic equations from a mathematical model to experimental data related to venous and arterial blood (HCO_3^-, PCO_2), exhaled VCO_2 and cardiac output (Qt) of a group of patients with chronic heart failure (CHF) belonging to the New York Heart Association class III were applied. The aim of this study was to verify whether the above measurable physiological parameters used to calculate pulmonary blood flow in pulmonary microcirculation (Qp) were significantly different among three different groups and to verify whether the algebraic equations used were useful for objectively diagnosing patients with CHF.

The comparison among the results of the three groups was extremely significant, so much to unquestionably highlight the class III CHF group compared with the other two groups and therefore allowing the CHF group to be objectively characterized both at rest and during exercise.

In particular, **at rest**: Group I: young and healthy subjects, aged 26.3±4.6 years, **Qp=4.15 L/min**; Group II: non-CHF normal controls, aged 62.3±10.3 years, **Qp=4.595 L/min**; Group III: CHF patients, who had New York Heart Association functional class III failure, aged 62.4±8.3 years, **Qp=5.51 L/min**.

During exercise: Group I, during exhaustive exercise at 340 W, **Qp=23.22 L/min;** Group II, during submaximal exercise at 50 W, **Qp=15.372 L/min;** Group III, during exhaustive exercise at 50 W, **Qp=8.45 L/min.**

This new diagnostic method performed a first objective pathophysiological characterization of CHF class III patients, laying the foundation for an objective classification of the four classes of CHF patients and subsequent precision medicine.

Keywords: Pulmonary blood flow; Cardiac output measurement; Shunt; Heart failure; NYHA classification; Pulmonary hypertension; Exercise

Introduction

In normal individuals, cardiac output (Qt), which originates from the right ventricle of the heart and enters the pulmonary artery, is considered to be equal to that which traverses the pulmonary microcirculation and exchanges with the external environment through the pulmonary epithelium [1,2]. This statement, however, is normally valid for healthy subjects but only under normoxia at rest.

The Fick principle [3] allows the calculation of cardiac output (Qt) on the basis of a mass balance for O_2 and for CO_2.

In my prior work [4], there is also a Fick equation for CO_2, but it is more detailed. In fact, it highlights the components of the total CO_2 content in

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the blood, namely, bicarbonate (the other form of CO_2) and dissolved CO_2.

However, when the above equation was applied to healthy and young subjects under different conditions [5], for all analyzed cases, the CO_2 leaving the blood multiplied by the cardiac output (Qt) was greater than the measured exhaled VCO_2 [4]. This result did not obey Lavoisier's law of conservation of mass. It indicated that the cardiac output (Qt) value was greater than that of **real blood circulating in the pulmonary microcirculation (Qp)**, which effectively exchanges gases with the external environment through the alveolar epithelium. Therefore, it was necessary to replace Qt with Qp. To calculate Qp, an appropriate equation was formulated [4].

The remaining flow of cardiac output can travel through pulmonary blood vessels known as intrapulmonary arteriovenous anastomosis (IPAVA), which are normally present in healthy lungs [6]. The opening of these anastomoses is inducible by various factors, including physical exercise [6,7] and hypoxia both at rest [8] and during exercise [9-11]. The flow that does not exchange could also be due to the presence of a cardiac shunt or right-to-left interatrial shunt passing through a patent foramen ovale (PFO), which is also present in ~30% of healthy individuals [12], or in large-diameter pulmonary arteriovenous malformations (PAVMs), which are present only in individuals with pulmonary vascular pathologies.

The potential health risks associated with blood flow through these shunt pathways include the ability to transport unfiltered emboli from the pulmonary microcirculation [10], increasing the risk of heart attack and stroke [6].

To measure the blood flow through the shunt (Q_{IPAVA}), an appropriate equation was formulated [4].

The same mathematical model may be used for patients with confirmed chronic heart failure (CHF).

Currently, cardiac patients are still classified with the **New York Heart Association (NYHA) functional classification**, first published in 1928 and updated in nine editions, the latest of which, "revised by the Criteria Committee of the American Heart Association, New York City Affiliate, was released on March 14, 1994" [13]. The “NYHA classes focus on exercise capacity and the symptomatic status of the disease” [14], and the “NYHA functional classification gauges the severity of symptoms in those with structural heart disease, primarily stages C and D. **It is a subjective assessment by a clinician**” [14] and is discordant between that assigned by the physician and the outcomes reported by the patient [15]; however, despite everything, “It is widely used in clinical practice and research and for determining the eligibility of patients for certain healthcare services” [14] and "has served as a fundamental tool for risk stratification of heart failure (HF) and determines clinical trial eligibility and candidacy for drugs and devices" [16]. Unfortunately, it has recently been verified that this classification "**poorly discriminates HF patients across the spectrum of functional impairment**. These findings raise important questions about the need for improved phenotyping of these patients to facilitate risk stratification and response to interventions” [16], as the clinical implications are that "Continued usage of NYHA class in guidelines and trials, for US Food and Drug Administration approval of therapies, and for clinical decision making may hinder efforts to bring precision medicine to the bedside of heart failure patients” [16].

Therefore, in this new study, the mathematical model in [4] was applied to measure Qp among three different groups to observe how Qp behaves at rest and during exercise. Specifically, the aim of this study was to verify whether Qp sufficiently characterizes a homogeneous group of 62-year-olds with CHF, previously classified as New York Heart Association (NYHA) class III, compared with a non-CHF normal control group of the same age, **to lay objective foundations for the classification of CHF**.

Additionally, the aim was to further compare the Qp of the above two groups with that of a third group of young, healthy and athletic individuals to verify how young age and sporting activity affect the Qp at rest and during exercise.

The experimental data entered into the equations were sourced from the scientific literature.

For comparisons between individuals of the same age with and without heart disease, experimental data from Rory Hachamovitch, MD et al. [17] were utilized.

For young, healthy, and athletic subjects, experimental data from Jonk et al. [5] were used.

These two publications were utilized because the mentioned physiological parameters were simultaneously measured as required by the equations.

Materials and Methods

As stated in the introduction, the fundamental parameter to calculate in the three groups is Qp, namely, the pulmonary blood flow that circulates in the pulmonary microcirculation and that actually exchanges with the alveoli.

The measured physiological parameters used in this study, which are involved in respiratory gas exchange, were HCO_3^-, PCO_2, VCO_2 (which are used to calculate Qp) and Qt.

Please note that physiological parameter measurements were taken simultaneously. Therefore, they obey Lavoisier’s law of conservation of mass.

As in previous work [4], VCO_2 is preliminarily transformed into $\Phi CO_{2(e)}$ in the following way:

Vanni R., Cardiol Cardiovasc Med 2024
DOI:10.26502/fccm.92920408

$$\Phi CO_{2(e)} = \frac{VCO_2}{VmCO_2} = \frac{VCO_2}{22.26} \quad (1)$$

where $\Phi CO_{2(e)}$ = the total molar flow rate per minute of expired CO_2 (measured with a metabolic cart), expressed in mmol/min.

$VCO_2 = \frac{mLCO_2}{\min}$ and $VmCO_2 = 22.26$ mL/mmol.

$VmCO_2$ is the molar volume at the STP (volume occupied by a mole of CO_2 to standard T° and P).

To calculate the blood flow in the pulmonary microcirculation (Qp) in all subjects, as in prior work [4], the following equation was used:

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

Qp = pulmonary blood flow in the pulmonary microcirculation, expressed in L/min

To calculate the shunt flow, which includes all forms of right-to-left shunt (IPAVA, PFO, PAVMs, etc.) where possible (for Qt greater than Qp), the following equation was used:

$$Qs = Qt - Qp \quad (3)$$

Qs = shunt blood flow, expressed in L/min.

In this study, we also need to compare Qp with the measured cardiac output (Qt) and with the Qt calculated with the Fick equation. Since the measured physiological parameters used for this study, as mentioned above, are HCO_3^-, PCO_2, VCO_2 and Qt, a modification of the Fick equation is necessary. Therefore, in the following steps, a rigorous mathematical proof allows to verify that the classical Fick equation to obtain the cardiac output (Qt), namely, Eq. 5 and Eq. 12 (modified Fick equation), are equivalent and lead to the same result.

The Fick equation for CO_2 is as follows:

$$VCO_2 = (cCO_{2v} - cCO_{2a}) \times Qt = \Delta cCO_{2(v-a)} \times Qt \quad (4)$$

where VCO_2 is CO_2 production; $cCO_{2\,v}$ and $cCO_{2\,a}$ are the mixed venous and arterial CO_2 contents in blood, respectively; $\Delta_c CO_{2(v\text{-}a)}$ is the difference in CO_2 content between the mixed venous and arterial blood; and Qt is the cardiac output.

To obtain Qt from Eq. (4), it can be reworked in this way:

$$Qt = \frac{VCO_2}{\Delta cCO_{2(v-a)}} \quad (5)$$

The form of the Henderson–Hasselbalch equation [19] used for the calculation of the content of CO_2 **in plasma**, $c[CO_2]$, is as follows:

$$c[CO_2] = \alpha PCO_2 \{1 + 10^{(pH-pK)}\} \quad (6)$$

where α is the solubility of CO_2 in plasma. Both α and pK are temperature dependent, and in addition, pK varies with pH [19].

By mathematically developing Eq. (6), the following equation is obtained:

$$c[CO_2] = \alpha PCO_2 + (\alpha PCO_2 \times 10^{(pH-pK)}) \quad (7)$$

The Henderson–Hasselbalch equation used for the calculation of $[HCO_3^-]$ is:

$$[HCO_3^-] = \alpha PCO_2 \times 10^{(pH-pK)} \quad (8)$$

Through the substitution of Eq. (8) in Eq. (7), the following equation is obtained:

$$c[CO_2] = \alpha PCO_2 + [HCO_3^-] \quad (9)$$

Because $\alpha PCO_2 = [CO_2]$, namely, the concentration of CO_2 dissolved in plasma, expressed in mmol/L, through its substitution, the following equation is obtained:

$$c[CO_2] = [CO_2] + [HCO_3^-] \quad (10)$$

After obtaining the CO_2 content in the plasma, $c[CO_2]$, Hachamovich [17] and Jonk [5] used their respective formulas [18,19] to determine the CO_2 content **in the blood**, so they obtained the bicarbonate concentrations and the concentration of the dissolved CO_2 ($[CO_2]$) in the venous and arterial blood.

The venous and arterial blood bicarbonate concentrations, expressed in mmol/L, and the venous and arterial PCO_2 values, which, multiplied by α, give the concentration of the dissolved CO_2 ($[CO_2]$), expressed in mmol/L, were extracted from Hachamovitch [17] and Jonk [5].

Therefore, $\Delta[HCO_3^-]_{v\text{-}a}$ and $\Delta[CO_2]_{v\text{-}a}$ were calculated for both experiments.

However, to convert $\Delta cCO_{2v\text{-}a}$ (expressed in mmol/L) to mL/L, we have to multiply it to 22.26 mL/mmol. In fact, a factor of 22.26 (molar volume of CO_2) converts the units from mmol CO_2/L of blood to mL CO_2/L of blood [19].

Therefore, to obtain $\Delta cCO_{2v\text{-}a}$ in mL/L, the following calculation was performed:

$$\Delta cCO_{2(v-a)} = (\Delta[HCO_3^-]_{(v-a)} + \Delta[CO_2]_{(v-a)}) \times 22.26 \quad (11)$$

where $\Delta[HCO_3^-]_{(v\text{-}a)}$ and $\Delta[CO_2]_{(v\text{-}a)}$ represent the concentration gradients of bicarbonate and dissolved CO_2, respectively, between venous and arterial blood (expressed in mL/L).

By substituting into Eq. (5) $\Delta cCO_{2v\text{-}a}$, with its equality given by Eq. (11), a modified Fick equation was obtained:

$$Qt = \frac{VCO_2}{(\Delta[HCO_3^-]_{(v-a)} + \Delta[CO_2]_{(v-a)}) \times 22.26} \quad (12)$$

Vanni R., Cardiol Cardiovasc Med 2024
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Characteristics of the subjects who participated in the Jonk and Hachamovitch experiments

In Jonk's work [5], the experiments were conducted on 6 male participants (aged 26.3 ± 4.6 years) who were healthy and who exercised at increasing intensities up to 340 watts on a cycle ergometer.

In the work of Hachamovitch [17], there were 26 men, 12 of whom were normal controls (aged 62.3 ± 10.3 years) and 14 of whom were heart failure patients (aged 62.4 ± 8.3 years). All the participants performed an incremental exercise on a cycle ergometer.

Patients with chronic heart failure (CHF) are a homogeneous group belonging to functional class III of the New York Heart Association (NYHA). "Heart failure patients were included in this study only if they could exercise for at least 10 minutes of incremental exercise to a workload of 50 W" [17]. "Immediately before exercise, the CHF patients and the normal subjects were monitored for 5 minutes. The duration of the exercise stages was 3 minutes, except at 50 W, when duration was prolonged to 4 minutes to accommodate additional data collection" [17].

"Each variable was measured during the last minute at rest and at each stage of exercise (unloaded pedaling, 25 and 50 W)" [17].

The Jonk [5] and Hachamovitch [17] experimental data, which were entered into the equations, are average measured values for the analyzed sample.

The following numbers were assigned to the three groups of the two different experiments [5,17]:

1: Group of 26-year-olds, healthy and athletic individuals [5]

2: Group composed of 62-year-olds, non-CHF control group [17]

3: Group of 62-year-olds with CHF (chronic heart failure, class III of the NYHA) [17]

Reference data for calculating Qp in the three groups

To calculate Qp with Eq. (2), the following data were used:

- For Group 1, the experimental data at rest and during heavy exercise were extracted from Jonk's paper [5]

- For Groups 2 and 3, the experimental data at rest and at 50 W were extracted from Hachamovitch's paper [17]

Application of the Experimental Data to the Equations

The data from the two previously mentioned papers were entered into the equations because, in the experiments conducted by Jonk and Hachamovitch, the parameters required by the equations were measured simultaneously, as specified by the equations (namely, venous and arterial PCO_2, venous and arterial bicarbonate concentration, Qt and VCO_2).

In fact, these experimental models faithfully reproduce 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.

Instruments and methods of measurement in Hachamovitch's experiment [17]

A right heart flotation catheter (Swan-Ganz) was placed in the pulmonary artery. It was used **to measure cardiac output** (Qt) and **to sample mixed venous blood**. Cardiac output (Qt) was measured by the **thermodilution technique** using a cardiac output computer. A catheter was placed in the radial artery **to sample arterial blood**. Blood analysis was performed with a blood gas analyzer (model 175, Dow Corning).

The VCO_2 was analyzed offline by a medical mass spectrometer (model MGA 1100, Perkin Elmer). The plasma CO_2 content was calculated from the standard formula derived from the Henderson–Hasselbalch equation.

The blood CO_2 content was calculated by the Douglas method [18]. All the data were analyzed during the steady state.

Instruments and methods of measurement in Jonk's experiment [5]

Cardiac output (Qt) was measured at rest and during steady-state exercise at 50% and ≥ 90% VO_2max **using the noninvasive open-circuit acetylene uptake method** [1, 5].

Venous blood was drawn through a catheter placed in the left femoral vein pointing distally. Arterial blood was drawn through a catheter placed in the radial artery of the nondominant arm.

The measured arterial and femoral venous data, PO_2, PCO_2, and pH, were all corrected to body temperature, together with Hb, Hct and standard P_{50} with the Kelman method 1967 [19] (see Calculation of *in vivo* P_{50}) [4,5].

The corrected blood data are presented in [5].

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. All the data were analyzed during the steady-state.

Results

After calculating the Qp values for the three groups with Eq. (2), it is possible to compare them with the respective Qt values measured by different methods in the experiments of Jonk et al. [5] and Hachamovitch et al. [17].

Figures 1 and 2 show the comparison between the

Vanni R., Cardiol Cardiovasc Med 2024
DOI:10.26502/fccm.92920408

calculated Qp in the three groups and the measured Qt using thermodilution, as presented by Hachamovitch et al. [17], and acetylene uptake, as presented by Jonk et al. [5].

By analyzing these data, we observed that Qt was correct only in two groups, as shown in **Figure 1**, namely, the 62-year-old non-CHF control group (Group 2) at rest and, in **Figure 2**, the 26-year-old healthy group (Group 1) during heavy exercise. In fact, only in these two cases is Qt higher than Qp. In all the other cases, Qt is lower than Qp. This is an impossible situation; therefore, all these Qt measurements are underestimated and should be discarded.

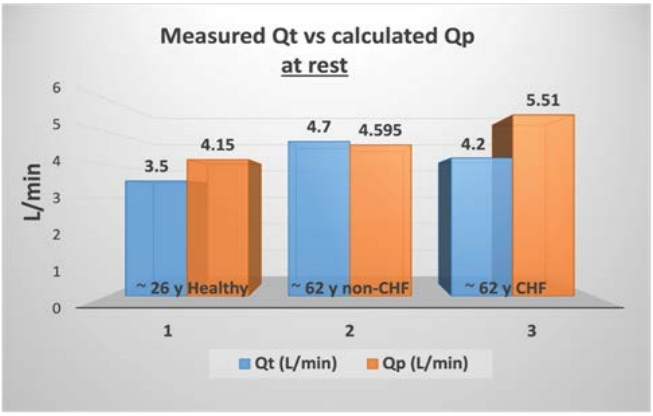

Figure 1: Comparison of measured Qt and calculated Qp at rest in the three groups: **1** (26 years old, healthy and athletic individuals), **2** (62 years old, non-CHF control group) and **3** (62 years old, CHF group). In 1, Qt was measured using acetylene uptake by Jonk [5], whereas in 2 and 3, Qt was measured using thermodilution by Hachamovitch [17]. The measured Qt values in Groups 1 and 3 are lower than the calculated Qp values and therefore are underestimated. Consequently, they should be discarded. In Group 2, the measure of Qt was correct because Qt is greater than Qp.

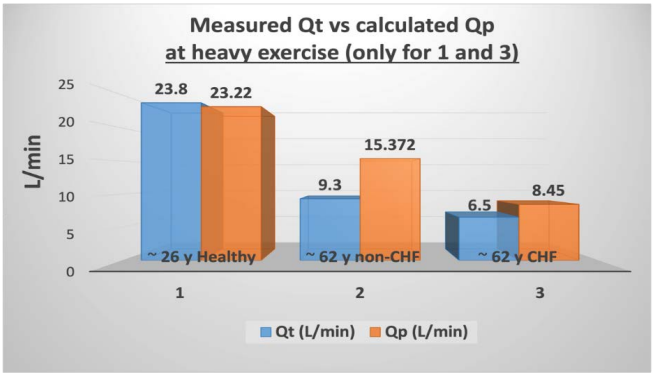

Figure 2: Comparison of the measured Qt and calculated Qp during heavy exercise (only 1 and 3) in the three groups: **1** (26 years old, healthy and athletic individuals), **2** (62 years old, non-CHF control group), and **3** (62 years old, CHF group). In 1, Qt was measured using acetylene uptake by Jonk [5], whereas in 2 and 3, Qt was measured using thermodilution by Hachamovitch [17]. The measured Qt values in groups 2 and 3 are lower than the calculated Qp values and therefore are underestimated. Consequently, they should be discarded. In Group 1, the measure of Qt was correct because Qt is greater than Qp.

Consequently, in Groups 1 and 3, at rest (**Figure 1**), and in Groups 2 and 3, during exercise (**Figure 2**), it was not possible to calculate the Qp/Qt ratio.

Comparison between the Qt measured with thermodilution and the Qt calculated with the modified Fick equation

To verify whether the cardiac output (Qt) measured using the thermodilution method, as indicated by Hachamovitch et al. [17], was indeed underestimated, it is possible to use Eq. (12).

The purpose of this approach is to ascertain whether the Qt measured by thermodilution aligns with the Qt calculated with the modified Fick equation, namely, Eq. (12).

Therefore, cCO_{2v} (in mixed venous blood) and cCO_{2a} (in arterial blood) were calculated with Eq. (9).

The $[HCO_3^-]$ and PCO_2 data from venous and arterial blood, which are shown in the Blood Gases section in [17], were used.

After the venous and arterial CO_2 contents were obtained, the difference between the two contents with Eq. (11), namely, $\Delta cCO_{2v\text{-}a}$, was calculated.

The modified Fick equation, Eq. (12), was subsequently applied to obtain Qt using the VCO_2 data presented in [17].

Figure 3 shows the Qt values (a) measured by Hachamovitch et al. [17] with the thermodilution method compared with the Qt values (b) calculated with the modified Fick equation, Eq. (12), using the VCO_2 , $[HCO_3^-]$ and PCO_2values data presented in the same paper [17]. Qt is expressed in L/min.

In **Figure 3**, when comparing the measured cardiac outputs, Qt (a), obtained through thermodilution with the

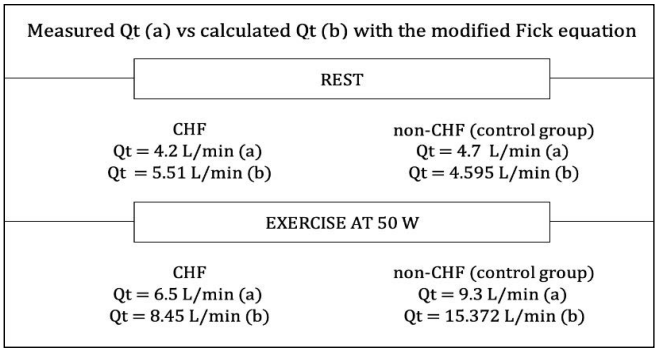

Figure 3: Comparison between the cardiac output values presented in [17], Qt (a), measured with the thermodilution method, and the cardiac output, Qt (b), calculated with the modified Fick equation, Eq. (12), using the VCO_2, $[HCO_3^-]$ and PCO_2 values data presented in [17]. Qt is expressed in L/min. This Figure shows that only the non-CHF (control group) at rest had a slightly greater measured Qt than that calculated with the modified Fick equation. All the other measured Qt values are significantly lower than those calculated with the modified Fick equation and are therefore underestimated.

Vanni R., Cardiol Cardiovasc Med 2024
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calculated cardiac outputs, Qt (b), using the modified Fick equation, Eq. (12), it is possible to observe that only the non-CHF (control group) at rest has a slightly greater measured Qt than that calculated with the modified Fick equation. All the other measured Qt values are significantly lower than those calculated with the modified Fick equation. This finding indicates that in all these cases, the cardiac output measured by thermodilution is underestimated.

Furthermore, it is possible to observe that in these cases of underestimation, the modified Fick equation, Eq. (12), used to obtain Qt, results in the same value as Qp (see **Figures 1 and 2**), which is derived from the calculation using Eq. (2); however, Eq. (2) specifies that it is actually Qp.

Comparison between cardiac output (Qt) measured with acetylene uptake and cardiac output (Qt) calculated with the modified Fick equation

In Group 1 (**Figures 1 and 2**), Qt was measured using acetylene uptake by Jonk et al. [5]. Unfortunately, even with this method, but only *at rest* (**Figure 1**), Qt was found to be inaccurate (underestimated). As further evidence of the incorrect measurement of Qt, when Eq. (12) was reworked to obtain VCO_2 and using the measured Qt, a VCO_2 value lower than the measured VCO_2 was obtained. However, when the value of Qp, which is calculated with Eq. (2), is entered into Eq. (12), instead of the measurement of Qt, the VCO_2 value matches the measured VCO_2.

Furthermore, by applying Eq. (12) using the measured VCO_2 and the $[HCO_3^-]$ and PCO_2 data from venous and arterial blood, we obtain a value of Qt that is exactly identical to Qp.

Qp at rest: comparison among the three studied groups

The Qp (L/min) at rest in the three groups (**Figure 4**) was significantly different among the 26-year-old group (**Figure 4** Group **1**), the 62-year-old non-CHF group (control group) (**Figure 4** Group **2**) and the 62-year-old CHF group (**Figure 4** Group **3**). Qp was calculated with Eq. (2).

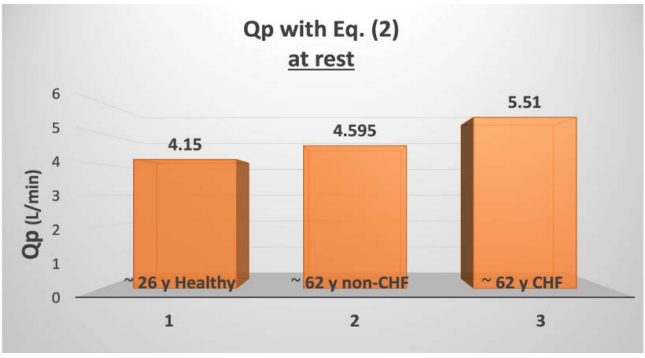

Figure 4: Comparison of Qp at rest among the three groups:
1: Group of 26-year-olds, healthy and athletic individuals.
2: Group of 62-year-old non-CHF (control group).
3: Group of 62-year-olds with CHF functional class III in NYHA.
Qp was calculated with Eq. (2). At rest, the Qp (L/min) significantly differed among the three groups.

Qp during exercise: comparison among the three studied groups

Figure 5 shows the comparison of Qp among the three groups. Qp was calculated with Eq. (2).

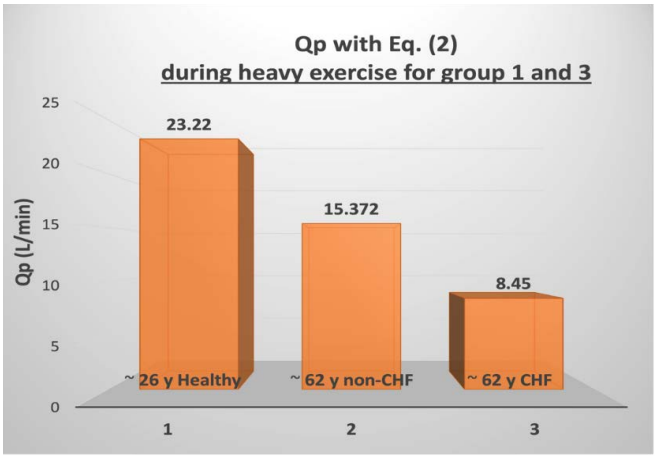

Figure 5: The three groups underwent exercise on a cycle ergometer. For the three groups, Qp was calculated with Eq. (2). Two groups were subjected to maximal exercise (Groups 1 and 3), whereas Group 2 underwent submaximal exercise. Specifically:

1: Group composed of 26-year-olds, healthy and athletic individuals. Qp (L/min) was calculated at **340 W** (≥ 90% VO_{2max}).

2: Group composed of 62-year-old non-CHF (control group). Qp (L/min) was calculated at **50 W** (VO_{2max} was not verified preliminarily).

3: Group composed of 62-year-olds with CHF functional class III in NYHA. Qp (L/min) was calculated at 50 W (VO_{2max} was not verified preliminarily).

The three groups underwent exercise on a cycle ergometer. In particular, two groups were subjected to maximal exercise (Groups 1 and 3), whereas Group 2 underwent submaximal exercise.

Specifically:

Group **1** (26-year-old healthy and athletic individuals) at 340 W underwent heavy exercise (≥ 90% VO_{2max}). In this group, the cardiac output (Qt) was 23.8 L/min, and the pulmonary blood flow (Qp) was **23.22 L/min,** with a shunt blood flow (Qs), calculated with Eq. (3), of 0.58 L/min (Qs represents 2.44% of Qt).

Group **2** (the 62-year-old non-CHF control group) "was not limited by the workload" [17] at 50 W of exercise, indicating that this group did not perform heavy exercise. Under these conditions (50 W), the average Qp was **15.372 L/min**. In this experiment [17], VO_{2max} was not verified preliminarily.

Vanni R., Cardiol Cardiovasc Med 2024
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Unfortunately, the inaccurate measurement of Qt did not allow us to calculate Qs, which normally occur during exercise.

Group **3** (62-year-old CHF patients) "was limited by fatigue and dyspnea at 50 W of exercise but had no symptoms of angina" [17]. These patients clearly demonstrated a marked limitation of physical activity (classified as CHF class III of the NYHA). The Qp of CHF patients during exhaustive exercise was only **8.45 L/min**. In this experiment [17], VO_{2max} was not verified preliminarily, but given the above statement in [17], it can be deduced that this group underwent heavy exercise. Even in this group, the inaccurate measurement of Qt did not allow us to calculate Qs.

Discussion

"It is a source of regret that the measurement of flow is so much more difficult than the measurement of pressure. This has led to an undue interest in the blood pressure manometer. Most organs, however, require flow rather than pressure. . ." Jarisch, 1928 [20]. This statement by Jarisch is still fully valid [21].

Currently, with these equations, it is possible to directly measure pulmonary blood flow (Qp) expressed in L/min through the pulmonary microcirculation and its exchange with the external environment in all subjects [4], including those with cardiovascular pathologies, even without knowing the cardiac output measurement.

Furthermore, in the case of wanting to proceed with the measurement of Qt and having the measurement of Qp available, it is possible to verify whether the cardiac output measurement is correct or incorrect, as seen in the cases depicted in **Figures 1 and 2**. It is also possible to measure, in terms of flow (L/min), the blood flowing through a shunt only if Qt is greater than Qp, as there are no shunts if Qt coincides with Qp.

However, to obtain a precise measurement of Qp, the data, which we use in the equations, **"**reflect the real values present in the mixed venous blood of the pulmonary artery and in the arterial blood at the end of the pulmonary capillaries. Only in this way can an accurate measurement of Qp be obtained" [4].

Qp analysis at rest: comparison among the three groups

An analysis of the resting-state Qp of the three groups (**Figure 4**) revealed that the 62-year-old non-CHF control group (Group 2) had an increase of 0.445 L/min compared with the 26-year-old healthy and athletic individuals (Group 1). Moreover, a characteristic feature of the CHF patients (Group 3) at rest was the manifestation of a particularly high Qp, which was 0.915 L/min higher than that of the non-CHF control group of the same age (Group 2) and almost 1.4 L/min higher than that of Group 1.

The Qp value of group 3, at rest, objectively characterizes CHF class III patients.

Qp analysis during exercise: comparison among the three groups

Figure 5 highlights the behavior of Qp during exercise in the three groups.

In particular:

Group 1 (26-year-old healthy and athletic individuals), **at 340 watts**, underwent **heavy exercise** (≥ 90% VO_{2max}). The Qp of these healthy, young and athletic subjects was **23.22 L/min.**

In **Group 2** (the 62-year-old **non-CHF control group**), **at 50 W**, the **Qp** was **15.372 L/min.** This group "was not limited by the workload" [17], indicating that the subjects were not performing heavy exercise and therefore could have increased the intensity of the work (wattage increase) with a further increase in their cardiac output and consequently of their Qp.

However, these considerations are imprecise because Hachamovitch's experiment [17] did not include a preliminary assessment of the VO_{2max} of Group 2. Only through this assessment could the percentage of VO_{2max} at which these subjects were exercising at 50 watts be known, and precise considerations could be made if blood samples were also taken during heavy exercise (≥ 90% VO_{2max}).

Unfortunately, inaccurate measurements of Qt did not allow us to verify Qs, which normally occur during exercise [6,7,9,11], even if "qualitatively measured exercise- and hypoxia-induced blood flow through IPAVA is significantly lower in older individuals compared with younger controls" [22], but "the reasons for the age-related decrease in blood flow through IPAVA are unknown" [22].

Group 3 (62-year-old **CHF patients**) "was limited by fatigue and dyspnea at 50 W of exercise but had no symptoms of angina" [17]. Therefore, Group 3, **at 50 W,** underwent **exhaustive exercise,** clearly demonstrating a marked limitation of physical activity (previously classified as CHF class III of NYHA). Under these conditions, **Qp** was only **8.45 L/min**.

In fact, as expected, the Qp **during heavy exercise** in CHF patients was almost half that of normal individuals of the same age; however, these individuals were performing a **submaximal effort** at the same wattage (50 W). In particular, Qp = 8.45 L/min for CHF patients, whereas Qp = 15.372 L/min for normal controls. Group 3 highlighted a rather significant form of heart failure.

The Qp value of Group 3, during heavy exercise, objectively characterizes CHF class III individuals.

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First characterization of CHF: objective classification of chronic heart failure class III

The present study allows for the first identification of some functional characteristics of CHF class III patients, which are fundamental for objectively classifying individuals exhibiting these features.

Currently, the gold standard for classifying **chronic heart failure** is the New York Heart Association (NYHA) classification [14-16], which has significant limitations related to subjectivity, both from the patient's and the physician's perspective [15].

This study lays the foundation for an objective characterization of CHF class III patients, as some features of the patients in Group 3, all of whom were previously classified as NYHA class III, exhibited significant differences in functional characteristics compared with those of the age-matched non-CHF control group.

In particular, a CHF class III is characterized by the following:

-At rest, the **Qp** was **significantly elevated** (average 5.51 L/min) and was approximately 1.00 L/min greater **than that of the non-CHF control group of the same age**.

-During exhaustive exercise, the **Qp** was **significantly lower** (8.45 L/min average) by approximately 7.00 L/min **than that of the non-CHF control group** of the same age, who, at the same workload intensity (50 W), had a Qp of 15.372 L/min. Unfortunately, from Hachamovich's experiment [17], it is not possible to deduce at what percentage of VO_{2max} the non-CHF control group, subjected to 50 W, were working, as this was not assessed preliminarily. We could only say that the non-CHF control group was far from the intensity of exhaustive exercise; therefore, their Qp during exhaustive exercise would also have further increased, widening the gap between the Qp of CHF patients and the Qp of the non-CHF control group of the same age.

-During exhaustive exercise, a very low wattage (50 W) was achieved by CHF patients. **This wattage was presumably lower than that of the age-matched non-CHF control group**, who, at the same wattage, were performing a submaximal effort. The maximal intensity of the control group, however, was not verified by Hachamovich et al. [17].

Two techniques for measuring cardiac output were compared: acetylene uptake and thermodilution

The thermodilution technique used to measure cardiac output (Qt) by Hachamovitch in 1991 [17] is invasive. The placement of a catheter (Swan-Ganz) in the pulmonary artery is needed, and the procedure carries significant risks, including pneumothorax, infection, bleeding, or damage to the vasculature, including pulmonary artery rupture [23]. Nonetheless, "pulmonary artery catheterization is becoming increasingly widely used for multiple interventional procedures. Pulmonary artery perforations have been described as a complication of Swan-Ganz catheters" [24], and "The mortality associated with large pulmonary artery perforations is extremely high" [24,25]. However, if pulmonary artery catheter insertion is justified in critical care settings and in interventional procedures, it has little significance in measuring cardiac output, especially in healthy subjects during exercise.

Furthermore, as already noted in [26], this study confirmed that compared with the noninvasive open-circuit acetylene uptake method used by Jonk et al. [5], thermodilution appears to be unreliable.

In fact, in Jonk's experiment [5], 72 measurements of Qt with acetylene uptake were taken**,** but only 12 measurements out of 72 total measurements of Qt were incorrect (that is, just over **16% are incorrect**); however, with **thermodilution**, 40 measurements of Qt out of 52 were incorrect (almost **77% are incorrect**).

The technique involving acetylene uptake not only allowed for the correct measurement of Qt in the vast majority of cases but also enabled us to calculate the Qp/Qt ratio and measure the shunt flow (Qs), owing to the use of Eq. (3), in experiments where cardiac output was found to be greater than Qp.

An inaccurate measurement of Qt represents a missed opportunity

In groups where the measurement of Qt is inaccurate (underestimated) and therefore to be discarded, we cannot determine whether Qt truly coincides with Qp or is higher than Qp. What is certain is the value of Qp, and if the measurement of Qt had been equal to that of Qp, we could have asserted that those subjects, under those conditions, did not exhibit a shunt.

Alternatively, if the measurement of Qt was greater, the Qp/Qt ratio and the measure of shunted blood flow (Qs) could be calculated with Eq. (3). This can only be done in two groups: Group 2 (62-year-old non-CHF control group) at rest (see number 2 in **Figure 1**), which exhibited a shunt of 0.105 L/min, corresponding to a reduction in Qp/Qt = 97.76%; and Group 1, composed of young subjects (see number 1 in **Figure 2**), with a shunt flow of 0.58 L/min during heavy exercise (at 340 watts), corresponding to a reduction in Qp/Qt = 97.56%.

Importance of the Qp/Qt ratio in diagnostic terms

Knowing the precise value of cardiac output allows for the calculation of the pulmonary blood flow in pulmonary microcirculation (Qp) and cardiac output (Qt) ratio. The Qp/Qt ratio is fundamentally important in the diagnosis of certain cardiovascular pathologies.

Indeed, the Qp/Qt ratio represents the efficiency of

pulmonary blood flow in relation to cardiac output and should be correlated with pulmonary arteriolar resistance. In fact, "the more Qp is less than Qt, the greater the resistance offered by the vessels through which the pulmonary blood flow of Qp flows and the lower the efficiency of pulmonary flow with respect to cardiac output" [4].

However, pulmonary arteriolar vasoreactivity normally occurs, and this ratio can vary even in healthy individuals; for example, in hypoxia, a decrease in the ratio was observed even at rest, and the Qp decreased up to 85.12% compared with the Qt during heavy exercise [4].

On the other hand, a Qp/Qt ratio significantly less than unity, when the subject is not under hypoxia and/or when vasoconstrictor drugs are not being used, could indicate other cardiovascular pathologies to be investigated.

For example, in Hachamovitch's study [17] involving patients with CHF in the third class, it would have been important to know if the Qp/Qt ratio was significantly different from unity, as "Pulmonary hypertension (PH) is a common and severe complication of heart failure (HF). Consequently, HF is the leading cause of PH" [27].

If a correct Qt measurement had been taken, this information would have been available. Consequently, having a precise measurement of Qt is of absolute importance in general and, particularly, in subjects with CHF.

Verification of shunt presence and the Qp/Qt ratio in the three groups

Despite the use of the invasive technique of thermodilution (gold standard), in Hachamovitch's work [17], the cardiac output measurements relating to CHF patients (Group 3) were all incorrect (see **Figures 1, 2, and 3**). Therefore, unfortunately, it was not possible to verify whether there was a shunt in Class III CHF patients, as cardiac output measurements were inaccurate (lower than pulmonary blood flow) both at rest and during heavy exercise. However, for subjects in Group 2 (same age, non-CHF control group), a shunt flow of 0.105 L/min was confirmed at rest, resulting in a reduction in Qp/Qt = 97.76% (see Group 2 of Figure 1).

The Qp/Qt ratio might be linked to aging, as in this comparative study, the ratio decreased with increasing age. Specifically, in Group 1 (26-year-old healthy and athletic individuals), it was possible to observe a ratio quite similar to that of Group 2 (62-year-old non-CHF control group). However, Group 1 presented this ratio during heavy exercise (**340 W** Qp/Qt = 97.56%), whereas in Group 2, a similar ratio (Qp/Qt = 97.76%) occurred at rest. This topic deserves further investigation and development in additional studies.

Regarding the path taken by shunted blood at rest in Group 2, it was not possible to determine whether the shunt flow was intrapulmonary (IPAVA) or extrapulmonary but only the magnitude of the flow in L/min. This is because the mathematical model cannot define the type of path taken by shunted blood, as stated in "Limitations of the mathematical model" [4]. However, by integrating this quantification of shunt flow in L/min with echocardiographic methods (transthoracic saline contrast echocardiography – TTSCE), which indicate the path taken by the shunt flow, which could be due to the presence of PFO and/or IPAVA [6,7,9,11], one could also determine its path.

Limitations and possibilities of the mathematical model

In this study, the equations were applied to only three groups: healthy and athletic young individuals, elderly normal control subjects, and elderly class III cardiac patients. Since this mathematical model consists of algebraic equations, it could be applied not only to the remaining three classes of cardiac patients but also to cardiovascular pathologies in general.

Specifically, by utilizing extensive and targeted samples with confirmed specific cardiovascular pathologies, it will be possible to characterize various cardiovascular diseases. The presence of these diseases should cause specific variations in Qt, Qp, Qs, and Qp/Qt, which are closely dependent on the type of disease.

These studies, which are of fundamental importance, will lead to precision medicine for the studied pathologies.

Clinicians can objectively diagnose cardiovascular pathology in individuals and effectively intervene with a personalized treatment plan, minimizing potential iatrogenic errors.

However, as already highlighted in a previous study [4], the model allows for the measurement of the flow related to the pulmonary microcirculation (Qp) and the measurement of shunted blood flow (Qs) in its entirety.

Conclusions and Future Directions

In summary, this comparative study included three groups, one of which was classified as CHF class III.

Owing to the use of these equations, it was possible to provide an initial objective pathophysiological characterization of CHF class III patients. This characteristic was particularly evident in their Qp at rest and during heavy exercise. The study also provided an initial understanding of the diagnostic significance of the Qp/Qt ratio.

Another aim of this study was to offer clinicians and researchers a simple, rapidly responsive, accurate, operator-independent, noninvasive, easy-to-use, cost-effective, and complication-free method for quantifying cardiac output (Qt), pulmonary blood flow through the pulmonary microcirculation (Qp), and shunt flow (Qs), if present, in an individual patient and for the use of the Qp/Qt ratio.

In particular, to obtain data for simultaneously measured parameters, as required by the equations, the instruments used by Jonk et al. [5] were minimally invasive. Only blood samples were collected for blood gas analysis, and no other invasive tools or associated risks were identified.

The instruments also exhibited high reliability, such as the metabolic cart (for measuring VCO_2) and the acetylene uptake method (for measuring cardiac output).

In the near future, these equations, coupled with noninvasive instruments/techniques, can be utilized to study and characterize homogeneous samples of various cardiovascular pathologies on a large scale. This could further develop an objective diagnosis of CVD patients and contribute to the advancement of precision medicine in this field.

Patents

From this work, I obtained a patent for industrial invention issued by the Italian Ministry of Economic Development with the following characteristics:

Invention Patent No. 102020000025801

Patent holder: Vanni Rosalba

Patent Title: Calcolatore di flusso sanguigno polmonare (Pulmonary Blood Flow Calculator)

Classification: G16H

Filing date: October 30, 2020

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Funding: This research received no external funding.

Data availability statement: The datasets analyzed during the current study are presented in these publicly available articles:

Jonk AM, Van Den Berg IP, Olfert IM, et al. Effect of acetazolamide on pulmonary and muscle gas exchange during normoxic and hypoxic exercise. J Physiol 579 (2007): 909-21.

Hachamovitch R, Brown HV, Rubin SA. Respiratory and Circulatory Analysis of CO2 Output During Exercise in Chronic Heart Failure. Circulation 84 (1991): 605-12.

Conflicts of interest: The author declares no conflicts of interest

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Vanni R., Cardiol Cardiovasc Med 2024
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Review comments

- Insightful and Innovative Approach: This article presents a highly innovative approach to objectively characterize CHF patients using algebraic equations and measurable physiological parameters. The focus on precision and objective diagnosis is both timely and important for advancing treatment options in cardiology.
- Clear and Meaningful Comparisons: The study effectively uses comparisons among different groups, highlighting significant physiological differences between healthy individuals, non-CHF controls, and CHF patients. The data provides a clear and quantitative distinction, especially under exercise conditions, which adds depth to our understanding of CHF progression.
- Important Step for Precision Medicine: By introducing a new diagnostic method that allows objective classification of CHF patients, the authors make an impressive step toward personalized treatment approaches. This could have substantial impacts on the accuracy of CHF diagnoses and treatment planning.
- Robust Experimental Design: The choice of variables, including Qp and specific exercise levels, offers a comprehensive view of how CHF impacts patients physiologically. The inclusion of exercise metrics further strengthens the article, showing practical implications for CHF patient management.
- Highly Relevant Findings: The findings are highly relevant to the medical community, particularly those focused on cardiovascular health. This study's approach in differentiating CHF patients based on measurable parameters could serve as a benchmark for future research.
- Contributes to CHF Research and Diagnostic Methods: This work sets a new standard for CHF diagnosis by proposing an objective diagnostic approach that leverages mathematical modeling. It paves the way for future research aimed at refining CHF classification and treatment across all functional classes.
- Well-Structured and Data-Rich Analysis: The authors provide a well-structured and data-rich analysis that supports their conclusions effectively. The thorough explanation of variables and groups enhances the reader's understanding, making the article both accessible and informative.
- Potential Impact on Clinical Practice: The use of algebraic equations for assessing CHF severity in a clinical setting is a noteworthy advancement. This study has the potential to influence clinical practices by promoting a more quantifiable approach to CHF diagnosis.