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ORIGINAL ARTICLE

Agreement of concomitant cardiac output measurement by thoracic bio-impedance and inert gas rebreathing in healthy subjects

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Abstract

Purpose: Inasmuch as they are deemed valid, noninvasive measurement of cardiac output techniques present advantages of ease and safety for use in humans. Few studies have compared the use of thoracic bioimpedance and inert gas rebreathing techniques for cardiac output (CO) assessment at rest and exercise. This manuscript reports on differences between Physioflow® and Innocor® CO measurements at rest and during cycling in a population of healthy subjects.

Methods: Fifty healthy subjects (52 ± 16 years) underwent an incremental cycle exercise testing (IET) during which standardized Physioflow® and Innocor® CO assessments were achieved. Measurements were completed in a subgroup of twelve subjects during two constant-load 10-min cycling bouts at moderate and high intensities.

Results: Mean difference between Physioflow® and Innocor® was of 0.002 ± 0.98 l/min at rest and 0.38 ± 1.31 l/min during IET without statistical difference. Correlation coefficient values were higher for exercise ($r = 0.83$) than resting ($r = 0.40$) measurements. Good reproducibility of the two devices was observed on different graded exercises with intraindividual variability lower than 6%, except for rest Innocor® CO measurements (CV = 18%).

Conclusion: Physioflow® and Innocor® can be easily used concomitantly for noninvasive measurement of CO. Despite finding a strong agreement between techniques for exercise CO, results should not be interpreted as being interchangeable as values are derived from different flow measurements: systemic blood flow for Physioflow® and pulmonary blood flow for Innocor®. However, the concomitant use of both techniques could be of value in clinical setting for noninvasive intrathoracic shunt quantification.

KEYWORDS

exercise test, healthy subjects, noninvasive cardiac output, pulmonary blood flow, shunt effect, systemic blood flow

1 | INTRODUCTION

The assessment of basic exercise hemodynamics such as cardiac output (CO) to guide and refine clinical diagnosis remains underused more on account of the complexity of use such as in the case of direct Fick techniques than the absence of valid indications. Over the past decades several noninvasive approaches using gas rebreathing or bioimpedance techniques have been introduced and validated (Peyton and Chong, 2010). Rebreathing techniques monitor end-expiratory gas tracer to assess pulmonary blood flow (Qp) with the standard assumption that it will reflect systemic blood flow (Qs) (Agostoni et al., 2005; Jarvis et al., 2007). Impedance cardiography continuously measures total thoracic electrical conductivity to detect changes in thoracic conductance reflecting systemic ventricular ejection and to allow the measurement of the Qs (Charloux et al., 2000; Richard et al., 2001). While both techniques have been perfected to be readily and safely used in clinical settings, there exists several pathological conditions where shunts or shunt-like effects may compromise the basis assumption of same Qp and Qs on which rebreathing techniques are grounded. Taken together the caveats associated with each of these techniques may serve as useful grounds for a new approach for shunt quantification as demonstrated by Peyton et al. (Peyton et al., 2004). Application of this concept presents the non-negligeable advantage of being noninvasive for quantification of shunts (Filaire et al., 2019; Perrault et al., 2016) or intrathoracic shunting effects while also enabling to track intracardiac shunts.

However, before applying the concomitant dual measurement approach in clinical populations, confirmation is required that when applied to a healthy population having received medical clearance for any shunts or shunting effects, the two techniques indeed provide same blood flow measurements across various physiological conditions of rest, submaximal and peak exercise.

This study therefore reports on the comparison of inert gas rebreathing (IGR) and thoracic bioimpedance (TB) cardiac output measurements obtained in a large population of healthy men and women submitted to cardiopulmonary exercise testing in a well-controlled clinical environment. A subgroup of subjects also completed repeated bouts of constant workload exercise to examine IGR and TB measurement reproducibility.

2 | METHODS

2.1 | Participants

Fifty healthy volunteers participated in this study after giving their written informed consent in accordance with the Declaration of Helsinki and with approval of the Institutional Review Board (IRB 00013468). During routine cardiopulmonary exercise testing (CPET), CO was systematically assessed using concomitant TB and IGR. Patients referred for exercise assessment were only included if they were non-smokers and did not present with clinical symptoms potentially related to intra-thoracic shunt or shunt-like effects.

2.2 | Exercise testing

Two cardiopulmonary cycling exercise testing (CPET), one incremental (IET) and one constant workload exercise (CWE), were performed on an electronically braked upright cycle ergometer (Medifit® 1000 S, Belgium). All subjects underwent the IET and twelve of them also completed the CWE within the same week, at the time of day, in an air-conditioned room (21°C). The IET consisted of continuous cycling with power output increments every minute starting at a power output equivalent to 20% of the theoretical predicted peak power (Hansen et al., 1984) and continuing until voluntary exhaustion. Subjects' maximal capacities were evaluated to determine the power associated with the first (i.e. lactate threshold (LT)) (Beaver et al., 1986) and second (i.e. respiratory compensation point (RCP)) ventilatory thresholds (Wasserman et al., 1990). Achievement of peak exercise capacity was confirmed by at least two of the following criteria: heart rate >90% of the theoretical maximum heart rate, respiratory exchange ratio (RER = $\dot{V}CO_2/\dot{V}O_2$) > 1.1 and/or $\dot{V}O_2$ plateau. $\dot{V}O_2$peak and peak power were taken as the average of the last 30 s of exercise just before exhaustion.

The CWE consisted to two 10-min work bouts at constant work rates at a pedalling frequency of 60 revolutions per minute, with seat and handlebar heights adjusted for each subject and held constant for all tests. Exercise intensities were equivalent to 45% (± 4%) and 73% (± 2%) of the peak power respectively, consistent with below (CWEb) and 10 min above (CWEa) the LT. The intensities of the CWE were calculated as follow: 80% of the LT power for the CWEb and intermediate between the LT and RCP powers for CWEa.

3 | MEASUREMENTS

3.1 | Gas exchanges

Minute ventilation (VE), tidal volume (V_T), breathing frequency and gas exchange parameters (VO_2, VCO_2) were obtained continuously through breath-by-breath open-circuit spirometry using a commercially available metabolic cart equipped with rapid O_2 and CO_2 analysers (Sensor Medics® MSE, France).

3.2 | Cardiac output measurements

Two noninvasive techniques for cardiac output (CO) determination were used concurrently, namely thoracic impedance cardiography (PhysioFlow®, Manatec, France) and a rebreathing technique using nitrous oxide (N_2O) as the inert gas tracer (Innocor®, Innovision, Odense, Denmark). Bio-impedance cardiac output (CO_{TB}) was derived from continuous recordings obtained throughout the exercise tests. The Innocor®

cardiac output (CO_{IGR}) was taken at rest before the IET and at the power output equivalent to 60% of peak power. During the CWE, CO_{IGR} were obtained twice before the start of the exercise test, at minutes 3 and 8 of a 10-min period, with subjects quietly. During the two periods of CWE, CO_{IGR} measurements were achieved at minutes 3, 6 and 9 of the 10-min work bout.

3.2.1 | Innocor® inert gas rebreathing

The assessment is derived while the subject is breathing through a rebreathing bag containing a bolus of 0.5% nitrous oxide N_2O, a blood soluble gas, 0.1% sulphur hexafluoride SF_6 as the insoluble gas and O_2 (28%) diluted with atmospheric air. Pulmonary blood flow was calculated from the rate of uptake of N_2O during the last three breaths of the rebreathing manoeuvre. Only measurements in which the expired SF_6 curve showed complete mixing of gases were included in the analysis.

The decrease in expired N_2O concentration was taken as circulatory wash-out rate and considered proportional to the Qp. In the absence of shunting, the latter is equivalent to the systemic flow or cardiac output (Qs). Subjects were instructed to empty the rebreathing bag with each breath and a constant rebreathing rate was ensured by having the subject breathe in synchrony with a graphical tachymeter on the computer screen. At rest, breath frequency, bag volume, and bolus fraction were 20 breath/min, 1.5 L and 20% respectively (Damgaard and Norsk, 2005) with at least 3 min intervals between each measurements to ensure a perfect body wash-out of N_2O. During exercise, parameters were adapted to the patient by the rebreathing system software with some limits (minimal O_2 content 13%, maximal CO_2 content 15% and bolus fraction 40%) (Fontana et al., 2009).

3.2.2 | Thoracic bioimpedance (Physioflow®, Manatec, France)

TB enables to derive systemic stroke volume from the time sequenced changes in thoracic impedance synchronized with the electrocardiographic recording to reflect cardiac ejection. Two sets of electrodes, one transmitting and one sensing were positioned above the supraclavicular fossa at the left base of the neck and along the xiphoid. Another set of two electrodes was used to monitor a single ECG (CM5 position). A complete description of the Physioflow® concept and the methodology was provided in an earlier publication from our group [appendix I of Charloux A et al.] (Charloux et al., 2000).

4 | STATISTICAL ANALYSES

All statistical analyses were conducted using Stata software (version 13, StataCorp, College Station, USA). Data were expressed as mean ± standard deviation (SD). Comparisons of resting and IET data obtained using TB and IGR were achieved using a paired Student *t*-test. The agreement between the IGR and TB methodologies was examined using the Lin concordance coefficient. A Bland-Altman plot was also generated to reflect the agreement between TB and IGR derived CO. Limits of agreement were defined as means ± 1.96 SD. The reproducibility of CO_{IGR} and CO_{TB} was assessed from the data sets obtained during the two CWE bouts. Intraclass correlation coefficient (ICC) were computed using random-effects models taking into account between and within subject variability (as random-effect). In this context, ICC represented the proportion of variation explained by subject (effect). Lin's concordance coefficient and coefficient of variation (CV) between each measure were also estimated. CV was calculated as:

CV (%) = (SD/μ) *100 where μ is the mean of the repeated test.

ICC and Lin's coefficient were expressed with 95% confidence intervals. A probability value of $p < 0.05$ was considered as significant with a two-sided type I error.

5 | RESULTS

5.1 | Population

Physical characteristics and functional capacities of the population are reported in Table 1. 80% of the subjects reached a peak power equal or higher to the theoretical value determined for healthy sedentary subjects.

5.2 | Incremental exercise test

At rest, mean CO_{TB} and CO_{IGR} were not statistically different (6.12 ± 1.58 l/min and 6.04 ± 1.40 l/min, respectively). Results from a Bland-Altman analysis reflect good limits of agreement (LOA) of −1.922 to 1.926, with a mean bias of 0.002 ± 0.98 l/min, and less than 20% of the values out of the LOA (Figure 1a).

At the lactate threshold, corresponding to the average of 109 ± 44 W (64% peak power), mean CO_{TB} and CO_{IGR} were 13.73 ± 3.30 l/min and 14.10 ± 2.86 l/min respectively without statistical difference. Mean difference between CO_{TB} and CO_{IGR} was −0.38 ± 1.31 l/min. Lower and upper LOA were −2.95 l/min and 2.18 l/min respectively with less than 20% of the values out of the LOA (Figure 1b). Agreement was enhanced from rest (r = 0.76; 95% CI 0.610–0.859) to exercise (r = 0.90; 95% CI 0.841–0.942). Figure 2 represents the relationship between CO and power output from rest to peak exercise. Slopes equations comparison revealed no statistically significant difference between Innocor® and Physioflow®.

5.3 | Constant workload exercise

Twelve subjects completed the CWE. No significant difference between CO_{TB} and CO_{IGR} measurements was observed. Mean CO_{TB} and CO_{IGR} at 45% of peak power (105 ± 33 W) were 11.13 ± 2.59 l/min and 11.51 ± 3.62 l/min respectively. At the second step of intensity equivalent to 73% of peak power (170 ± 56 W), mean CO_{TB} and CO_{IGR} were

TABLE 1 Baseline clinical characteristics.

Variables	All subjects ($n = 50$)	Subjects completing the CWE ($n = 12$)
Age, y	52 ± 16 (19–76)	37 ± 13 (19–58)
Sex (% male)	45	50
Height, cm	170 ± 9 (153–186)	173 ± 8 (160–185)
Weight, kg	71 ± 13 (50–100)	64 ± 10 (50–81)
Values at LT		
Power, W	84 ± 28 (35–145)	130 ± 42 (60–180)
$\dot{V}O_2$ (mL/min/kg)	15.65 ± 2.38 (11.92–19.47)	24.32 ± 6.17 (14.21–34.61)
$\dot{V}O_2$ (%$\dot{V}O_2$ max)	53 ± 6 (53–70)	62 ± 7 (50–76)
Incremental exercise testing		
Peak power, W	180 ± 82 (55–360)	233 ± 78 (110–340)
$\dot{V}O_2$ max, mL/min/kg	30.62 ± 12.31 (12.90–59.60)	39.33 ± 9.51 (28.30–59.60)
$\dot{V}O_2$ max, % $\dot{V}O_2$ theoretical	116 ± 28 (74–195)	119 ± 23 (85–163)
Constant work exercise		
Power 1, % PP		45 ± 4
Power 2, % PP		73 ± 2

Note: Values distributed normally are presented as mean ± SD (minimum-maximum).
Abbreviations: CWE, constant work exercise; LT, lactate threshold; PP, peak power; $\dot{V}O2$, oxygen consumption; W, Watt.

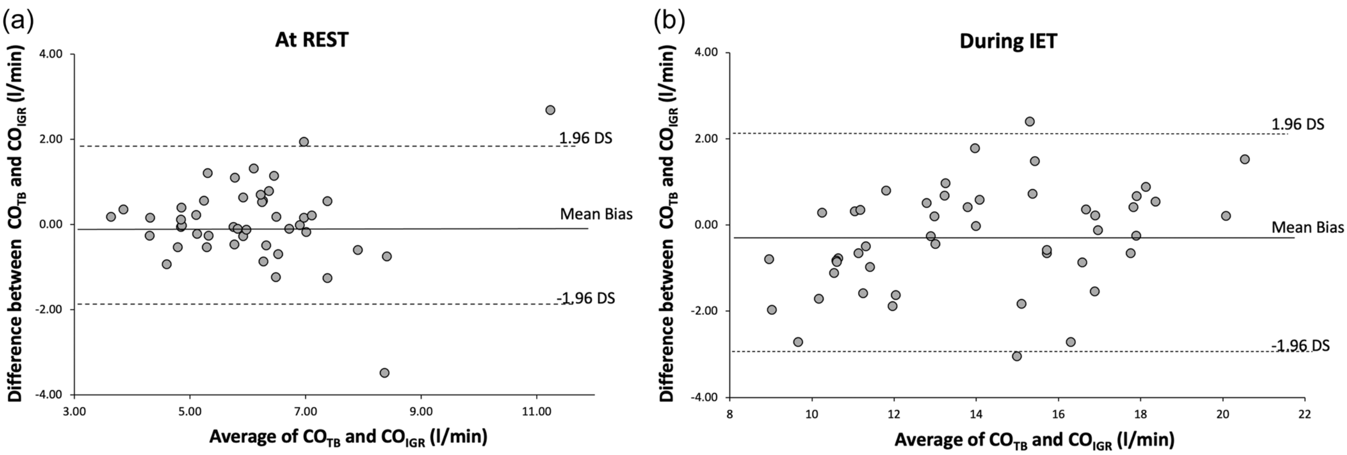

FIGURE 1 Bland–Altman plot showing limits of agreement between TB and IGR derived CO obtained at rest (a) and throughout the IET (b) ($n = 50$). The dotted lines represent the lower and upper limits of agreement, and the solid lines represent the mean bias of IGR compared to TB. CO, cardiac output; IGR, inert gas rebreathing; TB, thoracic bioimpedance.

14.96 ± 3.20 l/min and 14.70 ± 4.47 l/min respectively. Lin's coefficient enhanced from rest ($r = 0.40$) to exercise ($r = 0.81$ at CWEb; $r = 0.83$, at CWEa). TB and IGR were both highly reproducible at CWEb and CWEa. However, at rest, IGR had a lower interindividual reproducibility (ICC 0.41; 95% CI 0.06–0.88) than TB (ICC 0.84; 95% CI 0.52–0.96). Intraindividual reproducibility with Innocor® was stronger during exercise than under resting conditions. At rest, intraindividual variability was higher for IGR (CV 18%) than TB (CV 4.5%) (Table 2).

6 | DISCUSSION

In this study of healthy subjects, we assessed the concomitant use of two noninvasive CO measurements devices at rest, during incremental and two different submaximal exercise intensities. To the best of our knowledge, this is the largest standardized study comparing the noninvasive CO measurement by both inert gas rebreathing and thoracic bioimpedance. Our results revealed good agreement

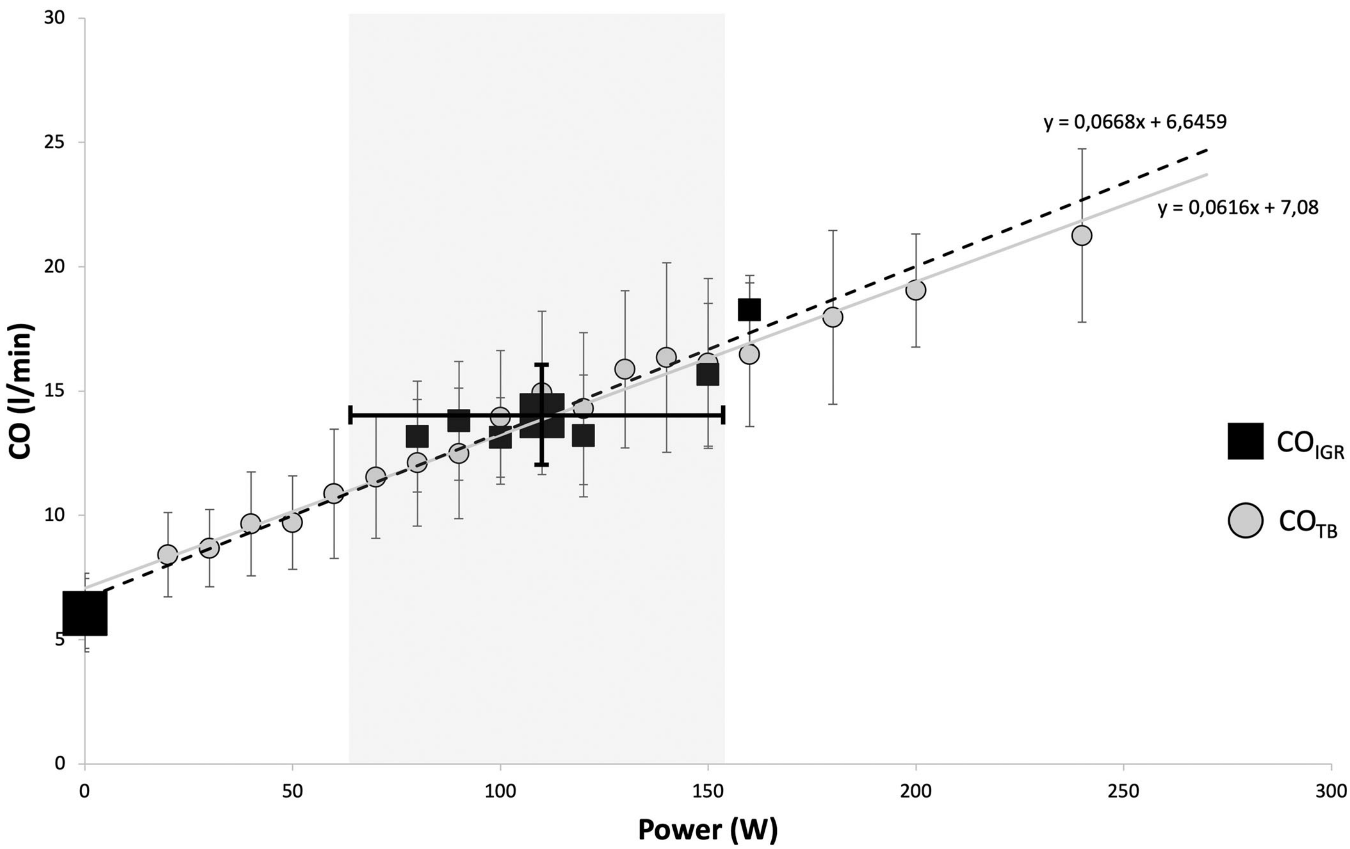

FIGURE 2 Mean TB and IGR derived cardiac output ± SD at each stage of the IET (n = 50). Dotted line links CO_{IGR} measurements made at set times during the exercise testing. The solid line shows the TB derived CO obtained continuously throughout the exercise test until peak exercise. The grey zone represents the range of power (standard deviation) at the lactate threshold during the IET. The largest black squares represent the mean CO_{IGR} at rest and at the lactate threshold.

between Innocor® and Physioflow® and the reproducibility of exercise measurements at two exercise intensities.

Overall, we observed a good agreement between CO_{IGR} and CO_{TB}. Findings of lower values measured using IGR as compared to TB are in line with previous reports (Okwose et al., 2018; Perrault et al., 2016) and could be related to the variability induced by the rebreathing manoeuvres at fixed rates required by IGR. Recommendations for these rebreathing manoeuvres advice a breath frequency around 20 breathes per min. This requirement being much higher than the spontaneous resting breathing frequency for some individuals introduces a greater variability at rest compared to the exercise-induced increase in breathing frequency. Some authors have already demonstrated that the rebreathing manoeuvre increases CO due to an increased heart rate and constitutes an extra-load to perform (Bartels et al., 2011; Ohlsson and Wranne, 1986). Consequently, higher correlation coefficients between CO_{IGR} and CO_{TB} were observed for exercise measurements in agreement with previous reports (Okwose et al., 2018).

With increasing intensity of exercise, N_2O recirculation time is decreased which reduces the contact time and the alveolar-arterial diffusion gradient for N_2O. At mild and submaximal exercise, this does not seem to interfere with the variability of CO, as in our study, where the variability of CO_{IGR} has a tendency to decrease, without influence of the time of CO_{IGR} measurement during each stage (Fontana et al., 2010).

The good agreements between CO_{IGR} and CO_{TB} at rest and exercise confirm that pulmonary blood flow is equivalent to the systemic blood flow. It reinforces that our subjects are healthy. In patients with atrial fibrillation, Osbak et al. noticed that CO_{IGR} were lower than CO measurements by echocardiography whereas CO_{TB} were found similar to CO by echocardiography. These differences in CO_{IGR} and CO_{TB} against echocardiography were not found in a control group (Osbak et al., 2011). In chronic obstructive pulmonary disease patients, CO_{IGR} were always lower than CO_{TB} at rest and exercise in contrary to healthy subjects where CO values did no differ significantly (Perrault et al., 2016). It highlighted that IGR and TB do not measure the same blood flow. As no difference in CO values is found in healthy subjects, the difference might not be due to the biological variation between the two devices but suggests the difference in CO values might be due to intrathoracic shunt (shunt effect).

Some limits must be highlighted. First in the subgroup CWE, the number of subjects is low with younger subjects. Second, by design we choose to not measure cardiac output at peak exercise intensity

TABLE 2 Reproducibility of cardiac output by inert gas rebreathing and thoracic bio-impedance during a constant workload exercise test (n = 12).

Type of exercise	Mean CO		Mean difference ± SD (p-value)	Lin coefficient (95% CI)	ICC (95% CI)		CV (%)	
	CO_{TB}	CO_{IGR}			TB	IGR	TB	IGR
Rest	5.50 ± 0.27	5.19 ± 0.99	0.24 ± 1.49 (0.4)	0.40 (0.01– 0.68)	0.84 (0.52– 0.96)	0.41 (0.06– 0.88)	4.5	18
CWEb	11.14 ± 0.57	11.42 ± 0.54	-0.37 ± 1.9 (0.26)	0.81 (0.68– 0.85)	0.94 (0.84– 0.97)	0.92 (0.84– 0.96)	4.8	5
CWEa	14.68 ± 0.70	14.53 ± 0.70	0.26 ± 2.3 (0.52)	0.83 (0.71– 0.90)	0.93 (0.82– 0.97)	0.95 (0.88– 0.98)	5.2	6

Note: Mean difference is presented as TB-IGR; ICC, intraclass correlation coefficient; IGR, inert gas rebreathing; TB, thoracic bioimpedance; CV, coefficient of variation; CWEb, constant workload exercise below lactate threshold; CWEa, constant workload exercise above lactate threshold.

to avoid technical difficulties in rebreathing manoeuvres at exhaustion. Moreover, this is the first study to compare Innocor® and Physioflow® CO measurements in various exercise intensities in daily healthy subjects.

7 | CONCLUSION

In conclusion, IGR an TB are both valid and reproducible techniques during various exercise intensities, with a preferential use of IGR at low and mild intensities of exercise to limit inert gas recirculation and get closer of the physiological respiratory rate. The concomitant noninvasive measurement of the pulmonary and systemic blood flow is feasible, reliable and easy to perform by Innocor® and Physioflow®. Their field of application could be the quantification of intrathoracic shunt.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author, Laura Filaire, upon reasonable request.

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