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Cardiac output during exercise: A comparison of four methods

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Several techniques assessing cardiac output (Q) during exercise are available. The extent to which the measurements obtained from each respective technique compares to one another, however, is unclear. We quantified Q simultaneously using four methods: the Fick method with blood obtained from the right atrium ($Q_{Fick\text{-}M}$), Innocor (inert gas rebreathing; Q_{Inn}), Physioflow (impedance cardiography; Q_{Phys}), and Nexfin (pulse contour analysis; Q_{Pulse}) in 12 male subjects during incremental cycling exercise to exhaustion in normoxia and hypoxia ($F_iO_2 = 12\%$). While all four methods reported a progressive increase in Q with exercise intensity, the slopes of the Q/oxygen uptake (VO_2) relationship differed by up to 50% between methods in both normoxia [4.9 ± 0.3, 3.9 ± 0.2, 6.0 ± 0.4, 4.8 ± 0.2 L/min per L/min (mean ± SE) for $Q_{Fick\text{-}M}$, Q_{Inn}, Q_{Phys} and Q_{Pulse}, respectively; $P = 0.001$] and hypoxia (7.2 ± 0.7, 4.9 ± 0.5, 6.4 ± 0.8 and 5.1 ± 0.4 L/min per L/min; $P = 0.04$). In hypoxia, the increase in the Q/VO_2 slope was not detected by Nexfin. In normoxia, Q increases by 5–6 L/min per L/min increase in VO_2, which is within the 95% confidence interval of the Q/VO_2 slopes determined by the modified Fick method, Physioflow, and Nexfin apparatus while Innocor provided a lower value, potentially reflecting recirculation of the test gas into the pulmonary circulation. Thus, determination of Q during exercise depends significantly on the applied method.

The assessment of cardiac output (Q) during exercise is important for both research and clinical settings. Unfortunately, the "gold standard" measurement of Q, e.g., the direct Fick or pulmonary thermodilution methods, requires catheterization of the pulmonary artery. In attempt to circumvent such intrusive methodology, a variety of less invasive techniques have been developed. The validity of these less invasive methods, however, is established by comparing values obtained from reference methods, which demonstrate inherent errors themselves (Stetz et al., 1982; Pugsley & Lerner, 2010). Accordingly, we compared measures of Q using four common methods in healthy individuals that performed incremental cycling exercise to exhaustion in normoxia and hypoxia and determined whether the results are exchangeable.

The first method evaluated was a modified Fick ($Q_{Fick\text{-}M}$) method with blood obtained from the right atrium. Although differences in O_2 content have been observed between the right atrium and the pulmonary artery (Hillis et al., 1986), sampling of blood from the right atrium has been used to assess the hemodynamic response to exercise (e.g., Mortensen et al., 2005). The second method evaluated was inert gas rebreathing (Laszlo, 2004) as established by Innocor (Innovision, Odense, Denmark) that derives Q from pulmonary uptake of N_2O. With this method, we thought that the hyperoxic Innocor test gas used during rebreathing may affect arterial oxygenation, particularly when subjects are exposed to hypoxia, and thereby influence Q (Roach et al., 1999). The third method evaluated was the Physioflow (PF05 Lab1^{TM}, Manatec Biomedical, Paris, France) that estimates Q by electrical impedance cardiography (Moshkovitz et al., 2004). Finally, the fourth method evaluated was the Nexfin (BMEYE, Amsterdam, Netherlands) that derives Q from arterial pressure by pulse contour analysis (Wesseling et al., 1993).

Methods

Twelve healthy males with physical activity ranging from sedentary to participating in elite endurance sport (25 ± 5 years, 182 ± 7 cm, and 76 ± 8 kg; mean ± SD) were included in this study following oral and written informed consent. The study was approved by the Ethical Committee of Copenhagen (H-4-2010-132) and conducted in accordance with the declaration of Helsinki.

Protocol

While the subjects were supine, a 20 G catheter was placed in the brachial artery of the non-dominant arm and a 2.2 mm catheter was inserted through the median cubital vein and advanced to the right atrium. Proper positioning of the catheter was confirmed by the pressure signal provided by a transducer (Edwards Life Sciences, Irvine, California, USA) placed at heart level. The transducer signals were registered (Dialogue-2000 IBC, Danica Electronic, Copenhagen, Denmark), analogue-digital converted (DI-720, Dataq Instruments Inc., Akron, Ohio, USA), and sampled at 100 Hz (Windaq, Dataq Instruments Inc.). After each intervention, the pressure trace was inspected and data were excluded if the atrial pattern had vanished ($n = 2$), i.e., indicating dislocation of the catheter from the atrium or, more likely, that the catheter was partially clotted.

All subject sat for 5 min in a seated position before resting measurements were obtained. The subjects were then transferred to a mechanically braked cycle ergometer (Monark, Varberg, Sweden) and sequentially pedalled for 3 min unloaded, 6 min at 112.5 W, and 10 min at 150 W. Thereafter, the workload was increased by 37.5 W every 1.5 min until exhaustion. The maximal workload completed was calculated as $W_{max} = W_{compl} + 37.5 \times (t/90)$ where W_{compl} is the last completed workload and t is the seconds maintained during the final incomplete step of progressive exercise.

After this first trial, the subjects rested supine for 90 min and had a light meal and drink. Thereafter, a second exercise trial was performed with the inspired O_2 fraction reduced by N_2 dilution (Altitrainer, SMTEC, Nyon, Switzerland) to 12% (~ 4000 m). This trial consisted of 3 min bouts of cycling at 75 W, 112.5 W and 150 W, respectively. The load was then increased as in the normoxic trial by 37.5 W every 1.5 min until exhaustion. In both trials, the subjects were instructed to maintain a pedaling cadence of 75/min and verbally encouraged to exercise to exhaustion (American Thoracic Society & American College of Chest Physicians, 2003).

The subjects wore face masks that covered mouth and nose for collection of expired air. Breath-by-breath ventilatory variables were measured with the Innocor that was calibrated for flow, gas analysis, and gas delay prior to each trial. The moving median over 10 consecutive values was calculated to even out these measures. Throughout both normoxic and hypoxic trials, Q was assessed by the four methods as specified below.

Q by the modified Fick method ($Q_{Fick\text{-}M}$)

At each workload, blood was collected simultaneously in heparinized syringes (Pico 50, Radiometer, Copenhagen, Denmark) from the arterial and central venous catheters. Syringes were immediately placed in ice-cold water and analyzed in a hemoximeter after the trial (ABL 800, Radiometer). The $Q_{Fick\text{-}M}$ was calculated as $VO_2 \times (c_aO_2\text{-}c_{cv}O_2)^{-1}$ with VO_2 being determined by the Innocor and $cO_2 = (1.34 \times [Hb] \times SO_2) + (0.003 \times PO_2)$ where [Hb] is the hemoglobin concentration, SO_2 hemoglobin O_2 saturation, PO_2 partial pressure of O_2 and VO_2 pulmonary oxygen uptake. The actual PO_2 was likely somewhat overestimated, especially in instances when hemoglobin was not fully saturated, as the blood samples were not temperature corrected (Stickland et al., 2013).

Q by Innocor (Q_{Inn})

The rebreathing technique assumes that pulmonary uptake of a blood soluble gas is proportional to pulmonary blood flow (Krogh & Lindhard, 1912). With the Innocor, every subject rebreathes a gas mixture consisting of 5% blood soluble N_2O, 1% blood insoluble SF_6, and 94% of O_2 that is filled, together with ambient air, into a rebreathing bag. The ratio between the test gas, the ambient air, and the volume of the bag is calculated based on tidal volume and VO_2. For each measurement, the subject is switched to rebreathing the test gas from a closed circuit while photo-acoustic analysis quantifies the gas concentrations. Pulmonary N_2O uptake is assessed as the decrease in N_2O over three expirations after a stable SF_6 concentration is established.

In normoxia, Q_{Inn} was determined at rest, at 112.5 W, 150 W, and at every second step of the incremental trial, i.e., every third minute after the 185.5 W workload. During hypoxia, Q_{Inn} was assessed at the same workloads and additionally at 75 W with the rebreathing manoeuvre started immediately after blood sampling, approximately 30 s before the end of the workload.

To assess a potential effect of the rebreathing manoeuvre on arterial oxygenation in normoxia and hypoxia, we obtained four arterial blood samples in quick succession at rest and at 150 W in both trials. The first sample was obtained immediately prior to the start of the rebreathing manoeuvre and further samples were collected 5 s, 15 s and 25 s thereafter. These measurements were completed in 10 subjects in normoxia and in nine subjects during hypoxia.

Q by Physioflow (Q_{Phys})

For electrical impedance cardiography, a low amplitude/high frequency current is transmitted through the chest and changes in impedance are detected (Strobeck et al., 2000). Calculation of stroke volume is based on the assumption that changes in aorta blood volume induce opposing changes in electrical impedance (Moshkovitz et al., 2004). Compared with other electrical impedance cardiography apparatus, the Physioflow algorithm does not take baseline thoracic impedance into consideration because it can be affected by, e.g., electrode contact and the subject's anatomy (Charloux et al., 2000). Six electrodes were attached to the subjects' upper body according to the manufacturer's instructions and the Physioflow calculated Q_{Phys} continuously (Kemps et al., 2008) with values averaged over 15 s.

Q by pulse contour analysis (Q_{Pulse})

The Nexfin (BMEYE, Amsterdam, Netherlands) derives Q by pulse contour analysis from arterial pressure measured either intra-arterially (as in the present study) or non-invasively by the volume clamp method on the fingertip (Bogert & van Lieshout, 2005). For the calculation of stroke volume and thus Q_{Pulse}, the systolic area of the arterial pressure waveform is divided and aortic input impedance is established according to a three-element Windkessel model (Westerhof et al., 2009; Bogert et al., 2010). The data were sent to BMEYE engineers who computed Q_{Pulse} using the Nexfin software with beat-to-beat values evened by calculation of a moving median over 30 consecutive values.

Statistics and data analysis

A mixed-effect random-intercept model evaluated relationships between Q and VO_2 as a random effect with unstructured covariance structure. Inspection of residuals revealed that square-root transformed VO_2 provided a better fit than non-transformed VO_2 and for statistical analysis, the model was modified accordingly. Levene's test was used to evaluate homogeneity of variance. If evidence was found for inhomogeneous variance between the four methods, the statistical model was adjusted accordingly with values expressed as mean ± SD and a P-value < 0.05 was considered statistically significant.

We identified Q_{Inn}, Q_{Phys}, and Q_{Pulse} values that were lower than what we considered plausible for a given VO_2: All Q values were entered together with the simultaneously determined VO_2 and c_aO_2

Table 1. Effect of the Innocor rebreathing manoeuvre on arterial oxygenation in normoxia and hypoxia

	Normoxia				Hypoxia			
	Rest		Exercise		Rest		Exercise	
	PaO_2	SaO_2	PaO_2	SaO_2	PaO_2	SaO_2	PaO_2	SaO_2
– 5 s	111 ± 13	99 ± 0.5	99 ± 7	98 ± 0.6	68 ± 22	92 ± 4	40 ± 5	72 ± 6
5 s	109 ± 9	98 ± 0.5	105 ± 6	98 ± 1	65 ± 15	92 ± 4	45 ± 8*	79 ± 6*
15 s	117 ± 16	99 ± 0.6	112 ± 14*	98 ± 1	80 ± 18	96 ± 2	52 ± 7*	84 ± 4*
25 s	122 ± 11	99 ± 0.4	101 ± 10	98 ± 1	79 ± 12	96 ± 4	44 ± 7*	77 ± 7

Arterial blood was collected 5 s before and as indicated after initialization of the rebreathing manoeuvre. Exercise measurements were obtained during steady state cycling at 150 W. PaO_2, arterial O_2 pressure; SaO_2, arterial O_2 saturation.
*$P < 0.05$ vs – 5 s.

into the Fick equation. If the calculated $c_{cv}O_2$ was < 0 mL/L, the Q value was flagged as not possible. Similarly, if the calculated $c_{cv}O_2$ was < 20 mL/L, i.e., the $c_{cv}O_2$ observed in elite endurance athletes during maximal exercise (Wagner, 2006), the Q value was considered not plausible. Thus, we identified cardiac outputs that required an implausible c_aO_2-$c_{cv}O_2$ to exist.

Results

Exercise response

The subjects reached exhaustion at an average workload of 327 ± 61 W in normoxia and 245 ± 49 W in hypoxia. VO_2 increased from 0.4 ± 0.1 L/min at rest to 4.1 ± 0.7 L/min and 3.3 ± 0.2 L/min in normoxia and hypoxia, respectively ($P < 0.001$ normoxia vs hypoxia) and (c_aO_2-$c_{cv}O_2$) widened from 47 ± 13 mL/L to 170 ± 20 mL/L and from 39 ± 12 mL/L to 122 ± 20 mL/L ($P < 0.001$).

Stroke volume during exercise varied considerably among the four methods: at rest in normoxia it ranged from 92 mL (Innocor) to 128 mL (Physioflow) and from 96 mL (Innocor) to 135 mL (Physioflow) in hypoxia. During high intensity exercise, stroke volume increased up to 122 mL (Nexfin), 158 mL (Physioflow), 122 mL (Innocor), and 181 mL (Fick-M). Heart rate was 79 ± 21/min and 86 ± 19/min ($P = 0.07$) at rest and increased to 182 ± 11/min and 172 ± 9/min ($P < 0.001$) during maximal exercise in normoxia and hypoxia, respectively.

Effect of the Innocor rebreathing on arterial oxygenation

The effect of the Innocor rebreathing manoeuvre on P_aO_2 and S_aO_2 at rest and during moderate exercise (150 W) is illustrated in Table 1. While inhalation of the test gas did not affect P_aO_2 and S_aO_2 at rest, the test gas increased P_aO_2 during exercise in both normoxia and hypoxia. Also, during inhalation of the test gas, S_aO_2 remained unaffected in the normoxic trial whereas it became elevated in hypoxia for ~ 15 s.

Q measurements

The Q responses to incremental exercise assessed by the four methods are presented in Fig. 1. Inhomogeneous variance between methods, both inter- and intrasubject, was found in both normoxia and hypoxia (Table 2). The average increase in $Q_{Fick\text{-}M}$, Q_{Inn}, Q_{Phys}, and Q_{Pulse} per L/min increase in VO_2 were 4.9 ± 0.3 L/min, 3.9 ± 0.2 L/min, 6.0 ± 0.4 L/min, and 4.8 ± 0.2 L/min ($P > 0.001$, mean ± SE) in normoxia and 7.2 ± 0.7 L/min, 4.9 ± 0.5 L/min, 6.4 ± 0.8 L/min, and 5.1 ± 0.4 L/min ($P = 0.04$) in hypoxia, respectively ($P < 0.05$ normoxia vs hypoxia for all methods except for the Nexfin data).

Impossible and implausible Q values

The number of Q measurements generated by Innocor, Physioflow, and Nexfin that would require an implausibly (< 20 mL/L) or impossibly (< 0 mL/L) low $c_{cv}O_2$ to fulfill the Fick equation are presented in Table 3. The Innocor and Nexfin produced more impossible/implausible values than the Physioflow ($P < 0.001$).

Discussion

We compared four techniques that assess Q during rest and throughout incremental exercise in normoxia and hypoxia. The principle finding was that the increase in Q during incremental exercise differs by as much as 50% depending on the method applied to determine Q. In hypoxia, the Fick-M method, the Innocor, and the Physioflow apparatus, but not Nexfin, detected the established increase in the Q/VO_2 slope whereas the Innocor rebreathing manoeuvre elevated SaO_2 for ~ 15 s, i.e., until O_2 in the rebreathing bag approached the arterial value.

The present analysis is based on a linear Q/VO_2 relationship from rest to maximal exercise (Faulkner et al., 1977). Recent evidence has, however, revealed a negative Q/VO_2 relationship curvature at high exercise intensities particularly in physically fit subjects (Beck et al., 2006). To minimize potential bias from those measures that deviated from a straight line, we initially excluded Q values measured at exercise intensities > 70%. Nevertheless, square-root transformation of VO_2 secured a linear relationship throughout the entire range of intensities and removing intensities between 50% and 100% did not affect the conclusions of the study. In normoxia, Q is expected to increase by ~ 5–6 L/min per L/min increase

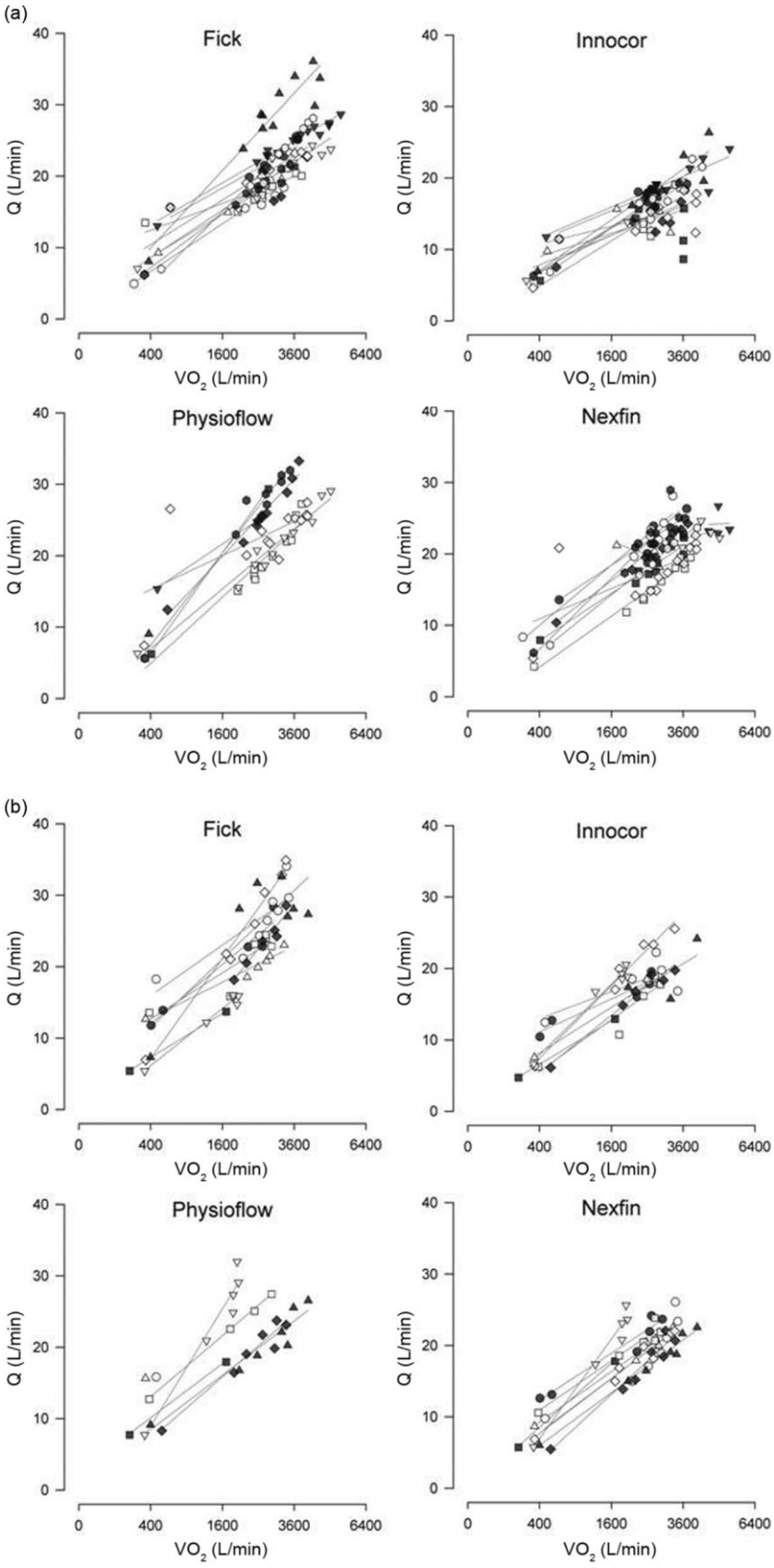

Fig. 1. Individual cardiac output as assessed by the Fick-M method and Innocor, Physioflow and Nexfin apparatus plotted against the corresponding oxygen uptake (VO_2). (a) normoxia; (b) normobaric hypoxia ($F_iO_2 = 12\%$). The average slopes of the cardiac output/VO_2 – relationships differed between methods (Normoxia, $P < 0.001$; hypoxia, $P = 0.04$) and increased in hypoxia for all methods except for the Nexfin.

Table 2. Variances from the individual and average cardiac output/oxygen uptake slopes generated by the Fick-M method and Innocor, Physioflow, and Nexfin apparatus

	Intrasubject variance		Intersubject variance	
	Normoxia	Hypoxia	Normoxia	Hypoxia
Fick-M method	1.4	5.3	10.5	15.1
Innocor	3.4	1.8	6.9	6.7
Physioflow	1.6	1.9	12.8	18.7
Nexfin	1.3	1.4	8.5	7.4
Levene's test (*P*-value)	0.0035	0.0028	0.12	0.0029

Table 3. Number of data that were deemed plausible, implausible, or impossible based on the Fick equation derived central venous O_2 content

Derived c_vO_2 =	$c_aO_2 - \frac{VO_2}{Q_{Inn}}$		$c_aO_2 - \frac{VO_2}{Q_{Phys}}$		$c_aO_2 - \frac{VO_2}{Q_{Pulse}}$	
	NX	HX	NX	HX	NX	HX
Impossible [$c_vO_2 < 0$]	13 (15%)	7 (13%)	0 (0%)	2 (6%)	2 (2%)	13 (20%)
Implausible [$c_vO_2 < 20$ ml/l]	12 (14%)	12 (23%)	0 (0%)	2 (6%)	13 (14%)	10 (16%)
Plausible [$c_vO_2 \geq 20$ ml/l]	59 (70%)	33 (63%)	59 (100%)	29 (88%)	77 (84%)	41 (64%)

NX, normoxia; HX, hypoxia. Q_{Inn}; Q_{Phys}; Q_{Pulse}, cardiac output assessed by Innocor, Physioflow, and Nexfin, respectively. Physioflow produced more plausible values than the two other methods ($P < 0.001$). Innocor has a similar performance in hypoxia compared with normoxia ($P = 0.46$), while the performances of Nexfin and Physioflow declined in hypoxia ($P < 0.001$ and $P = 0.015$).

in VO_2 (Faulkner et al., 1977; Proctor et al., 1998), which was within the 95% confidence intervals of the slopes for $Q_{Fick\text{-}M}$, Q_{Phys}, and Q_{Pulse}. However, the increase for Q_{Inn} was considerably smaller. The effect of interindividual variability for the Q/VO_2 relationship should also be considered when comparing variances between methods. These values might be used to express precision with the assumption that the Q/VO_2 relationship is linear (for intraindividual variance) and has the same slope (for intersubject variance) for each subject.

Convective O_2 transport is a determinant of exercise capacity and is relevant for research and clinical evaluations. Reference methods often require catheterization of the pulmonary artery, which is not only arduous but is also associated with risks (Evans et al., 2009) and thus alternative techniques have been developed. Our data, however, demonstrate that comparison of Q measured by different methods is problematic.

The Fick-M method based on central venous blood may be biased by incomplete blood mixing and/or catheter dislocation into the inferior or superior caval vein even in resting subjects (Hillis et al., 1986). With cycle exercise, muscle O_2 extraction increases in the skeletal leg muscles and accordingly, blood in the inferior v. cava is expected to be more desaturated than blood in the superior caval vein, and incomplete blood mixing and/or dislocation of the catheter tip becomes important. Nevertheless, the modified Fick method based on central venous sampling has previously been used for scientific purposes (e.g., Mortensen et al., 2005).

The Innocor has been validated by the direct Fick and thermodilution methods in patients with heart disease (Gabrielsen et al., 2002; Peyton & Thompson, 2004; Dong et al., 2005; Corte et al., 2010) and lung fibrosis (Agostoni et al., 2005). Difference between methods (< 1 L/min) and limits of agreement (< ± 2.5 L/min) were considered sufficient for clinical purposes. Alternatively, the Innocor determination of Q has not been validated during exercise, although it is used for that purpose (e.g., Ghofrani et al., 2004; Cockburn et al., 2010; Fontana et al., 2011). Here, the Innocor demonstrated lower Q values than the other methods and > 30% of the values were lower than what we considered plausible/possible (Table 2). Likely, the N_2O rebreathing technique underestimates Q because of recirculation of N_2O (Jarvis et al., 2007) and that could reduce the alveolar-arterial diffusion gradient for N_2O and attenuate further N_2O uptake (Chapman et al., 1950; Simmons & Shephard, 1971; Laszlo, 2004).

The manufacturers of the Innocor recommend a rebreathing time of < 25 s at rest and "less during exercise" but at rest, recirculation takes place already ~ 15 s after inspiration of a test gas (Sowton et al., 1968; Zeidifard et al., 1976). During exercise (VO_2 2.5 L/min) recirculation manifests already after 8.5 s and in less than 8 s at a VO_2 of 3 L/min (Rigatto et al., 1968; Zeidifard et al., 1976). The subjects in the present study completed the rebreathing manoeuvre in 16.1 ± 3.8 s at rest, which seems to be too long a period as all four methods used to determine Q indicated that Q was high (average 8.7 L/min), probably because of anticipation of strenuous exercise (Secher et al., 1977; Mortensen et al., 2005). Similarly, the 8.9 ± 1.3 s rebreathing manoeuvre used during maximal exercise may be too long considering that VO_{2max} in normoxia was ~ 4 L/min. We also

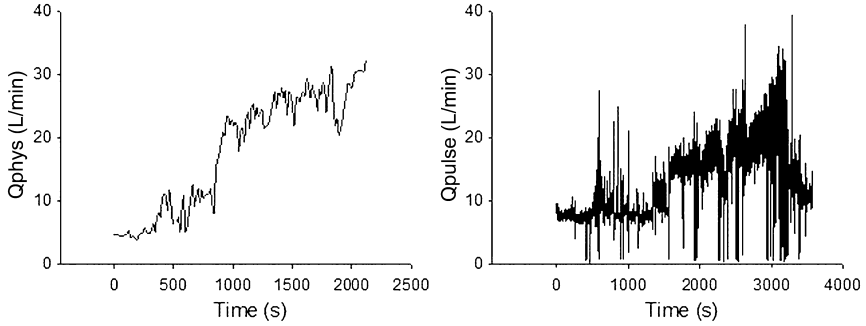

Fig. 2. Original tracings of cardiac output as generated by Physioflow (Q_{Phys}) and Nexfin (Q_{Pulse}). The Q_{Phys} signal is automatically averaged over 15 s whereas Q_{Pulse} illustrates beat-by-beat values.

believe that hemoconcentration could contribute to the low Q_{Inn} values. During exercise in both normoxia and hypoxia, arterial [Hb] increased by ~ 5% and thus the reduced plasma volume may affect the uptake of N_2O and thereby Q_{Inn}.

The Physioflow method reported the highest Q values. The Q determined by Physioflow is validated against the direct Fick method during exercise in both patients (Charloux et al., 2000; Bougault et al., 2005; Kemps et al., 2008) and healthy subjects (Richard et al., 2001) and may overestimate exercise Q by ~ 30–50% although that is not a consistent finding (Charloux et al., 2000; Richard et al., 2001; Robach et al., 2008). Both a small stroke volume (Kemps et al., 2008) and hyperinflation (Bougault et al., 2005) appear to affect a Physioflow determined Q.

Furthermore, some (Bougault et al., 2005) but not all (Charloux et al., 2000; Richard et al., 2001) studies find a low precision for the Physioflow determined Q with limits of agreement ranging up to ± 60% (Kemps et al., 2008). Physioflow is attractive as it only requires electrodes to be attached to the chest and the algorithm that computes Q_{Phys} is claimed to be insensitive to variations in electrode placement. Yet, strenuous exercise is likely to affect impedance cardiography by movement, respiratory artefacts, and possibly by accumulation of fluid in the lungs (Warburton et al., 1999b; Peng et al., 2005; Eldridge et al., 2006). Accordingly, Q_{Phys} was associated with the highest intersubject variance in this study.

The Nexfin has been compared with a determination of Q by pulmonary artery thermodilution in patients revealing a mean difference < 0.5 L/min and limits of agreement < ± 30% (Stover et al., 2009; Bogert et al., 2010). During exercise, Q_{Pulse} has been compared with Q assessed in an earlier study by dye dilution (Ide et al., 1998), but no bias or limits of agreement were presented. Dye dilution determination of Q is considered as reliable as the values derived by the Fick method during intense exercise (Warburton et al., 1999a). Yet, Nexfin did not detect the steeper Q/VO_2 slope in hypoxia, probably because Nexfin considers the characteristics of the arterial system to be known and therefore does not take hypoxia-induced peripheral vasodilatation (Blitzer et al., 1996a,b) into account. Similarly, Nexfin underestimates the increase in Q associated with heat stress, also dominated by peripheral vasodilatation (Shibasaki et al., 2011).

While the Physioflow and Nexfin both offer continuous measurement of Q and do not require the subject's collaboration, it is problematic that movement may influence the signals. Figure 2 illustrates tracings from the two devices with Q_{Phys} represented as the (automatically calculated) averages over 15 s whereas Q_{Pulse} represents the beat-by-beat values (i.e., before smoothing by a moving median over 30 s). For the present analysis, we have inspected the signals and excluded Q values from noisy segments.

There are several limitations to this study. We did not radiolografically secure that the catheter tip was in the right atrium but relied on that an atrial pressure pattern would indicate a correct position. Thus, if an atrial pressure pattern was not present or vanished during the study, we excluded the $Q_{Fick\text{-}M}$ data from the analysis ($n = 2$). Furthermore, we did not take blood temperature into account when analyzing arterial and venous cO_2 and therefore the calculated $Q_{Fick\text{-}M}$ may be slightly overestimated. Assuming (Severinghaus, 1979) changes in PO_2 between 1.3%/°C and 7.4%/°C at fully and low saturated hemoglobin, respectively, and temperature variations from 38°C to 40°C, the influence on $Q_{Fick\text{-}M}$ however becomes negligible. At the practical level, the storage of arterial blood in ice water has been shown to affect PO_2 but not SO_2 (Knowles et al., 2006) and in hypoxic blood temperature may have no effect on PO_2 or SO_2 (Mahoney et al., 1991). A further limitation to the study is that we did not establish/compare stroke volume responses reported by the different methods. Due to movement artefacts, we lack several Q and thus stroke volume values for each subject/measurement method. Furthermore, and in contrast to Q, the stroke volume response to exercise is not linear and is influenced by fitness. The present study included subjects ranging from sedentary to elite athletes.

In conclusion, this study demonstrates that four widely used and purportedly valid methods for determination of Q during exercise generate significantly different values. Thus, determination of Q during exercise depends on the applied method.

Perspective

There are several methods available to determine Q during exercise, each having both strengths and limitations. By comparing Q results obtained by four different techniques, it is illustrated in the present study that a continuous determination of Q can be obtained by Physioflow albeit the determined values for Q is then, with the present algorithm, probably too large. On the other hand, Nexfin can obtain a continuous Q provided that the subject is not exposed to circumstances that induce extreme vasodilatation, as illustrated here with hypoxia and previously shown by heat stress. If a continuous determination of Q is not required, then Innocor offers a non-invasive alternative, but the presented results suggest that the long rebreathing manoeuvre required to determine Q by Innocor makes an evaluation during exercise problematic because recirculation of the test gas attenuates its uptake in blood and even a high resting Q may be underestimated for the same reason. From the present evaluation, a Fick-based determined Q seems the most robust if subjects are to be exposed to a wide range of interventions as illustrated by strenuous exercise and hypoxia.

Q is the driving force for systemic O_2 delivery and a key determinant of aerobic exercise capacity. Therefore, the assessment of Q during exercise is not only relevant for researchers but also in sport medicine where it may help to quantify the success of a given training regime or facilitate diagnosing process in patients with a pathologically low exercise tolerance.

The methods evaluated here avoid the risks associated with pulmonary artery catheterization as required for the reference methods. Our findings, however, indicate that although all methods have been validated, they may generate significantly different Q values within the same subjects. Different measurement techniques for Q should be taken into account by researchers as well as physicians when comparing the outcome of evaluations.

Key words: Inert gas rebreathing, impedance cardiography, pulse contour analysis, hypoxia, maximal oxygen uptake.

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