Non-Invasive Estimate of Cardiac Output During Exercise Based on Impedance Cardiography and Oxygen Uptake in the Elderly

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Objective: This study assessed the agreement between cardiac output (Q) measurements generated by two indirect methods and their applicability in 54 men and 77 women (aged 60-90).

Methods: The subjects performed a cardiopulmonary test with incremental to maximal exercise on a cycle-ergometer. “Q” was estimated based on oxygen uptake and on impedance cardiography at 50% and 100% of the maximal workload (Wmax) reached during the test. The limits of agreement and mean differences (biases) were estimated using the methodology proposed by Bland-Altman, whereas the relationship between the methods was analyzed by linear regression and intra-class correlation (ICC).

Results: For the load equivalent do 50% of Wmax, the bias between the means of the two methods was -0.58 L•min⁻¹ (6.3% smaller for the impedance measurement) and the limit of agreement was ± 2.54 L•min⁻¹ (24.7%). At 100% of Wmax, the bias was 1.03 L•min⁻¹ (8.5% greater for the impedance measurement) with a limit of agreement of ± 3.35 L•min⁻¹ (27.6%). ICC values and the regression curves obtained between the methods were: Qimp=1.82+0.75QVO₂ (r²=0.765, p<0.001; ICC=0.727, p<0.01) at 50% Wmax, and Qimp=0.93+1.00QVO₂ (r²=0.755, p<0.001; ICC=0.796, p<0.01) at 100% Wmax.

Conclusion: These results suggest that there is a good agreement between the two methods for the measurement of Q during exercise in the elderly, which is compatible with the findings of similar studies with young subjects.

Key words: Exercise, exercise test, impedance, cardiography, aging.
selected among the members of thirteen senior citizen centers in Brussels, Belgium. We used a random number table to define how many would be drawn in each center. The following exclusion criteria were applied before the final draw of the participants: a) presence of cardiovascular, mobility and pneumopathological problems or recent surgeries; b) use of medication or substances that might affect acute cardiovascular physiological responses to exercise; c) use of food supplements; d) individuals who are substantially overweight (BMI > 35 kg/m²), smokers and athletes. An informed consent term was obtained prior to the subjects' participation in the study, following the recommendation of the Helsinki Convention which was ratified in Brazil by Resolution n° 196/96 of the National Health Council of Brazil on experiments with humans.

Exercise Protocol - The subjects performed a cardiopulmonary exercise test on a cycle-ergometer (Ergo-Line® the American Heart Association. 6 to 12 minutes of test, following the recommendation of work capacity in order to obtain maximal exertion between loads were selected according to the predicted maximum for the gender; (c) five minutes of recovery, without load. The initial load being added every two minutes, according to the gender; (b) work phase at 25 W for men and 20 W for women, with an incremental load equal to the initial load being added every two minutes, according to the gender; (c) five minutes of recovery, without load. The loads were selected according to the predicted maximum work capacity in order to obtain maximal exertion between 6 to 12 minutes of test, following the recommendation of the American Heart Association. 14. The criteria of interruption of the test followed the recommendations of the American College of Sports Medicine. 15. The test was considered maximal when at least two of the following criteria were observed: (a) respiratory quotient (R) ≥ 1.06; (b) VO₂ plateau despite the increase in load (increase in VO₂ ≤ 2.0 ml·kg⁻¹·min⁻¹ between the last two loads); (c) maximum voluntary exhaustion. The reproducibility of the test was previously tested in a subgroup of 12 elderly subjects (eight men and four women) randomly selected from the original sample.

Estimation of cardiac output based on impedance cardiography - Impedance cardiography was recorded on a Minnesota® (IFM 304b, USA) impedance recorder, with a tetrapolar configuration. The ECG and the HR were recorded on a Fukuda Denshi® (FD-36, Japan) electrocardiograph, and on a Fukuda Denshi® (PL-16, Japan) phonocardiograph. Hematocrit was quantified after a centrifugation process, and the blood sample was collected after the testing. Cardiac output (Q) and stroke volume were estimated every two minutes according to the following equation: Q (L·min⁻¹) = 0.001 stroke volume (ml·syst⁻¹·HR (bpm)). Considering that the variation in thoracic impedance due to blood ejection is related with the ejection volume, 16 stroke volume can be calculated based on the equation: stroke volume (ml·syst⁻¹) = (p) (L·Z,²) (LVET) (dz/dt), where p refers to blood resistivity (ohm·cm); p = 53.2e⁻0.22HV, where Hct is hematocrit; 17 L is the length between the signal detection electrodes (cm); Z, is the baseline thoracic impedance (ohm); LVET is the left ventricle ejection time (second); and dz/dt is the rate of thoracic impedance change (ohm·seg⁻¹). These equations have been previously validated by Miles and Cotshall 7 and Bogaard et al. 5 by comparison with direct measurements. The components of the equations presented were obtained according to previously described methods 18.

Estimation of cardiac output based on oxygen uptake - Oxygen uptake (VO₂), carbon dioxide output (VCO₂) and ventilation (VE) were assessed respectively by an O₂ paramagnetic analyzer, an infrared CO₂ analyzer and a pneumotachograph (Morgan®, UK). These ventilatory variables were determined in L·min⁻¹ STPD over the same period of the impedance data and their average was calculated every 30 seconds. The difference in O₂ arterial venous content (Diff. O₂) was estimated based on the equation: Diff. O₂ = 5.721 + (0.1047 x %VO₂max), and Q was estimated based on Fick's equation (Q = VO₂ / Diff. O₂).

Statistical procedure - The relation between the two methods was assessed by linear regression for the data at 50% of the maximum load (40-90%VO₂max) and at maximal exertion (100%VO₂max). The agreement between the methods was assessed based on the intra-class correlation coefficient (ICC), the limits of agreement and the differences between methods (bias) were assessed according to the methodology proposed by Bland and Altman. 19. The analyses were carried out using the STATA 8.2 and STATISTICA 5.5 software programs.

Results
Table 1 presents the mean and confidence interval (95%CI) for the variables measured/estimated at 50% and 100% of the exertion load. Table 2 and Figures 1, 2, 3 and 4 present the data of the comparison between the two methods. At 50% of the load, the difference between the methods was 0.58 L·min⁻¹ – corresponding to 6.3% in favor of the method of Stringer et al. 7 – and with a limit of agreement of ± 2.54 L·min⁻¹, corresponding to 24.7% (Tables 1 and 2; Figures 1 and 3). At maximal exertion, this trend, though slight, is reversed. The means presented a difference of 1.03 L·min⁻¹ in favor of impedance cardiography, corresponding to 8.5% of the bias between the methods. The limit of agreement was ± 3.35 L·min⁻¹, corresponding to 27.6% (Tables 1 and 2; Figures 2 and 4).

Discussion
When comparing different methods to measure the same variable, the values obtained will hardly agree in a perfect fashion, and provide identical results for all individuals. For this reason, Table 1 - Descriptive data at different exertion intensities

<table>
<thead>
<tr>
<th>Variable</th>
<th>50% (mean and 95%CI)</th>
<th>100% (mean and 95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>VO₂ (L·min⁻¹)</td>
<td>1.29 (1.24 – 1.34)</td>
<td>1.80 (1.72 – 1.88)</td>
</tr>
<tr>
<td>QO₂ (L·min⁻¹)</td>
<td>9.70 (9.30 – 10.11)</td>
<td>11.12 (10.61 – 11.62)</td>
</tr>
<tr>
<td>Qv (L·min⁻¹)</td>
<td>9.13 (8.78 – 9.47)</td>
<td>12.15 (11.57 – 12.73)</td>
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<tr>
<td>HR (bpm)</td>
<td>115 (113 – 118)</td>
<td>140 (137 – 143)</td>
</tr>
<tr>
<td>W (Watts)</td>
<td>55 (52 – 59)</td>
<td>100 (94 – 105)</td>
</tr>
</tbody>
</table>

W = Load; VO₂ = O₂ uptake; QO₂ = Estimated output based on O₂ uptake; Qv = Estimated output based on impedance; HR = Heart Rate.
differ from one another. Actually, the cut-off point of what would be considered acceptable differences depends on the variable analyzed, and there are some variables that are believed to admit greater variability than others.

Some previous studies have used similar testing protocols in elderly subjects. The choice of methods used to estimate Q in this study was determined considering its specific characteristics. Impedance cardiography was chosen in view of the fact that it is widely used. Although the method is based on some controversial premises and is even not recommended by some authors, its validity, accuracy and

<table>
<thead>
<tr>
<th>Load</th>
<th>50%</th>
<th>100%</th>
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<tr>
<td>Bias (mean and SD)</td>
<td>$-0.577 \pm 1.127$</td>
<td>$1.034 \pm 1.674$</td>
</tr>
<tr>
<td>Limits of agreement (2SD)</td>
<td>$\pm 2.254 or \pm 24.7%$</td>
<td>$\pm 3.348 or \pm 27.6%$</td>
</tr>
<tr>
<td>ICC</td>
<td>0.727 (p&lt;0.01)</td>
<td>0.796 (p&lt;0.01)</td>
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<tr>
<td>Linear regression</td>
<td>$Q_{\text{imp}} = 1.82 + 0.75Q_{\text{VO}_2}$, $r^2=0.765 / p&lt;0.001$</td>
<td>$Q_{\text{imp}} = 0.93 + 1.00Q_{\text{VO}_2}$, $r^2=0.755 / p&lt;0.001$</td>
</tr>
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</table>

*ICC = intra-class correlation index; $Q_{\text{imp}}$ = Estimated output based on O$_2$ uptake; $Q_{\text{imp}}$ = Estimated output based on impedance.*

Table 2 - Results of the comparison between impedance cardiography (IMP) and O$_2$ Uptake (VO$_2$).

Bland and Altman proposed an approach to compare to what extent a certain method differs from another. If the difference, which expresses the precision between the methods and the limits of agreement, which express the variability of measurements, are not elevated, there would be no problems, in principle, for the cross-interpretation of data (that is, comparing the data obtained by different methods). According to Bland and Altman, for this type of cross-interpretation to be possible, it is at the discretion of the researchers to define to what extent measurements can
reproducibility have been documented by several studies. However, previous laboratory studies, involving more than 150 individuals above 60 years of age, did not reveal difficulties as to their applicability, in comparison with younger subjects. In fact, there were no significant differences in the quality of the signs obtained and the values usually measured generally do not depart from those reported in the literature for the age groups and intensity of exertion observed.

The estimation of Q based on oxygen uptake is a relatively new method. It was developed by Stringer et al. in young individuals, based on the hypothesis that Dif.\(\Delta\)\(\text{O}_2\) would increase in a predictable manner via a percentage of VO\(_2\) max during exercise. Its major advantage is that it does not require the use of different pieces of equipment other than the ones used in cardiopulmonary exercise testing, or nonconventional maneuvers to take the measurements, which could facilitate its use in elderly subjects. This population would benefit from a less invasive estimate method that reflects the reality better during physical exercise.

Because it is a new method, the estimate of Q based on oxygen uptake lacks validation studies in elderly subjects. In the comparison with the direct measurement by Fick’s method in five young subjects doing an incremental to maximal exercise testing on a cycle-ergometer. Stringer et al. reported an r of 0.97 and a difference in the means between the values estimated and those effectively measured of ± 2 L·min\(^{-1}\), corresponding to 15% of the measurement obtained directly. In a study similar to this one, comparing indirect methods, Kaplan et al. evaluated 23 subjects aged between 24 and 43, in that two were women. Of them, 11 subjects performed an exercise protocol in steady-state on a cycle-ergometer, beginning with 25-50 W and with increments of equal magnitude every 10-15 minutes, during a period of 45 minutes, to compare the values measured based on inductance cardiography and CO\(_2\) rebreathing. Another group of 20 subjects did a progressive ramp test, on a cycle-ergometer, with increments of 15–30 W·min\(^{-1}\) until exhaustion. In this case, the objective was to compare the values measured based on the inductance and \(\text{O}_2\) uptake. The authors reported limits of agreement of ± 2.8 L·min\(^{-1}\) in the first group, corresponding to a variability of 21%, and of ± 2.8 L·min\(^{-1}\) in the second group, corresponding to 22%.

Charloux et al. published a study in which they compared impedance cardiography with Fick’s Direct Method. Subjects with different clinical conditions participated in the study, with a total of 40 patients, of which 14 had sleep apnea and 26 had chronic obstructive pulmonary disease. The subjects performed steady-state exercise on a cycle-ergometer in supine position with loads between 10 and 50 W. The results revealed a difference of 0.29 L·min\(^{-1}\) between the methods and limits of agreement between -2.34 and 2.92 L·min\(^{-1}\); the authors reveal that in only 9.3% of the cases did the differences between the method exceed 20%.

Some studies have analyzed other methods. Davis et al. for instance, reported limits of agreement of ± 20% between CO\(_2\) rebreathing and Fick’s Direct Method in 18 patients with severe pulmonary disease. Espersen et al. compared the methods of thermodilution and CO\(_2\) rebreathing with Fick’s Direct Method, in 11 apparently healthy subjects during exercise performed at 50 W. The differences found were 2.3 and -0.2 L·min\(^{-1}\), respectively, between thermodilution and CO\(_2\) rebreathing and between the first one and Fick’s Direct Method. In another study analyzing the validity of a variation of the CO\(_2\) rebreathing method, Olszowka et al. reported, in 14 subjects, from rest to maximal exercise, coefficients of variation for mean values of Q between 3 and 4%, in comparison with the traditional method. The differences were between 3 to 5% in the comparison with Fick’s Direct Method and between 2 to 3% as regards the thermodilution. The same authors mentioned a similar study, of the same group, in which coefficients of variation between 11 and 22% were found in comparison between thermodilution and acetylene rebreathing. Finally, Tordi et al., in a recent study, compared non-invasive methods (impedance and CO\(_2\) rebreathing) in eight young men during three different bouts of steady-state exercise controlled by HR (120, 140 and 160 bpm). The authors reported an r of 0.85 and a mean difference of 0.06 L·min\(^{-1}\) (corresponding to 0.12 %) in the three intensities. In the lowest intensity, the mean of the values of Q estimated by impedance was lower than the estimated by CO\(_2\) rebreathing. However, this trend reversed in higher intensities. This behavior was explained by the authors as resulting from a limitation of the CO\(_2\) rebreathing method in steady-state conditions for high intensities, due to progressive acidemia (decrease in blood pH).

In this study, the estimates were compared at two different times, 50% and 100% of the maximal exertion load during incremental exercise. This strategy allowed the perception of a reasonable agreement between the methods (differences of ± 6% to 8.5% and limits of agreement of ± 24% to 28%), although the variation between the values obtained from both increase as the absolute values of Q increase. When approaching maximum values, Q estimated based on oxygen uptake tended to be lower than the Q measured by the impedance cardiography technique, and we also observed an upward trend of the difference between the values estimated according to the proximity to maximal exertion.

This behavior was similar to that observed by Tordi et al., in the comparison between impedance and CO\(_2\) rebreathing. Although these authors have justified this behavior in view of the limitations of the CO\(_2\) rebreathing method, we may theorize that, at higher intensities, the impedance method would tend to overestimate Q values in view of artifacts in the impedance curves measured. However, it becomes clear that absolute and relative values for differences and limits of agreement approach those obtained by other studies that compare direct and indirect methods to measure Q. Additionally, they fall within the ± 15% range of variation reported in the work carried out by Miles e Gotshall.

In summary, this study suggests a good agreement in the estimate of Q in elderly subjects, between the impedance cardiography and oxygen uptake-based methods. The results seem to be compatible with those of other studies which compare methods of measurement during exercise in young subjects or in subjects with cardiorespiratory conditions. However, additional studies should be conducted to further the process of validation of the Q estimate method based on oxygen uptake in elderly subjects, either by comparing different methods or by verifying the reproducibility of the measurement during the exercise.
References


