

Northumbria Research Link

Citation: Louvaris, Zafeiris, Spetsioti, Stavroula, Andrianopoulos, Vasileios, Chynkiamis, Nikolaos, Habazettl, Helmut, Wagner, Harrieth, Zakynthinos, Spyros, Wagner, Peter and Vogiatzis, Ioannis (2019) Cardiac output measurement during exercise in COPD : A comparison of dye dilution and impedance cardiography. *The Clinical Respiratory Journal*, 13 (4). pp. 222-231. ISSN 1752-6981

Published by: Wiley

URL: <https://doi.org/10.1111/crj.13002> <<https://doi.org/10.1111/crj.13002>>

This version was downloaded from Northumbria Research Link:
<http://nrl.northumbria.ac.uk/id/eprint/37946/>

Northumbria University has developed Northumbria Research Link (NRL) to enable users to access the University's research output. Copyright © and moral rights for items on NRL are retained by the individual author(s) and/or other copyright owners. Single copies of full items can be reproduced, displayed or performed, and given to third parties in any format or medium for personal research or study, educational, or not-for-profit purposes without prior permission or charge, provided the authors, title and full bibliographic details are given, as well as a hyperlink and/or URL to the original metadata page. The content must not be changed in any way. Full items must not be sold commercially in any format or medium without formal permission of the copyright holder. The full policy is available online: <http://nrl.northumbria.ac.uk/policies.html>

This document may differ from the final, published version of the research and has been made available online in accordance with publisher policies. To read and/or cite from the published version of the research, please visit the publisher's website (a subscription may be required.)

1 **Cardiac output measurement during exercise in COPD:**
2 **A comparison of dye dilution and impedance**
3 **cardiography**

4 Zafeiris Louvaris^{1,2,3}, Stavroula Spetsioti², Vasileios
5 Andrianopoulos⁴, Nikolaos Chynkiamis^{2,5} Helmut Habazettl^{6,7},
6 Harrieth Wagner⁸, Spyros Zakyntinos², Peter Wagner⁸ and Ioannis
7 Vogiatzis^{2,3,5}

8
9 ¹Faculty of Movement and Rehabilitation Sciences, Division of Respiratory
10 Rehabilitation, Department Rehabilitation Sciences KU Leuven, University
11 Hospitals Leuven, Leuven, Belgium.

12 ²1st Department of Critical Care Medicine and Pulmonary Services, GP Livanos
13 and M Simou Laboratories, Medical School of Athens University, Evangelismos
14 Hospital, Athens, Greece.

15 ³National and Kapodistrian University of Athens, Department of Physical
16 Education and Sports Sciences. Athens, Greece.

17 ⁴Institute for Pulmonary Rehabilitation Research; Schoen Klinik
18 Berchtesgadener Land; Schoenau am Koenigssee, Germany

19 ⁵Department of Sport, Exercise and Rehabilitation, Faculty of Health and Life
20 Sciences, Northumbria University Newcastle, UK.

21 ⁶Institute of Physiology, Charite - University Medicine Berlin, corporate member
22 of Freie Universität Berlin, Humboldt-Universität zu Berlin, and Berlin Institute of
23 Health, Germany.

24 ⁷Institute of Anesthesiology, German Heart Institute Berlin, Berlin, Germany.

25 ⁸Department of Medicine, University of California San Diego, La Jolla,
26 California.

27
28
29 Short title: Impedance cardiography for cardiac output in COPD
30
31
32

33 **Correspondence:** Dr. Louvaris Zafeiris (zafeiris.louvaris@kuleuven.be)
34 Rehabilitation and Respiratory Division, UZ Gasthuisberg, Herestraat 49, O&N4
35 Building, Bus 1510, Leuven 3000, Belgium.

36 **Summary**

37 Impedance cardiography (IC) derived from morphological analysis of the thoracic
38 impedance signal is now commonly used for non-invasive assessment of cardiac
39 output (CO) at rest and during exercise. However, in COPD, the two published studies
40 disagree about its accuracy. We therefore compared concurrent CO measurements
41 captured by IC (PhysioFlow™: CO_{IC}) and by the indocyanine green dye dilution method
42 (CO_{DD}) in patients with COPD. Fifty paired CO measurements were concurrently
43 obtained using the two methods from 10 patients (FEV₁:50.5±17.5%predicted) at rest
44 and during cycling at 25%, 50%, 75% and 100% peak work rate. From rest to peak
45 exercise CO_{IC} and CO_{DD} were strongly correlated (r=0.986, p<0.001). The mean
46 absolute and percentage differences between CO_{IC} and CO_{DD} were 1.08 liters/min
47 (limits of agreement (LoA): 0.05 to 2.11 liters/min) and 18±2%, respectively, with
48 impedance cardiography yielding systematically higher values. Bland-Altman analysis
49 indicated that during exercise only 7 of the 50 paired measurements differed by more
50 than 20%. When data were expressed as changes from rest, correlations and
51 agreement between the two methods remained strong over the entire exercise range
52 (r=0.974, p<0.001, with no significant difference: 0.19 Liters/min; LoA: -0.76 to 1.15
53 liters/min). Oxygen uptake (VO₂) and CO_{DD} were linearly related: r=0.893 (p<0.001),
54 CO_{DD} = 5.94 x VO₂ + 2.27 liters/min. Similar results were obtained for VO₂ and CO_{IC} (r
55 =0.885, p<0.001, CO_{IC} = 6.00 x VO₂ + 3.30 liters/min). These findings suggest that
56 impedance cardiography provides an acceptable CO measurement from rest to peak
57 cycling exercise in patients with COPD.

58

59

60

61 **Keywords: Exercise, Central hemodynamics, Noninvasive techniques, Thoracic**
62 **impedance, Lung diseases**

63 Introduction

64 Measurement of cardiac output (CO) in patients with Chronic Obstructive Pulmonary
65 Disease (COPD) is important for comprehensively investigating the pathophysiological
66 mechanisms of exercise intolerance, as well as the efficacy of rehabilitative exercise
67 training interventions.

68 For many years, a number of invasive techniques such as the direct Fick,
69 thermodilution and dye dilution methods have been used for measuring CO during
70 exercise (Warburton *et al.*, 1999a). The direct Fick method requires trained personnel
71 and blood sampling from both pulmonary and systemic arteries to perform what is
72 regarded as the standard technique - if meticulously carried out- (Darovic, 1995).
73 Requiring discrete blood samples, it is a discontinuous method. Despite its extensive
74 use in clinical settings, the thermodilution method, which requires a systemic but not
75 pulmonary arterial catheter, is reported to yield a consistent overestimation of CO, both
76 at low values and during vigorous exercise compared to the direct Fick method (van
77 Grondelle *et al.*, 1983; Russell *et al.*, 1990; Esprersen *et al.*, 1999) This occurs
78 because unknown quantities of thermal indicator may be lost from the injectate before it
79 enters the circulation and/or through the vessel wall, or because of the temperature
80 difference between pulmonary blood and the injectate (Mackenzie *et al.*, 1986). This
81 method is also discontinuous, because each measurement requires a separate
82 injection of cold tracer.

83 The dye dilution technique, which also requires an arterial catheter, is more suited to
84 use during exercise, since it is relatively easier to use than the direct Fick method and
85 is more accurate than thermodilution (Russell *et al.*, 1990). However, in addition to the
86 arterial cannula, dye dilution requires post-hoc data analysis involving deconvolution of
87 the main dye appearance curve from its smaller recirculation curve. It also is a
88 discontinuous method as each estimate requires a separate injection of dye, precluding
89 rapid repetition of measurements.

90 Impedance cardiography is relatively newer as a method for measuring cardiac
91 output, is completely noninvasive, and also virtually continuous. If reliable, it would, for
92 these reasons, offer major advantages over earlier methods. It relies on thoracic
93 impedance waveform analysis to determine stroke volume, which, when multiplied by
94 heart rate recorded from the inbuilt ECG signal, provides CO (Charloux et al., 2000).
95 This method requires only the application of (six) surface electrodes, and CO can, if
96 desired, be measured on a beat-to-beat basis or averaged over selected time periods
97 (Charloux *et al.*, 2000; Bour & Kellett, 2008).

98 Two studies in patients with COPD have compared impedance cardiography -
99 derived from thoracic impedance waveform analysis- against the direct Fick method
100 during cycling. Charloux *et al.*, (2000) demonstrated clinically acceptable agreement
101 between these methods during exercise of moderate intensity. They reported that
102 during exercise only 6.2% of CO values obtained by impedance cardiography differed
103 from the reference Fick method by more than 20% (which is considered to indicate the
104 clinically acceptable difference between two CO evaluation methods, Stetz *et al.*, 1982;
105 La Mantia *et al.*, 1990). In contrast, Bougault *et al.*, (2005), found that impedance
106 cardiography overestimated CO by 25-31% compared to the Fick method during
107 maximal exercise in COPD, thus precluding the use of IC under these conditions.
108 Consequently the acceptability of impedance cardiography during cycling exercise in
109 patients with COPD is still uncertain, and the resolution of this uncertainty requires
110 additional comparisons.

111 Because of this conflicting evidence and the increasing use of impedance
112 cardiography in clinical studies, we analyzed, and here present, data obtained from an
113 exercise study we conducted in COPD patients in which impedance cardiography and
114 dye dilution had been concurrently applied (Vogiatzis *et al.*, 2010). The primary
115 purpose of that study was to examine respiratory muscle blood flow at rest and during
116 exercise in COPD. However, as we required cardiac output measurements (by the

117 established dye dilution method) in that study, we saw the opportunity to also measure
118 cardiac output by impedance cardiography and compare the two. Accordingly, the
119 purpose of the present report is to compare cardiac output obtained by both methods
120 across the full range of (cycling) exercise intensity in patients with COPD. We wish to
121 fully and clearly disclose that the dye dilution data appear in the 2010 paper, Figure 4,
122 panel B (Vogiatzis *et al.*, 2010), while impedance cardiography data do not appear
123 anywhere in that, or in any other, report. With this disclosure, we reason that it is
124 necessary to bring back those dye dilution data in order to accomplish direct
125 comparison with the impedance cardiography values. We have also brought back VO_2
126 from the same study to allow the relationship between cardiac output and VO_2 to be
127 examined for both methods. It would not be possible to perform that comparison
128 without so doing.

129 **Materials and methods**

130 **Study participants and experimental procedures**

131 As originally reported in greater detail (Vogiatzis *et al.*, 2010), 10 clinically stable
132 patients [2 females, mean \pm SD: FEV₁:50.5 \pm 17.5% predicted, age, 60 \pm 7 years, weight
133 77 \pm 18 kg, body surface area 1.90 \pm 0.24m²] with COPD but without cardiac disease
134 classified by the Global Initiative for Chronic Obstructive Lung Disease (GOLD, 2016)
135 as spirometric stages II (n = 4) and III (n = 3) and IV (n=3) were studied. Patients
136 demonstrated reduced exercise capacity (peak work rate 73 \pm 42 watts (mean \pm SD)
137 which was 41 \pm 19 %predicted; and peak oxygen uptake 15 \pm 4 ml/kg/min (39 \pm
138 13%predicted).

139 After resting measurements, all patients were studied while cycling at 25%, 50%.
140 75% and 90-100% of their peak work rate, each level sustained for 2-5 min. This
141 protocol therefore yielded 5 comparisons per subject, so that a total of 50 simultaneous
142 paired measurements of CO by impedance cardiography and dye-dilution were
143 available for comparison.

144 **Cardiac output measurements**

145 Procedures for determination of CO by the dye-dilution method (CO_{DD}) are
146 described in the on-line supplement to Vogiatzis *et al.*, (2010). For impedance
147 cardiography, a commercially available signal-morphology device, (PhysioFlow™
148 PF05; Manatec Biomedical, Macheren, France) was used for determining stroke
149 volume and heart rate, and from this, CO (CO_{IC}). A detailed technical description of this
150 method can be found elsewhere (Charloux *et al.*, 2000; Bougault *et al.*, 2005; Tonelli *et*
151 *al.*, 2011; Ferreira *et al.*, 2012). After careful skin preparation that included shaving,
152 application of a mildly abrasive gel (Nuprep, www.dowaver.com) and then cleaning (by
153 alcohol), six electrodes (Physioflow™ PF5; Manatec Biomedical, Macheren, France)
154 were placed according to the manufacturers' instructions in effect at the time, as shown
155 in Figure 1 of Nasis *et al.*, (2015): two on the neck on the left side (one vertically above
156 the other over the carotid artery above the supraclavicular fossa); two anteriorly in the
157 xiphoid region; and two in locations corresponding to the V1 and V6 positions used for
158 conventional ECG monitoring (Bougault *et al.*, 2005). After the subject had rested for
159 15 minutes, the system was auto-calibrated (a nominal, one-time, initial 30 second
160 procedure as recommended by the manufacturer).

161 Data were then recorded at 1 second intervals and stored on a disk in Excel for off-
162 line analysis. Verification of signal quality was performed according to the
163 manufacturers' instructions and as reported later by Ferreira *et al.*, (2012). The
164 Physioflow™ software includes real-time indication of signal quality (expressed in
165 percentage values i.e., 0-100%). In this study data points were excluded when signal
166 quality was less than 90% as performed in previous studies published by our group
167 (Vassilopoulou *et al.*, 2012; Nasis *et al.*, 2015; Louvaris *et al.*, 2015). The reason for
168 <90% signal quality is motion artefacts induced by exercise and exaggerated
169 ventilatory responses to exercise, or poor skin contact with electrodes (Edmunds *et*
170 *al.*, 1982; Warburton *et al.*, 1999b). Data were smoothed using a 5-point moving

171 average (Savitzky & Golay, 1964). The values were then time-aligned with the data
172 captured by the dye-dilution method (CO_{DD}). The value of CO_{IC} used for comparison
173 with the dye dilution estimate was the average of all smoothed values obtained over a
174 30-second period at rest and over a 15-second period during exercise, time periods
175 corresponding to the typical duration of the dye curves in each case. A representative
176 example of both raw and smoothed data for CO_{IC} is shown in Figure 1.

177 **Statistical analysis**

178 Data are presented as means \pm SEM. We chose SEM (standard error of the mean)
179 rather than SD (standard deviation) because the comparison of interest is between the
180 two methods' mean values. Pearson's correlation coefficient (r) was used to establish
181 associations between measurements. Two-way ANOVA with repeated measures and
182 post-hoc comparisons were used to identify statistically significant differences across
183 cycling work rates between the two methods. Analysis of agreement between the two
184 methods was performed by using Bland-Altman analysis. Limits of agreement were
185 defined as $\pm 1.96 \times$ standard deviation of the difference between the two methods,
186 corresponding to 95% confidence intervals. The level of statistical significance was set
187 at $P < 0.05$. All statistical analyses were performed using the SPSS statistical software
188 (v. 20 IBM SPSS Statistics, Chicago, IL, USA).

189 **Results**

190 **Central hemodynamic responses at rest and exercise**

191 CO measured by both methods reached a plateau at 75% of WR_{peak} (Figure 2a).
192 There were significant differences in absolute values of CO between CO_{IC} and CO_{DD} at
193 rest and during exercise ($p < 0.001$, Figure 2a) secondary to stroke volume that was
194 consistently higher with impedance cardiography (as compared to stroke volume
195 calculated by dye-dilution CO divided by heart rate, $p < 0.001$, Table 1). Specifically,
196 mean CO_{IC} at rest was 5.0 ± 0.4 liters/min and increased to 9.8 ± 0.9 liters/min at 100%
197 WR_{peak} whilst CO_{DD} increased from 4.1 ± 0.4 (rest) to 8.4 ± 1.0 liters/min (at

198 100%WRpeak, Figure 2a). Therefore, an approximately 1 l/min systematic difference
199 was observed between methods from rest to maximal exercise, with impedance
200 cardiography giving the higher values. (Figure 2a). Hence, when CO values were
201 expressed as changes from rest, there were no significant differences between the two
202 methods (Figure 2b).

203 **Association between cardiac output by both methods, and between cardiac** 204 **output and VO₂**

205 The association between all individual absolute values of CO_{IC} and CO_{DD} at rest and
206 during exercise was strong ($r=0.986$, $p<0.001$, Figure 3a). Similarly strong correlations
207 were obtained when looking at changes from rest to exercise ($r=0.974$, $p<0.001$, Figure
208 3b). The correlation coefficient between VO₂ and CO_{DD} was $r=0.893$ ($p<0.001$), and the
209 regression equation was $CO_{DD} = 5.94 \times VO_2 + 2.27$ liters/min (Figure 4a). The
210 correlation coefficient between VO₂ and CO_{IC} was $r=0.885$ ($p <0.001$), and the
211 regression equation was $CO_{IC} = 6.00 \times VO_2 + 3.30$ liters/min (Figure 4b). These two
212 equations also point out that the intercept values are different (by ~ 1.0 l/min) between
213 the methods while the slopes are essentially the same.

214 **Agreement between impedance cardiography and dye-dilution**

215 The differences between the two measurements plotted against their mean value of
216 the Bland-Altman analysis reference are presented in Figure 5. Specifically, at rest and
217 during exercise, the mean difference (CO_{IC}-CO_{DD}) was 1.08 liters/min with limits of
218 agreement of 0.05 liters/min and 2.11 liters/min (Figure 5a). The difference between
219 the two methods exceeded 20% in only 11 out of 50 measurements (4 cases at rest
220 and only 7 during exercise) whilst the mean percentage difference between the two
221 methods was $18 \pm 2\%$. When comparing changes from rest to peak exercise, the mean
222 difference (CO_{IC} -CO_{DD}) was +0.19 liters/min with the limits of agreement of -0.76
223 liters/min and 1.15 liters/min (Figure 5b) whilst only 8 out of 50 measurements
224 exceeded 20% difference between the two methods. In addition, when comparing

225 changes from rest to peak exercise the mean percentage difference between the two
226 methods ($CO_{IC} - CO_{DD}$) was ~~reduced to~~ $13 \pm 4\%$.

227 **Discussion**

228 **Main findings**

229 The present analysis compared measurements of cardiac output by impedance
230 cardiography against an established, older and invasive method (i.e., dye dilution) in
231 patients with COPD at rest and over a wide range of exercise workloads up to the limit
232 of tolerance. At rest the mean difference between the two methods was ~ 1.0 l/min
233 (impedance value higher than dye dilution), a difference that remained unchanged
234 during exercise up to the limit of tolerance (Figure 2). We found strong individual
235 correlations between the two methods (Figure 3) accompanied by highly significant and
236 comparable correlations between CO and VO_2 (Figure 4). These positive findings were
237 further supported by the acceptable agreement (Figure 5) between the two methods
238 (mean difference ~ 1.0 l/min or 18%) under all conditions examined. The results support
239 the use of impedance cardiography in these patients during exercise up to maximal
240 levels.

241 **Prior studies using impedance cardiography in COPD and other diseases**

242 Charloux *et al.*, (2000) compared PhysioFlow™ against the direct Fick method in 40
243 patients with moderate COPD at rest and during low to moderate exercise intensity
244 (between 10-50 watts, which was below patients' ventilatory threshold). They found a
245 mean difference between the two methods of 0.3 liters/min, with only 9.3% of
246 measurements (3 out of 32 measures) differing by more than 20% from the reference
247 method. Of interest, at rest, and in the same range of cardiac output as in the present
248 study, they found that the impedance technique resulted in a slightly higher value than
249 the reference method (Figure 3A of their paper, showing every data point in the 3-5
250 liters/min range on or above the regression line). Our study expands the Charloux *et*
251 *al.*, (2000) findings by presenting results from rest to the limit of exercise tolerance, and

252 by including patients with more severe COPD. The difference between the two studies
253 is in our results showing a continued difference of ~ 1.0 l/min across the entire exercise
254 range when compared to the chosen standard method.

255 Bougault *et al.*, (2005) compared cardiac output measured by the PhysioFlow™
256 device with the direct Fick method in 8 patients with moderately severe COPD during a
257 maximal incremental exercise test and an intermittent work exercise test up to maximal
258 levels. They found a mean difference between the two methods of 3.2 liters/min and
259 2.5 liters/min, respectively with impedance cardiography yielding the higher values.
260 These differences, especially in the incremental test, may be at least in part explained
261 by lack of a gas exchange steady state, since a steady state is required for proper use
262 of the Fick method (Guyton *et al.*, 1973; Warburton *et al.*, 1999a). That said, the slope
263 of the relationship between cardiac output and VO_2 by the Fick method (5.9 liters/min
264 per liter/min VO_2) was in the usually reported range, while that for the impedance
265 method was unusually high (9.7 liters/min per liter/min VO_2), suggesting a systematic
266 error in their application of the latter method. Note from Figure 5 in the present paper
267 that we found a slope of 6.0 liters/min per liter/min VO_2 , essentially the same as their
268 Fick-derived slope value, and a value in accord with the literature based on various
269 measurement methods. Furthermore, Granath *et al.*, (1964) employed the
270 thermodilution method in 27 individuals aged between 61-83 years during exercise in
271 supine and sitting position and reported a slope between CO-VO_2 of 5.8 liters/liter.
272 Julius *et al.* (1967) used the direct Fick method to measure CO in 18 subjects aged
273 between 50-69 years and in 36 subjects aged between 18-49 years old. They
274 established that the slope of the CO-VO_2 relationship was ~6.0 liters/liter, which was
275 not altered by aging or the level of physical fitness among subjects. Grimby *et al.*,
276 (1966) by using dye dilution method in middle-aged trained subjects reported a slope of
277 5.2 liters/liter during submaximal and maximal exercise. These findings have been
278 consistently confirmed by a number of investigators using noninvasive techniques for

279 assessing CO such as foreign gas measures methods (i.e., acetylene rebreathing) or
280 indirect Fick methods (i.e, CO₂ rebreathing.) (Faulkner, *et al.*, 1977; Hagberg *et al.*,
281 1985; McElvaney *et al.*, 1989; Makredis *et al.*, 1990; Proctor *et al.*, 1998). They
282 reported slopes from 4.6 to 6.0 liters/liter in subjects aged between 49-72 years old.

283 We have no technical explanation for the findings by Bougault *et al.*, (2005) noting
284 that we used the same version of the Physioflow™ system as did they. However, they
285 did not provide methodological details regarding how they used the PhysioFlow™
286 system or how they analyzed the data (i.e., smoothing procedure, if any; data sample
287 frequency, etc) nor did they report whether they followed the manufacturer's
288 instructions for using specific electrodes, subject calibration, software for data analysis,
289 information for skin preparation and signal quality inspection, as we report here (see
290 methods).

291 In support of our findings, a study by Bogaard *et al.*, (1997) in 19 patients with
292 moderate COPD compared a different impedance cardiography device (i.e., IPG-104
293 impedance;Mini-Lab; Detroit, MI) against the CO₂ re-breathing method during steady-
294 state exercise, ranging from light intensity to the limit of tolerance. They reported
295 similar results to ours - that the overall correlation during exercise between the two
296 methods was strong ($r=0.92$), with few measurements falling outside the limits of
297 agreement of 20%. The mean CO difference between impedance cardiography and the
298 reference method was only 0.01 liters/min with limits of agreement of 2.56 liters/min.

299 In summary, in examining the three published studies and our present data, two of
300 the published studies and our data set report adequate agreement with standard
301 methods at rest and during exercise in patients with COPD, while the remaining
302 published study did not, without apparent explanation. Our study is novel in providing
303 comparisons using the Physioflow™ system over the entire exercise range from rest to
304 maximal.

305 The PhysioFlow™ system has also been investigated in patients with chronic heart
306 failure (CHF) or pulmonary arterial hypertension (PAH) at rest and during exercise
307 against different reference methods (Tordi *et al.*, 2004; Kemps *et al.*, 2008; Tonelli *et*
308 *al.*, 2011; Ferreira *et al.*, 2012; Tonelli *et al.*, 2013). These studies also reported
309 adequate agreement with standard methods used simultaneously.

310 **The difference between cardiac output by dye dilution and by impedance** 311 **cardiography in the present study**

312 As the results of our study show (Figure 2a), impedance cardiography yielded
313 values 1 l/min higher than did dye dilution over the entire range from rest to maximal
314 exercise. The question that this poses is, which method was likely more accurate?
315 Using the regression equations of cardiac output against VO_2 in Figure 4 for both
316 methods, at a normal resting VO_2 of 300 ml/min, cardiac output by impedance
317 cardiography would be 5.1 liters/min while that by dye dilution would be only 4.1
318 liters/min. A similar calculation from the Charloux *et al.*, (2000) paper (their Figure 2)
319 estimates cardiac output at this VO_2 would be 6.3 liters/min, while that from Bogaard *et*
320 *al* (their Figure 5) estimates cardiac output would be 4.7 liters/min. Taken together with
321 the relatively high body mass of the subjects in our study of 77.0 kg, these calculations
322 suggest that the impedance-based values in our study may be more accurate than
323 those derived from dye dilution.

324 **Strengths, Limitations and Conclusions**

325 While the present study is limited by small sample size (10 patients), the group
326 spans the COPD severity and exercise capacity spectrum (i.e., GOLD stages II-IV and
327 WR_{peak} 11 to 69% predicted), and the measurements cover the entire range of
328 exercise from none to maximal, such that we were able to accumulate 50 paired
329 cardiac output measurements. Cardiac output is well-known to be an important
330 contributor to exercise capacity, but has proven difficult to measure in clinical exercise
331 testing because the usual methods (dye dilution, direct Fick, thermodilution, CO_2 re-

332 breathing) are technically complex and mostly invasive as well as being limited to
333 discrete rather than essentially continuous measurements that require often substantial
334 analysis of raw data before the result is known. Impedance cardiography on the other
335 hand is noninvasive, requires only the placement of skin electrodes thus saving
336 valuable time for operators, and gives an essentially continuous readout of cardiac
337 output. With the unexplained exception of one study described above, our study and
338 those that preceded it together suggest that impedance cardiography is well suited to
339 (clinical) exercise testing settings in patients with COPD.

340

341

342

343

344

345

346

347

348

349

350

351

352

353

354

355

356

357

358

359 Conflict of interest

360 The authors state explicitly that there are no conflicts of interest in connection with this
361 article and have no relevant financial disclosures, particularly in connection with the
362 manufacturer of the impedance cardiography system used in the study.
363

364 Acknowledgments

365 Dr. Louvaris Zafeiris is a is a post-doctoral research fellow of the FWO-Flanders
366 (12U5618N)

367

368

369

370

371

372

373

374

375

376

377

378

379

380

381

382 References

- 383 Bogaard HJ, Hamersma WB, Horsch JL, *et al.* Non-invasive assessment of cardiac
384 output during exercise in chronic obstructive pulmonary disease: comparison of the
385 CO₂-rebreathing method and electrical impedance cardiography. *Physiol*
386 *Meas* (1997);18:327-38.
- 387
388 Bougault V, Lonsdorfer-Wolf E, Charloux A, *et al.* Does thoracic bioimpedance
389 accurately determine cardiac output in COPD patients during maximal or intermittent
390 exercise? *Chest* (2005);127:1122-31.
- 391 Bour J, Kellett J. Impedance cardiography: a rapid and cost-effective screening tool
392 for cardiac disease. *Eur J Intern Med* (2008);19:399-405.
- 393 Charloux A, Lonsdorfer-Wolf E, Richard R, *et al.* A new impedance cardiograph device
394 for the non-invasive evaluation of cardiac output at rest and during exercise:
395 comparison with the "direct" Fick method. *Eur J Appl Physiol* (2000);82:313-20.
396
- 397 Darovic GO. Hemodynamic monitoring: invasive and noninvasive clinical application.
398 Philadelphia (PA): W.B. Saunders Company, 1995.
399
- 400 Edmunds AT, Godfrey S, Tooley M. Cardiac output measured by transthoracic impe-
401 dence cardiography at rest, during exercise and at various lung volumes. *Clin Sci*
402 *(Lond)*(1982);63:107-113.
403
- 404 Espersen K, Jensen EW, Rosenborg D, *et al.* Comparison of cardiac output
405 measurement techniques: thermodilution, Doppler, CO₂-rebreathing and the direct Fick
406 method. *Acta Anaesthesiol Scand* (1995);39:245-51.
407
- 408 Faulkner JA, Heigenhauser GF, Schork MA. The cardiac output-oxygen uptake
409 relationship of men during graded bicycle ergometry. *Med Sci Sports Exerc* (1977); 9:
410 148-154.
- 411 Ferreira EM, Ota-Arakaki JS, Barbosa PB, *et al.* Signal-morphology impedance
412 cardiography during incremental cardiopulmonary exercise testing in pulmonary arterial
413 hypertension. *Clin Physiol Funct Imaging* (2012);32:343-52.
414
- 415 van Grondelle A, Ditchey RV, Groves Jr BM, *et al.* Thermodilution method
416 overestimates low cardiac output in humans. *Am J Physiol* (1983);245: H690-2.
417
- 418 Granath A, Jonsson B, Strandell T. Circulation in healthy old men, studied by right
419 heart catheterization at rest and during exercise in supine and sitting position. *Acta*
420 *Med Scand* (1964);176:425-46.
- 421 Grimsby G, Nilsson NJ, Saltin B. Cardiac output during submaximal and maximal
422 exercise in active middle-aged athletes. *J Appl Physiol* (1966);21:1150-6.
- 423 Guyton AC, Jones CE, Coleman TG. Circulatory physiology: cardiac output and its
424 regulation. Philadelphia (PA): W.B. Saunders Company, 1973.
425
- 426 Hagberg JM, Allen WK, Seals DR, *et al.* A hemodynamic comparison of young and
427 older endurance athletes during exercise. *J Appl Physiol* (1985);58: 2041-2046.

- 428 Julius S, Amery A, Whitlock LS, *et al.* Influence of age on the hemodynamic response
429 to exercise. *Circulation* (1967);36: 222–230.
- 430 Kemps HM, Thijssen EJ, Schep G, *et al.* Evaluation of two methods for continuous
431 cardiac output assessment during exercise in chronic heart failure patients. *J Appl*
432 *Physiol* (2008);105:1822-9.
- 433
434 LaMantia KR, O'Connor T, Barash PG. Comparing methods of measurement: an
435 alternative approach. *Anesthesiology* (1990);72:781-3.
- 436 Louvaris Z, Kortianou EA, Spetsioti S, *et al.* Intensity of daily physical activity is
437 associated with central hemodynamic and leg muscle oxygen availability in COPD. *J*
438 *Appl Physiol* (1985) (2013);115:794-802.
- 439 Nasis I, Kortianou E, Vasilopoulou M, *et al.* Hemodynamic effects of high intensity
440 interval training in COPD patients exhibiting exercise-induced dynamic hyperinflation.
441 *Respir Physiol Neurobiol.* (2015);217:8-16.
- 442 Mackenzie JD, Haites NE, Rawles JM. Method of assessing the reproducibility of blood
443 flow measurement: factors influencing the performance of thermodilution cardiac output
444 computers. *Br Heart J* (1986);55:14-24
- 445 Makrides LG, Heigenhauser JF, Jones NL. High intensity endurance training in 20- to
446 30- and 60- to 70-yr-old healthy men. *J Appl Physiol* (1990); 69: 1792–1798.
- 447 McElvaney GN, Blackie SP, Morrison NJ, *et al.* Cardiac output at rest and in exercise in
448 elderly subjects. *Med. Sci. Sports Exerc.* (1989);21:293–298.
- 449 Proctor DN, Beck KC, Shen PH, *et al.* Influence of age and gender on cardiac output-
450 VO₂ relationships during submaximal cycle ergometry. *J Appl Physiol* (1998);84:599-
451 605.
- 452
453 Russell AE, Smith SA, West MJ, *et al.* Automated non-invasive measurement of
454 cardiac output by the carbon dioxide rebreathing method: comparisons with dye dilution
455 and thermodilution. *Br Heart J* (1990);63:195-9.
- 456
457 Savitzky A, Golay, MJE. Smoothing and Differentiation of Data by Simplified Least-
458 Squares Procedures. *Analytical Chemistry*, (1964); 36: 1627-1639.
- 459
460 Stetz CW, Miller RG, Kelly GE, *et al.* Reliability of the thermodilution method in the
461 determination of cardiac output in clinical practice. *Am Rev Respir*
462 *Dis.* (1982);126:1001-4.
- 463
464 Tonelli AR, Alnuaimat H, Li N, Carrie R, *et al.* Value of impedance cardiography in
465 patients studied for pulmonary hypertension. *Lung* (2011);189: 369–375.
- 466
467 Tonelli AR, Alkukhun L, Arelli V, *et al.* Value of impedance cardiography during 6-min-
468 ute walk test in pulmonary hypertension. *Clin Transl Sci* (2013);6:474–480.
- 469
470 Tordi N, Mourot L, Matusheski B, *et al.* Measurements of cardiac output during
471 constant exercises: comparison of two non-invasive techniques. *Int J Sports Med*
472 (2004);25:145–149.
- 473

474 Vasilopoulou MK, Vogiatzis I, Nasis I, et al. On- and off-exercise kinetics of cardiac
475 output in response to cycling and walking in COPD patients with GOLD Stages I-IV.
476 *Respir Physiol Neurobiol* (2012);181:351-8.

477
478 Vogiatzis I, Athanasopoulos D, Habazettl H, et al. Intercostal muscle blood flow
479 limitation during exercise in chronic obstructive pulmonary disease. *Am J Respir Crit*
480 *Care Med* (2010);182:1105-13.

481
482 Warburton DE, Haykowsky MJ, Quinney HA, et al. Reliability and validity of measures
483 of cardiac output during incremental to maximal aerobic exercise. Part I: Conventional
484 techniques. *Sports Med* (1999);1:23-41.

485 Warburton DE, Haykowsky MJ, Quinney HA, et al. Reliability and validity of measures
486 of cardiac output during incremental to maximal aerobic exercise. Part II: novel tech-
487 niques and new advances. *Sports Med* (1999);27: 241–260.

488

489

490

491

492

493

494

495

496

497

498

499

500

501

502

503

504

505

506 **Figures**

507 **Figure 1.** Representative example of cardiac output by impedance cardiography in an
508 individual subject, from rest to maximal exercise. Values were recorded at 1 second
509 intervals. A 5-point moving average was implemented to smooth (red dots) the raw
510 data (black dots).

511 **Figure 2.** (a). Group mean absolute values of cardiac output measured by impedance
512 cardiography and dye dilution at rest and during cycling (b). Relative changes from rest
513 in cardiac output measured by impedance cardiography and dye dilution. Data are
514 presented as mean \pm SEM. Asterisks denote significant differences from values at
515 100% of WRpeak. Cross denotes significant difference between the two methods,
516 $P=0.031$. (Cardiac output data by dye dilution reproduced from Vogiatzis *et al.*, 2010).

517 **Figure 3.** Correlation between (a) absolute values of cardiac output measured by
518 impedance cardiography and dye dilution during cycling (50 pairs) and (b) relative
519 changes from rest in cardiac output measured by impedance cardiography and dye
520 dilution during cycling (40 measured pairs). Linear regression equations and correlation
521 coefficients are shown. (Cardiac output data by dye dilution reproduced from Vogiatzis
522 *et al.*, 2010).

523 **Figure 4.** Correlation between oxygen uptake (VO_2) and absolute values of cardiac
524 output measured by (a) dye-dilution (b) impedance cardiography (50 pairs). Linear
525 regression equations and correlation coefficients are shown. (VO_2 data reproduced
526 from Vogiatzis *et al.*, 2010).

527 **Figure 5.** Bland-Altman plots comparing (a) cardiac output measured by impedance
528 cardiography and dye dilution at rest and during cycling trials (50 pairs) and (b) relative
529 changes from rest in cardiac output measured by impedance cardiography and dye
530 dilution in (40 pairs). (Cardiac output data by dye dilution reproduced from Vogiatzis *et*
531 *al.*, 2010).

532

533

534

535

536

Table 1. Central hemodynamic characteristics at rest and during exercise

Characteristics	Rest	25%WRpeak	50%WRpeak	75%WRpeak	100%WRpeak
HR IC, beats/min	74±4	89±5	98±6	109±8	112±7
ΔHR IC, beats/min	-	15±2	25±3	34±4	37±4
HR ECG, beats/min	75±4	90±6	100±6	110±7	112±6
ΔHR ECG, beats/min	-	15±3	26±4	35±5	38±4
SV IC, ml/beat	67.8±5.1*	87.4±6.2*	95.8±7.9*	90.1±8.2*	87.6±7.3*
ΔSV IC, ml/beat	-	20.4±2.5	28.1 ±3.4	23.1±3.7	20.1±3.1
SV DD, ml/beat	54.4±4.2	75.7±6.6	83.7±7.1	78.5±7.6	74.8±6.2
ΔSV DD, ml/beat	-	21.1±2.1	29.1±3.1	24.1±3.3	20.4±3.0
SBP (mmHg)	122±3	148±5	156±7	161±9	170±11
DBP (mmHg)	82±3	84±3	85±4	87±3	90±3
MAP(mmHg)	97±3	106±3	109±3	115±4	117±4
SpO ₂ , (%)	95.5±0.6	94.2±0.8	93.0±1.0	92.6±1.3	92.2±1.1

537

538 Data are presented as mean and SEM for 10 subjects. WRpeak, peak work rate, IC,
 539 impedance cardiography (PhysioFlow™); ECG, electrocardiography, DD, Dye dilution
 540 method; HR, heart rate; Δ, changes from rest, SV, stroke volume; SBP, systolic blood
 541 pressure; DBP, diastolic blood pressure; MAP, mean arterial blood pressure; SpO₂,
 542 arterial oxygen saturation measured by pulse oximetry. Asterisks denote significant
 543 differences between SV IC and SV DD, P values range between 0.010 and 0.020.

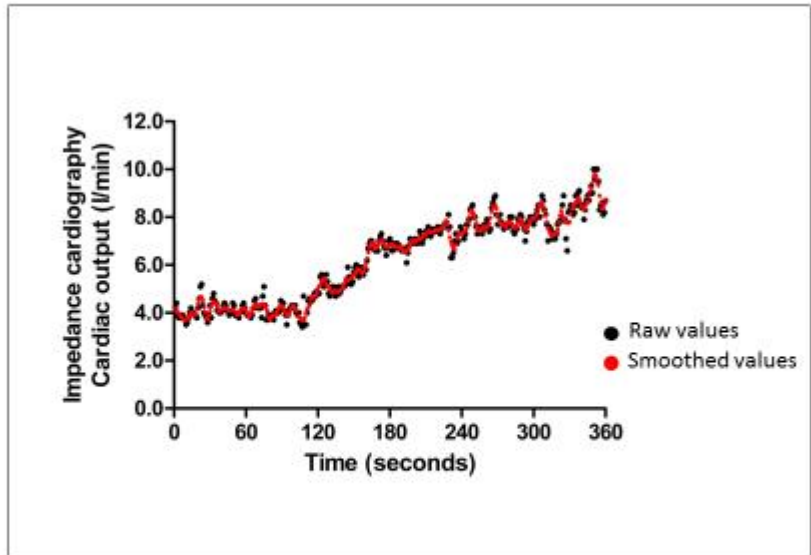
544

545

546

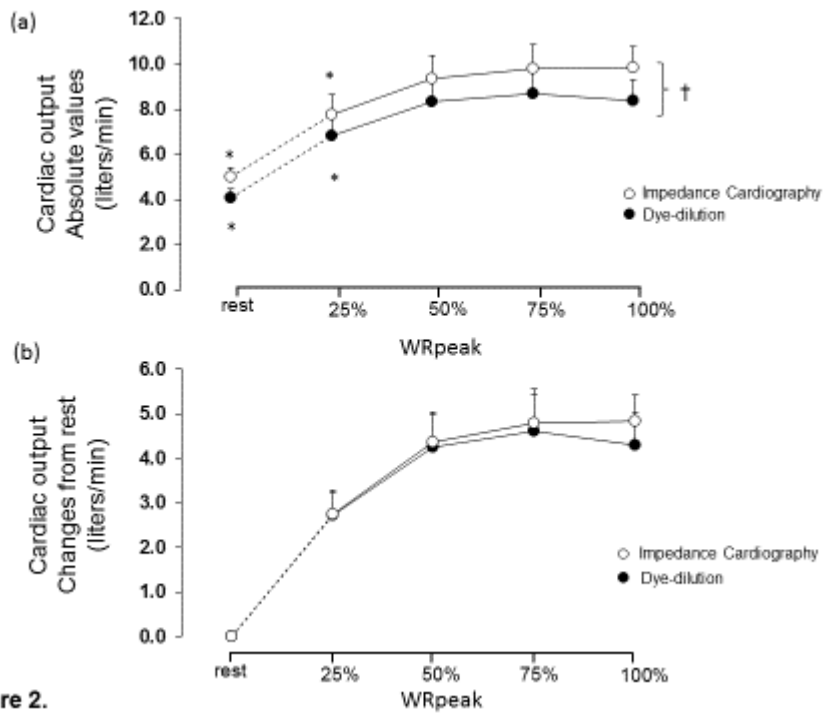
547

548



549 Figure 1.

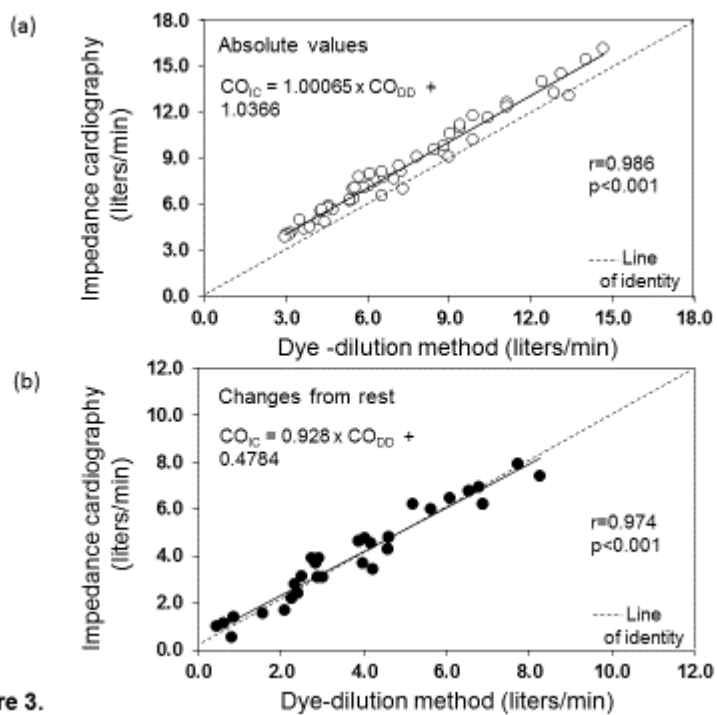
550



551 Figure 2.

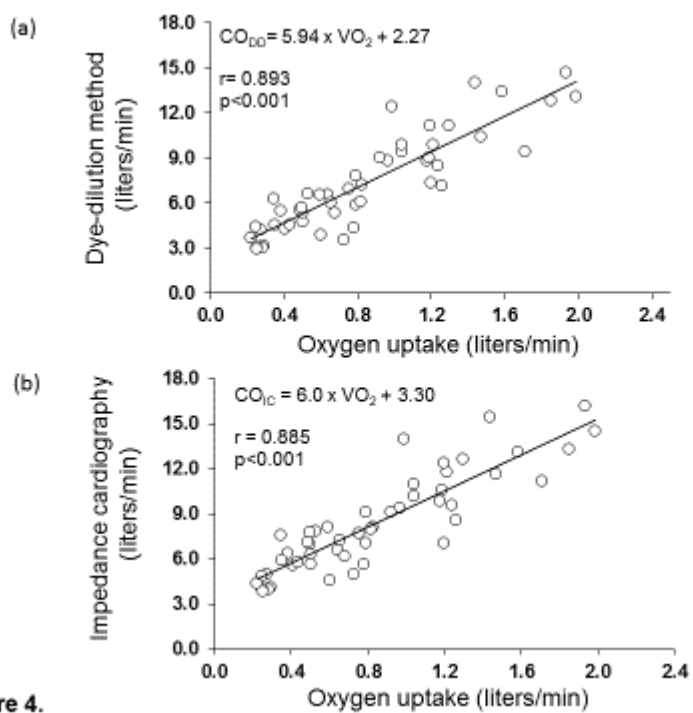
552

553



554 Figure 3.

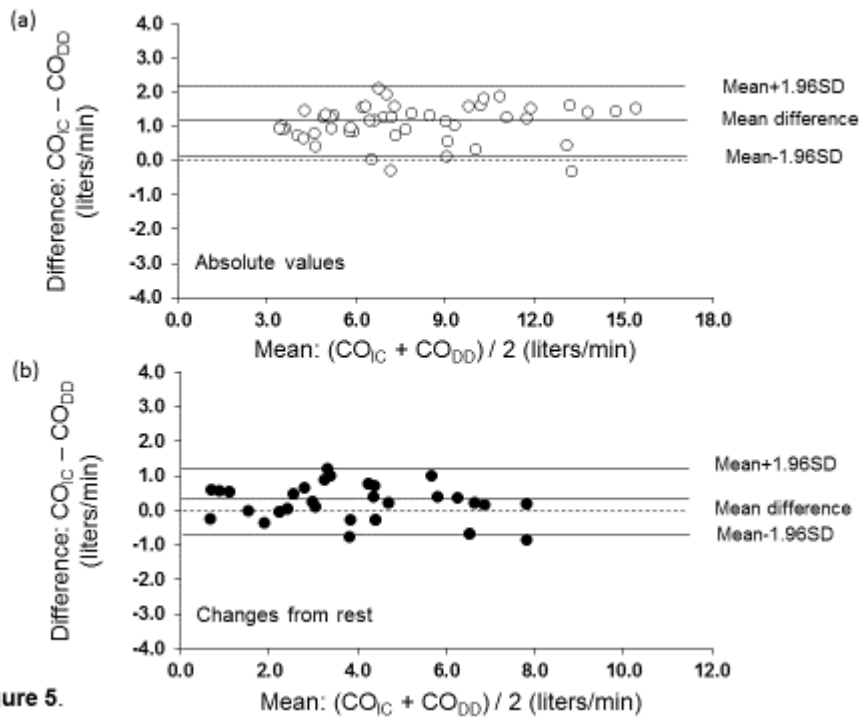
555



556 Figure 4.

557

558



559

Figure 5.