

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

4 Zafeiris Louvaris<sup>1,2,3</sup>, Stavroula Spetsioti<sup>2</sup>, Vasileios  
5 Andrianopoulos<sup>4</sup>, Nikolaos Chynkiamis<sup>2,5</sup> Helmut Habazettl<sup>6,7</sup>,  
6 Harrieth Wagner<sup>8</sup>, Spyros Zakyntinos<sup>2</sup>, Peter Wagner<sup>8</sup> and Ioannis  
7 Vogiatzis<sup>2,3,5</sup>

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

12 <sup>2</sup>1st 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 <sup>3</sup>National and Kapodistrian University of Athens, Department of Physical  
16 Education and Sports Sciences. Athens, Greece.

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

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

21 <sup>6</sup>Institute 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 <sup>7</sup>Institute of Anesthesiology, German Heart Institute Berlin, Berlin, Germany.

25 <sup>8</sup>Department of Medicine, University of California San Diego, La Jolla,  
26 California.

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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<sub>IC</sub>) and by the indocyanine green dye dilution method  
42 (CO<sub>DD</sub>) in patients with COPD. Fifty paired CO measurements were concurrently  
43 obtained using the two methods from 10 patients (FEV<sub>1</sub>: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<sub>IC</sub> and CO<sub>DD</sub> were strongly correlated (r=0.986, p<0.001). The mean  
46 absolute and percentage differences between CO<sub>IC</sub> and CO<sub>DD</sub> 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 (VO<sub>2</sub>) and CO<sub>DD</sub> were linearly related: r=0.893 (p<0.001),  
54 CO<sub>DD</sub> = 5.94 x VO<sub>2</sub> + 2.27 liters/min. Similar results were obtained for VO<sub>2</sub> and CO<sub>IC</sub> (r  
55 =0.885, p<0.001, CO<sub>IC</sub> = 6.00 x VO<sub>2</sub> + 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.

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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: FEV<sub>1</sub>:50.5  $\pm$  17.5% predicted, age, 60  $\pm$  7 years, weight  
133 77  $\pm$  18 kg, body surface area 1.90  $\pm$  0.24m<sup>2</sup>] 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  $5.0 \pm 0.4$  liters/min and increased to  $9.8 \pm 0.9$  liters/min at 100%  
197  $WR_{peak}$  whilst  $CO_{DD}$  increased from  $4.1 \pm 0.4$  (rest) to  $8.4 \pm 1.0$  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 VO<sub>2</sub>**

205 The association between all individual absolute values of CO<sub>IC</sub> and CO<sub>DD</sub> 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 VO<sub>2</sub> and CO<sub>DD</sub> 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 VO<sub>2</sub> and CO<sub>IC</sub> 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  $\sim 1.0$  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<sub>IC</sub>-CO<sub>DD</sub>) 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<sub>IC</sub> -CO<sub>DD</sub>) 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  $\sim 1.0$  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  $\sim 1.0$  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  $\text{VO}_2$  by the Fick method (5.9 liters/min  
264 per liter/min  $\text{VO}_2$ ) was in the usually reported range, while that for the impedance  
265 method was unusually high (9.7 liters/min per liter/min  $\text{VO}_2$ ), 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  $\text{VO}_2$ , 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  $\text{CO-VO}_2$  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  $\text{CO-VO}_2$  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, CO<sub>2</sub> 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 CO<sub>2</sub> 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  $\text{VO}_2$  in Figure 4 for both  
316 methods, at a normal resting  $\text{VO}_2$  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  $\text{VO}_2$  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  $\text{WR}_{\text{peak}}$  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,  $\text{CO}_2$  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.

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**359 Conflict of interest**

**360** The authors state explicitly that there are no conflicts of interest in connection with this  
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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).

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**Table 1. Central hemodynamic characteristics at rest and during exercise**

<b>Characteristics</b>	<b>Rest</b>	<b>25%WRpeak</b>	<b>50%WRpeak</b>	<b>75%WRpeak</b>	<b>100%WRpeak</b>
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 <sub>2</sub> , (%)	95.5±0.6	94.2±0.8	93.0±1.0	92.6±1.3	92.2±1.1

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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; SpO<sub>2</sub>,  
 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.

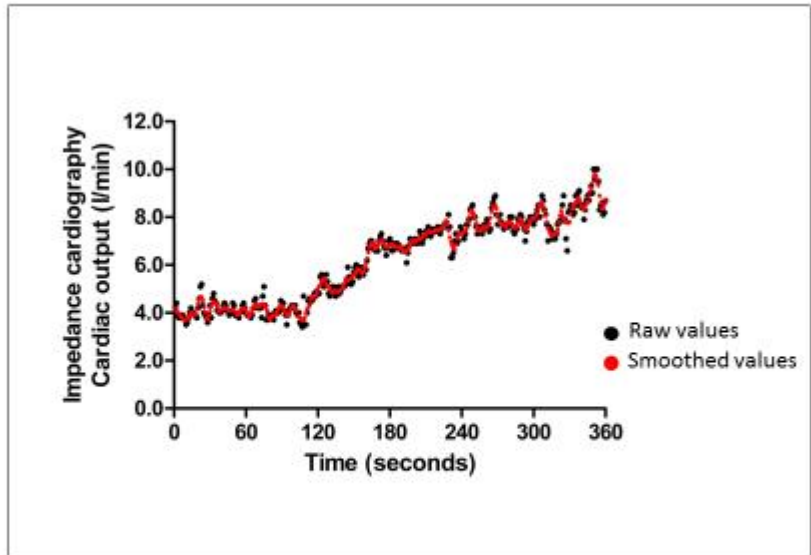
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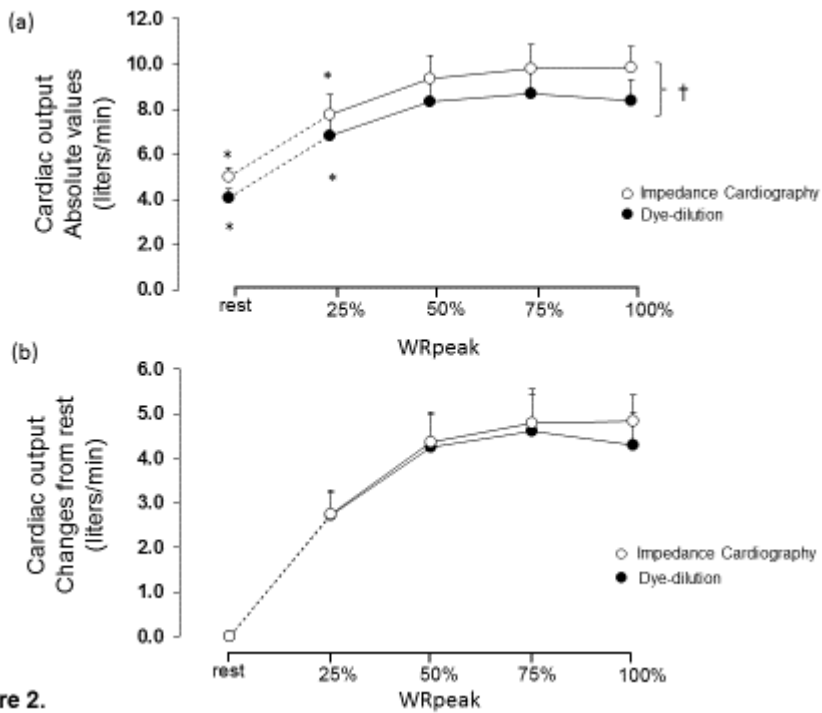
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549 Figure 1.

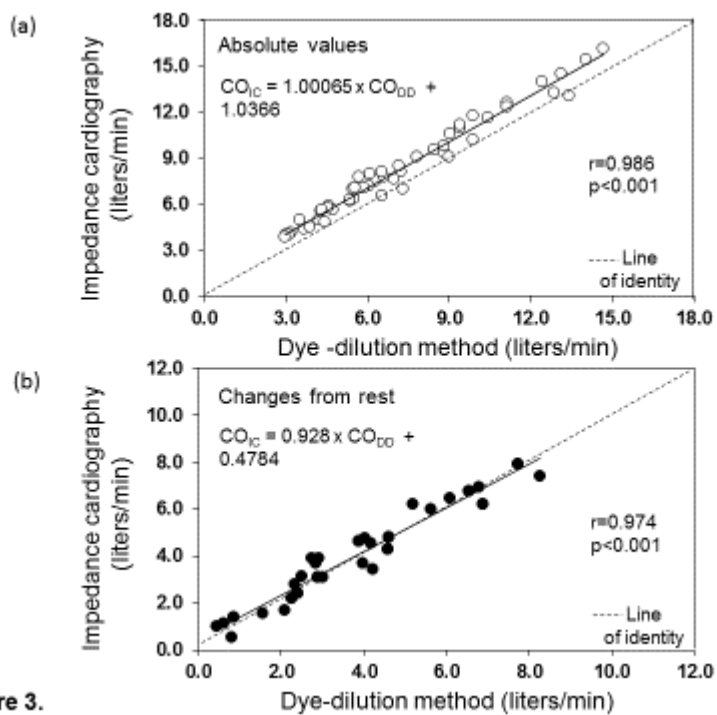
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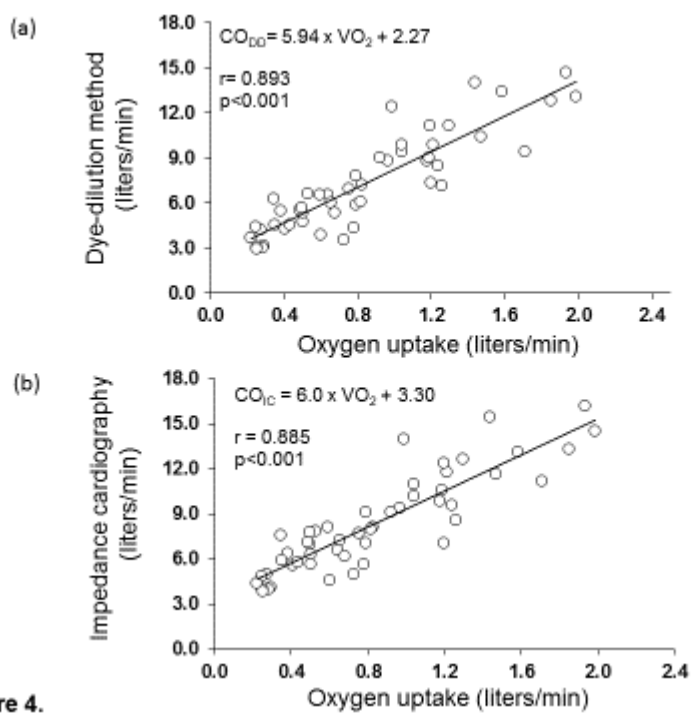
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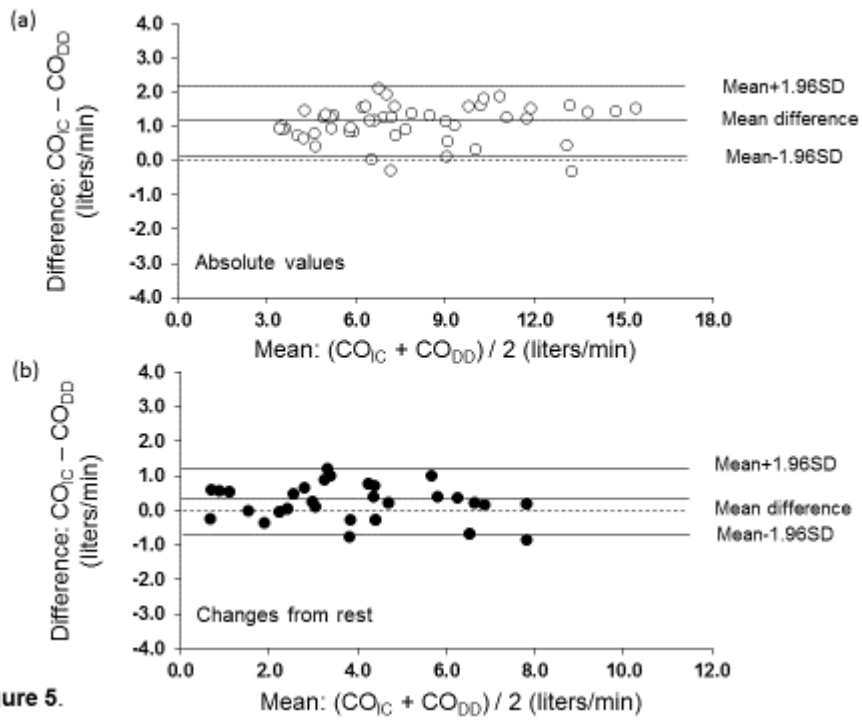
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556 Figure 4.

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Figure 5.