

# Cardiac output changes during exercise in heart failure patients: focus on mid-exercise

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## Abstract

**Aims** Peak exercise oxygen uptake ( $\text{VO}_2$ ) and cardiac output (CO) are strong prognostic indexes in heart failure (HF) but unrelated to real-life physical activity, which is associated to submaximal effort.

**Methods and results** We analysed maximal cardiopulmonary exercise test with rest, mid-exercise, and peak exercise non-invasive CO measurements (inert gas rebreathing) of 231 HF patients and 265 healthy volunteers. HF patients were grouped according to exercise capacity (peak  $\text{VO}_2 < 50\%$  and  $\geq 50\%$  pred, Groups 1 and 2). To account for observed differences, data regarding  $\text{VO}_2$ , CO, stroke volume (SV), and artero-venous  $\text{O}_2$  content difference [ $\Delta\text{C}(\text{a-v})\text{O}_2$ ] were adjusted by age, gender, and body mass index. A multiple regression analysis was performed to predict peak  $\text{VO}_2$  from mid-exercise cardiopulmonary exercise test and CO parameters among HF patients. Rest  $\text{VO}_2$  was lower in HF compared with healthy subjects; meanwhile, Group 1 patients had the lowest CO and highest  $\Delta\text{C}(\text{a-v})\text{O}_2$ . At mid-exercise, Group 1 patients achieved a lower  $\text{VO}_2$ , CO, and SV [0.69 (interquartile range 0.57–0.80) L/min; 5.59 (4.83–6.67) L/min; 62 (51–73) mL] than Group 2 [0.94 (0.83–1.1) L/min; 7.6 (6.56–9.01) L/min; 77 (66–92) mL] and healthy subjects [1.15 (0.93–1.30) L/min; 9.33 (8.07–10.81) L/min; 87 (77–102) mL]. Rest to mid-exercise SV increase was lower in Group 1 than Group 2 ( $P = 0.001$ ) and healthy subjects ( $P < 0.001$ ). At mid-exercise,  $\Delta\text{C}(\text{a-v})\text{O}_2$  was higher in Group 2 [13.6 (11.8–15.4) mL/100 mL] vs. healthy patients [11.6 (10.4–13.2) mL/100 mL] ( $P = 0.002$ ) but not different from Group 1 [13.6 (12.0–14.9) mL/100 mL]. At peak exercise, Group 1 patients achieved a lower  $\text{VO}_2$ , CO, and SV than Group 2 and healthy subjects.  $\Delta\text{C}(\text{a-v})\text{O}_2$  was the highest in Group 2. At multivariate analysis, a model comprising mid-exercise  $\text{VO}_2$ , carbon dioxide production ( $\text{VCO}_2$ ), CO, haemoglobin, and weight predicted peak  $\text{VO}_2$ ,  $P < 0.001$ . Mid-exercise  $\text{VO}_2$  and CO, haemoglobin, and weight added statistically significantly to the prediction,  $P < 0.050$ .

**Conclusions** Mid-exercise  $\text{VO}_2$  and CO portend peak exercise values and identify severe HF patients. Their evaluation could be clinically useful.

**Keywords** Heart failure; Cardiac output; Oxygen uptake; Exercise limitation

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## Backgrounds

In heart failure (HF), coupling of oxygen uptake ( $\text{VO}_2$ ) and haemodynamic measurements is of pivotal importance to understand causes of exercise limitation, as well as to assess HF prognosis.<sup>1</sup> Available data of the combination of  $\text{VO}_2$  and cardiac output (CO) refer mainly to rest and peak exercise, and limited information is available as regards mid-exercise.<sup>2–5</sup>

However, in severe HF, peak exercise may be difficult to achieve and precisely define and even risky. Moreover, the great majority of haemodynamic exercise evaluation is obtained, mainly for safety reasons, with patients in supine or semi-supine position,<sup>6–8</sup> being exercise with invasive haemodynamic monitoring in the upright position considered dangerous. Similarly, cardiac function and haemodynamic measurements estimated from cardiac ultrasound are usually

performed on a semi-recumbent position.<sup>9</sup> Thus, comparisons among invasive and cardiac ultrasound-derived haemodynamic measurements with non-invasive peak  $\text{VO}_2$  measurements obtained on a treadmill or cycle ergometer,<sup>10</sup> as well as with real-life physical activity, are difficult, if not impossible.

At present, it is unknown whether the combination of  $\text{VO}_2$  and haemodynamic measurements at mid-exercise bears useful clinical data and allows to separate healthy individuals from HF patients and patients with severe vs. moderate HF. From a metabolic/haemodynamic point of view, several issues characterize mid-exercise: (i) it is the threshold from a mainly stroke volume dependent to a mainly heart rate (HR)-dependent CO increase; (ii) it is the transit point between a CO independent to a CO-dependent  $\text{VO}_2$  increase<sup>11</sup>; (iii) it grossly corresponds to the anaerobic threshold; and finally, (iv) it is characterized, in HF patients, by an almost fixed artero-venous  $\text{O}_2$  content difference [ $\Delta\text{C(a-v)}\text{O}_2$ ].<sup>12,13</sup>

The present study was undertaken to describe  $\text{VO}_2$ , CO, stroke volume, and  $\Delta\text{C(a-v)}\text{O}_2$  behaviour during exercise in a sizable population of normal subjects and HF patients with different HF severity.

## Methods

### Study design and population

We retrospectively analysed the data of HF patients regularly followed at our HF unit and healthy volunteers who performed a maximal cardiopulmonary exercise test (CPET) with rest, mid-exercise, and peak exercise CO measurements by inert gas rebreathing (IGR) technique at our institution between 2006 and 2018. All subjects, both healthy individuals and HF patients, had been familiarized with CPET and IGR technique. Patients were in stable clinical conditions, mildly to moderately symptomatic (NYHA II–III), and on medical therapy according to up-to-date guidelines at the time of inclusion. Haemoglobin and plasma B-type natriuretic peptide levels measured within 7 days of CPET were collected in HF patients. Left ventricle ejection fraction measured by biplane disc summation method at a transthoracic echocardiography examination performed within 6 months of CPET was also collected. We excluded subjects with symptomatic angina, severe aortic stenosis, complex arrhythmias, primary pulmonary hypertension, pulmonary embolism, relevant cardiac or extra cardiac shunts, or any disease that could *per se* influence their exercise capacity.

### Cardiopulmonary exercise test with simultaneous cardiac output measurement

Cardiopulmonary exercise test was performed on a cycle ergometer with a progressive work rate increase protocol based on the familiarization with CPET. Workload was

personalized to achieve peak effort in about 10 min. Expiratory  $\text{O}_2$ ,  $\text{CO}_2$ , and ventilation (VE) were measured breath by breath (Innocor® Rebreathing System, Innovision A/S, Odense, Denmark). A 12 lead electrocardiogram was recorded (Quark PFT, COSMED, Roma, Italy). CO measurements were performed at rest (sitting on the cycle ergometer, after a few minutes of quiet breathing), after 4–5 min of loaded cycling (mid-exercise) and at peak exercise.  $\text{VO}_2$  and carbon dioxide flow ( $\text{VCO}_2$ ) were reported as mean values over 20 s of exercise preceding the rebreathing manoeuvre. Percentage of predicted peak  $\text{VO}_2$  was calculated according to Hansen *et al.*<sup>14</sup> Predicted CO was calculated according to Agostoni *et al.*<sup>15</sup> Subjects were strongly encouraged to perform a maximal test, but the maximum was self-determined when they approached maximal exercise, allowing the final 30 s for the rebreathing manoeuvre. In the rare cases when peak exercise CO measurement was not obtained, CPETs were repeated the day after, whenever possible. The  $\text{VE}/\text{VCO}_2$  slope was calculated as the slope of the relationship between VE and  $\text{VCO}_2$  from ~1 min after the beginning of loaded exercise to the end of the isocapnic buffering period, excluding breaths during IGR manoeuvres.<sup>16–18</sup> The IGR technique has been previously reported in detail.<sup>16</sup> In brief, the IGR technique uses an oxygen-enriched mixture of an inert soluble gas (0.5% nitrous oxide) and an inert insoluble gas (0.1% sulfur hexafluoride) inflated into a bag by the machine. Patients have to breathe into a respiratory valve via a mouthpiece and a bacterial filter with a nose clip. At the end of expiration, the valve is activated automatically so that subjects rebreathe from the prefilled bag for a period of 10–20 s. After that period, patients start breathing ambient air again. CO measurement is performed by a photoacoustic analyser that measures gas concentration over a five-breath interval. Sulfur hexafluoride, which is insoluble in blood, is used to determine lung volume, while the concentration of nitrous oxide, which is soluble in blood, decreases during rebreathing with a rate that is proportional to pulmonary blood flow (PBF). CO is equal to PBF only if arterial oxygen saturation ( $\text{SpO}_2$ ) is >98% at pulse oximeter, showing the absence of pulmonary shunt flow. If  $\text{SpO}_2$  is <98%, CO is equal to PBF plus shunt flow.<sup>16</sup>  $\Delta\text{C(a-v)}\text{O}_2$  was calculated as  $\text{VO}_2/\text{CO}$ . The study complies with the Declaration of Helsinki, and the locally appointed ethics committee approved the research protocol (approval number R435/16-CCM451). We obtained written informed consent before each CPET for the exercise procedure as well as for the blind research use of CPET-derived data and for all patients' clinical data.

### Statistical analysis

Continuous variables were expressed as means  $\pm$  standard deviation or as median and interquartile range (IQR) if not normally distributed. Comparisons between subgroups were

performed using two-tailed ANOVA tests for normally distributed variables and Mann–Whitney or Kruskal–Wallis test for non-normally distributed variables. The  $\chi^2$  test was used to compare frequencies distributions. Wilcoxon signed-rank test was used to compare medians of related samples. To account for observed differences among groups, data regarding  $\text{VO}_2$ , CO, stroke volume, and  $\Delta\text{C(a-v)}\text{O}_2$  were adjusted by age, gender, and body mass index (BMI). Univariate regression analysis was used to test for the association of peak  $\text{VO}_2$  with each mid-exercise CPET and CO parameter and with laboratory and anthropometric measures (such as age, weight, height, and sex). A forward stepwise multiple regression analysis was performed to predict peak  $\text{VO}_2$  from a model including the mid-exercise CPET and CO parameters and laboratory and anthropometric measures that had a linear relationship with peak  $\text{VO}_2$  with  $P < 0.100$ .  $P < 0.050$  was considered statistically significant. Statistical analyses were performed using SPSS 22.0 software (SPSS Inc., Chicago, IL, USA).

## Results

We retrieved data from 231 HF patients and 265 healthy subjects who performed CPET with rest, mid-exercise, and peak exercise non-invasive CO measurement in our laboratory. *Table 1* summarizes demographic, clinical, echocardiographic, and biochemical profiles. Healthy volunteers were younger, were more frequently female, and had a lower BMI.

Twenty-seven per cent of HF patients had idiopathic cardiomyopathy; 43% had ischemic heart disease; 16% had primary valvular disease; and the remaining patients had chronic myocarditis, toxic cardiomyopathy (chemotherapy or alcohol induced), tachycardiomyopathy, hypertensive heart disease, pulmonary hypertension, arrhythmogenic cardiomyopathy, peripartum cardiomyopathy, and hypertrophic cardiomyopathy. HF patients were treated with diuretics (83%), beta-blockers (83%), angiotensin-converting enzyme inhibitors (56%), angiotensin receptor blockers (13%), angiotensin receptor neprilysin inhibitor (5%), and mineralocorticoid receptor antagonists (40%). Finally, 38% of patients had an implantable cardioverter defibrillator or cardiac resynchronization therapy. HF patients were grouped according to exercise capacity: Group 1 included 68 patients who achieved  $<50\%$  of their predicted peak  $\text{VO}_2$ , and Group 2 included 163 patients who achieved  $\geq 50\%$  of their predicted peak  $\text{VO}_2$  (*Table 1*).

Cardiopulmonary exercise test and non-invasive CO measurements obtained at rest, mid-exercise, and peak exercise in healthy volunteers and HF patients are reported in *Table 2* (not adjusted data). Data regarding  $\text{VO}_2$ , stroke volume, CO, and  $\Delta\text{C(a-v)}\text{O}_2$  (adjusted for age, gender, and BMI intergroup differences) are shown in *Figure 1A–D*, respectively. As expected, CPET parameters and non-invasive CO measurements were different between healthy volunteers and HF patients. Respiratory exchange ratio at mid-exercise was similar between healthy volunteers and HF patients.

Group 1 patients had lower haemoglobin, higher B-type natriuretic peptide levels, and a more reduced left ventricular

**Table 1** Healthy volunteers', HF patients', and Group 1 and Group 2 patients' demographic, clinical, echocardiographic, and laboratoristic characteristics

	Healthy volunteers		HF patients		P value (HV vs. HF patients)	Group 1		Group 2		P value (HV vs. Group 1)	P value (HV vs. Group 2)	P value (Group 1 vs. Group 2)
	n = 265		n = 231			n = 68	n = 163					
Age (years)	45	33.5–55	67	57–73	<0.001	63	55–70	69	58–74	<0.001	<0.001	NS
Male (%)	n 144	54%	169	73%	<0.001	56	82%	113	69%	<0.001	0.003	NS
BMI (kg/23.5 m <sup>2</sup> )	21.4–25.4	25.7	23.4–28.4	25.7	<0.001	25.7	23.6–27.7	25.7	23.3–28.7	<0.001	<0.001	NS
Hb (g/dL)	N.A.	—	13.8	12.0–15.0	—	13.0	11.7–14.0	14.0	13.0–15.0	—	—	0.001
BNP (pg/mL)	N.A.	—	219	78–625	—	529	192–1098	175	41–428	—	—	<0.001
LVEF (%)	N.A.	—	37	29–54	—	32	25–37	39	30–56	—	—	<0.001
HFrEF (%)	n —	—	141	61%	—	57	84%	85	52%	—	—	<0.001
HFmrEF (%)	n —	—	23	10%	—	3	4%	20	12%	—	—	NS
HFpEF (%)	n —	—	67	29%	—	8	12%	58	36%	—	—	0.001

BNP, B-type natriuretic peptide; BMI, body mass index; Hb, haemoglobin; HF, heart failure; HV, healthy volunteers; HFmrEF, heart failure with mid-range ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; LVEF, left ventricle ejection fraction; N.A., not available, NS, non-significant P value.

Data are expressed as median and interquartile range or frequencies as appropriate. Haemoglobin, BNP, and LVEF values were compared only between Group 1 and Group 2 HF patients.

ejection fraction than Group 2 (Table 1). Rest  $\text{VO}_2$  values were similar among HF cohorts and lower compared with healthy subjects (Figure 1A); at rest, CO progressively increased from Group 1 to healthy subjects, while  $\Delta\text{C(a-v)}\text{O}_2$  decreased (Figure 1C,D).

Cardiac output determination at mid-exercise was obtained after 4.9 (IQR 4.8–5.0) and 4.8 (IQR 4.0–5.0) min of

loaded pedalling in healthy individuals and in HF patients, respectively, corresponding to 73 (IQR 49–98) and 31 (IQR 24–48) W and 51% (IQR 45–59%) and 54% (IQR 46–63%) of exercise tolerance, respectively. In HF Group 1 and Group 2 patients, mid-exercise CO determination was obtained after 4.8 (IQR 4.0–5.0) and 4.8 (IQR 4.4–5.0) min of loaded pedalling, respectively, corresponding to 24 (IQR 20–31) and 39

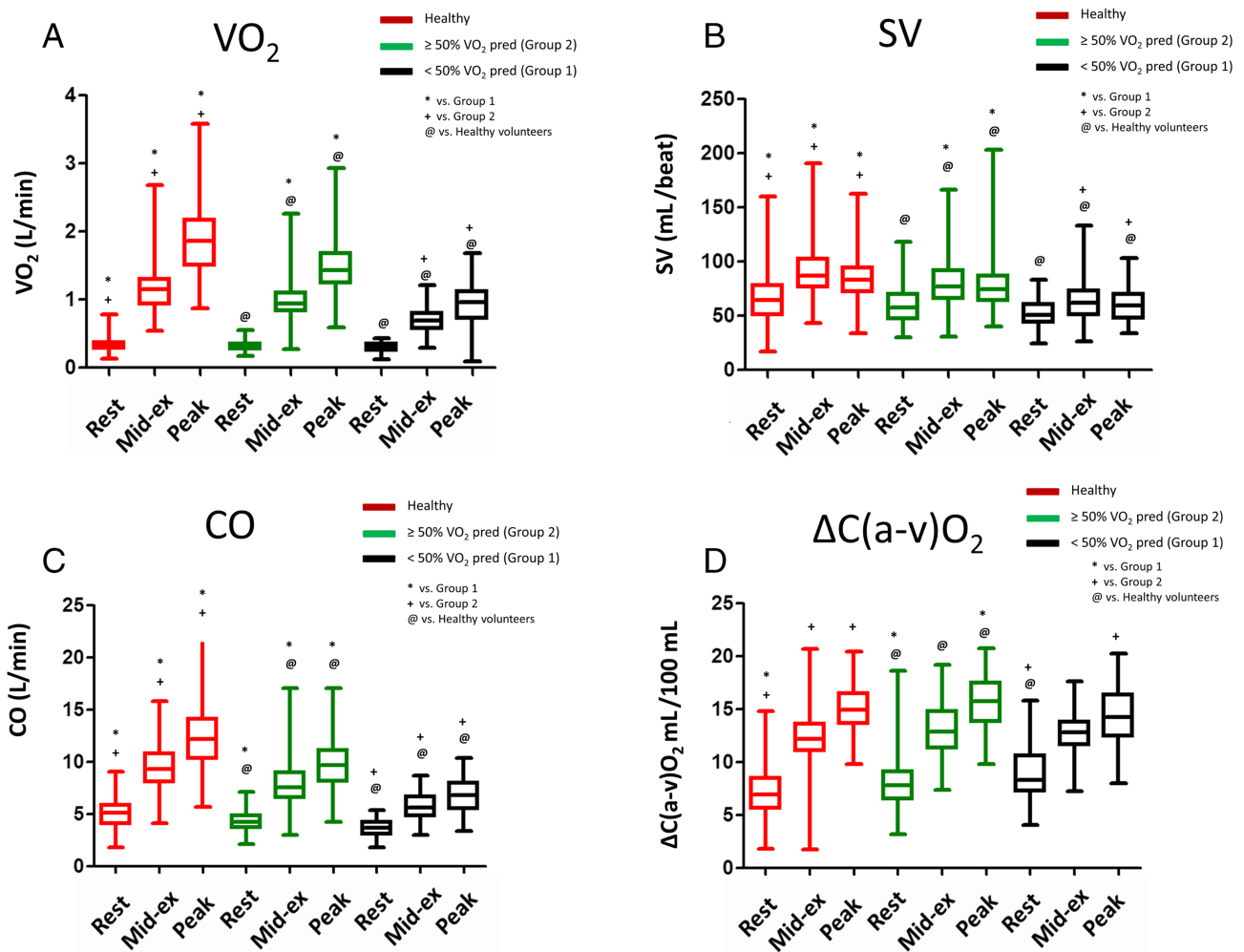
**Table 2** Healthy volunteers', HF patients', and Group 1 and Group 2 patients' CPET and CO measurements (not adjusted for gender, age, and BMI) at rest, mid-exercise, and peak exercise

	Healthy volunteers		HF patients		P value (HV vs HF patients)	Group 1		Group 2		P value (HV vs Group 1)	P value (HV vs Group 2)	P value (Group 1 vs Group 2)
	n = 265		n = 231			n = 68		n = 163				
Rest $\text{VO}_2$ (L/min)	0.314	0.279–0.376	0.300	0.256–0.350	0.039	0.300	0.257–0.350	0.300	0.252–0.350	NS	NS	NS
Rest $\text{VO}_2$ (mL/min/kg)	4.7	4.0–5.5	4.3	3.6–4.7	<0.001	4.2	3.5–4.7	4.2	3.5–4.8	<0.001	<0.001	NS
Rest CO (L/min)	5.5	4.6–6.6	3.5	2.8–4.2	<0.001	3.4	2.7–4.1	3.5	2.8–4.4	<0.001	<0.001	NS
Rest CI (L/min/m <sup>2</sup> )	3.1	2.6–3.6	1.8	1.6–2.2	<0.001	1.8	1.5–2.1	1.9	1.6–2.3	<0.001	<0.001	NS
Rest $\Delta\text{(a-v)}\text{O}_2$ (mL/100 mL)	5.8	4.9–7.6	9.1	7.4–10.6	<0.001	9.5	7.9–11.1	8.8	7.2–10.3	<0.001	<0.001	NS
Rest SV (mL)	67	55–84	50	41–63	<0.001	50	41–60	50	41–65	<0.001	<0.001	NS
Mid-exercise $\text{VO}_2$ (L/min)	1.200	0.990–1.500	0.750	0.600–0.900	<0.001	0.650	0.596–0.780	0.800	0.650–1.000	<0.001	<0.001	<0.001
Mid-exercise $\text{VO}_2$ (mL/min/kg)	17.5	14.8–20.1	10.0	8–11.8	<0.001	8.7	7.6–10.0	10.5	9.2–12.2	<0.001	<0.001	0.001
Anaerobic threshold $\text{VO}_2$ (L/min)	1.287	1.016–1.690	0.733	0.605–0.924	<0.001	0.625	0.528–0.730	0.791	0.640–1.041	<0.001	<0.001	<0.001
Mid-exercise CO (L/min)	10.3	8.7–12.4	5.6	4.5–6.9	<0.001	4.8	4.2–5.8	6.1	4.7–7.4	<0.001	<0.001	0.005
Mid-exercise CI (L/min/m <sup>2</sup> )	5.8	5.1–6.6	3.0	2.5–3.6	<0.001	2.7	2.3–3.1	3.2	2.7–3.8	<0.001	<0.001	0.012
Mid-exercise $\Delta\text{(a-v)}\text{O}_2$ (mL/100 mL)	11.6	10.4–13.2	13.6	11.8–15.3	<0.001	13.6	12.0–14.9	13.6	11.8–15.4	<0.001	<0.001	NS
Mid-exercise SV (mL)	93	76–113	67	54–84	<0.001	61	51–72	70	53–89	<0.001	<0.001	0.004
Mid-exercise workload (W)	73	49–98	31	24–48	<0.001	24	20–31	39	24–49	<0.001	<0.001	0.001
Mid-exercise RER	0.88	0.82–0.97	0.90	0.80–0.98	NS	0.92	0.85–0.98	0.89	0.80–0.97	NS	NS	NS
Time from beginning (min)	4.9	4.8–5.0	4.8	4.0–5.0	<0.001	4.8	4.0–5.0	4.8	4.4–5.0	<0.001	0.002	NS
Peak $\text{VO}_2$ (L/min)	1.953	1.522–2.579	1.018	0.800–1.323	<0.001	0.832	0.697–0.961	1.139	0.910–1.470	<0.001	<0.001	<0.001
Peak $\text{VO}_2$ (mL/min/kg)	28.1	23.7–34.2	14.1	11.4–16.8	<0.001	11.0	9.5–13.3	15.3	13.1–17.8	<0.001	<0.001	<0.001
Peak CO (L/min)	13.6	11.2–16.0	6.7	5.2–8.5	<0.001	5.5	4.7–6.6	7.1	5.8–9.2	<0.001	<0.001	0.001
Peak CI (L/min/m <sup>2</sup> )	7.5	6.7–8.5	3.5	3.0–4.5	<0.001	3.0	2.6–3.4	3.9	3.3–4.7	<0.001	<0.001	0.001
Per cent of predicted peak CO (%)	98	88–109	55	45–68	<0.001	42	36–50	60	52–72	<0.001	<0.001	<0.001
Peak $\Delta\text{(a-v)}\text{O}_2$ (mL/100 mL)	14.6	10.9–16.3	15.6	13.8–17.8	<0.001	14.9	12.9–17.0	16.0	14.3–18.1	NS	<0.001	0.024
Peak SV (mL)	85	71–104	65	53–85	<0.001	58	51–71	68	54–88	<0.001	<0.001	0.003
Peak workload (W)	135	110–190	60	42–87	<0.001	41	34–57	70	50–94	<0.001	<0.001	<0.001
Peak RER	1.11	1.04–1.20	1.04	0.97–1.12	<0.001	1.03	0.93–1.12	1.05	0.98–1.13	<0.001	<0.001	NS
Exercise duration (min)	10.0	8.7–11.0	8.8	7.5–10.0	<0.001	7.8	7.0–9.0	9.0	8.0–10.4	<0.001	<0.001	<0.001
Ramp protocol (W/min)	15	10.0–20.0	8	5.0–10.0	<0.001	5	5.0–8.0	8	5.0–10.0	<0.001	<0.001	0.001

$\Delta\text{(a-v)}\text{O}_2$ , artero-venous oxygen content difference; BMI, body mass index; CI, cardiac index; CO, cardiac output; CPET, cardiopulmonary exercise test; HF, heart failure; HV, healthy volunteers; NS, non-significant P value; SV, stroke volume; RER, respiratory exchange ratio;  $\text{VO}_2$ , oxygen uptake.

Data expressed as median and interquartile range. Anaerobic threshold  $\text{VO}_2$  values were compared between Group 1 and Group 2 HF patients.

**FIGURE 1** (A) Box plot depicting oxygen uptake ( $\text{VO}_2$ ) values (adjusted for age, gender, and body mass index) obtained at rest, mid-exercise, and peak exercise in healthy volunteers (red), Group 1 heart failure (HF) patients (black), and Group 2 HF patients (green), with pairwise comparisons among  $\text{VO}_2$  values of different groups at the same step of exercise. Statistical significance: \* vs. Group 1, + vs. Group 2, @ vs. healthy volunteers. (B) Box plot depicting stroke volume (SV) values (adjusted for age, gender, and body mass index) obtained at rest, mid-exercise, and peak exercise in healthy volunteers (red), Group 1 HF patients (black), and Group 2 HF patients (green), with pairwise comparisons among SV values of different groups at the same step of exercise. Statistical significance: \* vs. Group 1, + vs. Group 2, @ vs. healthy volunteers. (C) Box plot depicting cardiac output (CO) values (adjusted for age, gender, and body mass index) obtained at rest, mid-exercise, and peak exercise in healthy volunteers (red), Group 1 HF patients (black), and Group 2 HF patients (green), with pairwise comparisons among CO values of different groups at the same step of exercise. Statistical significance: \* vs. Group 1, + vs. Group 2, @ vs. healthy volunteers. (D) Box plot depicting artero-venous  $\text{O}_2$  content difference [ $\Delta\text{C(a-v)}\text{O}_2$ ] values (adjusted for age, gender, and body mass index) obtained at rest, mid-exercise, and peak exercise in healthy volunteers (red), Group 1 HF patients (black), and Group 2 HF patients (green), with pairwise comparisons among  $\Delta\text{C(a-v)}\text{O}_2$  values of different groups at the same step of exercise. Statistical significance: \* vs. Group 1, + vs. Group 2, @ vs. healthy volunteers.



(IQR 24–49) W and 57% (IQR 50–68%) and 51% (IQR 45–61%) of exercise tolerance, respectively. Mid-exercise  $\text{VO}_2$  values in HF patients did not differ significantly from their anaerobic threshold  $\text{VO}_2$  values (Table 2;  $P = 0.224$ ). Differently, in healthy volunteers, mid-exercise  $\text{VO}_2$  values was significantly lower compared with anaerobic threshold  $\text{VO}_2$  values [ $\text{VO}_2 = 1.200$  (IQR 0.990–1.500) and 1.287 (IQR 1.016–1.690) L/min at mid-exercise and anaerobic threshold, respectively,  $P < 0.001$ ]. At mid-exercise, Group 1 patients achieved a lower  $\text{VO}_2$ , stroke volume, and CO than Group 2

and healthy subjects (Figure 1A–C). Stroke volume increase between rest and mid-exercise was statistically different between Groups 1 and 2 [11 (IQR 1–20) and 19 (IQR 10–32) mL, respectively;  $P = 0.001$ ]. Notably,  $\Delta\text{C(a-v)}\text{O}_2$  was lower in healthy individuals compared with Group 2 patients but did not differ between the two HF groups at mid-exercise (Figure 1D).

Heart rate increase between rest [Group 1 rest HR 63 b.p.m. (IQR 59–72) vs. Group 2 68 b.p.m. (IQR 61–78)] and mid-exercise [Group 1 mid-exercise HR 80 b.p.m. (IQR 68–

93) vs. Group 2 HR 85 b.p.m. (IQR 73–97)] did not statistically differ between Group 1 and Group 2 [13 b.p.m. (IQR 8–20) and 15 b.p.m. (IQR 8–21), respectively;  $P = 0.542$ ]; mid-exercise HR was significantly lower in healthy individuals compared with Group 2 patients ( $P < 0.001$ ).

At peak exercise, Group 1 patients achieved a lower  $VO_2$ , stroke volume, and CO than Group 2 and healthy subjects (Figure 1A–C).  $\Delta C(a-v)O_2$  was the highest in Group 2 with no differences between healthy subjects and Group 1 HF patients (Figure 1D).

Among HF patients, at multivariate analysis, a model comprising mid-exercise  $VO_2$ ,  $VCO_2$ , CO, haemoglobin, and weight nicely predicted peak  $VO_2$ ,  $P < 0.001$ . Mid-exercise  $VO_2$  and CO, haemoglobin, and weight were independent predictors of peak  $VO_2$ , and each added statistically significantly to the prediction,  $P < 0.050$  (Table 3).

## Discussion

In the present study, we showed that CO can be measured during exercise by IGR and that peak exercise and mid-exercise  $VO_2$ , CO, and stroke volume are significantly lower in HF patients vs. healthy individuals and among HF patients, in those with the most severe exercise limitation (peak  $VO_2 < 50\%$  pred, Group 1), allowing to differentiate among HF patients with different severity and healthy individuals. Peak  $\Delta C(a-v)O_2$  value was the highest in moderate HF patients (peak  $VO_2 \geq 50\%$  pred, Group 2).

Inert gas rebreathing technique allows to directly measure PBF, which, added to an estimate of intrapulmonary shunt flow, allows to estimate CO. Intrapulmonary shunt is negligible in HF patients, and consequently, it is a small fraction of CO.<sup>16,19</sup> Several previous reports have shown that CO measurement by IGR technique during ramp protocol exercise at different steps is reliable.<sup>17,20–22</sup> Specifically, we have previously described a strong correlation between simultaneous CO measurements in HF patients at different steps of exercise by IGR technique, invasive thermodilution, and direct Fick measurement.<sup>17</sup>

**Table 3** Multivariate analysis to predict peak  $VO_2$  from a model including mid-exercise CPET and CO parameters among HF patients

	Coefficient	Standard error	t	P value
Mid-exercise $VO_2$	0.698	0.118	5.902	<0.001
Mid-exercise CO	0.067	0.013	5.313	<0.001
Haemoglobin	0.038	0.009	3.975	<0.001
Weight	0.003	0.001	2.829	0.005
Mid-exercise $VCO_2$	0.193	0.113	0.713	NS

CO, cardiac output; CPET, cardiopulmonary exercise test; HF, heart failure; NS, non-significant P value;  $VCO_2$ , carbon dioxide production;  $VO_2$ , oxygen uptake.

$F(5, 225) = 127.425$ ,  $P < 0.001$ .

Data of the present study confirm that in a large population, peak exercise  $VO_2$  and CO are the lowest in patients with the most severe HF with the worst exercise limitation and extend for the first time these findings to mid-exercise.<sup>23–26</sup> Several reports showed that peak CO measurements have a robust prognostic value in HF. Griffin *et al.* reported the superiority of CO-derived parameters to peak  $VO_2$  in predicting prognosis.<sup>24</sup> Notably, Chomsky *et al.* described that a reduced invasively measured peak exercise CO was the only predictor of survival independent of peak  $VO_2$ .<sup>26</sup> Moreover, Metra *et al.* intriguingly stated that exercise haemodynamics in patients with HF allow to identify patients whose functional limitation is caused mainly by skeletal muscle deconditioning, rather than by cardiovascular factors.<sup>25</sup>

However, obtaining peak exercise CO measurements is usually difficult in HF patients, mainly in advanced disease stages. On the other hand, daily life activities, which are most important for patients' well-being, are comparable with a submaximal exercise and not to a maximal exercise performance. Therefore, we sought to investigate the determinants of  $VO_2$  kinetics, i.e. CO and  $\Delta C(a-v)O_2$ , at different steps of exercise, focusing on mid-exercise measures and comparing healthy volunteers and patients at different HF stages.

Cardiac output kinetics have already been described by Stringer *et al.*<sup>3,4</sup> in healthy volunteers: stroke volume is the major determinant of CO in the first part of exercise, while HR increases linearly with  $VO_2$  up to 85–90% of maximal exercise capacity, when HR response starts to flatten and further  $VO_2$  is mediated by blood flow distribution towards exercise muscles and muscle oxygen extraction. CO kinetics measured with subjects sitting on a cycle ergometer and by means of invasive haemodynamic recording in a limited number of HF patients have been reported in their pioneering studies by Sullivan *et al.* and Weber and Janicki,<sup>2,5</sup> showing a kinetic behaviour of CO and  $\Delta C(a-v)O_2$  similar to that of healthy individuals, albeit with a lower CO and  $VO_2$ .<sup>3,4,13</sup>

In our population, rest  $VO_2$  values were lower in HF patients compared with healthy subjects, while they were similar between HF groups; CO and  $\Delta C(a-v)O_2$  were all statistically different between healthy subjects and HF patients, and between Group 1 and Group 2 HF patients. The higher HF patients'  $\Delta C(a-v)O_2$  documented that peripheral mechanism able to increase  $VO_2$  uptake are exploited even at rest in this population of patients.<sup>27</sup> Stroke volume values were significantly higher in healthy subjects compared with HF patients, while the difference between HF patients' values was at threshold for statistical significance ( $P = 0.05$ ).

In the present study, mid-exercise was predetermined between 4 and 5 min of active pedalling using a ramp protocol aimed at achieving peak effort in ~10 min and tailored from the familiarization CPET. Despite having been familiarized, exercise time was progressively shorter in patients with different HF stages compared with healthy individuals. A possible explanation may be related to the physical effort associated with

the IGR manoeuvres, which is likely more relevant in severe HF patients. In HF patients, mid-exercise CO values were acquired at about anaerobic threshold (*Table 2*), while in healthy volunteers, mid-exercise measures were collected before reaching the anaerobic threshold, as suggested by  $\text{VO}_2$  values.

At mid-exercise, Group 1 patients achieved a lower  $\text{VO}_2$  and CO than Group 2 and healthy subjects, as they were less able to increase stroke volume (stroke volume increase between rest and mid-exercise: 11 and 19 mL, respectively,  $P = 0.001$ ). Group 2 showed statistically higher values of mid-exercise  $\Delta\text{C(a-v)}\text{O}_2$  compared with healthy subjects ( $P = 0.002$ ; *Figure 1D*). Indeed, HF patients are known to rely on changes on  $\Delta\text{C(a-v)}\text{O}_2$  to increase oxygen uptake during exercise.<sup>28</sup>  $\Delta\text{C(a-v)}\text{O}_2$  did not differ between the two HF groups at mid-exercise, suggesting that in the first part of exercise, regardless of the severity of exercise performance limitation, HF patients use their peripheral mechanisms of oxygen distribution and uptake to the same extent. Differently, at peak exercise,  $\Delta\text{C(a-v)}\text{O}_2$  was lower in Group 1 compared with Group 2 (*Figure 1D*) patients, suggesting a reduced capacity of peripheral mechanisms to compensate for major cardiac inability to increase CO in patients with most severe HF.<sup>23,29,30</sup> It is likely that the different increase between HF groups of  $\Delta\text{C(a-v)}\text{O}_2$  induced by exercise is attributable, at least partially, to the lower rest haemoglobin level and to its expected lower increase during exercise in patients with more severe HF.<sup>13</sup>

Of note, independent predictors of peak  $\text{VO}_2$  among HF patients were mid-exercise  $\text{VO}_2$  and CO, haemoglobin, and weight. Mid-exercise  $\text{VO}_2$  and CO portend peak exercise values, whose prognostic value cannot be understated. Therefore, in upcoming studies, it will be of the utmost importance to investigate the prognostic value of mid-exercise parameters, to finally obtain clinically meaningful indications even from sub-maximal or precociously interrupted CPETs.

The present study has some limitations that must be acknowledged. First, measuring CO by IGR technique during exercise implies a relevant patient compliance and skill as well as a technical knowledge and expertise from the physicians responsible for the test. Second, the inert gases utilized for CO determination are relatively expensive, albeit much less than a haemodynamic procedure. These are undeniable limitations, which reduce a widespread use in clinical practice of IGR technique. Third, as rebreathing manoeuvres affect

respiration and ventilatory gases, reported data at mid-exercise and peak exercise are those immediately preceding the rebreathing manoeuvre. Therefore, peak measurements are just around the real peak of the exercise and not precisely at the maximal metabolic effort. Similarly, mid-exercise step has been set by the operator at arbitrarily predicted half-time: between peak and the start of exercise. Fourth, our population is not homogeneous: it is acknowledged that adjusting for age, gender, and BMI can temper this deficiency but does not solve it completely. Moreover, Group 1 patients had more frequently HF with reduced ejection fraction compared with Group 2 patients; conversely, HF with preserved ejection fraction patients were significantly more represented in Group 2 (*Table 1*). Finally, HF severity was classified by grouping patients according to peak  $\text{VO}_2$  using arbitrary cut-off values, which allowed us to divide the study population into two groups, although of unequal size. We chose peak  $\text{VO}_2$  as HF severity criterion because it is among the most reliable HF severity indexes.

## Conclusions

Mid-exercise non-invasive haemodynamic assessment, achieved in a standard sitting position, best mimics real-life activities and therefore represents a valuable tool for a comprehensive evaluation of HF patients' exercise capacity. Values collected at mid-exercise have a potential to herald peak exercise parameters, which is especially useful in patients who have difficulties in reaching peak exercise. Accordingly, whenever CPET is integrated with CO measurements, mid-exercise parameters should be recorded.

## Conflict of interest

None.

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