International Journal of Cardiology 248 (2017) 252–256

Contents lists available at ScienceDirect

International Journal of Cardiology

journal homepage: www.elsevier.com/locate/ijcard

Contribution of central and peripheral factors at peak exercise in heart failure patients with progressive severity of exercise limitation☆

Alberico Del Torto [a,b,1], Nicoletta Corrieri [a,b,1], Carlo Vignati [a,b], Piero Gentile [c], Gaia Cattadori [d], Stefania Paolillo [a], Piergiuseppe Agostoni [a,b,*]

[a] Centro Cardiologico Monzino, IRCCS, Milan, Italy
[b] Dept. of Clinical Sciences and Community Health, Cardiovascular Section, University of Milano, Milano, Italy
[c] Cardiovascular Department, Division of Cardiology, Azienda Sanitaria Universitaria Integrata and University of Trieste, Trieste, Italy
[d] Unità Operativa Cardiologia Riabilitativa, Multimedica IRCCS, Milano, Italy

ARTICLE INFO

Article history:
Received 9 May 2017
Received in revised form 21 June 2017
Accepted 14 July 2017

Keywords:
Heart failure
Peak exercise cardiac output
Peak exercise oxygen uptake

ABSTRACT

Background: A reduced cardiac output (CO) response during exercise is a major limiting factor in heart failure (HF). Oxygen consumption (VO_2) is directly proportional to CO. Peripheral mechanisms via arteriovenous oxygen difference ($\Delta(a\text{-}v)O_2$) play a pivotal role in chronic HF. We hypothesized a weak correlation between peak VO_2 and peak CO with a greater $\Delta(a\text{-}v)O_2$ variability in most severe HF.

Methods: We analyzed 278 HF patients (NYHA II–III) who performed maximal cardiopulmonary exercise test with non-invasive CO measurement by inert gas rebreathing.

Results: Median peakVO_2, CO and $\Delta(a\text{-}v)O_2$ were 0.96 (0.78–1.28) L/min, 6.3 (5.1–8.0) L/min and 16.0 (14.2–18.0) mL/100 mL respectively, with a linear relationship between VO_2 and CO: $CO = 5.3 \times VO_2 + 1.13$ ($r^2 = 0.705$, $p < 0.001$). Patients were grouped according to exercise limitation. Group 1 (101 patients) peakVO_2 < 50% pred: peakVO_2 0.80 (0.67–0.94) L/min, peakCO 5.6 (4.7–6.5) L/min, peak$\Delta(a\text{-}v)O_2$ 14.8 (12.9–17.1) mL/100 mL. Group 2 (89 patients) peakVO_2 ≥ 50–<65% pred: peakVO_2 1.02 (0.84–1.29) L/min, peakCO 6.4 (5.1–8.0) L/min, peak$\Delta(a\text{-}v)O_2$ 16.7 (15.0–18.5) mL/100 mL. Group 3 (88 patients) peakVO_2 ≥ 65% pred: peakVO_2 1.28 (0.93–1.66) L/min, peakCO 8.0 (6.2–9.7) L/min, peak$\Delta(a\text{-}v)O_2$ 16.8 (14.6–18.3) mL/100 mL. A peakVO_2 and peakCO linear relationship was observed in Group 1 ($r^2 = 0.381$, $p < 0.001$), Group 2 ($r^2 = 0.756$, $p < 0.001$) and Group 3 ($r^2 = 0.744$, $p < 0.001$).

Conclusions: With worsening HF we observed a progressive reduction of peak CO and peak VO_2. However in most compromised patients also peripheral mechanisms play a role as indicated by reduced $\Delta(a\text{-}v)O_2$.

© 2017 Elsevier B.V. All rights reserved.

1. Introduction

In heart failure (HF) patients, alterations in central hemodynamics, peripheral vasodilatory capacity, intrinsic skeletal muscle changes, pulmonary factors, iron deficiency, anemia and overall conditioning status can all impair effective oxygen delivery and utilization, as muscular work during exercise requires a complex integration of cardiac, pulmonary, vascular and peripheral mechanisms.

However, a reduced cardiac output (CO) response during exercise is thought to be an early and major factor limiting exercise performance [1–3]. According to Fick's law, CO is directly proportional to oxygen consumption (VO_2) and inversely proportional to arteriovenous oxygen difference ($\Delta(a\text{-}v)O_2$). Peak CO can be reliably estimated from peak VO_2 in normal subjects [3–6]. In HF patients peak exercise $\Delta(a\text{-}v)O_2$ is, on average, similar to that recorded in healthy subjects [3,7], but it shows a relevant interpatient variability [8]. Indeed $\Delta(a\text{-}v)O_2$ depends on three major factors: capillary O_2 availability, O_2 diffusion from capillaries to mitochondria, and muscle aerobic capacity. On its turn capillary O_2 availability is related to CO but also to blood hemoglobin concentration at rest, exercise induced hemoconcentration, arterial pO_2, pulmonary hypertension, other factors affecting the O_2-hemoglobin dissociation curve and peripheral blood flow distribution; O_2 diffusion from capillaries to mitochondria depends on capillary density in the working muscles and resistive conditions to O_2 diffusion such as fibrosis, cellularity and edema; muscle aerobic capacity depends on mitochondrial density and fibers metabolic efficiency [9]. Notably the role of the different peripheral mechanisms in determining exercise performance may vary at different stages of HF [8]. Hence peak exercise CO estimation by VO_2 in HF patients may not be completely reliable, and methods to non-invasively measure CO are believed important in this

☆ Funding: Centro Cardiologico Monzino RC2015: 2613322.
Conflict of interest: none declared.

* Corresponding author at: Dept. Of Clinical sciences and Community Health, Cardiovascular Section, Centro Cardiologico Monzino, IRCCS, University of Milan, Via Parea 4, 20138 Milan, Italy.
E-mail address: piergiuseppe.agostoni@unimi.it (P. Agostoni).

[1] These authors contributed equally to this work.

http://dx.doi.org/10.1016/j.ijcard.2017.07.071
0167-5273/© 2017 Elsevier B.V. All rights reserved.

setting [4,10,11]. Metra showed that direct assessment of exercise hemodynamics in patients with HF provides additive independent prognostic information, compared to peak exercise VO_2, identifying patients whose functional limitation is caused mainly by skeletal muscle deconditioning, rather than by cardiovascular factors [12]. Indeed a reduced peak VO_2 with a low peak CO, (hence with a calculated preserved $\Delta(a\text{-}v)O_2$), means that the usefulness of a further training is questionable and that major effort should be dedicated to the heart itself while vice versa, for the same peak VO_2, a preserved peak CO with a low $\Delta(a\text{-}v)O_2$, suggests the need of intensive rehabilitation [13–16].

We hypothesized that patients with the most severe exercise limitation have the greatest variability in peripheral mechanisms, making the correlation between peak exercise CO and VO_2 weaker in this specific setting. Therefore in severe HF patients, simultaneous measurement of CO and VO_2 at peak exercise seems most important. Hence we analyzed the correlation between peak exercise VO_2, CO and $\Delta(a\text{-}v)O_2$ at different degrees of exercise limitation.

2. Methods

2.1. Study design and population

We retrospectively analyzed data of 278 consecutive HF patients regularly followed at our HF unit, who performed a maximal cardiopulmonary exercise test (CPET) with simultaneous CO measurement (CPET-CO) by inert gas rebreathing (IGR) technique. All patients had been familiarized with CPET and IGR technique by repeated IGR teaching sections. At the time of inclusion, patients were either ambulatory or at hospital discharge, and all were in stable clinical conditions, mildly to moderately symptomatic (NYHA II–III), and on guideline-directed medical therapy. We excluded patients with symptomatic angina, severe valvular aortic stenosis, complex arrhythmias, pulmonary hypertension group 1, 3, 4 or 5 [17], pulmonary embolism or any disease which per se influenced their exercise capacity. For the present analysis, we evaluated resting hemoglobin and CPET-CO. On the same day of CPET-CO a blood sample was obtained to measure hemoglobin and brain natriuretic peptide (BNP) concentration; in a subset of patients, ferritin, serum iron, transferrin and transferrin saturation were also measured. Iron deficiency was defined as serum ferritin concentration < 100 μg/L or serum ferritin concentration between 100 and 300 μg/L and transferrin saturation < 20% [18].

The study complies with the Declaration of Helsinki, and the locally appointed ethics committee approved the research protocol (approval number R435/16-CCM451).

2.2. Cardiopulmonary exercise test with simultaneous CO measurement

CPET was performed with progressive work rate increase in a ramp pattern, after at least 3 min of rest and a brief unloaded cycling. CPET was performed using a personalized ramp protocol aimed at achieving peak exercise in around 10 min, while estimating exercise capacity from familiarization CPET [19]. Respiratory O_2, CO_2, and ventilation were measured breath by breath (Innocor® rebreathing system, Innovision A/S, Odense, Denmark). A 12-lead ECG was recorded (Quark PFT Cosmed, Roma, Italy). 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 maneuver.

We analyzed CPET using a standard methodology. Peak VO_2 was calculated as an average over 30 s and reported either as absolute value or as a percentage of the VO_2 peak predicted value [20]. The ventilation (VE)/carbon dioxide flow (VCO_2) slope was calculated as the slope of the relationship between VE and VCO_2 from approximately 1 min after the beginning of loaded exercise to the end of the isocapnic buffering period [19].

CO was measured at rest and at peak exercise using an IGR method [21–23]. The IGR technique has been previously reported in detail [24]. 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 patients rebreathe from the prefilled bag for a period of 10 to 20 s. After that period, patients start breathing ambient air again. CO measurement is performed by a photoacoustic analyzer that measures gas concentration over a three to 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 (SpO_2) is >98% at pulse oximeter, showing the absence of pulmonary shunt flow. If SpO_2 is <98%, CO is equal to pulmonary blood flow plus shunt flow [24]. In CPET-CO, respiratory gases and ventilation were measured breath by breath as in CPET. $\Delta(a\text{-}v)O_2$ was calculated as VO_2/CO. 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.

2.3. Statistical analysis

Continuous variables were expressed as means ± standard deviation (SD), or as median and interquartile range if not normally distributed. Comparisons between subgroups were performed using two-tailed ANOVA tests for normally distributed variables and Kruskal-Wallis test for non-normally distributed variables. Pearson regression analysis was performed after logarithmic transformation for non-normally distributed variables. Chi-squared analysis was performed to compare iron deficiency prevalence in each subgroup. $p < 0.05$ was considered statistically significant. Statistical analyses were performed using SPSS 22.0 software (SPSS Inc., Chicago, IL, USA).

3. Results

The overall data of 278 consecutive HF patients who performed cardiopulmonary exercise test and CO measurements at peak exercise by IGR technology were evaluated. Table 1 summarizes clinical characteristics, mean peak exercise CO, cardiac index (CI), VO_2 and $\Delta(a\text{-}v)O_2$ of the entire population. Median age was 69 years; 215 patients (77%) were men. Median left ventricular ejection fraction measured at transthoracic echocardiography by biplane disc summation method was 35% (including patients with severe mitral regurgitation). Median hemoglobin was 13.6 g/dL, and median BNP was 214 pg/mL. VO_2 increased from an average of 0.30 L/min to 0.96 L/min at peak exercise; CO increased from 3.4 L/min to 6.3 L/min, and $\Delta(a\text{-}v)O_2$ increased from 8.86 mL/100 mL to 16.00 mL/100 mL.

Treatment included diuretics (84%), angiotensin converting enzyme inhibitors (66%), beta blockers (84%), angiotensin receptor blockers (29%), mineralcorticoid receptor antagonists (63%). Finally 37% of patients had an ICD or CRT.

The HF etiology was: ischemic cardiomyopathy in 144 patients (52%); idiopathic dilated cardiomyopathy in 73 patients (26%); primary severe valvular disease in 41 patients (15%); the remaining patients had previous myocarditis, post-chemotherapy cardiomyopathy, tachycardiomyopathy, left ventricular non compaction cardiomyopathy, arrhythmogenic right ventricular cardiomyopathy and postpartum cardiomyopathy.

A strong linear relationship between VO_2 and CO at peak exercise was observed ($r^2 = 0.705$, $p < 0.001$, Fig. 1) and a linear regression model demonstrated the following equation: $CO = 5.3 \times VO_2 + 1.13$. No specific behavior of the VO_2 vs. CO relationship was observed as regards HF etiology.

We analyzed the correlations between peak CO and peak VO_2 by grouping patients according to exercise limitation (percent achieved of predicted peak exercise VO_2) with arbitrarily defined cutoffs.

Group 1 consisted of 101 patients with peak VO_2 < 50% of predicted peak VO_2; Group 2 consisted of 89 patients with peak VO_2 ≥ 50% and <65% of predicted peak VO_2; Group 3 consisted of 88 patients with peak VO_2 ≥ 65% of predicted peak VO_2. Clinical characteristics, mean peak exercise CO, CI, VO_2 and $\Delta(a\text{-}v)O_2$ of the three groups are reported in Table 1.

Group 1 patients had the most compromised exercise performance, with the lowest peak exercise CO and $\Delta(a\text{-}v)O_2$. Group 2 patients achieved a significantly lower peak exercise CO than Group 3 patients.

We observed a robust linear relationship between VO_2 and CO at peak exercise in Group 2 ($CO = 6.2 \times VO_2 – 0.1$, $r^2 = 0.756$, $p < 0.001$) and Group 3 ($CO = 5.2 \times VO_2 + 1.3$, $r^2 = 0.744$, $p < 0.001$) and, albeit weaker, in Group 1 ($CO = 4.7 \times VO_2 + 1.8$, $r^2 = 0.381$, $p < 0.001$) (Fig. 2).

Measures of serum ferritin, iron, transferrin, and transferrin saturation at time of CPET-CO were available in 21 patients in Group 1 (20.8%), 21 patients in Group 2 (23.6%) and 17 patients in Group 3 (19.3%), for a total amount of 59 patients. Median serum ferritin, iron, transferrin and transferrin saturation are reported in Table 2, as well as the number of patients with iron deficiency in each group. In these small subgroups, we observed a greater prevalence of iron deficiency in Group 1 trending toward statistical significance ($p = 0.059$).

Download English Version:

https://daneshyari.com/en/article/5604163

Download Persian Version:

https://daneshyari.com/article/5604163

Daneshyari.com