Relationship of resting hemoglobin concentration to peak oxygen uptake in heart failure patients

Piergiuseppe Agostoni,[1,2]* Elisabetta Salvioni,[1] Chiara Debenedetti,[1] Carlo Vignati,[1] Gaia Cattadori,[1] Mauro Contini,[1] Damiano Magrì,[1] Pietro Palermo,[1] Erica Gondoni,[1] Denise Brusoni,[1] Cesare Fiorentini,[1] and Anna Apostolo[1]

Anemia is frequent in chronic heart failure (HF). To calculate what change in peak oxygen uptake ($\dot{V}O_2$) should be expected in the event of changes in hemoglobin concentration, we studied the correlation between peak $\dot{V}O_2$ and hemoglobin concentration in a large HF population. We carried out retrospective analysis of all cardiopulmonary exercise tests (CPET) performed in our HF Clinic between June 2001 and March 2009 in HF patients who had a resting hemoglobin concentration measurement taken within 7 days of the CPET. We collected 967 CPETs, 704 tests were considered maximal and analyzed. We identified 181 patients (26%) as anemic. Peak $\dot{V}O_2$ was lower ($P < 0.001$) in anemic patients (971 ± 23 ml/min) compared with nonanemic (1243 ± 18 ml/min). The slope of the $\dot{V}O_2$ vs. hemoglobin ratio was 109 ml/min/g/dl at peak exercise. This correlation remained significant also when several confounding variables were analyzed by multivariate analysis. As an average, each gram of hemoglobin accounts, at peak exercise, for 109 ml/min change in $\dot{V}O_2$ which is equivalent to 0.97 ml/min/kg. Therefore, in HF patients anemia treatment should increase $\dot{V}O_2$ by 109 ml/min for each g/dl of hemoglobin increase. Am. J. Hematol. 85:414–417, 2010. © 2010 Wiley-Liss, Inc.

Introduction

Anemia and reduction of exercise capacity are both frequently reported in chronic heart failure (HF) and are both associated to worsening of HF prognosis [1–4]. The two are linked to each other indirectly, having heart failure as a common underlying origin, and directly. Indeed, the gold standard variable of exercise capacity evaluation is peak exercise oxygen uptake ($\dot{V}O_2$), which is a cardiac output x arterio-venous O_2 difference. The latter depends on hemoglobin, which reduction negatively affects the arterial oxygen concentration. Furthermore several reports showed that, in chronic HF patients, anemia is associated with low exercise capacity [5,6]. In principle, it is possible to calculate the amount of peak $\dot{V}O_2$ loss due to anemia if hemoglobin arterial oxygen saturation is normal, and if peak exercise cardiac output and peak exercise oxygen extraction are known. In 2 previous studies of our group in HF patients, we measured at peak exercise a mean extraction rate ~70% [7,8]. Therefore, because 1 g of hemoglobin binds 1.34 ml of oxygen and, at peak exercise extraction rate is ~70%, each gram of hemoglobin provides to the muscles ~1 ml of oxygen. The latter multiplied by the cardiac output is the amount of $\dot{V}O_2$ reduction resulting from a 1 g drop in hemoglobin [9]. For example, if peak exercise cardiac output is 10 l/min the loss of 1 g of hemoglobin is equivalent to a reduction of ~100 ml/min $\dot{V}O_2$. Unfortunately, neither cardiac output nor oxygen extraction at peak exercise are usually measured, so that we cannot calculate the reduction of $\dot{V}O_2$ directly due to anemia. It would be desirable, however, to understand, at least in a semi-quantitative fashion, the role of anemia on peak $\dot{V}O_2$ in HF patients. This study was undertaken to evaluate the correlation between peak exercise $\dot{V}O_2$ and hemoglobin concentration in a large HF population.

Methods

We carried out retrospective analysis of all cardiopulmonary exercise tests (CPET) performed in our HF Clinic between June 2001 and March 2009 in HF patients in stable clinical conditions, NYHA Class I to III, with left ventricle ejection fraction ≤50% who had performed a resting hemoglobin concentration measurement in our general laboratory within 7 days of the exercise test. We excluded subjects with history and/or clinical documentation of pulmonary embolism or primary valvular heart disease, pericardial disease, severe obstructive lung disease, primitive pulmonary hypertension or occupational lung disease, asthma, severe renal failure (serum creatinine >5 mg/dl), significant peripheral vascular disease, advanced atrio-ventricular block, exercise-induced angina and/or relevant ST changes. We also excluded patients whose exercise was interrupted as the result of a medical decision before maximal effort was reached, due to severe hypertension or severe arrhythmia.

CPETs were performed on a cycle-ergometer using a progressively increasing work load generated by a ramp protocol personalized for each patient, with the aim of reaching maximum exercise in about 10 min. Subjects were asked to pedal at 60 revolutions per minute. The used load for each individual of the personalized ramp protocol was decided by the physician in charge according to previous test results, if available, or to exercise performance as reported by patients. Tests too short (<5 min) or too long (>14 min) were repeated with a more appropriate ramp protocol [10]. Ventilation ($\dot{V}E$), $\dot{V}O_2$, and carbon dioxide production ($\dot{V}CO_2$) were measured breath by breath (V-max 2900 metabolic cart SensorMedics, Yorba Linda CA for tests performed between June 2001 and August 2004 and V-max metabolic cart SensorMedics, Yorba Linda CA for tests performed between September 2004 and March 2009). Twelve-leads ECG and heart rate were monitored continuously. Anaerobic threshold was measured by the V-slope method and confirmed by O_2 and CO_2 ventilatory equivalents and end-tidal O_2 and CO_2 pressure specific changes [11]. $\dot{V}E/\dot{V}CO_2$ slope was measured from the beginning of loaded pedaling to the end of the isocapnic buffering period. The latter was identified by an increase of the ventilatory equivalent for CO_2 ($\dot{V}E/\dot{V}CO_2$) and confirmed by reduction of end-tidal CO_2 pressure. The $\dot{V}O_2$/work ratio was measured throughout the entire exercise.

[1]Centro Cardiologico Monzino, IRCCS, Dipartimento di Scienze Cardiovascolari, Università di Milano, Milan, Italy; [2]Division of Critical Care and Respiratory Medicine, Department of Medicine, University of Washington, Seattle, Washington

Conflict of interest: Nothing to report.

*Correspondence to: P. Agostoni, Centro Cardiologico, IRCCS, Istituto di Scienze Cardiovascolari, Università di Milano, Via Parea 4, Milan 20138, Italy. E-mail: piergiuseppe.agostoni@unimi.it

Received for publication 25 January 2010; Revised 23 February 2010; Accepted 24 February 2010

Am. J. Hematol. 85:414–417, 2010.

Published online 2 March 2010 in Wiley InterScience (www.interscience.wiley.com).
DOI: 10.1002/ajh.21698

TABLE I. HF Patients Characteristics

	Total population n = 704	Anemic n = 181	Not-anemic n = 523	*P*
Age (year)	62.8 ± 0.4	65.3 ± 0.8	61.9 ± 0.5	<0.001
Gender				
m	571 (81%)	148 (26%)	423 (74%)	N.S.
f	133 (19%)	33 (25%)	100 (75%)	N.S.
NYHA				
I	101	10 (5%)	91 (17%)	<0.001
II	297	59 (33%)	238 (46%)	
III	306	112 (62%)	194 (37%)	
LVEF (%)	35.4 ± 0.3	35.3 ± 0.6	35.5 ± 0.4	N.S.
LVDV (ml)	189 ± 3	190 ± 5	189 ± 3	N.S.
Hemoglobin (g/dl)	13.6 ± 0.06	11.7 ± 0.07	14.3 ± 0.05	<0.001
Weight (Kg)	76.7 ± 0.5	73.8 ± 1	77.7 ± 0.6	0.001
Therapy				
B-Blockers	592 (84%)	151 (83%)	441 (84%)	N.S.
Diuretics	513 (73%)	157 (87%)	356 (68%)	<0.001
Ace-inhibitor	525 (75%)	133 (73%)	392 (75%)	N.S.
ARBs	135 (20%)	40 (22%)	95 (18%)	N.S.
Spironolactone	341 (50%)	94 (52%)	247 (47%)	N.S.

LVEF = left ventricular ejection fraction; LVDV = left ventricular diastolic volume.

TABLE II. Cardiopulmonary Exercise Test Results

	Total population	Anemic	Not-anemic	*P*
Peak $\dot{V}O_2$ (ml/min)	1173 ± 15	971 ± 23	1243 ± 18	<0.001
Peak $\dot{V}O_2$ (ml/Kg/min)	15.3 ± 0.2	13.2 ± 0.3	16.0 ± 0.2	<0.001
Peak $\dot{V}O_2$ (% of predicted value)	60 ± 01	51 ± 1	63 ± 1	<0.001
$\dot{V}E/\dot{V}CO_2$ slope	31 ± 0	34 ± 1	31 ± 0	<0.001
$\dot{V}O_2$ /Work (ml/min Watt)	9.6 ± 0.3	9.4 ± 0.4	9.7 ± 0.3	N.S.
$\dot{V}O_2$ AT (ml/min)	807 ± 11	680 ± 18	849 ± 13	<0.001
HR at rest (b/min)	74 ± 1	73 ± 1	74 ± 1	N.S.
HR max (b/min)	120 ± 1	111 ± 2	123 ± 1	<0.001
Delta HR (b)	47 ± 1	38 ± 2	49 ± 1	<0.001
Work load (Watt)	89 ± 1	71 ± 2	95 ± 2	<0.001
Exercise time (min)	8.8 ± 0.1	7.9 ± 0.1	9.1 ± 0.2	<0.001

$\dot{V}O_2$ = oxygen uptake; $\dot{V}E/\dot{V}CO_2$ = ventilation/carbon dioxide slope; AT = anaerobic threshold; HR = heart rate.

Echocardiography was performed in our laboratory on each patient within 6 months of the CPET test. Left ventricular diastolic volume and ejection fraction were measured in the left lateral decubitus position. Left ventricular volume was derived from the conventional apical 2- and 4-chamber images and the left ventricle ejection fraction was calculated using biplane Simpson's technique [12].

Anemia was defined by WHO criteria as hemoglobin concentration <12 g/dl in women and <13 g/dl in men [13]. The presence of coronary artery disease associated to HF was assessed by standard coronary angiography according to Felker et al. [14]. We considered only coronary angiography performed within one year of the CPET. In case of multiple exercise tests we selected the CPET used in the present analysis in a random manner. The study and the access of private health information were approved by the local intern review board.

Statistical analysis. Data are reported as mean ± SE. Differences between groups were analyzed by unpaired t-tests with a $P < 0.05$ considered as statistically significant. Categorical variables such as NYHA classification, gender differences or treatment were analyzed by chi-square test. Correlation between variables was assessed by linear regression analysis. We evaluated vs. peak $\dot{V}O_2$ several variables including: age, gender, NYHA class, left ventricle ejection fraction, $\dot{V}E/\dot{V}CO_2$ slope, peak heart rate and work load. Multivariate analysis was performed adding in the model all variables which were correlated to peak $\dot{V}O_2$ at monovariate analysis. A similar analysis was also performed using $\dot{V}O_2$ at the anaerobic threshold as the dependent variable.

All data were analyzed by SPSS 17.0 software collected in an Excel data base.

Results

We collected a total of 967 CPETs of HF patients who matched the clinical study criteria, who had both a blood test for hemoglobin concentration determination at rest taken at our central laboratory within one week and an echocardiographic evaluation taken within 6 months. 263 CPETs were discarded because effort was judged submaximal according to peak exercise gas exchange ratio (RQ < 1.05). Consequently, 704 patients were considered in this report. Population characteristics, treatment and heart failure severity are reported in Table I. Anemic patients were older, had clinically more severe HF and were more frequently treated with diuretics.

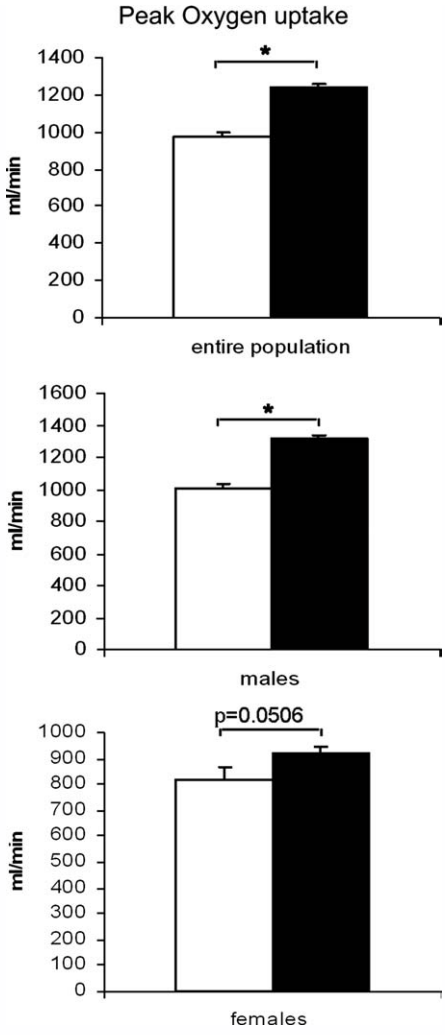

Figure 1. Peak oxygen uptake in anemic (white bar) and not anemic (black bar) HF patients. Entire HF population (upper panel), HF males (middle panel), and HF females (lower panel). * = $P < 0.05$.

Haemoglobin was 13.7 ± 0.1 g/dl ranging between 7.5 and 17.1 g/dl. One hundred eighty-one patients were anemic (26%), representing 33 (25%) of 133 women and 148 (26%) of 571 males. Nonanemic patients were 523 (74%), representing 100 (75%) of 133 women, and 423 (74%) of 571 males. Anaerobic threshold was not identified in 12% (n = 87) of the 704 patients. CPET results are reported in Table II for the entire study population and for the anemic and nonanemic patients, respectively. Anemic patients had a lower exercise capacity, with the work load achieved, the $\dot{V}O_2$ both at peak exercise and at anaerobic threshold being lower. Furthermore, anemic HF patients had a greater $\dot{V}E/\dot{V}CO_2$ slope. It should be noted that cardiac function and left ventricular volume at echocardiography were similar for anemic and nonanemic patients (Table I). Peak $\dot{V}O_2$ was lower in anemic male patients compared with nonanemic but not in women who showed only a trend toward the same difference ($P = 0.0506$) (Fig. 1).

TABLE III. Linear Regressions Between Peak $\dot{V}O_2$ and $\dot{V}O_2$ at the Anaerobic Threshold vs. Hemoglobin at Rest

Total population	HF+CAD	HF no-CAD
Peak $\dot{V}O_2$ = 109 Hb − 3189 R^2 = 0.180	Peak $\dot{V}O_2$ = 94 Hb − 161 R^2 = 0.168	Peak $\dot{V}O_2$ = 116 Hb − 363 R^2 = 0.182
$\dot{V}O_2$ AT = 74 Hb − 200 R^2 = 0.169	$\dot{V}O_2$ AT = 61 Hb − 60 R^2 = 0.146	$\dot{V}O_2$ AT = 82 Hb − 284 R^2 = 0.191

$\dot{V}O_2$ (ml/min) = oxygen uptake; AT = anaerobic threshold; HF = heart failure; CAD = coronary artery disease; Hb (g/dl) = hemoglobin.

TABLE IV. Monovariate Correlations Between Peak $\dot{V}O_2$ and Several Variables

	R^2	*P*
Age	0.197	<0.000
Gender	0.110	<0.000
LVEF(%)	0.08	<0.000
Hb (g/dl)	0.108	<0.000
$\dot{V}E/\dot{V}CO_2$ slope	0.2	<0.000
HR peak (b/m)	0.192	<0.000
Work load (Watts)	0.872	<0.000
NYHA class	0.589	<0.000

$\dot{V}O_2$ = oxygen uptake; $\dot{V}E/\dot{V}CO_2$= ventilation/carbon dioxide slope; HR = heart rate; Hb = hemoglobin.

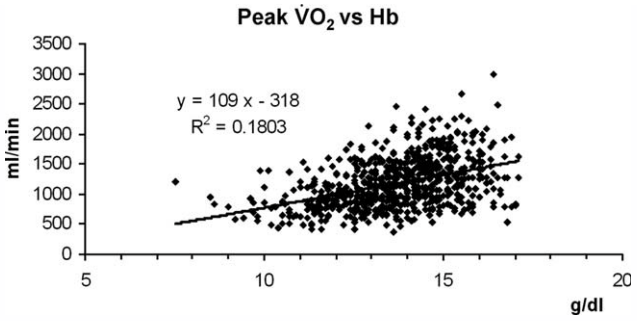

Figure 2. Linear regression between peak $\dot{V}O_2$ (oxygen uptake) and hemoglobin concentration in HF patients (n = 704).

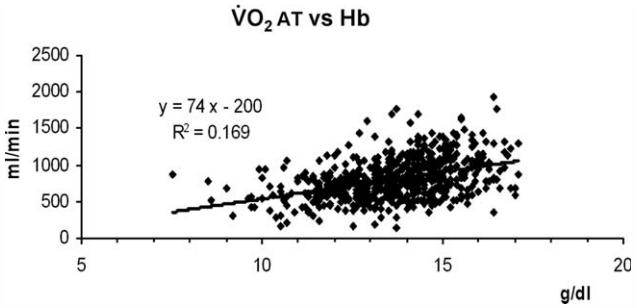

Figure 3. Linear regression between $\dot{V}O_2$T (oxygen uptake at anaerobic threshold) and hemoglobin concentration in HF patients (n = 617).

Coronary angiography was available for 692 of the 704 patients. 332 (47%) patients (30 female and 302 male) were classified as having HF associated to coronary artery disease and 360 (53%) (102 female and 258 male) as not associated to coronary artery disease, i.e., with angiografically normal epicardial coronary arteries. The presence of coronary artery disease did not significantly influenced the correlation between $\dot{V}O_2$ and hemoglobin both at peak exercise and at anaerobic threshold (Table III). Table IV shows the correlations between several variables and peak $\dot{V}O_2$. At multivariate analysis only gender ($P < 0.000$), hemoglobin ($P < 0.01$), $\dot{V}E/\dot{V}CO_2$ slope ($P < 0.000$), the work load achieved ($P < 0.000$) and NYHA class ($P < 0.000$) remained significantly correlated to peak $\dot{V}O_2$.

The correlation between peak exercise $\dot{V}O_2$ and hemoglobin at rest is reported in Fig. 2. Assessing $\dot{V}O_2$ as ml/min/kg the slope of the $\dot{V}O_2$ vs. hemoglobin relationship was 0.97 (ml/kg/min/g/dl). $\dot{V}O_2$ at anaerobic threshold was significantly correlated to the following variables: age ($P < 0.000$), gender ($P < 0.000$), NYHA class ($P < 0.000$), LVEF ($P < 0.000$), hemoglobin ($P < 0.000$), $\dot{V}E/\dot{V}CO_2$ slope ($P < 0.000$), peak heart rate ($P < 0.000$), and work load ($P < 0.000$). At multivariate analysis only age ($P < 0.05$), $\dot{V}E/\dot{V}CO_2$ slope ($P < 0.000$), and work load ($P < 0.000$) remained independently correlated to $\dot{V}O_2$. The $\dot{V}O_2$ vs. Hb relationship at the anaerobic threshold is reported in Fig. 3.

Discussion

This study shows, in accordance with several previous reports, that anemia is frequent in chronic HF patients and associated with a lower exercise capacity [1–6]. Indeed, the prevalence of anemia we observed (26%) is in agreement with what has been reported previously (between 10 and 55%) [4]. In HF the presence of anemia is associated with poor prognosis, with higher mortality risk both in hospitalized and ambulatory patients, higher hospitalization rate and, overall, with a more severe clinical condition for patients [4,15–17]. In our study, on average, peak $\dot{V}O_2$ and $\dot{V}E/\dot{V}CO_2$ slope, both of which are independent strong prognostic indicators of HF [18], were 22% lower and 10% higher, respectively, in HF patients with anemia compared with those without anemia.

It is commonly thought that anemia should be corrected to improve HF patients' quality of life and possibly prognosis, however, there is still a lack of a scientific evidence; consequently, anemia correction is not considered as mandatory in HF treatment guidelines [19,20]. Several studies have focused on the effect of anemia correction, usually by iron and erythropoietin or darbopoietin, on exercise performance, measured either by peak $\dot{V}O_2$, exercise tolerance or by distance walked at the 6 min walking test, in both HF and non-HF patients [21–29]. However, only four [21–23] reports all based on small studies, showed the effect of anemia correction on peak exercise $\dot{V}O_2$ in HF patients, with discordant findings. Indeed, three reports showed that anemia treatment increased exercise performance [21,22,24] while one did not [23].

Several factors influence exercise performance in HF, including, following the Fick principle, cardiac output and the arterio-venous oxygen difference. We limited our analysis only to hemoglobin. To extrapolate the role of hemoglobin, we studied the correlation between resting hemoglobin and $\dot{V}O_2$ at peak and anaerobic threshold. We observed a correlation between $\dot{V}O_2$ (ml/min) at peak and hemoglobin with a R^2 = 0.18, which means that hemoglobin accounts for 18% of the variance in peak $\dot{V}O_2$. This also means that 82% of peak $\dot{V}O_2$ variance is not related to hemoglobin. The slope of this ratio (Fig. 2) tells us that, on average, at peak exercise each gram of hemoglobin accounts for a 109 ml/min change in $\dot{V}O_2$ which is equivalent to 0.97 ml/min/kg.

We analyzed the correlation between $\dot{V}O_2$ at peak exercise and resting hemoglobin. Unfortunately peak exercise hemoglobin data is not available. However, exercise-induced hemoconcentration, which is well known and is

due to both spleen contraction and fluid shift away from the intravascular space due to an increase in intracellular lactic acid (30,31), probably did not significantly influence our findings. Indeed, exercise-induced hemoconcentration is responsible for approximately 20% of arterio-venous oxygen difference increase in HF subjects, being on average around 1.0 g/dl in normal subjects and 0.6 g/dl in HF patients (30). Had the exercise-induced hemoglobin increase been even in patients with different levels of HF severity, this would have only shifted the $\dot{V}O_2$/Hb ratio upward, with no effect on the slope of the ratio and, consequently, with no effect on the predicted $\dot{V}O_2$ change as a result of hemoglobin changes. Unfortunately this is not the case, because exercise-induced hemoglobin increase is greater in less compromised patients, so the lack of hemoglobin measurements at peak exercise weakens our results. However, when comparing severe and non-severe HF patients the difference in exercised-induced hemoglobin increase is trivial (30) and certainly not able to have a significant effect on our results.

Data at anaerobic threshold were analyzed because exercise-induced hemoconcentration takes place above the anaerobic threshold. The relationship between $\dot{V}O_2$ at anaerobic threshold and hemoglobin at rest is more shallow than the one observed at peak exercise being the slope 74 and 109 ml/min/g/dl, respectively. Furthermore at multivariate analysis the relationship between resting hemoglobin and $\dot{V}O_2$ AT loses the statistical significance. Indeed, at the anaerobic threshold, hemoglobin has a lower role in determining $\dot{V}O_2$ compared to $\dot{V}O_2$ at peak exercise. This finding is not surprising considering that, at the anaerobic threshold, a reduction in oxygen delivery due to anemia can be still partially counteracted by an increase in cardiac output.

This study has some structural limitations, which should be acknowledged. Indeed, the cross sectional nature of this study does not permit to define, but only to suggest, a causal relationship between hemoglobin levels and exercise capacity. Finally, we had described a relationship for a population but this may not be an appropriate prediction in a single individual.

In conclusion our data show that, analyzing a relevant number of HF patients, a correlation between peak $\dot{V}O_2$ and hemoglobin exists with a slope equal to 109 ml/min/g/dl. Thus, albeit totally unproven, it is possible to suggest that $\dot{V}O_2$ should increase by approximately 109 ml/min for each g/dl of hemoglobin increase. Studies analyzing the acute effects of hemoglobin changes on exercise performance in anemic HF patients are needed.

References

1. Anand IS. Anemia and chronic heart failure implications and treatment options. J Am Coll Cardiol 2008;52:501–511.
2. Felker GM, Adams KF, Gattis WA; et al. Anemia as a risk factor and therapeutic target in heart failure. J Am Coll Cardiol 2004;44:959–966.
3. Mitchell JE. Emerging role of anemia in heart failure. Am J Cardiol 2007; 99:15D–20D.
4. Tang YD, Katz SD. The prevalence of anemia in chronic heart failure and its impact on the clinical outcomes. Heart Fail Rev 2008;13:387–392.
5. Kalra PR, Bolger AP, Francis DP; et al. Effect of anemia on exercise tolerance in chronic heart failure in men. Am J Cardiol 2003;91:888–891.
6. Witte KK, Desilva R, Chattopadhyay S; et al. Are hematinic deficiencies the cause of anemia in chronic heart failure? Am Heart J 2004;147:924–930.
7. Perego GB, Marenzi GC, Guazzi M; et al. Contribution of PO2, P50, and Hb to changes in arteriovenous O2 content during exercise in heart failure. J Appl Physiol 1996;80:623–631.
8. Agostoni PG, Wasserman K, Perego GB; et al. Non-invasive measurement of stroke volume during exercise in heart failure patients. Clin Sci (Lond) 2000; 98:545–551.
9. Agostoni P, Cattadori G. Non invasive cardiac output measurement: A new tool in heart failure. Cardiology 2009, in press.
10. Agostoni P, Bianchi M, Moraschi A; et al. Work-rate affects cardiopulmonary exercise test results in heart failure. Eur J Heart Fail 2005;7:498–504.
11. Beaver WL, Wasserman K, Whipp BJ. A new method for detecting anaerobic threshold by gas exchange. J Appl Physiol 1986;60:2020–2027.
12. Feigenbaum HAW., Ryan T., editors. Feigenbaum's Echocardiography, Lippincott: Williams and Wilkins; 2005. pp 214–216.
13. WHO/UNICEF/UNU. Iron deficency anaemia: Assessment, prevention, and control, Geneva, Switzerland: World Health Organization; 2001.
14. Felker GM, Shaw LK, O'connor CM. A standardized definition of ischemic cardiomyopathy for use in clinical research. J Am Coll Cardiol 2002;39:210–218.
15. Mcmurray JJ. What are the clinical consequences of anemia in patients with chronic heart failure? J Card Fail 2004;10:S10–S12.
16. Ezekowitz JA, Mcalister FA, Armstrong PW. Anemia is common in heart failure and is associated with poor outcomes: Insights from a cohort of 12 065 patients with new-onset heart failure. Circulation 2003;107:223–225.
17. Horwich TB, Fonarow GC, Hamilton MA; et al. Anemia is associated with worse symptoms, greater impairment in functional capacity and a significant increase in mortality in patients with advanced heart failure. J Am Coll Cardiol 2002;39:1780–1786.
18. Lang CC, Agostoni P, Mancini DM. Prognostic significance and measurement of exercise-derived hemodynamic variables in patients with heart failure. J Card Fail 2007;13:672–679.
19. Dickstein K, Cohen-Solal A, Filippatos G; et al. ESC guidelines for the diagnosis and treatment of acute and chronic heart failure 2008: The task force for the diagnosis and treatment of acute and chronic heart failure 2008 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association of the ESC (HFA) and endorsed by the European Society of Intensive Care Medicine (ESICM). Eur Heart J 2008;29:2388–2442.
20. Jessup M, Abraham WT, Casey DE; et al. 2009 focused update: ACCF/AHA guidelines for the diagnosis and management of heart failure in adults: A report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines: Developed in collaboration with the International Society for Heart and Lung Transplantation. Circulation 2009;119:1977–2016.
21. Mancini DM, Katz SD, Lang CC; et al. Effect of erythropoietin on exercise capacity in patients with moderate to severe chronic heart failure. Circulation 2003;107:294–299.
22. Palazzuoli A, Silverberg D, Iovine F; et al. Erythropoietin improves anemia exercise tolerance and renal function and reduces B-type natriuretic peptide and hospitalization in patients with heart failure and anemia. Am Heart J 2006;152:e1099–e1015.
23. Ponikowski P, Anker SD, Szachniewicz J; et al. Effect of darbepoetin alfa on exercise tolerance in anemic patients with symptomatic chronic heart failure: A randomized, double-blind, placebo-controlled trial. J Am Coll Cardiol 2007;49:753–762.
24. Okonko DO, Grzeslo A, Witkowski T; et al. Effect of intravenous iron sucrose on exercise tolerance in anemic and nonanemic patients with symptomatic chronic heart failure and iron deficiency FERRIC-HF: A randomized, controlled, observer-blinded trial. J Am Coll Cardiol 2008;51:103–112.
25. Toblli JE, Lombrana A, Duarte P; et al. Intravenous iron reduces NT-pro-brain natriuretic peptide in anemic patients with chronic heart failure and renal insufficiency. J Am Coll Cardiol 2007;50:1657–1665.
26. Van Veldhuisen DJ, Dickstein K, Cohen-Solal A; et al. Randomized, double-blind, placebo-controlled study to evaluate the effect of two dosing regimens of darbepoetin alfa in patients with heart failure and anaemia. Eur Heart J 2007;28:2208–2216.
27. Ghali JK, Anand IS, Abraham WT; et al. Randomized double-blind trial of darbepoetin alfa in patients with symptomatic heart failure and anemia. Circulation 2008;117:526–535.
28. Kourea K, Parissis JT, Farmakis D; et al. Effects of darbepoetin-alpha on quality of life and emotional stress in anemic patients with chronic heart failure. Eur J Cardiovasc Prev Rehabil 2008;15:365–369.
29. Van Der Meer P, Groenveld H, Januzzi JL; et al. Erythropoietin treatment in patients with chronic heart failure: A meta-analysis. Heart 2009;95:1309-1314.
30. Agostoni P, Wasserman K, Guazzi M; et al. Exercise-induced hemoconcentration in heart failure due to dilated cardiomyopathy. Am J Cardiol 1999;83: 278–280.
31. Agostoni P, Cerino M, Palermo P; et al. Exercise capacity in patients with beta-thalassaemia intermedia. Br J Haematol 2005;131:278–281.