Activation of the Ergoreceptors in Cardiac Patients With and Without Heart Failure

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ABSTRACT

Background: The presence of ergoreflex activity and its current relationship to hyperventilation and prognosis in cardiac patients is unclear. Therefore, we evaluated ergoreflex activity in cardiac patients with and without heart failure (CHF) as well as in healthy subjects, and we examined how ergoreceptor activity was related to a mortality risk score in CHF (MAGGIC).

Methods and Results: Twenty-five healthy subjects and 76 patients were included, among whom were 25 with ischemic heart disease (IHD), 24 with stable CHF, and 27 with unstable CHF. Ergoreflex activity was measured with a dynamic handgrip exercise, followed by post-handgrip regional circulatory occlusion (PH-RCO). Ergoreflex activity contributed significantly to ventilation (median [interquartile range] %V) in unstable CHF (81 [73-91] %V without PH-RCO, 92 [82−107] %V with PH-RCO, and 11 [6−20] difference in %V; $P < .001$) and was positively correlated with the MAGGIC risk score (Spearman $\rho = 0.431$; $P = .002$). No ergoreflex activity was observed in healthy subjects (−4 [−10 to 5] difference in %V), IHD (0 [−8 to 3] Diff in %V) and stable CHF (−3 [−11 to 6] difference in %V).

Conclusions: Ergoreflex activity contributes to hyperventilation, but only in CHF patients with persistent symptoms, and is closely related to the MAGGIC risk score. Ergoreflex activity was not present in patients with IHD or stable CHF, suggesting other reasons for the increased ventilatory drive in those patients. (*J Cardiac Fail 2014;20:747−754*)

Key Words: Ergoreflex, ventilation, MAGGIC risk score, heart failure, ischemic heart disease, healthy subjects.

Chronic heart failure (CHF) has been mainly characterized by exercise intolerance with symptoms of fatigue and breathlessness,[1] with the latter being expressed by ventilatory inefficiency during exercise. A steep ventilatory slope has been demonstrated not only with CHF, but also with ischemic heart disease (IHD)[2] with a similar prognostic value.[3]

Overactivity of the ergoreceptors, ie, skeletal muscle afferents, has been shown to contribute to the excessive ventilatory response in CHF with a detrimental impact on prognosis.[4−8] Pharmacologic treatment has changed over the past decades, with neurohormonal agents being recommended in CHF with reduced left ventricular ejection fraction (LVEF) because of their beneficial effect on hospitalization and premature death.[9] Despite their obvious effect on survival, their influence on exercise intolerance and its determinants is less clear.

Notwithstanding the presence of an increased ventilatory slope in a substantial number of patients with IHD, information on the ergoreflex is currently lacking. Also in healthy subjects, the role of the ergoreflex in ventilatory control remains rather unclear, with some studies reporting a contribution of the ergoreflex to ventilation and others stating that there is no involvement.[4,5,7,10]

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Therefore, the primary aim of the present study was to evaluate the presence of ergoreflex activity and its current relationship to the ventilatory response to exercise and exercise intolerance in a broad spectrum of subjects, ranging from healthy subjects and patients with IHD to stable and unstable CHF patients. In addition, we examined how activity of the ergoreceptors was related to a recently validated prognostic risk score in CHF patients developed by the Meta-Analysis Global Group in Chronic Heart Failure (MAGGIC).[11]

Methods

Study Population

Twenty-nine healthy subjects and 76 patients were prospectively included from April 2011 to March 2013. Healthy subjects were free from clinical signs or history of heart disease, diabetes, or pulmonary disease. A 1st patient group consisted of patients who had an ischemic event without signs of heart failure >1 month preceding the study (IHD; n = 25). A 2nd group were stable heart failure patients with reduced LVEF (≤45%) who had an episode of decompensation >1 month preceding the study and had no signs of fluid retention on the moment of testing (stable CHF; n = 24). A third group consisted of heart failure patients with reduced LVEF (≤45%) who were recently decompensated (<1 mo) and were still symptomatic despite optimal medical treatment (unstable CHF; n = 27). Heart failure patients with ischemic or nonischemic heart disease and who were treated according to the recommendations of the European Society of Cardiology (ESC) regarding medication—β-blocker, angiotensin-converting enzyme (ACE) inhibitor or angiotensin receptor blocker (ARB), and mineralocorticoid receptor antagonist (MRA)—and devices[9] were included. Seriously limiting musculoskeletal or neurologic disorders, such as recent orthopedic surgery (<6 mo), rheumatoid arthritis, or a cerebrovascular accident, with potential influence of the performance of the tests, were considered to be exclusion criteria.

Ethics

This study protocol was approved by the local Ethical Committees of the two participating hospitals (AZ Maria Middelares, Ghent, and Onze-Lieve-Vrouw Hospital, Aalst) and each of the participants gave informed consent. The clinical investigations were conducted according to the principles of the Declaration of Helsinki.

Risk Score Calculation

An integer risk score for predicting mortality was calculated in CHF patients (n = 51) with the use of the online calculator from the MAGGIC group.[11] The following predictors were included in the risk calculation: age, sex, diabetes, chronic obstructive pulmonary disease (COPD), time since diagnosis, current smoker, New York Heart Association (NYHA) functional class, the use of β-blockers and ACE inhibitors or ARB, body mass index (BMI), systolic blood pressure at rest, serum creatinine, and LVEF. A progressively higher risk score identified an increased risk for mortality within 1 and 3 years, expressed as the median [interquartile range]. According to the cumulative mortality risk over 3 years, patients were categorized into 6 risk groups in the original study.[11] Because of the small sample in the present study, CHF patients were classified into 3 risk groups: 24 patients were classified as having a low risk with a score ≤20 (1-y risk 6% [4%−9%], 3-y risk 15% [11%−22%]), 14 patients had a medium risk with a score 21−28 (1-y risk 15% [12%−18%], 3-y risk 36% [29%−40%]), and 13 patients had a high risk with a score >28 (1-y risk 32% [25%−46%], 3-y risk 63% [52%−79%]).

Ergoreflex Activity

Before the test, maximal handgrip force was measured with the nondominant arm as the greatest of the peak forces produced by 3 brief maximal handgrip contractions with a baseline pneumatic squeeze dynamometer . Ergoreflex activity was evaluated with the post-handgrip regional circulatory occlusion (PH-RCO) method, consisting of 2 parts which were performed in random order. Ventilatory parameters were measured (Cortex Metalyzer 3B breath-by-breath analysis) during 3 minutes of resting, followed by a rhythmic handgrip exercise at 50% of the predetermined maximal capacity until exhaustion (30 squeezes/min) and a recovery period of 3 minutes. After a pause of 30 minutes, the same exercise protocol was used, but followed by 3 minutes of blood flow stasis in the exercising arm by inflation of a forearm tourniquet 30 mm Hg above systolic pressure (PH-RCO). After the cuff was inflated, the subject was instructed to relax. Four of the 29 healthy subjects complained of pain or serious discomfort and were excluded from further analysis. This protocol has been shown to isolate the metabolic state of the muscle and to prolong the activation of the ergoreceptors.[10,12] Because the performance was not equal during the 2 parts of the tests, with a difference in peak exercise, ergoreflex activity was expressed as the percentage exercise response that was maintained during PH-RCO (2nd and 3rd minutes) compared with the percentage exercise response maintained during normal recovery (2nd and 3rd minutes).[4] The difference between these 2 percentages represents the

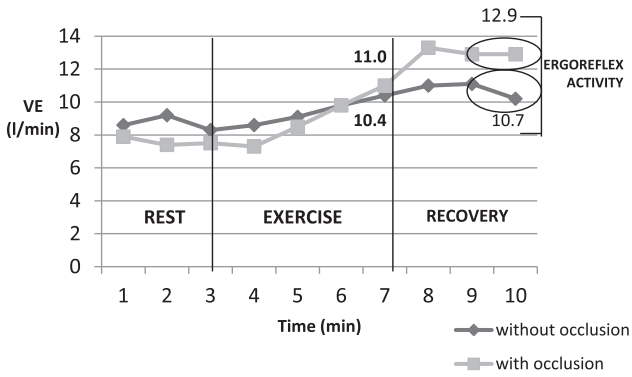

Fig. 1. Measurement of ergoreflex activity. Ergoreflex activity is expressed as the percentage exercise response that is maintained during recovery with occlusion (12.9/11.0 = 117%) compared with the percentage exercise response maintained during recovery without occlusion (10.7/10.4 = 103%). The difference between these 2 percentages represents the contribution of the ergoreflex activity to ventilation (difference in %V = 14%).