JACC: Heart Failure
© 2013 by the American College of Cardiology Foundation
Published by Elsevier Inc.

Vol. 1, No. 4, 2013
ISSN 2213-1779/$36.00
http://dx.doi.org/10.1016/j.jchf.2013.04.009

Adrenergic Activation, Fuel Substrate Availability, and Insulin Resistance in Patients With Congestive Heart Failure

Nir Uriel, MD, Jose Gonzalez-Costello, MD, Andrea Mignatti, MD, Kerry A. Morrison, BA, Nadav Nahumi, BA, Paolo C. Colombo, MD, Ulrich P. Jorde, MD

New York, New York

Objectives This study sought to investigate plasma levels of glucose and free fatty acids (FFA) and their relationship with adrenergic activation and insulin resistance (IR) in patients with advanced congestive heart failure (CHF).

Background Adrenergic activation and IR are hallmarks of advanced heart failure. The resulting changes in fuel substrate availability and their implications for exercise capacity have not been elucidated.

Methods Subjects with CHF underwent maximal exercise testing. Plasma glucose, FFA, insulin, and norepinephrine (NE) levels were measured at rest and at peak exercise. Beta-receptor sensitivity to NE was assessed using the Chronotropic Responsiveness Index (CRI). Homeostasis Model Assessment Index >2.5 defined IR. Left ventricular ejection fraction was estimated by 2-dimensional echocardiography.

Results Ninety-six subjects were enrolled. CHF subjects without IR (CHF/No-IR), but not those with IR (CHF/IR), significantly increased glucose and insulin in response to exercise. Only CHF/No-IR subjects increased FFA in response to exercise (0.14 ± 0.27 mmol/l; $p = 0.027$). NE increased significantly less with exercise, and CRI was lower in CHF/IR subjects compared with CHF/No-IR subjects (1.3 ± 1.4 vs. 2.5 ± 2.1; 6.4 ± 2.6 vs. 8.5 ± 3.4; $p = 0.069$). CRI correlated with the exercise-induced increase in FFA ($r = 0.41$; $p < 0.005$). These results stayed the same after excluding diabetic patients from the CHF/IR group.

Conclusions Circulating FFA levels increased during exercise in CHF subjects without IR, but not in those with IR or DM. Increased FFA availability during exercise may represent a catecholamine-dependent compensatory fuel shift in CHF. (J Am Coll Cardiol HF 2013;1:331–7) © 2013 by the American College of Cardiology Foundation

In congestive heart failure (CHF), profound changes in the rate of whole-body free fatty acids (FFA) and carbohydrate oxidation take place, although studies examining the direction of such fuel shifts, particularly in the failing human heart, have not led to clear conclusions (1). Some investigators have reported a shift away from FFA utilization (2), whereas others have reported a shift towards FFA utilization (3). Few studies have examined overall fuel utilization in patients with CHF during exercise and in vivo (4,5). In contrast to the prevailing paradigm that glucose is the preferred fuel in humans with CHF, at least 1 study suggests that FFA utilization is critically linked to reduced cardiac efficiency (5).

Overall fuel source utilization is governed by substrate availability and the organism's ability to use the substrate, which, in patients with CHF, may be affected by comorbid conditions such as diabetes (DM) or insulin resistance (IR), as well as pharmacotherapy and adrenergic activation (6,7). The availability of circulating fuel substrates in subjects with CHF receiving standard medical therapy during exercise has not been studied in regard to their status of IR. Accordingly, we examined resting and peak exercise levels of glucose, insulin, and norepinephrine (NE), as well as FFA, in subjects with advanced CHF on optimal medical therapy.

Methods

Patient population. Subjects with CHF were recruited from consecutive patients referred for a cardiopulmonary exercise test at New York Presbyterian Hospital–Columbia University Medical Center and were included if the following criteria were met: CHF, New York Heart Association class II to IV symptoms, left ventricular ejection fraction (LVEF) ≤40%, and optimal medical therapy including

From the Division of Cardiology, College of Physicians and Surgeons, Columbia University, New York, New York. This study was supported by National Institutes of Health grants R01HL45095 (to Dr. Jorde) and 1K23HL103795-01A1 (to Dr. Uriel). The authors have reported that they have no relationships relevant to the contents of this paper to disclose.

Manuscript received October 9, 2012; revised manuscript received April 2, 2013, accepted April 15, 2013.

JACC: Heart Failure Vol. 1, No. 4, 2013
August 2013:331–7

Abbreviations and Acronyms

BMI = body mass index
CHF = congestive heart failure
CRI = Chronotropic Responsiveness Index
DM = diabetes mellitus
FFA = free fatty acids
HOMA = Homeostasis Model Assessment
IR = insulin resistance
LVEF = left ventricular ejection fraction
NE = norepinephrine
pVo_2 = peak oxygen consumption

angiotensin-converting enzyme inhibitor or angiotensin receptor blocker and beta-blocker for at least 3 months unless contraindicated. Subjects were considered diabetic if this diagnosis had been made previously and they were taking antidiabetic medications. Nondiabetic subjects were categorized as insulin resistant if the Homeostasis Model Assessment (HOMA) Index was >2.5. Subjects were excluded if they had been hospitalized within 3 months for cardiovascular diseases or had noncardiac exercise-limiting illnesses, such as moderate-to-severe arthritis, peripheral vascular disease, or chronic obstructive pulmonary disease. Study approval was obtained from the institutional review board, and all subjects signed informed written consent.

Study protocol. Subjects were asked to withhold breakfast on the morning of the test and take their medication with water. After 20 min of supine rest, an 18- or 20-ga angiocatheter was inserted into a forearm vein, and blood for biochemical assessments was drawn. Subjects underwent a symptom-limited cardiopulmonary exercise test, and blood was again drawn immediately upon cessation of exercise. Samples were stored on ice after collection and promptly centrifuged at 1,550 *g* for 10 min. After separation, plasma aliquots were stored frozen at −80°C.

Study procedures. CARDIOPULMONARY EXERCISE TESTING. Peak oxygen consumption (pVo_2) in milliliters per kilogram per min (ml/kg/min) was assessed during graded treadmill exercise. Work rate increased continuously as a ramp function by augmenting the speed and grade of the treadmill according to the Naughton protocol (8). Heart rate and electrocardiograms were recorded continuously throughout the test, and blood pressure was measured at rest, every 2 min during exercise, and immediately upon cessation of exercise. Expired gases were collected throughout exercise, and oxygen consumption was calculated on a breath-by-breath basis using a metabolic cart (Medgraphics, St. Paul, Minnesota). Subjects exercised to exhaustion, and pVo_2 was defined as the highest value of oxygen uptake attained in the final 20 s of exercise.

Chronotropic Responsiveness Index (CRI), a measure of post-synaptic beta-receptor responsiveness to NE, was calculated using the following formula: (peak heart rate − baseline heart rate)/Log (peak norepinephrine − baseline norepinephrine) (9).

ECHOCARDIOGRAPHY. Echocardiograms were performed within 6 months of the Vo_2 study, and results were gathered from online charts. LVEF was estimated using 2-dimensional parasternal long, parasternal short, apical long, and apical short images.

BIOCHEMICAL ANALYSES. Plasma glucose was determined with a glucose oxidase method (GM7 Analyser, Analox Instruments, Hammersmith, United Kingdom). Insulin levels were determined in heparinized plasma by 2-site chemiluminescent immunometric assay (Diagnostic Products Corp., Los Angeles, California). Serum FFAs were determined with an enzymatic colorimetric method (Nefa C test, Wako Chemicals, Neuss, Germany). NE was determined by high-performance liquid chromatography separation and tandem mass spectrometric detection (API 4000, Applied Biosystems, Carlsbad, California) in the first 55 CHF patients.

We estimated IR using the HOMA Index, which is defined as fasting insulin (μU/ml) times fasting glucose (mmol/l) divided by 22.5 (10). A HOMA index >2.5 defined IR (11). Subjects using exogenous insulin were excluded from the HOMA index calculations.

Statistical analysis. Continuous variables are expressed as mean ± SD. Continuous variables were explored for normal distribution according to histograms and the Shapiro-Wilk test. In Tables 1 and 2, the comparison of quantitative variables between the CHF groups was performed using the Student *t* test for normally distributed variables and the Mann-Whitney *U* test for non-normally distributed variables. Categorical variables are expressed as number and percentage, and the chi-square test was used for comparisons with Fisher exact test when appropriate. In Figures 1 and 2, for the comparison of the change in glucose or FFA in response to exercise between diabetic patients, CHF subjects with IR (CHF/IR), and CHF subjects without IR (CHF/No-IR), we used the Kruskal-Wallis test. In Figure 3, for the comparison of the change in FFA in response to exercise according to the pVo_2 in quartiles, we used the Jonckheere-Terpstra test for trend. For the comparison between resting and exercise measurements (response to exercise), we used the paired-samples Wilcoxon test for non-normally distributed variables. Bivariate correlations were analyzed by the Pearson correlation coefficient, and the significance test was 2-tailed. For correlation analyses that involved the HOMA Index, we excluded patients with insulin-dependent DM because we did not control the administration of exogenous insulin before the study and the possible influence of this exogenous insulin on the HOMA Index. We performed backward method linear multiple regression analysis to predict the increase in FFA during exercise with an inclusion criteria of $p < 0.05$ and an exclusion criteria of $p > 0.10$. Analysis of residuals was performed. Significance was set at $p < 0.05$ (2-tailed). SPSS version 17 was used to perform all statistical evaluations (SPSS, Chicago, Illinois).

Results

Ninety-six subjects age 52.5 ± 12.5 years were enrolled. The etiology of CHF was ischemic cardiomyopathy in

Download English Version:

https://daneshyari.com/en/article/10165212

Download Persian Version:

https://daneshyari.com/article/10165212

Daneshyari.com