Clinical Trials

Identifying Biomarker Patterns and Predictors of Inflammation and Myocardial Stress

RUTH M. MASTERSON CREBER, PhD, MSc, RN,[1] CHRISTOPHER S. LEE, PhD, RN, FAHA, FAAN,[2] KENNETH MARGULIES, MD,[3] AND BARBARA RIEGEL, PhD, RN, FAAN, FAHA[4]

New York, New York; Portland, Oregon; and Philadelphia, Pennsylvania

ABSTRACT

Background: Regular exercise is recommended to improve outcomes in patients with heart failure. Exercise is known to decrease inflammation and thought to decrease myocardial stress; however, studies of exercise in heart failure have had mixed results on levels of N-terminal pro−B-type natriuretic peptide (NT-proBNP) and high-sensitivity C-reactive protein (hsCRP). A multimarker analysis may help to identify distinct subgroups of patients who respond to exercise. Our primary study objective was to identify common and distinct patterns of change in hsCRP and NT-proBNP and to quantify the influence of exercise therapy on the observed patterns of change.

Methods and Results: NT-proBNP and hsCRP were assessed in a random sample of 320 participants from the biomarker substudy of HF-ACTION, a randomized clinical trial of exercise training versus usual care in patients with stable and chronic heart failure. Growth mixture modeling was used to identify unique biomarker patterns over 12 months. Three statistically independent and clinically meaningful biomarker patterns of NT-proBNP and hsCRP were identified. Two patterns were combined and compared with the ''low/stable'' pattern, which was characterized by the lowest levels of NT-proBNP and hsCRP over time. Participants who were taking a loop diuretic and had hypertension or ischemic etiology were ∼2 times as likely to be in the ''elevated/worsening'' biomarker pattern. Participants randomized to the exercise intervention were less likely to be in the elevated/worsening pattern of NT-proBNP and hsCRP (relative risk ratio 0.56, 95% confidence interval 0.32−0.98; $P = .04$).

Conclusions: Exercise therapy was protective for reducing the frequency of membership in the elevated/worsening biomarker pattern, indicating that exercise may be helpful in delaying the progression of heart failure. (*J Cardiac Fail 2015;21:439−445*)

Key Words: Heart failure, biological markers, inflammation, exercise therapy.

From the [1]School of Nursing and Department of Biomedical Informatics, Columbia University, New York, New York; [2]School of Nursing, Oregon Health and Science University, Portland, Oregon; [3]School of Medicine, University of Pennsylvania, Philadelphia, Pennsylvania and [4]School of Nursing, University of Pennsylvania, Philadelphia, Pennsylvania.

Manuscript received August 19, 2014; revised manuscript received February 13, 2015; revised manuscript accepted February 20, 2015.

Reprint requests: Ruth M. Masterson Creber, PhD, MSc, RN, Columbia University, School of Nursing, 617 W 168th St, New York, NY 10032. Tel: 212-342-3755; Fax: 212-305-6937. E-mail: rm3284@cumc.columbia.edu

Funding: Predoctoral funding for Ruth Masterson Creber provided by NIH/NINR (F31NR014086−01) and the National Hartford Centers of Geriatric Nursing Excellence Patricia G. Archbold Scholarship program. Postdoctoral funding for Ruth Masterson Creber provided by NIH/NINR (T32 NR007969) at Columbia University School of Nursing. The original HF-ACTION trial was funded by 13 separate grants from NIH/NHLBI. The biomarker substudy was funded by a grant from Roche Diagnostics.

See page 444 for disclosure information.

1071-9164/$ - see front matter

© *2015 Elsevier Inc. All rights reserved.*

http://dx.doi.org/10.1016/j.cardfail.2015.02.006

Exercise therapy is considered to be a safe nonpharmacologic intervention to improve functional capacity[1] and clinical outcomes[2] for adults with heart failure. Moderate exercise routines (3−7 metabolic-equivalent hours per week) are associated with a decreased risk of clinical events.[3] Physiologically in patients with heart failure, exercise training improves myocardial contractility, perfusion, endothelial dysfunction,[4,5] angiogenesis,[6] and coronary and peripheral skeletal vessel dilation.[7] A challenge to the broad implementation of exercise training in heart failure is physiologic heterogeneity in response to exercise. That is, some patients respond to exercise therapy with reductions in peripheral hypoxia,[8] local inflammation[9] and resting heart rate,[10] whereas others do not. Accordingly, the primary aim of the present study was to identify common and distinct patterns of change in serum biomarkers

of systemic inflammation and myocardial stress among adults with stable heart failure who participated in an exercise trial. The secondary aim of this study was to identify sociodemographic and clinical predictors of the most unfavorable patterns of change in biomarkers of systemic inflammation and myocardial stress. We hypothesized that exercise therapy would be associated with more favorable patterns of change in biomarkers over time.

Materials and Methods

Study Population

This was a secondary analysis of data from a random selection of 320 participants in the biomarker substudy of Heart Failure: A Controlled Trial Investigating Outcomes of Exercise Training (HF-ACTION) randomized controlled trial. The full study design has been published previously.[2,11] Briefly, HF-ACTION was a multicenter randomized controlled trial designed to examine long-term safety and efficacy of aerobic exercise training in a large sample of medically stable chronic outpatients with heart failure. Enrollment criteria included reduced left ventricular ejection fraction (LVEF) of ≤35%, New York Heart Association (NYHA) functional class II−IV, and willingness to undergo exercise training. Patients were excluded if they could not exercise, were already habitual exercisers or had a cardiovascular event in the preceding 6 weeks. Participants were randomized from 82 centers within the United States, Canada, and France during 2003−2007 to a usual care or an aerobic exercise training group. The intervention entailed 36 supervised sessions followed by home-based training.

Participants performed a maximal exercise test with gas exchange measurements on a treadmill with the use of the modified Naughton protocol or a cycle ergometer with the use of a 10-W/min ramp protocol.[12] Functional exercise capacity was measured at baseline by means of peak oxygen consumption (mL kg^{-1} min^{-1}).[11] Blood samples were collected from a peripheral vein into EDTA-containing tubes, centrifuged immediately, and stored at −70°C.[11] All samples were obtained on the same day but before exercise testing at the baseline and 3- and 12-month visits.[13] Assays for all biomarkers were performed with the use of commercially available assays (Roche Diagnostics) at the Duke University central core laboratory.[13] Sociodemographic and clinical history characteristics were self-reported at baseline, and patients completed the Euroqol-5D questionnaire as a measure of baseline health status.[11]

The HF-ACTION randomized controlled trial was approved by all relevant Institutional Review Boards at the participating centers and the coordinating center.[11] This study was also approved by Institutional Review Boards at the University of Pennsylvania and Duke University.

Biomarker Measures

High-sensitivity C-reactive protein (hsCRP; mg/L) was selected as a marker of inflammation because it is associated with heart failure severity.[14,15] N-Terminal pro−B-type natriuretic peptide (NT-proBNP; pg/mL) was selected as a marker of myocardial stress and hemodynamic congestion because it is released in response to ventricular dilation, hypertrophy, and wall tension[16] and increases with the severity of ventricular dysfunction.[17] NT-proBNP is also used routinely in the clinical management of patients with heart failure as an indicator of heart failure progression.[13,18,19] In addition, standard, reproducible, and cost-effective assays are available for both biomarkers, making them useful for prognostication.[20,21] Both assays were also available in the HF-ACTION repository. Troponin was initially considered for this analysis, but it was not included because there were concerns about the analytic sensitivity and lack of variability (zero-inflation) of the assay.

Statistical Analysis

In the preliminary analysis, descriptive statistics of frequency, central tendency, and dispersion over time were used to describe hsCRP and NT-proBNP independently. Consistently with previous HF-ACTION publications,[13,22] raw values of NT-proBNP and hsCRP were log transformed to approximate normality. Mean values of ln(hsCRP) and ln(NT-proBNP) values were compared between the exercise training and usual care groups by means of analysis of covariance (ANCOVA), controlling for baseline biomarker values and treatment allocation. ANCOVA models that used the baseline biomarker value as the single covariate were used to test for differences between the usual care and intervention groups' mean ln(NTproBNP) and ln(hsCRP) values at baseline and 3 and 12 months.

The primary aim of this study was to identify common and distinct patterns of change in ln(hsCRP) and ln(NT-proBNP). Growth mixture modeling was used to identify subgroups of patients whose biomarker profiles differed at enrollment (ie, intercepts) and/or had unique patterns of change over time (ie, slopes). Common principles of model specification[23] were used, including: the significance of the adjusted and nonadjusted Lo-Mendell-Rubin likelihood ratio test,[24] entropy (close to 100%), the proportion of sample in each pattern (≥5%), and posterior probabilities (close to 1).[25] Individual growth mixture models for ln(NT-proBNP) and ln(hsCRP) were identified and then combined in a single model and each participant was assigned a ''most likely pattern'' based on conditional probabilities. Owing to the small size of 1 observed pattern, 2 related patterns were combined for further analyses. Baseline characteristics of the 2 patterns were described with the use of medians (interquartile ranges [IQRs]) or means (SDs) and frequencies (proportions) where appropriate. Unadjusted differences between the biomarker patterns were quantified with the use of t test, χ^2 analysis, or 1-way analysis of variance. Differences in peak oxygen consumption between the 2 patterns were compared to better understand the clinical relevance of the observed patterns.

Sociodemographic and clinical factors that influenced the likelihood of fitting in the unfavorable pattern were identified with the use of a model comparison approach[26] including bivariate analyses with the outcome ($P < .05$) and forward and backwards stepwise multivariable logistic regression modeling. Logistic regression was used to identify predictors of observed patterns; results are reported in adjusted odds ratios (ORs), 95% confidence intervals (CIs), and corresponding P values. Model fit was compared with the use of χ^2 likelihood ratio, pseudo R^2, Akaike information criterion, and bayesian information criterion tests. Mplus (version 7.0; Los Angeles, California) was used for all growth mixture modeling, and all other analyses were conducted with the use of StataMP v11.2(College Station, Texas).

Download English Version:

https://daneshyari.com/en/article/2958889

Download Persian Version:

https://daneshyari.com/article/2958889

Daneshyari.com