



6-2015

Identifying Biomarker Patterns and Predictors of Inflammation and Myocardial Stress


Ruth Masterson-Creber

Christopher S. Lee

Kenneth Margulies
University of Pennsylvania

Barbara Riegel
University of Pennsylvania, briegel@nursing.upenn.edu

Follow this and additional works at: <https://repository.upenn.edu/nrs>

 Part of the [Cardiology Commons](#), [Cardiovascular Diseases Commons](#), [Circulatory and Respiratory Physiology Commons](#), [Medical Humanities Commons](#), [Nursing Commons](#), and the [Preventive Medicine Commons](#)

Recommended Citation

Masterson-Creber, R., Lee, C. S., Margulies, K., & Riegel, B. (2015). Identifying Biomarker Patterns and Predictors of Inflammation and Myocardial Stress. *Journal of Cardiac Failure*, 21 (6), 439-445. <http://dx.doi.org/10.1016/j.cardfail.2015.02.006>

This paper is posted at ScholarlyCommons. <https://repository.upenn.edu/nrs/115>
For more information, please contact repository@pobox.upenn.edu.

Identifying Biomarker Patterns and Predictors of Inflammation and Myocardial Stress

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.

Keywords

Biomarkers, C-Reactive Protein, Exercise Test, Exercise Therapy, Female, Heart Failure, Humans, Inflammation, Male, Middle Aged, Myocardium, Natriuretic Peptide, Brain, Peptide Fragments, Predictive Value of Tests, Prognosis, Severity of Illness Index, Treatment Outcome

Disciplines

Cardiology | Cardiovascular Diseases | Circulatory and Respiratory Physiology | Medical Humanities | Medicine and Health Sciences | Nursing | Preventive Medicine



Published in final edited form as:

J Card Fail. 2015 June ; 21(6): 439–445. doi:10.1016/j.cardfail.2015.02.006.

Identifying Biomarker Patterns and Predictors of Inflammation and Myocardial Stress

Ruth M. Masterson Creber, PhD, MSc, RN,

Columbia University, School of Nursing and Department of Biomedical Informatics

Christopher S. Lee, PhD, RN, FAHA, FAAN,

Oregon Health & Science University

Kenneth Margulies, MD, and

University of Pennsylvania, School of Medicines

Barbara Riegel, PhD, RN, FAAN, FAHA

University of Pennsylvania, School of Nursing

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 multi-marker analysis may help identify distinct subgroups of patients who respond to exercise. The primary study objective was to identify common and distinct patterns of change in hsCRP and NT-proBNP and 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 sub-study 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 NTproBNP and hsCRP were identified. Two patterns were combined and compared to 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, had hypertension or ischemic etiology were about two 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, CI: 0.32–0.98, p=0.04).

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.

Corresponding Author: Ruth M. Masterson Creber, PhD, MSc, RN, Columbia University, School of Nursing, 617 W 168th St, NY, NY 10032, Tel: 212-342-3755, rm3284@cumc.columbia.edu.

Disclosures: The authors have nothing to disclose.

Keywords

heart failure; biological markers; inflammation; exercise therapy

Exercise therapy is considered a safe non-pharmacological intervention to improve functional capacity¹ and clinical outcomes² for adults with heart failure. Moderate exercise routines (3 to 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 inflammation⁹ and resting heart rate,¹⁰ while others do not. Accordingly, the primary aim of this 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 socio-demographic 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.

Methods

Study population

This was a secondary analysis of data from a random selection of 320 participants in the biomarker sub-study 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% or less, New York Heart Association (NYHA) class II to 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 from 2003–2007 to a usual care or 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, using the modified Naughton protocol, or a cycle ergometer, using a 10-Watt/min ramp protocol.¹² Functional exercise capacity was measured at baseline by peak oxygen consumption (mL/kg/min).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 prior to exercise testing at the baseline, 3-month, and 12-month visits.¹³ Assays for all biomarkers were performed using commercially available

assays (Roche Diagnostics, Inc.) at the Duke University central core laboratory.¹³ Socio-demographic and clinical history characteristics were self-reported at baseline and patients completed the EuroQol-5D 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 tension¹⁶ 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 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. Consistent 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 using 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, 3-and 12-months, respectively.

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 (i.e. intercepts) and/or had unique patterns of change over time (i.e. slopes). Common principles of model specification²³ were used including: the significance of the adjusted and non-adjusted Lo-Mendell-Rubin likelihood ratio test,²⁴ entropy (close to 100%), the proportion of sample in each pattern ($\geq 5\%$), 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. Due to the small size of one observed pattern, two related patterns were combined for further analyses. Baseline characteristics of the two patterns were described using medians (interquartile ranges) or means (SD) and frequencies (proportions) where

appropriate. Unadjusted differences between the biomarker patterns were quantified using t -test, χ^2 analysis or one-way analysis of variance. Differences in peak oxygen consumption between the two patterns were compared to better understand the clinical relevance of the observed patterns.

Socio-demographic and clinical factors that influenced the likelihood of fitting in the unfavorable pattern were identified using a model comparison approach²⁶ including: bivariate analyses with the outcome ($p < 0.05$) 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 using: χ^2 likelihood ratio, pseudo R^2 , AIC, and BIC tests. Mplus (version v.7.0, Los Angeles, CA) was used for all growth mixture modeling and all other analyses were conducted in StataMP v11.2 (College Station, Texas).

Results

Baseline characteristics for this sample ($n=320$) are reported in Table 1. Overall, the median age was 58 years, the majority of the sample was male (73%), NYHA class II (71%) with a median left ventricular ejection fraction (LVEF) of 24 percent. Just over one-third of participants had a history of diabetes (34%) or previous myocardial infarction (39%) and approximately two-thirds had hypertension (60%). The vast majority of participants in this study were treated with evidence-based therapies, including over 95% on an angiotensin-converting-enzyme inhibitor or angiotensin II receptor blocker and 93% on a beta-blocker. Almost 50% of the sample was on a statin medication and almost 14% had an implanted biventricular pacemaker.

Baseline socio-demographic and clinical characteristics were compared between the original parent cohort and this subgroup. In general, this subpopulation was representative of the parent cohort, but there were significant differences in the proportions of patients in NYHA class II at baseline in this sample versus the total population (71% versus 63%, $p=0.008$). There were no statistically significant differences between the means in the usual care and intervention groups for $\ln(\text{NT-proBNP})$ between baseline and 3 months ($p=0.499$) or baseline and 12 months ($p=0.471$). There were also no differences in $\ln(\text{hsCRP})$ from baseline to 3 months ($p=0.168$) or baseline to 12 months ($p=0.193$) between the usual care and intervention groups (Figure 1). Thus, growth mixture modeling was used to further identify and describe potential underlying patterns.

Identification of Multiple Patterns of Change in Biomarkers Over Time

Three statistically independent and clinically meaningful biomarker patterns of NTproBNP and hsCRP were identified (entropy = 0.79, Lo-Mendell Rubin adjusted likelihood ratio test $p=0.02$, and average posterior probabilities = 0.87–0.93 all indicating a good model solution) (Figure 2). Based on the observed characteristics of NT-proBNP and hsCRP, the first and smallest pattern of change ($n=15$ [5%]; average posterior probability was 0.90) had the highest levels of NT-proBNP at baseline that did not change over time ($p=0.827$) and hsCRP increased significantly over 12 months ($p < 0.001$). The second pattern of change

(n=197 [61%]; average posterior probability = 0.92) was characterized by lower levels of NT-proBNP and hsCRP at baseline, and there were significant declines in both NT-proBNP (p=0.006) and hsCRP (p<0.001) over the course of 12-months. The third pattern (n=108 [34%]; average posterior probability = 0.87) had higher hsCRP (p<0.001) and similar NT-proBNP levels (p=0.885) compared with the second pattern at baseline and improvements in hsCRP over the 12-month follow-up period (p=0.017). Due to the small size of the first pattern, the first and third patterns were combined and labeled “elevated/worsening” (n=123). On average, peak oxygen consumption was lower at baseline among patients with the *elevated/worsening* biomarker pattern compared with those with the *low/stable* biomarker pattern and this difference held over time (Figure 3).

Identification of Biomarker Pattern Determinants—Determinants of the *elevated/worsening* biomarker pattern are presented in Table 2, (model $\chi^2=67.31$, p<0.001, pseudo $R^2=16.5\%$). The odds of being in the *elevated/worsening* pattern were almost two times higher for patients with ischemic etiology, hypertension or for those on loop diuretics and 9% higher for each unit increase in body mass index. The variables in the model offer fair prognostication for the *elevated/worsening* pattern (area under the curve: 0.716). Having diabetes was associated with reduced odds of having the *elevated/worsening* biomarker pattern. Finally, participants who were randomized to the exercise group were much less likely than those in the usual care group to have the *elevated/worsening* biomarker pattern.

Discussion

In this random sample of 320 participants from the biomarker sub-study of the HF-ACTION trial, we observed two clinically relevant patterns of change in biomarkers of myocardial stress and systemic inflammation. One pattern was characterized by elevated myocardial stress and inflammation and the other was characterized by lower myocardial stress and decreasing inflammation over 12-months. Traditional markers of disease severity were associated with being in the elevated/worsening biomarker pattern. Exercise therapy provided a protective effect for not being associated with the elevated/worsening biomarker, which supports the potential for exercise therapy to contribute to slowing the progression of heart failure.²⁷

The finding that there are no mean differences in mean ln(NT-proBNP) or ln(hsCRP) over time between the exercise and usual care group are consistent with the study by Ahmad and colleagues that used a sample of 928 participants from the HF-ACTION study.²² Ahmad and colleagues reported that exercise training (measured by volume of exercise) was not associated with numerical decreases in NT-proBNP and hsCRP from baseline to 3-months.²² In an effort to further explain the relationship between these biomarkers (NT-proBNP and hsCRP) and exercise therapy, this study used growth mixture modeling to identify distinct multi-marker biomarker patterns. This methodology is especially relevant for a heterogeneous heart failure population, where being able to identify distinct patterns is clinically informative. When NT-proBNP and hsCRP were combined into distinct multi-marker patterns, we identified a small third pattern with rising hsCRP over 12-months. The characteristics of this pattern may partially explain why they did not find a statistically significant mean reduction in hsCRP in the exercise therapy group compared to usual care.

The findings reported here are consistent with results from the Cardiovascular Health Study (CHS), in which deFilippi and colleagues reported a protective effect of moderate physical activity on the risk of developing heart failure, neurohormonal activation (measured by NT-proBNP) and cardiac injury (measured by Troponin T).²⁸

When comparing the *elevated/worsening* and *low/stable* patterns, participants randomized to the exercise therapy intervention were less likely to have the *elevated/worsening* pattern. Hypertension was associated with two times the risk of being in the *elevated/worsening* compared to *low/stable* pattern, along with other measures of severity—being on a loop diuretic or having heart failure of ischemic etiology. Many patients with reduced renal function also have hypertension, which can cause left ventricular hypertrophy and elevated natriuretic peptides.²⁹ Hypertension and hsCRP have also been associated in other studies due to shared mechanisms of oxidative stress and endothelial dysfunction.³⁰ Specifically, hsCRP is known to attenuate nitric oxide production and decrease endothelial nitric oxide synthase expression leading to vasoconstriction and atherothrombosis.²⁰ The association between elevated hsCRP and hypertension is consistent across multiple racial and ethnic groups.^{31,32}

Higher BMI was associated with the *elevated/worsening* biomarker pattern. An inverse relationship between BMI and NT-proBNP has been reported in many other studies,^{33–37} one theory is that there is increased clearance of NT-proBNP by type C natriuretic peptide receptors on adipocytes.³⁸ In obese patients, natriuretic peptides are still routinely used for diagnostic purposes, but at lower cutoff levels.³⁶

Diabetes was also associated with a lower risk of being in the *elevated/worsening* pattern. This may be explained by a higher proportion of diabetic patients being on a statin medication compared to non-diabetics (59% versus 43%). Statins are associated with reduced hsCRP in diabetic patients.³⁹ The apparently protective effect of diabetes may be due to chance, or it might be related to the fact that diabetic participants were less likely than non-diabetic participants to have ischemic etiology (44% versus 56%). However, controlling for statin use and ischemic vs. non-ischemic etiology in post-hoc models did not change the strength of the relationship between diabetes and the risk of having the hazardous patterns of change in these biomarkers. More research is needed to further explore associations among diabetes and other comorbidities in heart failure and the systemic inflammatory and myocardial stress responses to exercise.

Strengths and Limitations

One potential limitation of this study is its generalizability because it was conducted on a random sample of the biomarker sub-study chosen from those with nearly complete data. Although it is unlikely that our results were solely a function of sample selection, it is possible that if this analysis were done on in the entire dataset that the results would be different. It should be noted that this random sample was representative of the larger HF-ACTION trial population. Although we successfully identified statistically distinct biomarker subgroups and corresponding predictors, further testing in a larger sample may increase the precision of the estimates. Given that the measure of exercise was randomization to the exercise intervention, rather than quantity, it is likely that the protective

effect of exercise would be stronger if adherence were accounted for. Another limitation is that we had data at three time points and this is the minimum number of data points for growth mixture modeling. Further description of the patterns, including possible curvilinear or nonlinear growth patterns would only be possible with additional measurement points. The final limitation is that the exercise therapy group tended to have lower NT-proBNP at baseline, though this difference was not statistically significant ($p=0.083$). This slight imbalance at randomization is unlikely to account for the protective effect of exercise therapy reported in this study.

The growth mixture modeling analytic approach was a major strength of this study because it allowed for the identification of previously unobserved biomarker patterns of change. Though traditionally biomarkers have been considered individually,¹⁶ multi-marker strategies are now recommended to improve risk stratification and prediction in chronic heart failure.^{16,40,41} As such, it is a useful analytic tool for helping to explain the heterogeneity in response to exercise therapy that is common among patients with heart failure. Another strength of this study was that it built on the results of the Ahmad study,²² demonstrating how different types of biomarker analyses can help to explain how exercise may be able to slow or prevent the progression of heart failure.²⁷

There are many related avenues for future research around exercise and heart failure, including further elucidation of mechanisms of benefit, identifying which biomarkers are modified by exercise, quantifying the dose of exercise needed to achieve a benefit, and identifying ways to engage heart failure patients in exercise.²⁷ There is also a strong need to identify different exercise regimens for patients with heart failure and prevalent comorbid conditions such as type 2 diabetes. In the future, multi-marker biomarker analyses of exercise interventions may also be able to clarify which patients can be expected to benefit from exercise by demonstrating the mechanism by which exercise slows the progression of heart failure.²⁷

Acknowledgments

We would like to thank Dr. Stephen Ellis from Duke University for developing the HF-ACTION dataset, approving the data analysis plan and summary and reviewing the final manuscript. We would also like to acknowledge Dr. Houry Puzantian for providing insight into the relationship between diabetes and the *elevated/worsening* pattern.

Funding: The authors gratefully acknowledge the pre-doctoral 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. We also acknowledge the post-doctoral funding for Ruth Masterson Creber 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 bio-marker sub-study was funded by a grant from Roche Diagnostics.

References

1. Pina IL, Apstein CS, Balady GJ, et al. Exercise and heart failure: A statement from the American Heart Association Committee on exercise, rehabilitation, and prevention. *Circulation*. Mar 4; 2003 107(8):1210–1225. [PubMed: 12615804]
2. O'Connor CM, Whellan DJ, Lee KL, et al. Efficacy and safety of exercise training in patients with chronic heart failure: HF-ACTION randomized controlled trial. *JAMA*. Apr 8; 2009 301(14):1439–1450. [PubMed: 19351941]

3. Keteyian SJ, Leifer ES, Houston-Miller N, et al. Relation between volume of exercise and clinical outcomes in patients with heart failure. *J Am Coll Cardiol*. Nov 6; 2012 60(19):1899–1905. [PubMed: 23062530]
4. Downing J, Balady GJ. The role of exercise training in heart failure. *J Am Coll Cardiol*. Aug 2; 2011 58(6):561–569. [PubMed: 21798416]
5. Kappagoda T, Amsterdam EA. Exercise and heart failure in the elderly. *Heart Fail Rev*. Sep; 2012 17(4–5):635–662. [PubMed: 22327748]
6. Piepoli MF, Davos C, Francis DP, Coats AJ. Exercise training meta-analysis of trials in patients with chronic heart failure (ExTraMATCH). *Bmj*. Jan 24.2004 328(7433):189. [PubMed: 14729656]
7. Hambrecht R, Fiehn E, Weigl C, et al. Regular physical exercise corrects endothelial dysfunction and improves exercise capacity in patients with chronic heart failure. *Circulation*. Dec 15; 1998 98(24):2709–2715. [PubMed: 9851957]
8. Niebauer J, Clark AL, Webb-Peploe KM, Boger R, Coats AJ. Home-based exercise training modulates pro-oxidant substrates in patients with chronic heart failure. *Eur J Heart Fail*. Mar 2; 2005 7(2):183–188. [PubMed: 15701464]
9. Gielen S, Adams V, Mobius-Winkler S, et al. Anti-inflammatory effects of exercise training in the skeletal muscle of patients with chronic heart failure. *J Am Coll Cardiol*. Sep 3; 2003 42(5):861–868. [PubMed: 12957433]
10. Gielen S, Schuler G, Adams V. Cardiovascular effects of exercise training: molecular mechanisms. *Circulation*. Sep 21; 2010 122(12):1221–1238. [PubMed: 20855669]
11. Whellan DJ, O'Connor CM, Lee KL, et al. Heart failure and a controlled trial investigating outcomes of exercise training (HF-ACTION): design and rationale. *Am Heart J*. Feb; 2007 153(2):201–211. {Whellan, 2007 #3165}. [PubMed: 17239677]
12. Wilson JR. Exercise and the failing heart. *Cardiol Clin*. 1987; 5:171–181. [PubMed: 3555795]
13. Felker GM, Whellan D, Kraus WE, et al. N-terminal pro-brain natriuretic peptide and exercise capacity in chronic heart failure: data from the Heart Failure and a Controlled Trial Investigating Outcomes of Exercise Training (HF-ACTION) study. *Am Heart J*. Oct; 2009 158(4 Suppl):S37–44. [PubMed: 19782787]
14. Elster SK, Braunwald E, Wood HF. A study of C-reactive protein in the serum of patients with congestive heart failure. *Am Heart J*. Apr; 1956 51(4):533–541. [PubMed: 13302128]
15. Seta Y, Shan K, Bozkurt B, Oral H, Mann DL. Basic mechanisms in heart failure: the cytokine hypothesis. *J Card Fail*. Sep; 1996 2(3):243–249. [PubMed: 8891862]
16. Braunwald E. Biomarkers in Heart Failure. *NEJM*. 2008; 258:2148–2159. [PubMed: 18480207]
17. Davis M, Espiner E, Richards G, et al. Plasma brain natriuretic peptide in assessment of acute dyspnoea. *Lancet*. Feb 19; 1994 343(8895):440–444. [PubMed: 7905953]
18. Hinderliter AL, Blumenthal JA, O'Conner C, et al. Independent prognostic value of echocardiography and N-terminal pro-B-type natriuretic peptide in patients with heart failure. *American Heart Journal*. 2008; 156(6):1191–1195. [PubMed: 19033018]
19. Felker GM, Petersen JW, Mark DB. Natriuretic peptides in the diagnosis and management of heart failure. *CMAJ*. Sep 12; 2006 175(6):611–617. [PubMed: 16966666]
20. Bassuk SS, Rifai N, Ridker PM. High-sensitivity C-reactive protein: Clinical Importance. *Current Problems in Cardiology*. 2004; 29(8):439–493. [PubMed: 15258556]
21. Apple FS, Wu AHB, Jaffe AS, et al. National Academy of Clinical Biochemistry and IFCC Committee for Standardization of Markers of Cardiac Damage Laboratory Medicine Practice Guidelines: Analytical Issues for Biomarkers of Heart Failure. *Circulation*. 2007; 116(5):e95–e98. [PubMed: 17630411]
22. Ahmad T, Fiuzat M, Mark DB, et al. The effects of exercise on cardiovascular biomarkers in patients with chronic heart failure. *Am Heart J*. Feb; 2014 167(2):193–202.e191. [PubMed: 24439980]
23. Ram N, Grimm KJ. Methods and measures: Growth mixture modeling: A method for identifying differences in longitudinal change among unobserved groups. *International Journal of Behavioral Development*. 2009; 33:565–576. [PubMed: 23885133]
24. Lo YMN, Rubin DB. Testing the number of components in a normal mixture. *Biometrika*. 2001; 88:767–778.

25. Nylund K, Muthen B. Deciding on the number of classes in latent class analysis and growth mixture modeling: A monte carlo simulation study. *Struct Equ Modeling*. 2007; 14:535–569.
26. Maxwell, SE.; Delancey, H. *Designing experiments and analyzing data: A model comparison perspective*. 2. Mahwah, NJ: Erlbaum; 2004.
27. O'Connor CM, Ahmad T. Can we prevent heart failure with exercise? *J Am Coll Cardiol*. Dec 18; 2012 60(24):2548–2549. [PubMed: 23158537]
28. deFilippi CR, de Lemos JA, Tkaczuk AT, et al. Physical activity, change in biomarkers of myocardial stress and injury, and subsequent heart failure risk in older adults. *J Am Coll Cardiol*. Dec 18; 2012 60(24):2539–2547. [PubMed: 23158528]
29. Slavin L, Daniels LB, Maisel AS. Use of biomarkers in evaluation of patients with heart failure. *Contrib Nephrol*. 2010; 164:88–117. [PubMed: 20427997]
30. Jialal I, Devaraj S, Siegel D. CRP induces hypertension in animal models: homo sapiens says no. *Hypertens Res*. Jul; 2011 34(7):801–802. [PubMed: 21593738]
31. Lakoski SG, Cushman M, Palmas W, Blumenthal R, D'Agostino RB, Herrington DM. The Relationship Between Blood Pressure and C-Reactive Protein in the Multi-Ethnic Study of Atherosclerosis (MESA). *Journal of the American College of Cardiology*. 2005; 46(10):1869–1874. [PubMed: 16286174]
32. Kong H, Qian YS, Tang XF, et al. C-reactive protein (CRP) gene polymorphisms, CRP levels and risk of incident essential hypertension: findings from an observational cohort of Han Chinese. *Hypertens Res*. Oct; 2012 35(10):1019–1023. [PubMed: 22763479]
33. Wang TJ, Larson MG, Levy D, et al. Impact of age and sex on plasma natriuretic peptide levels in healthy adults. *Am J Cardiol*. Aug 1; 2002 90(3):254–258. [PubMed: 12127613]
34. Mehra MR, Uber PA, Park MH, et al. Obesity and suppressed B-type natriuretic peptide levels in heart failure. *J Am Coll Cardiol*. May 5; 2004 43(9):1590–1595. [PubMed: 15120816]
35. Wang TJ, Larson MG, Levy D, et al. Impact of obesity on plasma natriuretic peptide levels. *Circulation*. Feb 10; 2004 109(5):594–600. [PubMed: 14769680]
36. Daniels LB, Clopton P, Bhalla V, et al. How obesity affects the cut-points for B-type natriuretic peptide in the diagnosis of acute heart failure. Results from the Breathing Not Properly Multinational Study. *Am Heart J*. May; 2006 151(5):999–1005. [PubMed: 16644321]
37. Das SR, Drazner MH, Dries DL, et al. Impact of body mass and body composition on circulating levels of natriuretic peptides: results from the Dallas Heart Study. *Circulation*. Oct 4; 2005 112(14):2163–2168. [PubMed: 16203929]
38. Sarzani R, Dessi-Fulgheri P, Paci VM, Espinosa E, Rappelli A. Expression of natriuretic peptide receptors in human adipose and other tissues. *J Endocrinol Invest*. Oct; 1996 19(9):581–585. [PubMed: 8957740]
39. Chu AY, Guilianini F, Barratt BJ, Nyberg F, Chasman DI, Ridker PM. Pharmacogenetic determinants of statin-induced reductions in C-reactive protein. *Circ Cardiovasc Genet*. Feb 1; 2012 5(1):58–65. [PubMed: 22230323]
40. Allen LA, Felker GM. Multi-marker strategies in heart failure: clinical and statistical approaches. *Heart Failure Reviews*. 2009; 15(4):343–349. [PubMed: 19412735]
41. Ky B, French B, Levy WC, et al. Multiple biomarkers for risk prediction in chronic heart failure. *Circ Heart Fail*. Mar 1; 2012 5(2):183–190. [PubMed: 22361079]

Highlights

- We model two biomarkers of hsCRP and NT-proBNP using growth mixture modeling.
- Growth mixture models are well suited for identifying variations in therapeutic responses in important patient subgroups in a heterogeneous syndrome like heart failure.
- Multi-marker analytic strategies can provide more information than single biomarker analyses alone.
- Exercise therapy may helpful for delaying the progression of heart failure.

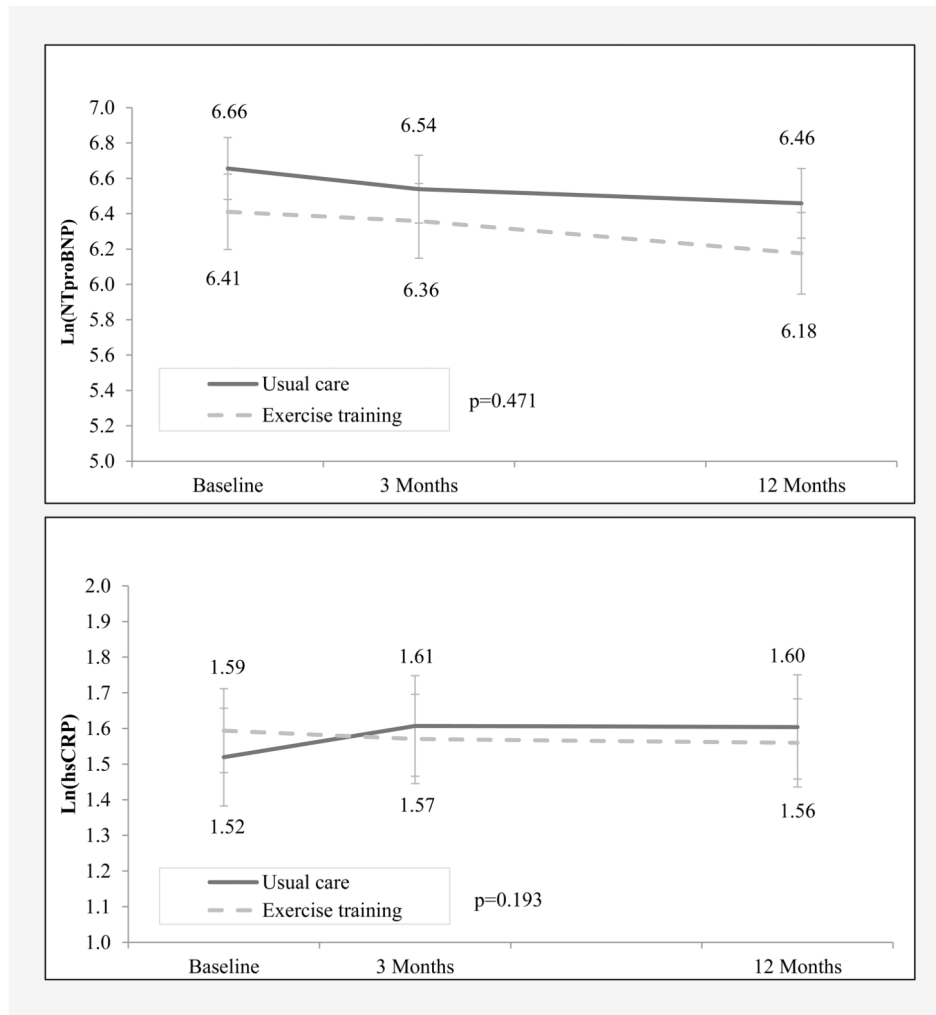


Figure 1.

This figure reports no statistically significant change in mean $\ln(\text{NT-proBNP})$ and $\ln(\text{hsCRP})$ between baseline and 12-months with 95% confidence intervals over time between the usual care and exercise training groups. P-values reported are from ANCOVA models adjusted for baseline biomarker values and treatment allocation.

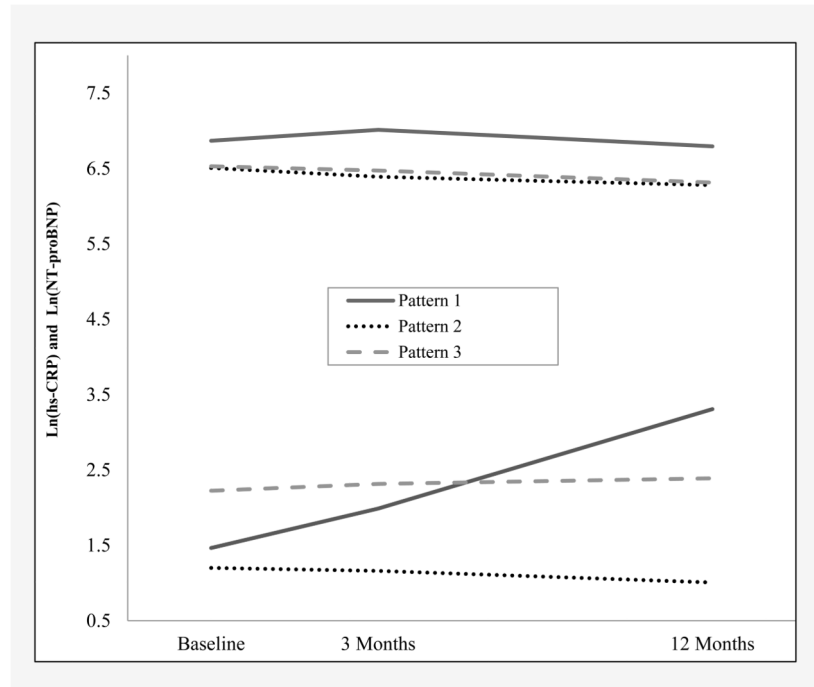


Figure 2. Three statistically independent and clinically meaningful biomarker patterns of $\ln(\text{NTproBNP})$ and $\ln(\text{hsCRP})$ are presented. Patterns 1 and 3 were combined and labeled “elevated/worsening” and compared to Pattern 2, labeled “low/stable.” For economy of presentation, error bars were not included in this figure.

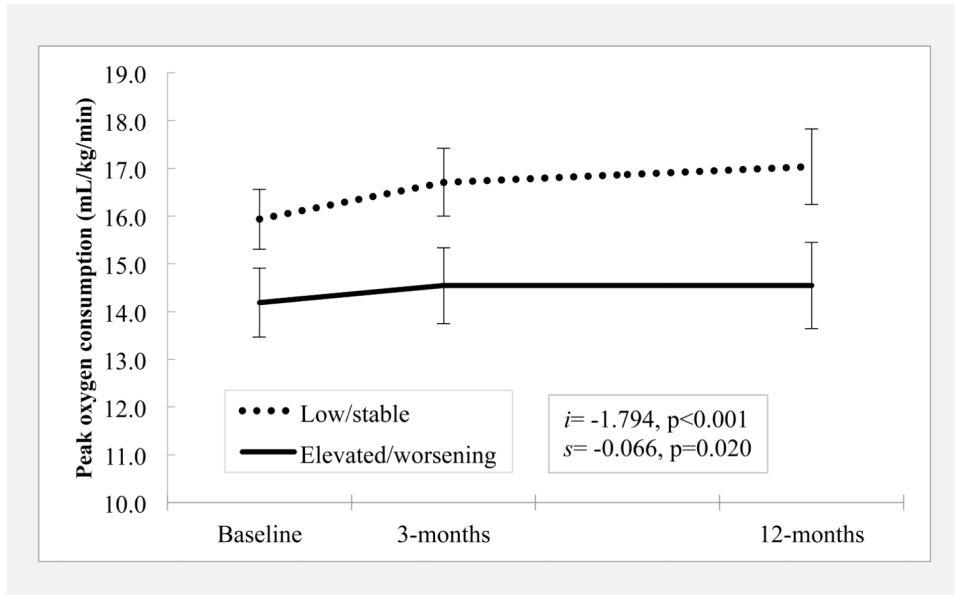


Figure 3. Differences in changes in peak oxygen consumption are presented comparing *elevated/worsening* (dotted line) and *low/stable* (solid line) patterns. Differences in the intercept (i) indicate that baseline values of peak oxygen consumption were higher in the *low/stable* pattern at baseline relative to the *elevated/worsening* pattern. Differences in the slope (s) indicate that the change over time was statistically significant ($p=0.020$) comparing the *elevated/worsening* and *low/stable* patterns over one-year.

Table 1a

Baseline demographic and clinical characteristics by biomarker pattern at baseline

| Variables (% , median/IQR) | Overall (N=320) | Low/stable (n=197) | Elevated/Worsening (n=123) | p-value |
|------------------------------------|-----------------|--------------------|----------------------------|---------|
| Usual care | 157 (49) | 92 (47) | 65 (53) | |
| Exercise training | 163 (51) | 105 (53) | 58 (47) | |
| Age | 58 (51, 67) | 59 (51, 69) | 57 (52, 65) | 0.18 |
| Female sex | 86 (27) | 48 (24) | 38 (31) | 0.20 |
| Race (n=315) | | | | 0.53 |
| Black or Other | 112 (36) | 66 (34) | 46 (38) | |
| White | 203 (64) | 127 (66) | 76 (62) | |
| New York Heart Association class | | | | 0.14 |
| II | 226 (71) | 145 (74) | 81 (66) | |
| III/IV | 94 (29) | 52 (26) | 42 (34) | |
| Ischemic etiology | 167 (52) | 96 (49) | 71 (58) | 0.12 |
| Diabetes mellitus | 108 (34) | 69 (35) | 39 (32) | 0.54 |
| Previous myocardial infarction | 126 (39) | 80 (41) | 46 (37) | 0.57 |
| Hypertension | 194 (60) | 113 (57) | 81 (66) | 0.13 |
| Atrial fibrillation | 64 (20) | 36 (18) | 28 (23) | 0.33 |
| Clinical values | | | | |
| Left ventricular ejection fraction | 24 (21, 30) | 25 (21, 30) | 24 (20, 30) | 0.46 |
| Systolic blood pressure, mm Hg | 112 (102, 130) | 113 (102, 130) | 110 (100, 130) | 0.41 |
| Diastolic blood pressure, mm Hg | 70 (61, 80) | 70 (60, 80) | 70 (62, 78) | 0.98 |
| Sodium, mEq/L | 139 (138, 141) | 140 (138, 141) | 139 (137, 141) | 0.68 |
| Creatinine, mg/dL, (n=294) | 1.2 (1.0, 1.5) | 1.1 (1.0, 1.4) | 1.2 (1.0, 1.5) | 0.13 |
| BUN, mg/dL, (n=292) | 20 (15, 27) | 19 (15, 25) | 22 (15, 31) | 0.09 |
| Beck Depression Index, (n=318) | 8 (4, 15) | 7 (4, 15) | 9 (4, 15) | 0.13 |

Data are complete for all 320 participants unless otherwise indicated, p-values indicate difference in mean values between biomarker subgroups for continuous variables.

Abbreviations: IQR: interquartile range; BUN: blood urea nitrogen

Table 1b

Medication use, functional status and EuroQol-5D by biomarker pattern at baseline

| Baseline use of medications and devices (%) | | | | |
|--|----------------------|----------------------|----------------------|---------|
| ACE inhibitor or ARB | 305 (95) | 189 (96) | 116 (94) | 0.50 |
| B-blocker | 299 (93) | 183 (93) | 116 (94) | 0.62 |
| Loop diuretic | 241 (75) | 135 (69) | 106 (86) | 0.001* |
| Statin | 156 (49) | 98 (50) | 58 (47) | 0.65 |
| ICD | 118 (37) | 63 (32) | 55 (45) | 0.02* |
| Pacer | 61 (19) | 33 (17) | 28 (23) | 0.18 |
| Biventricular pacemaker | 44 (14) | 20 (10) | 24 (20) | 0.02* |
| Functional measures (median, IQR) | | | | |
| PkV02, mL/kg/min | 15.2 (12.2, 17.8) | 15.6 (13.1, 18.2) | 13.5 (11.3, 16.9) | 0.001* |
| Body mass index, kg/m ² | 30 (26, 35) | 29 (25, 33) | 32 (28, 38) | <0.001* |
| 6 min walk, m (n=312) | 384.0 (314.9, 440.2) | 384.8 (320.0, 441.9) | 383.0 (306.3, 435.9) | 0.26 |
| EuroQol-5D (%) | | | | |
| Question 4: Pain/Discomfort (n=317) | | | | |
| No pain or discomfort | 149 (47) | 102 (52) | 41 (39) | 6 (40) |
| Moderate pain | 161 (51) | 90 (46) | 62 (59) | 9 (60) |
| Extreme pain | 7 (2.2) | 4 (2.0) | 3 (28) | 0 (0) |
| Question 5: Anxiety (n=318) | | | | |
| Not anxious | 187 (59) | 118 (61) | 62 (57) | 7 (47) |
| Moderately/Extremely anxious | 131 (41) | 77 (39) | 46 (43) | 8 (53) |

Data are complete for all 320 participants unless otherwise indicated, p-values indicate difference in mean values between biomarker subgroups for continuous variables.

Abbreviations: ACE: angiotensin-converting-enzyme; ARB: angiotensin II receptor blocker; ICD: implantable cardioverter-defibrillator; IQR: interquartile range; PkV02: Peak oxygen consumption

* p-values are significant (<0.05) between the biomarker patterns

Table 2

Predictors of the “elevated/worsening” biomarker pattern

| Variable | Odds Ratio | 95% Confidence Interval | p-value |
|-------------------------------------|------------|-------------------------|---------|
| Exercise group | 0.56 | 0.32 – 0.98 | 0.04 |
| Ischemic etiology | 1.93 | 1.03 – 3.65 | 0.04 |
| Loop diuretic | 2.32 | 1.16 – 4.63 | 0.02 |
| Hypertension | 2.00 | 1.10 – 3.63 | 0.02 |
| Body mass index | 1.09 | 1.04 – 1.14 | <0.01 |
| Diabetes | 0.49 | 0.27 – 0.90 | 0.02 |
| Peak oxygen consumption (mL/kg/min) | 0.92 | 0.86 – 1.00 | 0.06 |

Factors included in the models included: randomization to the exercise intervention or usual care, gender, race, age, heart failure etiology, baseline peak oxygen consumption, body mass index, pain or anxiety (assessed with EuroQol-5D), diabetes, hypertension, taking a loop diuretic, implantation of a pacemaker, bi-ventricular pacer or implantable cardioverter-defibrillator, treatment with an angiotensin-converting-enzyme inhibitor or angiotensin II receptor blocker and beta-blockers.

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript