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## N-terminal Pro-Brain Natriuretic Peptide and Exercise Capacity in Chronic Heart Failure: Data from the HF-ACTION Study

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### Abstract

**Objectives**—To examine the relationship between N-terminal pro-brain natriuretic peptide (NT-proBNP) and exercise capacity in a large contemporary cohort of patients with chronic heart failure.

**Background**—Natriuretic peptides such as NT-proBNP are important biomarkers in heart failure. The relationship between NT-proBNP and exercise capacity has not been well studied.

**Methods**—We analyzed the relationship between baseline NT-proBNP and peak  $VO_2$  or distance in the 6 minute walk test in 1383 subjects enrolled in the HF-ACTION study. Linear regression models were used to analyze the relationship between NT-proBNP and peak  $VO_2$  or distance in the 6 minute walk test in the context of other clinical variables. Receiver operator curve (ROC) analysis was used to evaluate the ability of NT-proBNP to accurately predict a peak  $VO_2 < 12$  mL/kg/min.

**Results**—NT-proBNP was the most powerful predictor of peak  $VO_2$  (partial  $R^2=0.13$ ,  $p<0.0001$ ) out of 35 candidate variables. Although NT-proBNP was also a predictor of distance in the 6 minute walk test, this relationship was weaker than that for peak  $VO_2$  (partial  $R^2 = 0.02$ ,  $p<0.0001$ ). For both peak  $VO_2$  and distance in the 6 minute walk test, much of the variability in exercise capacity remained unexplained by the variables tested. ROC analysis suggested NT-proBNP had moderate ability to identify patients with peak  $VO_2 < 12$  mL/kg/min (c-index=0.69).

**Conclusions**—In this analysis of baseline data from HF-ACTION, NT-proBNP was the strongest predictor of peak  $VO_2$  and a significant predictor of distance in the 6 minute walk test. Despite these associations, NT-proBNP demonstrated only modest performance in identifying patients with a low peak  $VO_2$  who might be considered for cardiac transplantation. These data suggest that, while hemodynamic factors are important determinants of exercise capacity, much of the variability in exercise performance in heart failure remains unexplained by traditional clinical and demographic variables.

### Keywords

Heart failure; exercise; biomarker; clinical trials

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Circulating biomarkers play an increasingly critical role in the diagnosis and management of patients with chronic heart failure<sup>1</sup>. Natriuretic peptides such as brain natriuretic peptide (BNP) and its N-terminal pro-brain natriuretic peptide (NT-proBNP) have been demonstrated to be powerful tools for the diagnosis, risk stratification, and management of

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patients with heart failure<sup>2</sup>. In addition to being useful for clinical management, biomarkers may suggest insights into the mechanisms underlying important physiologic relationships.

Exercise intolerance, typically manifest as exertional dyspnea, is the major morbidity of chronic heart failure. Both maximal (as measured by peak oxygen uptake (peak  $\text{VO}_2$ ))<sup>3, 4</sup> and sub-maximal (as measured by distance in the 6 minute walk test)<sup>5</sup> exercise capacity have been demonstrated to be of substantial prognostic importance in chronic heart failure. Assessment of peak  $\text{VO}_2$  plays a central role in risk stratification of patients with advanced heart failure being considered for cardiac transplantation<sup>6</sup>. Despite the clinical importance of exercise capacity, substantial controversy persists about the primary determinants of exercise intolerance in heart failure, and the relative contribution of cardiac performance, hemodynamic factors, pulmonary function, and peripheral skeletal muscle remain incompletely understood<sup>7-11</sup>. The purpose of this study was to evaluate the association of NT-proBNP with peak  $\text{VO}_2$  and distance in the 6 minute walk test in a large cohort of patients enrolled in a randomized trial of exercise training, the Heart Failure and a Controlled Trial Investigating Outcomes of Exercise Training (HF-ACTION) study.

## Methods

Details of design, rationale, and primary results of HF-ACTION have been published elsewhere<sup>12, 13</sup>. Briefly, HF-ACTION (clinicaltrials.gov, NCT00047437) was a randomized clinical trial evaluating the effect of exercise training on long term morbidity and mortality in patients with chronic heart failure due to left ventricular systolic dysfunction. Enrolled patients were randomized to exercise training in addition to usual care versus usual care alone. HF-ACTION was approved by local Institutional Review Boards, and all enrolled patients provided written informed consent.

### Exercise Testing

2329 of 2331 patients enrolled in the HF-ACTION study underwent baseline exercise testing as has been previously described<sup>12, 14</sup>. Patients underwent symptom limited cardiopulmonary exercise testing with gas exchange analysis to evaluate peak  $\text{VO}_2$ , utilizing either a motor driven treadmill or exercise cycle ergometer protocol. For treadmill exercise, a modified extended Naughton protocol was used; for cycle ergometer exercise, a ramped protocol was used with 10 watt/minute increases starting at 0 watts. A six minute walk test was to be performed as previously described<sup>5</sup> at least 2 hours before or after baseline cardiopulmonary exercise (CPX) testing. CPX testing data were interpreted by a central core laboratory (Duke University).

### NT- proBNP Assay

Patients enrolled in the HF-ACTION study and in the biomarker substudy underwent plasma collection at the baseline, 3-month, and 12-month visits. Baseline blood samples were obtained on the same day as baseline exercise testing, but were to be obtained prior to exercise. Samples were collected via peripheral vein into EDTA containing tubes, and then centrifuged immediately and stored at  $-70^\circ\text{C}$  for subsequent analysis. Assays for NT-proBNP were performed using a commercially available assay platform (Roche Diagnostics, Inc.) at a central core laboratory (Duke University).

### Statistical Analysis

Continuous variables were presented as medians with the 25th and 75th percentiles. Categorical data were presented as percentages. Patient characteristics were compared between patients above and below the median value of Peak  $\text{VO}_2$  using the Chi square test for categorical, and the t-test for continuous variables. Where specific distributional

assumptions for these tests were violated, the Fisher's Exact and Wilcoxon signed rank tests, respectively, were used instead. Because data on NT-proBNP were not normally distributed, we log transformed NT-proBNP values ( $\ln[\text{NT-proBNP}]$ ) for all statistical analyses.

The aim of this analysis was to evaluate the relationship between NT proBNP and measures of exercise capacity, specifically the ability of NT-proBNP to predict peak  $\text{VO}_2$  and distance in the 6 minute walk test alone and in combination with other clinical predictors. We used Pearson correlation coefficients to assess the univariable relationship between NT-proBNP and each of these primary endpoints, as well as other exercise parameters of interest (CPX test duration and  $\text{Ve}/\text{VCO}_2$  slope).

In order to understand the relationship between NT-proBNP and exercise capacity in the context of other clinical variables, we created multivariable linear regression models for both peak  $\text{VO}_2$  and distance in the 6 minute walk test, with the measure of exercise capacity as the dependent outcome variable. For each of these endpoints, the best predictive model was constructed using baseline clinical data from the overall trial population ( $n=2331$ ) in a backwards variable selection process. Variables were sequentially eliminated from an initial set of candidate predictors, the variable with the highest P-value eliminated at each step. This stage ended when all remaining variables had a P-value  $< 0.05$ . In order to further isolate factors most significant in determining functional capacity measures, all variables which remained in the model derived by this process, but which possessed a partial  $R^2 < 0.01$  after eliminating non-significant predictors, were also removed. Candidate variables considered for each model were 35 demographic and clinical variables thought to be potential predictors of exercise capacity based on review of the literature and clinical judgment (see Appendix for list of candidate variables). Once a best model was generated from the overall study population, this model was then applied to the subset of patients ( $n=1383$ ) for whom NT-proBNP data were available. Finally, NT-proBNP was added to the model to evaluate the relative contribution of NT-proBNP in the context of other predictors of exercise capacity. We also evaluated interaction terms for NT-proBNP with age, gender, and body mass index based on previous data showing that these were important potential determinants of both NT-proBNP levels and exercise capacity. The relative strength of association between each predictor variable and exercise capacity was based on the partial  $R^2$  in the final multivariable model. A p value  $< 0.05$  was considered statistically significant for all analyses.

Because peak  $\text{VO}_2 \geq 12$  mL/kg/min has been recommended as a clinically important cut point for cardiac transplant listing in patients treated with beta-blocker therapy<sup>6</sup>, we used receiver-operator curve (ROC) analysis to assess the ability of NT-proBNP to predict a peak  $\text{VO}_2 \geq 12$  mL/kg/min in the study population. The area under the curve for the ROC was used to assess the accuracy of NT-proBNP levels in predicting a peak  $\text{VO}_2 \geq 12$  mL/kg/min.

## Results

### Study Cohort

Baseline characteristics for the study cohort are shown in Table 1. Generally, the cohort in whom NT-proBNP data were available ( $n=1383$ ) was similar to the overall study population ( $n=2331$ ). The study cohort was diverse with regard to gender (29% women), race (34% African-American), and age (20% with age  $\geq 70$ ). The mean ejection fraction was 25% and most patients (66%) had NYHA class II heart failure symptoms. Notably, patients enrolled in HF-ACTION were exceptionally well-treated in terms of evidence-based therapies, with extremely high rates of utilization for beta-blockers (95%), angiotensin-converting enzyme

(ACE) inhibitors or angiotensin II receptor blockers (ARBs) (95%), and implantable cardioverter-defibrillators (ICDs) (39%).

### Exercise Capacity and NT-proBNP

The median peak  $\text{VO}_2$  in the study cohort was 14.4 mL/kg/min (inter-quartile range 11.5 – 17.5 mL/kg/min), consistent with moderate impairment of exercise capacity. The median distance in the 6 minute walk test was 372 meters (interquartile range 300 – 431 meters). The median NT-proBNP was 815 pg/mL (interquartile range 341 – 1805 pg/mL). In univariable analysis, there was a significant correlation between the logarithm of NT-proBNP and all measures of exercise capacity: peak  $\text{VO}_2$  ( $r = -0.38$ ,  $p < 0.0001$ ), distance in the 6 minute walk test ( $r = -0.23$ ,  $p < 0.0001$ ), CPX duration ( $r = -0.35$ ,  $p < 0.0001$ ), and  $\text{Ve}/\text{VCO}_2$  slope ( $r = 0.50$ ,  $p < 0.0001$ ). Scatter plots for each of the relationships are shown in Figure 1.

### NT-proBNP in the Context of Other Predictors: Multivariable Modeling

In order to understand the relationship between exercise capacity and NT-proBNP in the context of other demographic and clinical variables, we evaluated the added value of NT-proBNP in the context of those clinical variables most predictive of exercise capacity in the overall HF-ACTION cohort. In the HF-ACTION study as a whole, the most significant predictors of peak  $\text{VO}_2$  were age, race, body mass index, NYHA class, and gender. When NT-proBNP was entered into the multivariable model for peak  $\text{VO}_2$ ,  $\ln(\text{NT-proBNP})$  was strongly associated with peak  $\text{VO}_2$  even after adjustment for other determinants ( $p < 0.0001$ , partial  $R^2 = 0.13$ ). In the final model that included  $\ln(\text{NT-proBNP})$ ,  $\ln(\text{NT-proBNP})$  was the strongest overall predictor of peak  $\text{VO}_2$  (partial  $R^2 = 0.13$ ), followed by body mass index (partial  $R^2 = 0.13$ ) and age (partial  $R^2 = 0.09$ ). The addition of NT-proBNP to the best clinical model raised the  $R^2$  for the overall model from 0.38 (clinical model only) to 0.46 (clinical model + NT-proBNP). The final multivariable regression model for predicting peak  $\text{VO}_2$  is shown in Table 2.

Using the same approach, we investigated the added value of NT-proBNP in predicting distance in the 6 minute walk test. The strongest clinical predictors for distance in the 6 minute walk test were age, NYHA class, height, weight, race, and the presence of peripheral vascular disease. As for peak  $\text{VO}_2$ , the NT-proBNP remained a highly significant predictor of distance in the 6 minute walk test ( $p < 0.0001$ ) even after adjustment for other clinical predictors. Unlike peak  $\text{VO}_2$ , however, the relative contribution of NT-proBNP to prediction of distance in the 6 minute walk test was modest (partial  $R^2 = 0.020$ ). NT-proBNP was the 5<sup>th</sup> strongest overall predictor of performance in the 6 minute walk test, after NYHA class, age, height, and weight (Table 3). The addition of NT-proBNP to the best clinical model resulted in a modest improvement in overall model performance ( $R^2$  changed from 0.28 to 0.30).

### Impact of Age, Gender, and Body Mass Index

Because age, gender, and body mass index may affect both NT-proBNP levels and exercise capacity, we explored the possibility of differential relationship between NT-proBNP and peak  $\text{VO}_2$  and distance in the 6 minute walk test for each of these variables using interaction terms in the overall models. For each of gender and obesity (defined as body mass index  $> 30 \text{ kg/m}^2$ ), we found evidence for a quantitative interaction between NT-proBNP and peak  $\text{VO}_2$ . There was a stronger correlation between NT-proBNP and peak  $\text{VO}_2$  in men compared to women ( $R = -0.44$  for men vs.  $-0.33$  for women,  $p < 0.0001$  for interaction) and in non-obese patients compared to obese patients ( $R = -0.48$  for BMI  $\geq 30$  vs.  $-0.36$  for BMI  $< 30$ ,  $p = 0.04$  for interaction). There was also evidence for a quantitative interaction between age and the correlation of NT-proBNP and distance in the 6 minute walk test, with older patients

(above the median age of 58.5 years) having a stronger correlation between NT-proBNP and distance in the 6 minute walk test than younger patients ( $R = -0.24$  for age > median vs.  $-0.13$  for age < median,  $p < 0.001$  for interaction).

### NT-proBNP as a Surrogate for Peak $VO_2$

Since assessment of peak  $VO_2$  is central to the selection of patients for cardiac transplantation, we examined the sensitivity and specificity of NT-proBNP levels for predicting peak  $VO_2 < 12$  mL/kg/min. This cut-point was chosen based on recent guidelines for transplant evaluation in patients treated with beta-blockers (95% of patients in HF-ACTION were taking beta-blockers at enrollment)<sup>6</sup>. Three hundred ninety three patients (29%) in the study cohort had peak  $VO_2 < 12$  mL/kg/min. The optimal NT-proBNP cut-off for predicting a peak  $VO_2 < 12$  mL/kg/min was 876 pg/mL, which had a sensitivity of 0.67, a specificity of 0.61, positive predictive value of 0.63, and negative predictive value of 0.65. The area under the curve for the ROC curve was 0.69, suggesting modest discriminatory ability for NT-proBNP in predicting a low peak  $VO_2$  (Figure 2)

### Discussion

The primary finding of this analysis was that NT-proBNP levels were associated with both peak  $VO_2$  and distance in the 6 minute walk test in a large well-treated contemporary cohort of patients with chronic heart failure. NT-proBNP was the most significant overall predictor of peak  $VO_2$  even after adjustment for 35 demographic and clinical candidate variables. For distance in the 6 minute walk test, NT-proBNP was also a significant independent predictor of exercise capacity, although the relationship was weaker than that for peak  $VO_2$ . These data represent the largest analysis to date evaluating the relationship between natriuretic peptide levels and exercise capacity in heart failure.

Previous data on the relationship between exercise capacity and natriuretic peptide levels are primarily from small single center studies of patients referred for exercise testing. Smaller studies by Kruger et al, Kallistratos et al, and Passino et al have demonstrated significant correlations ( $r = -0.56$ ,  $-0.77$ , and  $-0.53$  respectively) between natriuretic peptide levels and peak  $VO_2$  in patients with heart failure referred for exercise testing<sup>15-18</sup>. Similarly, other studies have found higher BNP or NT-proBNP levels to be associated with shorter distance in the 6 minute walk test<sup>19, 20</sup>. Our findings regarding the relationship between NT-proBNP and exercise capacity are broadly consistent with these prior results, but extend them in several important areas. First, the detailed ascertainment of baseline characteristics, large sample size, and broadly representative study cohort of the HF-ACTION study allowed us to perform detailed adjustment for other demographic and clinical characteristics that might impact exercise capacity. Additionally, the size of our cohort also allowed us to evaluate the relationship in relevant subgroups. We found the relationship between peak  $VO_2$  and NT-proBNP was stronger for men and for non-obese patients, potentially due to the known effects of gender and obesity on NT-proBNP levels<sup>21, 22</sup>. Finally, ours is the first study to examine the differences between peak  $VO_2$  and distance in the 6 minute walk test in relation to the NT-proBNP levels in the same patient population. The correlation between NT-proBNP and exercise capacity, especially distance in the 6 minute walk test, seen in our study was somewhat weaker in absolute terms than that seen in previous studies, possibly due to variability introduced by a multi-center trial as compared to a single center study.

Although correlation coefficients and linear regression models are useful for quantifying relationships between continuous variables, they are not readily applicable to individual patients for clinical use. Notably, despite the strong association between NT-proBNP levels and peak  $VO_2$  in multivariable models, the performance of NT-proBNP in predicting a peak  $VO_2 < 12$  mL/kg/min was modest, with a c-index of 0.69, a sensitivity of 0.67, and a



specificity of 0.61 at an optimal NT-proBNP cut point of 876 pg/mL. These data suggest that NT-proBNP is not a sufficient predictor of peak  $\text{VO}_2$  to act as a clinically useful surrogate for identifying those patients with a low peak  $\text{VO}_2$  that might be considered for transplant listing. Notably, of the exercise variables evaluated, NT-proBNP was most strongly correlated with  $\text{Ve}/\text{VCO}_2$  slope, which has been suggested to be a more powerful predictor of prognosis than peak  $\text{VO}_2$  in several studies<sup>23, 24</sup>. Previous data have shown that natriuretic peptides and cardiopulmonary exercise testing provide independent and complementary information in predicting prognosis in patients with heart failure.<sup>25</sup>

### Mechanistic Considerations

The physiologic determinants of exercise capacity in heart failure have been the subject of substantial interest. Measures of cardiac systolic function such as ejection fraction have not been shown to correlate well with exercise capacity<sup>26</sup>. Although the relationship between hemodynamic measures (such as cardiac output or ventricular filling pressures) and maximal exercise capacity is stronger than that of ejection fraction, the invasive assessment of hemodynamics and exercise is technically challenging and has been limited to small studies of highly selected populations<sup>27, 28</sup>. A substantial component of exercise intolerance in heart failure remains unexplained, and is posited to be due to non-cardiac factors such as changes in peripheral skeletal muscle<sup>29</sup>. Although natriuretic peptide levels may reflect a variety of cardiac processes including ischemia, inflammation, and oxidative stress, they primarily reflect central hemodynamics<sup>30</sup>, and therefore serve as a non-invasive means to estimate the relative contribution of hemodynamic factors to exercise capacity in heart failure. The finding that NT-proBNP was the strongest overall predictor of peak  $\text{VO}_2$  out of 35 candidate variables suggests that hemodynamic factors play a significant role in mediating exercise performance in heart failure. Importantly, however, even with NT-proBNP included in the best clinical model, the overall model performance ( $R^2 = 0.46$ ) suggest that over half of the variability in exercise capacity among patients with heart failure is not explained by the factors analyzed in our models. This finding argues for the importance of other unmeasured variables (such as skeletal muscle abnormalities or genetic factors) as important determinants of exercise capacity in heart failure, and suggests the need for ongoing research into the mechanisms of exercise intolerance in these patients.

### Maximal vs. Sub-maximal Capacity

Although NT-proBNP was also a significant predictor of distance in the 6 minute walk test, this relationship was substantially less strong than that seen for peak  $\text{VO}_2$ . Previous data suggest that distance in the 6 minute walk test may be more influenced by non-physiologic factors (such as patient motivation and investigator prompting) than is peak  $\text{VO}_2$ .<sup>31</sup> In comparing the best clinical models with NT-proBNP for peak  $\text{VO}_2$  and distance in the 6 minute walk test, there was substantially more variability in distance in the 6 minute walk test that was not explained by our models, suggesting that unmeasured factors and possibly non-physiologic aspects may play a greater role in determining sub-maximal as compared to maximal exercise capacity.

### Limitations

As with any cross-sectional analysis, our study was able to demonstrate associations but is unable to establish causation. The study population was from a multi-center randomized trial, and patients enrolled in clinical trials are known to differ from the broader heart failure population in potentially important ways<sup>32</sup>. As in previous large heart failure trials, the population enrolled in HF-ACTION was somewhat younger and had a greater proportion of non-ischemic heart failure etiology than the general heart failure population. Specific strengths of this analysis include the use of a large, multi-center cohort with careful phenotyping of baseline characteristics, extremely high utilization of contemporary evidence

based therapy, and the use of centralized core laboratories to standardize analysis of both exercise data and biomarker assays.

## CONCLUSIONS

NT-proBNP was strongly associated with peak  $\text{VO}_2$  in a large well-treated cohort of patients with heart failure due to left ventricular systolic dysfunction. NT-proBNP was the strongest predictor of peak  $\text{VO}_2$ , even after adjustment for multiple other demographic and clinical characteristics. NT-proBNP was also significantly associated with distance in the 6 minute walk test, although this relationship was substantially weaker than for peak  $\text{VO}_2$ . These data support the concept that hemodynamic factors play an important role in determining exercise tolerance in heart failure, but also confirm that much of the variability in exercise capacity in heart failure remains unaccounted for by currently available clinical measures. Given that exertional limitation is the primary morbidity of heart failure, these findings highlight the need for ongoing research in the determinants of exercise capacity in patients with heart failure. Future analyses of data from the HF-ACTION trial will provide further insights into the relationships between changes in circulating biomarkers, exercise training, changes in exercise performance measures, and clinical outcomes over time.

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## Abbreviations

<b>BNP</b>	brain-natriuretic peptide
<b>NT-proBNP</b>	N-terminal pro-brain natriuretic peptide
<b>Peak <math>\text{VO}_2</math></b>	maximal oxygen uptake
<b>BMI</b>	body mass index
<b>ROC</b>	Receiver operator characteristic

## REFERENCES

1. Braunwald E. Biomarkers in heart failure. *New England Journal of Medicine*. 2008; 358(20):2148–2159. [PubMed: 18480207]
2. Felker GM, Petersen JW, Mark DB. Natriuretic peptides in the diagnosis and management of heart failure. *CMAJ*. 2006; 175(6):611–617. [PubMed: 16966666]
3. Aaronson KD, Schwartz JS, Chen TM, Wong KL, Goin JE, Mancini DM. Development and prospective validation of a clinical index to predict survival in ambulatory patients referred for cardiac transplant evaluation. *Circulation*. 1997; 95(12):2660–2667. [PubMed: 9193435]
4. Mancini DM, Eisen H, Kussmaul W, Mull R, Edmunds LH, Wilson JR. Value of peak exercise oxygen consumption for optimal timing of cardiac transplantation in ambulatory patients with heart failure. *Circulation*. 1991; 83:778–786. [PubMed: 1999029]
5. Bittner V, Weiner DH, Yusuf S, Rogers WJ, McIntyre KM, Bangdiwala SI, et al. Prediction of mortality and morbidity with a 6-minute walk test in patients with left ventricular dysfunction SOLVD Investigators. *Journal of the American Medical Association*. 1993; 270(14):1702–1707. [PubMed: 8411500]

6. Mehra MR, Kobashigawa J, Starling R, Russell S, Uber PA, Parameshwar J, et al. Listing Criteria for Heart Transplantation: International Society for Heart and Lung Transplantation Guidelines for the Care of Cardiac Transplant Candidates--2006. *The Journal of Heart and Lung Transplantation*. 2006; 25(9):1024–1042. [PubMed: 16962464]
7. Sullivan MJ, Higginbotham MB, Cobb FR. Increased exercise ventilation in patients with chronic heart failure: intact ventilatory control despite hemodynamic and pulmonary abnormalities. *Circulation*. 1988; 77(3):552–559. [PubMed: 3342486]
8. Sullivan MJ, Knight JD, Higginbotham MB, Cobb FR. Relation between central and peripheral hemodynamics during exercise in patients with chronic heart failure Muscle blood flow is reduced with maintenance of arterial perfusion pressure. *Circulation*. 1989; 80(4):769–781. [PubMed: 2791242]
9. Coats AJ, Adamopoulos S, Radaelli A, McCance A, Meyer TE, Bernardi L, et al. Controlled trial of physical training in chronic heart failure. Exercise performance, hemodynamics, ventilation, and autonomic function. *Circulation*. 1992; 85(6):2119–2131. [PubMed: 1591831]
10. Duscha BD, Annex BH, Green HJ, Pippen AM, Kraus WE. Deconditioning fails to explain peripheral skeletal muscle alterations in men with chronic heart failure. *J Am Coll Cardiol*. 2002; 39(7):1170–1174. [PubMed: 11923042]
11. Hambrecht R, Niebauer J, Fiehn E, Kalberer B, Offner B, Hauer K, et al. Physical training in patients with stable chronic heart failure: effects on cardiorespiratory fitness and ultrastructural abnormalities of leg muscles. *J Am Coll Cardiol*. 1995; 25(6):1239–1249. [PubMed: 7722116]
12. Whellan DJ, O'Connor CM, Lee KL, Keteyian SJ, Cooper LS, Ellis SJ, et al. Heart Failure and A Controlled Trial Investigating Outcomes of Exercise TraiNing (HF-ACTION): Design and rationale. *Am Heart J*. 2007; 153(2):201–211. [PubMed: 17239677]
13. O'Connor CM, Whellan DJ, Lee KL, Keteyian SJ, Cooper LS, Ellis SJ, et al. Efficacy and Safety of Exercise Training in Patients With Chronic Heart Failure: HF-ACTION Randomized Controlled Trial. *Jama*. 2009; 301(14):1439–1450. [PubMed: 19351941]
14. Bensimhon DR, Leifer ES, Ellis SJ, Fleg JL, Keteyian SJ, Piña IL, et al. Reproducibility of Peak Oxygen Uptake and Other Cardiopulmonary Exercise Testing Parameters in Patients With Heart Failure (from the Heart Failure and A Controlled Trial Investigating Outcomes of exercise traiNing). *The American Journal of Cardiology*. 2008; 102(6):712–717. [PubMed: 18773994]
15. Kruger S, Graf J, Kunz D, Stickel T, Hanrath P, Janssens U. brain natriuretic peptide levels predict functional capacity in patients with chronic heart failure. *J Am Coll Cardiol*. 2002; 40(4):718–722. [PubMed: 12204502]
16. Kruger S, Graf J, Merx MW, Stickel T, Kunz D, Hanrath P, et al. Brain natriuretic peptide kinetics during dynamic exercise in patients with chronic heart failure. *Int J Cardiol*. 2004; 95(1):49–54. [PubMed: 15159038]
17. Kallistratos MS, Dritsas A, Laoutaris ID, Cokkinos DV. N-terminal prohormone brain natriuretic peptide as a marker for detecting low functional class patients and candidates for cardiac transplantation: linear correlation with exercise tolerance. *J Heart Lung Transplant*. 2007; 26(5): 516–521. [PubMed: 17449423]
18. Passino C, Poletti R, Bramanti F, Prontera C, Clerico A, Emdin M. Neuro-hormonal activation predicts ventilatory response to exercise and functional capacity in patients with heart failure. *Eur J Heart Fail*. 2006; 8(1):46–53. [PubMed: 16112902]
19. Ingle L, Rigby AS, Nabb S, Jones PK, Clark AL, Cleland JGF. Clinical determinants of poor six-minute walk test performance in patients with left ventricular systolic dysfunction and no major structural heart disease. *European Journal of Heart Failure*. 2006; 8(3):321–325. [PubMed: 16266825]
20. Jourdain P, Funck F, Bellorini M, Guillard N, Loiret J, Thebault B, et al. Bedside B-type natriuretic peptide and functional capacity in chronic heart failure. *European Journal of Heart Failure*. 2003; 5(2):155–160. [PubMed: 12644005]
21. Das SR, Drazner MH, Dries DL, Vega GL, Stanek HG, Abdullah SM, et al. Impact of body mass and body composition on circulating levels of natriuretic peptides: results from the Dallas Heart Study. *Circulation*. 2005; 112(14):2163–2168. [PubMed: 16203929]



22. Redfield MM, Rodeheffer RJ, Jacobsen SJ, Mahoney DW, Bailey KR, Burnett. Plasma brain natriuretic peptide concentration: impact of age and gender. *J Am Coll Cardiol.* 2002; 40(5):976–982. [PubMed: 12225726]
23. Francis DP, Shamim W, Davies LC, Piepoli MF, Ponikowski P, Anker SD, et al. Cardiopulmonary exercise testing for prognosis in chronic heart failure: continuous and independent prognostic value from VE/VCO<sub>2</sub>slope and peak VO<sub>2</sub>. *Eur Heart J.* 2000; 21(2):154–161. [PubMed: 10637089]
24. Arena R, Myers J, Aslam SS, Varughese EB, Peberdy MA. Peak VO<sub>2</sub> and VE/VCO<sub>2</sub> slope in patients with heart failure: a prognostic comparison. *American Heart Journal.* 2004; 147(2):354–360. [PubMed: 14760336]
25. deGroot P, Dagorn J, Soudan B, Lamblin N, McFadden E, Bauters C. B-type natriuretic peptide and peak exercise oxygen consumption provide independent information for risk stratification in patients with stable congestive heart failure. *J Am Coll Cardiol.* 2004; 43(9):1584–1589. [PubMed: 15120815]
26. Marantz PR, Tobin JN, Wassertheil-Smoller S, Steingart RM, Wexler JP, Budner N, et al. The relationship between left ventricular systolic function and congestive heart failure diagnosed by clinical criteria. *Circulation.* 1988; 77(3):607–612. [PubMed: 3342491]
27. Higginbotham MB, Morris KG, Williams RS, McHale PA, Coleman RE, Cobb FR. Regulation of stroke volume during submaximal and maximal upright exercise in normal man. *Circ Res.* 1986; 58(2):281–291. [PubMed: 3948345]
28. Sullivan MJ, Higginbotham MB, Cobb FR. Exercise training in patients with chronic heart failure delays ventilatory anaerobic threshold and improves submaximal exercise performance. *Circulation.* 1989; 79(2):324–329. [PubMed: 2914350]
29. Duscha BD, Kraus WE, Keteyian SJ, Sullivan MJ, Green HJ, Schachat FH, et al. Capillary density of skeletal muscle: a contributing mechanism for exercise intolerance in class II-III chronic heart failure independent of other peripheral alterations. *J Am Coll Cardiol.* 1999; 33(7):1956–1963. [PubMed: 10362199]
30. Kazanegra R, Cheng V, Garcia A, Krishnaswamy P, Gardetto N, Clopton P, et al. A rapid test for B-type natriuretic peptide correlates with falling wedge pressures in patients treated for decompensated heart failure: A pilot study. *J Card Fail.* 2001; 7(1):21–29. [PubMed: 11264546]
31. Myers J, Zaheer N, Quaglietti S, Madhavan R, Froelicher V, Heidenreich P. Association of Functional and Health Status Measures in Heart Failure. *Journal of Cardiac Failure.* 2006; 12(6): 439–445. [PubMed: 16911910]
32. Heiat A, Gross CP, Krumholz HM. Representation of the Elderly, Women, and Minorities in Heart Failure Clinical Trials. *Arch Intern Med.* 2002; 162(15):1682–1688. [PubMed: 12153370]

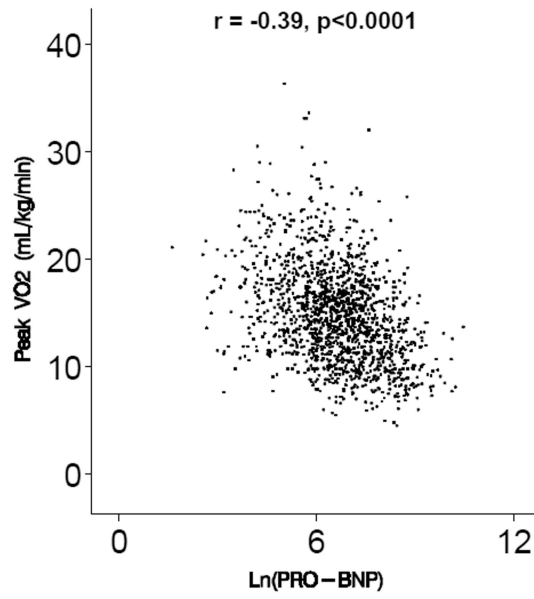
## APPENDIX

Candidate Variables for Linear Regression Models for Predicting Peak V<sub>O<sub>2</sub></sub> and distance in the 6 minute walk test

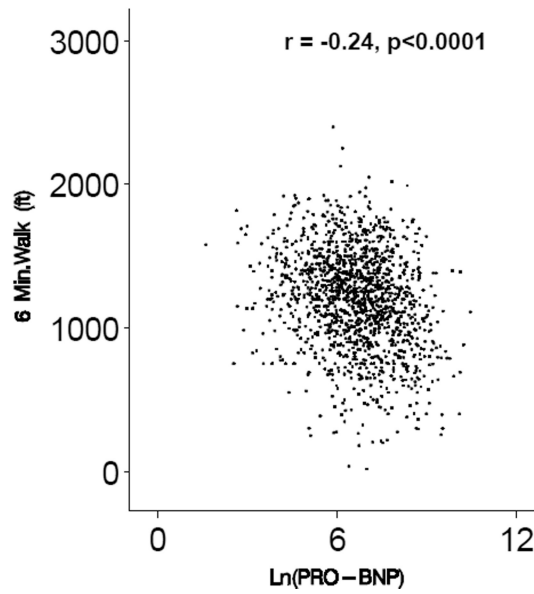
- sex
- diabetes (history of)
- stroke (history of)
- hypertension (history of)
- prior CABG
- prior valve surgery
- prior percutaneous coronary intervention
- prior myocardial infarction
- peripheral vascular disease (history of)

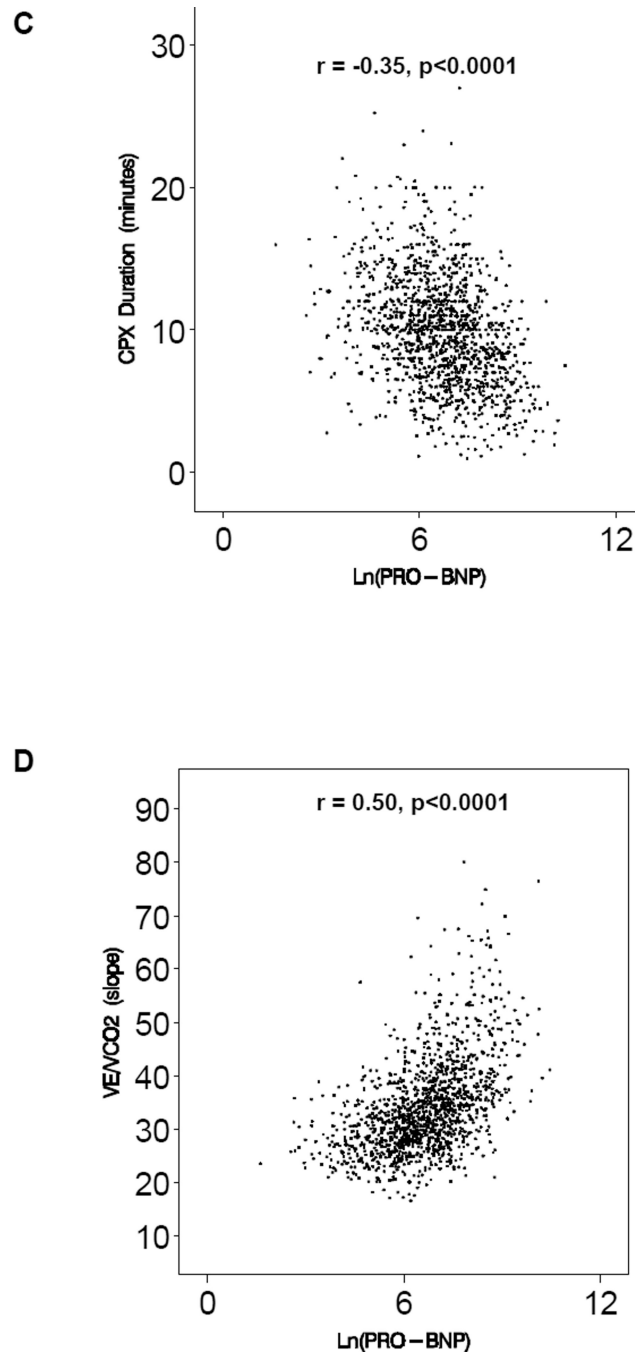
- chronic obstructive pulmonary disease (history of)
- depression (history of)
- atrial fibrillation/atrial flutter (history of)
- pacemaker
- bi-ventricular pacemaker
- on an ACE inhibitor at baseline
- on a beta blocker at baseline
- etiology of heart failure
- CPX mode (treadmill or bicycle)
- heart failure hospitalizations in the last 6 months (0, 1, 2, or 3+)
- region (4 regions of US, Canada, or France)
- race (Black or African American, White, or Other)
- NYHA class (II vs. III/IV) at baseline
- CCS angina class at baseline
- rest ECG ventricular conduction prior to baseline CPX test (normal, LBBB, RBBB, IVCD, or paced)
- rest ECG rhythm prior to baseline CPX test (sinus, atrial fibrillation, or other)
- smoking status (never, current, or past)
- diastolic BP
- systolic BP
- height
- weight
- BMI
- resting HR (clinic visit)
- resting HR (CPX test)
- LVEF
- age

**A**

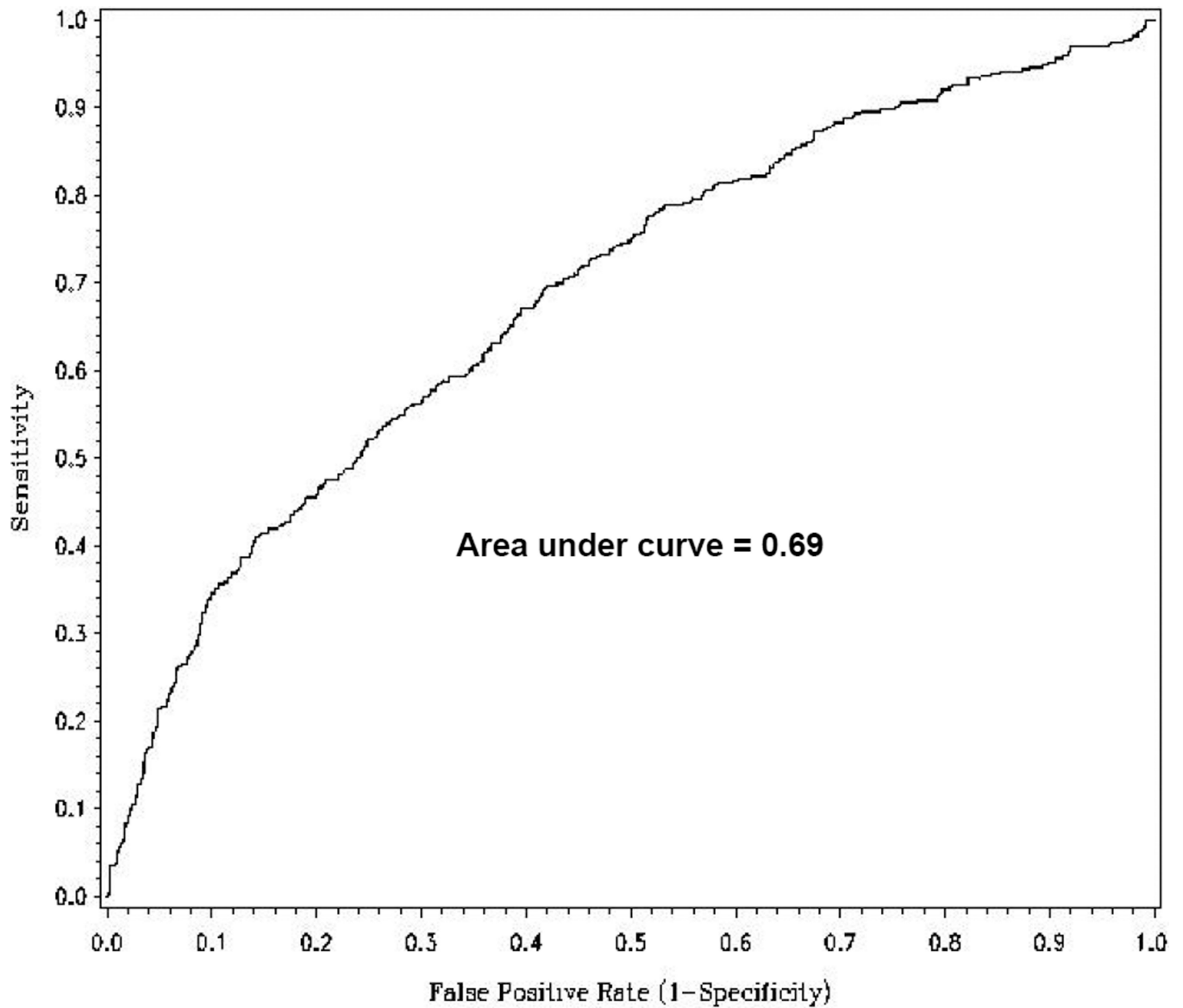


**B**





**Figure 1.** Association between ln (NT-proBNP) and Measures of Exercise Capacity; A. peak V<sub>O2</sub>, B. distance in the 6 minute walk test, C. CPX duration, and D. Ve/VCO<sub>2</sub> slope.



**Figure 2.** Receiver operator curve for NT-proBNP predicting peak  $V_{O2} < 12$  mL/kg/min. Optimal cut point for maximizing performance was NTproBNP of 876 (sensitivity = 0.67, specificity = 0.61).



**Table 1**

Baseline Characteristics of Study Cohort

Variable	Total Cohort N = 1383	Peak VO <sub>2</sub> 14.4 N = 694	Peak VO <sub>2</sub> > 14.4 N = 675	P value
Age (years) Median (Q1, Q3)	59 (50, 68)	66 (53, 71)	56 (48, 64)	<0.001
Female sex	29%	35%	23%	<0.001
Race (%)				
White	60%	55%	65%	0.001
Black or African American	34%	38%	29%	
Other	7%	7%	6%	
LVEF (%)	25 (20, 30)%	24 (19, 29)%	26 (21, 31)%	<0.001
NYHA Class				<0.001
II	66%	52%	80%	
III/IV	34%	48%	20%	
Ischemic etiology of heart failure	49%	53%	45%	0.003
Diabetes mellitus	32%	39%	25%	<0.001
Hospitalizations (last 6 months)				0.025
0	59%	59%	58%	
1	29%	26%	32%	
2	12%	15%	10%	
Hypertension	62%	65%	59%	0.014
Stroke	10%	12%	8%	0.018
Active smoking	16%	16%	16%	0.006
Resting heart rate (beats/min)	70 (63, 78)	70 (64, 78)	70 (62, 78)	0.204
SBP (mmHg)	112 (101, 128)	110 (100, 126)	114 (104, 128)	0.001
DBP	70 (62, 80)	70 (60, 78)	70 (62, 80)	<0.001
Weight (kg)	91 (78, 107)	91 (78, 110)	91 (78, 105)	0.225

Variable	Total Cohort	Peak VO <sub>2</sub> 14.4	Peak VO <sub>2</sub> > 14.4	P value
	N= 1383	N = 694	N = 675	
Height (cm)	173 (166, 180)	173 (165, 178)	175 (168, 180)	<0.001
BMI (kg/m <sup>2</sup> )	30 (26, 36)	31 (26, 37)	30 (26, 34)	<0.001
Peak VO <sub>2</sub> (mL/kg/min)	14.4 (11.5, 17.5)	11.6 (9.8, 13.1)	17.5 (16.0, 20.0)	<0.001
Distance in the 6 minute walk test (m)	372 (300, 431)	329 (259, 385)	414 (357, 472)	<0.001
KCCQ overall summary score	68 (51, 83)	64 (48, 80)	73 (56, 87)	<0.001
Beck Depression Inventory II score	8 (4, 15)	9 (5, 16)	8 (4, 13)	0.016
ACE or ARB	95%	95%	95%	0.999
Beta blocker	95%	95%	95%	0.809
ICD	39%	43%	36%	0.005
NT-proBNP (pg/mL)	815 (341, 1805)	1210 (503, 2921)	524 (241, 1171)	<0.001

**Table 2**Final Multivariable model for prediction of peak V02 (listed in order of R<sup>2</sup>)

Variable	Parameter Estimate	P-value	Partial R-square
<b>ln NT-proBNP</b>	<b>-1.15</b>	<b>&lt;0.0001</b>	<b>0.129</b>
BMI	-0.02	<0.0001	0.125
Age	-0.10	<0.0001	0.086
Sex	-2.17	<0.0001	0.075
Race	--	<0.0001	0.058
NYHA class (II vs. III/IV)	-1.61	<0.0001	0.048
CPX mode	2.35	<0.0001	0.029
PVD	-1.86	<0.0001	0.020
ECG ventricular conduction	--	0.0002	0.017
Diabetes mellitus	-0.64	0.0020	0.007
Region	--	0.0017	0.002
LVEF	0.02	0.15	0.0016

Reference categories: sex = male, NYHA Class = Class II, CPX mode = bicycle

**Table 3**Final Multivariable model for prediction of distance in the 6 minute walk test (listed in order of R<sup>2</sup>)

Variable	Parameter Estimate	P-value	Partial R-square
NYHA class (II vs. III/IV)	-59.19	<0.0001	0.091
Age	-2.41	<0.0001	0.086
Height	-2.41	<0.0001	0.057
Weight	-1.10	<0.0001	0.056
<b>ln NT-proBNP</b>	<b>-10.49</b>	<b>&lt;0.0001</b>	<b>0.020</b>
Race	--	<0.0001	0.019
Heart Failure hospitalizations	--	<0.0001	0.018
PVD	-35.95	0.0002	0.010
Region	--	0.0233	0.009

Reference categories: NYHA Class = Class II