Published in final edited form as:

Am Heart J. 2009 October ; 158(4 Suppl): S45–S52. doi:10.1016/j.ahj.2009.07.015.

Relationship of Doppler-Echocardiographic left ventricular diastolic function to exercise performance in systolic heart failure: The HF-ACTION study

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Abstract

Introduction—Patients with systolic heart failure often have concomitant left ventricular (LV) diastolic dysfunction. Although in animal models diastolic dysfunction is associated with worsening exercise capacity and prognosis, information regarding these relationships in patients with established systolic heart failure (HF) is sparse.

Methods—HF-ACTION was a large, multicenter National Institutes of Health–funded trial of exercise training in systolic HF (LV ejection fraction [LVEF] $\leq 35\%$) and included detailed Doppler-echocardiographic (echo) and cardiopulmonary exercise testing at baseline. We tested the hypothesis that echo measures of LV diastolic function predict key cardiopulmonary exercise outcomes, including aerobic exercise capacity (peak exercise oxygen consumption, VO_2), distance in the 6-minute walk test (6MWD), and ventilatory efficiency (VE/VCO_2 slope) in patients with systolic HF.

Results—Overall, 2,331 patients (28% women, median age 59 years, median LVEF 25%) were enrolled. There were significant bivariate correlations between echo diastolic function variables and peak VO_2 (inverse) and VE/VCO_2 slope (direct) that were strongest for ratio of early diastolic peak transmitral (MV) to myocardial tissue velocity (E/E'), peak MV early-to-late diastolic velocity ratio (E/A), and left atrial dimension (range of absolute $r = 0.16$ – 0.28). Both MV E/A and E/E' were more

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Presented in part at the 57th Annual Scientific Sessions of the American College of Cardiology, April 1, 2008.

Disclosures

J. Gardin, E. Leifer, J. Fleg, D. Whellan, P. Kokkinos, M. LeBlanc, E. Wolfel, and D. Kitzman have no conflicts of interest to disclose.

A complete list of the HF-ACTION investigators is available as an appendix in the introduction of this supplement.

strongly related to all 3 exercise variables than was LVEF. The relationships of E/A and E/E' with 6MWD were weaker than with peak VO_2 or VE/VCO₂ slope. A multivariable model with peak VO_2 as the dependent variable, which included MV E/A and 9 demographic predictors including age, sex, race, body mass index, and New York Heart Association class, explained 40% of the variation in peak VO_2 , with MV E/A explaining 6% of the variation. Including LVEF in the model explained less than an additional 1% of the variance in peak VO_2 . In a multivariable model for VE/VCO₂ slope, MV E/A was the strongest independent echo predictor, explaining 10% of the variance. The relationship of LV diastolic function variables with 6MWD was weaker than with peak VO_2 or VE/VCO₂ slope.

Conclusion—In patients with systolic HF, LV early diastolic function is a modest independent predictor of aerobic exercise capacity and appears to be a better predictor than LVEF.

Exercise intolerance is the primary chronic symptom in patients with systolic heart failure (HF), is the primary determinant of their severely reduced quality of life, and can be quantified with cardiopulmonary exercise (CPX) testing.¹ However, the mechanisms of reduced exercise capacity in systolic HF are not fully understood. Prior studies have suggested that resting ejection fraction is a relatively poor predictor of exercise capacity² and that a variety of other factors may be important contributors, particularly left ventricular (LV) diastolic dysfunction, which appears to be present in a large proportion of patients with systolic HF.^{3–5} Although in animal models diastolic dysfunction is associated with reduced exercise capacity, information regarding this relationship in patients with systolic HF is sparse.^{6,7} In addition, it has recently been recognized that ventilatory efficiency, as assessed by VE/VCO₂ slope during the CPX test, may be a stronger predictor of clinical outcomes and prognosis in patients with HF than is peak VO_2 . Distance in the 6-minute walk test (6MWD) is frequently used as a quicker, lower-cost means than CPX testing for assessing exercise performance in patients with HF. However, little is known regarding the relationships between LV function and these newer exercise measures.

HF-ACTION was a large National Institutes of Health–funded multicenter, randomized, controlled trial designed to test the long-term safety and efficacy of exercise training versus usual care in patients with systolic HF.^{8,9} In addition to standardized CPX and 6MWD testing, the study also included a Doppler-echocardiography (echo) ancillary study for detailed measurements of LV size, mass, and systolic and diastolic function at baseline. This provided a unique opportunity to examine the relative influence of demographic, clinical, and echo variables on the key exercise testing outcomes of peak VO_2 , VE/VCO₂ slope, and 6MWD in a large cohort of patients with systolic HF and to test the specific hypothesis that echo measures of LV diastolic function are independent predictors of exercise performance in patients with systolic HF.

Methods

The design⁸ and primary outcome⁹ have been previously published. Enrollment criteria included an LV ejection fraction (LVEF) $\leq 35\%$, New York Heart Association (NYHA) class II–IV HF, and sufficient ability to undergo exercise training. Patients were excluded if they were unable to exercise, if they were already exercising regularly, or if they had experienced a cardiovascular event in the prior 6 weeks. Patients were optimally treated by current practice guidelines.⁹ Overall, 2,331 patients were randomly assigned to receive either a program consisting of 36 sessions of facility-based exercise training followed by home-based exercise training for the remainder of the trial, in addition to usual care or usual care alone; median follow-up was approximately 2.5 years.

Cardiopulmonary exercise testing

At study entry, patients underwent a symptom-limited CPX test on a treadmill ($n = 2,100$) using a modified Naughton protocol or a cycle ergometer ($n = 211$) as previously described.⁸ Patients were strongly encouraged to achieve a peak respiratory exchange ratio >1.10 and a Borg rating of perceived exertion >16 . Expired gases were collected continuously throughout exercise and analyzed for ventilatory volume (VE) and for oxygen (O₂) and carbon dioxide (CO₂) content using dedicated analyzers. Expired gases were reported every 15 seconds and forwarded after test completion to a core exercise laboratory for quality assurance and further analysis. The following variables were derived from the CPX results: peak oxygen consumption (VO₂) expressed as milligram per kilogram per minute; peak respiratory exchange ratio defined by the ratio of CO₂ production to O₂ consumption at peak effort; VE/VCO₂ slope defined as the slope of the increase in peak ventilation/increase in CO₂ production throughout exercise. In addition, a 6MWD was performed on each patient during the baseline visit using standard procedures.⁹

Doppler-echocardiography

Doppler-echocardiography was performed during the baseline visit using standard methodology; echo recordings were forwarded to a core echo laboratory for analysis.^{10,11} Studies were read blinded as to demographic information by a primary reader and overread by an experienced level III echocardiographer using a Digisonics measurement workstation (Digisonics, Inc, Houston, TX). The following echo variables were measured or derived: LV mass, dimensions, volumes, EF, left atrial (LA) dimension, peak transmitral valve (MV) early diastolic (E) velocity, the average of septal and lateral myocardial annular tissue velocity (E'), the E/E' ratio, and the MV E/A ratio, where A is peak late diastolic transmitral velocity.^{11–14} The E/E' velocity ratio has been shown to be a good measure of preload or pulmonary capillary wedge pressure.^{15,16} Left ventricular dimension, wall thicknesses, and mass, as well as LA dimension, were measured from 2-dimensionally derived M-mode echocardiograms. If these M-mode echocardiograms were felt to be suboptimal, linear dimensions were measured from 2-dimensional images.¹⁷ Left ventricular volumes were measured, when possible, using a biplane approach. If either, but not both, the apical 2-chamber or 4-chamber view was considered inadequate for measurement, a single-plane method was used to measure ventricular volumes. Peak early and late diastolic transmitral velocities were measured using the pulsed-Doppler technique with the sample volume placed at the level of the mitral leaflet tips during diastole in the apical 4-chamber view. The septal and lateral myocardial annular tissue velocities were recorded with the pulsed-Doppler sample volumes positioned within 1 cm of the septal and lateral insertion sites, respectively, of the anterior and posterior mitral leaflets.¹⁸

Baseline demographic and clinical variables

A range of baseline demographic and clinical variables were acquired in HF-ACTION, and their independent relationships to exercise performance are reported in a separate article. Based on those findings and on prespecified plans, demographic and clinical variables (see Table I) were included in the present analysis to determine what information echo variables added to the prediction of key exercise performance outcome variables: peak VO₂, VE/VCO₂ slope, and 6MWD.

Statistical methods

The bivariate correlations between continuous demographic and clinical variables and echo-Doppler variables were assessed by Pearson's correlation coefficient r . The bivariate correlations between categorical demographic and clinical variables and Doppler-echo variables were assessed by the square root of the explained variation r^2 , which corresponds to

the Pearson's correlation coefficient for continuous variables. The bivariate correlations between the functional variables (peak VO₂, VE/VCO₂ slope, 6MWD) and Doppler-echo variables were also assessed by Pearson's correlation coefficient.

Separate multivariable linear regression models were fit for peak VO₂ and VE/VCO₂ slope, respectively. For each multivariable model, a list of 31 candidate demographic and clinical variables, chosen by the HF-ACTION Executive Committee, and 5 Doppler-echo variables was considered for inclusion in the multivariable model. These variables are listed in Table I. From the 36 variables, those with the highest likelihood ratio test (χ^2) *P* values were eliminated one at a time from inclusion in the multivariable model until all those remaining had partial *R*² values $\geq .01$. The 5 Doppler-echo variables were selected from Table II as those having the highest univariate correlations with peak VO₂, VE/VCO₂ slope, and 6MWD, respectively. A multi-variable model for 6MWD was also fit using the same 36 candidate variables, but no echo-Doppler variables were selected for inclusion in the model; that model is not included in this article.

Statistical analyses were performed using SAS version 9.0 (SAS Institute, Inc, Cary, NC) and R version 2.7.1 (R Foundation for Statistical Computing, Vienna, Austria). All statistical *P* values are 2-tailed.

Results

Selected demographic, clinical, and echo variables are presented in Table III in the overall cohort and in subgroups in whom in addition to LVEF, only M-mode echo, or M-mode, and Doppler MV E/A (with or without E/E' velocity) were available. Note that most patients in the cohort were men (72%), white (62%), and exhibited NYHA class II (63%) and class III (36%) HF. There were no qualitative differences in demographic (age, sex, BMI, and race), exercise, and LVEF variables between the overall cohort and the echo subgroups as outlined. The percent of the cohort in whom various echo variables were available ranged from 99% for LVEF; 71% for LA and LV internal dimensions and LV mass; 69% for LV deceleration time and 67% for MV E/A; to 39% for E' velocity and 34% for E/E' velocity ratio. Pulsed Doppler recordings of E' were not performed at all centers because it was not the routine at some centers to record tissue velocity measurements.

Table IV outlines the bivariate correlations (or square root of the explained variation *r*² for categorical variables) between age, sex, race, NYHA class, HF etiology (ischemic vs nonischemic), ventricular conduction, geographic region, CPX mode, and presence or absence of diabetes mellitus and peripheral vascular disease versus echo-Doppler variables. Note that sex, followed by age and NYHA class, generally demonstrated the strongest correlations with the echo-Doppler variables considered and that none of the correlations were extraordinarily high.

Bivariate correlations between echo-Doppler variables and CPX variables and distance in the 6MWD are shown in Table II. The correlation between echo-Doppler variables tended to be the least with 6MWD. E/E', a measure of LV diastolic function (and preload), was inversely related to peak VO₂ (*r* = -0.23) and directly related to VE/VCO₂ slope (*r* = 0.19). The MV E/A was inversely related to peak VO₂, but was directly related to VE/VCO₂ slope. Left atrial dimension was inversely related to peak VO₂ and directly related to VE/VCO₂ slope. The LVEF correlated directly with peak VO₂ and inversely with VE/VCO₂ slope. E/E' was a stronger bivariate correlate of peak VO₂, VE/VCO₂ slope, and 6MWD than was E' velocity. E/E', MV E/A, and LA dimension correlated more strongly than did LVEF with both peak VO₂ and VE/VCO₂ slope. Left ventricular mass was weakly and nonsignificantly related to peak VO₂.

In a multivariable model (Table V) with peak VO_2 as the dependent variable and including 10 clinical and echo predictor variables with partial r squares ≥ 0.01 , MV E/A ratio as the only echo-Doppler variable explained 6% of the variation in peak VO_2 , and the overall 10-variable model explained 40% of the variation. In this model, age was the strongest predictor, followed by BMI and NYHA classification (sex had a partial r^2 of 0.07).

If MV E/A was replaced by LA dimension, LV early deceleration time, E' , E/E' , or LVEF in the multivariable model for peak VO_2 , the partial r^2 for the echo variable decreased from 0.06 to 0.02–0.05, and the overall model r^2 decreased from 0.40 to 0.37–0.39. Furthermore, the addition to MV E/A of LV mass, LVEF, LA dimension, E' , deceleration time, or any other Doppler variables added nothing to the predictive model for peak VO_2 and 6MWD (data not shown). Adding LVEF to MV E/A in the model explained less than an additional 1% of the variability in peak VO_2 .

In a multivariable model (Table VI) including 5 predictor variables with VE/VCO₂ slope as the dependent variable (Table VI), MV peak E/A was the strongest predictor, explaining 10% of the variation in VE/VCO₂ slope, and the overall model explained 24%. If MV E/A was replaced by LA dimension, E/E' , or LVEF, the partial r^2 decreased from 0.10 to 0.02–0.03, and the overall model r^2 decreased from 0.24 to 0.18–0.19. Adding any echo-Doppler variables to MV E/A in the model provided no additional predictive ability for VE/VCO₂ slope. None of the echo-Doppler variables were predictors for 6MWD in a multivariable model.

Patients who were categorized as having an ischemic etiology of their systolic HF were compared with those with a nonischemic etiology for differences in diastolic functional measures. There were no statistical differences in E , E/A , or E/E' velocity ratio between the ischemic and nonischemic subgroups, respectively (E : 73.9 ± 26 vs 74.3 ± 28 cm/s, t test $P = .76$; E/A : 1.42 ± 0.99 vs 1.37 ± 0.92 , $P = .26$; and E/E' : 10.9 ± 6.9 vs 11.5 ± 8.0 , $P = .27$). The etiology of systolic HF (ischemic vs nonischemic) contributed virtually nothing to the multivariable prediction model for peak VO_2 .

Discussion

The HF-ACTION echo ancillary study provided a unique opportunity to examine detailed echo assessments of LV structure and function and their relationships to demographics and exercise performance in a large cohort of patients with systolic HF. Abnormal aerobic exercise performance is a pivotal feature of the HF syndrome. Furthermore, exercise performance can be quantified by standardized exercise testing. Key exercise measures, particularly peak VO_2 , VE/VCO₂ slope, and 6MWD, are predictive of clinical events and prognosis and are frequently used as outcomes in intervention trials in HF.¹⁹ However, the relationship of these exercise outcomes to the LV function abnormalities present in HF is not well understood. Although abnormal EF is the most obvious abnormality in systolic HF, it is now recognized that significant abnormalities in LV diastolic function are also frequently present^{3–5} and may play a role in abnormal exercise performance. However, we are not aware of published data from a large, multicenter study that has examined the relationships between LV diastolic function, as compared to LV systolic function, and exercise performance. The current analysis focused on 3 key exercise performance outcomes: peak VO_2 , VE/VCO₂ slope, and 6MWD.

The findings of this study indicate that several echo variables were related significantly to exercise performance on bivariate analysis, including diastolic function measures MV E/A, E' , E/E' , early diastolic deceleration time, and LA dimension, as well as LVEF. The MV E/A and E/E' were the echo measures most strongly related to both peak VO_2 (bivariate $r = -0.17$ and -0.23 for MV E/A and E/E' , respectively, both $P < .001$) and VE/VCO₂ slope (bivariate $r = 0.28$ and 0.19 , for MV E/A and E/E' , respectively, both $P < .001$). The bivariate relationships

of MV E/A and E/E' with 6MWD ($r = -0.07$, $P = .004$, and $r = -0.13$, $P < .001$) were weaker than with peak VO_2 or VE/VCO₂ slope. Both MV E/A and E/E' were considerably more strongly related to all 3 exercise test outcomes than was LVEF. In a multivariable model with peak VO_2 as the dependent variable and including MV E/A as the echo variable (which explained 6% of the variance), adding LVEF into the model explained <1% additional variability in peak VO_2 . Furthermore, MV E/A was the strongest multivariable predictor of VE/VCO₂ slope, explaining 10% of the variance. Thus, among patients with systolic HF, echo measures of LV diastolic function appear to be stronger independent predictors of exercise performance than is LVEF.

Of additional interest in this study, there were significant relationships found between specific echo-Doppler variables and key clinical characteristics (Table IV). Some of these may have been expected, given their reported relationships in healthy subjects. However, it is noteworthy that LA and ventricular size retained modest relationships to sex (signed square root of explained variation = -0.25 and -0.21 , respectively) even after the severe remodeling of these chambers that usually accompanies the development of HF with severely decreased EF. Left atrial dimension was also very modestly correlated with NYHA class and ischemic etiology. Not surprisingly, LV dimension and EF and LA dimension were all modestly related to ventricular conduction pattern on resting ECG. The Doppler diastolic function variables MV E/A and early diastolic deceleration time are known to be strongly related to age in healthy subjects; these were significantly, but only modestly ($r = -0.10$ and $r = 0.17$, respectively) related to age in the present cohort of patients with systolic HF (median age 59 years); however, E/E', an estimate of LV filling pressure, was not related to age (data not shown).

There was no significant relationship between BMI and either MV E/A or E/E' in this study. Furthermore, the etiology of the systolic HF (ischemic versus non-ischemic) contributed <1% to explaining peak VO_2 in a multivariable model (data not shown).

Our findings both extend and complement those of other studies. In a study of 75 patients with HF and LVEF $\leq 45\%$ compared to 20 age- and sex-matched healthy controls, LA diastolic dimension indexed to body surface area was the only independent predictor (odds ratio 1.43, $P < .001$) of low treadmill exercise capacity (< 5 metabolic equivalent of task).¹² Independent predictors of cardiovascular events over a period ranging from 330 to 480 days were LA systolic dimension indexed for body surface area and transmitral peak early-to-late velocity ratio (odds ratio 1.10, $P < .027$). However, no expired gas analysis measurements were reported in that study.

In a recent large cross-sectional study of patients undergoing echocardiography after treadmill exercise using the Bruce protocol ($n = 2,867$)—in which patients with evidence of exercise-induced ischemia, LVEF $< 50\%$, or significant valvular heart disease were excluded—LV diastolic dysfunction was strongly and inversely associated with estimated aerobic capacity.²⁰ Increased left ventricular filling pressure as measured by resting E/E' ≥ 15 was associated with a reduction in exercise capacity (-0.41 METs, $P = .007$) in multivariable analysis. Other independent correlates of exercise capacity were age, female sex, and BMI $> 30 \text{ kg/m}^2$ (all $P < .001$). The authors concluded in this cross-sectional study that among patients—not specifically those with HF—referred for exercise echocardiography and not limited by ischemia, abnormalities of LV diastolic function were independently associated with reduced exercise capacity.

Limitations

There are caveats in using Doppler velocity measurements to evaluate LV diastolic function and LV filling pressure. For example, in a recently published study of 106 patients with severe HF, Mullens et al²¹ reported that E/E' ratio was not reliable in predicting intracardiac filling

pressures, particularly in patients with large LV volumes. Other variables, including regional contractility, may modify E/E' ratio. Furthermore, E/A may be pseudonormalized and unmasked by Valsalva maneuver, especially in patients with high filling pressures.²² To date, there is no perfect Doppler-echo measurement of diastolic dysfunction.²³

Tissue Doppler E' and E/E' velocity ratio were unavailable in a substantial percentage of individuals in this study because some of the echocardiographic laboratories involved in the study did not routinely record these measurements. Nonetheless, as shown in Table III, it is expected that our findings should be generalizable to the entire cohort—even those in whom the tissue Doppler E' was not recorded—because there were no meaningful differences in demographic variables between the subgroups in whom this variable was available versus missing. Furthermore, the Valsalva maneuver was only performed during the recordings of Doppler transmitral flow velocity in 25% of patients, and pulmonary venous velocity was not recorded. Even in a well-regarded echocardiography clinical laboratory—and even more so in multicenter studies that generally rely on a spectrum of expertise and practice among participating laboratories—the success of obtaining adequate recordings of these 2 measures is often suboptimal and less than that for the other measures of diastolic function reported in this study.^{24,25} In addition, some of the data that were recorded suffered from outliers in some of the echo variables. Finally, Bensimhon et al²⁶ showed in a representative subset of 405 HF-ACTION patients who performed 2 baseline CPX tests, there is a fairly high degree of within-patient variability in peak $\dot{V}O_2$.

Implications

An important finding of this study is that neither LV diastolic function—as measured by transmitral E/A velocity ratio, tissue Doppler E/E' velocity ratio, or LA dimension—nor LV mass or systolic function, as measured by ejection fraction, is nearly as important in explaining functional capacity as age, sex, and body size in patients with systolic HF. Moreover, because the model including MV peak E/A and 9 other demographic variables only explained 40% of the variance in peak $\dot{V}O_2$, it is clear that other, unmeasured factors are important in explaining human functional capacity. Specifically, it is now well-accepted that peripheral factors, such as muscle mass, mitochondrial energetics, blood flow, and blood hemoglobin, are important contributors to human functional capacity as measured by peak $\dot{V}O_2$.¹ Clearly both cardiac and noncardiac factors should be taken into account in evaluating functional capacity in patients with systolic HF.

In contrast to peak $\dot{V}O_2$ for VE/ $\dot{V}CO_2$ slope, LV diastolic function, as assessed by MV E/A, was the strongest independent predictor of outperforming clinical variables such as age, BMI, and NYHA class. The predictive power of LV diastolic function for VE/ $\dot{V}CO_2$ slope is intriguing, given the strong prognostic value of this latter variable in patients with HF, exceeding that of peak $\dot{V}O_2$.¹⁹

Conclusion

In patients with systolic HF, measures of LV early diastolic function (eg, MV E/A or E/E' velocity ratios and LA dimension) are modest independent predictors of exercise performance and are stronger predictors than is LVEF.

Acknowledgments

This research was supported by National Institutes of Health grants: 5U01HL063747, 5U01HL068973, 5U01HL066501, 5U01HL066482, 5U01HL064250, 5U01HL066494, 5U01HL064257, 5U01HL066497, 5U01HL068980, 5U01HL064265, 5U01HL066491, 5U01HL064264, R37AG18915, P60AG10484.

References

1. Kitzman DW, Groban L. Exercise intolerance. *Heart Fail Clin* 2008;4:99–115. [PubMed: 18313628]
2. Little, WC.; Cheng, CP. Response of left ventricular filling to exercise before and after heart failure. In: Ingels, NB.; Daughters, GT.; Baan, J.; Covell, JW.; Reneman, RS.; Yin, FCP., editors. *Systolic and diastolic function of the heart*. Amsterdam: Ohmsha Ltd; IOS Press; Tokyo: 1996. p. 157–66.
3. Baicu CF, Zile MR, Aurigemma GP, et al. Left ventricular systolic performance, function, and contractility in patients with diastolic heart failure. *Circulation* 2005;111:2306–12. [PubMed: 15851588]
4. Kitzman DW, Little WC, Brubaker PH, et al. Pathophysiological characterization of isolated diastolic heart failure in comparison to systolic heart failure. *JAMA* 2002;288:2144–50. [PubMed: 12413374]
5. Rivas-Gotz C, Manolios M, Thohan V, et al. Impact of left ventricular ejection fraction on estimation of left ventricular filling pressures using tissue Doppler and flow propagation velocity. *Am J Cardiol* 2003;91:780–4. [PubMed: 12633827]
6. Hundley WG, Kitzman DW, Morgan TM, et al. Cardiac cycle dependent changes in aortic area and aortic distensibility are reduced in older patients with isolated diastolic heart failure and correlate with exercise intolerance. *J Am Coll Cardiol* 2001;38:796–802. [PubMed: 11527636]
7. Kitzman DW, Higginbotham MB, Cobb FR, et al. Exercise intolerance in patients with heart failure and preserved left ventricular systolic function: failure of the Frank-Starling mechanism. *J Am Coll Cardiol* 1991;17:1065–72. [PubMed: 2007704]
8. 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* 2007;153:201–11. [PubMed: 17239677]
9. O'Connor CM, Whellan DJ, Lee KL, et al. Investigators. Efficacy and safety of exercise training in patients with chronic heart failure: HF-ACTION randomized controlled trial. *JAMA* 2009;301:1439–50. [PubMed: 19351941]
10. Guyatt GH, Sullivan MJ, Thompson PJ, et al. The 6-minute walk: a new measure of exercise capacity in patients with chronic heart failure. *Can Med Assoc J* 1985;132:919–23. [PubMed: 3978515]
11. Gardin JM, Wong ND, Bommer W, et al. Echocardiographic design of a multi-center investigation of free-living elderly subjects: the Cardiovascular Health Study. *J Am Soc Echocardiogr* 1992;5:63–72. [PubMed: 1739473]
12. Quinones MA, Otto CM, Stoddard M, et al. Recommendations for quantification of Doppler echocardiography: a report from the Doppler Quantification Task Force of the Nomenclature and Standards Committee of the American Society of Echocardiography. *J Am Soc Echocardiogr* 2002;15:167–84. [PubMed: 11836492]
13. Redfield MM, Jacobsen SJ, Burnett JC, et al. Burden of systolic and diastolic ventricular dysfunction in the community: appreciating the scope of the heart failure epidemic. *JAMA* 2003;289:194–202. [PubMed: 12517230]
14. Acaturk E, Koc M, Bozkurt A, et al. Left atrial size may predict exercise capacity and cardiovascular events in patients with heart failure. *Tex Heart Inst J* 2008;35:136–43. [PubMed: 18612491]
15. Nagueh SF, Middleton KJ, Kopelen HA, et al. Doppler tissue imaging: a non-invasive technique for evaluation of left ventricular relaxation and estimation of filling pressures. *J Am Coll Cardiol* 1997;30:1527–33. [PubMed: 9362412]
16. Ommen SR, Nishimura RA, Appleton CP, et al. Clinical utility of Doppler echocardiography and tissue Doppler imaging in the estimation of left ventricular filling pressures: a comparative simultaneous Doppler-catheterization study. *Circulation* 2000;102:1788–94. [PubMed: 11023933]
17. Gottdiener JS, Bednarz J, Devereux R, et al. American Society of Echocardiography recommendations for use of echocardiography in clinical trials. *J Am Soc Echocardiogr* 2004;17:1086–119. [PubMed: 15452478]
18. Nagueh SF, Appleton CP, Gillebert TC, et al. Recommendations for the evaluation of left ventricular diastolic function by echocardiography. *J Am Soc Echocardiogr* 2009;22:107–33. [PubMed: 19187853]

19. Arena R, Myers J, Guazzi M. The clinical and research applications of aerobic capacity and ventilatory efficiency in heart failure: an evidence-based review. *Heart Fail Rev* 2008;13:245–69. [PubMed: 17987381]
20. Grewal J, McCully RB, Kane GC, et al. Left ventricular function and exercise capacity. *JAMA* 2009;301:286–94. [PubMed: 19155455]
21. Mullens W, Borowski AG, Curtin RJ, et al. Tissue Doppler imaging in the estimation of intracardiac filling pressure in decompensated patients with advanced systolic heart failure. *Circulation* 2009;119:62–70. [PubMed: 19075104]
22. Dumesnil JG, Paulin C, Pibarot P, et al. Mitral annulus velocities by Doppler tissue imaging: practical implications with regard to preload alterations, sample position, and normal values. *J Am Soc Echocardiogr* 2002;15(10 Pt 2):1226–31. [PubMed: 12411909]
23. Dumesnil JG, Pibarot P. Doppler assessment of diastolic function at rest and during exercise: distinguishing myth from reality. *J Am Soc Echocardiogr* 2009;22:350–3. [PubMed: 19345304]
24. Khan S, Bess RL, Rosman HS, et al. Which echocardiographic Doppler left ventricular diastolic function measurements are most feasible in the clinical echocardiographic laboratory? *Am J Cardiol* 2004;94:1099–101. [PubMed: 15476639]
25. Bess RL, Khan S, Rosman HS, et al. Technical aspects of diastology: why mitral inflow and tissue Doppler imaging are the preferred parameters? *Echocardiography* 2006;23:332–9. [PubMed: 16640715]
26. Bensimhon DR, Leifer ES, Ellis SJ, 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 (HF-ACTION)). *Am J Cardiol* 2008;102:712–7. [PubMed: 18773994]

Table I**Demographic and clinical variables**

Demographic and clinical variables

- Sex
- Diabetes (history of)
- Stroke (history of)
- Hypertension (history of)
- Prior coronary artery bypass graft
- Prior valve surgery
- Prior PCI
- Prior myocardial infarction
- Peripheral vascular disease (history of)
- Chronic obstructive pulmonary disease (history of)
- Depression (history of)
- Atrial fibrillation/flutter (history of)
- Pacer
- Biventricular pacer
- On an angiotensin-converting enzyme inhibitor at baseline
- On a β -blocker at baseline
- Etiology of HF
- CPX mode (treadmill or bicycle)
- HF hospitalizations in the last 6 m (0, 1, 2, or 3+)
- Region (4 regions of United States, 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 before baseline CPX test (normal, LBBB, RBBB, IVCD, or paced)
- Rest ECG rhythm before baseline CPX test (sinus, atrial fibrillation, or other)
- Smoking status (never, current, or past)
- Diastolic blood pressure
- Systolic blood pressure
- BMI
- Resting heart rate
- Age

Echo-Doppler variables

- LVEF
- E/E' ratio
- E/A ratio
- LV mass
- LA dimension

PCI, Percutaneous coronary intervention; *CCS*, Canadian Cardiovascular Society.

Table IICorrelations (*r*) between key echocardiographic and exercise variables

	Peak VO ₂ (mL kg ⁻¹ min ⁻¹)	VE/VCO ₂ slope	Distance in 6MWD (m)
LA dimension (cm)	-0.18 [*]	0.16 [*]	-0.08 [†]
LVIDd (cm)	-0.01	0.01	-0.01
LV mass (g)	-0.08 [‡]	-0.01	-0.07 [‡]
LVEF (%)	0.13 [*]	-0.16 [*]	0.03
MV E/A	-0.17 [*]	0.28 [*]	-0.07 [‡]
LV deceleration time (ms)	0.10 [†]	-0.09 [†]	0.02
E' velocity (cm/s)	0.07 [‡]	-0.04	0.06
E/E' velocity ratio	-0.23 [*]	0.19 [*]	-0.13 [†]

Abbreviations as in prior tables.

^{*} *P* < .0001.[†] *P* < .001.[‡] *P* < .05.

Table III

Baseline characteristics of participants as a function of echocardiographic measurement availability

	Overall	M-Mode only	M-mode and Doppler MV E/A velocity	M-mode, MV E/A and E/E' velocities
	n = 2331	n = 1484	n = 1230	n = 693
Age, y	59 ± 13	59 ± 13	58 ± 13	58 ± 13
BMI, kg/m ²	31 ± 7	31 ± 7	31 ± 7	32 ± 7
Sex, % female	28	28	30	31
Race (white/nonwhite), %	62/38	62/38	60/40	60/40
NHVA class (II, III), %	63, 36	64, 35	65, 35	65, 35
Ventricular conduction (IVCD, LBBB, normal, paced, RBBB), %	13, 17, 43, 24, 4	12, 16, 43, 25, 4	12, 16, 45, 23, 3	13, 16, 45, 22, 4
Geographic region (West, Midwest, Northeast, South, Canada, France), %	12, 31, 11, 36, 8, 3	12, 32, 10, 35, 9, 3	12, 32, 10, 36, 7, 3	12, 38, 11, 31, 8, 0
CPX mode (treadmill), %	91	91	92	95
Diabetes mellitus, % yes	32	31	32	31
LVEF, %	25 ± 7	26 ± 7	26 ± 7	26 ± 7
PVD, % yes	7	7	7	7
Peak VO ₂ (mL kg ⁻¹ min ⁻¹)	14.9 ± 4.7	15.0 ± 4.7	15.2 ± 4.6	15.2 ± 4.5
Distance in the 6MWD (m)	365 ± 105	365 ± 105	369 ± 104	370 ± 101

Continuous variables are expressed as mean ± SD. *IVCD*, Intraventricular conduction delay; *LBBB*, left bundle branch block; *RBBB*, right bundle branch block; *PVD*, peripheral vascular disease.

Table IV
Correlation* Between Key Selected Demographic/Clinical Variables and Echo-Doppler Variables

	LA dimension (ccm)	LVIDd (cm)	LVEF (%)	MV E/A	LV deceleration time (ms)	E' velocity (cm/s)	E/E' velocity ratio
Age	0.09 [‡]	-0.07 [§]	0.05 [§]	-0.10 [‡]	0.17 [‡]	-0.08 [§]	0.04
Sex (male/female)	-0.25 [‡]	-0.21 [‡]	0.05 [§]	0.08 [‡]	0.00	-0.03	0.11 [§]
Race (white/nonwhite)	0.04	0.06 [§]	-0.02	0.01	0.11 [‡]	0.06	-0.10 [§]
NYHA class (II vs III/IV)	0.11 [‡]	0.07 [§]	0.10 [§]	0.08 [§]	0.04 [§]	0.01 [§]	0.06 [§]
HF etiology (ischemic/nonischemic)	-0.11 [‡]	-0.02	-0.01	-0.03	-0.04	-0.01	0.04
Ventricular conduction	0.18 [‡]	0.13 [‡]	0.16 [‡]	0.09 [§]	0.05	0.06	0.08
Geographic region	0.10 [§]	0.08	0.07 [§]	0.06	0.10 [§]	0.13 [§]	0.11 [§]
CPX mode (treadmill vs bike)	-0.04	-0.02	0	-0.03	0	-0.03	0
Diabetes mellitus (no vs yes)	0.12 [‡]	0	0.03	0.10 [‡]	0.04	-0.01	0.06
PVD (no vs yes)	0	-0.02	0.02	0.01	-0.03	-0.04	0.05

* For dichotomous demographic or clinical variables, the table reports the signed square root of the explained variation r^2 of the corresponding echo-Doppler variable. For each of these variables, the category listed first is the reference category so a negative sign value corresponds to the nonreference category having the lower mean echo-Doppler variable value. For nondichotomous, categorical variables, the table reports the (unsigned) square root of r^2 . For continuous variables, Pearson correlation coefficient is reported. LVIDd, LV internal dimension in diastole. Other abbreviations as in Table I.

[‡] $P < .0001$.

[‡] $P < .001$.

[§] $P < .05$.

Table VMultivariable model for peak VO_2 ($\text{mL kg}^{-1} \text{ min}^{-1}$)

Variable	Coefficient	95% CI	P	Partial r^2
Age, y	-0.13	-0.16 to -0.12	<.0001	0.15
BMI, kg/m^2	-0.19	-0.22 to -0.16	<.0001	0.10
Sex	-2.2	-2.7 to -1.8	<.0001	0.07
MV peak E/A	-1.0	-1.2 to -0.8	<.0001	0.06
NYHA class (II vs III/IV)	-2.0	-2.4 to -1.6	<.0001	0.06
Race			<.0001 (overall)	0.05 (overall)
African American	-1.9	-2.3 to -1.4		
Other	-0.6	-1.5 to 0.3		
Region			<.0001 (overall)	0.03 (overall)
West United States	0.7	0.1 to 1.4		
Midwest United States	0.5	0.1 to 1.0		
Northeast United States	-0.8	-1.5 to -0.2		
Canada	-0.7	-1.5 to 0.2		
France	2.5	1.0 to 3.9		
CPX mode (treadmill vs bike)	-2.5	-3.3 to -1.6	<.0001	0.02
ECG ventricular conduction			<.0001 (overall)	0.02 (overall)
IVCD	-1.3	-1.9 to -0.7		
LBBB	-0.6	-1.2 to -0.1		
Paced	-1.3	-1.8 to -0.8		
RBBB	-1.1	-2.2 to -0.1		
PVD	-2.3	-3.0 to -1.5	<.0001	0.02

Model $r^2 = 0.40$. Reference categories: CPX mode = treadmill, ECG ventricular conduction = normal, sex = male, PVD = no, race = white, region = south United States. Abbreviations as in prior tables.

Table VIMultivariable model for peak VE/VCO₂ Slope

Variable	Coefficient	95% CI	P	Partial r^2
MV peak E/A	2.6	2.3 to 3.1	<.0001	0.10
Age, y	0.16	0.13 to 0.20	<.0001	0.05
NYHA class (II vs III/IV)	3.2	2.4 to 4.1	<.0001	0.04
BMI (kg/m ²)	−0.20	−0.25 to −0.14	<.0001	0.03
ECG ventricular conduction			<.0001 (overall)	0.01 (overall)
IVCD	2.1	0.9 to 3.4		
LBBB	2.1	0.9 to 3.2		
Paced	1.2	0.2 to 2.3		
RBBB	1.2	−0.9 to 3.4		

Model $r^2 = 0.24$. Reference categories: ECG ventricular conduction = normal. Abbreviations as in prior tables.