Accelerometer-Measured Daily Activity in Heart Failure With Preserved Ejection Fraction

Clinical Correlates and Association With Standard Heart Failure Severity Indices

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Background—Daily physical activity assessed by accelerometers represents a novel method to assess the impact of interventions on heart failure (HF) patients’ functional status. We hypothesized that daily activity varies by patient characteristics and correlates with established measures of HF severity in HF with preserved ejection fraction.

Methods and Results—In this ancillary study of the NEAT-HFpEF trial (Nitrate’s Effect on Activity Tolerance in HF With Preserved Ejection Fraction), average daily accelerometer units (ADAU) and hours active per day were assessed during a 14-day period before starting isosorbide mononitrate or placebo (n=110). Baseline ADAU was negatively associated with age, female sex, height, and body mass index, and these variables accounted for 28% of the variability in ADAU (P<0.007 for all). Adjusting for these factors, patients with lower ADAU were more likely to have had an HF hospitalization, orthopnea, diabetes mellitus and anemia, be treated with β-blockers, have higher ejection fraction, relative wall thickness and left atrial volume, and worse New York Heart Association class, HF-specific quality of life scores, 6-minute walk distance, and NT-proBNP (N-terminal pro-B-type natriuretic peptide; P<0.05 for all). Associations between hours active per day and clinical characteristics were similar. Relative to baseline, there were no significant associations between changes in ADAU or hours active per day and changes in standard functional assessments (New York Heart Association, quality of life, 6-minute walk distance, and NT-proBNP) with isosorbide mononitrate.

Conclusions—Daily activity is a measure of HF-related and global functional status in HF with preserved ejection fraction. As compared with intermittently assessed standard HF assessments, change in daily activity may provide unique information about the impact of HF interventions on functional status.

Clinical Trial Registration—URL: https://www.clinicaltrials.gov/. Unique identifier: NCT02053493

Key Words: anemia ■ body mass index ■ diabetes mellitus ■ functional capacity ■ heart failure ■ lifestyle

Clinical trials of heart failure (HF) therapies determine effects of an intervention on patients’ functional status by assessing New York Heart Association (NYHA) functional class, HF-specific quality of life (QOL) scores, cardiopulmonary exercise testing (CPXT), or 6-minute walk distance (6MWD). Safety and tolerability are assessed by the incidence of adverse events, and the investigator assessed relatedness of the adverse event to the study intervention. These measures each have strengths but may not be sensitive to clinically meaningful changes in functional status (NYHA class and adverse events), assess functional capacity rather than performance (CPXT and 6MWD), and rely on patient perception and memory (QOL scores). Importantly, these measures provide low-density data because they are typically assessed only a few times during the course of a study. The CPXT and 6MWD are difficult for some patients to perform.

See Clinical Perspective

There is a need for high-density, quantitative, patient-centric clinical trial end points that are reflective of a therapy’s global effect on functional status. Patient-worn accelerometers can provide high-density, quantitative data from continuous assessment of physical activity during usual daily life.12 Daily activity may be sensitive to both the therapeutic effects and off-target side effects of an HF therapy. In the NEAT-HFpEF trial (Nitrate’s Effect on Activity Tolerance in HF...
With Preserved Ejection Fraction), relative to placebo, isosorbide mononitrate (ISMN) therapy decreased accelerometer-assessed daily activity in a dose-related fashion but did not significantly affect standard HF end points. In this analysis from the NEAT-HFpEF study, we sought to further understand the determinants of daily activity in HFpEF and its relationship to standard functional assessments. Accordingly, we determined the clinical correlates of daily activity in HFpEF at baseline (in the absence of study drug administration). Because sex, age, and body size are known to influence measures of functional capacity (6MWD and CPXT), we first assessed their impact on daily activity measures. Adjusting for these variables, we examined the association of daily activity with clinical features and standard HF assessments (NYHA class, 6MWD, HF QOL scores, and NT-proBNP [N-terminal pro-B-type natriuretic peptide]) at baseline and the relationship between changes in activity and changes in standard HF assessments with ISMN relative to baseline.

**Methods**

The study rationale, design, and primary findings of NEAT-HFpEF have been reported. NEAT-HFpEF was a multicenter, randomized, double-blind, placebo-controlled, 2-period, 12-week crossover study (Figure I in the Data Supplement) of 110 patients with HFpEF designed to test the hypothesis that extended release ISMN would enhance daily activity as assessed by patient-worn accelerometers. Throughout the entire study and for 24 hours each day (except while bathing), patients wore a belt outfitted with 2 kinetic activity monitors (Kersh Health, Plano, TX) containing high-sensitivity, triaxis accelerometers (KXUD9-2050; Kionix, Ithaca, NY; Figure II in the Data Supplement). Institutional review board approvals were obtained by each study site, and all subjects gave informed consent.

Patients were eligible for study participation if they had NYHA class II to IV symptoms of HF, were at least 50 years of age, had preserved (25%) ejection fraction (EF), and demonstrated objective evidence of HF (either prior HF hospitalization or invasive hemodynamic, Doppler echocardiographic or natriuretic peptide criteria). Patients were randomized to ISMN or placebo for the first 6-week study period. Patients took no study drug for the first 2 weeks of the first period to provide a baseline and then underwent weekly scheduled uptitration (30–60 to 120 mg once daily) of study drug and remained on the maximally tolerated dose for the final 2 weeks of the first study period. Patients then returned for a second study visit, underwent repeat NYHA functional class assignment, 6MWD, QOL questionnaires, and NT-proBNP measurement (Core Laboratory). Patients were randomized to ISMN or placebo for the first 6-week study period. Patients took no study drug for the first 2 weeks of the first period to provide a baseline and then underwent weekly scheduled uptitration (30–60 to 120 mg once daily) of study drug and remained on the maximally tolerated dose for the final 2 weeks of the first study period. Patients then returned for a second study visit, underwent repeat NYHA functional class assignment, 6MWD, QOL questionnaires, and NT-proBNP measurements, received new accelerometers, were crossed over to the alternate therapy, and completed study procedures as in the first study period. Complete study design is represented in Figure I in the Data Supplement. The NEAT-HFpEF primary end point was daily activity, quantified as average daily accelerometer units (DAU) during the 120-mg (or maximally tolerated) dose of ISMN versus placebo. Secondary end points included hours active per day (HAPD) during the 120-mg dose.

**Accelerometer**

Acceleration sensing is based on the principle of differential capacitance. Differential capacitance results from acceleration-induced motion of a silicon sense element within a microelectromechanical systems chip and is measured in 3 orthogonal axes (x, y, and z). Body movement causes the silicon sense element to shift in position, changing capacitance, which is measured as changes in voltage. The cumulative vector of the 3 capacitances in 3 dimensions for each body movement is expressed as arbitrary accelerometer units.

The kinetic activity monitoring devices were activated at the study visits providing time and date-stamped data to match to the study periods. The kinetic activity monitors did not display any information about duration or intensity of activity to the patient. Data were continuously recorded, and cumulative accelerometer units were stored in 15-minute epochs, providing a total of 96 different data points per day, which were averaged to provide ADAU. For the baseline or dose-specific study drug periods, the daily ADAU were averaged for the respective study or study drug periods. The ADAU provides a composite index reflective of both the intensity and duration of activity. In contrast, the HAPD reflects the duration of activity but provides no information about the intensity of activity. The HAPD was calculated from the daily number of 15-minute cumulative accelerometer units >50 (activity threshold described previously) and averaged for the baseline or dose-specific study drug periods. When wearers are sedentary, the effect of breathing and shifting in sitting/lying position is evident as low-level accelerometer output. A 15-minute cumulative accelerometer unit of 50 may be reflective of this type of activity and at a maximum equates to walking at 1.0 mph for 1 minute or 0.5 mph for 4 minutes interspersed with sitting or lying for the 15-minute epoch. In contrast, if the accelerometer is left on a surface, the 15-minute accelerometer unit values are zero unless the surface itself is moved. The threshold for not wearing the accelerometer was set at a 15-minute accelerometer unit value of <5, present for at least 4 consecutive 15-minute epochs. Days with <10 hours of wear time per day were considered inadequate for analysis because of noncompliance. The accelerometer core laboratory (Mayo Clinic, Rochester, MN, and Scottsdale, AZ) prepared the devices, downloaded and processed the raw data (blinded to treatment assignment), and supplied the cleaned raw data to the data coordinating center.

**Statistical Analysis**

To investigate factors influencing daily activity in HFpEF, the relationship between baseline (study visit 1) clinical characteristics and ADAU or HAPD measured over the ensuing 14-day baseline period (before any intervention) was assessed. First, stepwise, general linear models were used to assess the relationship between ADAU or HAPD and sex, age (normalized), and body size measures. Because the distribution of ADAU was skewed (Figure), log transformation was used in this and all subsequent models.

To assess the relationship between ADAU or HAPD and clinical characteristics, data were displayed according to tertiles of the baseline ADAU or HAPD and analyzed using general linear models, including the clinical variables of interest, ADAU or HAPD as continuous variables and age, sex, and appropriate body size covariates. Associations between ADAU or HAPD and echocardiographic indices or standard HF functional assessments (NYHA functional class, QOL scores, 6MWD, and NT-proBNP levels) were assessed using linear regression.

To investigate the relationship between changes in ADAU or HAPD and changes in standard HF functional assessments from baseline to the 120-mg (or maximally tolerated) dose of ISMN, changes in variables were displayed according to tertiles of the change in ADAU or HAPD. Data were analyzed using a general linear model that included the baseline values of the standard assessment and ADAU or HAPD, the treatment period (first or second) where active drug was received, and the changes in the variables. P<0.05 were considered significant, and statistical analyses were performed using SAS statistical software (SAS Institute Inc, Cary, NC).

**Results**

Of the 110 patients enrolled in NEAT-HFpEF, 11 did not have adequate baseline accelerometer data because of withdrawal
of consent (n=1), site lost accelerometer after patient returned it (n=1), or poor compliance (n=9) with wearing of the accelerometer. NEAT-HFpEF patients included in this study were a mean of 69 years of age, 60% women, predominantly white, and obese with controlled blood pressure, multiple comorbidities, and use of multiple cardiovascular medications (Table I in the Data Supplement). Participants had NYHA functional class II or III symptoms. The mean EF was 63.9%, and 45% of participants had evidence of concentric remodeling or hypertrophy (relative wall thickness >0.41).

During the baseline period, the median (25th, 75th percentiles) days with usable data were 12.0 (10.0, 13.0) days. As outlined in methods, all days used in analysis had at least 10 hours of wear time. The distribution of ADAU but not HAPD was skewed (Figure A through C). During the baseline period, there was excellent correlation ($r=0.99$, $P<0.0001$ for ADAU and $r=0.99$, $P<0.0001$ for HAPD) and agreement between data from the 2 accelerometers on the accelerometer belt worn by each patient (Figure III in the Data Supplement). During the baseline period, ADAU and HAPD were correlated but in an exponential fashion reflecting the fact that some patients had higher intensity of activity but not a (linearly related) increase in duration of activity in (Figure D).

### Association of Daily Activity Measures With Age, Sex, and Body Size

Although sex, age, and body size variables displayed several associations with each other, in the multivariable model, daily activity assessed by ADAU was negatively associated with older age, female sex, greater height, and greater body mass index (BMI; Table 1). Age, sex, height, and BMI accounted for 28% of the variation in ADAU. Similarly, daily activity as assessed by HAPD was negatively associated with older age, female sex, greater height, and greater body weight (Table 1). Age, sex, height, and weight accounted for 25% of the variation in HAPD.

### Association of Daily Activity Measures With Clinical Characteristics

Adjusted for age, sex, height, and BMI, ADAU did not vary according to ethnicity, heart rate, blood pressure, or the presence of elevated jugular venous pressure (Table 2). Patients with lower ADAU tended ($P=0.08$) to have more edema and were more likely to report orthopnea. Patients with lower ADAU were more likely to have had an HF hospitalization in the year before enrollment and have diabetes mellitus or anemia, but there was no association between ADAU and history of coronary disease, lung disease, obstructive sleep apnea, depression, or renal dysfunction. Patients treated with β-blockers had lower ADAU ($P=0.0054$), but ADAU did not vary according to treatment with other standard HF therapies (loop diuretics, inhibitors).

### Table 1. Association of Daily Activity Indices With Age, Sex, and Body Size

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Estimate</th>
<th>95% Confidence Interval</th>
<th>$P$ Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Log average daily accelerometer units (model $R^2=0.28$)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (per SD)</td>
<td>−0.24</td>
<td>−0.33, −0.14</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Sex (female)</td>
<td>−0.52</td>
<td>−0.79, −0.24</td>
<td>0.0003</td>
</tr>
<tr>
<td>Height (per SD)</td>
<td>−0.19</td>
<td>−0.32, −0.05</td>
<td>0.0062</td>
</tr>
<tr>
<td>Body mass index (per SD)</td>
<td>−0.21</td>
<td>−0.31, −0.11</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Hours active per day (model $R^2=0.25$)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (per SD)</td>
<td>−0.68</td>
<td>−1.13, −0.24</td>
<td>0.0031</td>
</tr>
<tr>
<td>Sex (female)</td>
<td>−2.41</td>
<td>−3.64, −1.17</td>
<td>0.0002</td>
</tr>
<tr>
<td>Height (per SD)</td>
<td>−0.54</td>
<td>−1.16, 0.09</td>
<td>0.0902</td>
</tr>
<tr>
<td>Body weight (per SD)</td>
<td>−1.12</td>
<td>−1.64, −0.61</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

Data are results of stepwise multivariable linear regression retaining variables with a $P<0.15$. 

![Figure. Distribution of accelerometer-assessed activity measures during the baseline period in NEAT-HFpEF (Nitrate’s Effects on Activity Tolerance in HF With Preserved Ejection Fraction). Distribution of average daily accelerometer units (ADAU, A), log-transformed ADAU (B), hours active per day (HAPD, C), and the correlation between ADAU and HAPD (D) during the baseline period.](http://circheartfailure.ahajournals.org/doi/figure/10.1161/CIRCHEARTFAILURE.117.002715)
**Table 2. Association of ADAU With Clinical Characteristics**

<table>
<thead>
<tr>
<th>ADAU range</th>
<th>Lowest ADAU Tertile (n=32)</th>
<th>Middle ADAU Tertile (n=34)</th>
<th>Highest ADAU Tertile (n=33)</th>
<th>Adjusted P Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADAU</td>
<td>2281–6736</td>
<td>6779–10 730</td>
<td>10 736–30 148</td>
<td></td>
</tr>
</tbody>
</table>

Demographics

- **Age, y**
  - 72.6±9.9
  - 67.7±9.1
  - 67.6±7.7
  - <0.0001
- **Female sex**
  - 75% (24)
  - 47% (16)
  - 58% (19)
  - 0.0003
- **Minority race†**
  - 22% (7)
  - 3% (1)
  - 6% (2)
  - 0.38

Physical examination

- **BMI, kg/m²**
  - 35.7±9.6
  - 36.2±8.3
  - 33.8±6.7
  - <0.0001
- **Heart rate, bpm**
  - 71±11
  - 72±14
  - 69±10
  - 0.15
- **Systolic BP, mm Hg**
  - 129±15
  - 128±15
  - 133±18
  - 0.25
- **Elevated JVP**
  - 26% (8)
  - 41% (14)
  - 24% (8)
  - 0.35
- **Mod/severe edema**
  - 22% (7)
  - 15% (5)
  - 0
  - 0.076

Clinical data

- **Orthopnea**
  - 63% (20)
  - 53% (18)
  - 42% (14)
  - 0.032
- **HF Hsp in last year**
  - 25% (8)
  - 29% (10)
  - 3.0% (1)
  - 0.0066
- **Ischemic pathogenesis**
  - 66% (21)
  - 50% (17)
  - 70% (23)
  - 0.43
- **COPD**
  - 16% (5)
  - 18% (6)
  - 9% (3)
  - 0.19
- **OSA**
  - 42% (13)
  - 64% (21)
  - 47% (15)
  - 0.12
- **Diabetes mellitus**
  - 47% (15)
  - 44% (15)
  - 12% (4)
  - 0.0071
- **Depression**
  - 34% (11)
  - 35% (12)
  - 27% (9)
  - 0.39
- **Anemia‡**
  - 41% (13)
  - 45% (15)
  - 12% (4)
  - 0.022
- **eGFR, mL/min per 1.73 m²§**
  - 56±18
  - 58±22
  - 66±16
  - 0.62

Medications

- **Loop diuretic use**
  - 69% (22)
  - 74% (25)
  - 55% (18)
  - 0.85
- **β-Blocker use**
  - 81% (26)
  - 82% (28)
  - 48% (16)
  - 0.0054
- **ACE/ARB use**
  - 66% (21)
  - 62% (21)
  - 58% (19)
  - 0.89
- **MRA use**
  - 31% (10)
  - 35% (12)
  - 9% (3)
  - 0.22

Echocardiography

- **Ejection fraction**
  - 66±6
  - 62±10
  - 63±9
  - 0.021
- **Relative wall thickness**
  - 0.47±0.13
  - 0.43±0.10
  - 0.39±0.10
  - 0.0079
- **LA volume index, mL/m²**
  - 43±13
  - 43±19
  - 35±13
  - 0.012
- **E/e’ medial**
  - 16.5±7.2
  - 13.8±6.2
  - 15.4±12.3
  - 0.070

Data are % (n) or mean±SD. ACE/ARB indicates angiotensin-converting enzyme/angiotensin receptor blocker; ADAU, average daily accelerometer unit; BMI, body mass index; BP, blood pressure; COPD, chronic obstructive lung disease; eGFR, estimated glomerular filtration rate; HF, heart failure; Hsp, hospitalization; JVP, jugular venous pressure; LA, left atrial; MRA, mineralocorticoid receptor antagonist; and OSA, obstructive sleep apnea.*Adjusted for age, sex, height, and body mass index.
†Self-identified.
‡Hemoglobin <13 in men or <12 in women.
§Modified diet in renal disease equation.

\(P=0.85\); angiotensin-converting enzyme/angiotensin receptor blocker, \(P=0.89\); mineralocorticoid receptor, \(P=0.22\). Patients with lower ADAU had higher EF, more concentric left ventricular remodeling (higher relative wall thickness) and larger left atrial volume, and tended to have higher Doppler estimated filling pressures (higher \(E/e’\), \(P=0.07\)).

Adjusted for age, sex, and weight, HAPD did not vary according to ethnicity, heart rate, blood pressure, or the presence of elevated jugular venous pressure, edema, or orthopnea (Table II in the Data Supplement). Patients with lower HAPD were more likely to have had an HF hospitalization in the year before enrollment and tended to have a higher prevalence.
of diabetes mellitus ($P=0.13$) or anemia ($P=0.09$), but there was no association between HAPD and history of coronary disease, lung disease, obstructive sleep apnea, depression, or renal dysfunction. Patients treated with $\beta$-blockers had lower HAPD, but HAPD did not vary according to treatment with other standard HF therapies. Patients with lower HAPD had higher EF, more concentric left ventricular remodeling (higher relative wall thickness), and tended to have larger left atrial volume ($P=0.12$) but did not have higher Doppler estimated filling pressures ($E/\text{e}’$).

### Daily Activity Measures and Standard HF Functional Assessments

Patients with lower ADAU were more likely to have NYHA class III/IV symptoms, less favorable (lower) Kansas City Cardiomyopathy Questionnaire physical and overall QOL scores, lower 6MWD and higher NT-proBNP levels, and tended to have less favorable (higher) Minnesota Living with Heart Failure Questionnaire physical ($P=0.08$) and overall ($P=0.16$) QOL scores (Table 3). HAPD had similar associations with standard HF functional assessments (Table 3).

### Changes in Daily Activity Measures and Standard HF Assessments With ISMN

During the primary end point 120-mg dose phase, 101 participants during period 1 and 91 participants during period 2 had usable accelerometer data with a median of 16 (interquartile range, 12–20) complete days of accelerometer data in period 1 and 14 (interquartile range, 10–18) complete days of accelerometer data in period 2. Although activity measures correlated with standard HF functional assessments at baseline, there were no significant relationships between changes (baseline to ISMN) in activity (ADAU or HAPD) measures and changes in standard HF functional assessments (Table 4).

### Table 3. Association of Daily Activity Indices With Standard Heart Failure Assessments

<table>
<thead>
<tr>
<th>Variable</th>
<th>ADAU</th>
<th>HAPD</th>
</tr>
</thead>
<tbody>
<tr>
<td>NYHA III/IV</td>
<td>59% (19)</td>
<td>48% (16)</td>
</tr>
<tr>
<td>KCCQ physical*</td>
<td>48±26</td>
<td>48±27</td>
</tr>
<tr>
<td>KCCQ overall*</td>
<td>50±25</td>
<td>48±26</td>
</tr>
<tr>
<td>MLWHF, physical†</td>
<td>24±11</td>
<td>25±22</td>
</tr>
<tr>
<td>MLWHFQ, total†</td>
<td>49±24</td>
<td>50±22</td>
</tr>
<tr>
<td>6MWD, m</td>
<td>242±105</td>
<td>269±116</td>
</tr>
<tr>
<td>NT-proBNP, pg/mL</td>
<td>713±929</td>
<td>245±584</td>
</tr>
</tbody>
</table>

Data are mean±SD or % (n). 6MWD indicates 6-minute walk distance; ADAU, average daily accelerometer unit; HAPD, hours active per day; KCCQ, Kansas City Cardiomyopathy Questionnaire; MLWHFQ, Minnesota Living with Heart Failure Questionnaire; NT-proBNP, N-terminal pro-B-type natriuretic peptide; and NYHA, New York Heart Association.

*Higher KCCQ score indicates better status.
†Lower MLWHFQ score indicates better status.

### Table 4. Association of Changes in Daily Activity Indices With Changes in Standard Heart Failure Assessments

<table>
<thead>
<tr>
<th>Variable Change</th>
<th>Lowest Change</th>
<th>Middle Change</th>
<th>Highest Change</th>
<th>$P$ Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADAU tertile</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Change in ADAU (range)</td>
<td>−8230 to −977</td>
<td>−942 to −218</td>
<td>231 to 4835</td>
<td></td>
</tr>
<tr>
<td>NYHA −0.03±0.8</td>
<td>−0.06±0.6</td>
<td>−0.07±0.7</td>
<td>0.12</td>
<td></td>
</tr>
<tr>
<td>KCCQ physical†</td>
<td>−2±18</td>
<td>1±14</td>
<td>−3±18</td>
<td>0.94</td>
</tr>
<tr>
<td>KCCQ overall†</td>
<td>−0.3±16</td>
<td>−2±13</td>
<td>−4±12</td>
<td>0.27</td>
</tr>
<tr>
<td>MLWHF, physical‡</td>
<td>1±8</td>
<td>0.4±8</td>
<td>0.8±8</td>
<td>0.75</td>
</tr>
<tr>
<td>MLWHFQ, total‡</td>
<td>4±14</td>
<td>−3±16</td>
<td>1±14</td>
<td>0.89</td>
</tr>
<tr>
<td>6MWD, m</td>
<td>7±61</td>
<td>14±40</td>
<td>−8±48</td>
<td>0.97</td>
</tr>
<tr>
<td>NT-proBNP, pg/mL</td>
<td>−65±459</td>
<td>169±508</td>
<td>−42±148</td>
<td>0.97</td>
</tr>
</tbody>
</table>

Data are mean±SD for change (value during 120-mg dose of isosorbide mononitrate—baseline value). 6MWD indicates 6-minute walk distance; ADAU, average daily accelerometer unit; HAPD, hours active per day; KCCQ, Kansas City Cardiomyopathy Questionnaire; MLWHFQ, Minnesota Living with Heart Failure Questionnaire; NT-proBNP, N-terminal pro-B-type natriuretic peptide; and NYHA, New York Heart Association.

*P value based on a general linear model that included the baseline value of the standard heart failure assessments and ADAU or HAPD, the treatment period where active drug was received and the (continuous) change in the variable.
†Positive value indicates improvement.
‡Negative value indicates improvement.
Discussion

The ADAU derived from patient-worn accelerometers is a measure reflective of daily activity duration and intensity. In HFpEF, ADAU was negatively associated with age, female sex, height, and obesity (BMI). Adjusting for these factors, ADAU was lower in patients with HFpEF with a previous HF hospitalization and in those with more severe HF signs and symptoms (edema and orthopnea), comorbidities (diabetes mellitus or anemia), β-blocker therapy, higher EF, worse concentric left ventricular remodeling, and greater left atrial enlargement. At baseline, ADAU was correlated with standard HF severity indices (NYHA class, HF-specific QOL scores, 6MWD, and NT-proBNP levels). An activity index reflective of duration of activity alone (HAPD) showed directionally similar but numerically weaker associations. These findings suggest that accelerometer-assessed daily activity provides a measure of global and HF-related functional status in HFpEF. However, with the maximally tolerated dose (≤120 mg/d) of ISMN, changes in ADAU from baseline did not correlate with changes in standard HF severity indices. In the NEAT-HFpEF trial, relative to placebo, ISMN therapy was associated with dose-related decreases in activity without significant changes in standard HF end points.6 Collectively, these findings may suggest that as compared with intermittently assessed standard HF indices, daily activity may be more sensitive to the impact of an intervention on global functional status.

Daily Physical Activity as a Measure of Functional Status in the Context of This Study

There are 4 domains of functional status, including functional capacity (maximal potential to perform daily activities), functional performance (actual daily activity), functional reserve (the difference between capacity and performance), and functional capacity use (degree of capacity used on daily basis).8 In NEAT-HFpEF, we measured functional performance using accelerometers and an index of functional capacity (6MWD). Although CPXT provides a more robust measure of maximal functional capacity, the 6MWD is a commonly used assessment of functional capacity in HF and is believed to more closely approximate the capacity to perform activities of daily living. Furthermore, the majority of studies that have compared CPXT and 6MWD demonstrate strong correlation between the 2 and many patients with HF exercise close to or at their maximal energy expenditure during a 6-minute walk test.9 We hypothesized that ISMN would improve functional capacity and that patients would improve their functional performance in proportion to their capacity. However, we also recognized the potential for adverse side effects with ISMN, which could impair functional performance, even with stable or improved functional capacity. In NEAT-HFpEF, relative to placebo, ISMN therapy was associated with decreased activity but not decreased 6MWD, consistent with an effect of ISMN on functional capacity use. In the current analysis, relative to baseline, changes in activity (ADAU or HAPD) with ISMN showed neither a significant nor directional relationship to changes in 6MWD, again suggesting that changes in activity were related to changes in functional capacity use rather than changes in functional capacity. More recently, Zamani et al50 tested a higher dose of organic nitrates (in the form of isosorbide dinitrate) in HFpEF and showed no change in 6MWD but a high incidence of adverse side effects (60% with isosorbide dinitrate) and study drug discontinuation. Although this study did not include assessment of daily activity, the findings support our interpretation of the mechanism of decreases in functional performance (daily activity) in the absence of decreases in functional capacity (6MWD).

Accelerometer-Assessed Activity and Its Use in HF

Arbitrary values for accelerometer units, or time active per day based on such units, are highly sensitive to the device design (uniaxial versus triaxial), body location, wear time (hours per day and days worn), data acquisition mode (sampling frequency and storage epochs), analytics, activity threshold values, and patient population.12 At present, there are no consistent and universally accepted methods for converting accelerometer-assessed activity units into recognized intensity levels for direct clinical interpretation.11 Each accelerometer was calibrated during production, but there were no previous studies with this accelerometer in patients with HF. Similar accelerometers have been shown to sensitively capture low levels of daily physical activity.1

Previous studies have converted accelerometer units into steps using assumptions about accelerometer units per step or reported the duration or percent of wear time with accelerometer units for a certain threshold. Commercially available devices for activity monitoring and accelerometers imbedded in cardiac devices eliminate data corresponding to walking speeds of <1.5 to 2.0 miles/h.12 Such devices may be suboptimal for monitoring functional performance in elderly patients with chronic diseases, such as HFpEF.

Measures of time or percent time active are widely used but are sensitive to thresholds for activity. Studies focused on population health status have stratified time active by different accelerometer unit threshold values to provide time spent in non-sedentary versus moderate to vigorous activity.13 Although less intuitive to clinicians, ADAU provides an index of both intensity and duration of activity and showed numerically more robust associations with HF clinical characteristics and functional assessments than HAPD in our analysis.

Prior studies of accelerometer-assessed activity in HF have been largely restricted to patients with HF and reduced EF but have demonstrated correlations between variously quantitated accelerometer data and NYHA,14 6MWD,12,14 peak oxygen consumption,14,15 estimated (Seattle Heart Failure Model) or observed mortality risks,16,17 non-HF-specific QOL questionnaires,18 therapeutic response to cardiac resynchronization,19,20 and changes in clinical status.17,21 Our findings document that accelerometer-assessed activity is similarly associated with HF functional measures in HFpEF. However, other sources of variation in activity in HF have not been well described, particularly in HFpEF.

Sources of Daily Activity Variation in HFpEF

Studies in healthy young cohorts have identified interindividual variation, intraindividual variation, and week day as sources of variation in accelerometer-assessed daily physical activity and suggested that 1 week of monitoring is sufficient to establish activity pattern.7 In NEAT-HFpEF, we used a 2-week period to establish both baseline and therapeutic effect. Compliance with wearing the accelerometer in our study was good but not perfect.
The belt was used to reduce loss of the accelerometer devices, and no patient reported losing the accelerometer device.

**Associations of Daily Physical Activity With Age, Sex, and Body Size**

In NEAT-HFpEF, daily activity (ADAU or HAPD) was lower in women and in older, taller, or more obese patients with HFpEF. Measures of functional capacity (6MWD or maximal exercise capacity)\(^6\) are known to be lower in women and older or more obese patients, but sex-, age-, and obesity-related behavioral factors could also influence functional performance, independent of capacity. Studies in non-HF adult cohorts have established that accelerometer-assessed activity decreases with age independent of muscle mass,\(^2\) is lower in women than men,\(^2\) decreases with increased height\(^2\) (likely because of stride length and fewer steps per distance traveled), and decreases with increasing severity of obesity.\(^24\) Because these demographic variables may covary with clinical characteristics in HF, adjusting for their impact is important.

In addition, it is interesting to note that on average, across the tertiles of activity, all patients were obese (based on BMI range). Other studies may demonstrate additional relationships not seen among this patient population because most patients were obese and obesity may independently reduce ADAU or HAPD.

**Associations of Daily Activity With Clinical Characteristics**

Although the lower activity observed in patients with HFpEF with orthopnea and edema are expected, lower activity was also observed in patients with anemia and diabetes mellitus. These factors have been associated with lower functional capacity (6MWD or peak oxygen consumption) in HFpEF.\(^6\) Patients with lower activity were more likely to be treated with \(\beta\)-blockers. \(\beta\)-Blockers can worsen chronotropic incompetence, a factor related to reduced exercise capacity in HFpEF.\(^27\) Although observational studies in HF have documented lower activity in patients with depression,\(^28\) we did not see lower activity in patients with HFpEF with a history of depression recorded in the case report forms. It may be that patients enrolling in a clinical trial are less likely to have active depression. Studies of accelerometer-assessed activity in non-HF cohorts have documented that activity is lower in patients with more severe lung disease,\(^29\) angina,\(^13\) renal disease,\(^30\) and sleep apnea.\(^31\) We did not see an association with these conditions and activity, but the NEAT-HFpEF trial excluded patients whose clinical status was felt to be prominently influenced by these conditions.

It was of interest that EF, relative wall thickness, and left atrial volume were negatively associated with activity levels. These factors were not associated with functional capacity (peak oxygen consumption) in HFpEF after adjustment for age, sex, body size, chronotropic competence, and hemoglobin.\(^6\) We speculate that these phenotypic markers of HFpEF may covary with HFpEF severity and comorbidity burden.

**Strengths and Potential Limitations**

This study provides data collected exclusively in patients with HFpEF in a multicenter setting enhancing relevance to future use of accelerometers in clinical trials and provided a comprehensive assessment of factors influencing activity in HFpEF. Although our sample size was small, it was larger than many studies assessing accelerometer data in HF. Daily activity is sensitive to non-HF–related physical, behavioral, or environmental factors, but in the context of a clinical trial, these factors should be addressed by the randomization process. In addition, it should be noted that on average, the patients with HFpEF enrolled in NEAT-HFpEF were obese. Further validation of the relationships between daily activity and HFpEF clinical characteristics and therapeutic effect is needed. Accelerometer data are currently being collected in a similarly designed HFpEF trial testing the impact of inhaled inorganic nitrite on peak oxygen consumption\(^1\) (NCT02742129). The current analysis pertained to use of daily activity as a clinical trial end point and does not provide information on use of activity for clinical disease monitoring.

**Conclusions**

Accelerometer-assessed daily activity varies with age, sex, and body size, as well as standard assessments of HF severity and physiologically relevant comorbidities in HFpEF. As such, accelerometer provides a measure of HF-related and global functional status in HFpEF. With ISMN, changes in activity measures were not associated with changes in standard assessments of HF severity. As compared with intermittently assessed standard HF assessments, change in daily activity may provide unique information about the global impact of HF interventions on functional status.

**Disclosures**

None.

**References**


Accelerometer-Measured Daily Activity in Heart Failure With Preserved Ejection Fraction: Clinical Correlates and Association With Standard Heart Failure Severity Indices

David Snipelisky, Jacob Kelly, James A. Levine, Gabriel A. Koepp, Kevin J. Anstrom, Steven E. McNulty, Rosita Zakeri, G. Michael Felker, Adrian F. Hernandez, Eugene Braunwald and Margaret M. Redfield

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As outlined in the primary NEAT manuscripts (Supplemental Materials), patients enrolled in NEAT were screened to determine if heart failure symptoms were the primary factor limiting their activity as indicated by answering # 2 to the following question administered during the screening process.

My ability to be active is most limited by:

1. Joint, foot, leg, hip or back pain
2. Shortness of breath and/or fatigue and/or chest pain
3. Unsteadiness or dizziness
4. Lifestyle, weather, or I just don’t like to be active

**Supplemental Methods:**

As outlined in the primary NEAT manuscripts (Supplemental Materials), patients enrolled in NEAT were screened to determine if heart failure symptoms were the primary factor limiting their activity as indicated by answering # 2 to the following question administered during the screening process.

My ability to be active is most limited by:

1. Joint, foot, leg, hip or back pain
2. Shortness of breath and/or fatigue and/or chest pain
3. Unsteadiness or dizziness
4. Lifestyle, weather, or I just don’t like to be active
### Supplemental Table 1. Patient characteristics

<table>
<thead>
<tr>
<th>Included Patients (n=99)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age-yr</strong></td>
</tr>
<tr>
<td>Female sex – n (%)</td>
</tr>
<tr>
<td>Self-reported white race – n (%)</td>
</tr>
<tr>
<td>Body Mass Index (weight/height$^2$) – kg/m$^2$</td>
</tr>
</tbody>
</table>

#### Functional measures

- **NYHA functional classification – n(%)‡**
  - II: 52 (53%)
  - III: 45 (45%)

- **KCCQ clinical score (range 1-100, higher better)**: 56.8 ± 24.2
- **MLHFQ total Score (range 0-105, lower better)**: 44.4 ± 23.5
- **Six minute walk distance - meters**: 316.4 ± 119.2

#### Physical examination

- **Systolic blood pressure - mmHg**: 129.7 ± 16.1
- **Heart rate – beats/min**: 70.5 ± 11.8
- **Elevated jugular venous pressure – n (%)**: 30/98 (31%)
- **Moderate or severe edema – n (%)**: 58/98 (59%)

#### Medical History

- **Heart failure hospitalization in previous year – n (%)**: 19/99 (19%)
- **Hypertension**: 88 (89%)
- **Ischemic heart disease– n (%)**: 38 (38%)
- **Diabetes mellitus– n (%)**: 34 (34%)
- **Chronic obstructive pulmonary disease– n (%)**: 14 (14%)
- **Sleep Apnea – n(%) (n=107)**: 49/96 (51%)
- **Anemia (Hemoglobin < 13 for men or < 12 for women) – n (%)** (n=109): 32/98 (33%)
- **≥ Stage 3 chronic kidney disease – n (%)** (n=109): 46/98 (47%)
- **Depression treated with prescription drug**: 32 (32%)

#### Cardiovascular medications at enrollment

- **Loop diuretic – n (%)**: 65 (66%)
- **ACE inhibitor or angiotensin II receptor blocker –n (%)**: 61 (62%)
- **Beta blocker – n (%)**: 70 (71%)
- **Aldosterone antagonist – n (%)**: 25 (25%)

#### Laboratory and Echocardiographic variables

- **Local laboratory creatinine – mg/dL†**: 1.14 ± 0.35
- **Core laboratory NT-proBNP – pg/ml,**: 484.8 ± 686.5
- **Ejection fraction - %**: 63.9 ± 8.5
- **Relative wall thickness ≥ 0.42 – n(%)**: 43 (45%)
- **Medial E/e’**: 15.2 ± 8.8
- **Left atrial volume/body surface area – ml/m²**: 40.4 ± 15.5
### Supplemental Table 2. Association of hours active per day (HAPD) with clinical characteristics

<table>
<thead>
<tr>
<th></th>
<th>Lowest HAPD Tertile (n=33)</th>
<th>Middle HAPD Tertile (n=34)</th>
<th>Highest HAPD Tertile (n=32)</th>
<th>Adjusted p value**</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>HAPD range</strong></td>
<td>3.9 – 8.4</td>
<td>8.4 – 10.3</td>
<td>10.4 – 14.9</td>
<td></td>
</tr>
<tr>
<td><strong>HAPD</strong></td>
<td>7.0 ± 1.2</td>
<td>9.4 ± 0.6</td>
<td>12 ± 1.2</td>
<td></td>
</tr>
<tr>
<td><strong>Demographics</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, years</td>
<td>70.3 ± 10.1</td>
<td>69.2 ± 8.8</td>
<td>68.1 ± 8.7</td>
<td>0.0018</td>
</tr>
<tr>
<td>Female sex</td>
<td>73% (24)</td>
<td>53% (18)</td>
<td>53% (17)</td>
<td>0.0005</td>
</tr>
<tr>
<td>Minority Race*</td>
<td>18.2% (6)</td>
<td>5.9% (2)</td>
<td>6.3% (2)</td>
<td>0.96</td>
</tr>
<tr>
<td><strong>Physical Exam</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>37.2 ± 10</td>
<td>35.3 ± 6.4</td>
<td>33.1 ± 7.7</td>
<td>0.14</td>
</tr>
<tr>
<td>Heart rate, bpm</td>
<td>70 ± 13</td>
<td>71 ± 13</td>
<td>70 ± 11</td>
<td>0.34</td>
</tr>
<tr>
<td>Systolic BP, mmHg</td>
<td>129 ± 15</td>
<td>129 ± 15</td>
<td>131 ± 19</td>
<td>0.16</td>
</tr>
<tr>
<td>Elevated JVP</td>
<td>28% (9)</td>
<td>41% (14)</td>
<td>22% (7)</td>
<td>0.57</td>
</tr>
<tr>
<td>Mod/Severe Edema</td>
<td>24% (8)</td>
<td>9% (3)</td>
<td>3% (1)</td>
<td>0.18</td>
</tr>
<tr>
<td><strong>Clinical Data</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Orthopnea</td>
<td>58% (19)</td>
<td>59% (20)</td>
<td>41% (13)</td>
<td>0.14</td>
</tr>
<tr>
<td>HF Hsp in last year</td>
<td>36% (12)</td>
<td>8.8% (3)</td>
<td>13% (4)</td>
<td>0.012</td>
</tr>
<tr>
<td>Ischemic etiology</td>
<td>61% (20)</td>
<td>62% (21)</td>
<td>63% (20)</td>
<td>0.48</td>
</tr>
<tr>
<td>COPD</td>
<td>21% (7)</td>
<td>5.9% (2)</td>
<td>16% (5)</td>
<td>0.13</td>
</tr>
<tr>
<td>OSA</td>
<td>47% (15)</td>
<td>61% (20)</td>
<td>45% (14)</td>
<td>0.26</td>
</tr>
<tr>
<td>Diabetes</td>
<td>48% (16)</td>
<td>32% (11)</td>
<td>22% (7)</td>
<td>0.13</td>
</tr>
<tr>
<td>Depression</td>
<td>36% (12)</td>
<td>32% (11)</td>
<td>28% (9)</td>
<td>0.35</td>
</tr>
<tr>
<td>Anemia†</td>
<td>38% (12)</td>
<td>35% (12)</td>
<td>25% (8)</td>
<td>0.095</td>
</tr>
<tr>
<td>eGFR*, ml/min/1.73m²</td>
<td>57 ± 18</td>
<td>57 ± 20</td>
<td>67 ± 18</td>
<td>0.20</td>
</tr>
<tr>
<td><strong>Medications</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Loop Diuretic Use</td>
<td>73% (24)</td>
<td>76% (26)</td>
<td>47% (15)</td>
<td>0.33</td>
</tr>
<tr>
<td>Beta Blocker Use</td>
<td>82% (27)</td>
<td>74% (25)</td>
<td>56% (18)</td>
<td>0.018</td>
</tr>
<tr>
<td>ACE/ARB Use</td>
<td>61% (20)</td>
<td>65% (22)</td>
<td>59% (19)</td>
<td>0.92</td>
</tr>
<tr>
<td>MRA Use</td>
<td>27% (9)</td>
<td>38% (13)</td>
<td>9.4% (3)</td>
<td>0.10</td>
</tr>
<tr>
<td><strong>Echocardiography</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ejection Fraction</td>
<td>67 ± 7</td>
<td>63 ± 9</td>
<td>62 ± 9</td>
<td>0.023</td>
</tr>
<tr>
<td>Relative wall thickness</td>
<td>0.45 ± 0.09</td>
<td>0.44 ± 0.13</td>
<td>0.40 ± 0.11</td>
<td>0.0154</td>
</tr>
<tr>
<td>LA volume index, ml/m²</td>
<td>41 ± 12</td>
<td>42 ± 18</td>
<td>39 ± 16</td>
<td>0.12</td>
</tr>
<tr>
<td>E/e’ medial</td>
<td>15.7 ± 7.9</td>
<td>13.7 ± 5.9</td>
<td>16.3 ± 11.9</td>
<td>0.52</td>
</tr>
</tbody>
</table>
Data are % (n) or mean ± SD

* Self-identified; † hemoglobin < 13 in men or <12 in women; ‡ Modified Diet in Renal Disease equation; ** Adjusted for age, sex and weight

Abbreviations: ACE/ARB, angiotensin converting enzyme inhibitor or angiotensin receptor blocker; BP, blood pressure; COPD, chronic obstructive lung disease; eGFR, estimated glomerular filtration rate; HF, Heart Failure; Hsp, hospitalization; JVP, jugular venous pressure; LA, left atrial; Mod, moderate; MRA, mineralocorticoid receptor antagonist; OSA, obstructive sleep apnea
SUPPLEMENTAL FIGURE 1. NEAT-HFpEF STUDY DESIGN DEMONSTRATING CROSS-OVER STUDY DESIGN WITH PATIENTS RANDOMIZED TO EITHER PLACEBO OR ACTIVE DRUG FIRST.

At study visit 1, all patients underwent echocardiography, NYHA functional class assignment, Kansas City Cardiomyopathy Questionnaire (KCCQ), Minnesota Living with Heart Failure Questionnaire (MLHQ), 6MWD, and NT-proBNP measurement (Core laboratory). Patients were randomized to ISMN or placebo for the first six-week study period. Patients took no study drug for the first two weeks of the first period to provide a baseline and then underwent weekly forced up-titration (30 to 60 to 120 mg once daily) of study drug and remained on the maximally tolerated dose for the final two weeks of the first study period. Patients then returned for a second study visit, underwent repeat NYHA functional class assignment, 6MWD, QOL questionnaires and NT-proBNP measurements, received new accelerometers and were crossed over to the alternate therapy. Patients again took no study drug for the first two weeks to provide a washout and then underwent weekly forced up-titration and two weeks of maximally tolerated dose of study drug as in the first period. Patients then returned for a final study visit where all assessments obtained in study visit two were repeated.

* or maximally tolerated dose, BL, baseline; wk, week; WO, washout
SUPPLEMENTAL FIGURE 2. THE NEAT-HFpEF ACCELEROMETER DEVICE

Patients were supplied with an elastic, hip worn belt outfitted with two Kinetic Activity Monitors (KAMs, Kersh Health, Plano, Texas) containing high-sensitivity, tri-axis, silicon micro-machined accelerometers (model KXUD9-2050, Kionix, Ithaca, NY).
SUPPLEMENTAL FIGURE 3. CORRELATION BETWEEN THE TWO ACTIVITY MONITORS USED IN THE NEAT-HFpEF ACCELEROMETER DEVICE AT BASELINE

Two accelerometers were used to provide reproducibility data and help insure data availability in the case of a single device failure. During the primary baseline periods, there was excellent correlation and agreement between the two devices for average daily accelerometer units (ADAU) and hours active per day (HAPD). As 8 patients had data from only one accelerometer, the n for this analysis is 91. These data support the concept that data from different accelerometers used in different phases of studies would give similar data.