Physical Activity Measured With Implanted Devices Predicts Patient Outcome in Chronic Heart Failure

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Background—Physical activity (PA) predicts cardiovascular mortality in the population at large. Less is known about its prognostic value in patients with chronic heart failure (HF).

Methods and Results—Data from 836 patients with implantable cardioverter defibrillator without or with cardiac resynchronization therapy enrolled in the Sensitivity of the InSync Sentry OptiVol feature for the prediction of Heart Failure (SENSE-HF) study and the Diagnostic Outcome Trial in Heart Failure (DOT-HF) were pooled. The devices continuously measured and stored total daily active time (single-axis accelerometer). Early PA (average daily activity over the earliest 30-day study period) was studied as a predictor of time to death or HF-related hospital admission (primary end point). Data from 781 patients were analyzed (65±10 years; 85% men; left ventricular ejection fraction, 26±7%). Older age, shorter height, ischemic cause, peripheral artery disease, atrial fibrillation, diabetes mellitus, rales, peripheral edema, higher New York Heart Association class, lower diastolic blood pressure, and no angiotensin II receptor blocker/angiotensin-converting enzyme inhibitor use were associated with reduced early PA. The primary end point occurred in 135 patients (15±7 months of follow-up). In multivariable analysis including baseline variables, early PA predicted death or HF hospitalization, with a 4% reduction in risk for each 10 minutes per day additional activity (hazard ratio [HR], 0.96; confidence interval [CI], 0.94–0.98; P=0.0002 compared with a model with the same baseline variables but without PA). PA also predicted death (HR, 0.93; CI, 0.90–0.96; P<0.0001) and HF hospitalization (HR, 0.97; CI, 0.95–0.99; P=0.011).

Conclusions—Early PA, averaged over a 30-day window early after defibrillator implantation or cardiac resynchronization therapy in patients with chronic HF, predicted death or HF hospitalization, as well as mortality and HF hospitalization separately, accounting for baseline HF severity.

Clinical Trial Registration Information—URL: http://www.clinicaltrials.gov. Unique identifiers: NCT00400985, NCT00480077.

Key Words: heart failure ■ mortality ■ physical activity

Despite significant improvements in the treatment of chronic heart failure (CHF), mortality remains as high as 20% to 30% after 3 years. The costs for heart failure (HF) care approach 2% of the total health care expenditure in Western countries, primarily due to hospitalization for decompensation. As a result, the past decade has witnessed a surge in finding reliable markers to identify patients at risk of early death and impending decompensation.

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Physical fitness predicts cardiovascular mortality in the population at large. The collection of multiple parameters derived during cardiorespiratory exercise testing, in particular the minute ventilation/carbon dioxide production relationship (the VE/ V\textsubscript{CO\textsubscript{2}} slope) in conjunction with peak \textit{V}\textsubscript{O\textsubscript{2}} uptake, allows prognostic stratification in patients with CHF. However, repetitive cardiopulmonary exercise testing, which may be required for a dynamic condition such as CHF, is demanding in clinical practice. Daily physical activity (PA) has been shown to predict outcome in various chronic diseases. However, data for the CHF population are scarce and are often based on qualitative subjective patient and physician reports or questionnaires or
short-term measurement with pedometers and accelerometers. Continuous recording of PA, through accelerometers incorporated in implanted devices, may more accurately address the question whether PA merely reflects disease severity or whether it is an independent prognostic marker.

The Sensitivity of the InSync Sentry OptiVol feature for the prediction of Heart Failure (SENSE-HF) study and the Diagnostic Outcome Trial in Heart Failure (DOT-HF) are recent prospective trials conducted to evaluate the utility of intrathoracic impedance measurement, incorporated as a diagnostic feature in implantable cardioverter defibrillator without (ICD) or with cardiac resynchronization therapy (CRT-D). These devices also measured and stored total daily active time. We analyzed the pooled patient data from SENSE-HF and DOT-HF to determine whether and to what extent daily PA as measured by implanted devices is related to patient outcome.

Methods

Patient Population
Detailed descriptions of the design and results of SENSE-HF and DOT-HF have been published previously. Briefly, SENSE-HF enrolled 501 patients <34 days after implantation of an ICD or CRT-D with the OptiVol feature (Medtronic Inc, Minneapolis, MN), which measures intrathoracic impedance. After a waiting period of 34 days to ensure correct measurement of intrathoracic impedance, patients were followed up for 6 months to determine the sensitivity and the positive predictive value of OptiVol intrathoracic fluid monitoring for the detection of HF-related hospitalizations (phase I, blinded). Phase I was followed by maximally 18 months with full access to the device data. PA was recorded and stored during the entire study period, starting at day 35 postimplant.

DOT-HF tested whether physician access to device-based diagnostic information, including audible patient alerts for decreasing intrathoracic impedance, would improve outcome in patients with HF. In total, 335 patients were randomized to an access versus a control arm between 35 days and 6 months after implantation with an ICD or CRT-D. Patients were followed up for 15 months, during which PA was continuously measured and stored.

The Table in the Data Supplement describes end points and the major inclusion and exclusion criteria for both studies. Both studies were approved by the local ethics committees, and written informed consent was obtained from all patients. Given the similarities in patient population and treatment, and because all devices in SENSE-HF and DOT-HF recorded and stored PA during daily life on a continuous basis, it was decided to pool and analyze patient data from both trials. The authors had full access to the study data.

Study End Points
The primary end point of the present analysis was time to death or HF-related hospital admission. Time to death and time to first HF-related hospital admission were analyzed as secondary end points. HF hospitalizations were adjudicated by study-specific, independent, blinded Adverse Event Advisory Committees. Device Measurement of Daily PA
The activity measurement in the devices is designed to capture normal daily activities in patients with HF, including walking at a slow pace. A single-axis accelerometer is used to capture patient motion as an electric signal. The number of minutes a patient is active per day is counted, where a minute is considered active if a threshold is reached that incorporates both the number and magnitude of deflections in the accelerometer signal. The devices store the number of active minutes for the most recent 425 days (Figure 1), and this information was retrieved from device memory for this analysis. The sensor provides a quantification of patient activity that, due to the specifics of the algorithm, may numerically differ from measurements obtained from other devices such as pedometers or external accelerometers.

Analyses Methods
We defined early PA as the average daily activity over the earliest 30-day period in the study (the activity window). For patients in SENSE-HF, this window started 35 days after implant and continued until day 64. For patients in DOT-HF, the activity window started after randomization, which was between day 35 and day 183 post-implant. We averaged 30 daily values to account for within-patient variability. Patients were excluded from analysis if they died or had a HF hospitalization during or before the 30-day activity window, or if there were <7 days with valid activity data in the window.

Because lower activity was expected to be associated with a generally worse condition of patients, we investigated the relation of early activity with baseline characteristics. The relation of early PA and outcome as well as the incremental value of activity as a risk marker when added to known risk factors was assessed in line with the American Heart Association scientific statement on evaluation of novel markers of cardiovascular risk. As measures of known risk, we determined the best predictive model based on baseline patient characteristics, and we used The Candesartan in Heart failure Assessment of Reduction in Mortality and morbidity (CHARM) programme risk score, a validated score for risk of all-cause death in patients with HF. For both approaches, time-to-event models including and excluding early activity are compared to determine incremental predictive value.

Statistical Analyses
Results are reported with mean and standard deviation for continuous, and counts and percentages for categorical variables. The relation between baseline characteristics and early PA was analyzed with t test for dichotomous and linear regression for ordinal and continuous characteristics. Reported effect sizes (Table 1) are observed differences for dichotomous characteristics, and regression coefficients otherwise. Multivariable linear regression with backward variable elimination was used to assess joint association with early activity.

For calculation of the CHARM risk score, coefficients were taken from the study by Pocock et al. Multiple imputation was used to account for missing values, using the multivariate normal specification. For categorical variables, the imputed value was rounded to the nearest coded category value. Ten completed data sets were generated. The CHARM risk score was calculated for each completion separately. Finally, Rubin rule was used to determine a single risk score value per patient.

Cox proportional hazards regression was used to analyze the relation between events and early PA, which was included as a continuous variable. Patients were considered at risk starting at the end of the activity window (time zero). Hazard ratio (HR) with associated 95% confidence interval (CI) is reported for 10 minutes per day incremental activity. The incidence of end points is illustrated with Kaplan–Meier graphs with patients divided into 2 or 3 equal-sized groups using medians or tertiles as cut points. Multivariable proportional hazards models using model reduction with backward selection are used to define predictive models based on baseline characteristics. To assess the incremental predictive value of early activity, multivariable models including and excluding early activity are compared using likelihood ratio tests. The predictive ability of models is quantified using the Harrell C-index, which extends the area under the receiver operating characteristic curve to the context of time-to-event data with censoring.

All analyses were done using SAS (version 9.3; SAS Institute Inc, Cary, NC) or R (version 3.0.1; the R project for statistical computing; www.r-project.org), and P values <0.05 were considered significant. No correction for multiple testing was applied.

Results

Patients
SENSE-HF and DOT-HF together enrolled 836 patients between 2005 and 2009 in 100 centers across Europe (91%
of patients), the Middle East, and Asia. Fifty-five patients were removed from analysis because they experienced events before the end of the activity window (35 patients; 11 deaths and 28 HF hospital admissions), early study exit (5 patients), or because device data were not available for analysis (15 patients).

Demographic and clinical characteristics are presented in Table 1. At enrollment, the majority of patients was in New York Heart Association (NYHA) class II/III, with severely impaired left ventricular ejection fraction (26±7%) and implanted with a CRT-D (80%).

**Correlates of Early PA**

Early PA was 199±106 minutes per day and was comparable between studies (SENSE-HF: 199 minutes per day; DOT-HF: 198 minutes per day; P=0.90; see Figure in the Data Supplement). As a result of the design of both studies, the activity window started 35 days after implantation in all SENSE-HF patients, and on average 86 days after implantation in DOT-HF patients. Time between implant and start of the activity window did not affect early activity (linear regression; P=0.83) or its prognostic value for DOT-HF patients.

Table 1 illustrates the relation between early PA and baseline characteristics. Multivariable analysis identified older age, shorter height, ischemic cause, peripheral artery disease, atrial fibrillation, diabetes mellitus, rales, peripheral edema, higher NYHA class, lower diastolic blood pressure, and absence of angiotensin receptor blocker (ARB)/angiotensin-converting enzyme (ACE) inhibitor therapy as jointly associated with reduced early PA.

**Patient Outcome and Early PA**

During follow-up (15±7 months), 65 deaths and 141 HF hospitalizations were recorded in 100 patients. The primary end
Early PA was significantly associated with the primary end point, with 5% relative reduction of risk for each 10 minutes per day additional activity (HR, 0.95; CI, 0.94–0.97; P < 0.0001). There were also significant associations with death (HR, 0.92; CI, 0.89–0.95; P < 0.0001) and HF hospitalization (HR, 0.97; CI, 0.95–0.99; P = 0.0011). Figure 2 shows event incidence with patients stratified into 3 equal-sized groups according to early PA. The cut points are 235 minutes per day between high and medium activity and 146 minutes per day between medium and low activity. The incidence of primary end point at 18 months is 12.5% for high activity, 17.5% for medium activity, and 19.5% for low activity. Table 1. Baseline Characteristics and Relation to Early Physical Activity

<table>
<thead>
<tr>
<th>Baseline Characteristics</th>
<th>Analysis Cohort (n=781)</th>
<th>Effect Size (min/d)</th>
<th>Univariable P Value</th>
<th>P Value From Multivariable Model</th>
<th>P Value From Reduced Multivariable Model</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>65±10</td>
<td>−3.19</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Men</td>
<td>661 (85%)</td>
<td>16.01</td>
<td>0.13</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Body height, cm</td>
<td>171±8</td>
<td>1.40</td>
<td>0.002</td>
<td>0.012</td>
<td>0.003</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>80±16</td>
<td>0.29</td>
<td>0.22</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>27±5</td>
<td>−0.32</td>
<td>0.70</td>
<td></td>
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</tr>
<tr>
<td>Underweight (BMI ≤ 21 kg/m²)</td>
<td>47 (6%)</td>
<td>6.99</td>
<td>0.56</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HF hospitalization in last 6 mo*</td>
<td>406 (87%)</td>
<td>7.39</td>
<td>0.61</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HF hospitalization in last 12 mo</td>
<td>774 (99%)</td>
<td>40.36</td>
<td>0.32</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ischemic cause</td>
<td>445 (57%)</td>
<td>−37.61</td>
<td>&lt;0.0001</td>
<td>0.032</td>
<td>0.002</td>
</tr>
<tr>
<td>Previous myocardial infarction</td>
<td>364 (47%)</td>
<td>−30.20</td>
<td>&lt;0.0001</td>
<td>0.79</td>
<td></td>
</tr>
<tr>
<td>Mitral insufficiency</td>
<td>360 (46%)</td>
<td>3.60</td>
<td>0.64</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peripheral artery disease</td>
<td>45 (6%)</td>
<td>−41.23</td>
<td>0.011</td>
<td>0.055</td>
<td>0.020</td>
</tr>
<tr>
<td>Left bundle branch block</td>
<td>418 (54%)</td>
<td>−1.95</td>
<td>0.80</td>
<td></td>
<td></td>
</tr>
<tr>
<td>History of atrial fibrillation</td>
<td>292 (37%)</td>
<td>−31.26</td>
<td>&lt;0.0001</td>
<td>0.025</td>
<td>0.009</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>232 (30%)</td>
<td>−35.86</td>
<td>&lt;0.0001</td>
<td>0.09</td>
<td>0.015</td>
</tr>
<tr>
<td>Diabetes mellitus (type I)</td>
<td>27 (3%)</td>
<td>−63.78</td>
<td>&lt;0.0001</td>
<td>0.18</td>
<td></td>
</tr>
<tr>
<td>Dyspnea</td>
<td>552 (71%)</td>
<td>−33.08</td>
<td>&lt;0.0001</td>
<td>0.08</td>
<td></td>
</tr>
<tr>
<td>Dyspnea at rest</td>
<td>8 (1%)</td>
<td>−45.11</td>
<td>0.24</td>
<td></td>
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</tr>
<tr>
<td>Rales</td>
<td>48 (6%)</td>
<td>−54.21</td>
<td>&lt;0.0001</td>
<td>0.033</td>
<td>0.043</td>
</tr>
<tr>
<td>Peripheral edema</td>
<td>119 (15%)</td>
<td>−43.19</td>
<td>&lt;0.0001</td>
<td>0.008</td>
<td>0.007</td>
</tr>
<tr>
<td>Pulmonary edema</td>
<td>64 (8%)</td>
<td>−31.87</td>
<td>0.021</td>
<td>0.12</td>
<td></td>
</tr>
<tr>
<td>NYHA classification</td>
<td>38 (5%)</td>
<td>−32.96</td>
<td>&lt;0.0001</td>
<td>0.013</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Class I</td>
<td>381 (49%)</td>
<td>26±7</td>
<td>0.23</td>
<td>0.66</td>
<td></td>
</tr>
<tr>
<td>Class II</td>
<td>346 (44%)</td>
<td>146±36</td>
<td>−0.12</td>
<td>0.27</td>
<td></td>
</tr>
<tr>
<td>Class III</td>
<td>15 (2%)</td>
<td>36±23</td>
<td>−0.52</td>
<td>0.002</td>
<td>0.26</td>
</tr>
<tr>
<td>Heart rate, beats/min</td>
<td>72±12</td>
<td>0.21</td>
<td>0.53</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic blood pressure, mmHg</td>
<td>117±18</td>
<td>0.39</td>
<td>0.064</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diastolic blood pressure, mmHg</td>
<td>71±11</td>
<td>−1.42</td>
<td>&lt;0.0001</td>
<td>0.033</td>
<td>0.003</td>
</tr>
<tr>
<td>LVEF, %</td>
<td>26±7</td>
<td>0.23</td>
<td>0.66</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intrinsic QRS duration, ms</td>
<td>146±36</td>
<td>−0.12</td>
<td>0.27</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MLHF score, points</td>
<td>36±23</td>
<td>−0.52</td>
<td>0.002</td>
<td>0.26</td>
<td></td>
</tr>
<tr>
<td>Current smoker</td>
<td>48 (6%)</td>
<td>3.05</td>
<td>0.71</td>
<td></td>
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</tr>
<tr>
<td>CRT-D</td>
<td>621 (80%)</td>
<td>10.20</td>
<td>0.32</td>
<td></td>
<td></td>
</tr>
<tr>
<td>b-Blocker</td>
<td>689 (88%)</td>
<td>16.99</td>
<td>0.15</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACE inhibitor or ARB</td>
<td>682 (87%)</td>
<td>24.90</td>
<td>0.029</td>
<td>0.005</td>
<td>0.027</td>
</tr>
<tr>
<td>Total diuretics dose, mg/kg</td>
<td>0.88±1.02</td>
<td>−10.98</td>
<td>0.003</td>
<td>0.09</td>
<td></td>
</tr>
</tbody>
</table>

Characteristics were taken at baseline, which could be up to 6 mo after device implantation. Effect size is the average difference in early physical activity for patients with characteristic versus without (dichotomous) or the average change in activity per unit increase (ordinal, continuous). ACE indicates angiotensin-converting enzyme; ARB, angiotensin receptor blocker; BMI, body mass index; CRT-D, defibrillator with cardiac resynchronization therapy; HF, heart failure; LVEF, left ventricular ejection fraction; MLHF, Minnesota Living with Heart Failure questionnaire; and NYHA, New York Heart Association.

*Data not collected in Diagnostic Outcome Trial in Heart Failure (DOT-HF) so that denominator is 469, the number of Sensitivity of the InSync Sentry OptiVol feature for the prediction of Heart Failure (SENSE-HF) study patients in the analysis cohort.
Outcome and Early PA Accounting for Disease Severity

To assess the incremental value of early PA as a risk marker for clinical events when added to other risk factors, 2 approaches were used.

First, baseline characteristics were tested for their relation with patient outcome. Fourteen characteristics were significantly related to the primary end point (age, height, weight, underweight, left bundle branch block, diabetes mellitus, dyspnea, systolic blood pressure, diastolic blood pressure, QRS duration, QRS ≥120 ms, QRS ≥150 ms, ARB/ACE inhibitor, daily diuretic dosage). Additionally, peripheral edema was predictive of mortality. These 15 variables were included in multivariable models, from which nonsignificant parameters were iteratively removed. In the final multivariable model for death or HF hospitalization, age (P=0.0011), systolic blood pressure (P=0.0001), daily diuretic dosage (P=0.0004), and absence of ARB/ACE inhibitor (P=0.04) were retained as joint predictors of outcome. The c-index for this model was 0.66 (CI, 0.61–0.71). The addition of early PA to the model significantly improved the predictive ability (likelihood ratio P=0.0002). The model with activity has a c-index of 0.68 (CI, 0.63–0.73). Accounting for the effect of other factors, there was a 4% reduction in risk for each 10 minutes per day additional activity (HR, 0.96; CI, 0.94–0.98). These results are summarized in Table 2, which also includes results for mortality and HF hospitalization separately.

Next, we determined the predictive value of the validated CHARM risk score on the current patient cohort. On its own, the score was significantly associated with the incidence of death or HF hospitalization (P<0.0001; c-index 0.61; CI, 0.56–0.66; Table 2). Figure 3 shows event incidence with patients stratified into low-, medium-, and high-risk groups. The CHARM score and early PA were significantly correlated (r=−0.33; P<0.0001).

The addition of early PA to the model significantly improved the predictive ability (likelihood ratio P<0.0001), establishing lower activity as a predictor of increased event rates when accounting for baseline risk. The c-index increased to 0.65 (CI, 0.60–0.70). With CHARM score in the model, there was a 4% reduction in risk of death or HF hospitalization for each 10 minutes per day additional activity (HR, 0.96; CI, 0.94–0.98). Figure 4 illustrates these findings by showing the incidence of death or HF hospitalization for patients stratified by the CHARM score and early PA. For both parameters, patients are classified as above or below the median value, creating 4 groups. Table 2 also shows that for death and HF hospitalization separately, early activity significantly improved the predictive value when added to the CHARM score in time-to-event models.

Discussion

The main finding of the present study is that early PA, measured by the accelerometer sensor of implanted ICD and CRT-D devices, strongly predicts outcome in patients with CHF. Early PA was defined as the average activity over a 30-day window, measured either starting 35 days after implant for SENSE-HF patients or after randomization, and between 35 days and 6 months after implant for DOT-HF patients. Despite the expected

activity, and 30.0% for low activity. Mortality is 2.5%, 9.9%, and 18.2%, respectively. The incidence of HF hospitalization is 11.7%, 10.2%, and 22.0%.

Figure 2. Kaplan–Meier estimates for the incidence of clinical events. A, All-cause death or heart failure (HF) hospitalization (primary end point). B, All-cause death. C, HF hospitalization. Patients are stratified in 3 equal-sized groups based on their early activity with cut points 145.6 and 235.0 min/d (tertiles). Events are counted after the activity window used to determine early activity.
Population-based studies show that PA and a high level of cardiorespiratory fitness predict longevity. Literature on the prognostic impact of daily PA in patients with HF is scarce and almost exclusively based on subjective evaluation of patients’ reports or data gathered by intermittent application of pedometers and external accelerometers. Continuous measurement of daily PA with accelerometers incorporated in implanted devices can exclude nonadherence and avoid bias of deliberate changes in patients’ habits at the time of planned assessments. Surprisingly, few studies have investigated the clinical utility of continuous measurements and have mainly concentrated on short-term prediction of acute decompensated HF. The Program to Access and Review Trending Information and Evaluate Correlation to Symptoms in Patients with Heart Failure (PARTNERS-HF) demonstrated that a combination of device-measured parameters, including activity, predicted a 5.5-fold higher HF hospitalization risk in CRT-D patients, but results for activity are not reported separately. Only Shoemaker retrospectively related PA recordings in 102 ICD or CRT-D patients to long-term outcome. They found a moderate correlation between mean daily activity, calculated for a 2-week period, and estimated short- and long-term outcome, based on the Seattle Heart Failure Score.

The present study support the notion that daily PA reflects disease severity, measured by means of a validated HF risk score. However, the fact that early PA predicted outcome, taking well-recognized traditional risk factors into account, is an important finding. Significant relation between early PA and HF severity, low early PA was a significant predictor of the combined primary end point of death and HF hospitalization, as well as of both components separately, when correcting for HF severity.

Table 2. Incremental Value of Early Physical Activity as Risk Marker

<table>
<thead>
<tr>
<th></th>
<th>Risk Model Based on Study Data</th>
<th>Risk Model With CHARM Risk Score</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Without Activity</td>
<td>With Activity</td>
</tr>
<tr>
<td><strong>Death and HF hospitalization</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Variables in model</td>
<td>Age, SBP, diuretic dose, ARB/ACE absence</td>
<td>Age, SBP, diuretic dose, ARB/ACE absence, early activity</td>
</tr>
<tr>
<td>Hazard ratio, activity increase by 10 min/d</td>
<td>0.96 (0.94–0.98)</td>
<td>0.6114 (0.5601–0.6627)</td>
</tr>
<tr>
<td>Harrell c-index</td>
<td>0.6585 (0.6064–0.7106)</td>
<td>0.6803 (0.6282–0.7324)</td>
</tr>
<tr>
<td>P value comparing models</td>
<td>0.0002</td>
<td></td>
</tr>
<tr>
<td><strong>Death</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Variables in model</td>
<td>Age, SBP, diuretic dose</td>
<td>Age, SBP, diuretic dose, early activity</td>
</tr>
<tr>
<td>Hazard ratio, activity increase by 10 min/d</td>
<td>0.93 (0.90–0.96)</td>
<td>0.6108 (0.5348–0.6869)</td>
</tr>
<tr>
<td>Harrell c-index</td>
<td>0.7123 (0.6350–0.7897)</td>
<td>0.7535 (0.6762–0.8309)</td>
</tr>
<tr>
<td>P value comparing models</td>
<td>&lt;0.0001</td>
<td></td>
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<tr>
<td><strong>HF hospitalization</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Variables in model</td>
<td>Weight, SBP, diabetes mellitus</td>
<td>Weight, SBP, diabetes mellitus, early activity</td>
</tr>
<tr>
<td>Hazard ratio, activity increase by 10 min/d</td>
<td>0.97 (0.95–0.99)</td>
<td>0.6031 (0.5441–0.6621)</td>
</tr>
<tr>
<td>Harrell c-index</td>
<td>0.6246 (0.5643–0.6849)</td>
<td>0.6450 (0.5847–0.7053)</td>
</tr>
<tr>
<td>P value comparing models</td>
<td>0.011</td>
<td></td>
</tr>
</tbody>
</table>

Cox proportional hazards models were used to assess the relation of baseline risk markers and early physical activity with outcome. The first 2 data columns report on predictive models derived from the study data, comparing the model with only baseline risk factors to the model with these risk factors and early activity added. Reported P values are from likelihood ratio tests. Similarly, the last 2 columns compare a model with only the CHARM risk score to a model with CHARM score and early physical activity. ACE indicates angiotensin-converting enzyme; ARB, angiotensin receptor blocker; CHARM, The Candesartan in Heart failure Assessment of Reduction in Mortality and morbidity (CHARM) programme; HF, heart failure; and SBP, systolic blood pressure.

Figure 3. Kaplan–Meier estimates for the incidence of death or heart failure (HF) hospitalization. Patients are stratified in 3 equal-sized groups based on their baseline CHARM (The Candesartan in Heart failure Assessment of Reduction in Mortality and morbidity programme) risk score value with cut points 2.0 and 8.0 (tertiles).
account, is novel and may be of use in the management of patients with CHF.

As shown by a subanalysis of the Heart Failure: A Controlled Trial Investigating Outcomes of Exercise Training (HF-ACTION), improved patient outcome, as well as increased exercise capacity, depends on exercise volume.29 Our data support a similar dose–response effect with regard to daily PA. Patients in the lowest tertile for early activity (<146 minutes per day) had 2.3 times higher risk for the combined end point (HR, 2.3), compared with those in the highest tertile (>235 minutes per day), and even a 5-fold risk for mortality (HR, 5.0). The advice provided to patients by SENSE-HF16 and DOT-HF17 physicians based on stored PA data was not part of the study protocols. Therefore, a prospective study is necessary to confirm the current findings and to establish clinical recommendations.

In this study, several patient and disease characteristics, as well as comorbidities, were associated with early PA. A significant effect of age and NYHA functional class on 6-minute walking distances30 and cardiorespiratory fitness, 31 as well as a detrimental effect of raised jugular venous pressure on PA, is described.30 The decline of cardiorespiratory fitness with age32 likely increases exercise-induced symptoms of fatigue and dyspnea in patients with HF. These effects may hamper the motivation and ability of patients with HF to engage in daily PA. A similar argument may explain lower levels of PA in patients presenting with higher NYHA functional class, rales, and peripheral edema.

After multivariable analysis, height was retained as a predictor of PA. Without providing a physiological justification, Witham et al30 described a significant effect of height on accelerometer-based quantification of PA in patients with HF in univariate analysis. One plausible explanation may involve the larger excursion of the body during movements in taller people, which may be sensed by the accelerometer.

The fact that atrial fibrillation significantly determined low levels of PA may be related to lower cardiac output during exertion due to poorly controlled ventricular rate and atrioventricular dyssynchrony. The functional substudy of the Atrial Fibrillation Follow-Up Investigation of Rhythm Management (AFFIRM) trial33 demonstrated a significantly larger increase in functional status, assessed with the 6-minute walk test, in HF patients with atrial fibrillation allocated to the rhythm versus the rate control group. Similar findings were reported in the Pharmacological Intervention in Atrial Fibrillation (PIAF) trial through 2 years of follow-up.34 Recently, Izawa et al35 described a significantly reduced step count and estimated daily PA energy expenditure obtained with uniaxial accelerometers in diabetic versus non-diabetic HF patients. Skeletal muscle wasting as well as bioenergetic changes at the level of peripheral skeletal musculature are plausible mechanisms.36

Exercise-induced pain and significant lower limb ischemia change gait pattern and lead to lower walking performance as well as poor daily PA.37 HF patients with peripheral artery disease have lower exercise capacity and lower response to exercise training intervention.38 Patients with ischemic cause, compared with those with nonischemic cause, demonstrate lower peak oxygen uptake and a steeper VE/VCO₂ slope.31 Impaired PA may result from chronotropic incompetence, exercise-induced myocardial ischemia, and mitral regurgitation.39 Treatment with an ACE inhibitor improves exercise duration40 as well as peak aerobic capacity.41 There is a direct benefit on cardiac performance through the inhibition of the renin–angiotensin–aldosterone system. Additionally, facilitated alveolar–capillary gas transfer,42 as well as restoration of peripheral endothelial function, have been described.43

Limitations

For this post hoc analysis, we pooled data from 2 studies with different design. As a result, the 30-day activity window was collected for a period between 35 and 183 days. Nevertheless, prognostic information derived from this pooled data set remains strong and seems not affected by this approach.

The devices used the same type of accelerometer, and it is not known whether the present results can be extrapolated to other activity sensors. Literature on the validation of the device’s activity sensor is limited. Gulati et al44 found that the 6-minute walk test and daily activity measured within the preceding or subsequent 24 hours were correlated (r=0.42 and
0.49, respectively). A similar relation was found in a subset of 83 patients enrolled in SENSE-HF in whom the 6-minute walk test was conducted ($r=0.43; P<0.0001$). Braunsweg et al calculated weekly means of PA in a group of 56 patients after the novo device implant using the same accelerometer. There was a steady increase in weekly PA, which was clearly related to NYHA functional class with absolute values after 4 weeks that were well within the range of current observations (283±97, 206±132, and 186±53 minutes per day for NYHA II, III, and IV, respectively).

The CHARM risk score was developed from a large number of nondevice patients across a broad spectrum of HF. Nevertheless, the risk score strongly predicted outcome for the currently analyzed cohort of patients, characterized by broad QRS complexes, impaired systolic left ventricular function, and implanted with either an ICD or a CRT-D.

The studies analyzed here did not enroll patients in the United States. Therefore, clinical recommendations for daily PA derived from the present analyses may not be applicable to the American HF population. Finally, >30 tests were performed to assess the relation between activity and baseline characteristics so that some of the significant findings may be spurious.

Conclusions

Early PA, averaged over a 30-day window early after ICD or CRT-D implant in patients with CHF, predicted death or HF hospitalization, as well as mortality and HF hospitalization separately, also corrected for disease severity. These findings underscore the validity of spontaneous PA as a clinical status marker. Whether regular follow-up of PA, provided by accelerometers in implanted devices, will aid physicians in modifying patients’ lifestyle and whether this will improve outcome may need to be prospectively studied.

Sources of Funding

This study was funded by the Medtronic Bakken Research Center. M.R.C. receives salary support from the National Institute for Health Research Cardiovascular Biomedical Research Unit at the Royal Brompton Hospital. D. J. v. V. is an established investigator of the Netherlands Heart Foundation (grant No. D97.017). V. M. C. was supported by Fonds Wetenschappelijk Onderzoek-Flanders as a clinical postdoctoral fellow.

Disclosures

Drs Borggrefe, Braunsweg, Conraads, Cowie, van Veldhuisen, and Tavazzi received consultancy fees or research grants from Medtronic and from other device companies. Drs Conraads, Cowie, and Tavazzi served on the Steering Committee of the SENSE-HF study. Drs Borggrefe, Braunsweg, Conraads, Cowie, and van Veldhuisen served on the Steering Committee for DOT-HF. Drs Hill, Jacobs, and Gerritse are employees of Medtronic. Dr Gerritse reports having equity in Medtronic. Dr Spruit has no conflicts to report.

References


**CLINICAL PERSPECTIVE**

This study shows that patient activity measured by implanted devices predicts death and hospitalization for worsening heart failure. It included 781 heart failure patients with implanted defibrillators (most with resynchronization therapy). The patient activity measured by device accelerometers was averaged over a 30-day period shortly after device implantation. The resulting early physical activity (PA) level was strongly predictive of later clinical events. Each 10 minutes per day of incremental activity was associated with 8% reduction of the risk of death (P<0.0001), 3% reduction of the risk of heart failure hospitalization (P=0.001), and 5% reduction of the risk of the composite event (P<0.0001). Similar results were observed after correction for known heart failure risk factors. Risk stratification based on device-measured early PA may contribute to efficient patient management. However, further research is needed to assess if device-measured activity can be used to monitor patient status, or whether and to what extent increasing activity levels by exercise programs or patient counseling will result in better outcomes.
Physical Activity Measured With Implanted Devices Predicts Patient Outcome in Chronic Heart Failure

Viviane M. Conraads, Martijn A. Spruit, Frieder Braunschweig, Martin R. Cowie, Luigi Tavazzi, Martin Borggrefe, Michael R.S. Hill, Sandra Jacobs, Bart Gerritse and Dirk J. van Veldhuisen

Circ Heart Fail. 2014;7:279-287; originally published online February 11, 2014;
doi: 10.1161/CIRCHEARTFAILURE.113.000883

Circulation: Heart Failure is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 1941-3289. Online ISSN: 1941-3297

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circheartfailure.ahajournals.org/content/7/2/279

Data Supplement (unedited) at:
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SUPPLEMENTAL MATERIAL

Physical activity, measured with implanted devices, predicts patient outcome in Chronic Heart Failure.

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Methods

The table below (eTable 1) provides additional details of the designs of SENSE-HF and DOT-HF. Investigators may have influenced patient behavior based on physical activity records, which were accessible after Phase I for SENSE-HF (unblinding after Phase I) and for patients in the access arm of DOT-HF. We therefore investigated the interaction effect between access to device diagnostic data and early physical activity. Both studies were approved by the local ethics committees, and written informed consent was obtained from all patients. The authors had full access to study data.

To evaluate the possible confounding effect of a positive response to CRT, in terms of exercise tolerance, as well as outcome, we compared patients implanted with an ICD only to those with an implanted CRT-D device.

Influences of access to diagnostics and CRT were assessed from interaction terms.

Results:

The average early physical activity is 199 minutes per day, with a standard deviation of 106 min/day. Further descriptive statistics are: range: 3-579 min/day; and quartiles 120 and 259 min/day. eFigure 1 provides the frequency distribution.

Access to device diagnostic data for patients enrolled in DOT-HF did not influence the relation between early activity and the primary endpoint (HR=0.96 in patients with, and HR=0.95 in patients without access, interaction p=0.58). Patients with ICD and CRT-D were comparable with respect to early activity (p=0.32) and incidence of primary endpoints (p=0.17). The association between early activity and primary endpoints did also not differ significantly (HR=0.92 in ICD patients and HR=0.96 in CRT-D patients, interaction p=0.15).
**eTable 1. Design of SENSE-HF and DOT-HF**

<table>
<thead>
<tr>
<th></th>
<th>SENSE-HF</th>
<th>DOT-HF</th>
</tr>
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<tbody>
<tr>
<td><strong>Trial registration</strong></td>
<td>NCT00400985</td>
<td>NCT00480077</td>
</tr>
<tr>
<td><strong>Design</strong></td>
<td>single arm</td>
<td>randomized parallel two arm</td>
</tr>
<tr>
<td><strong>Treatment</strong></td>
<td>ICD/CRT-D device</td>
<td>ICD/CRT-D device</td>
</tr>
<tr>
<td><strong>Main inclusion criteria</strong></td>
<td>chronic heart failure with impaired LVEF (≤ 35%) despite OMT, HF hospitalization in last 12 months, recent implant (≤ 34 days) of ICD or CRT-D with OptiVol</td>
<td>chronic heart failure with impaired LVEF (≤ 35%) despite OMT, HF hospitalization in last 12 months, recent implant (≤ 6 months) of ICD or CRT-D with OptiVol</td>
</tr>
<tr>
<td><strong>Main exclusion criteria</strong></td>
<td>post heart transplant or on waiting list, COPD, pulmonary hypertension, dialysis</td>
<td>post heart transplant or on waiting list, COPD, pulmonary hypertension, dialysis, cardiac surgery in last 90 days</td>
</tr>
<tr>
<td><strong>Access to device data</strong></td>
<td>phase I: 6 months, no access</td>
<td>control arm: no access</td>
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<tr>
<td></td>
<td>phase II/III: 18 months, full access</td>
<td>access arm: full access</td>
</tr>
<tr>
<td><strong>Primary endpoint</strong></td>
<td>phase I: sensitivity and PPV of OptiVol threshold crossing for detection of HF hospitalization phase II/III: PPV of first detected OptiVol alert for worsening HF</td>
<td>all-cause death and HF hospitalization</td>
</tr>
</tbody>
</table>

**Abbreviations:** COPD=Chronic Obstructive Pulmonary Disease; CRT=Cardiac Resynchronization Therapy; CRT-D=Defibrillator with CRT; HF=Heart Failure; ICD=Implantable Cardioverter Defibillator; LVEF=Left Ventricular Ejection Fraction; OMT=Optimal Medical Therapy; PPV=Positive Predictive Value
eFigure 1. Histogram for early physical activity.