Speed of Heart Rate Recovery in Response to Orthostatic Challenge
A Strong Risk Marker of Mortality

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Rationale: Speed of heart rate recovery (HRR) may serve as an important biomarker of aging and mortality.
Objective: To examine whether the speed of HRR after an orthostatic maneuver (ie, active stand from supine position) predicts mortality.
Methods and Results: A longitudinal cohort study involving a nationally representative sample of community-dwelling older individuals aged ≥50 years. A total of 4475 participants completed an active stand at baseline as part of a detailed clinic-based cardiovascular assessment. Beat-to-beat heart rate and blood pressure responses to standing were measured during a 2-minute window using a finometer and binned in 10-s intervals. We modeled HRR to the stand by age group, cardiovascular disease burden, and mortality status using a random effects model. Mortality status during a mean follow-up duration of 4.3 years served as the primary end point (n=138). Speed of HRR in the immediate 20 s after standing was a strong predictor of mortality. A 1-bpm slower HRR between 10 and 20 s after standing increased the hazard of mortality by 6% controlling for established risk factors. A clear dose–response relationship was evident. Sixty-nine participants in the slowest HRR quartile died during the observation period compared with 14 participants in the fastest HRR quartile. Participants in the slowest recovery quartile were 2.3× more likely to die compared with those in the fastest recovery quartile.

Conclusions: Speed of orthostatic HRR predicts mortality and may aid clinical decision making. Attenuated orthostatic HRR may reflect dysregulation of the parasympathetic branch of the autonomic nervous system.

Key Words: autonomic nervous system ■ cardiovascular disease ■ epidemiology ■ heart rate ■ mortality

Much recent work has focused on the prognostic value of heart rate recovery (HRR) postexercise as a risk factor for cardiovascular disease (CVD) and mortality. Vagal reactivation plays an integral role in modulating the rate at which the heart rate recovers after exercise, especially during the first 30 s and ≤2 minutes. A reduction in vagal tone and an increase in activity of the sympathetic nervous system are associated consistently with an increased risk of cardiovascular events, including sudden death and with all-cause mortality. More recently, the vagus nerve has also been shown to have a reflexive role in modulating proinflammatory signaling, which may, in part, contribute to the association with CVD and mortality.

The autonomic nervous system plays a central role in regulation of cardiovascular and humoral responses to orthostasis. Orthostasis evokes a rapid physiological response involving the coordinated action of several systems, including the skeletal-muscle pump and arterial and cardiopulmonary baroreflexes. The orthostatic response reflects a balance between cardiac output and total peripheral resistance modulated by the autonomic nervous system and baroreflexes and most commonly measured using changes in heart rate and blood pressure. When resting in the supine position, venous and arterial reservoirs are at the same height, but standing up reduces venous return by displacing ≈500/700 mL (10 mL/kg) of central blood into the peripheral system.

Heart rate increases rapidly in the first few seconds after standing to counteract the gravitational forces acting on blood pressure that propels blood toward the lower extremities (Figure 1). The initial surge in heart rate that occurs in the first few seconds after standing results from abrupt inhibition of vagal activity. The peak heart rate that is reached at about 10 s after standing is a product of vagal inhibition and (slower acting) sympathetic systems acting in concert. Heart rate declines rapidly after this point as a result of rebounding arterial pressure. There is a particularly steep drop in heart rate between 10 and 20 s and an age gradient with heart rate and blood pressure responses.
The Irish Longitudinal Study on Ageing (TILDA) is a population-based nationally representative cohort study of aging in the Republic of Ireland that measures continuous noninvasive beat-to-beat heart rate and blood pressure responses to orthostatic change in community-dwelling older individuals aged ≥50 years as part of a comprehensive multidisciplinary assessment.22 In this article, we describe the development and validation of a new biomarker of cardiovascular aging derived from the active stand procedure, specifically the speed of HRR between 10 and 20 s after standing, and show that this parameter has clinical relevance as a marker of aging, CVD, and all-cause mortality.

Methods

Study Design and Participants

TILDA is a large prospective cohort study examining the social, economic, and health circumstances of 8175 community-dwelling older adults, aged ≥50 years, resident in the Republic of Ireland. The sample was generated using a 2-stage clustered sampling process and the Irish Geodirectory as the sampling frame. The Irish Geodirectory is a comprehensive listing of all addresses in the Republic of Ireland, which is compiled by the national post service and ordnance survey Ireland. The primary sampling units were 640 geographic regions selected by random selection, stratified on proportion of head of households in the professional class, proportion of the population aged ≥265 years, and geographical location. The second stage involved the selection of a random sample of 40 addresses from within each primary sampling unit, resulting in an initial sample of 25600 addresses. Addresses were then assessed for eligibility, and members of eligible households aged ≥50 years were canvassed to participate. Consequently, the response rate was defined as the proportion of sampled households, including an eligible participant from whom an interview was successfully obtained. A response rate of 62.0% was achieved at the household level. The baseline survey (wave 1) occurred in 2009/2011.

Respondents completed a computer-assisted personal interview (n=8175) in the home. All participants were subsequently invited to undergo a detailed clinic-based health assessment in 1 of 2 national centers using trained nursing staff. A total of 5035 people attended the health center assessment at wave 1. One hundred fifteen individuals were unable to complete the active stand, and data for a further 445 individuals were excluded because of poor signal quality, incomplete data, or poor compliance with protocol. This left a final total of 4475 people who completed the active stand procedure. Online Figure I presents the flow diagram for study participation.

With a few exceptions,2 most of the studies examining HRR in response to exercise have been conducted in symptomatic, clinically referred samples so the ecological validity of these findings for the general population remains questionable. Furthermore, there is no standard protocol for measuring HRR.16,17 Recovery values have been measured at time intervals ranging from 1 to 5 minutes after the cessation of treadmill exercise, and what constitutes a slow HRR has varied from study to study. Few studies have explored the hemodynamics of the HRR during the time period when the speed of recovery toward baseline is at its most pronounced; that is, in the immediate 30 s after the cessation of exercise.18 Finally, HRR to orthostasis has not been widely studied, despite the fact that the results of at least 2 studies suggest that shifts in cardiac autonomic balance in response to standing may have promise as predictors of mortality.19,20

Given that standing can be easily performed by anyone who is functionally mobile and is a potent cardiovascular stressor that demands the full capabilities of the reflexes that govern cardiovascular function,21 we examined the predictive value of HRR to standing in a large adult population study and further describe a novel measure of autonomic dysregulation.

The hemodynamics of the cardiovascular response to standing among the 4475 The Irish Longitudinal Study on Ageing participants who completed the active stand is shown in Figure 1. Baseline values for heart rate (HR) and BP are obtained 60 s before standing. There is a brief initial increase in BP on standing owing to the strain of the maneuver, but SBP and DBP drop quickly thereafter, reaching a nadir at about 10 s and recovering quickly toward baseline between 10 and 20 s. HR increases rapidly in the first 10 s to counteract the gravitational forces acting on BP, peaks at about 10 s and declines rapidly between 10 and 20 s.
Ethics Statement

Ethical approval for the study was obtained from the Trinity College Dublin Research Ethics Committee. Signed informed consent was obtained from all participants.

Heart Rate and Blood Pressure Measurement

A detailed description of the active stand protocol used in TILDA is available elsewhere. Briefly, participants who attended the health center completed an active stand from a supine position as part of a detailed cardiovascular health assessment. A pressure cuff was applied to the finger of each participant to measure their phasic blood pressure. Participants rested comfortably in the supine position for 10 minutes before performing the stand in a silent room with an ambient temperature ranging between 21 and 23°C. Participants were asked to stand in a timely manner (≤5 s) under the supervision of a nurse and were assisted to stand if this proved necessary.

The zero time point for each individual was set by the clinical nurse at the point where the participant began to rise from the supine position. Beat-to-beat variability in heart rate and blood pressure during the stand was captured using noninvasive digital photoplethysmography (Finometer, Finapres Medical Systems, Arnhem, The Netherlands). Data were corrected for hydrostatic changes in finger pressure because of standing using the Height Correction Unit used by the Finometer device. The following parameters were extracted:

1. The supine baseline values of heart rate (HR), systolic blood pressure (SBP), and diastolic blood pressure (DBP) occurring 60 s before standing.
2. Recovery values for heart rate, SBP, and DBP at 10-s time intervals between 10 and 110 s after the stand. The full beat-to-beat data traces were filtered using a nonstationary moving average filter. Recovery values at each 10-s time interval represented a moving average ±2.5 s around that time point. These values are denoted HR(t), SBP(t), and DBP(t), where t is time in seconds after standing and takes on values of 10 to 110 s.
3. Difference from baseline measures were obtained by subtracting values of HR(t) at each time point from the baseline resting heart rate (supine baseline values of heart rate). These values are denoted ΔHR(t). This process was repeated for SBP and DBP. These values are denoted ΔSBP(t) and ΔDBP(t).

End Points: All-Cause Mortality

Mortality status was established through attempts at contact with participants at wave 2 (≥2 years after baseline) and wave 3 (≥4 years after baseline). In total, 549 of the 8175 individuals or 6.7% of the sample who were initially recruited were confirmed as deceased by up to a maximum of 6-year follow-up. Of the 4475 individuals who completed the active stand at wave 1, 141 were confirmed as dead as a 3-level variable: primary, secondary, and tertiary education.

Primary Predictor Variable

We initially explored variation in HRR across the stand using 3 broad age groups: 50 to 59, 60 to 69, and ≥70 years. Preliminary investigation of the data revealed that the speed of HRR in the early part of the stand differentiated strongly between age groups; specifically the speed of HRR between 10 and 20 s after standing. We extracted an additional parameter to describe the speed of HRR during this time window (described in the statistical analysis section below), and it served as the primary predictor variable in the analysis.

Covariates

The covariates were chosen based on their association with mortality and speed of HRR in the literature. All of the covariates were measured at baseline during the wave 1 sweep of data collection. In addition to age, sex, resting HR (bpm), and resting SBP (mm Hg), we control for the use of anticoagulant medications. The international nonproprietary name for any regularly taken medications was assigned and coded using anatomic therapeutic classification codes. Cardiovascular medications were antiadrenergics (C02), diuretics (C03), β-blockers (C07), calcium channel blockers (C08), and angiotensin-converting enzyme inhibitors (C09). Medical history including pre-existing doctor-diagnosed CVDs that represent hard end points (angina, heart attack, congestive heart failure, stroke, and transient ischemic attack) were ascertained during the household interview. Participants with atrial fibrillation were identified as such if they self-reported having an abnormal heart rhythm and this was confirmed from the ECG recording. These data were then pooled to create a 3-level CVD disease measure: CVD free, 1 CVD, and ≥2 CVDs, for use in the analysis. We also include controls for several specific comorbidities that could affect exercise and exertion levels required when actively standing from the supine position. Having ever received a doctor diagnosis of cancer, lung disease, or diabetes mellitus is represented by a series of binary variables in the analysis. Limitations in activities of daily living (ADLs) and instrumental activities of daily living (IADLs) are included as a proxy for the participant’s general physical condition. ADLs included difficulties with (1) dressing, (2) walking across a room, (3) bathing or showering, (4) eating, such as cutting up food, (5) getting in or out of bed, and (6) using the toilet. IADLs included (1) difficulties in preparing a hot meal, (2) doing household chores, (3) shopping for groceries, (4) making telephone calls, (5) taking medications, and (6) managing money. We summed the number of conditions separately with respect to ADLs and IADLs, and the count of these conditions is used in the analysis. Lifestyle factors included smoking history, which is represented as a 3-level variable: never smoked, past smoker, current smoker; body mass index (measured weight/measured height m2); and serum lipids. Body mass index was measured at the clinic visit by trained nursing staff using scientifically approved and calibrated measuring equipment. Participants also provided a blood sample during the course of the health assessment, and these were sent for immediate analysis to derive a detailed lipid profile, which included high-density lipoprotein, low-density lipoprotein, and triglycerides. Finally, we also include a control for educational attainment, which is represented as a 3-level variable: primary, secondary, and tertiary education.

Statistical Analysis

Repeated observations of HR at 10-s intervals within a cross-section allows treatment of the data as a panel (measurement occasions nested within individuals) and fitting of a random effects model using generalized least squares estimation. We explored age-related variation in HRR across the stand for different age groups (50–59, 60–69, and ≥70 years) controlling for sex, existing CVD, and use of cardiovascular medications by fitting the following model (Equation 1) to the data of n individuals, with an individual denoted by i at time t (t ≥ i) poststand:

\[ y_{ij} = \alpha + \beta_1 Y_{ij} + \gamma X_{ij} + \delta_i X_{ij} + u_i + e_{ij} \]
where $i$=1,…,n, $j$=1,…,11, and $y_i$ represents the difference in HR from baseline (ΔHR) at $t_j$; $α$ is the intercept; $β_j$ is the coefficient for each time point at the reference level of each covariate; $X_j$ a vector of individual-level covariates: age group (50–59, 60–69, ≥70 years), sex, existing CVD (none, 1, and ≥2 CVDs), and use of cardiovascular medications (no and yes); and $γ_j$, the related row vector of coefficients. A cross-level interaction term between time ($t_j$ - level 1) and individual-level covariates ($X_j$ - level 2) is given by $τ_j$ $X_j$ and where $δ$ is the related row vector of coefficients. This allows HRR to vary over time by age group and by other covariate groups. The terms $u_i$ and $e_i$ are residuals representing an unobserved individual effect and an error term for individual $i$ at time $j$, sampled from normal distributions with variances $τ_j^2$ and $σ_j^2$, respectively. The model, thus, contains 77 fixed-effects parameters and 2 random-effects parameters. The predictive margins at the means and the associated 95% confidence intervals for the cross-level (time×age group) interaction were derived and plotted.

Visual inspection of the results plotting revealed that the speed of HRR in the early part of the stand (ie, initial 20 s) was the orthostatic feature that most clearly distinguished younger from older participants. Older people experienced a less vigorous increase in HR on standing and a slower recovery toward baseline between 10 and 20 s relative to those aged 50 to 59 years. Additional parameters were, therefore, extracted to represent the speed of HRR during this time frame by subtracting the difference from baseline value of HR at 10 s from the value at 20 s (Equation 2). This is equivalent to simply calculating the absolute difference in heart rate values between 10 and 20 s after standing.

\[
\text{Speed of HRR}_{10\text{s}|20\text{s}} = (\Delta HR_{20\text{s}} - \Delta HR_{10\text{s}})
\]

Differences in the rate of change (ie, slope) across age groups between 10 and 20 s after the stand was confirmed by performing significance tests for difference. Because it is clinically difficult to uncouple the speed of HRR from the BP response, parameters were also extracted to represent the speed of the SBP (Equation 3) and DBP recovery occurring at the same time point (Equation 4).

\[
\text{Speed of SBP recovery}_{10\text{s}|20\text{s}} = (\Delta SBP_{20\text{s}} - \Delta SBP_{10\text{s}})
\]

\[
\text{Speed of DBP recovery}_{10\text{s}|20\text{s}} = (\Delta DBP_{20\text{s}} - \Delta DBP_{10\text{s}})
\]

The bivariate association of each of the parameters extracted from the stand with participants’ age at baseline was examined using Spearman rank-order correlation coefficient. This analysis confirmed that the speed of HRR$_{10\text{s}|20\text{s}}$, was the parameter that was most strongly correlated with age. To check clinical relevance, we compared the speed of HRR$_{10\text{s}|20\text{s}}$, in those with and without CVD and examined its association with the probability of mortality during an average 4.3-year follow-up.

We also calculated the receiver operating characteristic curves predicting mortality in a series of separate univariate analyses with respect to each of the HR, SBP, and DBP parameters extracted from the stand, which was implemented using the ROCtab (receiver operating characteristic)$^{23}$ procedure in STATA.

We followed the American Heart Association’s recommendations for the evaluation of a novel risk marker$^{24}$ to assess the prognostic value of the speed of HRR$_{10\text{s}|20\text{s}}$. Cox proportional hazards models$^{25}$ were fitted to the data to determine whether the speed of HRR$_{10\text{s}|20\text{s}}$, was associated with time to death (month and year of death) up to a maximum of 6 years after initial assessment. The crude model (model 1) estimated the impact of a 1-bpm change in the speed of HRR$_{10\text{s}|20\text{s}}$, on the hazard of mortality. Model 2 adjusted additionally for a range of covariates measured at baseline: (resting HR, resting SBP, sex, cardiovascular medications, CVDs, cancer, lung disease, diabetes mellitus, ADLs, IADLs, smoking status, body mass index, serum lipid profile, and educational status) to determine whether the speed of HRR$_{10\text{s}|20\text{s}}$, was independently associated with hazard of mortality in a multivariable model. Model 3 added age and an age squared term to the equation to determine whether the speed of HRR$_{10\text{s}|20\text{s}}$, predicted mortality independently of age.

Discrimination performance was assessed using Harrell C index and Somer D index. As described by Pennell et al,$^{26}$ the C index estimates the probability of concordance between the predicted risk and the observed order of events for a randomly selected pair of participants. The D index estimates the mean log hazard ratio for the event of interest for a randomly selected pair of participants: one in the top half and one in the bottom half of the predicted risk distribution. We estimate first the model with the established risk markers and then we estimate the model with the established risk markers and the novel risk marker (HRR$_{10\text{s}|20\text{s}}$) to determine whether it leads to an improvement in prediction. The predictive accuracy of the novel risk marker was further assessed using the net reclassification improvement index$^{27}$ based on continuous predictions from a binary model predicting probability of mortality at the end of the surveillance period for each individual as described in the Methods section in the Online Data Supplement.

**Missing Data and Nonresponse**

Only 110 participants, 3 (2.3%) of the 141 confirmed deceased and 107 (2.5%) of the 4227 alive, at last contact had 21 missing covariates, so we report the results from the complete case analysis. SEs of estimates were adjusted to account for the clustered design effect and stratification, and data were weighted using survey weights to account for the fact that respondents who attended the health center were younger, better educated, and in better health.$^{23}$

**Results**

Mean age of the sample was 62.8 years (SD=9.2), 51.3% were female, and 35.5% were taking cardiovascular medications. Almost 12% of the sample had a doctor-diagnosed CVD. The mean HRR$_{10\text{s}|20\text{s}}$, was −5.78 bpm (SD=7.06). Table 1 describes the baseline characteristics of the sample and how they vary according to quartiles of HRR$_{10\text{s}|20\text{s}}$. For example, mean age of those in the slowest HRR quartile was 67.8 years compared with a mean age of 57.7 years among those in the fastest HRR quartile. Similarly, 49.1% of those in the slowest HRR quartile were taking cardiovascular medications compared with 19.3% of those in the fastest HRR quartile. Figure 1 illustrates the mean unadjusted orthostatic HR, SBP, and DBP response to standing for the sample. It shows that HR increases rapidly in the first 10 s after standing and then declines quickly between 10 and 20 s. This pattern is more or less reversed with respect to SBP and DBP, which fall rapidly in the first 10 s but recover quickly between 10 and 20 s.

Table 2 summarizes the bivariate association between age and the array of HR, SBP, and DBP parameters extracted from the stand. The speed of HRR between 10 and 20 s (HRR$_{10\text{s}|20\text{s}}$) after standing was the parameter that was most strongly correlated with age (r=0.40). It was more strongly correlated with age than any of the difference from baseline measures of HR, SBP, or DBP or indeed the speed of the SBP$_{10\text{s}|20\text{s}}$, (r=−0.23). The ΔHR$_{10\text{s}|20\text{s}}$, was the only other variable extracted from the stand that correlated >0.30 (r=−0.33) with age.

Figure 2A through 2D shows that older participants were characterized by a slower HRR toward baseline in the immediate 20 s after standing compared with younger participants in the sample. The speed of HRR$_{10\text{s}|20\text{s}}$, was −8.21 bpm for those aged 50 to 59 years (Figure 2A), −5.25 bpm for those aged 60 to 69 years (Figure 2B), and −2.51 bpm for those aged ≥70 years (Figure 2C). Figure 2D shows the speed of recovery for all age groups simultaneously.

Figure 3A through 3D shows slower HRR$_{10\text{s}|20\text{s}}$, among those with higher CVD burden. Individuals who were free of CVD at wave 1 experienced a greater deceleration in heart
rate between 10 and 20 s after standing (−6.30 bpm, Figure 3A) compared with those who had 1 CVD (−5.50 bpm, Figure 3B) or ≥2 CVDs (−4.26 bpm, Figure 3C). Figure 3D shows these relationships simultaneously. Formal statistical tests confirmed that the speed of HRR10s|20s was significantly faster among those who were CVD free compared with those who had ≥2 CVDs.

The speed of HRR10s|20s also distinguished those who completed the stand at baseline and had died during a mean 4.3-year follow-up. Figure 4A through 4C illustrates this relationship graphically showing that the average HRR10s|20s at wave 1 for those who subsequently died was −3.53 bpm compared with an average HRR10s|20s of −6.30 bpm for those who were still alive at follow-up. The results of the receiver operating characteristic analyses are presented in Online Table 1.

The majority of the difference from baseline measures of HR, SBP, and DBP did not perform significantly better than chance in predicting mortality. Notably, the area under the curve was greatest for the speed of HRR10s|20s (area under the curve=0.69; 95% CI, 0.64–0.73), although comparable to the difference from baseline value of heart rate at 10 s: ΔHRR10s (area under the curve=0.66; 95% CI, 0.62–0.71).

The speed of HRR10s|20s was related to all-cause mortality in univariable and multivariable Cox regression analyses. In the crude analysis (model 1), a 1 bpm slower HRR10s|20s was associated with a 10% increase (hazard ratio, 1.10; 95% CI, 1.08–1.13; \( P < 0.001 \)) in the hazard of all-cause mortality during a mean 4.3-year follow-up period. The association was robust to adjustment for a broad range of established risk markers measured at baseline (model 2), including resting HR, resting SBP, sex, use of cardiovascular medications, existing CVD burden, lung disease, cancer, diabetes mellitus, ADLs, IADLs, smoking, body mass index, serum lipids, and education (hazard ratio, 1.09; 95% CI, 1.06–1.13; \( P < 0.001 \)). The speed of HRR10s|20s remained a significant predictor of all-cause mortality even when adjusted additionally for age and age2 in model 3 (hazard ratio, 1.06; 95% CI, 1.03–1.10; \( P < 0.001 \)).

Table 1. Baseline Characteristics of the Study Population According to Quartiles of HRR (n=4365)

<table>
<thead>
<tr>
<th>First Quartile (Fastest HRR)</th>
<th>Second Quartile</th>
<th>Third Quartile</th>
<th>Fourth Quartile (Slowest HRR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean (SD) or n (%)</td>
<td>Mean (SD) or n (%)</td>
<td>Mean (SD) or n (%)</td>
<td>Mean (SD) or n (%)</td>
</tr>
<tr>
<td>Age</td>
<td>57.7 (7.1)</td>
<td>60.3 (7.9)</td>
<td>64.2 (8.9)</td>
</tr>
<tr>
<td>Female (%)</td>
<td>614 (51.1)</td>
<td>626 (53.6)</td>
<td>586 (52.3)</td>
</tr>
<tr>
<td>Resting HR</td>
<td>65.6 (9.5)</td>
<td>64.8 (10.0)</td>
<td>65.3 (10.0)</td>
</tr>
<tr>
<td>Resting SBP</td>
<td>135.2 (23.0)</td>
<td>136.6 (21.7)</td>
<td>139.3 (23.4)</td>
</tr>
<tr>
<td>Resting DBP</td>
<td>74.8 (11.7)</td>
<td>73.9 (11.4)</td>
<td>73.6 (11.3)</td>
</tr>
<tr>
<td>Cardiovascular medications (%)</td>
<td>207 (19.3)</td>
<td>297 (28.6)</td>
<td>412 (40.9)</td>
</tr>
<tr>
<td>No CVD (%)</td>
<td>1046 (95.1)</td>
<td>1016 (92.2)</td>
<td>969 (87.0)</td>
</tr>
<tr>
<td>1 CVD (%)</td>
<td>35 (3.7)</td>
<td>58 (6.0)</td>
<td>100 (10.4)</td>
</tr>
<tr>
<td>≥2 CVDs (%)</td>
<td>11 (1.2)</td>
<td>17 (1.9)</td>
<td>22 (2.6)</td>
</tr>
<tr>
<td>Cancers (%)</td>
<td>49 (4.3)</td>
<td>50 (4.8)</td>
<td>74 (7.6)</td>
</tr>
<tr>
<td>Lung disease (%)</td>
<td>28 (3.4)</td>
<td>31 (3.3)</td>
<td>36 (3.6)</td>
</tr>
<tr>
<td>Diabetes mellitus (%)</td>
<td>37 (3.5)</td>
<td>49 (4.8)</td>
<td>96 (9.9)</td>
</tr>
<tr>
<td>ADLs (%)</td>
<td>0.06 (0.37)</td>
<td>0.08 (0.45)</td>
<td>0.11 (0.42)</td>
</tr>
<tr>
<td>IADLs (%)</td>
<td>0.04 (0.31)</td>
<td>0.07 (0.48)</td>
<td>0.09 (0.47)</td>
</tr>
<tr>
<td>Never smoked (%)</td>
<td>558 (48.5)</td>
<td>533 (45.9)</td>
<td>499 (43.2)</td>
</tr>
<tr>
<td>Past smoker (%)</td>
<td>427 (39.2)</td>
<td>402 (34.8)</td>
<td>414 (36.5)</td>
</tr>
<tr>
<td>Current smoker (%)</td>
<td>107 (12.3)</td>
<td>156 (19.3)</td>
<td>178 (20.3)</td>
</tr>
<tr>
<td>BMI</td>
<td>29.1 (4.9)</td>
<td>28.6 (4.8)</td>
<td>28.4 (4.7)</td>
</tr>
<tr>
<td>Triglycerides (mmol/L)</td>
<td>1.76 (1.13)</td>
<td>1.75 (1.19)</td>
<td>1.78 (1.12)</td>
</tr>
<tr>
<td>Low-density lipoprotein (mmol/L)</td>
<td>3.10 (0.92)</td>
<td>3.02 (0.99)</td>
<td>2.86 (0.94)</td>
</tr>
<tr>
<td>High-density lipoprotein (mmol/L)</td>
<td>1.55 (0.42)</td>
<td>1.56 (0.44)</td>
<td>1.51 (0.43)</td>
</tr>
<tr>
<td>Primary education (%)</td>
<td>156 (23.1)</td>
<td>204 (29.6)</td>
<td>272 (39.3)</td>
</tr>
<tr>
<td>Secondary education (%)</td>
<td>505 (53.6)</td>
<td>467 (48.6)</td>
<td>445 (43.3)</td>
</tr>
<tr>
<td>Tertiary education (%)</td>
<td>431 (23.3)</td>
<td>420 (21.8)</td>
<td>374 (17.4)</td>
</tr>
<tr>
<td>( n )</td>
<td>1092</td>
<td>1091</td>
<td>1091</td>
</tr>
</tbody>
</table>

ADL indicates activities of daily living; BMI, body mass index; CVD, cardiovascular disease; DBP, diastolic blood pressure; HRR, heart rate recovery; IADL, instrumental activities of daily living; and SBP, systolic blood pressure.

Figures reported in the table are survey-weighted means, SDs, or percentages.
We observed small incremental gains in the C index (0.810 versus 0.816) and D index (0.620 versus 0.633) when we added speed of HRR10s|20s to the model containing the established risk factors predicting mortality. Net reclassification resulted in 78 deaths having greater predicted risk and 60 deaths having lower predicted risk in the model with HRR10s|20s compared to the model without. Similarly, 2503 nondeaths had lower predicted risk, and 1724 nondeaths had greater predicted risk in the model with HRR10s|20s compared with the model without. The continuous net reclassification improvement was 0.315 (95% CI, 0.147–0.483).

To facilitate exploration of dose–response effects, we calculated the hazard ratio and associated 95% confidence intervals for all-cause mortality according to quartiles of HRR10s|20s. The mean HRR10s|20s for those in the fastest recovery quartile was −15.31 bpm. By comparison, the mean HRR10s|20s for those in the slowest recovery quartile was positive (+2.11 bpm), which means that on average, these individuals experienced an increase in heart rate between 10 and 20 s after standing.

Kaplan–Meier survival curves according to quartiles of HRR10s|20s are depicted in Figure 5. Table 3 (model 1) shows that in the crude model, those in the slowest quartile of HRR10s|20s were 7.0× (95% CI, 3.7–13.4; \( P < 0.001 \)) more likely to experience mortality during a mean follow-up duration of 4.3 years compared with those in the fastest recovery quartile; and there was a clear dose–response relationship between the speed of HRR10s|20s and hazard of all-cause mortality. In the full multivariable adjusted model, those in the slowest quartile were also significantly more likely to experience mortality (HR 5.3×, 95% CI, 2.5–11.2; \( P < 0.001 \)).

Table 2. Correlation of HR, SBP, and DBP Parameters Extracted From the Active Stand With Age at the Time of Interview

<table>
<thead>
<tr>
<th>HR Parameters</th>
<th>( r )</th>
<th>SBP Parameters</th>
<th>( r )</th>
<th>DBP Parameters</th>
<th>( r )</th>
</tr>
</thead>
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<tr>
<td>ΔHR10s</td>
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<td>ΔDBP10s</td>
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<td>ΔHR30s</td>
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<td>−0.13</td>
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<td>−0.23</td>
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<td>ΔSBP50s</td>
<td>−0.07</td>
<td>ΔDBP50s</td>
<td>−0.18</td>
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<td>−0.03</td>
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<td>−0.15</td>
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<td>0.00</td>
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<td>ΔDBP rec.</td>
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<td>−0.16</td>
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<td>−0.23</td>
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Estimated using Spearman rank order correlation coefficient. DBP indicates diastolic blood pressure; HR, heart rate; and SBP, systolic blood pressure.

Figure 2. Speed of heart rate recovery after orthostatic challenge by age group. The hemodynamics of the heart rate response to standing during the 2-min time horizon is presented separately for different age groups: 50 to 59 y (A), 60 to 69 y (B), and ≥70 years (C). The estimates were derived controlling for sex, existing cardiovascular disease burden, and use of cardiovascular medications. The speed of heart rate recovery between 10 and 20 s after standing declines with age. Younger individuals are characterized by a steeper initial increase in heart rate and a faster return toward baseline (ie, more precipitous drop) during this time period. D The relationships for all age groups simultaneously. Note that the speed of heart rate recovery between 10 and 20 s is the time point where the difference between age groups is most pronounced. Error bars represent the 95% confidence intervals. HR indicates heart rate.
Circulation Research  August 19, 2016

recovery quartile remained 2.3× (95% CI, 1.1–4.5; \( P < 0.05 \)) more likely to experience all-cause mortality compared with those in the fastest recovery quartile.

**Discussion**

In this large epidemiological study of aging, the speed of HRR between 10 and 20 s (HRR\(_{10\text{–}20\text{s}}\)) after standing was a clear risk marker for mortality during a mean 4.3-year follow-up. The reason why this slope parameter performs better than simply using difference from baseline measures at each time point is that it takes account of how far HR increases on standing and how quickly it recovers toward baseline. To some extent, we think it may be useful to conceive of the slope parameter as a measure of heart rate elasticity because it reflects both the capacity of the system to mount a vigorous response to cardiovascular challenge and to quickly re-establish homeostatic equilibrium. Viewed in this context, an attenuated HRR to the active stand may reflect dysregulation of the parasympathetic branch of the autonomic nervous system because parasympathetic inhibition is largely responsible for the initial surge in HR after the stand,\(^{13}\) whereas parasympathetic reactivation is thought to be responsible for the speed of HRR in the early phase of recovery.\(^{30,31}\) Imai et al\(^{30}\) found that pharmacological blockade of parasympathetic reactivation using atropine delayed cardiac heart rate deceleration, particularly in the initial 30 s of the postexercise recovery phase.

Consistent with expectations for a powerful risk marker, the speed of HRR\(_{10\text{–}20\text{s}}\) distinguishes between different age groups, demarcates those with existing CVD from those who are CVD free, and has predictive power as an indicator of all-cause mortality independent of other established risk markers. In the crude analysis, a 1-bpm slower HRR\(_{10\text{–}20\text{s}}\) was associated with a 10% increase in the hazard of all-cause mortality during a mean 4.3-year follow-up period. The risk of mortality increased as the speed of HRR\(_{10\text{–}20\text{s}}\) declined. An individual in the slowest quartile of HRR\(_{10\text{–}20\text{s}}\) was 7.0× more likely to die at follow-up compared with those in the fastest recovery quartile. These associations were robust to adjustment for established risk factors and remained significant even when adjusted for age, although the latter strongly attenuated the associations. What seems clear is that the speed of HRR\(_{10\text{–}20\text{s}}\) has clinical value as a marker of health and may help identify individuals at risk of mortality. Given that we have limited mortality data, the magnitude of the effect sizes would seem to indicate that we have identified a parameter from the stand that has important clinical relevance.

It should be acknowledged that the novel risk marker led to, at most, moderate gains in the discrimination and accuracy of prediction as assessed using measures of concordance (C index and D index) and net reclassification improvement. This is perhaps not unexpected given that, as a prospective
epidemiological study of aging, the TILDA sample is so well characterized in terms of established risk markers. However, in the context of a clinical setting where all of these covariates are not readily available to the clinician, the speed of HRR_{10|20s} may serve as a useful adjunct to help guide clinical decision making.

Figure 4. Speed of heart rate recovery after orthostatic challenge by incident mortality status. The hemodynamics of the heart rate response to standing during the 2-min time horizon is presented separately for those who completed the stand at wave 1 and were still alive at follow-up (A) and those who had died at follow-up (B). The estimates were derived controlling for age, sex, existing cardiovascular disease burden, and use of cardiovascular medications. Respondents who died were characterized by a slower heart rate recovery between 10 and 20 s relative to those who were still alive. C shows these relationships simultaneously. Error bars represent the 95% confidence intervals. HR indicates heart rate.

Figure 5. Kaplan–Meier survival probability curves according to quartiles of heart rate recovery between 10 and 20 s after standing (n=4385). HRR indicates heart rate recovery.
Table 3. Hazard Ratio for Mortality During a Mean 4.3-Year Follow-Up Duration by Speed of HRR Quartiles Between 10 and 20 s After Standing in Crude and Multivariable-Adjusted Models (n=4365)

|               | Model 1          | Model 2          | Model 3          | HRR$_{10\text{s}|20\text{s}}$ Died | n  |
|---------------|------------------|------------------|------------------|-------------------------------------|----|
|               | Hazard Ratio     | 95% CI           | Hazard Ratio     | 95% CI                             |     |
| Quartile 1 (fastest) | REF              | ...              | REF              | ...                                |     |
| Quartile 2     | 1.98             | 0.92–4.27        | 1.63             | 0.75–3.52                          |     |
| Quartile 3     | 2.95**           | 1.43–6.08        | 1.97             | 0.95–4.08                          |     |
| Quartile 4 (slowest) | 7.05***         | 3.72–13.35       | 4.32***          | 2.20–8.48                          |     |

Model 1: Crude. Model 2: Resting HR, resting systolic blood pressure, sex, cardiovascular medications, cardiovascular diseases, diabetes mellitus, cancer, lung disease, activities of daily living, instrumental activities of daily living, smoking status, body mass index, lipid profile, and educational status. Model 3: model 2 + age2. CI indicates confidence interval; HRR, heart rate recovery; and REF, reference category. ***Significant at the 0.001 level; **significant at the 0.01 level; *significant at the 0.05 level.

Limitations

Only a small number of cases who completed the stand (n=138) and had full information on covariates had died at follow-up, so the confidence intervals around the estimates are large. Despite this, the magnitude of the effect sizes support the use of orthostatic HRR as a robust risk marker. Second, information was not available about cause of death and the numbers would likely be too small to disaggregate and analyze by disease type. It is entirely possible that the predictive power of HRR$_{10\text{s}|20\text{s}}$ would be higher if we were predicting cardiovascular as opposed to all-cause mortality. Future research with this cohort will be directed toward this end, particularly if we are able to link individual-level clinical data to administrative sources of data (ie, National Death Registry). Finally, another criticism that could be leveled at the study is that a sizeable proportion of the sample did not attend the health center assessment, and a sizeable subset of individuals who did attend the health center assessment did not complete the stand, which may raise concerns about the ecological validity of the findings for the general population. Notwithstanding this caveat, it is important to acknowledge that individuals who attended the health center assessment tended to be younger and in better health compared with those who did not attend.32 This can be adduced from the fact that the mortality rate was 6.7% in the overall sample compared with 3.2% among those who completed the stand. As the derived estimates were likely to be conservative, we used survey weights in the analysis to take account of nonparticipation in the health center component.

Strengths

The study also has a significant number of strengths. First, it uses a large representative sample of the community-dwelling older population and a novel measure of cardiovascular functioning (ie, active stand) that is rare in the context of an epidemiological study. Second, beat-to-beat measurement of heart rate and blood pressure affords us the resolution to explore features of the cardiovascular response to standing during a time period (ie, initial 20 s) that is of potential theoretical interest because it is arguably indexing the balance of sympathetic and parasympathetic systems. The study also benefits from the strong in-depth characterization of the sample, which means that we are able to control for a large range of variables that could potentially confound the relationship between our putative measure of cardiovascular aging and mortality.

Conclusions

The speed of orthostatic HRR between 10 and 20 s identifies those who are at high risk of mortality. This has important clinical applications because the speed of HRR is a clinical variable that may be useful for population screening. Although HRR is modifiable by, for example, physical activity interventions,33–35 whether modifying HRR directly reduces mortality requires further study. Future intervention studies should be designed to explore this possibility.

Acknowledgments

We thank the Irish Longitudinal Study on Ageing (TILDA) participants who provided the data for this article.

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Disclosures

None.

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Novelty and Significance

**What Is Known?**
- Impaired heart rate recovery after treadmill stress testing is an established risk factor for cardiovascular and all-cause mortality. It is hypothesized that this is because of dysregulation of autonomic balance unmasked by the test.

**What New Information Does This Article Contribute?**
- Impaired heart rate recovery in the immediate 20 s after an orthostatic maneuver (ie, active stand from a supine position) predicts all-cause mortality independently of other established risk factors.
- Heart rate monitoring (ie, with ECG) during active stand is a simpler test to determine autonomic responsiveness compared with alternative methods, such as treadmill stress testing.

To orthostatic challenge (ie, active stand from a supine position) has clinical value as a marker of risk. The active stand represents a potent cardiovascular stressor that elicits a rapid physiological response involving the coordinated action of several systems, including the skeletal-muscle pump and arterial and cardiopulmonary baroreflexes. Peak heart rate is reached ≈10 s after standing and declines rapidly thereafter as a result of rebounding arterial pressure. There is a particularly steep drop in heart rate between 10 and 20 s after standing and an age gradient with heart rate and blood pressure responses. We show that speed of HRR during this time window distinguishes those with existing cardio-
vascular disease from those who are cardiovascular disease free and has predictive power as a marker of all-cause mortality. We hypothesize that speed of HRR during this time window reflects the capability of the system to mount a vigorous response to cardio-
vascular challenge and to quickly re-establish homeostatic equilibrium.
Speed of Heart Rate Recovery in Response to Orthostatic Challenge
Cathal McCrory, Lisa F. Berkman, Hugh Nolan, Neil O'Leary, Margaret Foley and Rose Anne Kenny

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doi: 10.1161/CIRCRESAHA.116.308577

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SUPPLEMENTARY MATERIAL

Title: Speed of Heart Rate Recovery in Response to Orthostatic Challenge: A Strong Risk Marker of Mortality

Authors: Cathal McCrory (PhD)1, Lisa Berkman (PhD)2, Hugh Nolan (PhD)1, Neil O’Leary (PhD)1 Margaret Foley, & Rose Anne Kenny (MD)1

1 The Irish Longitudinal Study on Ageing, Department of Medical Gerontology, Trinity College Dublin, Dublin 2, Ireland; and 2 Center for Population and Development Studies, Harvard School of Public Health, 9 Bow Street, Cambridge, MA 02139, USA

Running Title: Orthostatic Heart Rate Recovery and Mortality.

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Net Reclassification Improvement

The net-recategorization index (NRI) can be interpreted as the net change in the proportion of subjects assigned a more appropriate risk or risk category under the new model. We define the category-free population-weighted NRI as follows:

\[ NRI = \text{NRI}_E P(E) + \text{NRI}_{NE} P(NE) \]

Here \( P(E) \) is the probability of an event \( E \), in this case death, and the probability of a non-event \( NE \) is given by \( P(NE) = (1 - P(E)) \). These probabilities act as prevalence weighting for calculating the NRI from \( \text{NRI}_E \), the NRI for events (deceased) and \( \text{NRI}_{NE} \) the NRI for non-events (survivors).

Furthermore we define:

\[ \text{NRI}_E = P(q^* > q | E) - P(q^* < q | E) \]
\[ \text{NRI}_{NE} = P(q^* < q | NE) - P(q^* > q | NE) \]

The predicted risk from the model with and without the novel risk marker are given by \( q^* \) and \( q \) respectively, and \( P(q^* > q | E) \) is the probability of a higher risk being assigned by the model with the novel risk marker compared to that without given an event \( E \), \( P(q^* < q | E) \) is the probability of a lower risk being assigned by the model with the novel risk marker given an event \( E \) (death). Similarly \( P(q^* < q | NE) \) and \( P(q^* > q | NE) \) represent the probabilities of lower and higher risk respectively from the model with the novel risk marker compared to the model without, given no event (survivor).

We calculated the standard error of \( \text{NRI}_E \) and \( \text{NRI}_{NE} \) as follows:

\[ SE(\text{NRI}_E) = \sqrt{ \frac{(P(q^* > q | E) + P(q^* < q | E))P(E)}{n_E} - \frac{(\text{NRI}_E P(E))^2}{n_E} } \]
\[ SE(\text{NRI}_{NE}) = \sqrt{ \frac{(P(q^* > q | E) + P(q^* < q | E))P(NE)}{n_{NE}} - \frac{(\text{NRI}_{NE} P(NE))^2}{n_{NE}} } \]

Then combine for the standard error of the population-weighted NRI

\[ SE_{NRI} = \sqrt{ P(E)^2 SE(\text{NRI}_E)^2 + (1 - P(E))^2 SE(\text{NRI}_{NE})^2 } \]

And we compute normal-approximated 95% confidence intervals for the NRI as follows:

\[ (L_{NRI}, U_{NRI}) = (NRI - 1.96 SE_{NRI}, NRI + 1.96 SE_{NRI}) \]
Online Figure I: Flow Diagram for Study Participation

N=8175 respondents at Wave 1

- No health centre assessment
  N = 3139

N=5035

- Unable to complete the active stand
  N= 115

N=4920

- Poor quality active stand
- Incomplete data
- Poor compliance with protocol
  N=445

N=4475

- Missing on covariates
  N= 110

N=4365

- Alive (at right censoring)
  N=4227
- Dead
  N=138
Online Table I: Receiver Operating Characteristic Curves Predicting Risk of Mortality for the various Heart Rate, Systolic Blood Pressure and Diastolic Blood Pressure Parameters extracted from the Active Stand.

<table>
<thead>
<tr>
<th>HR parameters</th>
<th>SBP parameters</th>
<th>DBP parameters</th>
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<td>ΔSBP 10 secs</td>
<td>ΔDBP 10 secs</td>
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<tr>
<td><strong>0.66</strong>* [0.62, 0.71]</td>
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<td>ΔSBP 20 secs</td>
<td>ΔDBP 20 secs</td>
</tr>
<tr>
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<td>0.57** [0.52, 0.63]</td>
<td>0.56* [0.51, 0.62]</td>
</tr>
<tr>
<td>ΔHR 30 secs</td>
<td>ΔSBP 30 secs</td>
<td>ΔDBP 30 secs</td>
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<tr>
<td>0.53 [0.48, 0.58]</td>
<td>0.56* [0.51, 0.62]</td>
<td>0.57** [0.52, 0.62]</td>
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<td>0.61*** [0.56, 0.66]</td>
</tr>
</tbody>
</table>

AUC = area under the curve

***significant at the 0.001 level; **significant at the 0.01 level; * significant at the 0.05 level