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Association of Holter-Derived Heart Rate Variability Parameters With the Development of Congestive Heart Failure in the Cardiovascular Health Study

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ABSTRACT

OBJECTIVES This study sought to determine whether Holter-based parameters of heart rate variability (HRV) are independently associated with incident heart failure among older adults in the CHS (Cardiovascular Health Study) as evidenced by an improvement in the predictive power of the Health Aging and Body Composition Heart Failure (Health ABC) score.

BACKGROUND Abnormal HRV, a marker of autonomic dysfunction, has been associated with multiple adverse cardiovascular outcomes but not the development of congestive heart failure (CHF).

METHODS Asymptomatic CHS participants with interpretable 24-h baseline Holter recordings were included (n = 1,401). HRV measures and premature ventricular contraction (PVC) counts were compared between participants with (n = 260) and without (n = 1,141) incident CHF on follow-up. Significantly different parameters between groups were added to the components of the Health ABC score, a validated CHF prediction tool, using stepwise Cox regression.

RESULTS The final model included components of the Health ABC score, ln PVC counts (adjusted hazard ratio [aHR]: 1.12; 95% confidence interval [CI]: 1.07 to 1.19; $p < 0.001$) and the following HRV measures: abnormal heart rate turbulence onset (aHR: 1.52; 95% CI: 1.11 to 2.08; $p = 0.009$), short-term fractal scaling exponent (aHR: 0.27; 95% CI: 0.14 to 0.53; $p < 0.001$), in very low frequency power (aHR: 1.28; 95% CI: 1.02 to 1.60; $p = 0.037$), and coefficient of variance of N-N intervals (aHR: 0.94; 95% CI: 0.90 to 0.99; $p = 0.009$). The C-statistic for the final model was significantly improved over the Health ABC model alone (0.77 vs. 0.73; $p = 0.0002$).

CONCLUSIONS Abnormal HRV parameters were significantly and independently associated with incident CHF in asymptomatic, older adults. When combined with increased PVCs, HRV improved the predictive power of the Health ABC score. (J Am Coll Cardiol HF 2017;■:■–■) © 2017 by the American College of Cardiology Foundation.

The development of congestive heart failure (CHF) is associated with significant morbidity and mortality. It is estimated that the annual cost of care for CHF patients in the United States will increase from $31 billion in 2012 to $70 billion in 2030, largely due to aging of the American population (1). Currently, care for these patients begins after the development of symptoms that lead to the diagnosis of the disease. Improved tools to identify patients at risk for the development of CHF

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ABBREVIATIONS AND ACRONYMS

CAD = coronary artery disease

CHF = congestive heart failure

ECG = electrocardiogram

GND = Greenwood-Nam-D'Agostino

HRT = heart rate turbulence

HRV = heart rate variability

MI = myocardial infarction

NT-proBNP = N-terminal pro-B-type natriuretic peptide

PVC = premature ventricular contraction

TO = turbulence onset

TS = turbulence slope

may result in targeted interventions for primary prevention. Several risk models have been created to predict the development of CHF using known risk factors such as diabetes mellitus, coronary artery disease (CAD), hypertension, and chronic kidney disease (2,3). Although predictive in the specific populations from which they were derived, most of these models have not been externally validated (4). However, the Health Aging and Body Composition Heart Failure (Health ABC) score, originally developed in the Health ABC study, was externally validated in the CHS (Cardiovascular Health Study), a longitudinal study of community dwelling, older adults (5). In addition, a subset of CHS participants volunteered to undergo 24-h Holter monitoring, making it possible to determine whether Holter-based parameters, including heart rate variability (HRV), improves the ability of the Health ABC model to identify participants who are at risk of developing CHF.

HRV is a set of parameters that capture the magnitude and organization of the intervals between consecutive normal heart beats. These parameters reflect cardiac autonomic function and are abnormal in patients with CAD, diabetes mellitus, and CHF, but are also affected by the normal aging process (6–9). Abnormal HRV has been shown to be an independent predictor of mortality after myocardial infarction (MI) and sudden cardiac death in patients with CHF (10–13). In the CHS, abnormal HRV has been shown to be associated with increased cardiovascular mortality in community-dwelling adults without signs or symptoms of heart failure (14).

Ventricular ectopy is a commonly recognized electrocardiogram (ECG) finding that can be an ominous sign in the post-MI phase, but may also be seen on routine ECGs in otherwise healthy individuals (15–17). Multiple studies have examined the prognostic significance of premature ventricular contractions (PVCs) in the general population, and a 2013 meta-analysis showed that frequent PVCs were associated with a markedly increased risk of both sudden death and cardiac death (18). In the CHS, PVCs from 24-h Holter recordings were significantly associated with the development of heart failure (19).

Given the relationship among HRV, ectopy, and cardiovascular mortality, we hypothesized that abnormal HRV on 24-h Holter recordings could improve the ability of the Health ABC model to identify participants who are at an increased risk for the development of CHF in the CHS.

METHODS

STUDY POPULATION. The design, rationale, and recruitment methods for the CHS have been previously described (20,21). Briefly, noninstitutionalized individuals who were 65 years of age or older were recruited from Medicare eligibility lists in 4 communities. The original cohort included 5,201 participants, recruited from 1989 to 1990. An additional 687 African-American individuals were recruited from 1992 to 1993. Baseline physical examinations, laboratory tests, and questionnaires were obtained for all participants. A subset of participants from the CHS cohort that had baseline 24-h Holter monitoring were studied (n = 1,764) (14). The original cohort underwent Holter recording at year 2 of the CHS, whereas the African-American cohort, which had baseline assessments at year 5, had Holter recordings performed in year 7. Participants with unusable Holter data (i.e., paced rhythms, atrial fibrillation, wandering atrial pacemaker, or >20% ectopic beats) were excluded (n = 275). Additionally, those with heart failure at the time of Holter monitoring were excluded (n = 42), as well as those with unknown baseline heart failure status (n = 4). Participants with missing components of the Health ABC score were also excluded, as only complete case data were utilized in our analysis (n = 39). Three participants were excluded due to incomplete follow-up data. This yielded a final sample size of 1,401 participants.

COMPONENTS OF THE HEALTH ABC HEART FAILURE SCORE. The Health ABC score components were recorded in all participants who underwent Holter monitoring using baseline physical examination findings, laboratory values, and testing, as shown in **Figure 1**. Of note, the 687 African-American participants who were recruited later had baseline laboratory values assessed 2 years before their 24-h Holter monitoring. The individual components of the Health ABC score, as defined in **Table 1**, were compared between participants who did and did not develop CHF by the end of follow-up.

OUTCOMES. The primary outcome was incident CHF. The methods used to define incident CHF have been reported previously (22,23). To summarize, in the CHS, incident events (e.g., heart failure, MI, and stroke) were tabulated through regular surveys, clinic visits, and calls through which participants were questioned regarding any recent hospitalizations or new diagnoses. Additionally, participants were able to contact the local field centers to report any changes in their medical care. Finally, incident events could be explored through review of medical records