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Abnormal Heart Rate Turbulence Predicts Cardiac Mortality in Low, Intermediate and High Risk Older Adults

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Abstract

Introduction—We examined whether heart rate turbulence (HRT) adds to traditional risk factors for cardiac mortality in older adults at low, intermediate and high risk.

Methods and Results—N=1298, age ≥65 years, with 24-hour Holter recordings were studied. HRT, which quantifies heart rate response to ventricular premature contractions, was categorized as: both turbulence onset (TO) and turbulence slope (TS) normal; TO abnormal; TS abnormal; or both abnormal. Independent risks for cardiac mortality associated with HRT or, for comparison, elevated C-reactive protein (CRP) (>3.0 mg/L), were calculated using Cox regression analysis adjusted for traditional cardiovascular disease risk factors and stratified by the presence of no, isolated subclinical (*i.e.*, intermediate risk) or clinical CVD. Having both TS and TO abnormal compared to both normal was associated with cardiac mortality in the low risk group [HR 7.9, 95% CI 2.8–22.5, (p<0.001)]. In the high and intermediate risk groups, abnormal TS and TO ([HR 2.2, 95% CI 1.5–4.0, p=0.016] and [HR 2.7, 95% CI 1.2–5.9, p=0.012]), respectively, were also significantly associated with cardiac mortality. In contrast, elevated CRP was associated with increased cardiac mortality risk only in low risk individuals [HR 2.5, 95% CI 1.3–5.1, p=0.009]. In the low risk group, the c-statistic was 0.706 for the base model, 0.725 for the base model with CRP, and 0.767 for the base model with HRT.

Conclusions—Abnormal HRT independently adds to risk stratification of low, intermediate and high risk individuals but appears to add especially to the stratification of those considered at low risk.

INTRODUCTION

Traditional cardiovascular disease (CVD) risk factors (*e.g.*, age, gender, cholesterol, hypertension, smoking, diabetes) explain much but not all cardiac disease mortality risk [1]. Efforts, therefore, have continued to identify other factors that could further explain risk of mortality. One candidate risk factor is elevated C-reactive protein (CRP), a global measure of the inflammation that underlies the development of cardiovascular disease. Adding elevated CRP levels (>3 mg/dL) to predictive models such as the Framingham Risk Score or the National Cholesterol Education Program Global Risk Score improves classification of people at intermediate risk for cardiac mortality into either low or high risk groups [2]. However, CRP does not appear to add to risk stratification among people at low or high risk of cardiac events using several risk calculators [3,4].

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Previously, we investigated whether abnormal heart rate turbulence (HRT), another potential risk factor, could add value to the Framingham risk score as a predictor of CVD mortality in older adults. HRT is a Holter-based measure that quantifies the autonomically-mediated oscillatory behavior of the heart rate response to ventricular premature beats (VPC). Loss of this response is believed to signify impaired baroreflex sensitivity and loss of the cardiovascular system's ability to adapt to hemodynamic changes [5]. We found that abnormal HRT identified a high risk group of individuals *independent* of Framingham risk score, diabetes and the presence of clinical CVD and that it was especially powerful among those with a low Framingham risk scores [6].

In the current study we extended this analysis to simultaneously examine the risks associated with abnormal HRT and elevated CRP for cardiac mortality in a cohort of older adults at low, intermediate and high risk of cardiac events based on cardiovascular clinical status [7]. Analyses were adjusted for traditional risk factors and abnormalities in left ventricular ejection fraction. Participants for this study were from the Holter monitoring sub-study of the Cardiovascular Health Study (CHS), an epidemiological study of cardiovascular risk factors in adults, ages ≥ 65 years.

METHODS

Study Population

Recruitment methods for the CHS have been published [8]. In brief, a random sample of individuals ≥ 65 years of age, derived from government-sponsored health insurance (Medicare) eligibility lists from 4 communities, and other household members, age ≥ 65 years, were invited to participate in the study. Potential participants were excluded if they were institutionalized, were unable to attend clinic visits, or had illnesses that were expected to lead to early death. 5201 participants were recruited in 1989–1990 (original cohort) and 687 in 1992–1993 to provide additional representation of African-Americans (new cohort). All participants signed informed consent upon entry into the study. This study conforms to the Declaration of Helsinki and was approved by the local Human Research Protection Organization.

The 24-hour Holter recordings for this study (N=1429) were obtained in the original cohort at the time of the baseline examination. Although 375 members of the new cohort had Holter recordings, they were obtained two years after the detailed assessment of cardiovascular risk factors; therefore they were not included in the current analyses. Tapes with atrial fibrillation or a paced rhythm, or of inadequate quality or length (<8 hours of usable signals) were not analyzed, leaving 1298 recordings. Our prior analysis has shown that the demographic and clinical factors in those who volunteered for Holter recordings and the total CHS cohort were similar [9].

Baseline Examination and CVD Status

Participants completed standardized interviews and answered questions regarding past medical history [10]. They underwent an electrocardiogram, cardiac ultrasound, measurement of the ankle-arm index and blood pressure, and fasting laboratory tests [11]. Details of laboratory measurements, including hs-CRP and lipid fractions, and quality control of cardiovascular measures, have been published [11].

CVD status was determined based on the baseline cardiovascular testing. *Clinical CVD* was defined as the presence of one or more of the following: coronary heart disease, defined as a history of myocardial infarction, angina pectoris, or a revascularization procedure (coronary artery bypass grafting or percutaneous transluminal coronary angioplasty); history of stroke or transient ischemic attack; or a history of claudication [7]. CVD diagnoses were

adjudicated by a committee that reviewed medical records according to standardized procedures. *Isolated sub-clinical CVD* was defined as the presence of any of the following in the absence of any clinical CVD: ankle arm index <0.9 , major ECG changes, common or internal carotid artery intimal medial thickness in the upper 20% of the distribution, or common carotid stenosis $>25\%$ [7]. Diabetes was defined as a baseline fasting glucose value ≥ 126 mg/dl or use of hypoglycemic agents.

Outcome Variable

Mortality from cardiac causes was the outcome for these analyses. These deaths were due primarily to coronary heart disease (CHD) (N=169) but also included deaths associated with heart failure (N= 23). Confirmation of deaths was ascertained through reviews of obituaries, medical records (including hospital and nursing home records, as well as physician questionnaires), death certificates and the National Death Index and the Medicare utilization database for hospitalizations. Through these methods, there was 100% ascertainment of vital status [12].

Covariates

To assess the independent impact of HRT and of CRP on cardiac mortality, analyses were stratified on CVD status (none, isolated subclinical, clinical CVD) [7], and adjusted for traditional risk factors: age, gender, ejection fraction (categorized as normal, borderline [45%–54%] or abnormal [$<45\%$]) [13], diabetes, current smoking, total to HDL cholesterol ratio and hypertension (systolic BP ≥ 140 mmHg or diastolic BP ≥ 90 mmHg or use of anti-hypertensive medication).

Ambulatory ECG Monitoring and Assessment of HRV

Holter tapes were recorded on Del Mar Avionics recorders which have a calibrated timing signal and processed by research technicians at the Washington University School of Medicine Heart Rate Variability Laboratory (St Louis, Missouri), using a GE Marquette MARS 8000 Holter analyzer (GE-Marquette, Milwaukee, WI). All Holter analyses were reviewed in detail by one of us (PKS) with special attention paid to ensuring that only normal beats with uniformly detected onsets were labeled as normal (N). The longest and shortest true N-N intervals were identified for each tape, and intervals outside of these limits, including blocked atrial premature contractions (APCs) excluded from all calculations. Participants with a paced rhythm, atrial fibrillation or wandering atrial pacemaker were excluded from the analysis. Heart rate turbulence (HRT) was calculated from annotated beat-to-beat files exported to a Sun Enterprise 450 server (Sun Microsystems, Santa Clara, CA) using validated research software [14].

Heart Rate Turbulence

Heart rate turbulence (HRT) quantifies the response of the sinus node to ventricular premature complexes (VPCs) [14,15]. Two indices are calculated: turbulence onset (TO) and turbulence slope (TS). In healthy hearts, there is generally a brief sinus tachycardia after a VPC. TO measures the magnitude of this tachycardia as the percent change in N-N interval of the sinus rhythm two beats after the VPC compared to the two beats before. In healthy hearts this index is negative or zero. Thus, a $TO \geq 0$ is abnormal (no immediate tachycardia or possibly bradycardia). TS quantifies the slower oscillation in heart rate (tachycardia, bradycardia then return to baseline) that follows a VPC as the largest fitted slope of the N-N intervals between any 5 beats within 15 sinus beats of the VPC. These indices require ≥ 5 VPCs for calculation and are determined as a signal-average of all of the VPCs on the recording. HRT could not be calculated in 26 cases with ≥ 5 VPCs since there

were not enough VPCs with 2 sinus beats before and 15 sinus beats after to permit HRT calculation. These cases were excluded from the analysis.

HRT is generally analyzed as a categorical variable. The usual cut point for abnormal TS is <2.5 ms/beat and for TO ≥ 0 based on data from post-MI patients in the Autonomic Tone and Reflex after Acute Myocardial Infarction (ATRAMI) study [16]. Because CHS examines a different population - the elderly, with or without prevalent CHD - we had previously explored other cut points for TS and TO using univariate Cox regression analysis [6]. We found the cut points that maximally separated those who did or did not die of cardiovascular causes to be $TS < 3$ and $TO > 0$. Thus, for the present analyses, participants were categorized as having abnormal HRT if either TS or TO was abnormal using these cut points. Participants with < 5 VPCs (in whom HRT cannot be calculated) were categorized as having normal HRT. Those in whom HRT could not be calculated ($N=26$) were excluded from further analysis.

Statistical Analysis

Multivariate Cox regression analyses tested the relationship of clinical and demographic risk factors with cardiac mortality. The initial models were run for the entire cohort using either HRT or CRP (categorized as low or average ≤ 3 mg/L or high > 3 mg/L) or both [1]. Models stratified by cardiovascular clinical status included both CRP and HRT. Because participants with < 5 VPCs on their recordings were categorized as having normal HRT, a categorical variable of having < 5 VPCs or having ≥ 5 VPCs was added to the models. A $p < 0.05$ was considered statistically significant.

The c-statistic, a measure of the accuracy of discrimination that can be thought of as an extension of the binary ROC curve to multivariate survival analysis, was calculated for clinical and demographic factors [17]. The effect of the addition of either HRT or CRP or both on the cstatistic was then determined by cardiovascular clinical status. SPSS 16 (SPSS, Inc, Chicago, IL) software was used for these analyses.

RESULTS

Clinical and Demographic Characteristics of Study Population (Table I)

When compared with those still alive or who had died of non-cardiac causes, those who died of cardiac causes were significantly less likely to be female (40 vs. 57%) and more likely to have diabetes (27 vs. 12%), more likely to have hypertension (87 vs. 69%) and more likely to be classified as high risk (52 vs. 25%). They were less likely to be classified as low (18 vs. 39%) or intermediate risk (29 vs. 37%). Current smoking was not common (~10% in each group). Thirty-eight percent of those who died of cardiac causes had elevated CRP levels vs. 26% who did not and 47% had either one or two abnormal HRT tests vs. 25% among those who did not. The prevalence of more than 5 VPCs on the recording was markedly higher among those who died (82% vs. 18%). The cohort was 95% white.

HRT, CRP and Cardiac Mortality

When the entire HRT-eligible population (1272 participants, 196 cardiac deaths over 11.7 ± 3.8 years follow up) was considered together, high CRP levels (> 3 mg/L) compared with a $CRP \leq 3$ mg/L was associated with a hazard ratio (HR) of 1.4 for cardiac mortality (95% CI=1.1–2.0, $p=0.015$) in the multivariate model. Having > 5 VPCs on the recording was significantly associated with outcome (HR=1.7, 95% CI 1.2–2.4, $p=0.005$). When the model was repeated for HRT, abnormal turbulence slope (TS) was associated with an HR of 1.7 (95% CI=1.2–2.5, $p=0.008$) compared to both HRT factors normal. Combined TS and TO abnormal yielded an HR of 3.1 (95% CI=2.0–4.7, $p<0.001$). When CRP and HRT were both

added to the model, CRP remained significant (HR=1.4, 95% CI=1.0–1.8, $p=0.050$), as was HRT [TS abnormal, 1.7 (95% CI=1.1–2.5, $p=0.009$), both TS and TO abnormal, HR=2.9 (95% CI=1.9–4.5, $p<0.001$)]. Survival curves for different levels of HRT in the fully adjusted model are shown in Figure 1.

Among participants with low cardiac risk, the prevalence of TS and TO abnormal was 5%, but was 19% among the 39 who died of cardiac causes. Among those with intermediate risk, prevalence of TS and TO abnormal was 7% (33/451) and was 27% among the 59 who died of cardiac causes. Among those at high risk, prevalence of abnormal HRT was 9.0 % but was 40% of the 105 who died of cardiac causes.

Among participants with low cardiac risk, an elevated CRP was present in 25% (113/461) but was present in 43% of the 39 who died of cardiac causes. In the intermediate risk group, prevalence of elevated CRP was 27% (122/461) and was 32% among the 59 who died of cardiac causes. In the high risk group, elevated CRP was found in 33.3 % (125/376) and found in 40% of the 105 who died of cardiac causes.

Stratified Survival Models for Prediction of Cardiac Mortality (Table II)

Among participants without measurable subclinical or clinical CVD (Table II, Figure 2) both elevated CRP (HR=2.5, 95% CI=1.3–5.1, $p=0.009$) and abnormal HRT (both TS and TO abnormal, HR=7.9, 95% CI=2.8–22.5, $p<0.001$) were associated with cardiac mortality. Among those with isolated subclinical CVD (intermediate risk) (Table II Figure 3), high CRP was not associated with cardiac mortality. This was true whether or not HRT was in the model. Abnormal HRT (both TS and TO abnormal, HR=2.7, 95% CI=1.2–5.9, $p=0.012$) did enter the model. Among participants with known cardiovascular disease (high risk participants), (Table II, Figure 4), elevated CRP levels were also not associated with cardiac mortality while having both TS and TO abnormal (HR=2.2, 95% CI=1.2–4.1, $p=0.016$) remained a significant predictor of cardiac mortality. Again high CRP did not enter this model even when HRT was removed.

C-Statistics

In the model for the full cohort, the c-statistic for the base model without HRT or CRP but including clinical status as a covariate, was 0.748. Addition of CRP raised the c-statistic to 0.754. Addition of HRT alone raised it to 0.766. Having both CRP and HRT in the model resulted in a c-statistic of 0.768.

In the stratified analysis, among those without any evidence for CVD, the c-statistic was 0.706 for the base model, 0.725 for the base model with CRP, and 0.767 for the base model with HRT, 0.774 with both HRT and CRP. Elevated CRP levels were not associated with cardiac death for the other two groups and therefore the effect on the c-statistic was not tested. For isolated subclinical CVD, the c-statistic was 0.712 for the base model and 0.725 with HRT. For clinical CVD, the c-statistic was 0.706 for the base model and 0.721 with HRT.

DISCUSSION

In this prospective study of adults, aged ≥ 65 years, both abnormal HRT and elevated CRP levels contributed to the identification of higher risk older adults originally classified as being at low risk for cardiac death. Elevated CRP levels, however, did not add to the prediction of future cardiac mortality in participants at intermediate or higher risk, whereas abnormal HRT added to prediction models in all three groups. These findings can be interpreted to mean that in the absence of detectable atherosclerosis, elevated CRP levels and abnormal HRT reflect two separate disease processes, each of which leads to elevated

cardiac risk. On the other hand, in the presence of atherosclerosis, CRP loses its ability to predict cardiac mortality even when HRT is not in the model. This latter finding is consistent with results from the Framingham Heart Study. In that study, elevated CRP levels were not significantly associated with CHD events on multivariate analysis (RR 1.22 [95% CI, 0.81–1.84]) nor did they add to the c statistic which was based on traditional CHD risk factors. Also in that study, CRP levels were associated with CHD risk only for those with a low Framingham Risk Score (similar to our findings) and not with intermediate or high scores, again similar to our findings [18].

Prior studies have shown HRT to be a strong risk factor for CHD. Abnormal HRT predicted mortality among patients with cardiac disease in the Multi-Center Post-Infarction Project (MPIP-median follow up 22 months) and in the placebo arm of the European Myocardial Infarction Amiodarone Trial (EMIAT-21 month median follow up) with a multivariate-adjusted relative risk of mortality associated with the combination of TS and TO abnormal of 3.2 in each cohort [19]. Our results generalize this finding to population-dwelling adults ≥ 65 years, especially including those without evidence of CVD. Although the main purpose of our study was to measure the association of HRT with risk at different strata of the CHS, the overall hazard ratio for cardiac mortality for having both abnormal TS and TO in the entire cohort was 3.1, a remarkably similar finding, albeit over a much longer follow up period (median 14 years)

HRT quantifies autonomic responses to the change in arterial pressure associated with a VPC, the post-VPC compensatory pause, and the normal heart beats that follow the VPC [15]. Cardiac output and blood pressure decline during a VPC, resulting in a baroreflex-mediated compensatory vagal withdrawal and possibly a slightly delayed increase in sympathetic activity leading to an immediate increase in heart rate (TO). As blood pressure increases during the post-compensatory pause, there is a baroreflex-mediated slowing of the heart beat and then a return to baseline. This results in the oscillation of heart rate that is captured by TS. This is hypothesized to reflect both sympathetic and parasympathetic activity. Thus, abnormal HRT may be seen as reflecting dysfunction in the interaction of cardiac sympathetic and parasympathetic control of heart rate and blood pressure. Whether these abnormalities are directly involved in CVD mortality or reflect underlying CVD pathology is not known.

As compared to classic CVD risk factors, HRT is a “dynamic” measure that reflects an integrated physiologic response, *i.e.*, the effect of the underlying risk factors rather than their degree. It is non-invasive and it does not require complex or costly testing. While HRT measurement is available for clinical use on only one commercial Holter system (GE Medical Systems), the algorithm is available without charge for research purposes [14].

Our findings, coupled with the work of others [19], may result in an increased availability of this measure on other commercially-available Holter analyzers. For a test to be considered a “CVD risk factor” it must fulfill several criteria [20]. These include: (1) a statistically significant association with a hard endpoint (e.g., mortality) when tested (preferably) prospectively; (2) incremental prognostic information over and above that of traditional risk factors, using tests such as the c-statistic; (3) replicable in other studies and measured accurately; and (4) assessment readily available and cost effective. These criteria were met by measurement of HRT in our study. Of note, HRT was most effective in increasing cardiac mortality risk prediction in participants with no evidence of atherosclerosis. Thus its use may be considered, for example, in healthy adults embarking on a program of vigorous exercise or strenuous work.

In conclusion, we report that both HRT and CRP contribute significantly to risk stratification of older adults without evidence for CVD; while HRT added to risk prediction among older adults with isolated subclinical or established CVD. Results suggest that abnormal HRT may provide a novel risk factor for risk of future cardiac mortality risk independent of known cardiovascular risk factors.

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Figure 1. Survival curves for different categories of HRT in the entire cohort. Model is adjusted for clinical and demographic factors and for CRP.

Figure 2. Survival curves for different categories of HRT in those at low risk of cardiovascular outcomes. Model is adjusted for clinical and demographic factors and for CRP.

Figure 3. Survival curves for different categories of HRT in those at intermediate risk of cardiovascular outcomes. Model is adjusted for clinical and demographic factors and for CRP.

Figure 4. Survival curves for different categories of HRT in those at high risk of cardiovascular outcomes. Model is adjusted for clinical and demographic factors and for CRP.

Table 1

Clinical and Demographic Characteristics of the CHS Holter Cohort Alive at the End of Follow Up or Dead of Non-Cardiac Causes vs. Those Who Died of Cardiac Causes. Mean $\pm$ SD or Number and %).

	Alive or Non-Cardiac Death (N=1097)	Cardiac Death (N=201)	p-value for difference
Age (years)	71.4 $\pm$ 4.6	73.7 $\pm$ 5.3	<0.001
Female Gender	630 (57%)	83 (40%)	<0.001
Diabetes	130 (12%)	55 (27%)	<0.001
Hypertension	755 (69%)	174 (87%)	<0.001
Cardiovascular Clinical Status			
Healthy (Low Risk)	424 (39%)	37 (18%)	<0.001
Subclinical CVD (Intermediate Risk)	402 (37%)	59 (29%)	
Clinical CVD (High Risk)	271 (25%)	105 (52%)	
Current Smoking	102 (9%)	19 (10%)	0.515
Total/HDL Cholesterol Ratio	4.3 $\pm$ 1.3	4.6 $\pm$ 1.4	0.004
Borderline or Abnormal LVEF	73 (6%)	48 (21%)	<0.001
CRP (mg/L)	3.3 $\pm$ 6.2	4.7 $\pm$ 9.3	0.036
C-Reactive Protein Categories			
Low or Average CRP ($\leq$ 3 mg/L)	814 (74%)	124 (62%)	<0.001
High CRP ($>$ 3 mg/L)	283 (26%)	77 (38%)	
Heart Rate Turbulence Categories			
TS and TO normal	803 (75%)	104 (53%)	<0.001
TO abnormal only ($>$ 0%)	89 (8%)	17 (9%)	
TS abnormal only ($<$ 3.0 ms/beat)	130 (12%)	42 (21%)	
TS and TO abnormal (both)	54 (5%)	33 (17%)	
VPC Category ($\geq$ 5 VPCs)	37 (18.4%)	164 (81.6%)	<0.001

Legend: CVD=cardiovascular disease; LVEF=left ventricular ejection fraction; TS=heart rate turbulence slope (normal $\Rightarrow$ 3ms/beat); TO=heart rate turbulence onset (normal= $>$ 0%)

Table II

Survival models for clinical and demographic factors, CRP and HRT in participants classified as low (*i.e.*, without subclinical or clinical CVD), intermediate (*i.e.*, isolated subclinical CVD) and high risk (*i.e.*, with clinical CVD) of cardiac death.

	Low N=461, 37 deaths		Intermed N=461, 57 deaths		High N=376, 102 deaths	
	Hazard Ratio [95% CI]	p-value	Hazard Ratio [95% CI]	p	Hazard Ratio [95% CI]	p-value
Age	1.1 [1.02–1.2]	0.017	1.1 [1.1–1.2]	<0.001	1.1 [1.1–1.2]	<0.001
Male Gender	2.0 [1.02–4.1]	0.044	NS	0.800	1.7 [1.1–2.6]	0.025
Borderline LVEF	6.0 [1.7–21.8]	0.006	2.5 [1.1–5.5]	0.024	1.9 [1.2–3.1]	0.007
CRP>3.0 mg/L	2.5 [1.3–5.1] N=111	0.009	NS N=119	0.961	NS N=122	0.441
TS&TO Abnormal vs. Both Normal	7.9 [2.8–22.5] N=21	<0.001	2.7 [1.2–5.9] N=33	0.012	2.2 [1.5–4.0] N=33	0.016
TO Abnormal	NS	0.224	NS	0.883	NS	0.640
TS Abnormal	NS	0.244	NS	0.173	NS	0.486
Smoking	NS	0.381	3.7 [1.8–7.5]	<0.001	NS	0.765
Diabetes	NS	0.266	1.9 [1.003–3.6]	0.049	2.3 [1.4–3.6]	<0.001
Hypertension	NS	0.564	NS	0.054	NS	0.080
Total to HDL Ratio	NS	0.333	NS	0.824	NS	0.231
Having >5 VPCs	NS	0.792	NS	0.574	NS	0.119

See Legend Table I