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Prognostic significance of electrocardiographic right ventricular hypertrophy in the general population☆

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ABSTRACT

Background: Echocardiographically detected right ventricular hypertrophy (RVH) is associated with cardiovascular disease (CVD) and mortality. However, the prognostic significance of electrocardiographic (ECG)RVH criteria as predictors of poor outcomes in the general population is unclear.
Methods: This study included 7857 participants (59.8 ± 13.4 years, 52.6% women) from the Third National Health and Nutrition Examination Survey. Sixteen different ECG-RVH criteria were created from digitally recorded and centrally processed electrocardiograms. All-cause mortality was ascertained using the National Death Index. Cox proportional hazards analysis was used to examine the association between baseline ECG-RVH criteria and all-cause mortality.
Results: The prevalence of RVH varied widely among the criteria. The lowest ECG-RVH prevalence was 0.09% (using S > R in I, II, III) while the highest prevalence was 20.7% (using (R I + S III) − (S I + R III) < 15 mm). During a median follow-up of 14 years, 2812 deaths occurred. The mortality rate was highest among participants with ECG-RVH defined as R:S ratio V_5 < 0.75. In multivariable adjusted models, 9 out of the 16 ECG-RVH criteria were significantly associated with all-cause mortality. When ECG-RVH was defined as the presence of any ECG-RVH criteria, each additional ECG-RVH criteria was associated with 6% increased risk of all-cause mortality (HR (95% CI):1.06(1.03,1.10)).
Conclusions: There is a wide variation in the prevalence of ECG-RVH when different criteria are applied in the general population. However, the presence of ECG-RVH by most criteria regardless of prevalence was associated with poor prognosis suggesting that appropriate choice of criteria may enhance the utilization of these ECG markers in risk stratification.

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Introduction

There is increasing recognition of the significance of right ventricular hypertrophy (RVH) as a risk factor and predictor for cardiovascular disease (CVD) [1–3]. Echocardiographically detected RVH has been shown to be predictive of heart failure (HF), CVD death and atrial fibrillation (AF) [2,3] and abnormalities in RV morphology and function are frequently associated with poor outcomes in various cardiopulmonary conditions [4–7].

The detection of RVH is frequently delayed, resulting in underdiagnosis of RVH in the clinical practice [8]. Because even mild RVH is associated with poor outcomes, early detection may facilitate prompt treatment and improve clinical outcomes [2,8,9]. RVH is traditionally detected using 2-dimensional echocardiography and cardiac magnetic resonance imaging (cMRI). Both are relatively expensive and not widely available and hence not appropriate for screening. On the other hand, electrocardiogram (ECG) based scores have shown excellent predictive ability in assessing CVD risk in asymptomatic individuals [10]. And the presence of any ECG abnormality has been associated with increased risk of poor outcomes in the future [11]. However, ECG has low sensitivity in screening for mild RVH in adults without CVD compared with cMRI [12]. Although ECG has limited utility in detecting RVH in otherwise healthy adults, it is possible that ECG-RVH still carries significant prognostic information. This assertion has not been tested yet, but it is a plausible assertion given the lessons learned from prior studies on the diagnostic yield and prognostic significance of electrocardiographic left ventricular hypertrophy (ECG-LVH). Although all ECG-LVH criteria have poor diagnostic performance, their role as predictors of poor

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outcomes is undeniable and continues to grow [13,14]. We expect that this will be the same case for ECG-RVH. Therefore, we examined the relationship between 16 commonly used ECG-RVH criteria and all-cause mortality using data from the Third National Health and Nutrition Examination Survey (NHANES-III).

Material and methods

NHANES III is a survey conducted by the National Center for Health Statistics (NCHS) between the years 1988–1994 using a representative sample of the United States civilian non-institutionalized individuals. The purpose of the survey was to determine disease prevalence and the overall health of the United States population. All study participants signed written informed consent prior to participation [15].

This analysis was limited to NHANES III participants who underwent ECG recording as part of their exam. We excluded participants with poor quality ECG data or those with major conduction abnormalities that interfere with ECG-RVH calculation including complete left or right bundle branch blocks or QRS ≥ 120 msec. We also excluded those without complete medical and anthropometric measurements or mortality data. After all exclusions (n = 794), 7857 participants remained and were included in the analysis.

Baseline covariates

Participant baseline data were collected during an in-home interview and a subsequent visit to a mobile examination center between 1988 and 1994. Age, gender, race/ethnicity, history of previous cardiovascular disease (CVD) (heart failure, stroke, coronary heart disease), history of chronic obstructive pulmonary disease (COPD) (bronchial asthma and chronic bronchitis) and smoking history were self-reported. A physical examination was performed to obtain body mass index (BMI), blood pressure, blood draw and ECG. Blood pressure readings were taken during the in-home evaluation and again during their visit at the mobile examination center and averaged for each participant. Hypertension was defined as systolic blood pressure ≥ 140 mmHg or diastolic ≥90 mmHg or use of antihypertensive medications. Obesity was defined as BMI ≥ 30 kg/m^2 computed as weight in kilograms divided by the square of height in meters. Diabetes was defined as fasting plasma glucose ≥126 mg/dl, glycosylated hemoglobin A1c values ≥6.5% or a history of diabetic medication use.

Electrocardiogram

Trained technicians recorded standard 12-lead ECG using a Marquette MAC 12 system (Marquette Medical Systems, Milwaukee, Wisconsin) during the study visit at the mobile examination center. Computerized automated analysis of the electrocardiographic data was performed with visual inspection of outlier values by a trained technician in a central electrocardiogram core laboratory (Epidemiological Cardiology Research Center (EPICARE), Wake Forest School of Medicine, Winston Salem, North Carolina). Using the automatically generated measurements of the amplitudes and durations of the ECG waveforms, we calculated 16 RVH criteria [16] (Table 2). Our choice of those 16 criteria was based on the availability of raw ECG data at NHANES-III that enable calculation, and for the ECG-RVH criteria to be listed in the 2009 American Heart Association (AHA)/American College of Cardiology Foundation (ACCF)/Heart Rhythm Society (HRS) recommendations for the standardization of ECG recognition of cardiac chamber hypertrophy [16].

Follow up and mortality

The participants of NHANES III were followed up for mortality until December 31, 2006. The probabilistic matching method was used to link NHANES III participants with the National Death Index for vital status and the cause of death in deceased participants. Name, social security number, and date of birth were part of 12 identifiers used to match the participants. The follow-up duration was defined as the period between the initial examination for NHANES III participation and December 31, 2006, or date of death, whichever occurred first.

Statistical analysis

Categorical variables were reported as frequency and percentage whereas continuous variables were reported as mean and standard deviation (SD). The mortality rate was reported per 1000 person-years.

Cox proportional-hazards regression analysis was used to compute hazard ratio (HR) and 95% confidence interval (CI) for the association between each of the 16 ECG-RVH criteria with all-cause mortality. In addition, we defined ECG-RVH as the presence of RVH by any of the ECG-RVH criteria and examined the risk of mortality associated per each additional extra ECG-RVH. Models were adjusted as follows: Model 1 was adjusted for age, sex, and race (non-Hispanic black vs. other races); Model 2 adjusted for Model 1 plus hypertension, diabetes, obesity, and current smoker; Model 3 adjusted for Model 2 covariates plus prior CVD, COPD and Cornell Index.

All statistical analyses were performed using with SAS version 9.4 (SAS Institute Inc., Cary, NC) and p-values were considered significant if <0.05.

Results

A total of 7857 participants (59.8 ± 13.4 years, 52.6% women, 23.4% non-Hispanic blacks) were included in the analysis. Table 1 shows the baseline characteristic of the study participants.

The prevalence of RVH varied widely based on the criteria used as shown in Table 2. The lowest ECG-RVH prevalence was 0.09% when Supporting Criteria (S > R in I, II, III) was used while the highest prevalence was 20.7% when Lewis ((R I + S III) − (S I + R III) < 15 mm) was used.

Over a median follow-up of 14 years, a total of 2812 (35.7%) deaths occurred. Table 2 shows the number of deaths and the mortality rates per 1000 person-years among the study participants with and without baseline ECG-RVH defined by different criteria. As shown, most criteria tended to be associated with increased mortality. The mortality rate was highest among participants with ECG-RVH defined as reduced R:S ratio V_5 < 0.75 (105.2 deaths per 1000 person-years) and the lowest was among participants with ECG-RVH defined by Lewis ((R I + S III) − (S I + R III) < 15 mm) (24.92 deaths per 1000 person-years).

In models adjusted for demographics and CVD risk factors, 9 out of the 16 ECG-RVH criteria were significantly associated with all-cause mortality and several others were borderline significant (Table 3). Also, when ECG-RVH was defined as the presence of any ECG-RVH

Table 1
Baseline characteristic of study participants (n = 7857).

Characteristics	Mean ± SD or n (%)
Age (years)	59.85 ± 13.4
Women	4136(52.6%)
Non-Hispanic Black	1840(23.4%)
Hypertension	2845(36.1%)
Diabetes	913(11.6%)
Obesity	1483(18.8%)
Current smoker	1713(22.5%)
COPD	546(6.9%)
CVD	873(11.1%)
Cornell Voltage Index (microvolt)	1312.9 ± 548.3
Cornell Voltage ECG-LVH	225(2.86%)

COPD = Chronic obstructive pulmonary disease; CVD = Cardiovascular disease; LVH = Left Ventricular Hypertrophy.

Table 2
Prevalence of ECG-RVH by different criteria and rates of mortality associated with each set of criteria.

ECG-RVH				All-cause mortality			
Criteria		Number (n)	Prevalence (%)	ECG-RVH Absent		RVH- Present	
				Events (n)	Rate (1000 person-years)	Events (n)	Rate (1000 person-years)
Myers [31]	Increased R:S ratio $V_1 > 1.0$	228	2.90	2714	28.2	98	34.8
	Deep S $V_5 > 10$ mm	49	0.62	2781	28.3	31	67.8
	Deep S $V_6 > 3$ mm	362	4.60	2638	27.8	174	42.8
	Small S $V_1 < 2$ mm	745	9.40	2387	26.3	425	52.9
	Small R $V_{5,6} < 3$ mm	59	0.75	2775	28.2	37	67.1
	Reduced R:S ratio $V_5 < 0.75$	37	0.47	2784	28.2	28	105.3
	QR V_1 present	41	0.52	2783	28.2	29	75.6
	Tall R $V_1 > 6$ mm	147	1.80	2761	28.5	51	26.46
Sokolow [32]	Tall R aVR > 4 mm	34	0.43	2794	28.3	18	49.2
	R:S V_5 to R:S $V_1 < 0.04$	31	0.39	2786	28.2	26	98.7
	R V1 + $SV_{5,6} > 10.5$ mm	151	1.92	2729	28.1	83	49.4
Lewis [33]	(R I + S III) − (S I + R III) < 15 mm	1627	20.70	2291	29.4	521	24.9
Supporting criteria [16]	S > R in I, II, III present	7	0.09	2807	28.4	5	74.2
	S I and Q III present	1447	18.40	2331	29.0	481	25.9
	Negative T-wave V_1 through V_3	140	1.78	2744	28.2	68	44.1
	P II amplitude > 2.5 mm	120	1.53	2750	28.2	62	47.8
Any criteria	At least one the 16 criteria	3248	41.3	1561	26.4	1251	31.4

ECG-RVH = Electrocardiographic Right Ventricular Hypertrophy.

criteria, each additional ECG-RVH criteria was associated with 6% (p-value < 0.01) increased risk of all-cause mortality (Table 3).

Discussion

In this analysis from the NHANES-III, we examined the prognostic significance of 16 different ECG-RVH criteria. The key findings from this analysis are: 1) There was a wide variation in the prevalence of ECG-RVH when different criteria are applied in the general population; 2) Despite the wide variation in prevalence, the presence of ECG-RVH by most criteria was associated with poor prognosis but with variable strength in the association. Our findings suggest that with appropriate choice of ECG-RVH criteria, these simple ECG markers may enhance the risk stratification and identification of those at risk of poor outcomes despite the known low performance as diagnostic tools.

The prognostic role of the RV in various cardiopulmonary conditions including HF, pulmonary arterial hypertension (PAH), and acute myocardial infarction (MI) has been overlooked for many years. However, more recent studies have placed greater importance on the RV in prognostic assessments [6,17–19]. Several studies have shown that RV function is a significant, independent predictor of poor outcomes in patients with left ventricular dysfunction complicating acute MI [20,21]. Steiner et al. found that RV systolic function and hypertrophy predicted mortality in patients with significant PAH in a retrospective study of 152 participants. Decreased RV systolic function assessed by tricuspid annular plane systolic excursion and increased RV thickness were independently associated with mortality in patients with significant pulmonary artery systolic pressure > 60 mmHg [1]. In a retrospective study on 106 patients with known hypertrophic cardiomyopathy utilizing cMR to detect RVH, defined as RV maximum wall thickness > 5 mm, Nagata et al. found that RVH was associated with greater incidence of CVD events [22]. In a multiethnic population free of clinical CVD at baseline, RV hypertrophy determined by cMR was associated with more than twice the risk of heart failure or death [2].

There are several explanations why RVH may predict an increased risk of mortality. RVH has been frequently linked to disease states

Table 3
Association between different Electrocardiographic Right Ventricular Hypertrophy (ECG-RVH) with all-cause mortality.

ECG-RVH criteria		Model 1	p-value	Model 2	p-value	Model 3	p-value
Myers [31]	Increased R:S ratio $V_1 > 1.0$	0.93(0.76–1.14)	0.53	0.87(0.71–1.07)	0.20	0.91(0.74–1.11)	0.37
	Deep S $V_5 > 10$ mm	1.98(1.38–2.82)	<0.01	1.72(1.20–2.46)	<0.01	1.65(1.15–2.37)	<0.01
	Deep S $V_6 > 3$ mm	1.13(0.97–1.32)	0.09	1.07(0.92–1.25)	0.34	1.06(0.90–1.24)	0.45
	Small S $V_1 < 2$ mm	1.25(1.12–1.39)	<0.01	1.14(1.02–1.26)	0.01	1.12(1.00–1.24)	0.03
	Small R $V_{5,6} < 3$ mm	1.58(1.14–2.19)	<0.01	1.74(1.25–2.41)	<0.01	1.67(1.20–2.32)	<0.01
	Reduced R:S ratio $V_5 < 0.75$	3.30(2.27–4.79)	<0.01	3.34(2.30–4.86)	<0.01	3.07(2.11–4.47)	<0.01
	QR V_1 present	1.79(1.24–2.58)	<0.01	1.33(0.922–1.92)	0.12	1.34(0.93–1.95)	0.11
	Tall R $V_1 > 6$ mm	1.03(0.78–1.37)	0.07	1.11(0.84–1.47)	0.44	1.13(0.86–1.50)	0.36
Sokolow [32]	Tall R aVR > 4 mm	1.59(1.00–2.53)	0.04	1.56(0.98–2.48)	0.06	1.53(0.96–2.44)	0.07
	R:S in V_5 to R:S $V_1 < 0.04$	1.78(1.21–2.62)	<0.01	1.44(0.98–2.13)	0.06	1.45(0.99–2.15)	0.05
	R V_1 + $SV_{5,6} > 10.5$ mm	1.28(1.02–1.59)	0.02	1.20(0.96–1.49)	0.10	1.18(0.94–1.47)	0.14
Lewis [33]	(R I + S III)– (S I + R III) > 1 .5mm	1.21(1.10–1.34)	<0.01	1.13(1.03–1.25)	<0.01	1.17(1.06–1.30)	0.01
Supporting criteria [16]	S > R in I, II, III present	2.81(1.17–6.78)	0.02	3.14(1.30–7.57)	0.01	3.17(1.31–7.65)	0.01
	S I and Q III present	1.09(0.98–1.20)	0.08	1.02(0.93–1.13)	0.60	1.00(0.91–1.11)	0.88
	Negative T-wave V_1 through V_3	1.47(1.15–1.87)	0.01	1.36(1.07–1.73)	0.01	1.33(1.04–1.69)	0.01
	P II amplitude > 2.5 mm	1.69(1.31–2.18)	<0.01	1.55(1.20–2.00)	<0.01	1.56(1.20–2.01)	<0.01
The 16 criteria	Per each additional criteria	1.10(1.07–1.14)	<0.01	1.07(1.03–1.10)	<0.01	1.06(1.03–1.10)	<0.01

Model 1 adjusted for age, sex, race.
Model 2 adjusted for model 1 plus hypertension, diabetes, current smoker, obesity.
Model 3 adjusted for model 2 plus prior cardiovascular disease, chronic obstructive pulmonary disease and Cornell Voltage Index.

which are associated with poor outcomes such as PAH, obstructive sleep apnea (OSA), AF, emphysema, obesity as well as markers of inflammation [3,23–26]. LV systolic or diastolic dysfunction results elevated left atrial pressure and PAH leading to RVH. Thus, RVH may serve as a marker of severity of the LV dysfunction or HF, or it may directly contribute to the development of HF due to impaired RV filling [2]. Finally, a dilated hypertrophied RV may act as a substrate for malignant arrhythmias [27,28].

ECG pattern resulting from RVH is variable and depends on intrinsic and extrinsic factors such as the hemodynamic pattern of RV load, severity of LVH, coexistence of branch block, heart rotation and changes in lung volumes altering diaphragm position [29]. The ECG changes invoked by RVH are different from those produced by LVH because the RV is considerably smaller than the LV and produces electrical forces that are largely canceled by those generated by the larger LV. Thus, for RVH to be manifested in ECG, the RV mass must be sufficiently large to overcome the LV forces. ECG changes associated with RVH include abnormally tall R waves in anteriorly and rightward directed leads (aVR, V1, V2) and deep S waves and abnormally small r waves in leftward directed leads (I, aVL and lateral precordial leads V5, V6). Less severe RVH, especially when limited to the outflow tract of the RV that is activated late during the QRS complex, produces less marked changes. ECG abnormalities may be limited to an rSr' pattern in V1 persistence of s or S waves in the left precordial leads [30]. Upon comparing traditional ECG-RVH criteria to RVH measured by cMRI, Whitman et al. found that the ECG-RVH criteria had poor sensitivity and specificity for detection of mild RVH in participants without clinically overt CVD.

Despite having poor utility to screen for mild RVH in the general population, we have shown that several common ECG-RVH have prognostic significance relating to all-cause mortality even after the rigorous adjustment for potential confounders. Of these, at least three criteria had a high degree of prevalence within the study population, including Myers (small S V_1 < 2 mm), Lewis ((R I + S III) − (S I + R III) > 1 .5mm) and Supporting Criteria (S 1 and Q III present). Although cardiac imaging demonstrates greater sensitivity and specificity to detect RVH, echocardiogram and cMR are relatively expensive when compared to surface ECG. The prognostic significance of these ECG criteria may have public health implications as we develop interventions to reduce CVD burden in the US.

Our study has certain limitations. ECG-RVH was ascertained only at baseline, and hence we could not assess changes over time and how this change may impact its association with mortality. Similar to other studies with similar design, residual confounding remains a possibility despite adjusting for potential confounders. Also, several variables were self-reported, and thus, there is a potential for recall or interview bias. Despite these limitations, to our knowledge, this is the first report examining the prognostic significance of a large number of ECG-RVH criteria in the general population. Also, our study has several strengths including the centralized processing of ECG data collected via standardized methods, long-term follow-up and large sample size with better generalizability to the US population.

Conclusion

Despite the known poor sensitivity of ECG to detect RVH in the general population, ECG-RVH criteria carry significant prognostic information. Appropriate choice of ECG-RVH criteria may enhance the utilization of these markers in risk stratification.

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Declarations of interest

None.

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