Interrelations Between Hypertension and Electrocardiographic Left Ventricular Hypertrophy and Their Associations With Cardiovascular Mortality

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Electrocardiogram (ECG) is the most common method for assessment of left ventricular hypertrophy (LVH) in contemporary clinical trials. However, our understanding of the relation between hypertension and LVH is based on studies used imaging to ascertain LVH. To fill this gap in knowledge, we examined the interrelationships between hypertension, ECG-LVH and cardiovascular disease (CVD) mortality in 6,105 patients free of CVD who were followed for 14.0 years (median). The was an exponentianl ECG-LVH prevalence rates (2.40%, 4.45%, 5.75%, 8.51%, 14.38%) were exponentially increases as systolic blood pressure increases (< 120 mm Hg, 120 to 129 mm Hg, 130 to 139 mm Hg, 140 to 159 mm Hg, > 160 mm Hg, respectively); trend p value < 0.001. Hypertension was associated with more than double the risk of ECG-LVH (odds ratio (95% confidence interval [CI]) 2.45 [1.83, 3.30]), and each standard-deviation increase in systolic blood pressure (19 mm Hg) was associated with 49% increased odds of ECG-LVH (odds ratio [95% CI] 1.49 [1.38, 1.61]). During follow-up, 733 CVD-deaths occurred. In separate Cox models, both ECG-LVH and hypertension were associated with CVD mortality (hazard ratio [95% CI] 1.39 [1.07, 1.81] and 1.39 [1.18, 1.62], respectively). However, when ECG-LVH and hypertension were entered together in the same model, the risk of CVD mortality was essentially unchanged for hypertension after adjusting for ECG-LVH, but markedly attenuated for ECG-LVH after adjusting for hypertension. In conclusion, the relation between hypertension and ECG-LVH follows a similar pattern to that reported in literature for imaging-LVH which provides support for the current practice of using ECG for assessment of LVH in contemporary hypertension clinical trials. The inability of ECG-LVH to explain the association between hypertension and CVD mortality suggests that LVH is only one of many factors by which hypertension exerts its impact on CVD.
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Observational studies have demonstrated graded associations between higher systolic blood pressure (SBP) and increased cardiovascular disease (CVD) risk.[1,2] Left ventricular hypertrophy (LVH) is the most common complication of hypertension, and it is a risk factor for CVD morbidity and mortality independent of BP levels.[3−5] Studies in which LVH was ascertained by imaging (imaging-LVH) have shown a linear relation between increasing prevalence of LVH with higher levels of SBP.[6-9] However, although the electrocardiogram (ECG) is the most common tool for assessment of LVH in contemporary clinical trials,[10−16] the relation between SBP levels and electrocardiographic-LVH (ECG-LVH) has not been examined in a large racially diverse cohort. Given the inherent differences between ECG-LVH and imaging-LVH suggesting that they are two different entities,[17−19] we thought to examine the interrelation between SBP and ECG-LVH and their associations with CVD mortality. Filling these gaps in knowledge could enhance our understanding of the results coming out from the contemporary clinical trials that used ECG to ascertain LVH.

Methods

We used data from the Third National Health and Nutrition Examination Survey (NHANES III). The protocol for NHANES-III was approved by the National Center for Health Statistics of the Center for Disease Control and Prevention institutional review board. Written consent was obtained from all study participants. The NHANES-III survey included a representative sample of the noninstitutionalized civilian of the US population, with an overall aim to estimate disease prevalence and health status. Participants' baseline data were collected during an in-home interview and a subsequent visit to a mobile examination center from 1988 to 1994. Data obtained during the in-home interview included medical history, demographics, body mass index, BP measurements, serum creatinine, and total serum cholesterol levels.

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BP was measured 3 times during the household interview followed by an additional 3 readings in mobile examinations centers. Each blood pressure measurement was performed with the participant seated, using a standard mercury sphygmomanometer. After resting quietly in a seated position for 5 minutes and once the participant's maximum inflation level had been determined, 3 consecutive blood pressure readings were obtained. If a blood pressure measurement was interrupted or incomplete, a fourth attempt was made. BP for each individual participant was reported as the arithmetic average of all measured systolic and diastolic pressures. Hypertension was defined by reported use of antihypertensives or having an average measured BP $\geq$ 140 mm Hg systolic or 90 mm Hg diastolic. Obesity was defined as having a body mass index $>$ 30 kg/m^2. Participants were identified as diabetic if they had a fasting plasma glucose $>$ 126 mg/dl, nonfasting plasma glucose $>$ 200 mg/dl or current use of antidiabetic medications. Participants were considered as having dyslipidemia if they their total cholesterol $\geq$ 240 mg/dl or low-density lipoprotein $\geq$ 160 mg/dl or high-density lipoprotein $\leq$ 40 mg/dl or on cholesterol-lowering medication. Smoking status was ascertained through self-report as never, current, or past.

NHANES-III participants who were 40 to 90 years old were invited to undergo 12-lead standard ECG by trained technicians during their visit to the mobile examination center. A Marquette MAC 12 electrocardiograph (Marquette Medical Systems, Milwaukee, Wisconsin) was used to record digital ECGs, which were then transmitted via phone lines for automatic processing at a central ECG core laboratory after being visually inspected for errors. ECG-LVH was determined using gender specific Cornell voltage product (CVP): ([R amplitude aVL+ S amplitude V3] + 0.6 mV for females) $\times$ QRS duration. Participants with CVP values $>$ 244 mV s were considered to have ECG-LVH. In addition to using LVH as a categorical/binary variable, CVP was also examined as a continuous variable, referred to in this article as CVP-index. Using CVP-index as a continuous variable has the advantage of independence from cut-off points selected to define LVH and could be used as a surrogate measure for left ventricular mass.[10,11]

Mortality data for NHANES-III participants were available through December 31, 2006. A probabilistic matching algorithm based on 12 identifiers was used to link participants with death information captured in the National Death Index. Matching identifiers included social security number, gender, and date of birth. Participants who were unable to be matched with a death record were considered to be alive through the entire follow-up period. The International Classification of Diseases, Tenth Revision codes were used to identify cause of death. CVD mortality was defined by codes 100 to 178. Follow-up was defined as the interval between the NHANES-III examination and either of the following, depending on whichever came first: date of death, date of censoring, or end of follow-up.

Out of the 8,561 NHANES-III participants who underwent 12-lead ECG, we excluded participants with previous history of CVD, or with ECG evidence of major intraventricular conduction delay (complete bundle branch block, Wolf Parkinson-White Syndrome, or QRS duration $\geq$ 120 milliseconds). We also excluded those with missing ECG or follow-up mortality data. After all exclusions, 6,105 participants remained and were included in the analysis.

Characteristics of the study participants were examined and compared across categories stratified by ECG-LVH and hypertension status using analysis of variance for continuous variables and chi-square test for categorical variables. The prevalence rates of ECG-LVH across levels of SBP were tabulated and a p value for trend was calculated. The correlation between SBP and CVP-index was examined using Pearson Correlation.

Multivariable logistic regression models were used to examine the cross-sectional associations between hypertension and 1-standard deviation increase in SBP (19 mm Hg), separately, with ECG-LVH. Models were initially unadjusted, then adjusted for demographics (age, gender, and race), then further adjusted for CVD risk factors (diabetes, dyslipidemia, obesity, smoking, serum creatinine, use of insulin, use of lipid lowering medications, and use of blood pressure lowering medications). Similar linear regression models were used to examine the cross-sectional associations between hypertension and 1-standard deviation increase in SBP, separately, with CVP-index as a continuous variable.

The CVD mortality rates were calculated per 1,000 person-years, overall and stratified by ECG-LVH and hypertension status. The impact of the interrelationship between ECG-LVH and hypertension on each other in terms of their association with CVD mortality was assessed using 3 approaches: First, we used multivariable Cox proportional hazard models to examine the associations between hypertension and ECG-LVH, in isolation and combined, with the risk of CVD mortality. In these models, different combinations of ECG-LVH and hypertension were included in the models as follows: concomitant presence of hypertension and ECG-LVH, isolated hypertension, isolated ECG-LVH, and no ECG-LVH or hypertension (reference group). This approach aimed to examine whether there is a graded additive increase in the risk of CVD mortality when hypertension and ECG-LVH coexist together compared with the presence of each one of them in isolation. Second, we examined the attenuation of the magnitude of risk of CVD mortality associated with ECG-LVH when the model is adjusted for hypertension, and vice versa. This was achieved by using multivariable Cox proportional hazard models to examine the risk of CVD mortality associated with ECG-LVH and hypertension when entered in 2 separate models, and with both entered in the same model as 2 separate variables adjusting for each other. This approach aimed to determine how much of the observed risk of CVD mortality associated with ECG-LVH is explained by hypertension, and vice versa. Third, we examined the effect modification of baseline ECG-LVH on the association of hypertension with CVD mortality, and vice versa, by stratifying the analysis sample by baseline ECG-LVH and examining the associations of hypertension with CVD mortality by baseline ECG-LVH status. The same approach was done for ECG-LVH after stratifying the sample by hypertension status. Interaction p value was calculated as a formal test to estimate the significance of effect modification. In all approaches, models were initially unadjusted (model 1),

then adjusted for demographics (age, gender, race; model 2), and then finally adjusted further for diabetes, dyslipidemia, obesity, smoking, serum creatinine, use of insulin, use of lipid lowering medications (model 3).

In additional analysis, we examined the associations between different combinations of ECG-LVH and hypertension in subgroups of the participants stratified by age (using 65 years as a cutpoint), gender, race, diabetes, dyslipidemia, obesity, and smoking in models adjusted in a similar fashion to model 3 mentioned above. The purpose was to examine possible effect modification of these demographic and CVD risk factors on the associations between different combinations of ECG-LVH and hypertension with CVD mortality.

All analyses were done using SAS 9.3 (SAS Institute Inc., Cary, North Carolina). Statistical significance was determined as a 2-sided $p < 0.05$.

Results

This analysis included 6,105 participants (mean age 58.4 ±13.1 years; 54.2% women; 50.3% non-Hispanic whites). Hypertension was present in 40% (n = 2,464) of the participants, of whom 9.3% (n = 229) had ECG-LVH. ECG-LVH was present in 5.6% (n = 342), of whom 50.9% (n = 174) had hypertension. Participants with concomitant presence of hypertension and ECG-LVH were more likely to be women, and with higher values of SBP and CVP-index. In contrast, those without hypertension or ECG-LVH tended to be young, non-Hispanic white, never smokers, and had the least prevalence of diabetes, dyslipidemia, and obesity as well as the lowest values of SBP and CVP-index (Table 1).

The prevalence of ECG-LVH increased exponentially with higher levels of SBP. The ECG-LVH prevalence rates were 2.40%, 4.45%, 5.75%, 8.51%, and 14.38% in those with SBP levels of < 120 mm Hg, 120 to 129 mm Hg, 130 to 139 mm Hg, 140 to 159 mm Hg, and > 160 mm Hg, respectively; trend p value < 0.001. Also, the mean CVP-index increased with higher levels of SBP. The mean (standard deviation) of CVP-index in those with SBP < 120 mm Hg, 120 to 129 mm Hg, 130 to 139 mm Hg, 140 to 159 mm Hg, and > 160 mm Hg were 138.2 (47.4), 148.3 (52.2), 154.1 (54.4), 165.4 (54.4), and 179.9 (56.0) mV s, respectively, with p value for differences in mean < 0.001 (Figure 1). Pearson correlation coefficient (r) between CVP-index and SBP was 0.24 (0.30 in women and 0.21 in men); $p < 0.001$.

In multivariable logistic regression models, hypertension was associated with more than double the risk of ECG-LVH ($p < 0.001$). In similar models each 1-standard deviation increase in SBP (19 mm Hg) was associated with a 49% increased odds of ECG-LVH ($p < 0.001$; Table 2). Also, in separate multivariable linear regression models, hypertension and each 1-standard deviation increase in SBP were associated with 21.2 mV s ($p < 0.001$) and 11.4 mV s ($p < 0.001$) increase in CVP-index, respectively (Table 2).

During a median follow-up of 14.0 years, 733 CVD deaths occurred (incidence rate of 9.1 deaths per 1000-person years). The CVD mortality rate was highest in participants with concomitant ECG-LVH and hypertension (20.2 deaths per 1000-person years) followed by those with

Table 1
Baseline characteristics stratified by hypertension and ECG-LVH status

Characteristics*	No Hypertension (n = 3,641)		Hypertension (n = 2,464)		p value†
	No ECG-LVH (n = 3,528)	ECG-LVH (n = 113)	No ECG-LVH (n = 2,235)	ECG-LVH (n = 229)	
Age (y)	54.6 ± 12.0	56.7 ± 12.6	64.1 ± 12.7	63.8 ± 13.3	< .001
Women	1891 (53.6%)	56 (49.6%)	1209 (54.1%)	152 (66.4%)	< .001
Race					< .001
Non-Hispanic white	1762 (49.9%)	36 (31.9%)	1175 (52.6)	100 (43.7%)	
Non-Hispanic black	675 (19.1%)	27 (23.9%)	561 (25.1%)	73 (31.9%)	
Mexican-American	911 (25.8%)	47 (41.6%)	437 (19.6%)	46 (20.1%)	
Other	180 (5.1%)	3 (2.7%)	62 (2.8%)	10 (4.4%)	
Diabetes Mellitus	248 (7.0%)	22 (19.5%)	309 (13.8%)	41 (17.9%)	< .001
Dyslipidemia	768 (21.8%)	23 (20.4%)	581 (26.0%)	58 (25.3%)	.002
Smoking Status					< .001
Never	1533 (43.5%)	59 (52.2%)	1045 (46.8%)	130 (56.8%)	
Current	918 (26.0%)	20 (17.7%)	428 (19.2%)	32 (14.0%)	
Past	1077 (30.5%)	34 (30.1%)	762 (34.1%)	67 (29.3%)	
Obesity	590 (16.7%)	33 (29.2%)	480 (21.5%)	63 (27.5%)	< .001
Systolic blood pressure (mm Hg)	120.1 ± 10.7	124.3 ± 9.8	146.8 ± 16.6	152.8 ± 20.2	< .001
Cornell voltage product (mV s)	137.23 ± 44.6	269.3 ± 26.5	156.4 ± 46.1	277.2 ± 31.0	< .001
Serum creatinine	1.06 ± 0.35	1.05 ± 0.23	1.14 ± 0.36	1.12 ± 0.29	< .001
Use of antihypertensives	0 (0%)	0 (0%)	1107 (49.5%)	133 (58.1%)	< .001
Use of insulin	51 (1.5%)	9 (8.0%)	94 (4.2%)	12 (7.2%)	< .001

BP = Blood pressure; ECG-LVH = electrocardiographic left ventricular hypertrophy; Hypertension = BP ≥ 140 mm Hg systolic or 90 mm Hg diastolic or use of antihypertensives; Dyslipidemia = total cholesterol > 240 mg/dl or low-density lipoprotein (LDL) > 160 mg/dl or high-density lipoprotein (HDL) < 40 mg/dl or current use of cholesterol-lowering medication; Diabetes = fasting plasma glucose > 126 mg/dl, nonfasting plasma glucose > 200 mg/dl or current use of antidiabetic medications; Obesity = body mass index > 30 kg/m^2.

* Values expressed as mean ± SD or n (%).

† p value for ANOVA for continuous variables and chi-square for proportions.

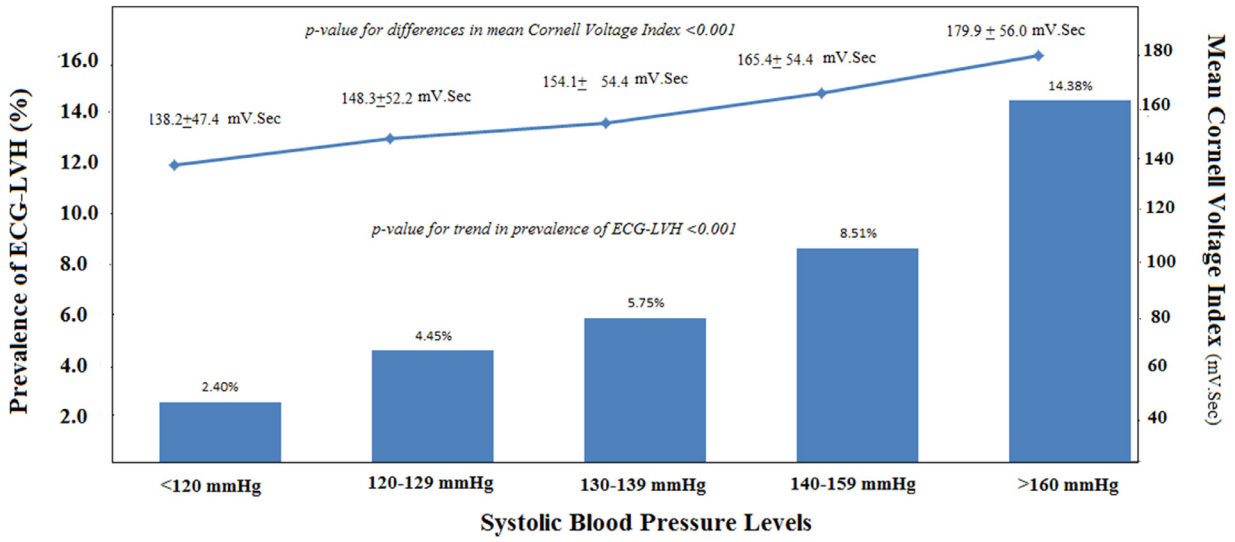


Figure 1. Prevalence of ECG-LVH and trend of mean Cornell voltage product across levels of blood pressure.

hypertension but no ECG-LVH (15.1 deaths per 1000-person years). In contrast, the mortality rate was similarly very low in those with isolated ECG-LVH (5.2 deaths per 1000-person years) and those in the reference group without hypertension or ECG-LVH (5.4 deaths per 1000-person years). Figure 2 shows the mortality rate per 1000-person years whereas Figure 3 shows Kaplan Meier Survival curves stratified by different combinations of ECG-LVH and hypertension (isolated hypertension, isolated ECG-LVH, concomitant ECG-LVH and hypertension, and no ECG-LVH or hypertension; Table 3).

Table 4 shows the results of Cox proportional hazard analysis where different combinations of ECG-LVH and hypertension were used in the models. As shown, compared with no ECG-LVH and no hypertension, concomitant presence of ECG-LVH and hypertension showed stronger association with CVD mortality than hypertension alone. In contrast, isolated ECG-LVH without hypertension was not associated with CVD mortality. These results were consistent in subgroup analyses stratified by gender, race/ethnicity, diabetes, dyslipidemia, obesity, and smoking status but differed by age where the associations were stronger in those younger than compared with those older than 65 years old (Figure 4).

Table 4 shows the risk of CVD mortality associated with each of ECG-LVH and hypertension using separate models. As shown, hypertension and ECG-LVH, entered separately in different sets of models, were associated with increased risk of CVD mortality, which remained significantly high in the multivariable adjusted models. More importantly, when ECG-LVH and hypertension were entered together in the same model and subsequently adjusted for on another, the risk of CVD mortality was essentially unchanged for hypertension after adjusting for ECG-LVH but markedly attenuated for ECG-LVH after adjusting for SBP.

There were signs of effect modification by hypertension status on the association between ECG-LVH with CVD mortality, although the interaction p value did not reach

Table 2
Associations between hypertension and levels of blood pressure with ECG-LVH and Cornell voltage product index

Associations between levels of blood pressure with Cornell voltage product index in linear regression models	Difference (95% confidence interval) mV s		
	Model 1*	Model 2†	Model 3‡
Difference in Cornell voltage product per 1-SD increase in SBP (19 mm Hg)	13.1 (11.8, 14.4)	13.1 (11.7, 14.6)	11.4 (9.9, 12.9)
Difference in Cornell voltage product in participants with vs without hypertension	26.2(23.5,28.9)	24.8 (22.0, 27.6)	21.2 (17.8, 24.7)
Associations between hypertension with ECG-LVH in logistic regression models	**Odds ratio (95% confidence interval)**		
	Model 1*	Model 2†	Model 3‡
Odds of ECG-LVH per 1-SD increase in systolic blood pressure (19 mm Hg)	1.78 (1.62, 1.96)	1.75 (1.57, 1.95)	1.49 (1.38, 1.61)
Odds of ECG-LVH in participants with vs without hypertension	3.12 (2.54, 4.03)	2.95 (2.30, 3.79)	2.45 (1.83, 3.30)

ECG-LVH = Electrocardiographic left ventricular hypertrophy.
* Model 1: unadjusted.
† Model 2: adjusted for age, gender, and race.
‡ Model 3, additional adjustment for diabetes, dyslipidemia, obesity, smoking, serum creatinine, use of insulin, use of lipid lowering medications, and use of blood pressure lowering medications.

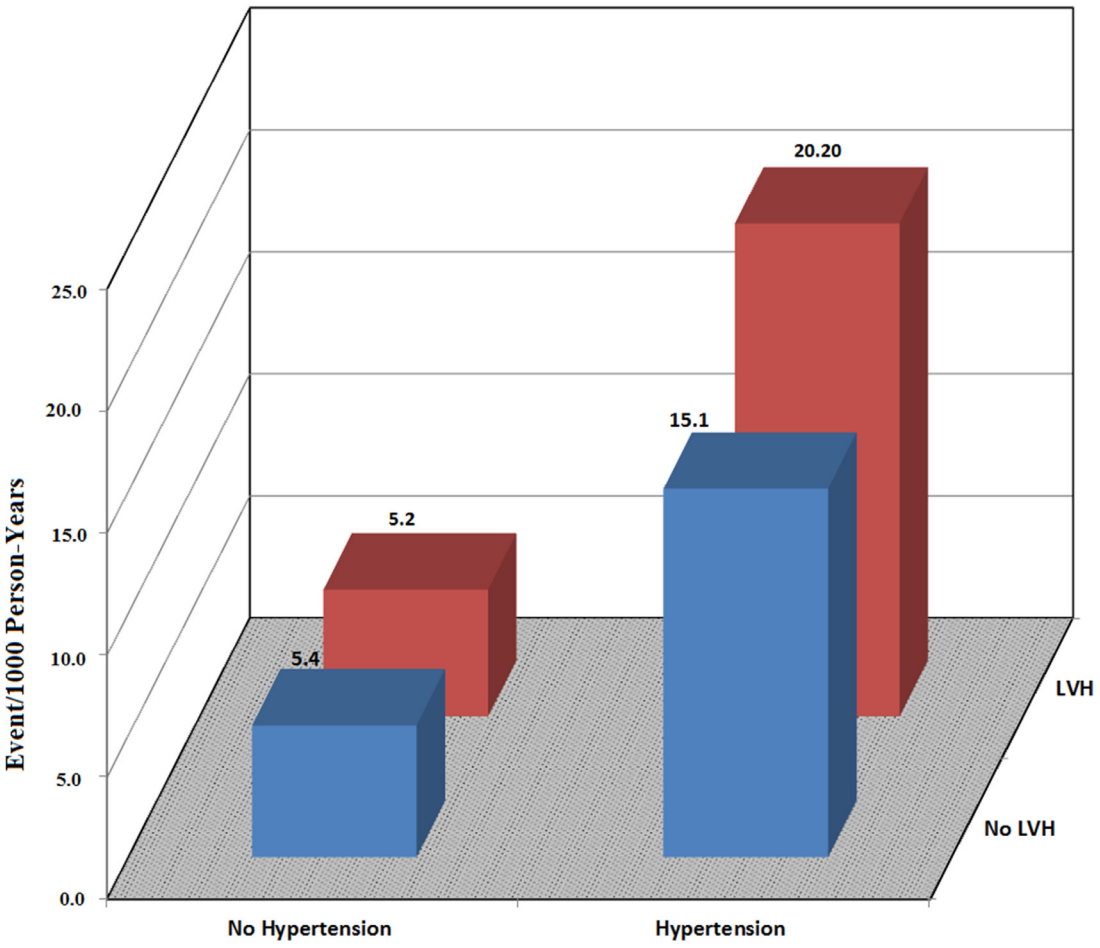
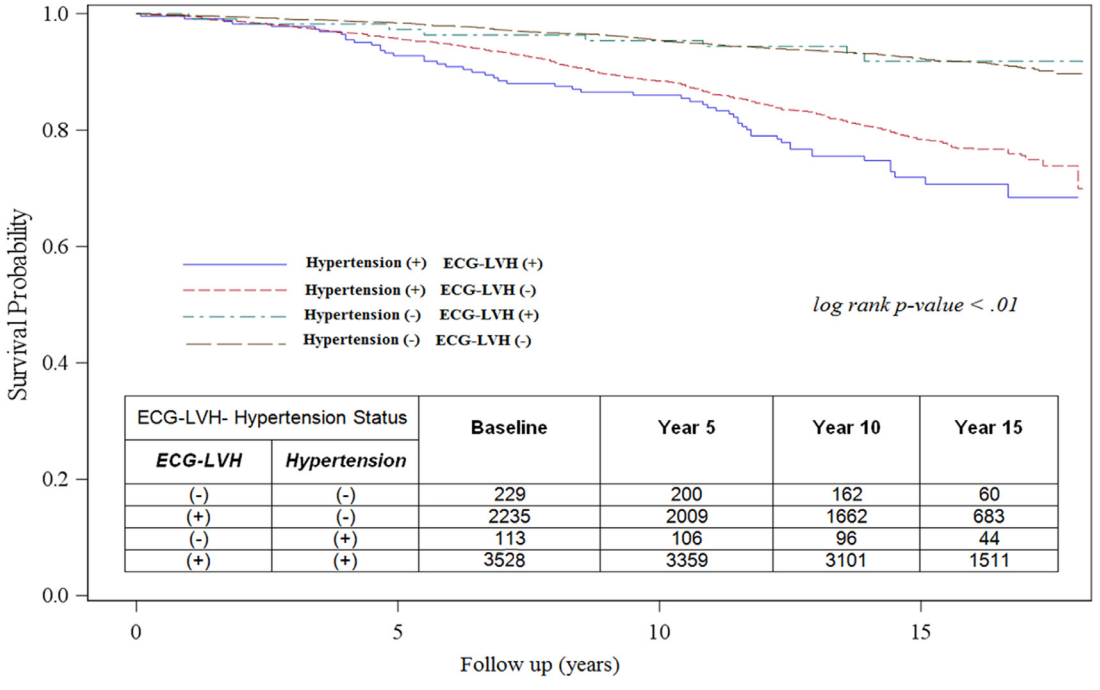


Figure 2. Cardiovascular mortality rates by presence of ECG-LVH and hypertension.



ECG-LVH- Hypertension Status		Baseline	Year 5	Year 10	Year 15
ECG-LVH	*Hypertension*				
(-)	(-)	229	200	162	60
(+)	(-)	2235	2009	1662	683
(-)	(+)	113	106	96	44
(+)	(+)	3528	3359	3101	1511

Figure 3. Kaplan-Meier event-free survival probability stratified by presence of ECG-LVH and hypertension.

Table 3
Concomitant presence of ECG-LVH and hypertension and risk of cardiovascular mortality

ECG-LVH-hypertension status					Hazard ratio (95% confidence interval)		
ECG-LVH	Hypertension	Participants n	Events n (%)	Event rate 1000-person year	Model 1*	Model 2†	Model 3‡
(−)	(−)	3528	259 (7.3%)	5.4	Reference	Reference	Reference
(+)	(−)	113	8 (7.1%)	5.2	0.97(0.48, 1.97)	0.84 (0.42, 1.70)	0.86 (0.43,1.75)
(−)	(+)	2235	411(18.4%)	15.1	2.91(2.49, 3.40)	1.36 (1.16, 1.60)	1.33 (1.13, 1.57)
(+)	(+)	229	55 (24.0%)	20.2	3.95 (2.95, 5.29)	2.04 (1.52, 2.74)	1.94 (1.43, 2.63)

ECG-LVH = Electrocardiographic left ventricular hypertrophy; (−) = absent; (+) = present.
* Model 1, unadjusted.
† Model 2, adjusted for age, gender, and race.
‡ Model 3, additional adjustment for diabetes, dyslipidemia, obesity, smoking, serum creatinine, use of insulin, use of lipid lowering medications.

statistical significance. ECG-LVH was associated with CVD mortality in those with hypertension (demographic and CVD adjusted hazard ratio [HR; 95% confidence interval {CI}] 1.47 [1.11, 1.96]), but not in those without hypertension (demographic and CVD adjusted HR [95% CI] 0.78 [0.39, 1.58]). In contrast, hypertension was associated with CVD mortality in those with and without baseline ECG-LVH (demographic and CVD adjusted HR [95% CI] 2.62 [1.22, 5.61] and 1.32 [1.12, 1.55, respectively]), but the association was stronger in those with ECG-LVH; interaction p value 0.13.

Discussion

The assumption that the associations of ECG-LVH with BP and cardiovascular outcomes are similar to those of imaging-LVH has been one of the reasons for using ECG-LVH in contemporary hypertension clinical trials.[10−16] However, there is no evidence from large studies to support this assumption, and the validity of this assumption is in question given the current thinking that ECG-LVH criteria do not have a straightforward relation with left ventricular mass.[18,19] Since our current understanding of the relation between BP and LVH and their associations with outcomes is based on studies that used imaging to assess LVH,[6−9] we extensively examined the interrelation between hypertension and ECG-LVH, and how their associations with CVD were impacted by this interrelation. Our analysis revealed several findings.

We found a strong association between higher levels of SBP and ECG-LVH. The patterns of associations of ECG-LVH with SBP in our study were similar to the reported relations between imaging-LVH and SBP. In our study, hypertension was associated with two and half the odds of ECG-LVH compared with those without hypertension, which is in agreement with previous studies in which LVH was ascertained by imaging.[6−9] We noticed a dose-response relation between SBP and ECG-LVH; the prevalence of ECG-LVH almost doubled as the levels of SBP increased in severity from normal BP to elevated BP to stage-1 hypertension to more severe hypertension according to the current hypertension guidelines.[20] A similar dose-response relation between SBP and the prevalence of ECG-LVH has been reported in the Framingham Heart study.[9] The correlation between SBP and CVP-index in our study is also similar to the correlation (r = 0.22 in men and 0.23 in women) between resting SBP and echocardiographic LV mass reported in the Framingham Heart Study[9] and several other studies.[21−24] The similarity between ECG-LVH and imaging-LVH in relation to SBP in these studies support the current practice of using ECG-LVH in studies examining the impact of resting casual BP on LVH. The feasibility of using ECG in clinical trials is another reason to continue this practice.

Our study also showed that SBP partially explains the associations of ECG-LVH with CVD mortality, but ECG-LVH virtually has no impact on the SBP associations. This suggests that LVH is probably only one of many factors by which SBP exerts its impact on CVD. Also, this may explain the recent results from the systolic blood pressure intervention trial which showed that the benefit of intensive BP lowering on the risk of CVD events was not meaningfully influenced by its favorable effect on ECG-LVH.[10]

Both ECG-LVH and SBP were associated with increased risk of CVD mortality when entered separately in different models. Further, compared with no ECG-LVH

Table 4
Impact of ECG-LVH and hypertension on each other's association with cardiovascular mortality

	Hazard ratio (95% confidence interval)		
	Model 1*	Model 2†	Model 3‡
Hypertension	3.01 (2.59, 3.50)	1.43 (1.22, 1.67)	1.39 (1.18, 1.62)
Hypertension with further adjustment for ECG-LVH	2.96 (2.54, 3.44)	1.41 (1.20, 1.65)	1.38 (1.17, 1.61)
ECG-LVH	1.70 (1.31, 2.20)	1.43 (1.10, 1.85)	1.39 (1.07, 1.81)
ECG-LVH with further adjustment for hypertension	1.29 (0.99, 1.67)	1.35 (1.04, 1.75)	1.33 (1.02, 1.73)

ECG-LVH = Electrocardiographic left ventricular hypertrophy.
* Model 1, unadjusted.
† Model 2, adjusted for age, gender, and race.
‡ Model 3, further adjustment for diabetes, dyslipidemia, obesity, smoking, serum creatinine, use of insulin, use of lipid lowering medications.

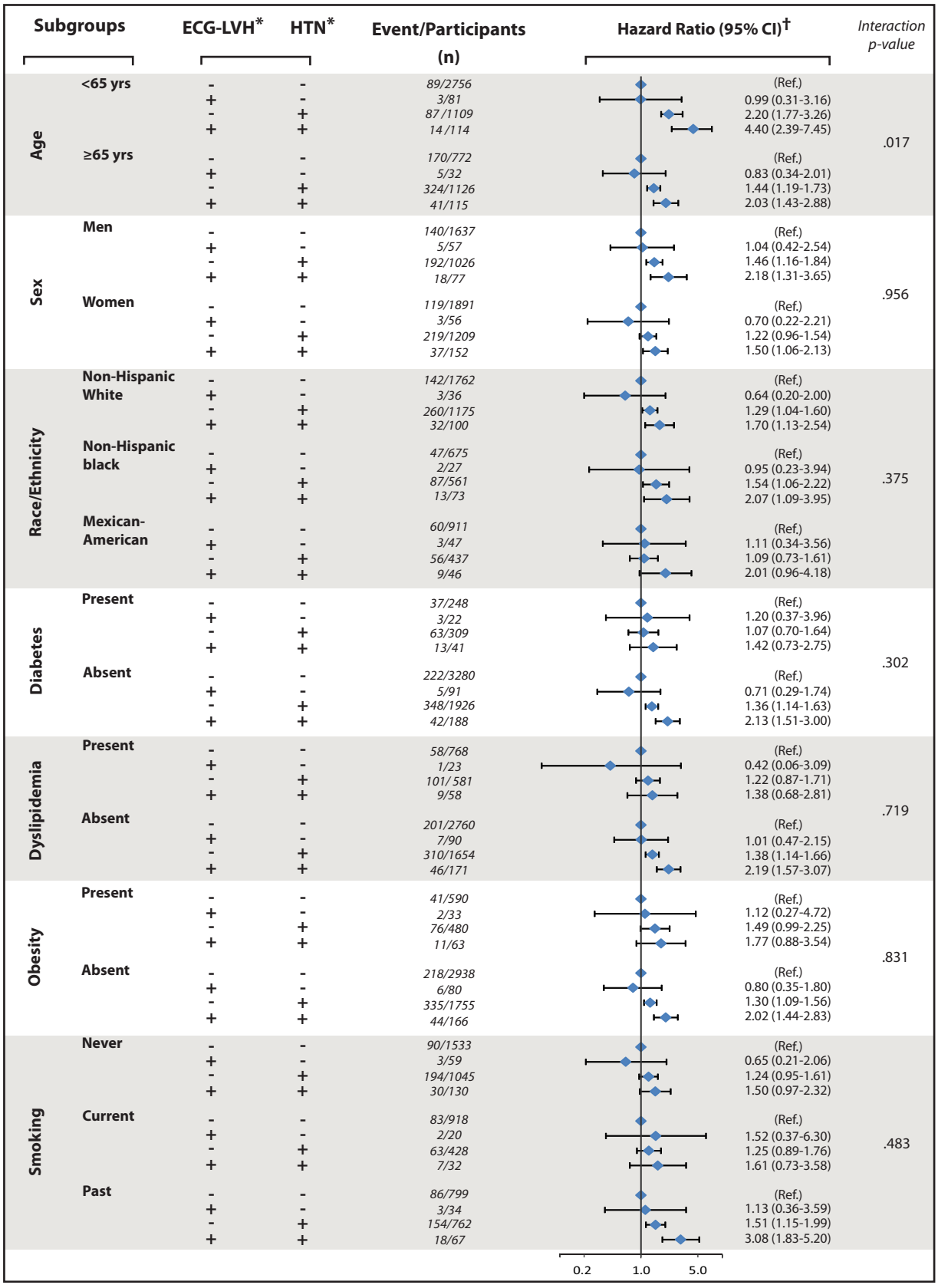


Figure 4. Concomitant presence of ECG-LVH and hypertension and cardiovascular mortality risk in subgroups. *(−) = absent (+) = present; ECG-LVH = electrocardiographic left ventricular hypertrophy by Cornell voltage product † model adjusted for age, gender race diabetes, dyslipidemia, obesity, and smoking.

and no hypertension, concomitant presence of ECG-LVH and hypertension showed stronger association with CVD mortality than hypertension alone. This suggests ECG-LVH provides added independent predictive information to SBP. This finding agrees with previous reports showing the independent usefulness of SBP and LVH as predictors of CVD outcomes.[1−5] Presence of ECG-LVH in those with hypertension may indicate severity, and hence an increased risk of CVD mortality. Notably, the risk of CVD mortality in those with ECG-LVH without hypertension was not different from those without ECG-LVH or hypertension. True positive ECG-LVH has shown to be a stronger predictor of CVD outcomes, and hence these findings suggest that ECG-LVH in those without hypertension in our study is more likely to be falsely positive. Using ECG to screen those at high risk instead of the general population is believed to improve the predictive ability of ECG.[25] In this context, ECG-LVH is expected to be a better predictor of outcomes in those with hypertension than in those without, as we observed. Noteworthy, however, echocardiographic-LVH is not uncommon in patients with normal SBP, and LVH could be developed as a physiologic adaptation in athletes.[26,27] Therefore, although LVH is the most common complication of hypertension, the latter is not the only etiology for LVH. This was the reason we included participants with and without hypertension.

We observed effect modification by age in the associations between different combinations of ECG-LVH and hypertension with CVD mortality where the associations were stronger in those younger than 65 years old. Since we adjusted for several potential risk factors, it is unlikely that differences in risk profile are the reason, and further research is needed to explain these differences by age.

Despite the known low-sensitivity of ECG to detect LVH, its usefulness as a predictor of CVD outcomes is well established,[17] which is independent from the presence of LVH detected by imaging.[28] The established prognostic usefulness beyond anatomy, simplicity, and low cost of ECG are reasons for the wide use for the use of ECG-LVH in both research and clinical settings. Nevertheless, myocardial remodeling that occurs with LVH is a complex process that cannot be captured by a single cardiac investigation method. Although ECG can capture the electrical phenomenon that accompany myocardial remodeling and hence could monitor the disease process, there are other important pathophysiologic dynamics that cannot be observed by ECG. For example, ECG cannot quantify myocardial fibrosis. Myocardial fibrosis can occur independent of cardiomyocyte hypertrophy and has been associated with adverse outcomes.[29] Therefore, for better understanding of the mechanistic relation between BP and LVH, assessment of LVH by more than 1 cardiac investigation method may be needed.

Our study has some limitations. We did not use the most recent 2017 definitions of hypertension.[20] Instead, we used the traditional definition of SBP/DBP $\geq$140/90 mm Hg or use of BP medications in order to facilitate the comparison of our results to previous studied using similar hypertension definition. However, we provided results for SBP as a continuous variable using SBP value ranges that enable interpreting the results in the context of the definition of hypertension according to the new high blood pressure guidelines. We decided to use Cornell voltage product to define LVH because of its common use and simple calculation that incorporates gender-specific cutoff points and QRS duration. Also, Cornell voltage product has shown good diagnostic performance in multiethnic settings compared with other LVH criteria as well as its high prognostic significance as a predictor for CVD events. Further, the current recommendations for the use of ECG criteria for detection of cardiac chamber enlargement[30] do not favor or recommend 1 set of LVH criteria over the other (i.e., any LVH criteria could be used as long as the criteria are specifically named). Another limitation is that in the Cox models we used LVH and SBP at 1 time point and not as time-updated variables. Despite these limitations, our report provides a comprehensive analysis of the interrelation in SBP, ECG-LVH, and CVD mortality. This study builds on the strengths of the NHANES-III survey including its large sample size, and community-based racially diverse population with well-ascertained outcomes.

Disclosures

The investigators have no conflicts of interest to disclose.

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