Determinants and Prognostic Significance of Electrocardiographic Left Ventricular Hypertrophy Criteria in Chronic Kidney Disease

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Summary

Background and objectives The diagnosis of left ventricular hypertrophy (LVH) has prognostic value in the general population. However, among those with chronic kidney disease (CKD), the determinants of electrocardiographic (EKG) LVH and its prognostic value are not clear.

Design, setting, participants, & measurements A cross-sectional study was performed among 387 consenting consecutive patients from a veterans hospital with a longitudinal follow-up.

Results The overall prevalence of EKG-LVH by the Sokolow–Lyon criteria was 8% and by the Cornell voltage-duration product was 11%. Compared with non-CKD controls, CKD patients had unadjusted odds ratio (OR) for LVH by Cornell criteria of 2.52 (95% CI 1.18 to 5.42). Significance was lost after adjustment. The unadjusted OR for LVH by Sokolow–Lyon criteria was 2.24 (95% CI 0.95 to 5.33). This OR remained statistically insignificant after multivariate adjustment. Anemia, proteinuria, and 24-hour ambulatory systolic BP were associated with EKG-LVH regardless of diagnostic criteria. After a 7.5-year median follow-up, the hazard ratio for all-cause mortality was not associated with EKG-LVH diagnosed by the Sokolow–Lyon criteria; however, multivariable adjustments made EKG-LVH significant. A statistically significant relationship was seen between mortality and Cornell criteria; however, multivariable adjustments made EKG-LVH nonsignificant.

Conclusions The Sokolow–Lyon and Cornell EKG-LVH criteria cannot be used interchangeably to diagnose LVH or determine prognosis. Among those with CKD, ambulatory systolic BP predicts all-cause mortality. Moreover, the duration and severity of BP elevation presumably reflected in EKG-LVH diagnosed by Sokolow–Lyon criteria is also of prognostic significance; the Cornell criteria do not carry independent prognostic information.

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Introduction

Electrocardiography can identify the presence of left ventricular hypertrophy (LVH). LVH has prognostic significance in the general population as has been demonstrated by numerous studies (1,2). In recent years, compared with electrocardiography, several imaging modalities such as two-dimensional echocardiography, three-dimensional echocardiography, computerized tomography, and magnetic resonance imaging have been used to provide a more accurate assessment of myocardial mass. However, electrocardiograms are more convenient and less costly compared with the imaging modalities. Furthermore, regression of electrocardiographic (EKG) LVH is associated with reduction in adverse cardiovascular outcomes (3,4). Therefore, the EKG-LVH remains of value for the diagnosis and follow-up of target organ damage among patients with hypertension.

People who have chronic kidney disease (CKD) and those who are older are more likely to have LVH. However, among patients with CKD, the prevalence of EKG-LVH, its determinants, and its prognostic value have been inadequately studied. Given the important role of EKG in detecting LVH among patients without CKD, the role of this simple procedure needs to be examined among patients with CKD.

Accordingly, the objective of this study was to ascertain the prevalence, determinants, and prognostic value of LVH among patients with CKD. As a comparison, we used a control group of patients without CKD to answer the question whether the increased prevalence of LVH in those with CKD is mediated by hypertension or whether it occurs independent of hypertension. We also compared two commonly used EKG criteria for LVH to ascertain their prognostic significance.

Materials and Methods

Study Cohort

In this prospective cohort study, consecutive consenting patients ($n = 423$) were recruited from the renal clinic and a general medicine clinic of the Richard L. Roudebush Veterans Affairs (VA) Medical Center in Indianapolis. Patients were excluded for body mass index (BMI) >40 kg/m^2, acute renal failure, receiving renal replacement therapy or having stage 5 CKD, atrial fibrillation, or change in their antihypertensive drugs within 2 weeks of study enrollment. CKD was defined as presence of proteinuria on a spot urine specimen when the protein/creatinine ratio was ≥0.22 g/g or estimated GFR (eGFR) was <60 ml/min per 1.73 m^2 by the four-component Modification of Diet in Renal Disease formula: $186 \times creatinine^{-0.154} \times age^{-0.203} \times 0.74$ (if female) and $\times$ 1.21 (if black) (5). Serum creatinine was not calibrated to the Cleveland Clinic. A urine protein/creatinine ratio of >0.22 g/g correlates with a urine protein excretion of >300 mg/d, the standard definition of clinical proteinuria (6). Accordingly, we selected this threshold of urine protein/creatinine ratio to reflect CKD. The ascertainment of other diagnoses and determinations has been previously reported (7).

The Institutional Review Board of Indiana University and the Research and Development Committee of the Veterans Affairs Medical Center approved this study. All patients gave their written, informed consent.

EKG Measurements

Resting 12-lead electrocardiograms were performed in each patient using a standard 12-lead electrocardiogram. Two independent technicians measured the voltages. Discrepancies of >2 mm were resolved by a third reader. QRS duration was taken as that directly measured by the EKG machine. The product of QRS duration times the Cornell voltage combination (RaVL + SV3, with 6 mm added in women) ≥2440 mm/ms was used to identify LVH (8). The Sokolow–Lyon criteria were also used (RV5/6 + SV1 ≥ 35 mm) to diagnose EKG-LVH (9).

Ascertainment of Mortality

The ascertainment of death was established using the computerized VA electronic medical record system; the exact date was recorded. The last date of visit to any VA facility was used to determine the last date of follow-up. When patients were not seen at a VA facility in the prior 6 months, the social security death index was checked for mortality. Finally, the Renal Network, which keeps accurate records of all dialysis patients in the region, was contacted to assess vital status in those patients who were on dialysis but had not been seen recently (within 6 months) within the VA system.

Statistical Analyses

Data were first plotted to evaluate for any outliers and to examine distributions. The prevalence of EKG-LVH by Cornel voltage-duration product and Sokolow–Lyon criteria were analyzed separately. To ascertain the association of LVH in those with and without CKD, we used logistic regression. The model was adjusted for the following variables known to be determinants of LVH in the general population: age, sex, race, EKG evidence for myocardial infarction, and diabetes mellitus. We call this model the multivariate adjusted model. Finally, we added 24-hour ambulatory systolic BP to the multivariate adjusted model. To examine the association of eGFR with EKG-LVH, we fitted a similar logistic model with 1 SD change in eGFR as the independent variable. Adjusted models were created as above. Next, to examine the independent association of 24-hour systolic BP with EKG-LVH, we used an unadjusted logistic model. We calculated the odds ratio (OR) per 1 SD change in ambulatory systolic BP. This unadjusted model was adjusted for the following variables: age, sex, race, myocardial infarction, and diabetes mellitus. Finally, we added presence or absence of CKD to the model.

To derive independent determinants of EKG-LVH from our data set, we performed the best possible subset regression. From among eight variables found to be associated with EKG-LVH in our population (age, race, weight, eGFR, log of urine protein/creatinine, hemoglobin, systolic 24-hour ambulatory BP, and number of BP medications), we selected the best four by selecting all permutations and combinations. Those variables that resulted in the lowest log likelihood function of the logistic model were deemed best (10).

Survival analyses were performed using the Cox model with the outcome of all-cause mortality. The proportionality assumption was tested by interacting the predictors with time and testing the model fit of the nested model by the likelihood ratio test and by analyzing the Schoenfeld residuals (11). No evidence for nonproportionality of hazards was found. To test the comparative value of the two EKG-LVH criteria, we created three models: one with both criteria (combination model), one with Cornell criteria, and one with Sokolow–Lyon criteria. We compared the combination model with the Cornell criteria and the combination model with the Sokolow–Lyon criteria with the likelihood ratio test.

All analyses were performed using Stata 11.0 (Stata Corporation, College Station, TX). P values are two sided and significance was set at 0.05.

Results

Between October 2000 and June 2002, 423 consecutive patients were recruited into the study and were followed up until July 2010. Thirty-six patients were excluded for the following reasons: 12 were excluded for lack of an EKG, 10 were excluded for lack of information on urine protein or GFR, and 14 were excluded for EKGs with insufficient information to compute LVH.

Table 1 shows the baseline characteristics of the remaining 387 patients. Approximately 37% of the patients had no CKD. Compared with patients without CKD, those with CKD were older and were more often male, black, diabetic, and smokers. They had lower hemoglobin and total cholesterol and had higher BP despite taking nearly twice the number of antihypertensive medications. Statin and aspirin use was higher and coronary and peripheral revascularization rates were more frequent. The prevalence of EKG-LVH (Cornell criteria) was more frequent in those with CKD. However, the prevalence of EKG-LVH by Sokolow–Lyon criteria was only marginally different between groups.

Table 2 shows the baseline characteristics by EKG-LVH criteria. Overall, 44 (11%) of the patients had LVH by

Table 1. Clinical characteristics of the study sample by presence or absence of CKD

Clinical Characteristic	No CKD	CKD	Overall	*P*
n	144 (37%)	243 (63%)	387 (100%)	
Age (years)	58.4 ± 12.9	67.1 ± 11.5	63.9 ± 12.8	<0.0001
Men	131 (91%)	237 (98%)	368 (95%)	<0.0001
Race				<0.0001
white	128 (89%)	152 (63%)	280 (72%)	
black	15 (10%)	86 (35%)	101 (26%)	
other	1 (1%)	5 (2%)	6 (2%)	
Weight (kg)	94.5 ± 23.1	93.6 ± 21.7	93.9 ± 22.2	0.7
Height (in.)	69.7 ± 3.1	69.1 ± 3.0	69.4 ± 3.0	0.07
BMI (kg/m^2)	30.1 ± 6.6	30.2 ± 6.1	30.1 ± 6.3	0.8
Diabetes mellitus	33 (23%)	108 (44%)	141 (36%)	<0.0001
Current smoker	58 (40%)	144 (59%)	202 (52%)	<0.0001
eGFR (ml/min per 1.73 m^2)	81.1 ± 14.6	34.5 ± 14.0	51.8 ± 26.7	<0.0001
Spot urine protein/creatinine ratio (g/g)	0.2 ± 0.4	1.1 ± 2.0	0.8 ± 1.7	<0.0001
Albumin (g/dl)	3.8 ± 0.4	3.8 ± 0.4	3.8 ± 0.4	0.9
Hemoglobin (g/dl)	14.4 ± 1.5	13.0 ± 1.8	13.5 ± 1.8	<0.0001
Cholesterol (g/dl)	194.9 ± 39.8	181.1 ± 35.7	186.0 ± 37.7	<0.01
Seated clinic systolic BP (mmHg)	137.9 ± 18.4	148.7 ± 22.4	144.6 ± 21.6	<0.0001
Seated clinic diastolic BP (mmHg)	82.5 ± 10.8	82.0 ± 12.7	82.2 ± 12.1	0.7
Seated clinic heart rate (bpm)	74.7 ± 12.4	70.2 ± 12.6	71.9 ± 12.7	<0.001
24-hour ambulatory systolic BP (mmHg)	127.9 ± 13.0	135.7 ± 17.0	132.7 ± 16.0	<0.0001
24-hour ambulatory diastolic BP (mmHg)	74.5 ± 8.6	73.9 ± 10.8	74.2 ± 10.0	0.6
24-hour ambulatory heart rate (bpm)	74.4 ± 11.2	70.0 ± 11.0	71.7 ± 11.3	<0.001
Number of antihypertensives drugs	1.5 ± 1.4	2.8 ± 1.5	2.3 ± 1.6	<0.0001
Nature of antihypertensive agent				
thiazide diuretics	36 (25%)	65 (27%)	101 (26%)	0.7
loop diuretics	18 (13%)	112 (46%)	130 (34%)	<0.0001
dihydropyridine CCBs	20 (14%)	85 (35%)	105 (27%)	<0.0001
nondihydropyridine CCBs	13 (9%)	23 (9%)	36 (9%)	0.9
beta-blockers	41 (28%)	113 (47%)	154 (40%)	<0.0001
alpha-blockers	22 (15%)	78 (32%)	100 (26%)	<0.0001
centrally acting agents	4 (3%)	27 (11%)	31 (8%)	<0.0001
vasodilators	1 (1%)	10 (4%)	11 (3%)	0.05
ACE inhibitors	59 (41%)	124 (51%)	183 (47%)	0.06
ARBs	9 (6%)	47 (19%)	56 (14%)	<0.0001
Statin use	47 (33%)	145 (60%)	192 (50%)	<0.0001
Aspirin use	56 (39%)	133 (55%)	189 (49%)	<0.0001
Myocardial infarction	28 (19%)	63 (26%)	91 (24%)	0.2
Coronary artery bypass surgery	11 (8%)	40 (16%)	51 (13%)	<0.01
Percutaneous coronary revascularization	15 (10%)	47 (19%)	62 (16%)	0.02
Stroke	19 (13%)	35 (14%)	54 (14%)	0.7
Peripheral vascular bypass	1 (1%)	18 (7%)	19 (5%)	<0.0001
Cornell voltage-duration product	1405.1 ± 727.9	1645.0 ± 865.4	1555.7 ± 824.2	<0.01
Cornell voltage LVH	9 (6%)	35 (14%)	44 (11%)	<0.01
Sokolow–Lyon voltage	21.3 ± 7.9	21.4 ± 10.3	21.4 ± 9.5	0.9
Sokolow–Lyon voltage LVH	7 (5%)	25 (10%)	32 (8%)	0.06

± indicates SD. Parentheses have percent of patients. Continuous variables tested by ANOVA and discrete variables tested by χ^2 test. CCB, calcium-channel blockers; ACE, angiotensin converting enzyme; ARBs, angiotensin receptor blockers.

Cornell criteria and 32 (8%) had LVH by Sokolow–Lyon criteria. The prevalence of EKG-LVH (Cornell criteria) was similar in patients with moderate (30 to 59 ml/min per 1.73 m^2) (12.9%) and severe (15 to 29 ml/min per 1.73 m^2) (13.7%) reductions in GFR compared with those with higher GFR without proteinuria (no CKD) (6.3%, $P = 0.101$ for differences between groups).

Significant differences between the presence and absence of LVH by Cornell criteria were seen for the following clinical characteristics: age, eGFR, CKD, systolic BP (clinic and ambulatory), ambulatory diastolic BP, number of antihypertensive medications, and for certain classes of drugs (nondihydropyridine calcium-channel blockers, beta-blockers, central agents, angiotensin converting enzyme inhibitors, statins, and aspirin) and for strokes. Significant differences between the presence and absence of LVH by Sokolow–Lyon criteria were seen for the following clinical characteristics: race, weight, eGFR, urine protein/creatinine ratio, hemoglobin, systolic BP (clinic and ambulatory), and clinic diastolic BP.

Figure 1A shows the OR for EKG-LVH for Cornell criteria with CKD. Unadjusted, the OR was 2.52 (95% confidence interval [CI] 1.18 to 5.42, $P = 0.02$). After multivar-

Table 2. Clinical characteristics of the study sample by presence or absence of EKG-LVH

Clinical Characteristic	Cornell LVH Negative	Cornell LVH Positive	*P*	Sokolow–Lyon LVH Negative	Sokolow–Lyon LVH Positive	*P*
n	343 (89%)	44 (11%)		355 (92%)	32 (8%)	
Age (years)	63.4 ± 12.8	67.6 ± 11.4	0.04	64.1 ± 12.6	61.1 ± 14.6	0.2
Men	327 (95%)	41 (93%)	0.5	339 (95%)	29 (91%)	0.2
Race			0.4			<0.0001
white	251 (73%)	29 (66%)		268 (75%)	12 (38%)	
black	86 (25%)	15 (34%)		81 (23%)	20 (63%)	
other	3 (1%)	0 (0%)		3 (1%)	0 (0%)	
Weight (kg)	94.6 ± 22.9	89.0 ± 15.3	0.1	94.7 ± 22.5	85.6 ± 17.5	0.03
Height (in.)	69.4 ± 3.1	68.8 ± 2.9	0.2	69.4 ± 3.0	68.4 ± 3.0	0.07
BMI (kg/m^2)	30.3 ± 6.5	28.8 ± 4.2	0.1	30.3 ± 6.4	28.3 ± 5.4	0.08
Diabetes mellitus	121 (35%)	20 (45%)	0.2	128 (36%)	13 (41%)	0.6
Current smoker	95 (28%)	10 (23%)	0.7	96 (27%)	9 (28%)	0.9
eGFR (ml/min per 1.73 m^2)	53.2 ± 26.7	41.4 ± 24.0	<0.01	52.6 ± 26.9	42.6 ± 22.3	0.04
Spot urine protein/ creatinine ratio (g/g)	0.7 ± 1.7	1.2 ± 1.9	0.1	0.7 ± 1.4	2.2 ± 3.8	<0.0001
CKD	208 (61%)	35 (80%)	<0.01	218 (61%)	25 (78%)	0.06
Albumin (g/dl)	3.8 ± 0.4	3.8 ± 0.3	1	3.8 ± 0.4	3.8 ± 0.5	0.5
Hemoglobin (g/dl)	13.6 ± 1.8	13.1 ± 2.1	0.1	13.6 ± 1.8	12.8 ± 2.2	0.02
Cholesterol (g/dl)	186.8 ± 38.3	179.5 ± 32.4	0.3	185.7 ± 37.8	189.1 ± 37.1	0.7
Seated clinic BP (mmHg)	143.4 ± 21.4/ 81.9 ± 11.9	154.3 ± 21.3/ 83.9 ± 13.4	<0.01/0.3	143.7 ± 21.0/ 81.8 ± 11.9	155.3 ± 25.8/ 86.2 ± 13.5	<0.01/0.05
Seated clinic heart rate (bpm)	72.1 ± 12.9	69.9 ± 10.9	0.3	72.0 ± 12.8	69.7 ± 10.8	0.3
24-hour ambulatory BP (mmHg)	131.4 ± 14.9/ 73.8 ± 9.8	142.3 ± 20.6/ 77.2 ± 11.0	<0.0001/0.05	132.7 ± 16.0/ 74.2 ± 10.0	144.3 ± 19.2/ 77.0 ± 14.4	<0.001/0.2
24-hour ambulatory heart rate (bpm)	71.7 ± 11.3	71.2 ± 11.2	0.8	71.7 ± 11.4	71.4 ± 9.7	0.9
Number of antihypertensives drugs	2.3 ± 1.6	3.0 ± 1.3	<0.01	2.3 ± 1.6	2.6 ± 1.6	0.3
Nature of antihypertensive agent						
thiazide diuretics	89 (26%)	12 (27%)	0.9	92 (26%)	9 (28%)	0.8
loop diuretics	112 (33%)	18 (41%)	0.3	118 (33%)	12 (38%)	0.6
dihydropyridine CCBs	94 (27%)	11 (25%)	0.7	94 (26%)	11 (34%)	0.3
nondihydropyridine CCBs	28 (8%)	8 (18%)	0.03	34 (10%)	2 (6%)	0.5
beta-blockers	130 (38%)	24 (55%)	0.03	138 (39%)	16 (50%)	0.2
alpha-blockers	88 (26%)	12 (27%)	0.8	94 (26%)	6 (19%)	0.3
centrally acting agents	24 (7%)	7 (16%)	0.04	27 (8%)	4 (13%)	0.3
vasodilators	9 (3%)	2 (5%)	0.5	11 (3%)	0 (0%)	0.3
ACE inhibitors	156 (45%)	27 (61%)	0.05	164 (46%)	19 (59%)	0.2
ARBs	47 (14%)	9 (20%)	0.2	51 (14%)	5 (16%)	0.9
Statin use	163 (48%)	29 (66%)	0.02	176 (50%)	16 (50%)	1
Aspirin use	160 (47%)	29 (66%)	0.02	176 (50%)	13 (41%)	0.3
Myocardial infarction	78 (23%)	13 (30%)	0.3	84 (24%)	7 (22%)	0.8
Coronary artery bypass surgery	42 (12%)	9 (20%)	0.1	47 (13%)	4 (13%)	0.9
Percutaneous coronary revascularization	51 (15%)	11 (25%)	0.08	58 (16%)	4 (13%)	0.6
Stroke	43 (13%)	11 (25%)	0.02	48 (14%)	6 (19%)	0.4
Peripheral vascular bypass				18 (5%)	1 (3%)	0.6
Cornell voltage-duration product	1333.7 ± 492.9	3286.7 ± 840.6	<0.0001	1503.0 ± 762.8	2140.3 ± 1195.5	<0.0001
Cornell voltage LVH				32 (9%)	12 (38%)	<0.0001
Sokolow–Lyon voltage	20.5 ± 9.0	28.4 ± 10.4	<0.0001	19.6 ± 7.4	41.7 ± 5.7	<0.0001
Sokolow–Lyon voltage LVH	20 (6%)	12 (27%)	<0.0001			

± indicates SD. Parentheses have percent of patients. Continuous variables tested by ANOVA, discrete variables tested by χ^2 test.

iate adjustment, the OR was reduced to 1.87 (95% CI 0.78 to 4.48, $P = 0.2$), and after adjustment of 24-hour ambulatory systolic BP it was further reduced to 1.54 (95% CI 0.57 to 4.17, $P = 0.4$). Figure 1A (bottom panel) shows the OR for EKG-LVH for Sokolow–Lyon criteria with CKD. Unadjusted, the OR was 2.24 (95% CI 0.95 to 5.33, $P = 0.07$). After multivariate adjustment, the OR was reduced to 1.74 (95% CI 0.61 to 4.98, $P = 0.3$), but after adjustment of 24-hour ambulatory systolic BP it was increased to 2.42 (95% CI 0.53 to 11.08, $P = 0.3$).

Compared with patients without CKD (GFR ≥ 60 ml/min per 1.73 m^2) and no proteinuria, those with a severe

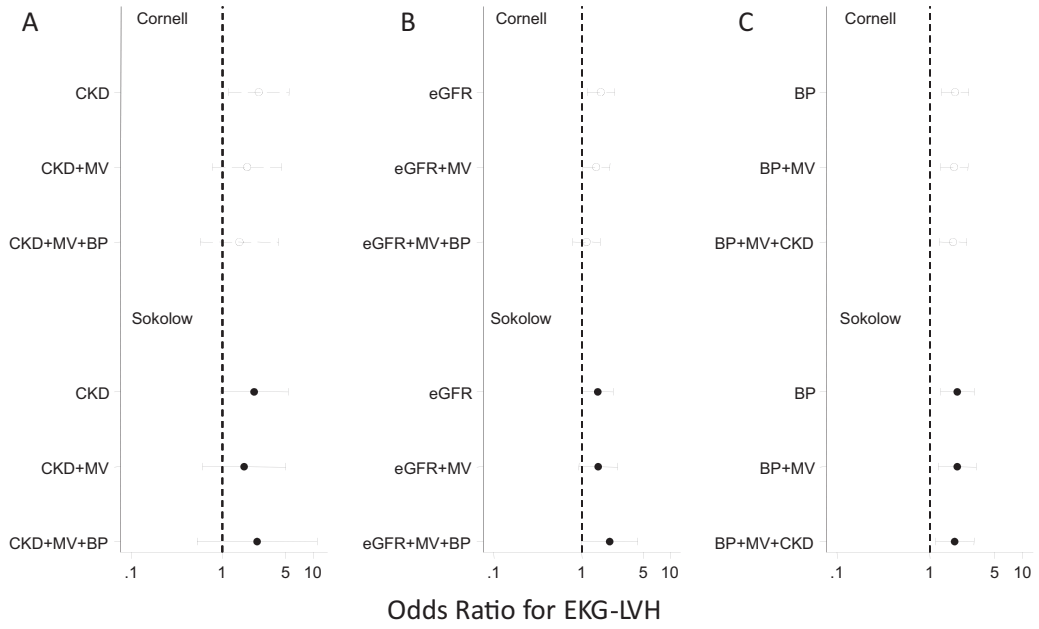

Figure 1. | **OR for EKG-LVH.** The top panels show the OR for Cornell criteria (dotted line, ○) and the bottom panels show the OR for Sokolow–Lyon criteria for LVH (solid line, ●). (A) ORs for presence of CKD unadjusted, multivariate adjusted (CKD + MV), or multivariate adjusted and further adjusted for ambulatory systolic BP (CKD + MV + BP). (B) ORs for 1 SD change in eGFR (26.7 ml/min per 1.73 m^2) unadjusted (eGFR),? multivariate adjusted (eGFR + MV), or multivariate adjusted and further adjusted for ambulatory systolic BP (eGFR + MV + BP). (C) ORs for 1 SD change in 24-hour ambulatory systolic BP (14.9 mmHg) unadjusted (BP), multivariate adjusted (BP + MV), or multivariate adjusted and further adjusted for CKD (BP + MV + CKD).

reduction in GFR (<30 ml/min per 1.73 m^2) had a >2-fold increase (OR, 2.3; $P = 0.06$) in the prevalence of ECG-LVH (Cornell criteria), although marginally significant. Compared with those without CKD, patients with a moderate reduction in GFR (30 to 59 ml/min per 1.73 m^2) also had a marginally significant increased risk (OR, 2.21; $P = 0.07$) for Cornell EKG-LVH. However, after multivariate adjustment, these differences vanished (OR for severe eGFR reduction 1.57, $P = 0.4$; for moderate eGFR reduction 1.72, $P = 0.3$).

To better understand the relationship of eGFR with EKG-LVH, we directly explored the relationship of these two variables. Figure 1B shows the OR for EKG-LVH by Cornell criteria for 1 SD change in eGFR. Unadjusted, the OR was 1.64 (95% CI 1.14 to 2.35, $P = 0.007$). After multivariate adjustment, the OR was reduced to 1.44 (95% CI 0.95 to 2.20, $P = 0.08$), and after adjustment of 24-hour ambulatory systolic BP it was further reduced to 1.12 (95% CI 0.69 to 1.82, $P = 0.6$). Figure 1B (bottom panel) shows the OR for EKG-LVH by Sokolow–Lyon criteria for 1 SD change in eGFR. Unadjusted, the OR was 1.51 (95% CI 1.01 to 2.27, $P = 0.04$). After multivariate adjustment, the OR was unchanged at 1.52 (95% CI 0.92 to 2.53, $P = 0.1$), and after adjustment of 24-hour ambulatory systolic BP it increased to 2.07 (95% CI 0.99 to 4.31, $P = 0.052$).

Figure 1C shows the OR for 24-hour ambulatory systolic BP with EKG-LVH for Cornell criteria. Unadjusted, the OR for 1 SD change in ambulatory systolic BP was 1.87 (95% CI 1.34 to 2.62, $P < 0.001$). After multivariate adjustment, the OR was 1.83 (95% CI 1.28 to 2.62, $P = 0.001$), and after adjustment of CKD it was 1.78 (95% CI 1.24 to 2.56, $P = 0.002$). Figure 1C (bottom panel) shows the OR for 24-hour ambulatory systolic BP with EKG-LVH for Sokolow–Lyon criteria. Unadjusted, the OR for 1 SD change in ambulatory systolic BP was 1.97 (95% CI 1.30 to 3.00, $P = 0.001$). After multivariate adjustment, the OR was 1.97 (95% CI 1.23 to 3.15, $P = 0.005$), and after adjustment of CKD it was 1.85 (95% CI 1.15 to 2.98, $P = 0.01$).

The ORs for the best four determinants of EKG-LVH are shown in Table 3. Both criteria identified 24-hour ambulatory systolic BP, hemoglobin, and proteinuria as determinants of EKG-LVH. However, the Sokolow–Lyon criteria identified more blacks, whereas Cornell criteria identified thinner individuals.

The median duration of follow-up was 7.5 years. One hundred and sixty-one (42%) patients died over 2532 years of cumulative follow-up, yielding a crude mortality rate of 6.36/100 patient-years. Figure 2A shows the hazard ratios (HRs) for mortality between patients with and without EKG-LVH by the Cornell criteria. The unadjusted HR was significant for the Cornell criteria (HR 1.66, 95% CI 1.09 to 2.55, $P = 0.02$). Adjusting for CKD, other variables (age, sex, race, myocardial infarction, and diabetes mellitus) reduced the strength of the relationship between Cornell EKG-LVH and mortality. Further adjustment for 24-hour ambulatory systolic BP reduced the relationship even further. In comparison, LVH diagnosed by Sokolow–Lyon criteria showed no relationship with mortality (HR for unadjusted analysis 1.04, $P = 0.9$) (Figure 2B). Adjustment for CKD did not change the significance. However, adjustment for other variables increased the strength of the relationship between Sokolow–Lyon LVH and mortality. Further adjustment for 24-hour ambulatory systolic BP increased

Table 3. Best subset of four determinants of EKG-LVH

Variable	EKG-LVH by Sokolow–Lyon Criteria				EKG-LVH by Cornell Criteria			
	OR	Lower 95% CI	Upper 95% CI	*P*	OR	Lower 95% CI	Upper 95% CI	*P*
Black race	2.56	0.90	7.29	0.08				
Weight (per 10 kg)					0.87	0.71	1.06	0.17
Log urine protein/creatinine (g/g)	1.21	0.83	1.75	0.3	0.92	0.69	1.23	0.6
Hemoglobin (g/dl)	0.77	0.58	1.02	0.07	0.90	0.73	1.11	0.3
24-hour systolic BP (per 1 SD)	1.54	0.86	2.76	0.14	2.05	1.30	3.22	0.002
Model fit	log likelihood = −58.7, χ^2 = 22.5, $P <$ 0.001				log likelihood = −95.3, χ^2 = 19.0, $P <$ 0.001			

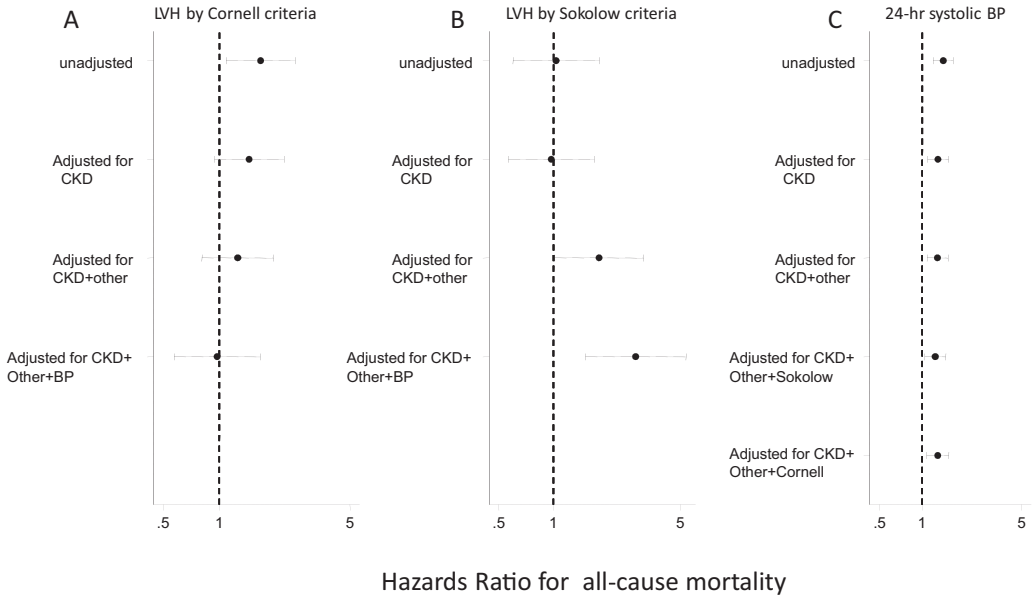

Figure 2. | **HRs for all-cause mortality.** HRs for death by EKG-LVH are shown in panels A and B and by 24-hour ambulatory systolic BP in panel C. (A) HRs for presence of EKG-LVH by Cornell criteria unadjusted, adjusted for CKD, multivariate adjusted (CKD + other), or multivariate adjusted and further adjusted for ambulatory systolic BP (CKD + other + BP). (B) HRs for presence of EKG-LVH by Sokolow–Lyon criteria following the same scheme as in panel A. (C) HR for 1 SD change in ambulatory systolic BP adjusted, adjusted for CKD, or multivariate adjusted (CKD + other). The final model was further adjusted for EKG-LVH by Sokolow–Lyon criteria (CKD + other + Sokolow) or for EKG-LVH by Cornell criteria (CKD + other + Cornell).

the strength of the relationship even further (HR 2.84, 95% CI 1.50 to 5.37, $P < 0.001$). Comparing the EKG-LVH models revealed that the Sokolow–Lyon model was superior to the Cornell model ($\chi^2 = 0.09$, $P < 0.01$). Figure 2C shows that 1 SD (14.9 mmHg) change in 24-hour systolic ambulatory BP resulted in increased hazards for death (HR 1.41, 95% CI 1.09 to 1.53, $P < 0.001$). Adjusting for CKD, other variables, including EKG-LVH, did not diminish the statistical significance of ambulatory BP and the HR for mortality remained between 1.23 and 1.29. In fact, the likelihood ratio test comparing models that contained ambulatory BP and EKG-LVH revealed that the model containing ambulatory BP was superior to that containing EKG-LVH ($P < 0.001$), attesting to the superiority of ambulatory BP in predicting all-cause mortality.

Discussion

Prevalence of EKG-LVH

The prevalence of EKG-LVH by the Sokolow–Lyon criteria was 8% and by the Cornell criteria was 11%. Thus, compared with the Sokolow–Lyon voltage criteria, the overall prevalence of EKG-LVH diagnosed by sex-adjusted Cornell criteria was slightly higher. In the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT), EKG-LVH was evaluated by Minnesota code 3-1 or 3-3 with ST/T wave changes (Minnesota codes 4 and 5) (12). The prevalence of EKG-LVH was higher in patients with moderate (6.0%) and severe (11.2%) reductions in GFR than those with a normal GFR (3.9%) or a mild reduction (4.2%; $P < 0.05$ for differences between groups). Although the prevalence of EKG-LVH between ALLHAT and our study is comparable, it should be noted

that the different diagnostic criteria used in the two studies do not allow for a head-to-head comparison. In a Spanish general practice multicenter study of 13,687 older (>55 years) hypertensive patients, 20.3% of the participants had EKG-LVH by Cornell criteria (13). This is nearly twice the prevalence compared with our study. In part, this higher prevalence in the Spanish cohort may be explained by inclusion of older patients (4.2 years older than in our study) and those with stage 5 CKD (of which we had only a few). Furthermore, compared with our study, in the Spanish study the Cornell criteria used a different definition of EKG-LVH in that it did not include the QRS duration to calculate the voltage-duration product; thus, head-to-head comparison is difficult. Krane *et al.* reported the prevalence of EKG-LVH diagnosed by Sokolow–Lyon criteria among 1253 patients participating in the German Diabetes and Dialysis 4D study (14). All of these patients were on hemodialysis and had type 2 diabetes mellitus; therefore, the patient population was substantially different from the study presented here. Overall, 12.4% had EKG-LVH by Sokolow–Lyon criteria. This prevalence is nearly 1.5 times what we noted, which is in keeping with more advanced CKD.

It should be noted that compared with EKG-LVH, anatomical LVH is more prevalent in the general population. For example, Kannel reported that in the 60- to 64-year age group, in the Framingham Heart Study, EKG-LVH was noted in 11.6% of men and only 3.1% of women (2). In contrast, x-ray evidence of anatomical LVH was noted in 27.9% of men and 32.8% of women. Thus, compared with EKG-LVH, anatomical LVH even in people without CKD may be 2.5 to 3.0 times higher in men and >10 times higher in women. In people with CKD, the prevalence of echocardiographic LVH has been reported to be approximately 40% (15). Among chronic hemodialysis patients, the prevalence of echocardiographic LVH is approximately 70% (16,17). The low prevalence rates of EKG-LVH therefore likely grossly underestimate the true prevalence of anatomical LVH.

Determinants of EKG-LVH

In the general population, the prevalence of LVH increases with age. For example, in the Framingham Heart Study, the prevalence of EKG-LVH increases from 8% in men <30 years of age to 33% among men 70 years or older (2). Other determinants are sex, BP, height and weight, glucose intolerance, valve disease, and coronary disease (2).

We found, as expected, that age and systolic ambulatory BP were independent determinants of EKG-LVH by either criterion. As in the general population, a strong and significant relationship was observed between ambulatory systolic BP and EKG-LVH (OR for 1 SD change in systolic BP 2.0 for Sokolow–Lyon and 1.9 for Cornell). These relationships remained significant despite multivariable adjustment. However, eGFR was only an independent predictor of EKG-LVH by the Sokolow–Lyon criteria.

Some determinants of EKG-LVH in patients without CKD are similar to those seen among patients with CKD. For example, in patients with mild or moderate hypertension, Okin *et al.* have reported that the Cornell criteria for EKG-LVH characterize older patients who are obese and female, whereas Sokolow–Lyon criteria are more characteristic of patients who are younger, male, black, and nonobese (18). We confirmed that the Cornell criteria identify older patients and the Sokolow–Lyon criteria identify black and nonobese patients at least in univariate analysis. That blacks have greater QRS voltage has been reported previously (19). However, among those with CKD, anemia, proteinuria, and systolic hypertension were stronger independent determinants of EKG-LVH. These findings confirm those of Levin *et al.* who have shown that among patients with nondialysis CKD followed longitudinally, anemia and systolic hypertension are independent determinants of echocardiographic LVH (20).

Only a few studies have evaluated the determinants of EKG-LVH among patients with CKD. The largest of these was ALLHAT. In ALLHAT, after adjustment for age, race, sex, BMI, baseline BP, LDL-cholesterol, HDL-cholesterol, triglycerides, diabetes, and smoking, eGFR was independently associated with EKG-LVH (12). A 10-ml/min per 1.73 m^2 decrease in GFR was associated with a 14% higher risk of LVH (OR, 1.14 per 10 ml/min per 1.73 m^2; $P < 0.001$). Patients with a severe reduction in GFR (<30 ml/min per 1.73 m^2) had a >3-fold increase (OR, 3.19; $P < 0.001$) in the prevalence of ECG-LVH compared with the reference group (GFR ≥ 90 ml/min per 1.73 m^2). Patients with a mild reduction in GFR (30 to 59 ml/min per 1.73 m^2) also had a significantly increased risk (OR, 1.26; $P = 0.001$) for EKG-LVH. We did not discover such associations. The stronger association between EKG-LVH and CKD in ALLHAT compared with our study may be due to several reasons. First, we used proteinuria to diagnose CKD. This is consistent with the clinical guidelines and was not the case for ALLHAT. Notably, those with EKG-LVH had a stronger association with proteinuria compared with eGFR (see Table 1). Second, we used 24-hour ambulatory BP monitoring to measure the most important risk factor for LVH; ALLHAT simply used a seated baseline BP. Third, we used Cornell and Sokolow–Lyon criteria for EKG-LVH, which was not the case for ALLHAT. Fourth, nearly half of the participants in ALLHAT were women. At least one study has shown that the relationship between EKG-LVH and CKD stage was much stronger in women but absent in men (13). However, we acknowledge that ALLHAT was a much larger study, so it could discover relationships between eGFR and EKG-LVH with greater power.

In a Spanish general practice multicenter study of 13,687 older (>55 years) hypertensive patients, lower eGFR was associated with greater prevalence of EKG-LVH only among women. However, 24-hour ambulatory BP recording was not performed. Nonetheless, in keeping with our study, in multiple logistic regression analysis (after adjusting for age, sex, BMI, diabetes, systolic and diastolic BP, and smoking) a lower eGFR was not associated with a higher prevalence of EKG-LVH among men.

Prognostic Value of EKG-LVH

An intriguing finding of our study was that in unadjusted analyses, EKG-LVH by Cornell criteria was of prognostic value but EKG-LVH diagnosed by Sokolow–Lyon voltage criteria was not of prognostic significance; the

prognostic significance was judged by all-cause mortality, the most specific "hard" endpoint. However, after multivariate adjustment, the EKG-LVH by Cornell criteria became nonsignificant (positive confounding), but EKG-LVH by Sokolow–Lyon criteria became of stronger prognostic importance (negative confounding). This would imply that EKG-LVH diagnosed by Sokolow–Lyon criteria are of prognostic importance over and above that observed with traditional risk factors (age, sex, race, diabetes, prior myocardial infarction, and ambulatory BP). Thus, EKG-LVH diagnosed by Sokolow–Lyon criteria carries prognostic information above and beyond ambulatory BP. In fact, this model was found to be statistically superior to the Cornell criteria. In the case of Cornell criteria, the confounding variables may lie in the mediating pathway.

The prognostic value of 24-hour systolic ambulatory BP remained strong despite multivariable adjustment including that for EKG-LVH whether it was diagnosed by Sokolow–Lyon or Cornell criteria. Thus, 24-hour systolic ambulatory BP is important in predicting mortality. However, the duration and severity of elevation that likely result in EKG-LVH are also important. Why Sokolow–Lyon criteria should be prognostically more informative than the Cornell criteria remains unclear.

Krane *et al.* reported the association of EKG-LVH diagnosed by Sokolow–Lyon criteria with cardiovascular events and mortality (14). These 1253 patients participating in the German Diabetes and Dialysis 4D study were all on hemodialysis and had type 2 diabetes mellitus; therefore, the patient population was substantially different from the study presented here. EKG-LVH was associated with all-cause mortality and cardiovascular events in the univariate analyses; however, significance was lost after multivariate adjustment. In contrast to their results, we found the Sokolow–Lyon criteria to be nonsignificant in unadjusted analyses, but they became significant after multivariate adjustment. An important difference between our study and the 4D study was that we adjusted for 24-hour ambulatory systolic BP. It was after adjustments that the HR for mortality increased; thus, BP may be the suppressor variable between EKG-LVH and mortality (21). It would imply that those with EKG-LVH by the Sokolow–Lyon criteria have a higher mortality. However, those without EKG-LVH at baseline have a higher mortality should they be exposed to higher 24-hour ambulatory systolic BP. Removal of ambulatory BP from the model may show no relationship between EKG-LVH, but inclusion of this variable may make EKG-LVH significant (21).

Limitations

There are some limitations of our study. Our population was predominantly men because US veterans are mostly men. We did not directly record EKG voltages from digital recordings, therefore the measurement of voltages reflect routine practice. However, QRS duration was recorded as directly reported by the digital EKG machine. We did not record the presence of LVH by echocardiograms, so we are unable to determine diagnostic test performance of EKG-LVH in this population. Although our cohort was modestly large, we may have missed relationships that may have been significant if the strength of the relationship was not high.

In conclusion, our data suggest that the EKG-LVH criteria cannot be used interchangeably to diagnose LVH. CKD is independently associated with LVH using Sokolow–Lyon criteria. However, EKG-LVH seen in patients with and without CKD appears to be largely mediated by systolic hypertension. Controlling hypertension would therefore be an attractive option for the prevention and treatment of LVH. However, diagnosing EKG-LVH by Sokolow–Lyon criteria provides prognostic information independent of BP and other risk factors. Because Sokolow-Lyon criteria are associated with hypertension, CKD, and all-cause mortality, it would appear that they would be superior to the Cornell criteria for determining the prognosis of patients with CKD.

Disclosures

None.

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