Hypertension Research (2019) 42:541–548
https://doi.org/10.1038/s41440-018-0164-8

ARTICLE

Cornell product in an electrocardiogram is related to reduced LV regional wall motion

Joji Ishikawa[1] · Yuko Yamanaka[2] · Shintaro Watanabe[3] · Ayumi Toba[1] · Kazumasa Harada[1]

Received: 27 June 2018 / Revised: 11 September 2018 / Accepted: 20 September 2018 / Published online: 12 December 2018

Abstract

Electrocardiographic left ventricular hypertrophy (LVH) diagnosed by Cornell product and the Sokolow–Lyon voltage are associated with anatomical LVH; therefore, we investigated whether Cornell product and the Sokolow–Lyon voltage were associated with echocardiographic regional wall motion (measured by 2D-strain imaging). We reviewed data on 288 consecutive hypertensive patients who underwent both echocardiography and electrocardiography. Electrocardiographic LVH was calculated as follows: Cornell voltage, S in lead V3 + R in lead aVL; Cornell product, Cornell voltage (+0.6 mV for females) × QRS duration; and Sokolow–Lyon voltage, S in lead V1 + R in lead V5. The mean age of the subjects was 64.3 ± 13.2 years; 47.9% were men, and 65.2% were taking antihypertensive medications. Both Cornell product ($r = 0.392$, $P < 0.001$) and the Sokolow–Lyon voltage ($r = 0.315$, $P < 0.001$) were significantly related to left ventricular mass index (LVMI), and the relationship between Cornell product and LVMI (beta = 0.24, $P = 0.001$) was independent of the Sokolow–Lyon voltage (beta = 0.25, $P < 0.001$). In multivariate linear regression analysis in which the two ECG-LVH were included together, Cornell product was related to global longitudinal strain (beta = 0.24, $P = 0.002$), even after adjusting for the Sokolow–Lyon voltage ($P = 0.835$). Additionally, the Cornell voltage was related to the inner/outer ratio of circumferential strain (beta = 0.17, $P = 0.033$) after adjusting for the Sokolow–Lyon voltage ($P = 0.318$). By contrast, the Sokolow–Lyon voltage was related to the relative wall thickness and E/e' on tissue Doppler imaging, even after adjusting for Cornell product. In conclusion, Cornell product and voltage were associated with longitudinal regional wall motion and with the transmurality of regional wall motion in the short axis direction.

Keywords Cornell product · Cornell voltage · Sokolow–Lyon voltage · hypertension · left ventricular hypertrophy

Introduction

Left ventricular hypertrophy (LVH) is associated with an increased risk of cardiovascular events in hypertensive patients [1]. On the electrocardiogram, the Sokolow–Lyon voltage and, more recently, Cornell voltage and product are used to estimate anatomical LVH corresponding to the left ventricular mass index (LVMI) [2, 3]. Both the Sokolow–Lyon voltage and Cornell product are reported to be independent predictors of future cardiovascular events and stroke [4–6], with Cornell product and voltage being stronger predictors of future stroke than the Sokolow–Lyon voltage in the general population [5]. LVH diagnosed by the Cornell product has been associated with obesity [7] and diabetes [5, 8], in addition to aging and high systolic blood pressure, but LVH diagnosed by the Sokolow–Lyon voltage has not demonstrated this association. Therefore, LVH diagnosed by Cornell product could develop when metabolic abnormalities cause microvascular damage and fibrosis in the heart.

Patients with LVH could have myocardial fibrosis and diastolic dysfunction, leading to an increased risk of heart failure with preserved ejection fraction (HFpEF) [9, 10]. In hypertrophic myocardium, the inner layer of the myocardium contracts more than the outer layer of myocardium; therefore, the systolic function, measured as EF, could overestimate the left ventricular systolic function [11, 12]. Longitudinal myocardial function, measured by tissue Doppler imaging (TDI) [13] and global longitudinal strain (GLS), could be sensitive

✉ Joji Ishikawa
joji_ishikawa@tmghig.jp
george@jichi.ac.jp

[1] Department of Cardiology, Tokyo Metropolitan Geriatric Hospital, Tokyo, Japan

[2] Division of Cardiovascular Medicine, Department of Medicine, Jichi Medical University School of Medicine, Tochigi, Japan

[3] Department of Cardiology, Sano Kosei General Hospital, Tochigi, Japan

markers of decreased myocardial function in patients with LVH [14, 15]. Additionally, the inner/outer ratio of circumferential strain (CS) and the inner/outer ratio of radial strain (RS) have been reported to be markers of hypertensive heart disease and cardiac fibrosis [16, 17].

Therefore, we evaluated whether the Cornell product, Cornell voltage, and Sokolow–Lyon voltage were associated with abnormal regional wall motion measured as myocardial 2D-strain on echocardiography.

Methods

Subjects

We reviewed echocardiography data obtained when screening consecutive hypertensive outpatients for target

Table 1 Characteristics of the patients

Age, years	63.4 ± 13.2
Male, %	47.9
Body mass index, kg/m^2	24.8 ± 4.4
Systolic blood pressure, mmHg	147.9 ± 24.1
Diastolic blood pressure, mmHg	86.2 ± 15.0
Pulse rate, beats/min	72.5 ± 11.8
Antihypertensive drug use, %	65.2
Smoking status	
Past smokers, %	20.5
Current smokers, %	16.1
Regular alcohol intake, %	26.1
Diabetes, %	15.3
Dyslipidemia, %	41.1
Sokolow–Lyon voltage ≥ 3.8 mV, %	5.9
Cornell product ≥ 244 ms × mV	24.5

Data are shown as the mean ± standard deviation or percentage

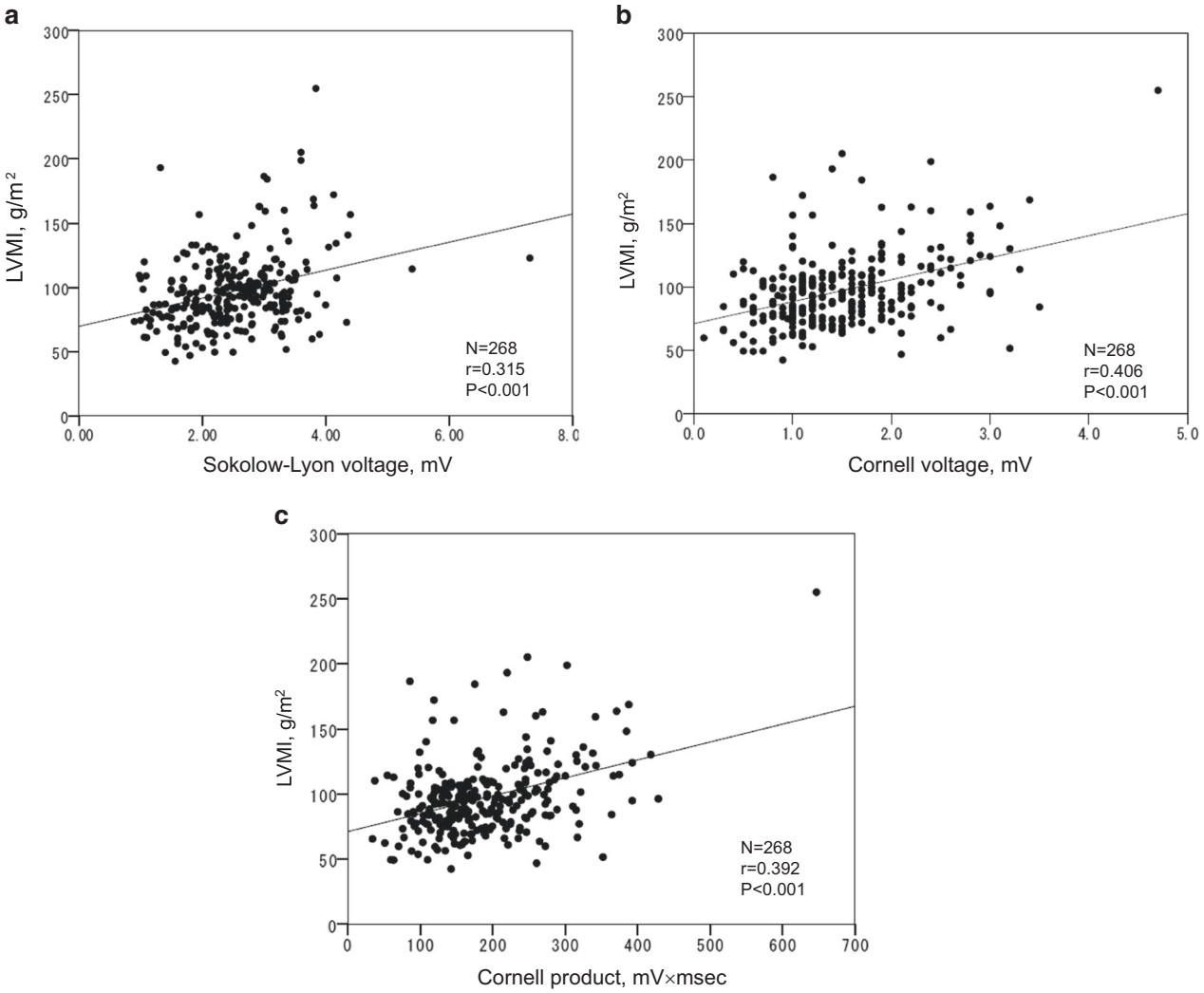

Fig. 1 **a** Relationship of the Sokolow–Lyon voltage to the left ventricular mass index. **b** Relationship of the Cornell voltage to the left ventricular mass index. **c** Relationship of the Cornell product to the left ventricular mass index

organ damage at a general hospital between January 2010 and June 2014. There were 345 sets of echocardiographic and electrocardiographic data [3], after excluding patients with the following: (1) significant arrhythmia, (2) complete left or right bundle branch block, (3) unclear echocardiographic images, (4) a history of ischemic heart disease, and (5) asynergy of left ventricular wall motion. In the present investigation, we analyzed data on 288 patients after excluding duplicate echocardiography studies ($N = 57$).

ECG recording and interpretation

ECGs were recorded using an automated12-lead ECG monitor (Fukuda Denshi, Inc., Tokyo, Japan). The monitor automatically measured the QRS duration, S in lead V1, and R in lead V5 (Sokolow–Lyon criteria), while R in lead aVL and S in lead V3 (Cornell voltage) were measured manually. Then, the Cornell product was calculated as the Cornell voltage (+0.6 mV in females) × QRS duration. A Cornell voltage ≥2.8 mV in males and ≥2.0 mV in females, a Cornell product ≥244 mV × ms and a Sokolow–Lyon voltage ≥3.8 mV were the diagnostic criteria for ECG-LVH in the Losartan Intervention For Endpoint (LIFE) Reduction in Hypertension Study [8].

Echocardiography

The first author performed most of the echocardiography examinations using an Altida (Toshiba, Japan) with a 3.5 MHz transducer. The absence of apparent asynergy of LV wall motion was confirmed in all patients. Two-dimensional B-mode images were recorded according to the guidelines of the American Society of Echocardiography [18]. Then, the LV mass was calculated using the following formula: $0.8 \times 1.04 \times [(\mathrm{IVS} + \mathrm{LVID} + \mathrm{PW})^3 - (\mathrm{LVID})^3] + 0.6$, where IVSd is the diastolic interventricular septal diameter, LVDd is the diastolic LV dimension, and PWd is the diastolic posterior wall diameter. LVMI was calculated as LV mass divided by body surface area [19]. The mean inter-observer difference of LVMI was 6.6 ± 19.5 g/m^2.

Analyses of TDI and strain were performed with an off-line system (ULTRA EXTENDED ver. 2.7, Toshiba, Japan). TDI was performed in the apical 4-chamber view. The mitral valve annulus velocity was measured at the septal wall, and the septal peak longitudinal systolic (s') and early diastolic (e') velocities were used for analysis. The transmitral E to e' ratio (E/e') was also calculated.

Two-dimensional strain imaging was performed using a semi-automatic speckle-tracking method. GLS, RS, and CS were measured in 12 segments, with the region of interest being placed on both the inner and outer layers of the LV wall in each segment. Mid-wall strain was also measured for GLS. Total RS and CS were also calculated as the total average of the inner and outer myocardial layers in the 12 segments. The inner/outer strain ratio was also calculated to evaluate the transmurality of regional wall motion.

When intra-operator reproducibility was assessed in 10 randomly selected patients, the results were as follows: RS was 1.13 ± 8.29% (inner layer, 0.93 ± 9.73%; outer layer, 0.93 ± 8.30%), CS was 0.39 ± 2.12% (inner layer 0.95 ± 3.84%; outer layer, 0.20 ± 1.23%), and GLS was 0.38 ± 1.33% (inner layer 0.26 ± 1.42%; outer layer, 0.16 ± 1.96%).

Informed consent

The institutional review board of the General Hospital approved this study. We did not obtain written informed consent because this was a retrospective analysis of routine clinical data.

Statistical analysis

Results are shown as the means ± SD for continuous variables or as percentages for categorical variables. Correlations were evaluated between the ECG indexes of LVH and LVMI, RWT, septal e', E/average of septal and lateral e' (E/e'), or strain by calculating Pearson's correlation coefficients. Independent associations between ECG-LVH and echocardiographic LVH parameters were assessed by multiple linear regression analysis in unadjusted and adjusted models (age, sex, BMI, diabetes, dyslipidemia, SBP, and antihypertensive drug use). The results of multiple linear regression analysis are shown by unstandardized B and 95% confidence interval (CI), and standardized beta. The odds ratio for an increased transmitral E/average of

Table 2 Multiple linear regression analysis of the relation between LVMI and the Cornell voltage or Cornell product and the Sokolow–Lyon voltage

	B	LCI	UCI	Beta	*P*
Cornell voltage					
Unadjusted model					
Sokolow–Lyon voltage	8.12	3.29	12.95	0.24	0.001
Cornell voltage	10.63	4.55	16.71	0.25	0.001
Model adjusted for conventional risk factors					
Sokolow–Lyon voltage	9.00	4.27	13.73	0.26	0.000
Cornell voltage	7.95	2.06	13.85	0.19	0.008
Cornell product					
Unadjusted model					
Sokolow–Lyon voltage	8.83	4.06	13.60	0.26	0.000
Cornell product	0.08	0.03	0.13	0.22	0.002
Model adjusted for conventional risk factors					
Sokolow–Lyon voltage	8.55	3.90	13.20	0.25	0.000
Cornell product	0.08	0.04	0.13	0.24	0.001

Age, sex, BMI, diabetes, dyslipidemia, SBP, and antihypertensive drug use were included in the adjusted models

B indicates unstandardized coefficient, *LCI* lower 95% confidence interval, *UCI* upper 95% confidence interval, *beta* standardized coefficient

septal and lateral e' (>14) to ECG-LVH was calculated using logistic regression analysis. There were no significant collinearities (all variance inflation factors <2.0) or interactions between Cornell product and the Sokolow–Lyon voltage. IBM SPSS statistical software (version 25.0, Chicago, IL, USA) was used for all analyses, and $P < 0.05$ was considered to indicate statistical significance.

Results

Subjects

The characteristics of the subjects ($N = 288$) are displayed in Table 1. Their mean age was 63.4 ± 13.2 years, and 47.9% were men. In addition, 65.2% of the patients were taking antihypertensive drugs, 15.3% had diabetes, and 41.1% had hyperlipidemia.

Relationship between ECG-LVH and LVMI or RWT

Scatter plots of LVMI vs. the Sokolow–Lyon voltage, Cornell voltage, and Cornell product are shown in Fig. 1. These ECG-LVH criteria were all significantly related to LVMI. Both the Cornell voltage and Sokolow–Lyon voltage were independently correlated with LVMI, as was Cornell product (Table 2).

While the Sokolow–Lyon voltage ($r = 0.137$, $P = 0.024$), Cornell voltage ($r = 0.151$, $P = 0.023$), and Cornell product ($r = 0.156$, $P = 0.010$) were all significantly related to the relative wall thickness (RWT), the Sokolow–Lyon voltage ($B = 0.028$, 95%CI 0.005–0.052, beta = 0.186, $P = 0.018$) was related to RWT even after adjusting for the Cornell voltage ($B = 0.013$, 95%CI −0.016 to 0.043, beta = 0.068, $P = 0.378$) in the multivariate adjusted model. The Sokolow–Lyon voltage ($B = 0.029$, 95%CI 0.005–0.052, beta = 0.186, $P = 0.017$) was also related to RWT even

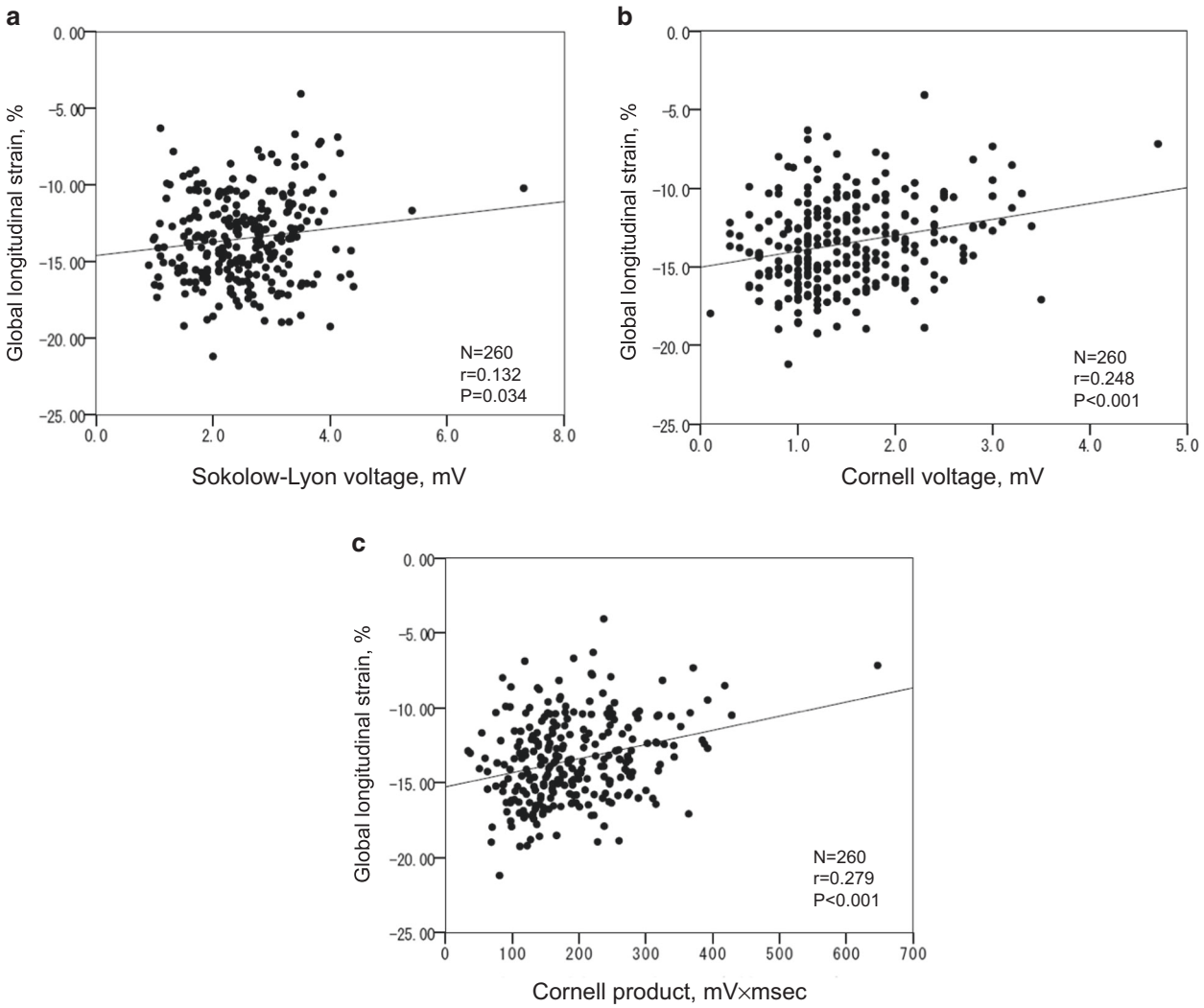

Fig. 2 **a** Relationship of the Sokolow–Lyon voltage to global longitudinal strain. **b** Relationship of the Cornell voltage to global longitudinal strain. **c** Relationship of the Cornell product to global longitudinal strain

Table 3 Multiple linear regression analysis of the relation between global longitudinal strain and the Cornell voltage or Cornell product and the Sokolow–Lyon voltage

	B	LCI	UCI	Beta	*P*
Cornell voltage					
Unadjusted model					
Sokolow–Lyon voltage	0.05	−0.45	0.55	0.02	0.843
Cornell voltage	0.87	0.24	1.50	0.21	0.007
Model adjusted for conventional risk factors					
Sokolow–Lyon voltage	0.19	−0.32	0.70	0.06	0.455
Cornell voltage	0.86	0.23	1.49	0.21	0.008
Cornell product					
Unadjusted model					
Sokolow–Lyon voltage	0.05	−0.436	0.54	0.02	0.835
Cornell product	0.01	0.003	0.01	0.24	0.002
Model adjusted for conventional risk factors					
Sokolow–Lyon voltage	0.05	−0.436	0.54	0.02	0.835
Cornell product	0.01	0.003	0.01	0.24	0.002

Age, sex, BMI, diabetes, dyslipidemia, SBP, and antihypertensive drug use were included in the adjusted models

B indicates unstandardized coefficient, *LCI* lower 95% confidence interval, *UCI* upper 95% confidence interval, *beta* standardized coefficient

after adjusting for Cornell product (beta = 0.068, $P = 0.375$) in the multivariate adjusted model.

Relationships of ECG-LVH to the *E/A* ratio, *e′* and *E/e′* on Doppler imaging

The Sokolow–Lyon voltage ($r = 0.013$, $P = 0.829$), Cornell voltage ($r = 0.042$, $P = 0.494$), and Cornell product ($r = 0.031$, $P = 0.616$) were not correlated with the *E/A* ratio of mitral valve inflow. By contrast, the Sokolow–Lyon voltage ($r = 0.264$, $P < 0.001$), Cornell voltage ($r = 0.202$, $P = 0.001$), and Cornell product ($r = 0.260$, $P < 0.001$) were all significantly correlated with *E/e′* on TDI. However, the Sokolow–Lyon voltage ($B = 1.488$, 95%CI 0.887–2.088, beta = 0.348, $P < 0.001$) was related to *E/e′* even after adjusting for the Cornell voltage (beta = 0.014, $P = 0.848$) in the multivariate adjusted model. The Sokolow–Lyon voltage ($B = 0.1486$, 95%CI 0.888–2.083, beta = 0.348, $P < 0.001$) was also related to *E/e′* even after adjusting for Cornell product (beta = 0.016, $P = 0.823$) in the multivariate adjusted analysis. In logistic regression analysis, the Sokolow–Lyon voltage had a marginally increased risk for $E/e' > 14$ (odds ratio 2.02 per 1 mV increase, 95% CI 0.94–4.37, $P = 0.073$), but Cornell product did not (odds ratio 0.99 per 1 mV × ms increase, 95% CI 0.983–1.005, $P = 0.272$).

The Sokolow–Lyon voltage ($r = -0.163$, $P = 0.008$), Cornell voltage ($r = 0.261$, $P < 0.001$), and Cornell product ($r = 0.273$, $P < 0.001$) were all significantly correlated with *e′* of septal mitral annulus velocity on TDI. The Cornell voltage ($B = -0.463$, 95%CI −0.856 to −0.070, beta = −0.178, $P = 0.021$) was related to *e′* even after adjusting for the Sokolow–Lyon voltage (beta = −0.103, $P = 0.180$) in multivariate adjusted analysis. Both Cornell product ($B = -0.004$ per 1 mV × ms increase, 95%CI −0.007 to −0.001, beta = −0.200, $P = 0.003$) and the Sokolow–Lyon voltage ($B = -0.320$ per 1 mV increase, 95%CI −0.594 to −0.045, beta = −0.155, $P = 0.023$) were independently related to reduced septal *e′* in multivariate adjusted analysis.

Relationship of ECG-LVH to GLS, RS, and CS

The Sokolow–Lyon voltage, Cornell voltage, and Cornell product were all related to GLS (Fig. 2). However, the Cornell voltage and Cornell product were related to GLS even after adjusting for the Sokolow–Lyon voltage (Table 3). The Sokolow–Lyon voltage ($r = 0.118$, $P = 0.058$), Cornell voltage ($r = 0.103$, $P = 0.097$), and Cornell product ($r = 0.046$, $P = 0.461$) were not related to the inner/outer ratio of GLS.

In addition, the Sokolow–Lyon voltage, Cornell voltage, and Cornell product were not related to RS or to the inner/outer ratio of RS.

The Cornell voltage ($r = 0.184$, $P = 0.003$) and Cornell product ($r = 0.160$, $P = 0.010$) were related to CS, while the Sokolow–Lyon voltage was not ($r = 0.055$, $P = 0.378$). However, the relationship of the Cornell voltage (beta = 0.072, $P = 0.375$) or Cornell product ($r = 0.066$, $P = 0.408$) to CS disappeared after adjusting for confounding factors, including the Sokolow–Lyon voltage. In addition, the Cornell voltage and Cornell product were significantly related to the inner/outer ratio of CS, but the Sokolow–Lyon voltage was not (Fig. 3). The Cornell voltage was still significantly related to the inner/outer ratio of CS even after adjusting for confounding factors, including the Sokolow–Lyon voltage (Table 4).

Discussion

This study showed that the Cornell voltage, Cornell product, and the Sokolow–Lyon voltage were all independently related to LVMI, but the Sokolow–Lyon voltage was related to RWT and *E/e′* even after adjusting for the Cornell voltage or Cornell product. Additionally, the Cornell voltage and product were related to GLS even after adjusting for the Sokolow–Lyon voltage, and the Cornell voltage was related to the transmurality (i.e., the inner/outer ratio) of CS.

In patients with hypertension, GLS and the transmurality of CS were reported to be sensitive markers of reduced regional wall motion and end-systolic wall stress due to fibrosis of the inner layer of the myocardium [17]. The inner

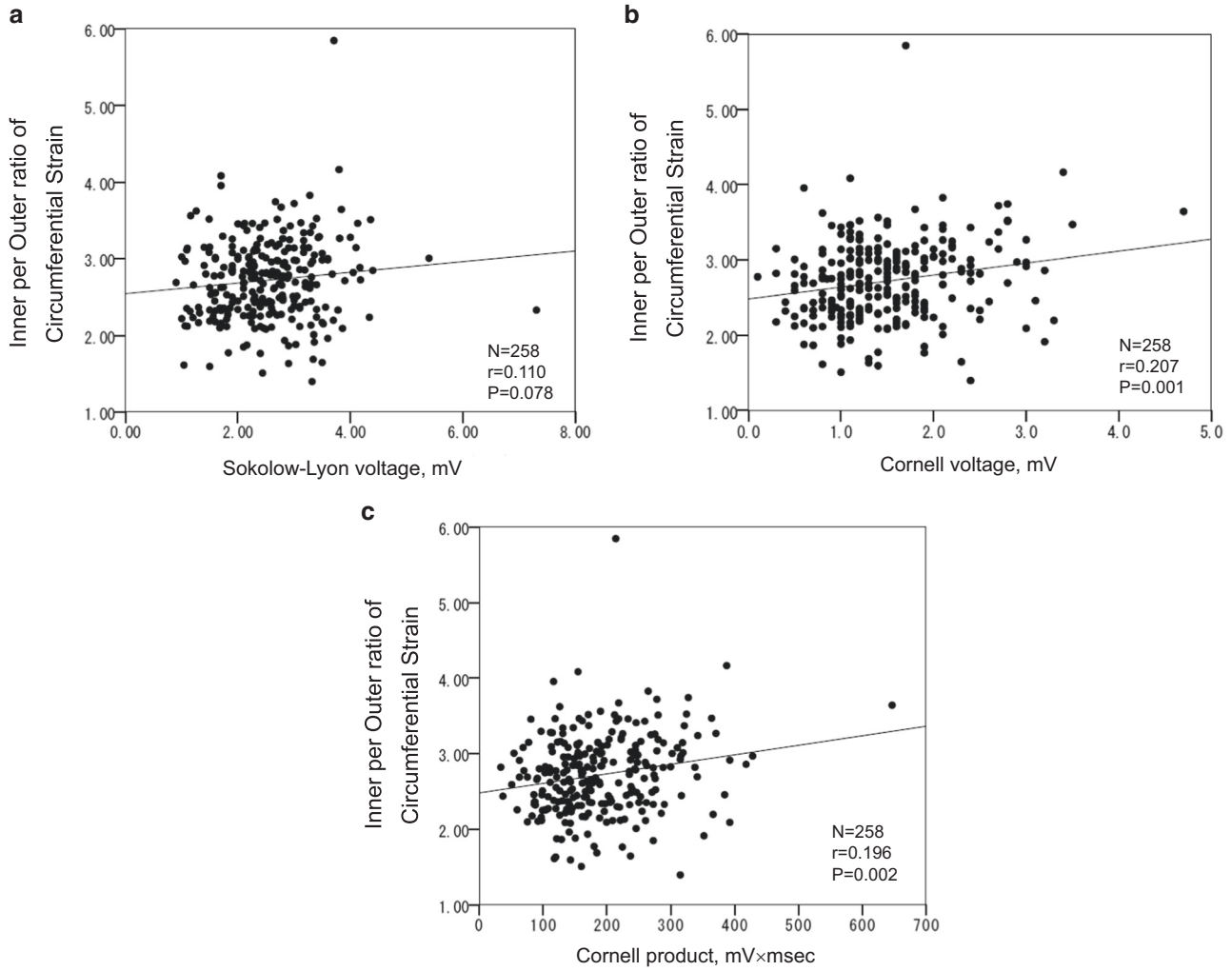

Fig. 3 **a** Relationship of the Sokolow–Lyon voltage to the inner/outer ratio of circumferential strain. **b** Relationship of the Cornell voltage to the inner/outer of circumferential strain. **c** Relationship of the Cornell product to the inner/outer of circumferential strain

layer of the myocardium contracts greater than the outer layer; therefore, in hypertensive patients with LV hypertrophy, the EF (measured at the endomyocardial layer) may overestimate LV systolic function [12]. Cardiac function of longitudinal direction by TDI (i.e., e' or E/e') had been evaluated to be a marker of diastolic function in patients with LVH. Recently, regional systolic wall motion in the longitudinal direction could be reduced in patients with LVH, and GLS has been evaluated in patients with a HFpEF [15]. Patients with LVH had an increased risk of developing reduced EF, which could cause a reduction in wall motion in the short axis direction (RS and CS) in the future (eccentric remodeling). Cornell product and voltage could be markers of reduction of GLS in patients with preserved EF and could also be markers of the beginning of the reduction of wall motion in the short axis direction (i.e., CS).

Cornell product and the Sokolow–Lyon voltage might have some different associations with left ventricular function. The Cornell voltage and Cornell product were influenced by obesity and diabetes, probably because R in lead aVL and S in lead V3 are more likely to be affected by obesity. Thus, the Cornell voltage might reflect metabolic LVH caused by myocardial fibrosis. By contrast, R in lead V5 is more likely to be affected by the distance from the chest wall to the cardiac apex, and patients with obesity could have an underestimated R in lead V5. In the present study, the Sokolow–Lyon voltage was related to RWT, which is an age-related change of LV geometry [20, 21]. E/e' was reported to show an association with elevation of LA pressure, a marker of diastolic dysfunction in elderly hypertensive patients with LV concentric remodeling. Thus, the Sokolow–Lyon voltage might be a marker of age-related LVH.

Both the Cornell voltage and Sokolow–Lyon voltage were independently related to LVMI and e' of mitral annulus velocity in TDI, which has been reported to show

Table 4 Multiple linear regression analysis of the relation between the inner/outer ratio of circumferential strain and the Cornell voltage or Cornell product and the Sokolow–Lyon voltage

	B	LCI	UCI	Beta	*P*
Cornell voltage					
Unadjusted model					
Sokolow–Lyon voltage	0.05	−0.05	0.15	0.08	0.324
Cornell voltage	0.16	0.04	0.29	0.20	0.013
Model adjusted for conventional risk factors					
Sokolow–Lyon voltage	0.05	−0.05	0.16	0.08	0.314
Cornell voltage	0.14	0.01	0.27	0.17	0.033
Cornell product					
Unadjusted					
Sokolow–Lyon voltage	0.06	−0.041	0.16	0.09	0.247
Cornell product	0.001	0.00	0.00	0.19	0.014
Model adjusted for conventional risk factors					
Sokolow–Lyon voltage	0.06	−0.04	0.17	0.09	0.240
Cornell product	0.001	0.00	0.00	0.13	0.093

Age, sex, BMI, diabetes, dyslipidemia, SBP, and antihypertensive drug use were included in the adjusted models

B indicates unstandardized coefficient, *LCI* lower 95% confidence interval, *UCI* upper 95% confidence interval, *beta* standardized coefficient

an association with increased left ventricular stiffness. It was reported that Cornell product and the Sokolow–Lyon voltage were independent predictors of future cardiovascular events in previous studies [5, 6].

LVH includes hypertrophy of myocardial cells and interstitial fibrosis in the heart. It was reported that an increased LVM was associated with a larger Cornell voltage and Sokolow–Lyon voltage, but an increase of diffuse myocardial fibrosis quantified by myocardial extracellular volume fraction, which was measured by contrast-enhanced cardiovascular magnetic resonance imaging, was associated with a lower Cornell voltage and Sokolow–Lyon voltage [22]. ECG-LVH could be influenced by the proportion of hypertrophy of myocardial cells and cardiac fibrosis. Since we enrolled outpatients with hypertension in this study, it was unclear whether the results of this study were applied to those with an advanced stage of hypertensive target organ damage in the heart and to those with HFpEF. Additionally, we need to evaluate the results in a prospective study.

Conclusion

The Cornell voltage and Cornell product were related to the reduction of regional wall motion detected by measurement of the GLS and inner/outer ratio of the CS even after adjusting for the Sokolow–Lyon voltage.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

References

1. Levy D, Garrison RJ, Savage DD, Kannel WB, Castelli WP. Prognostic implications of echocardiographically determined left ventricular mass in the Framingham Heart Study. N Engl J Med. 1990;322:1561–6.
2. Okin P, Roman M, Devereux R, Kligfield P. Electrocardiographic identification of increased left ventricular mass by simple voltage-duration products. J Am Coll Cardiol. 1995;25:417–23.
3. Ishikawa J, Yamanaka Y, Toba A, Watanabe S, Harada K. Gender-adjustment and cutoff values of Cornell product in hypertensive Japanese patients. Int Heart J. 2017;58:933–8.
4. Okin PM, Devereux RB, Jern S, Kjeldsen SE, Julius S, Nieminen MS. et al.for the LIFE Study Investigators Regression of electrocardiographic left ventricular hypertrophy during antihypertensive treatment and the prediction of major cardiovascular events. JAMA. 2004;292:2343–9.
5. Ishikawa J, Ishikawa S, Kabutoya T, Gotoh T, Kayaba K, Schwartz JE. et al.for the Jichi Medical School Cohort Study Investigators Group Cornell product left ventricular hypertrophy in electrocardiogram and the risk of stroke in a general population. Hypertension. 2009;53:28–34.
6. Ishikawa J, Ishikawa S, Kario K. Levels of Cornell voltage and Cornell product for predicting cardiovascular and stroke mortality and morbidity in the general Japanese population. Circ J. 2014;78:465–75.
7. Okin PM, Jern S, Devereux RB, Kjeldsen SE, Dahlof B.Group ftLS Effect of obesity on electrocardiographic left ventricular hypertrophy in hypertensive patients: the Losartan Intervention For Endpoint (LIFE) Reduction in Hypertension Study. Hypertension. 2000;35:13–8.
8. Okin PM, Devereux RB, Gerdts E, Snapinn SM, Harris KE, Jern S. et al.for the LIFE Study Investigators Impact of diabetes mellitus on regression of electrocardiographic left ventricular hypertrophy and the prediction of outcome during antihypertensive therapy: The Losartan Intervention For Endpoint (LIFE) Reduction in Hypertension Study. Circulation. 2006;113:1588–96.
9. O'Neal WT, Mazur M, Bertoni AG, Bluemke DA, Al-Mallah MH, Lima JAC, et al. Electrocardiographic predictors of heart failure with reduced versus preserved ejection fraction: the Multi-ethnic Study of Atherosclerosis. J Am Heart Assoc. 2017;6:e006023.
10. Zile MR, Baicu CF, Gaasch WH. Diastolic heart failure—abnormalities in active relaxation and passive stiffness of the left ventricle. N Engl J Med. 2004;350:1953–9.
11. Aurigemma GP, Zile MR, Gaasch WH. Contractile behavior of the left ventricle in diastolic heart failure: with emphasis on regional systolic function. Circulation. 2006;113:296–304.
12. de Simone G, Devereux RB, Roman MJ, Ganau A, Saba PS, Alderman MH, et al. Assessment of left ventricular function by the midwall fractional shortening/end-systolic stress relation in human hypertension. J Am Coll Cardiol. 1994;23:1444–51.
13. Borges MCC, Colombo RCR, Goncalves JGF, de Ferreira JO, Franchini KG. Longitudinal mitral annulus velocities are reduced in hypertensive subjects with or without left ventricle hypertrophy. Hypertension. 2006;47:854–60.
14. Shah AM, Claggett B, Sweitzer NK, Shah SJ, Anand IS, Liu L, et al. The prognostic importance of impaired systolic function in heart failure with preserved ejection fraction and the impact of

spironolacton. Circulation. 2015. https://doi.org/10.1161/CIRCULATIONAHA.115.015884.
15. Morris DA, Ma XX, Belyavskiy E, Aravind Kumar R, Kropf M, Kraft R, et al. Left ventricular longitudinal systolic function analysed by 2D speckle-tracking echocardiography in heart failure with preserved ejection fraction: a meta-analysis. Open Heart. 2017;4:e000630.
16. Ishikawa J, Matsui Y, Russo C, Hyodo E, Arai K, DiTulio MR, et al. Increased aortic wave reflection and longitudinal regional diastolic dysfunction in patients with left ventricular hypertrophy. Artery Res. 2012;6:97–102.
17. Ishizu T, Seo Y, Kameda Y, Kawamura R, Kimura T, Shimojo N, et al. Left ventricular strain and transmural distribution of structural remodeling in hypertensive heart disease. Hypertension. 2014;63:500–6.
18. Marwick TH, Gillebert TC, Aurigemma G, Chirinos J, Derumeaux G, Galderisi M, et al. Recommendations on the use of echocardiography in adult hypertension: a report from the European Association of Cardiovascular Imaging (EACVI) and the American Society of Echocardiography (ASE). J Am Soc Echocardiogr. 2015;28:727–54.
19. Du BD, Du BE. Clinical calorimetry: tenth paper a formula to estimate the approximate surface area if height and weight be known. Arch Intern Med. 1916;XVII:863–71.
20. de Simone G, Daniels SR, Kimball TR, Roman MJ, Romano C, Chinali M, et al. Evaluation of concentric left ventricular geometry in humans: evidence for age-related systematic underestimation. Hypertension. 2005;45:64–8.
21. Toba A, Kariya T, Aoyama R, Ishiyama T, Tsuboko Y, Takeda K, et al. Impact of age on left ventricular geometry and diastolic function in elderly patients with treated hypertension. Blood Press. 2017;26:264–71.
22. Maanja M, Wieslander B, Schlegel TT, Bacharova L, Abu Daya H, Fridman Y, et al. Diffuse myocardial fibrosis reduces electrocardiographic voltage measures of left ventricular hypertrophy independent of left ventricular mass. J Am Heart Assoc. 2017;6:1161.