

# Deterioration of Deceleration Capacity of Heart Rate is Associated with Left Ventricular Hypertrophy in End-Stage Renal Disease Population

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**Background:** Left ventricular hypertrophy (LVH) is prevalent in patients with end-stage renal disease (ESRD), and may be secondary to arterial stiffness and volume overload. It is unclear whether LVH is caused by autonomic nerve dysregulation (AND), a frequent condition in patients with ESRD that is characterized by sympathetic hyperactivity and vagal withdrawal. We hypothesized that AND estimated by heart rate variability (HRV) may be associated with LVH in patients with ESRD.

**Methods:** We prospectively enrolled patients with ESRD undergoing hemodialysis. Cardiac function and LVH were assessed using echocardiography according to the recommendations of the American Society of Echocardiography. Holter recordings were used to quantify HRV and deceleration capacity (DC). Data on comorbidities and medications, and serum markers were obtained. Logistic regression analysis was performed.

**Results:** Among the 281 included patients, 63% had LVH. The patients with LVH were older, had more comorbidities and advanced diastolic dysfunction than those without LVH. The root mean square of successive differences (rMSSD) ( $9.10 \pm 5.44$  versus  $13.25 \pm 8.61$ ;  $p = 0.004$ ) and DC ( $2.08 \pm 1.90$  versus  $3.89 \pm 1.45$ ;  $p = 0.021$ ) were lower in the patients with LVH than that in those without LVH. Multivariate regression analysis showed that hypertension, asymmetrical dimethylarginine (ADMA), advanced diastolic dysfunction grade, rMSSD, and DC were independently associated with LVH. Among these variables, DC and ADMA showed the highest diagnostic value for LVH with areas under curves of 0.701 and 0.751, respectively.

**Conclusions:** AND is independently associated with LVH in patients with ESRD.

**Key Words:** Deceleration capacity • ESRD • Left ventricle hypertrophy • Vagal withdrawal

## INTRODUCTION

Left ventricular hypertrophy (LVH) is a common finding in patients with end-stage renal disease (ESRD) with a reported incidence of 70%.<sup>1</sup> LVH is also a major risk factor for cardiovascular events, and worsening of LVH is a strong predictor of sudden cardiac death.<sup>1,2</sup> Among dialysis patients, the risk factors for LVH include hypertension, reduced arterial compliance, chronic volume overload, anemia, and arteriovenous fistula created for hemodialysis access.<sup>3-6</sup> In addition, prevalent autonomic nerve dysregulation (AND) in ESRD patients, which is caused by sympathetic overactivity and vagal withdraw, also contributes to worse cardiovascular out-

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comes.<sup>7</sup> While the relationship between LVH and sympathetic hyperactivity has been associated with an increased level of plasma norepinephrine in LVH patients, plasma norepinephrine is not a suitable marker for sympathetic activity.<sup>8,9</sup> Using Holter electrocardiography and heart rate variability (HRV) analysis, emerging evidence has demonstrated that sympathetic hyperactivity is related to an increased left ventricle mass index (LVMI).<sup>7,10,11</sup> Similarly, vagal withdrawal has also been shown to cause AND in patients with ESRD.<sup>7,10,12</sup> However, few studies have investigated the relationship between vagal withdrawal and the incidence of LVH. Recently, a new index called deceleration capacity (DC), which is derived by using phase-rectified signal averaging (PRSA) to characterize heart rate deceleration behavior, has been shown to be a better surrogate for vagal tone and predictor for cardiovascular outcomes than other conventional HRV measures.<sup>13,14</sup> Therefore, DC may be a better tool to assess the relationship between vagal withdrawal and incident LVH. We conducted this cross-sectional study to investigate the magnitude of AND in patients with ESRD and the possible clinical and biomarkers associated with LVH.

## METHODS

### Participants

We enrolled ESRD patients who had received maintenance hemodialysis for > 6 months from April 2015 to September 2016. Approval was obtained from the local ethics committee before initiating the study, and written informed consent was collected from all patients prior to enrollment. After enrollment, 24-hour Holter recordings were performed on the hemodialysis day, and baseline evaluations included a physical examination, 12-lead electrocardiography, laboratory assessments, and transthoracic echocardiography. Blood pressure was measured before and after hemodialysis on the same day of the Holter recording. After excluding 18 patients with atrial fibrillation, we enrolled 281 patients (143 males and 138 females) who had received hemodialysis therapy three times weekly for at least six months (median duration of hemodialysis 49 months, inter-quartile range 25 to 165 months). Dry weight was targeted in each case to achieve a normotensive edema-free state,

and all of the patients were all virtually anuric. Baseline data including comorbidities, history of myocardial infarction and stroke and medications were recorded.

### HRV

Holter recordings were performed using a Zymed-DigiTrakPlus 24 Hour Holter Monitor Recorder and DigiTrak XT Holter Recorder 24 Hour (Philips, Amsterdam, Netherlands). The 24-hour electrocardiography data were reviewed by an experienced technician using commercial software (Zymed 2010 Holter Software). The RR interval was deduced from the adjacent normal sinus beat, and missing intervals were interpolated using the cubic spline method. The mean heart rate, standard deviation of N-N interval (SDNN) and root mean square of successive differences of N-N intervals (rMSSD) were used as time-domain parameters. We determined very low frequency (VLF) power (VLF, 0.0033 to 0.04 Hz), low frequency power (0.04 to 0.15 Hz), and high frequency power (HF, 0.15 to 0.4 Hz) from each 24-hour segment. The power spectrum densities were estimated using Welch's averaged periodogram method.

PRSA was performed according to a previously published method.<sup>15</sup> The PRSA software was benchmarked against a freely available download from the Technical University of Munich. The PRSA method is used to extract periodicities from complex time series, including noise, artefacts, non-stationarities as well as periodic components. Non-periodic components were thus eliminated. DC-quantified spontaneous increases in NN intervals were calculated from short (four beats) overlapping segments.

### Laboratory measurements

On the same day as the Holter recordings, the patients were placed in a semi-recumbent position after resting for 20-30 minutes. Blood sampling was performed before hemodialysis and samples were placed into pre-chilled ethylene diamine tetraacetic acid vacutainers, centrifuged within 30 minutes at 4 °C and the plasma was stored at -80 °C until analysis. Serum hemoglobin, lipids, albumin, hemoglobin A1c (HbA1c), and parathyroid hormone were measured using standard clinical laboratory methods. Plasma high sensitive C-reactive protein (hs-CRP) levels were measured using a commercially available kit (Dade Behring, Marburg, Germany). The upper normal value of hs-CRP is 0.5 mg/dl in our laboratory.

Plasma levels of asymmetrical dimethylarginine (ADMA) were measured using commercially available enzyme-linked immunosorbent assay (ELISA) kits (DLD Diagnostika, Hamburg, Germany).<sup>16</sup> The correlation coefficient between liquid chromatography-mass spectrometry ADMA and ELISA ADMA was 0.98. The recovery rate for ADMA was > 90%, and the within-assay and between-assay variation coefficients were not more than 7% and 8%, respectively.<sup>17</sup>

### Transthoracic echocardiography

Transthoracic echocardiography (TTE) was performed during a mid-week non-dialysis day using an ultrasound system (iE33 xMATRIX Echocardiography System, Philips Healthcare, Best, The Netherlands). Two-dimensional images were acquired with standard parasternal and apical (apical 4-chamber, apical 2-chamber, and apical long-axis) views at a frame rate of 30 frames per second, and three cardiac cycles were recorded. Using M-Mode echocardiography in particular, we measured LV internal dimensions, interventricular septum and posterior wall thicknesses according to the recommendations of the American Society of Echocardiography.<sup>18</sup> LV mass was indexed to body surface area, and LVH was defined as the presence of a LVMI  $\geq 134$  and  $\geq 110$  g/m<sup>2</sup> body surface area in men and women, respectively.<sup>18</sup>

In terms of diastolic dysfunction (DD), the patients were divided into three groups according to DD grade as recently proposed by the American Society of Echocardiography and the European Association of Cardiovascular Imaging in 2016.<sup>19</sup> The 2016 DD grade was evaluated using several parameters including the ratio of mitral inflow velocity to mitral peak velocity of late filling (E/A), peak E velocity, peak velocity of tricuspid regurgitation jet, medial and lateral e', E/e' ratio, and left atrial volume index. Advanced DD was defined as grade II and grade III DD.

### Statistics

Continuous variables are presented as mean values  $\pm$  standard deviations, while categorical variables are presented as frequencies. The chi-square test was used for categorical variables and the Student's t test or Wilcoxon rank sum test was used for continuous variables, as appropriate. The influence of demographic, echocardiographic, laboratory and HRV parameters on the

development of LVH was investigated first using univariate logistic regression. To identify the most relevant parameters for each category, a separate multiple regression model was used for statistically significant variables ( $p < 0.05$ ) in univariate analysis in the respective category using a stepwise procedure. Results were expressed as odds ratios with 95% confidence intervals (CI). The link between the most relevant parameters and LVH was further tested using receiver operating characteristic (ROC) curve analysis, by plotting sensitivity against 1-specificity. The DeLong test was used to compare areas under the curves (AUCs) of the relevant parameters for LVH. The cut-off value of DC was determined using the maximal Youden's index (sensitivity + specificity - 1). Statistical analysis was performed using IBM SPSS Statistics version 21.0 (IBM, Armonk, New York). Two-sided  $p$  values  $< 0.05$  were considered to indicate statistical significance.

## RESULTS

### Baseline characteristics

The baseline characteristics are summarized in Table 1. Our analytic cohort included 281 subjects with male preponderance (143 males, 51%), mean age of  $63 \pm 12$  years, and prevalent hypertension (86.7%) and diabetes (60.2%). According to the guidelines of the Taiwan Hypertension Society, the control of blood pressure (BP) was not achieved, especially systolic BP.<sup>20</sup> The 178 (63.3%) subjects with LVH had higher systolic BP than those without LVH ( $n = 103$ ). In addition, the subjects with LVH were older and had more hospitalizations for heart failure. Furthermore, the subjects with LVH had higher rates of hypertension and coronary artery disease, and were more frequently taking spironolactone and calcium channel blockers (CCBs). A much higher LVMI was noted in the LVH group ( $148 \pm 48.3$  vs.  $87 \pm 15.9$  g/m<sup>2</sup>,  $p < 0.001$ ) compared to the control group. The possible explanations were poor blood pressure (BP) control and longer hemodialysis duration (mean hemodialysis duration  $8.2 \pm 3.5$  vs.  $3.8 \pm 4.1$  years) in the LVH group.

With respect to laboratory parameters, the overall cohort had anemia and higher levels of ADMA, HbA1c, parathyroid hormone, and hs-CRP compared with normal ranges. Of note, the subjects with LVH had a higher

**Table 1.** Baseline characteristics

	Total	No LVH	LVH	p value
N, %	281	103 (36.6)	178 (63.3)	
Male	143 (51)	42 (40.5)	101 (56.7)	< 0.001
Age, year	63 ± 12	61 ± 11	66 ± 12	0.02
BMI, kg/m <sup>2</sup>	25.3 ± 3.68	25.3 ± 3.78	25.2 ± 3.60	0.214
Hemodialysis duration, years	5.7 ± 3.3	3.8 ± 4.1	8.2 ± 3.5	0.012
Systolic BP, mmHg	142 ± 14	138 ± 11	153 ± 16	0.034
Diastolic BP, mmHg	78 ± 9	77 ± 11	79 ± 8	0.751
Hypertension	243 (86.7)	77 (74.7)	166 (93.2)	< 0.001
Diabetes	169 (60.2)	63 (61.1)	106 (59.5)	0.391
CAD	109 (38.8)	30 (29.1)	79 (44.4)	0.015
History of HF hospitalization	94 (33.3)	19 (18.4)	75 (42.1)	< 0.001
History of CVA	34 (12.2)	9 (8.7)	25 (14.4)	0.478
Medications				
Anti-platelets	132 (46.9)	44 (43.1)	88 (49.4)	0.392
Aldactone	89 (31.6)	20 (19.4)	79 (44.3)	0.004
ACEIs/ARBs	92 (32.7)	33 (32.5)	59 (33.1)	0.124
Beta-blockers	52 (18.5)	15 (14.5)	37 (20.8)	0.218
CCBs	100 (35.5)	27 (26.2)	73 (41.0)	0.032
Statins	20 (7.1)	6 (5.8)	14 (7.9)	0.184
Laboratory parameters				
Hemoglobin, g/dl	10.93 ± 1.5	10.90 ± 1.72	10.97 ± 1.17	0.482
HbA1c, %	7.50 ± 1.89	7.43 ± 2.27	7.58 ± 1.45	0.651
Albumin, g/dl	3.97 ± 0.33	4.00 ± 0.32	3.92 ± 0.35	0.194
Parathyroid hormone, pg/ml	379.27 ± 191.2	365.95 ± 183.71	394.38 ± 196.50	0.221
C-reactive protein, md/dl	14.6 ± 24.9	15.4 ± 29.3	12.9 ± 19.3	0.186
ADMA (μmol/L)	1.08 ± 0.17	0.87 ± 0.17	1.26 ± 0.16	0.014
Urea reduction ratio, %	75 ± 6.6	74 ± 5.3	75 ± 7.9	0.229
Echocardiographic parameters				
LVDD, mm	44.9 ± 6.68	40.2 ± 5.58	47.7 ± 5.64*	< 0.001
LVEDD, mm	29.0 ± 6.10	24.8 ± 4.30	31.5 ± 5.68*	< 0.001
IVS, mm	12.6 ± 2.91	11.6 ± 1.42	13.2 ± 3.37*	< 0.001
PWd, mm	12.0 ± 2.54	11.2 ± 1.55	12.5 ± 2.88*	0.021
LA, mm	39.2 ± 6.26	36.0 ± 6.54	41.1 ± 5.32*	< 0.001
LVEF, %	63 ± 10	64 ± 8	62 ± 10	0.228
TRPG, mmHg	28 ± 12.2	21 ± 9.7	41 ± 12.2	0.017
E/A ratio	0.86 ± 0.25	0.81 ± 0.17	0.89 ± 0.28	0.712
LVMI, g/m <sup>2</sup>	127 ± 49.6	87 ± 15.9	148 ± 48.3	< 0.001
Advanced diastolic dysfunction, %	124 (44.1)	27 (26.2)	97 (54.5)	0.002

ACEIs, angiotensin-converting enzyme inhibitors; ADMA, asymmetrical dimethylarginine; ARBs, angiotensin II receptor blocker; BMI, body mass index; BP, blood pressure; CAD, coronary artery disease; CCBs, calcium channel blockers; CVA, cerebral vascular accident; E/A, the ratio of peak velocity flow in early diastole (the E wave) to peak velocity flow in late diastole caused by atrial contraction (the A wave); HbA1c, hemoglobin A1c; IVS, interventricle septum; LA, left atrium dimension; LVEDD, left ventricle end-diastolic dimensions; LVEDS, left ventricle end-systolic dimensions; LVMI, left ventricle mass index; PWd, posterior wall thickness; TRPG, tricuspid regurgitation pressure gradient.

level of ADMA as compared with the subjects without LVH ( $1.26 \pm 0.16$  vs.  $0.87 \pm 0.17$  μmol/L,  $p < 0.05$ ). In terms of echocardiographic parameters, the mean LVMI was  $127 \pm 49.6$  g/m<sup>2</sup>, and  $148 \pm 48.3$  g/m<sup>2</sup> in the LVH

group. Compared with the control, the elevated tricuspid regurgitation pressure gradient (TRPG) ( $41 \pm 12.2$  mmHg), E/A ratio and enlarged left atrium in the subjects with LVH reflected increased LV filling pressure.

Therefore, the subjects with LVH had more advanced diastolic dysfunction (54.5% vs. 26.2%). Both groups had a preserved LV ejection fraction, and there was no systolic dysfunction in our cohort.

### HRV parameters

Missing intervals interpolated with the cubic spline method accounted for 5% to 8% of all R-R intervals. The results are demonstrated in Table 2. In time-domain parameters, the subjects without LVH had a higher SDNN ( $56.2 \pm 40.7$  vs.  $42.0 \pm 29.6$ ,  $p = 0.028$ ) and rMSSD ( $13.25 \pm 8.61$  vs.  $9.10 \pm 5.44$ ,  $p = 0.004$ ) compared with the subjects with LVH. For frequency-domain parameters, lower value of ln VLF ( $5.75 \pm 1.10$  vs.  $6.27 \pm 1.42$ ,  $p = 0.043$ ) and ln LF ( $4.78 \pm 1.38$  vs.  $5.45 \pm 1.65$ ,  $p = 0.034$ ) were observed in the subjects with LVH, whereas there were no significant differences in ln HF and LF/HF ratio between both groups. In the subjects with LVH, the DC was also lower ( $2.08 \pm 1.90$  vs.  $3.89 \pm 1.45$ ,  $p = 0.021$ ) than in those without LVH.

### Multivariate analysis of the determinants of LVH

Logistic regression models to delineate the variables associated with LVH are shown in Table 3. With respect to each parameter cluster, the following variables were independently associated with LVH: 1) clinical comorbidities: hypertension ( $p = 0.016$ ); 2) higher ADMA ( $p = 0.021$ ); 3) TTE: advanced DD grade ( $p = 0.011$ ); and 4) HRV: higher rMSSD ( $p = 0.032$ ) and lower DC ( $p = 0.044$ ) (Table 3).

The AUCs of four different parameters were 0.701 (95% CI 0.568-0.833,  $p = 0.007$ ) for DC, 0.667 (95% CI 0.529-0.804,  $p = 0.025$ ) for DD grade, 0.751 (95% CI 0.625-0.878,  $p = 0.001$ ) for ADMA, and 0.662 (95% CI 0.531-0.793,  $p = 0.029$ ) for rMSSD, all of which were significantly greater than the threshold of indifference (50%). Furthermore, among these variables, DC ( $p = 0.031$ ) and ADMA ( $p = 0.013$ ) showed a higher diagnostic value for LVH compared with rMSSD and DD grade. The cut-off value of DC to detect LVH was 0.27 along with 81% sensitivity (95% CI 72-88%) and 58% specificity (95% CI 47-68%). The ROC curves are shown in Figure 1.

## DISCUSSION

LVH is associated with worse cardiovascular out-

comes in patients receiving dialysis therapy, and regression of LVH may reduce the cardiovascular risk.<sup>21,22</sup> Conventionally, the incidence of LVH has been attributed to pressure and volume overload among ESRD patients. However, the corresponding AND has also been associated with remodeling of the left ventricle. Our study showed a significant correlation between autonomic dysfunction and LVH in dialysis patients, suggesting a potential pathological link between vagal withdrawal and sympathetic hyperactivity and LVH in patients with ESRD.

Among dialysis patients, concentric LV hypertrophy is a primarily adaptive remodeling process to deal with pressure overload (e.g. hypertension, arterial stiffness and aortic stenosis) and volume fluctuations (e.g. anemia, hemodialysis and uremia).<sup>4,23</sup> However, this population are also characterized by LVH and sympathetic hyperactivity.<sup>7,8,10,11</sup> Mechanisms of increased sympathetic activity include renal injury and ischemia, chemoreflex activation, endothelial dysfunction, and reduced nitric oxide (NO) activity.<sup>7</sup> Consequently, the accumulation of ADMA due to increased oxidative stress inhibits NO production, promotes atherosclerosis, increases sympathetic activity, and thereafter the development of LVH and adverse cardiovascular events.<sup>7,24,25</sup> In our cohort, the mean ADMA level was higher than normal range and was 40% higher in the subjects with LVH than in those without LVH.<sup>26</sup> In addition, ADMA was a good marker for LVH (AUC = 0.751), which is consistent with a previous study.<sup>24</sup>

Decreased HRV is a feature of patients with ESRD

**Table 2.** Parameters of heart rate variability comparison between subjects with and without LVH

Parameters	No LVH	LVH	p value
Mean HR, bpm	79 ± 17	84 ± 17	0.216
SDNN	56.2 ± 40.7	42.0 ± 29.6	0.028
rMSSD, ms	13.25 ± 8.61	9.10 ± 5.44	0.004
VLF ln, ms <sup>2</sup>	6.27 ± 1.42	5.75 ± 1.10	0.043
LF ln, ms <sup>2</sup>	5.45 ± 1.65	4.78 ± 1.38	0.034
HF ln, ms <sup>2</sup>	4.32 ± 1.19	4.99 ± 1.39	0.132
LF/HF	1.80 ± 0.90	1.82 ± 0.79	0.965
DC, ms	3.89 ± 1.45	2.08 ± 1.90	0.021

DC, deceleration capacity; HR, heart rate; HF, high-frequency; LF, low-frequency; rMSSD, root mean square of the successive differences; SDNN, standard deviation of N-N interval; VLF, very low frequency.

**Table 3.** Determinants of left ventricular hypertrophy by univariate and multivariate logistic regression analysis

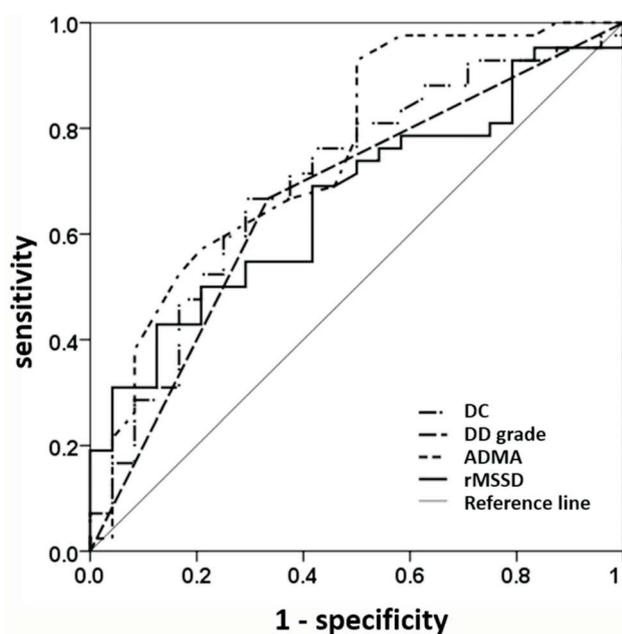
Variables	Univariate		Multivariate	
	Odds ratio (95% CI)	p value	Odds ratio (95% CI)	p value
<b>Clinical parameters</b>				
Age	1.039 (1.002-1.078)	0.036		
Male	0.542 (0.221-1.327)	0.180		
Body mass index	1.023 (0.901-1.161)	0.301		
Hypertension	3.231 (1.918-6.531)	0.014	3.521 (1.413-6.571)	0.016
Systolic BP	1.212 (0.871-1.982)	0.022		
Diabetes	0.778 (0.471-1.317)	0.363		
CAD	1.231 (0.461-3.182)	0.668		
History of HF hospitalization	1.294 (0.991-2.279)	0.673		
History of CVA	1.060 (0.889-2.887)	0.930		
<b>Laboratory parameters</b>				
Hemoglobin	1.002 (0.534-1.958)	0.948		
HbA1c	0.648 (0.357-1.176)	0.154		
Albumin	0.994 (0.822-1.686)	0.137		
iPTH	1.000 (0.997-1.004)	0.814		
CRP	1.123 (1.003-1.756)	0.045		
ADMA	1.901 (1.664-3.121)	0.009	1.892 (1.541-2.987)	0.021
Urea reduction ratio	1.153 (0.983-1.352)	0.032		
Total Cholesterol	1.001 (0.993-1.016)	0.869		
<b>Echocardiographic parameters</b>				
LVEF	0.925 (0.865-0.989)	0.022		
E/A ratio	1.892 (1.019-2.856)	0.044		
E/e' ratio	1.127 (1.012-1.232)	0.022		
TRPG	1.079 (1.007-1.157)	0.031		
Advanced DD grade	4.459 (1.996-7.957)	< 0.001	3.341 (1.321-6.819)	0.011
<b>Heart rate variability parameters</b>				
Heart rate (mean)	0.985 (0.960-1.010)	0.220		
<b>SDNN</b>				
rMSSD	1.091 (1.023-1.164)	0.008	1.089 (1.007-1.177)	0.032
LnLF	1.341 (1.018-1.767)	0.037		
LnHF	1.499 (1.082-2.078)	0.015		
LnVLF	1.399 (1.005-1.946)	0.046		
LF/HF	1.011 (0.629-1.624)	0.965		
DC	0.435 (0.297-0.964)	0.040	0.420 (0.281-0.975)	0.044

p values were derived from simple or multiple logistic regression analysis.

CI, confidence interval, other abbreviations as in Table 1 and Table 2.

and is also considered to be an independent predictor of cardiovascular events.<sup>27,28</sup> Our study demonstrated that traditional HRV parameters including SDNN, VLF, LF and rMSSD were lower in the subjects with LVH, indicating autonomic imbalance. These results are similar to previous reports, thereby supporting the validity of our analysis.<sup>10,27,28</sup> However, among these traditional HRV parameters, only rMSSD reached statistical significance in the multivariate model. It is possible that HF power of

the frequency domain reflects modulation of parasympathetic activity, and several previous studies have reported an inverse association between LVMI and HF power.<sup>10,11</sup> However, our results did not show a significant correlation between HF power and LVH. A possible reason maybe due to the fact that HF power is sensitive to the status of respiration,<sup>29,30</sup> which varies widely in ESRD patients. As with HF power, rMSSD reflects parasympathetic activity, however rMSSD has been proven to be



Parameters	AUC	95% CI	P value
DC	0.701	0.568-0.833	0.007
DD grade	0.667	0.529-0.804	0.025
ADMA	0.751	0.625-0.878	0.001
rMSSD	0.662	0.531-0.793	0.029

**Figure 1.** Receiver operating characteristic curves for deceleration capacity (DC) [area under the curve (AUC) = 0.701], diastolic dysfunction (DD) grade (AUC = 0.667), asymmetrical dimethylarginine (ADMA) (AUC = 0.751) and root mean square of the successive differences (rMSSD) (AUC = 0.662) in predicting left ventricular hypertrophy.

more reliable in reflecting parasympathetic activity in disease status than HF.<sup>31</sup>

Possible mechanisms contributing to AND in ESRD patients include altered baroreceptor and chemoreceptor reflexes, increased renin-angiotensin-aldosterone system activity, and activation of renal afferent arteries.<sup>32</sup> Among patients receiving renal replacement therapy, hemodialysis may trigger sympathetic overactivity and vagal withdrawal as a result of acute fluid removal. Intradialytic hypotension may cause recurrent cardiac injuries and impaired baroreflex sensitivity.<sup>33</sup> It has also been reported that DC is capable of distinguishing the vagal component of cardiac autonomic regulation irrespective of the lack of stationary nature of analyzed data.<sup>15,34</sup> While several studies have demonstrated that DC is a more powerful risk predictor than conventional HRV measures in patients with prior myocardial infar-

tion,<sup>14,34</sup> the prognostic value of DC in patients with ESRD has yet to be fully explored. Suzuki et al. reported that non-surviving ESRD patients had significantly decreased DC values after 87 months of follow-up, but that DC was not an independent predictor in multivariate analysis.<sup>35</sup> To the best of our knowledge, this study is the first to demonstrate a significant association between DC and LVH in multivariate analysis, implying the role of vagal withdrawal and the development of LVH in ESRD patients. Our findings support the hypothesis that improved vagal modulation after intensive hemodialysis leads to regression of LVH and a reduction in ventricle volume.<sup>36,37</sup>

### Limitations

There are several limitations to our analysis given its observational single-center nature. While the cohort included 281 patients on hemodialysis, the overall sample size could have limited the significance of other potential risk factors for LVH. Instead of cardiac magnetic resonance imaging, the diagnosis of LVH was made by echocardiography, which may have led to inter-observer variability and overestimation of LVM. Regarding the assessment of autonomic activity, we did not perform tests other than Holter recording to assess autonomic dysfunction. Because our analyses were cross-sectional, we could not determine whether the associations we found were causal. Longitudinal analyses may provide additional insight into the prognostic value of DC for cardiovascular outcomes in patients with ESRD.

### CONCLUSIONS

Our study showed that HRV assessed by rMSSD and DC was independently associated with LVH in patients with ESRD. DC appeared to be more predictive of LVH than rMSSD. Since DC is considered to be a better surrogate marker of cardiac vagal activity, our findings support the development of therapeutic strategies to target cardiac vagal activity in patients with ESRD.

### DISCLOSURE

All of the authors declared no competing interests.

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