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ORIGINAL RESEARCH

Left Atrial Reservoir Strain by Speckle Tracking Echocardiography: Association With Exercise Capacity in Chronic Kidney Disease

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BACKGROUND: Left atrial (LA) function plays a pivotal role in modulating left ventricular performance. The aim of our study was to evaluate the relationship between resting LA function by strain analysis and exercise capacity in patients with chronic kidney disease (CKD) and evaluate its utility compared with exercise E/e'.

METHODS AND RESULTS: Consecutive patients with stage 3 and 4 CKD without prior cardiac history were prospectively recruited from outpatient nephrology clinics and underwent clinical evaluation and resting and exercise stress echocardiography. Resting echocardiographic parameters including E/e' and phasic LA strain (LA reservoir [LASr], conduit, and contractile strain) were measured and compared with exercise E/e'. A total of 218 (63.9±11.7 years, 64% men) patients with CKD were recruited. Independent clinical parameters associated with exercise capacity were age, estimated glomerular filtration rate, body mass index, and sex (P<0.01 for all), while independent resting echocardiographic parameters included E/e', LASr, and LA contractile strain (P<0.01 for all). Among resting echocardiographic parameters, LASr demonstrated the strongest positive correlation to metabolic equivalents achieved (r=0.70; P<0.01). Receiver operating characteristic curves demonstrated that LASr (area under the curve, 0.83) had similar diagnostic performance as exercise E/e' (area under the curve, 0.79; P=0.20 on DeLong test). A model combining LASr and clinical metrics showed robust association with metabolic equivalents achieved in patients with CKD.

CONCLUSIONS: LASr, a marker of decreased LA compliance is an independent correlate of exercise capacity in patients with stage 3 and 4 CKD, with similar diagnostic value to exercise E/e'. Thus, LASr may serve as a resting biomarker of functional capacity in this population.

Key Words: chronic kidney disease ■ diastolic dysfunction ■ exercise capacity ■ exercise echocardiography ■ left atrial strain ■ left atrium

Exercise capacity is an established prognostic determinant of adverse cardiovascular outcomes and mortality, providing incremental value over established cardiovascular risk factors.[1,2] In patients with chronic kidney disease (CKD), reduced exercise capacity is common and similarly correlates with high cardiovascular risk.[3,4] The cause of reduced exercise capacity in CKD is multifactorial, in part related to the increasingly sedentary lifestyle and frailty that accompanies progression of renal disease.[4] Additionally, diastolic dysfunction, driven by left ventricular (LV) hypertrophy, increased vascular stiffness and systemic hypertension, is considered to be another contributory factor for poor cardiorespiratory capacity in these patients.[5]

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CLINICAL PERSPECTIVE

What Is New?

- This study evaluated the relationship between resting left atrial function by strain analysis and exercise capacity in patients with chronic kidney disease.
- Left atrial reservoir strain was the strongest resting echocardiographic parameter associated with exercise capacity and had similar diagnostic performance as exercise E/e' in detection of reduced exercise capacity.

What Are the Clinical Implications?

- Left atrial reservoir strain may serve as a biomarker of functional capacity in chronic kidney disease populations and can be useful in patients who are unable to exercise because of limiting comorbidities or frailty.
- As exercise capacity is a known prognostic marker for adverse cardiovascular outcomes, identifying patients with chronic kidney disease with impaired left atrial reservoir strain may also improve cardiovascular risk stratification.

Nonstandard Abbreviations and Acronyms

LAScd	left atrial conduit strain
LASct	left atrial contractile strain
LASr	left atrial reservoir strain
LAVI	left atrial volume indexed

The ratio of the transmitral E velocity to tissue Doppler mitral annular e' velocity following exercise (exercise E/e'), has recently been shown to refine diagnosis of diastolic dysfunction and predict poor exercise capacity in patients with CKD.[6] However, stress testing to evaluate exercise E/e' can be technically challenging, particularly in patients with CKD with high frailty levels and exercise-limiting comorbid disease.[7] Therefore, a marker of cardiorespiratory fitness that can be obtained at rest is easier and more practical and would aid risk stratification in these patients.

The left atrium has an important role in modulating LV performance, contributing up to a third of cardiac output.[8] Given its dynamic relationship with the LV chamber, left atrial (LA) function has been considered to predominantly reflect changes in LV systolic and diastolic function. More recently, there is evidence that LA dysfunction in patients with CKD is independently modulated by renal function,[9] that may be indicative of a CKD-associated atrial myopathy. Additionally, in disease states associated with systemic inflammation such as CKD, alterations in LA function independent of diastolic dysfunction have been described.[10]

Though a variety of parameters have been defined, there is no single parameter that best defines LA function. Conventionally, LA function is assessed by volumetric measures. Recently, however, evaluation of LA phasic function by strain analysis has been shown to be feasible and reproducible, with alterations in LA strain occurring before changes in LA volumes.[11,12] Based on these considerations, the objective of our study was to evaluate the relationship between LA function by strain analysis and exercise capacity in patients with CKD that may provide additional insights into exercise physiology beyond diastolic function. Further, we sought to compare the utility of resting echocardiographic parameters to exercise E/e' with regard to its association with reduced exercise capacity.

METHODS

The data that support the findings of the present study are available from the corresponding authors on reasonable request.

Study Population

Patients with stage 3 (estimated glomerular filtration rate [eGFR], 30–60 mL/min per 1.73 m^2) and stage 4 (eGFR, 15–29 mL/min per 1.73 m^2) CKD by the Modification of Diet in Renal Disease formula were prospectively recruited from outpatient nephrology clinics across 2 tertiary hospitals in New South Wales, Sydney, Australia, from January 2011 to December 2017.

Recruited patients were ≥18 years of age without prior cardiac history and had "stable" renal function, defined as <5% change in baseline eGFR for 3 months before enrollment, which was independently adjudicated by the patient-treating nephrologist. All patients were in sinus rhythm on ECG with no evidence of ischemia on exercise stress testing.

We excluded patients with preexisting cardiac disease, including coronary artery disease, heart failure, or arrhythmias, as well as patients with active malignancy, disabling stroke, or concomitant medical comorbidity limiting life span to <12 months. Patients with greater than mild valvular disease or moderate mitral annular calcification and those with impaired LV ejection fraction (LVEF) were also excluded.

Study Protocol

Included participants received clinical evaluation (including history for coexistent cardiac risk factors and

medications), blood pressure assessment, and ECG was recorded at rest. All patients underwent a comprehensive resting transthoracic echocardiogram immediately followed by an exercise stress echocardiogram. Our study was approved by the Human Research and Ethics Committee of New South Wales (HREC/14/LPOOL/304). All participants provided written informed consent.

Transthoracic Echocardiogram

Transthoracic echocardiogram was performed using commercial ultrasound systems (GE Healthcare, Horten, Norway) in accordance with recommendations of the American Society of Echocardiography.[13] Additional dedicated images optimizing the left ventricle and left atrium were acquired at high frame rates (>70 frames/s). All images were stored digitally, and analysis was performed offline.

LV end-diastolic and end-systolic volumes were traced in the apical 4- and 2-chamber views. LVEF was calculated by Simpson's biplane method. Normal LVEF was defined as ≥52% for men and ≥54% for women.[14] LV mass was calculated using the Devereux formula at end diastole and indexed to body surface area to derive the LV mass index. LV hypertrophy was defined as mass index of ≥95 g/m^2 for women and ≥114 g/m^2 for men.[14]

Diastolic function was evaluated from transmitral E and A velocities, E/A ratio, average of the septal and lateral annular e' velocity and E/e' ratio.[15] Diastolic grade was evaluated as per current guidelines.[15] Biplane LA volume was evaluated from apical 4- and 2-chamber views by the modified method of discs and indexed to body surface area to derive the indexed LA volume (LAVI).[16] LA emptying volume was determined by the difference between LA maximum and LA minimum volume. LA ejection fraction (LAEF) was calculated by the LA emptying volume/LA maximum volume.[16]

Speckle-Tracking Echocardiography

Strain analysis was performed with customized computer software (EchoPAC Version BT13, GE Healthcare).

The LV endocardium was traced at end systole in the 3 apical views; software analysis provided a region of interest,) which was adjusted when required to accommodate the thickness of the LV myocardium. An 18-segment LV model (6 segments in each apical view) was obtained; global longitudinal strain was measured as the average of 18 segments.[17] We defined impaired LV global longitudinal strain as ≤–17%, based on previously published lower limit reference value.[18]

For LA strain, the LA endocardium was manually traced in end systole and software automatically tracked the myocardium throughout the cardiac cycle using R-to-R gating on electrocardiography.[19] The region of interest was adjusted to the smallest LA wall thickness for tracking. The LA wall was divided into 6 segments (basal, mid, and apical segments) in the apical 4- and 2-chamber views.[19] Figure 1 shows the LA strain curve throughout the cardiac cycle. In the reservoir phase, as the left atrium fills and stretches, there is positive atrial strain that reaches its peak in systole at the end of LA filling and before opening of the mitral valve, which is measured as LA reservoir strain (LASr). Following this, passive LA emptying ensues with opening of the mitral valve, resulting in decreased atrial strain with negative deflection of the strain curve up to a plateau period, which is analogous to diastasis and is measured as LA conduit strain (LAScd). A second negative deflection in the strain curve is then observed corresponding to atrial systole, representing LA contractile strain (LASct).[17]

LASr is measured at the end of the reservoir phase as the average of the peak systolic strain from 12 segments, LASct is measured as the peak positive strain following *P* wave (atrial contraction) and LAScd as the difference between peak reservoir and contractile strain.[17,19] We defined impaired LASr as ≤23% based on a previously reported lower limit reference value for LASr.[20]

Exercise Echocardiography

Exercise stress testing was performed using standard treadmill protocols with 12-lead ECG monitoring. Patients were encouraged to exercise to maximal effort. Medications likely to suppress heart rate response with exercise were withheld for 24 hours before stress testing. In the event of resting hypertension, antihypertensive therapy was commenced or up titrated. Exercise echocardiogram would be performed following improvement in hypertension.

Post-exercise images were obtained according to standardized protocols for stress echocardiography from apical and parasternal images.[21] Additionally, transmitral peak E velocity and septal and lateral anannular e' velocities were obtained; post-exercise E/e' was calculated with an average of septal and lateral e' measurements.[22]

The maximum predicted heart rate was calculated according to age [100%×(220-age)][17] with a maximal heart rate of ≥85% considered to be the target heart rate. The rate pressure product was calculated as the product of heart rate and systolic blood pressure at peak exercise. Exercise capacity was assessed as estimated metabolic equivalents (METs), calculated from the peak exercise intensity treadmill speed and grade.

Statistical Analysis

Statistical analyses were performed using IBM SPSS Statistics version 22.0 (SPSS, Inc., Chicago, Illinois). All tests were 2-tailed with a *P* value <0.05 considered

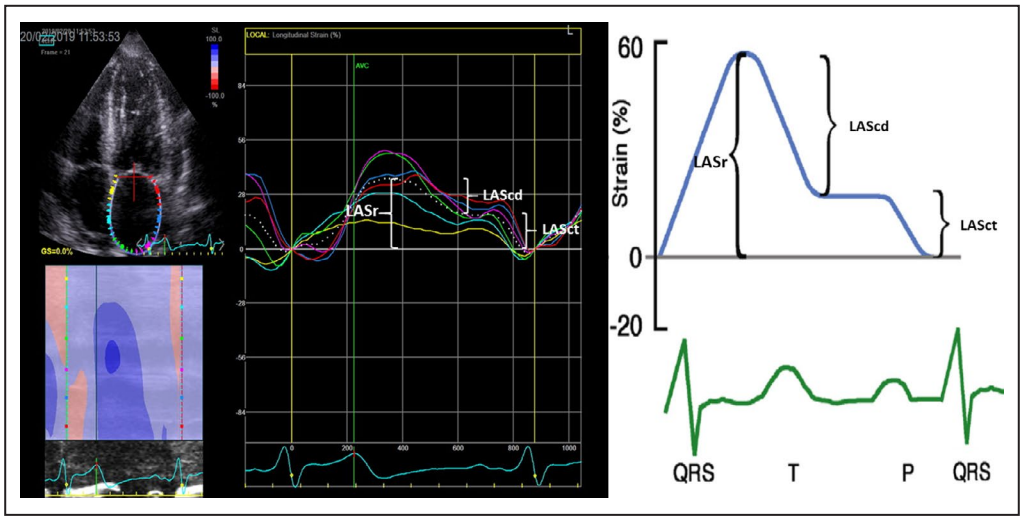


Figure 1. LA strain curve.
Left panel: Two-dimensional speckle tracking strain demonstrating phasic LA strain (LASr, LAScd, and LASct) from the apical 4 chamber view. Segmental strain from 6 segments as well as global LA strain (white dotted line) is shown. Right panel: Phasic LA function relative to the ECG. LA indicates left atrial; LAScd, left atrial conduit strain; LASct, left atrial contractile strain; and LASr, left atrial reservoir strain.

statistically significant. Data were presented as mean±SD for continuous variables and as number and percentage for categorical variables. To facilitate clinical interpretation, the summaries of baseline clinical and echocardiographic data were presented overall and by tertile of METs. The association between tertiles of METs and ordered categorical variables were assessed by chi-squared trend tests. One-way ANOVA with Bonferroni correction or its nonparametric equivalent, the Kruskal-Wallis test, was used for continuous variables. Pearson or Spearman correlation coefficients (for normally distributed and non–normally distributed data, respectively) were used to quantify the strength of linear association between continuous variables.

General linear regression analysis was used to evaluate the relative contribution of the clinical and resting echocardiographic variables to exercise capacity. The variables that exhibited significant univariable association with METs achieved were considered as candidate variables for inclusion in the multivariate models used to determine the independent predictors of METs. Partial r was the association between the variable and METs achieved. The standardized coefficient was the change in METs achieved associated with a 1 SD change in the variables.

Receiver operating characteristic curves and the area under the curve (AUC) was used to quantify the global performance of LASr and other echocardiographic parameters of interest in classifying those with reduced exercise capacity. DeLong tests were used for pairwise comparisons of the AUC. Inter- and intraobserver variability for LA strain indices were evaluated by estimating intraclass correlation coefficients.

RESULTS

Patient Characteristics

The final cohort consisted of 218 (mean age, 63.9±11.7 years; 64% men) prospectively recruited patients with stage 3 and 4 CKD (Figure 2). Nine patients were excluded—4 with atrial fibrillation on ECG, 2 attributable to impaired LVEF, and 3 with evidence of myocardial ischemia on exercise stress echocardiography.

The mean eGFR was 40.0±16.1 mL/min per 1.73 m^2, and the mean creatinine was 170.3±94.2 μmol/L. Hypertensive nephrosclerosis (32%) accounted for the most common cause of CKD in the cohort. This was followed by diabetic nephropathy (30%) and primary and secondary glomerulonephropathies (17%).

Table 1 describes the clinical and echocardiographic parameters in the cohort. As per study protocol, all patients were in sinus rhythm with stable renal function for at least 3 months before enrollment and without prior cardiac disease or ischemia on stress testing. A high prevalence of vascular risk factors was present in the cohort (90% with hypertension, 45% with diabetes mellitus, and 73% with hypercholesterolemia). Anemia, defined as a hemoglobin level of <120 g/L for women and <130 g/L for men,[23] was present in 24% of patients.

The mean resting systolic and diastolic blood pressure of the cohort was 132.4±17.4 mm Hg and

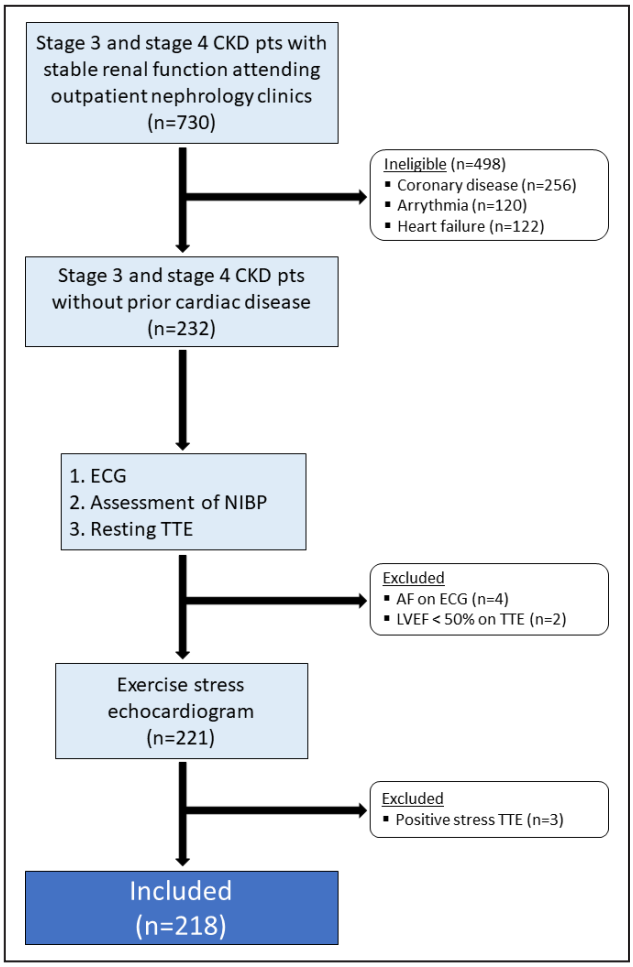


Figure 2. Study protocol and patient characteristics.
A total of 218 patients with stable renal function without prior cardiac history included. Nine patients were excluded, 3 because of myocardial ischemia on stress testing, 2 with impaired LVEF, and 4 with AF. AF indicates atrial fibrillation; CKD, chronic kidney disease; NIBP, noninvasive blood pressure; and TTE, transthoracic echocardiogram.

76.7±11.4 mm Hg, respectively. The average resting heart rate was 77.4±13.3 bpm.

Resting Echocardiography

All patients had normal LVEF. Thirty-four percent of the cohort had increased LV mass index, and 33% had an elevated resting E/e' ratio of >14. The mean LV global longitudinal strain was –19.4±3.8%, and using the lower limit of normal reference value of ≤–17%,[18] 24% had impaired LV global longitudinal strain.

Of the atrial indices, the mean LAVI was 31.3±8.8 mLs/m^2 and 32% had LA enlargement with LAVI ≥34 mL/m^2. The mean LASr, LAScd, and LASct were 24.1±7.6%, 16.4±6.5%, and 17.2±5.3%, respectively. Based on the lower limit of reference value of ≤23%,[20] half of the cohort (50%) had impaired LASr.

Based on current recommendations of diastolic grading, 42% of patients had normal diastolic function, 19% had indeterminate diastolic function, and 39% had impaired diastolic function.

Reduced Exercise Capacity

Table 1 summarizes the baseline clinical and echocardiographic data by tertile of METs achieved. Patients with the poorest exercise capacity (tertile 1: METs ≤5.2) were more often women of older age with higher body mass index (BMI) and lower eGFR (P<0.01 for all). Higher rates of vascular risk factors (hypertension, diabetes mellitus, and hypercholesterolemia; P<0.01 for all) were noted among these patients in addition to higher rates of anemia (P<0.01). No differences in blood pressures at rest or at peak exercise were appreciated.

Of the echocardiographic variables evaluated, higher rates of diastolic dysfunction (P<0.01) were observed among patients with CKD with reduced exercise capacity. These patients also had higher E velocity (P<0.01), lower average e' velocity (P<0.01), higher resting E/e' ratio (P<0.01), and higher exercise E/e' ratio (P<0.01). There were no differences in pulmonary pressures.

With regard to atrial metrics, lower LASr, LAScd, and LASct (P<0.01 for all) were observed in patients with CKD with reduced exercise capacity. Though there was a trend toward larger LAVI (P=0.05), this failed to reach statistical significance. No difference in LA ejection fraction (P=0.56) was seen.

Independent Associations of Exercise Capacity

METs achieved with exercise had a moderate inverse correlation with age (r=–0.49; P<0.01) and BMI (r=–0.30, P<0.01) and a modest positive correlation to eGFR (r=0.33; P<0.01). As expected, men had greater exercise capacity than women (P<0.01) and the magnitude of this difference increased only marginally with age (Figure 3). Of the echocardiographic variables, LASr (r=0.70; P<0.01) showed the strongest correlation to METs achieved followed by exercise E/e' (r=–0.65; P<0.01). Other echocardiographic correlates include resting E/e' (r=–0.41; P<0.01), LAScd (r=–0.38; P<0.01), LASct (r=–0.35; P<0.01), diastolic grade (r=–0.27; P≤0.01), and LAVI (r=–0.18; P<0.01), all of which demonstrated only modest correlations.

To determine the independent associations of exercise capacity, we performed linear regression models based on candidate clinical and echocardiographic variables that showed a significant univariable association with METs achieved. The clinical variables included age, sex, hypertension, diabetes mellitus, eGFR, anemia, and BMI. Although hypercholesterolemia was associated with reduced exercise capacity, it was not included in multivariable models to prevent overfitting, in particular given its low association with

Table 1. Clinical, Echocardiographic, and Exercise Characteristics Based on Tertiles of METs Achieved

Variable	All Patients (n=218)	Tertile 1 METs ≤5.20 (n=74)	Tertile 2 METs 5.21–8.30 (n=72)	Tertile 3 METs ≥8.31 (n=72)	*P* Value
Demographic and comorbidities					
Age, y, mean (SD)y	63.9 (11.7)	69.4 (9.7)*,†	65.3 (10.3)*	56.8 (11.4)	<0.01
Female sex, n (%)	76 (36)	39 (53)*,†	24 (33)	16 (22)	<0.01
BMI, kg/m^2, mean (SD)	29.7 (6.1)	32.2 (7.0)*,†	29.2 (5.6)	27.5 (4.5)	<0.01
eGFR, mL/min per 1.73 m^2, mean (SD)	40.0 (16.1)	33.9 (13.8)*,†	41.6 (13.7)	44.8 (18.4)	<0.01
Hypertension, n (%)	196 (90)	71 (96)*	66 (92)	59 (82)	0.02
Diabetes mellitus, n (%)	99 (45)	42 (57)*	32 (44)	25 (35)	0.03
Hypercholesterolemia, n (%)	158 (73)	63 (85)*,†	48 (67)	47 (65)	0.01
Anemia, n (%)	53 (24)	27 (37%)*	15 (21)	11 (15)	<0.01
SBP, mm Hg, median (IQR)	131.0 (127.0–140.0)	133.0 (125.0–145.0)	130.0 (120.0–140.5)	130.0 (120.0–143.0)	0.39
DBP, mm Hg, median (IQR)	79.0 (70.0–85.0)	75.0 (68.0–82.0)	72.0 (69.5–81.0)	80.0 (71.5–90.0)	0.06
HR, beats/min, median (IQR)	76.0 (67.0–86.0)	77.0 (67.0–86.0)	78.0 (65.5–88.0)	75.0 (69.0–85.0)	0.93
Baseline echocardiography					
LVMI, g/m^2, mean (SD)	97.6 (28.7)	100.6 (30.5)	98.7 (28.7)	93.4 (26.8)	0.30
LVEDV, mL, mean (SD)	69.1 (26.3)	70.7 (28.7)	65.7 (27.1)	70.9 (22.9)	0.41
LVESV, mL, mean (SD)	28.1 (13.9)	28.0 (14.8)	27.4 (15.1)	29.1 (11.7)	0.74
LVEF, %, mean (SD)	59.9 (6.2)	60.7 (6.5)	59.6 (6.1)	59.4 (6.0)	0.41
LVGLS, %, mean (SD)	19.4 (3.8)	19.3 (4.0)	19.2 (4.2)	19.7 (3.3)	0.69
E, mean (SD), m/sec	0.7 (0.2)	0.8 (0.2)*	0.7 (0.2)	0.7 (0.2)	<0.01
E/A, mean (SD)	1.0 (0.5)	1.0 (0.8)	0.9 (0.4)	1.0 (0.5)	0.80
E', mean (SD), cm/s	0.06 (0.02)	0.06 (0.02)*	0.06 (0.02)*	0.07 (0.02)	<0.01
E/e', mean (SD)	13.6 (5.3)	15.5 (5.9)*	14.3 (5.3)*	10.9 (3.3)	<0.01
Diastolic grade					
* Normal, n (%)	91 (42)	22 (30)*	25(35)*	44(61)	<0.01
* Indeterminate, n (%)	41 (19)	13 (18)	16(22)	12(17)	0.66
* Diastolic dysfunction, n (%)	86 (39)	39 (53)*	31(43)*	16(22)	<0.01
LAVI, mL/m^2, mean (SD)	31.3 (8.8)	32.7 (9.5)*	30.8 (8.1)	29.3 (8.6)	0.05
LAEF, %, mean (SD)	62.7 (9.9)	62.0 (11.3)	62.5 (9.9)	63.7 (8.3)	0.56
LASr, %, mean (SD)	24.1 (7.6)	19.1 (5.3)*,†	23.1 (6.2)*	30.1 (6.6)	<0.01
LAScd, %, mean (SD)	16.4 (6.5)	13.4 (5.2)*,†	16.3 (5.7)*	19.3 (7.1)	<0.01
LAScr, %, mean (SD)	17.2 (5.3)	15.3 (5.1)*	16.9 (5.1)*	19.4 (5.0)	<0.01
PASP, mm Hg, mean (SD)	16.9 (11.4)	18.0 (13.3)	14.8 (10.6)	16.9 (11.4)	0.22
Exercise parameters					
Peak SBP, mm Hg, median (IQR)	166.0 (150.0-180.0)	160.0 (145.0-180.0)	165.0 (150.0-170.0)	170.0 (160.0-180.0)	0.06
Peak DBP, mm Hg, median (IQR)	80.0 (70.0-95.0)	80.0 (70.0-98.0)	80.0 (70.0-95.0)	80.0 (70.0-94.0)	0.55
Peak HR, beats/min, median (IQR)	139.0 (121.0-151.0)	127.0 (110.0-146.0)*,†	141.0 (123.0-152.0)*	148.0 (136.5-160.0)	<0.01
Exercise duration, min, mean (SD)	7.1 (4.1)	4.9 (2.7)*,†	6.6 (2.6)*	10.0 (4.9)	<0.01
Exercise E/e', mean (SD)	14.2 (5.6)	17.7 (6.5)*,†	14.4 (4.3)*	10.4 (2.6)	<0.01

BMI indicates body mass index; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; HR, heart rate; IQR, interquartile range; LAEF, left atrial ejection fraction; LAScd, left atrial conduit strain; LASct, left atrial contractile strain; LASr, left atrial strain; LAVI, left atrial volume indexed; LVEDV, left ventricular end diastolic volume; LVEF, left ventricular ejection fraction; LVESV, left ventricular end systolic volume; LVGLS, left ventricular global longitudinal strain; LVMI, left ventricular mass indexed; PASP, pulmonary artery systolic pressure; and SBP, systolic blood pressure.

*P<0.05 to tertile 3.

†P<0.05 to tertile 2.

METs achieved and the lack of biological plausibility on its impact on exercise capacity. As our aim was to determine the optimal resting echocardiographic parameter that predicted exercise capacity, the candidate echocardiographic variables we included were LASr, LAScd, LASct, resting E/e', LAVI, and diastolic grade.

The multivariate models are shown in Table 2; separate models were fitted for LASr, LAScd, and LASct. To avoid

overfitting, we used nested models: model 1, comprising clinically significant variables; model 2a, 2b, 2c, comprising echocardiographic variables for LASr, LAScd, and LASct; model 3a, 3b, 3c, comprising combined independent clinical and echocardiographic variables of model 1 and model 2. A final model was performed combining all the independent variables from the nested model (model 4). Normal probability plots of the residuals in each model showed a good fit with no departure from normality, and there was no collinearity between variables in the models assessed with all variation inflation figures <2 on collinearity diagnostics. Correlation analysis was also performed for age and eGFR, which showed no significant correlation between both variables.

Age, sex, BMI, and eGFR were independent clinical predictors of METs achieved in the multivariable model. Of the echocardiographic parameters, LASr, LAScd, LASct, and resting E/e' were associated with exercise capacity in the echocardiographic models, but only LASr, LASct, and resting E/e' remained independent predictors of METs achieved in the combined clinical and echocardiographic models (models 3a, 3b, 3c). In the final model (model 4), LASr was the only independent echocardiographic predictor of METs achieved.

To evaluate the performance of the independent echocardiographic variables, we compared the AUC of receiver operating characteristic curves of LASr, LASct, and resting E/e' to exercise E/e' (Figure 4). Overall, LASr (AUC, 0.83; 95% CI, 0.78–0.88; $P<0.01$) was the strongest resting echocardiographic predictor of reduced exercise capacity, with a similar diagnostic performance to exercise E/e' (AUC, 0.79; AUC area difference, 0.05; 95% CI, −0.02 to 0.12; $P=0.20$ on DeLong test). Exercise E/e' remained superior to LASct and resting E/e' in predicting reduced exercise capacity.

Relationship of LASr to METs Achieved With Exercise

To assess the clinical value of LASr, we constructed a linear regression model combining LASr and the independent clinical predictors of exercise capacity (age, sex, eGFR, and BMI). Using unstandardized coefficients derived from the model, we performed overlay scatter plots of METs achieved with exercise and predicted METs derived from the model. A strong positive linear relationship between the predicted METs of the model to METs achieved with exercise was observed. In patients with CKD, the addition of LASr to age, sex, BMI, and eGFR provided a robust prediction of METs achieved with exercise.

Inter- and Intraobserver Variability

LA strain was analyzed by 2 different individuals and by the same individual on a different day to evaluate inter- and intra-observer variability. There was good overall agreement and reproducibility of LA strain indices. The inter- and intraobserver interclass correlation for LASr was 0.97 (0.92–0.99) and 0.98 (0.95–0.99), for LAScd was 0.96 (0.93–0.98) and 0.96 (0.93–0.99), and for LASct was 0.98 (0.94–0.99) and 0.97 (0.93–0.99).

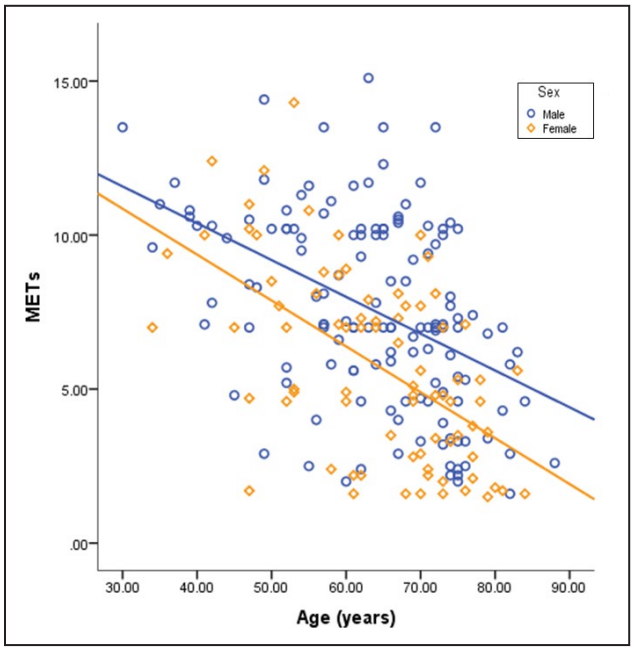


Figure 3. METs achieved during exercise with increasing age in men and women.
Men had greater exercise capacity than women and the magnitude of this difference increased only marginally with age. METs indicates metabolic equivalents.

DISCUSSION

In this study, we demonstrated for the first time the association between resting LA function by strain assessment, and exercise capacity in patients with CKD. In patients with stage 3 and stage 4 CKD, LASr was the strongest resting echocardiographic parameter associated with reduced exercise capacity, with similar diagnostic performance as exercise E/e' in detection of reduced exercise capacity. A multivariable model combining LASr and clinical correlates of exercise (older age, female sex, higher BMI, and reduced eGFR) provided a robust prediction of METs achieved with exercise in patients with CKD.

Exercise Capacity in CKD

Reduction in physical function and exercise capacity in patients with CKD is common and evident even in the early stages of renal disease.[24] The underlying pathophysiological processes are multifactorial and

Table 2. Multivariate Regression Models

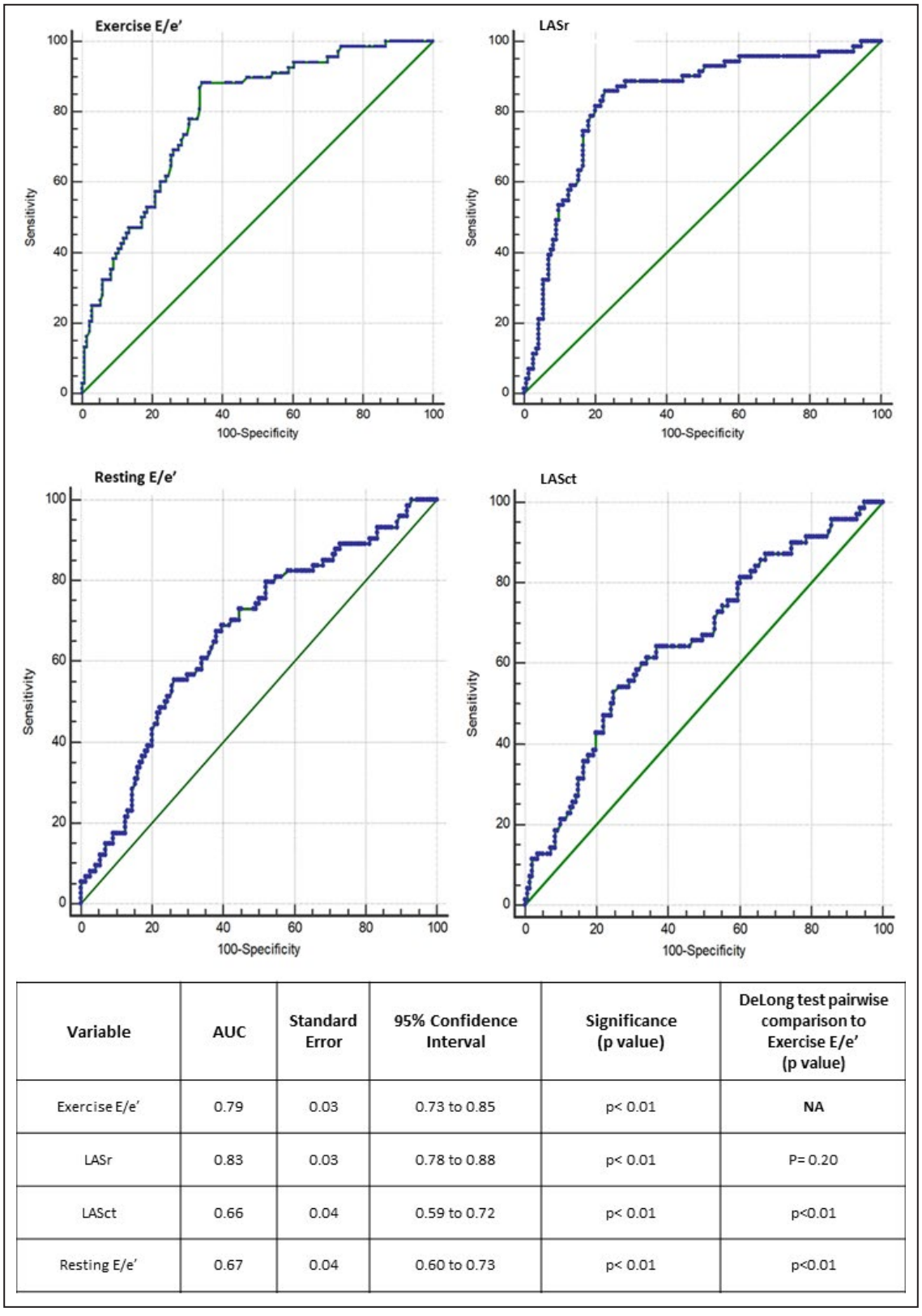
Model	Partial R	Unstandardized Coefficients		B Unstandardized 95% CI		Standardized Coefficients B	Significance (*P* Value)
		B	SE	Lower	Upper		
Model 1: Clinical variables							
Age	−0.505	−0.120	0.014	−0.148	−0.092	−0.438	<0.01
Female sex	−0.268	−1.391	0.346	−2.072	−0.710	−0.209	<0.01
BMI	−0.337	−0.143	0.028	−0.197	−0.089	−0.271	<0.01
eGFR	0.283	0.048	0.011	0.026	0.071	0.242	<0.01
Anemia	−0.057	−0.345	0.418	−1.170	0.479	−0.046	0.41
Hypertension	−0.060	−0.495	0.568	−1.614	0.625	−0.047	0.39
Diabetes mellitus	−0.048	−0.239	0.345	−0.919	0.442	−0.037	0.49
Model 2: Echocardiographic variables							
Model 2a (LASr)							
LASr	0.536	0.226	0.025	0.177	0.275	0.540	<0.01
LAVI	0.041	0.015	0.025	−0.034	0.064	0.038	0.55
Diastolic grade	−0.026	−0.094	0.249	−0.584	0.396	−0.027	0.71
E/e'	−0.205	−0.114	0.038	−0.188	−0.039	−0.192	<0.01
Model 2b (LAScd)							
LAScd	0.263	0.134	0.034	0.066	0.202	0.273	<0.01
LAVI	−0.038	−0.015	0.029	−0.072	0.041	−0.040	0.59
Diastolic grade	−0.028	−0.119	0.293	−0.696	0.459	−0.034	0.69
E/e'	−0.221	−0.145	0.045	−0.234	−0.056	−0.242	<0.01
Model 2c (LASct)							
LASct	0.248	0.147	0.040	0.067	0.226	0.241	<0.01
LAVI	0.003	0.001	0.029	−0.056	0.059	0.003	0.97
Diastolic grade	−0.087	−0.358	0.288	−0.925	0.209	−0.102	0.21
E/e'	−0.243	−0.159	0.044	−0.246	−0.071	−0.264	<0.01
Model 3: Combined clinical and echocardiographic variables							
Model 3a (LASr)							
Age	−0.372	−0.080	0.014	−0.108	−0.053	−0.293	<0.01
Female sex	−0.300	−1.396	0.308	−2.003	−0.788	−0.210	<0.01
BMI	−0.196	−0.076	0.026	−0.128	−0.024	−0.140	<0.01
eGFR	0.259	0.037	0.010	0.018	0.056	0.187	<0.01
LASR	0.431	0.159	0.023	0.114	0.205	0.377	<0.01

(*Continued*)

Table 2. Continued

Model	Partial R	Unstandardized Coefficients		B Unstandardized 95% CI		Standardized Coefficients B	Significance (*P* Value)
		B	SE	Lower	Upper		
E/e'	−0.107	−0.047	0.031	−0.108	0.013	−0.079	0.12
Model 3b (LAScd)							
Age	−0.428	−0.107	0.016	−0.138	−0.076	−0.386	<0.01
Female sex	−0.270	−1.379	0.345	−2.060	−0.699	−0.208	<0.01
BMI	−0.297	−0.127	0.029	−0.184	−0.071	−0.235	<0.01
eGFR	0.285	0.045	0.011	0.024	0.066	0.229	<0.01
LAScd	0.073	0.032	0.031	−0.028	0.092	0.065	0.30
E/e'	−0.162	−0.083	0.035	−0.153	−0.013	−0.137	0.02
Model 3c (LASct)							
Age	−0.466	−0.109	0.015	−0.138	−0.080	−0.393	<0.01
Female sex	−0.271	−1.351	0.336	−2.013	−0.689	−0.203	<0.01
BMI	−0.294	−0.121	0.028	−0.175	−0.067	−0.223	<0.01
eGFR	0.293	0.045	0.010	0.025	0.065	0.228	<0.01
LASct	0.239	0.112	0.032	0.049	0.175	0.186	<0.01
E/e'	−0.138	−0.067	0.034	−0.134	−0.001	−0.111	0.05
Model 4: Final model with all independent variables							
Age	−0.367	−0.081	0.014	−0.110	−0.053	−0.292	<0.01
Female sex	−0.295	−1.379	0.313	−1.996	−0.761	−0.207	<0.01
BMI	−0.203	−0.079	0.027	−0.132	−0.026	−0.146	<0.01
eGFR	0.259	0.037	0.010	0.018	0.056	0.188	<0.01
LASr	0.365	0.155	0.028	0.100	0.210	0.367	<0.01
LASct	0.023	0.011	0.035	−0.057	0.080	0.019	0.74
Resting E/e'	−0.092	−0.042	0.032	−0.105	0.021	−0.069	0.19

BMI indicates body mass index; eGFR, estimated glomerular filtration rate; LAScd, left atrial conduit strain; LASct, left atrial contractile strain; LASr, left atrial reservoir strain; LAVI, left atrial volume indexed.



Variable	AUC	Standard Error	95% Confidence Interval	Significance (p value)	DeLong test pairwise comparison to Exercise E/e' (p value)
Exercise E/e'	0.79	0.03	0.73 to 0.85	p< 0.01	NA
LASr	0.83	0.03	0.78 to 0.88	p< 0.01	P= 0.20
LASct	0.66	0.04	0.59 to 0.72	p< 0.01	p<0.01
Resting E/e'	0.67	0.04	0.60 to 0.73	p< 0.01	p<0.01

Figure 4. ROC curves of exercise E/e', LASr, LASct, and resting E/e' with DeLong tests.
LASr was the strongest independent predictor of reduced exercise capacity amongst resting echocardiographic parameters. AUC indicates area under the curve; LASct, left atrial contractile strain; and LASr, left atrial reservoir strain.

broadly relate to both irregularities in oxygen delivery (eg, vascular dysfunction) and extraction mechanisms (eg, skeletal muscle). With advancing renal disease, altered vascular tone attributable to endothelial dysfunction and increased vascular stiffness impair the capacity of peripheral vessels to dilate in response to increased shear stress during exercise.[25] Moreover, oxidative stress and proinflammatory states, both associated with CKD and heart failure with preserved ejection fraction, contribute to muscle wasting and have been found to correlate with physical fitness.[26,27] Microvascular endothelial inflammation is also associated with endothelial dysfunction and microvascular rarefaction, disease processes integral to tissue oxygenation.[28]

LA Function and Exercise Capacity

There is mounting evidence that LA dysfunction is a contributor to cardiorespiratory symptoms and exercise capacity.[29,30] Among unselected individuals referred for exercise stress echocardiogram, Kusunose et al[31] showed a strong association between reduced LA strain and impaired exercise capacity. Impaired LASr and LASct has also been associated with abnormal exercise dynamics and elevated pulmonary pressures among patients with heart failure and preserved ejection fraction.[32]

As the interplay between atrial phasic function and ventricular mechanics is essential for modulation of cardiovascular performance, these findings are unsurprising.[16] Impaired LA function can impose greater hemodynamic stress on the pulmonary vasculature and has been shown to be a robust correlate of elevated pulmonary vascular resistance and peak volume of oxygen, above and beyond traditional markers of diastolic function including the E/e' ratio and LA volume.[33] Additionally, chronic pulmonary venous congestion in the setting of abnormal LA mechanics results in altered pulmonary artery compliance, which hinders oxygen delivery and gas exchange.[34]

Of interest, although diastolic dysfunction has been linked with impaired exercise capacity in unselected patients [35] and patients with CKD,[6] our study demonstrated that impaired LASr in the absence of diastolic dysfunction was also strongly associated with impaired exercise capacity. This would suggest that in addition to the hemodynamic changes consequent to diastolic dysfunction, pathophysiological mechanisms specific to CKD likely contribute to LA remodeling and dysfunction, that is, development of an atrial myopathy.

Mechanism for LA Dysfunction in CKD

Studies have shown that CKD is an independent factor affecting LA function[36,37] and that alterations in LA strain occur before changes in LA volumes.[10] In patients with heart failure with preserved ejection fraction, Unger et al[9] demonstrated incremental reductions in LASr parallel to reductions in eGFR that was independent of clinical and other echocardiographic covariates, implying that pathophysiological mechanisms specific to CKD are also additive and worsen with progression of renal impairment.

Inflammation, consequent to uremia and local wall stress, have been proposed as a contributing mechanism, with a strong relationship between LA dilatation and high-sensitivity C-reactive protein reported in patients with stage 3 to 5 CKD.[38] This is similar to observations in patients with atrial fibrillation in whom increased inflammatory markers, including C-reactive protein and interleukin-6, have been linked to atrial size.[39] Additionally, neurohormonal changes, oxidative stress attributable to anti-oxidative imbalance as well as excessive sympathetic nerve excitation also play a role.[40] Enhanced angiotensin II activity by renin-angiotensin-aldosterone system upregulation, together with other downstream mediators such as transforming growth factor-beta 1, results in progressive myocardial fibrosis,[41] which manifests earlier and is more evident in the atrium, a thin-walled structure. Furthermore, changes in autonomic activity may trigger profibrotic signaling pathways, further driving atrial dysfunction.[42]

Clinical Relevance

Though utility of LA strain is largely confined to the research arena at present, a growing body of literature supports its use particularly in the evaluation of specific populations with diastolic dysfunction, where it has been shown to be an independent predictor of all-cause mortality.[43]

As exercise capacity is a known prognostic marker for adverse cardiovascular outcomes,[1,44] the potential application of our findings cannot be understated. In patients who are unable to exercise because of limiting comorbidities or frailty, resting LASr can be used as an alternative to exercise E/e'. Identifying patients with CKD with impaired LASr may also improve cardiovascular risk stratification and intensification of risk factor management in this patient group at risk of developing adverse cardiovascular events.

STRENGTHS AND LIMITATIONS

Our study had stringent eligibility criteria and included only patients with stable stage 3 and stage 4 CKD with low cardiovascular risk without myocardial ischemia on stress testing recruited across 2 large tertiary centers. Though our sample size was modest, more than half the cohort had reduced exercise capacity.

Furthermore, although strain measurement has an intrinsic limitation of variability, we had good level of reproducibility of measurements.

We used calculated METs as a measure of exercise tolerance rather than oxygen consumption, which although a more robust measure, is seldom used in routine clinical practice and was beyond the scope of this study. Further, B-type natriuretic peptide levels were not available in this group as patients were low risk, asymptomatic, and without cardiovascular disease. Finally, although LA strain is increasingly used, it is currently measured using a software package developed for the evaluation of LV strain, which has intrinsic limitations.

CONCLUSIONS

In patients with stable stage 3 and 4 CKD without prior cardiac disease, LASr had the strongest association with reduced exercise capacity, superior to other resting echocardiographic parameters and with similar diagnostic performance as exercise E/e'. The use of LASr may serve as a biomarker of functional capacity in this population and could be used as a therapeutic target to monitor effects of treatments.

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Disclosures

None.

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