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ORIGINAL RESEARCH ARTICLE

Diagnostic accuracy of left atrial remodelling and natriuretic peptide levels for preclinical heart failure

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Abstract

Aims Left atrial (LA) remodelling is an important predictor of cardiovascular events of heart failure (HF) and atrial fibrillation. Data regarding diagnostic value of LA remodelling on diastolic dysfunction (DD) and preclinical HF remain largely unexplored.
Methods and results We assessed LA dimension (LAD) in 8368 consecutive asymptomatic Asians (mean age: 49.7, 38.9% women) and related such measure to updated American Society of Echocardiography (ASE) DD criteria and newly revised N-terminal pro-brain natriuretic peptide (NT-proBNP) cut-off (≥125 pg/mL) and HF with preserved ejection fraction criteria incorporating NT-proBNP and echocardiography parameters by the European Society of Cardiology (ESC). LAD and indexed LAD (LADi) were both inversely correlated with myocardial relaxation e′ and positively associated with indexed LA volume, left ventricular E/e′, and tricuspid regurgitation velocity (all $P < 0.001$) and showed significantly graded increase across ASE-defined ‘normal’, ‘inconclusive’, and ‘DD’ categories (30.9, 34.4, and 36.5 mm; 16.7, 19.1, and 20.6 mm/m^2, for LAD/LADi, both P for trend: <0.001, respectively). Substantial differences of LAD/LADi (31.3 vs. 33.6 mm/16.7 vs. 19.2 mm/m^2, both $P < 0.001$) between ESC low and high HF probability using NT-proBNP cut-off were also observed. Multivariate linear and logistic models demonstrated that LAD set at 34 mm was independently associated with ASE-defined diastolic indices, DD existence, and elevated NT-proBNP (all $P < 0.05$). The use of LAD further yielded high diagnostic accuracy in DD (area under receiving operative characteristic curve: 0.77, 95% confidence interval [0.73, 0.80]; negative predictive value: 97.9%) and in ESC-recommended HF with preserved ejection fraction criteria (area under receiving operative characteristic curve: 0.70, 95% confidence interval [0.65, 0.75]; negative predictive value: 98.7%) with high predictive value in LA remodelling (>34 mL/m^2; positive predictive value: 96%) and well-discriminated ESC-recommended NT-proBNP (≥125 pg/mL, LAD: 37 mm) for HF.
Conclusions Single utilization of atrial remodelling is highly useful for ruling out presence of DD and provides practical threshold for identifying preclinical HF based on most updated guidelines.

Keywords Left atrium; ESC; Diastolic dysfunction; Heart failure; Atrial fibrillation; Echocardiography

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Introduction

The left atrium (LA) serves as a sensitive marker of clinical and subclinical cardiovascular disease.[1] Left atrial (LA) size is increased in a variety of cardiovascular disorders and is an indicator of chronically increased LA afterload and/or volume, especially in heart failure (HF).[2–5] Increased LA size has also been implicated in atrial fibrillation (AF)[6,7] and may be an indicator of early structural remodelling in senescence or in subjects with multiple clinical co-morbid conditions including obesity[8] or hypertension.[9] LA size also appears to be a useful predictor of several cardiovascular outcomes.[10,11]

Left atrium as a barometer may adapt to long-standing diastolic dysfunction (DD) or HF owing to chronically elevated left ventricular (LV) filling pressure, even with preserved ventricular function.[12–14] Therefore, accurate assessment of LA size or remodelling remains the cornerstone in recognizing DD as a clinical precursor for HF and forms the essential diagnostic key component for HF with preserved ejection fraction (HFpEF).[15,16] Because a standardized definition and index parameter for DD or clinical high-risk population of HF remains obscure, a more recent update of DD scoring system issued by the American Society of Echocardiography (ASE) recommended the use of a cluster of quantitative diastolic measures for objective definition.[17] Recently, the European Society of Cardiology (ESC)[16] also provided relevant clinical N-terminal pro-brain natriuretic peptide (NT-proBNP) cut-off, which predicts high probability for HF. However, the association of such measures with LA remodelling in a large asymptomatic population remains largely unexplored. This study therefore aimed to characterize LA remodelling and explore its association with DD or NT-proBNP threshold for HF based on guideline-recommended cut-offs in an asymptomatic Asian population.

Methods

Study subjects

This cross-sectional study analysed data of subjects who underwent annual cardiovascular evaluations at the MacKay Memorial Hospital (a tertiary medical centre in Northern Taiwan) between July 2003 and December 2012. For study participants who had multiple visits, only the visits for which echocardiogram data were available were included. Participants with missing key baseline variables and participants who did not have electrocardiography data for LA size were also excluded. Additional exclusion criteria were presence of an implanted pacemaker, pulmonary hypertension (defined as peak systolic pulmonary artery pressure ≥60 mmHg), impaired LV systolic function (LV ejection fraction <50%), hypertrophic cardiomyopathy, AF, thyroid dysfunction, significant primary valvular heart diseases (aortic or mitral valves) or history of valvular surgery, prior HF history or current symptoms of HF, or ongoing chest pain. Among totally 11 376 visits with echocardiography data available, we identified 8368 subjects with sufficient baseline information after exclusion criteria with part of this population published elsewhere.[13] This study was approved by the local ethics committee in accordance with the Declaration of Helsinki in our hospital (MacKay Memorial Hospital), and patient information was de-identified prior to analysis.

Conventional echocardiography and left atrial dimension determination

Echocardiography was performed as described previously,[13] using the Philips Hewlett-Packard (HP) Sonos 5500 ultrasound or the GE system (Vividi, Vingmed, Horten, Norway) equipped with the 2–4 MHz transducer. For both echocardiography systems, a standard imaging protocol was performed where M-mode, linear-based measures of LA dimension (LAD), LV end-diastolic/systolic diameter, wall thickness, and LV mass (and indexed to body surface area) were all obtained and calculated using the ASE criteria.[18] Further, LV volumes (both end-diastolic and end-systolic), LA volumes (LAVs) at maximum point, and derived LV ejection fraction were all determined by the modified biplane Simpson method using two-dimensional (2D) echocardiography (from LV apical four-chamber and two-chamber views). Indexed LAV (LAVi) and LAD/LADi were calculated by dividing LAV and LAD by body surface area. All M-mode images were acquired and recorded at a speed of 60–100 mm/s with the transducer placed at the third to the fifth inter-costal space. All echocardiography loops were obtained for at least three beats for 2D-based images and for at least 5–8 beats for M-mode-based measures. Image acquisition was performed with study participants in a left lateral decubitus position. Study participants were requested to hold their breath for 5–10 s if the image quality was suboptimal.

Assessment of diastolic functional indices and criteria for diastolic dysfunction

Diastolic assessment including transmitral inflow pulsed-wave Doppler of LV early (E) and late diastolic (A) velocities were measured from the tip of the mitral leaflets of the LV apical four-chamber view. Deceleration time (DT) and isovolumic relaxation time were also determined from same LV apical views, with minor adjustment and sliding of echo beam angle for continuous wave-based Doppler isovolumic relaxation time acquisition from LV apical five-chamber view. Peak tricuspid regurgitation (TR) systolic jet velocity was obtained during systole at the leading edge of spectral waveform from the four-chamber view, with angle-adjusted alignment of continuous wave Doppler echo beam. This also made it possible to assess the difference of pressure between the right ventricle and the right atrium. The simplified Bernoulli equation ($P = 4 \times [\text{TR max}]^2$) was used to quantify pressure differences using peak TR velocity, because this has been well validated with pulmonary artery systolic pressure utilizing the invasive right heart catheterization method.[19]

High frame rate myocardial velocity tissue Doppler imaging technique was used to determine early myocardial relaxation velocity (e', both septal and lateral mitral annular areas were evaluated). LV filling pressure was estimated

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by dividing mitral inflow (E) by early myocardial relaxation velocity (e′). We further categorized diastolic function based on four variables recommended by the ASE[17]: (i) mitral annular velocity e′: septal e′ < 7 cm/s or lateral e′ < 10 cm/s; (ii) average E/e′ ratio > 14; (iii) LAV index >34 mL/m^2; and (iv) peak TR velocity >2.8 m/s. Similarly, enlarged LAV was also part of HFpEF diagnostic components by more recent ESC criteria.[16] We further developed ASE DD scores by calculating the summation of any available 'positive' diastolic index based on ASE in any individual (*Figure 1*), which reflected total numbers of abnormal diastolic parameters that met ASE cut-off values. LV diastolic function was classified as 'normal' if more than half of the available diastolic indices did not meet the cut-off values of ASE-defined abnormal criteria, was defined as 'DD' if more than half of the variable parameters met the abnormal cut-off values, and was classified as 'inconclusive' if half of the parameters did not meet the cut-off values (*Figure 1*). Based on this, ASE DD scores were graded as 0, 1, 2, 3, or 4, respectively, for number of diastolic indices categorized as 'abnormal', with DD ratio defined as the 'abnormal' diastolic parameters divided by the total numbers of diastolic indices available. Finally, we further examined the diagnostic utilization of LAD/LADi measures for ESC-proposed HFpEF criteria[16] in current study, incorporating NT-proBNP and three additional echocardiography parameters including indexed LAV (>34 mL/m^2), sex-specified LV mass index, and average E/e′ ratio and averaged e′ in study participants.

Determination of serum N-terminal pro-brain natriuretic peptide and renal function

N-terminal pro-brain natriuretic peptide (pg/mL) was determined using the electrochemiluminescence immunoassay (Roche E170, Roche Diagnostics) on samples collected by venipuncture. Renal function in terms of estimated glomerular filtration rate was assessed using the Modification of Diet in Renal Disease formula. Based on ESC clinical practice guideline criteria for high probability of HF, NT-proBNP ≥ 125 pg/mL was categorized as high probability of clinical HF in our current study.

Statistical analysis

Continuous data were presented as mean and standard deviation. The independent two sample *t*-test was performed to compare the continuous data between women and men (Supporting Information, *Table S1*). The one-way ANOVA test with *post hoc* Bonferroni corrections was performed to compare the continuous data among any three categorization groups (e.g. as 'normal', 'inconclusive', and 'DD' in *Table 1*).

Figure 1 The classification and categorization of study participants and relevant diastolic dysfunction (DD) scoring developed based on American Society of Echocardiography (ASE)-recommended criteria for diastolic functional measures. All participants had left ventricular ejection fraction (LVEF) > 50%. LAVi, left atrial volume index; LV, left ventricular; TDI, tissue Doppler imaging; TR, tricuspid regurgitation.

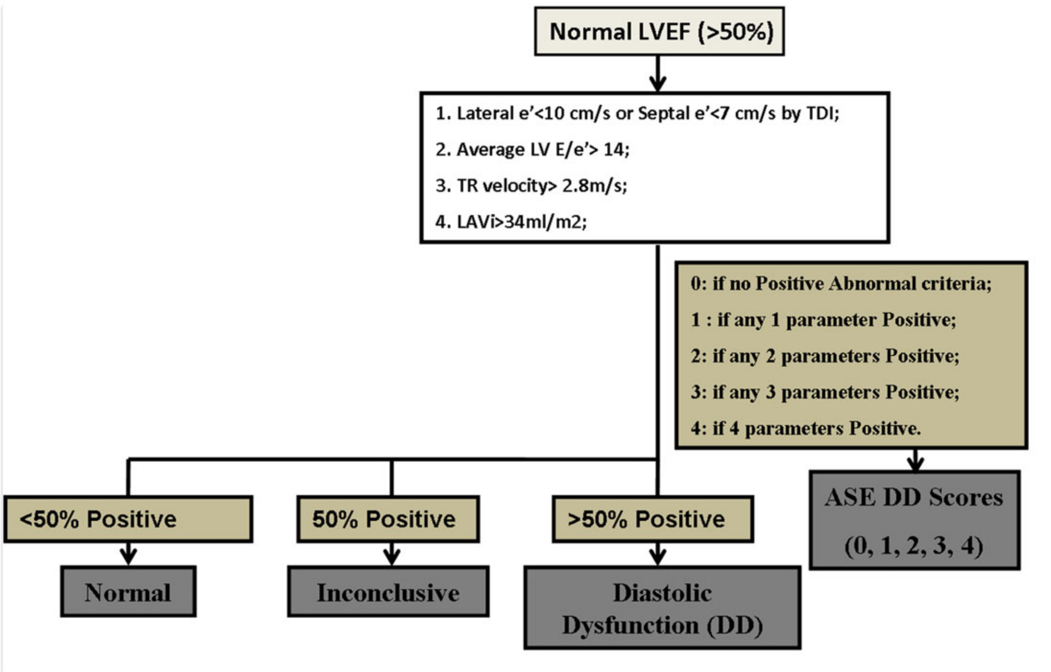

Table 1 Baseline demographics, clinical characteristics, and diastolic indices of study participants stratified by ASE DD criteria

	ASE-defined DD categorization			
	Normal (n = 7628)	Inconclusive (n = 521)	DD (n = 165)	P (trend test/χ^2)
Baseline characteristics				
Age, years	48.8 (11.3)	58.9 (11.8)*	60.1 (10.9)*	<0.001
Sex, female, %	2886 (37.8)	239 (45.9)	96 (58.2)	<0.001
BMI, kg/m^2	24.2 (3.6)	25.2 (3.7)*	24.7 (3.8)	<0.001
SBP, mmHg	122.4 (17.3)	131.7 (19.3)*	133.7 (20.7)*	<0.001
Heart rate, b.p.m.	74.2 (10.3)	73.6 (10.5)	73.4 (10.6)	<0.001
Medical history/co-morbidity				
HTN, n (%)	1360 (17.8)	200 (38.4)	62 (38.0)	<0.001
Hyperlipidaemia, n (%)	495 (6.5)	59 (11.3)	20 (12.1)	<0.001
CVD, n (%)	559 (7.3)	94 (18.0)	27 (16.4)	<0.001
CAD, n (%)	402 (5.3)	70 (13.4)	23 (13.9)	<0.001
DM, n (%)	473 (6.2)	69 (13.2)	24 (14.6)	<0.001
Diastolic and left atrial indices				
PR interval, ms	164.3 (20.6)	169.9 (25.4)*	171.6 (26.1)*	<0.001
LAD, mm	30.9 (4.6)	34.4 (5.8)*	36.5 (5.0)*	<0.001
LADi, mm/m^2	16.7 (2.5)	19.1 (3.3)*	20.6 (3.2)*	<0.001
LAV (max), mL	29.3 (10.4)	36.1 (15.0)*	40.9 (16.2)*,**	<0.001
LAVi, mL/m^2	15.6 (5.1)	20.1 (8.0)*	22.7 (9.0)*,**	<0.001
TDI e′ (average), cm/s	9.4 (2.3)	6.7 (1.7)*	6.4 (1.3)*	<0.001
TDI E/e′ (mean)	7.5 (2.0)	11.7 (3.7)*	13.8 (3.4)*,**	<0.001
TR velocity	2.1 (0.3)	2.4 (0.5)*	2.8 (0.4)*,**	<0.001
No. of ASE DD scores	0.34 (0.47)	1.7 (0.5)*	2.2 (1.1)*,**	<0.001
NT-proBNP, pg/mL (IQR: 25th–75th)	39.1 (12.5–50.3)	108.9 (30.3–119)*	160.5 (33.4–145.8)*,**	<0.001

ASE, American Society of Echocardiography; BMI, body mass index; CAD, coronary artery disease; CVD, cardiovascular disease; DD, diastolic dysfunction; DM, diabetes mellitus; HTN, hypertension; IQR, interquartile range; LAD, left atrial diameter; LADi, left atrial diameter index; LAV, left atrial volume; LAVi, left atrial volume index; NT-proBNP, N-terminal pro-brain natriuretic peptide; SBP, systolic blood pressure; TDI, tissue Doppler imaging; TR, tricuspid regurgitation.
*ANOVA $P < 0.05$ vs. normal group.
**ANOVA $P < 0.05$ vs. inconclusive group.

Categorical data (e.g. gender, medical history, and co-morbidity) were presented as numbers and percentages with the χ^2 test. The associations between LAD and LADi (which is clinically more practical without index) and all individual ASE-defined four diastolic indices [including myocardial relaxation e′, LV E/e′, degree of LA enlargement (LAVi), and elevated TR velocity] were presented in univariate and multivariate linear regression models with age, gender, body size (body mass index), blood pressure, heart rate, fasting sugar level, lipid profiles including total cholesterol, high-density lipoprotein, renal function in terms of estimated glomerular filtration rate, and baseline medical history of hypertension, diabetes mellitus, cardiovascular diseases, coronary artery diseases, and LV mass in a full model as confounders (*Table 2*). Paired comparisons of LAD/LADi in both genders were performed between the 'normal', 'inconclusive', and 'DD' groups by the ANOVA test (Supporting Information, *Figure S2*).

We also examined the clinical odds ratio (OR) of individual abnormal ASE-defined diastolic indices or presence of DD by logistic regression models, with (adjusted OR) and without (crude OR) adjusting for the same confounders. Area under receiving operative characteristic (AUROC) curves and the corresponding 95% confidence intervals (CIs) were calculated for prediction of individual abnormal diastolic indices and presence of DD using LAD/LADi measures separately. For LAD, optimal cut-off was chosen from the largest summation of sensitivity and specificity, with positive (PPV) and negative predictive values (NPV) also reported.

All statistical analyses were evaluated at a two-sided significance level of 0.05 and were performed using IBM SPSS software, version 22 (IBM Corp., Armonk, NY, USA).

Results

Baseline characteristics and echocardiography measures of study subjects

Among totally 8368 participants (mean age of 49.7 ± 11.7 years) met the inclusion/exclusion criteria for this study (Supporting Information, *Table S1*), 8314 had any given (1-4) echocardiography parameters for DD grading. The final study population comprised 3221 women and 5093 men, respectively. Echocardiography demonstrated that men had significantly greater LAD (32.1 vs. 29.9 mm), LV wall thickness, and volumes and larger total LV mass (indexed to height^2) compared with women (all $P < 0.05$), although significantly lower mitral inflow E/A ratio, smaller LADi (16.4 vs.

Table 2 The associations of LAD with ASE-recommended diastolic indices or DD and ESC NT-proBNP cut-offs for HF

	All		Women		Men	
	Coefficient (95% CI)	*P*-value	Coefficient (95% CI)	*P*-value	Coefficient (95% CI)	*P*-value
Linear regression models						
Unadjusted univariate models (per 10 units + of LAD)						
NT-proBNP level (pg/mL)	20.4 (15.6, 25.3)	<0.001	49.5 (40.0, 59.0)	<0.001	16.5 (11.0, 22.0)	<0.001
LA volume (max) (mL)	10.47 (9.95, 10.98)	<0.001	9.98 (9.20, 10.75)	<0.001	10.40 (9.70, 11.11)	<0.001
LAVi (also ESC HFpEF[16]) (mL/m^2)	4.14 (3.86, 4.41)	<0.001	4.88 (4.43, 5.34)	<0.001	4.37 (4.01, 4.72)	<0.001
Adjusted multivariate models (per 10 units + of LAD)						
NT-proBNP level (pg/mL)	20.9 (14.6, 27.1)	<0.001	49.8 (37.3, 62.4)	<0.001	6.1 (−0.61, 12.8)	0.075
LAVi (also ESC HFpEF[16]) (mL/m^2)[a]	3.3 (3.0, 3.6)	<0.001	3.2 (2.6, 3.8)	<0.001	3.3 (2.9, 3.7)	<0.001
TDI e′ (averaged) (cm/s)	−0.18 (−0.32, −0.03)	0.016	−0.4 (0.6, −0.1)	0.004	−0.1 (−0.3 0.08)	0.28
TDI E/e′ (mean)	0.56 (0.39, 0.74)	<0.001	1.1 (0.7, 1.4)	<0.001	0.33 (0.13, 0.54)	0.002
TR velocity	2.3 (2.0, 2.6)	<0.001	2.7 (2.1, 3.3)	<0.001	2.0 (1.6, 2.4)	<0.001
OR						
NT-proBNP Abn (>125 pg/mL)	2.0 (1.47, 2.77)	<0.001	2.10 (1.39, 3.17)	<0.001	2.10 (1.27, 3.42)	0.004
LAVi Abn (also ESC HFpEF[16])[a]	1.16 (1.11, 1.21)	<0.001	1.15 (1.08, 1.3)	<0.001	1.17 (1.10, 1.24)	<0.001
TDI e′ (both) Abn	1.02 (1.003, 1.04)	0.025	1.05 (1.01, 1.09)	0.02	1.02 (0.99, 1.04)	0.21
TDI E/e′ Abn	1.11 (1.07, 1.16)	<0.001	1.10 (1.05, 1.17)	<0.001	1.12 (1.07, 1.19)	<0.001
TR velocity Abn	1.23 (1.19, 1.27)	<0.001	1.21 (1.16, 1.27)	<0.001	1.25 (1.20, 1.31)	<0.001
NT-proBNP	2.08 (1.45, 2.71)	<0.001	4.98 (3.72, 6.23)	<0.001	0.61 (−0.06, 1.28)	0.075
DD Abn by ASE	1.31 (1.25, 1.37)	<0.001	1.30 (1.22, 1.39)	<0.001	1.32 (1.23, 1.42)	<0.001
NT-proBNP ≥ 125 pg/mL	1.07 (1.04, 1.11)	<0.001	1.08 (1.03, 1.12)	<0.001	1.08 (1.02, 1.13)	0.004

Abn, abnormal; ASE, American Society of Echocardiography; CI, confidence interval; DD, diastolic dysfunction; ESC, European Society of Cardiology; HF, heart failure; HFpEF, heart failure with preserved ejection fraction; LAD, left atrial dimension; LA, left atrial; LAVi, left atrial volume index; NT-proBNP, N-terminal pro-brain natriuretic peptide; OR, odds ratio; TDI, tissue Doppler imaging; TR, tricuspid regurgitation. For all study participants, models were adjusted for age, gender, body mass index, systolic blood pressure, heart rate, fasting sugar, total cholesterol, high-density lipoprotein, estimated glomerular filtration rate, hypertension, diabetes mellitus, cardiovascular disease, and left ventricular mass; for men or women, models were adjusted for age, body mass index, systolic blood pressure, heart rate, fasting sugar, total cholesterol, high-density lipoprotein, estimated glomerular filtration rate, hypertension, diabetes mellitus, cardiovascular disease, and left ventricular mass.
[a]In which model BMI was not included.

17.8 mm/m^2)/LAVi, lower myocardial relaxation e′ and LV E/e′, slightly smaller TR jet velocity (Supporting Information, *Table S1*), and significantly lower prevalence of individual ASE-defined abnormal diastolic components of LAVi, LV E/e′, and TR velocity in men compared with women counterpart (all $P < 0.05$) (Supporting Information, *Table S2*).

Patients in the 'inconclusive' and 'DD' were accompanied by more prolonged PR intervals, greater LAD (30.9, 34.4, and 36.5 mm)/LADi (16.7, 19.1, and 20.6 mm/m^2, respectively), larger LAVs, markedly lower myocardial relaxation e′, higher LV E/e′, and higher TR velocities compared with 'normal' group (*Table 1*, all $P < 0.001$). In addition, patients in the 'DD' group showed higher number of individual abnormal ASE-defined diastolic indices (2.2 vs. 1.7 and 0.34, respectively) and higher NT-proBNP levels compared with patients in the 'inconclusive' and 'normal' group (*Table 1*, all $P < 0.001$).

The associations among left atrial dimension, guideline-recommended diastolic dysfunction, and N-terminal pro-brain natriuretic peptide cut-off for heart failure

Among 8314 subjects eligible after exclusion, 7628 subjects (91.7%) were categorized as 'normal', with 521 (6.3%) categorized as 'inconclusive' and 165 (2.0%) categorized as 'DD' using the ASE DD criteria (*Table 1*). LAD correlated positively with PR interval ($r = 0.18$), LADi ($r = 0.73$), LAVs and LAV index (r = 0.45 and 0.35), and NT-proBNP level ($r = 0.11$, all $P < 0.001$). Each 10 mm LAD increase was associated with 10.5 mL and 4.14 mL/m^2 expansion of LAV (without and with indexing to body surface area, respectively) (*Table 2*). LAD and LAV indices were all inversely associated with myocardial relaxation e′ and were positively correlated to higher LV E/e′, TR velocity, numbers of abnormal DD indices, and higher NT-proBNP (Supporting Information, *Table S3*, all $P < 0.001$). Increasing age was associated with greater LAD/LADi (r = 0.26 and 0.40, both $P < 0.001$, respectively), lower myocardial relaxation e′, higher LV E/e′ (r = −0.62 and 0.44, both $P < 0.001$), more elevated NT-proBNP ($r = 0.23$, $P < 0.001$), and higher TR velocity ($r = 0.29$, $P < 0.001$), with higher risk of DD increased with higher risk of DD (unadjusted OR: 2.31, 95% CI [2.02, 2.65], $P < 0.001$, for 10 year increment). In general, LAD/LADi showed better correlations with individual ASE-based diastolic index than LAV parameters. The consistent associations among LAD and ASE-based diastolic indices, DD, and NT-proBNP were further confirmed by linear/logistic regression models (with and without adjustment) (*Table 2*, all $P < 0.001$).

Higher DD scores, ratios, or grading were all related to markedly ordered increase in LAD/LADi (30.9, 34.4, and

36.5 mm/16.7, 19.1, and 20.6 mm/m^2, for LAD/LADi across ‘normal’, ‘inconclusive’, and ‘DD’ groups, both *P* for trend: <0.001) for both genders (Supporting Information, *Figure S1A* and *B*). Men in general showed significantly larger LAD than women (32.1 vs. 29.9 mm) (Supporting Information, *Figure S2*), although LADi appeared to be higher in women (17.8 vs. 16.4 mm, $P < 0.001$), especially with larger LAD (r = 0.85 and 0.81 for women and men, $P_{\text{interaction}}$ for sex: <0.001; *Figure 2A*). Both LAD and LADi seemed to be significantly larger using the NT-proBNP cut-off for high HF probability (≥125 pg/mL) when compared with the low probability (<125 pg/mL) group (33.6 vs. 31.3 mm/19.2 vs. 16.7 mm/m^2, for LAD and LADi, respectively, $P < 0.001$) regardless of gender differences (Supporting Information, *Figures S1C* and *D* and *S2*).

The diagnostic yield of left atrial dimension of guideline-recommended diastolic dysfunction criteria and N-terminal pro-brain natriuretic peptide level

The optimal LAD cut-off for identifying DD defined by ASE criteria was 34 mm (AUROC: 0.77, 95% CI [0.73, 0.80]) with high OR (OR: 6.27, 95% CI [4.47, 8.81]), 34 and 31.6 mm for men and women, respectively (AUROC: 0.77/0.81, 95% CI [0.71, 0.83]/[0.77, 0.85] for men and women) (*Figure 2B* and *Table 3*). LAD set at 37 mm yielded a high PPV (96%) and high specificity (86.7%) for identifying abnormally high LAVi (>34 mL/m^2) and showed high NPV values by using LAD cut-offs in identifying DD in both sexes. Compared with

Figure 2 The linear relationships between left atrial dimension (LAD) (as *X*-axis) and sex-specified LAD indexed to body surface area (LADi) showed greater slope of LADi with larger LAD in women than men (A). The area under receiver operating characteristic (AUROC) curves of LAD/LADi for men and women, respectively, in identifying diastolic dysfunction (DD) using American Society of Echocardiography-recommended guideline criteria. (B and C) Both LAD and LADi showed good diagnostic yield for such purpose. CI, confidence interval.

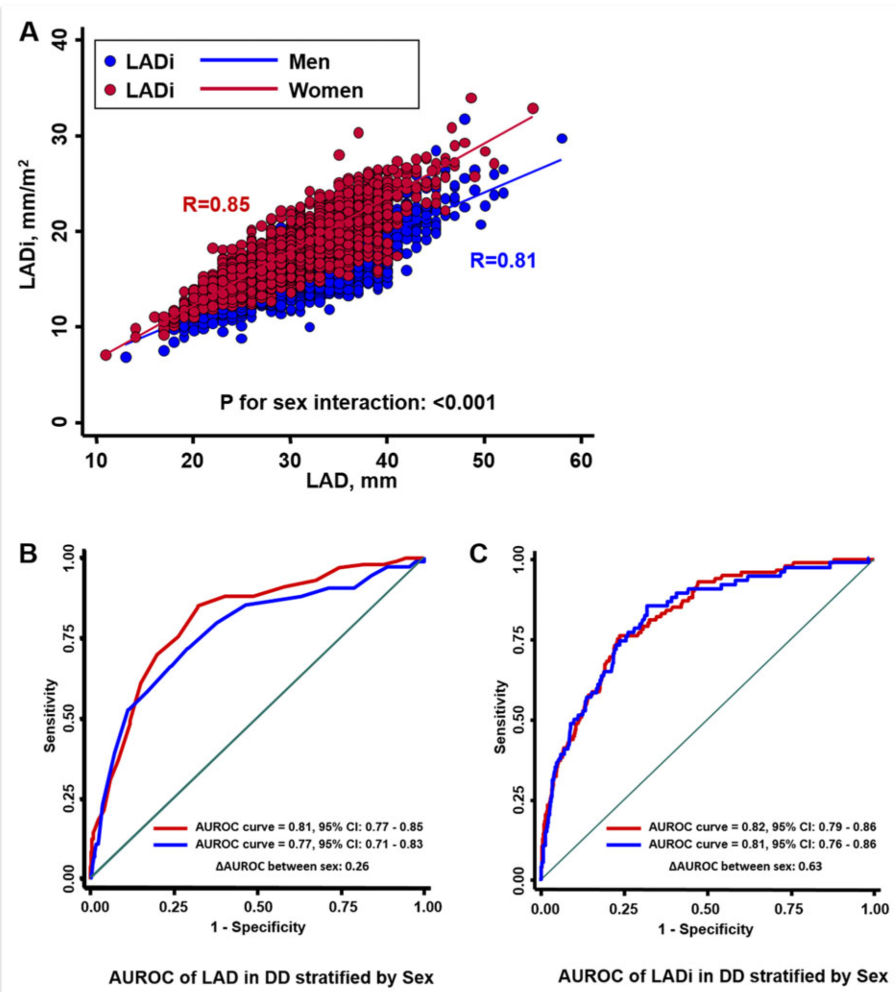

Table 3 Diagnostic yield of LAD in relation to ASE-recommended diastolic indices or DD and ESC NT-proBNP cut-offs for HF

	LAD							
C-statistics	Odds ratio (95% CI)	AUROC	95% CI	Cut-off (mm)	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
NT-proBNP Abn (≥125 pg/mL)	2.34 [1.85, 2.94]	0.63	[0.59, 0.66]	34	50.5	69.6	50.49	69.62
Echocardiography indices by ASE								
LAVi Abn (also ESC HFpEF[16])	2.24 [1.70, 2.96]	0.57	[0.54, 0.61]	37	25.60	86.70	96	8
TDI e′ (both) Abn	2.45 [2.19, 2.73]	0.65	[0.64, 0.66]	31	61.10	61.20	66.10	55.60
TDI E/e′ Abn	2.85 [2.17, 3.74]	0.68	[0.64, 0.71]	32	67.30	58.40	7.50	95.20
TR velocity Abn	5.50 [4.41, 6.84]	0.74	[0.71, 0.77]	35	62.10	77.20	11.60	95.40
DD Abn by ASE								
All	6.27 [4.47, 8.81]	0.77	[0.73, 0.80]	34	74	68.80	5.30	97.90
Women	11.48 [6.70, 19.68]	0.81	[0.77, 0.85]	31.6	86.50	70	8.70	96.80
Men	6.46 [3.65, 11.41]	0.77	[0.71, 0.83]	34	82.60	63.70	3.20	98.60
ESC criteria for HFpEF[16]	3.86 [2.70, 5.52]	0.70	[0.65, 0.75]	35	53.6	77.0	4.9	98.7

Abn, abnormal; ASE, American Society of Echocardiography; AUROC, area under receiver operating characteristic curve; CI, confidence interval; DD, diastolic dysfunction; ESC, European Society of Cardiology; HF, heart failure; HFpEF, heart failure with preserved ejection fraction; LAD, left atrial dimension; LAVi, left atrial volume index; NPV, negative predictive value; NT-proBNP, N-terminal pro-brain natriuretic peptide; PPV, positive predictive value; TDI, tissue Doppler imaging; TR, tricuspid regurgitation.

LAD 37 mm as cut-off in identifying abnormal LAVi (>34 mL/m^2), which offered a relatively high specificity (86.7%) and low sensitivity (25.6%) (*Table 3*), LAD set at 34 mm provided better sensitivity (42%) at the cost of lower specificity (69%). By defining abnormally high NT-proBNP for high probability of HF, the LAD cut-off for all study participants again was 34 mm (AUROC: 0.63) (OR: 2.34, 95% CI [1.85, 2.94]) (34 [AUROC: 0.68] and 31.0 mm [AUROC: 0.67] for men and women, respectively) (*Table 3*). Similar AUROC by LADi for both gender groups was also observed (*Figure 2C*). Finally, LAD set at 35 mm further yielded a sensitivity of 53.6% and acceptable specificity (69%) in identifying subjects who fulfilled ESC-defined HFpEF criteria (AUROC: 0.70) (OR: 3.86, 95% CI [2.70, 5.52]), with relatively better NPV (98.7%) in total study subjects.

Discussion

This study evaluated the impact of ASE-recommended quantitative echo-defined diastolic measures as well as ESC NT-proBNP cut-off for high probability of HF on LA remodelling in a large, asymptomatic Asians. Our results showed that increasing numbers of abnormal diastolic indices or presence of DD recommended by ASE as well as abnormal NT-proBNP level (>125 pg/mL) were significantly associated with greater LA remodelling, defined by greater LAD. Our data suggested that LAD set at 34 mm yielded high negative predictive value for guideline-based DD with high predictive accuracy for enlarged LAV (>34 mL/m^2) and also discriminate high NT-proBNP cut-off (≥125 pg/mL) defined for HF well in a preclinical stage.

Our current findings were consistent with previous data showing that men had a significantly greater LAD compared with women (40 vs. 36 mm, respectively) and the correlation with DD existence,[7] likely driven by increased myocardial stiffness, excessive extracellular matrix turnover/fibrosis from ageing, or associated co-morbidities (such as hypertension and obesity).[8,20–24] Our findings further extended previous studies to a population with relatively low hypertension prevalence (<20%), indicating that subclinical LA remodelling might occur at a relatively early clinical stage. Because LA enlargement in adults may strongly predict cardiovascular diseases (e.g. HF, AF, and stroke[25,26]), early recognition of LA remodelling in subjects with progressive pathological conditions plays a critical step for clinical risk stratification and preventive treatment. Maladaptive LA enlargement reflecting chronically increased afterload as a consequence of subclinical LV dysfunction or HF (American College of Cardiology Stage B)[27] may indicate a stage beyond presence of DD, which could be load-dependent and short-term based.[28] The thin-walled structure makes LA particularly vulnerable to volume and pressure-load conditions from long-standing elevated LV filling pressure, resulting in chamber dilation or geometric alterations with greater susceptibility for AF.[29] While atrial contraction may participate actively in LV filling during late diastolic phase, LA emptying function may deteriorate as LA remodelling continues with excessive interstitial fibrosis (or scar formation), causing retrograde elevation of pulmonary artery pressure and higher TR velocity.[19] Owing to the complex geometry, it has been proposed that LAD may not enlarge equally as atrial remodelling progresses, which makes precise quantification of LA size clinically challenging.[18]

Our data showed a significant difference between guideline-defined ‘normal’ and ‘DD’ groups (30.9 vs. 36.5 mm for all participants, $P < 0.001$) in both sexes, which challenges the traditional concept that LAD may be neither sensitive enough nor clinically feasible for assessment of LA remodelling in daily practice. Surprisingly, the differences in LAD between the ASE-defined ‘normal’ and ‘DD’ groups remained significantly different (31.1 vs. 33.1 mm, $P < 0.001$) even after adjusting for several baseline covariates and LV mass (Supporting Information, *Figure S2*). Our data also suggested the potential use of LAD (34 mm) as useful threshold in identifying DD with relatively high accuracy (AUROC: 77%; sensitivity/specificity: 74/68.8%; and NPV: >95%) and relatively high specificity (86.7%) in identifying LA enlargement (>34 mL/m^2; LAD: 37 mm) with good PPV (*Table 3*), indicating the potential feasibility in 'labelling' Stage B HF and help establish the clinical diagnosis of HFpEF recommended by most updated ESC HF guideline criteria.[16] Taken together, these results suggested that lower LAD appears be particularly useful in excluding the possible existence of 'DD' as defined by ASE, whereas larger LAD actually implies true LAV expansion. Although LADi in general demonstrated similar accuracy, calculation of such information needs body surface area for indexation. Further, caution should be exercised during clinical interpretation of LADi, which possibly shows gender differences as in current study. Nonetheless, we are not claiming that LAD is superior to LADi for clinical use.

Our current findings are consistent with several recent large epidemiological reports showing that LAD may still be a useful marker for early stage hypertension,[9] in identifying HFpEF,[30,31] and serve as a useful surrogate for AF prediction for regular drinkers.[32] In the Strong Heart Study, LAD was used as a surrogate of target organ damage for cardiovascular events and diabetes incidence.[33] In fact, the Cardiovascular Health Study reported that LA may actually remodel more severely from anteroposterior direction with HF.[34] On the other hand, Armstrong *et al*.[35] (CARDIA study) reported that LAD may be as useful as LAVs in predicting cardiovascular outcomes in a relatively healthy population. In a recent large meta-analysis from population-based cohort, arterial stiffness, a powerful clinical risk factor of development of DD was shown to independently predict LAD.[36] Despite the traditional concept on the advantageous use of volume-based LA measures over LAD, our data supported the clinical use of LAD for assessing DD and were concordant with Strong Heart Study and CARDIA studies as mentioned earlier.[33,35] This may be partly explained by the fact that LAD assessment is a relatively robust, simple measure with potentially higher reproducibility.[30] Instead, LAVs are more prone to assessment errors or are less reproducible, with potentially higher technical dependency. Additionally, it is likely that in daily practice, more attention was paid to optimize LV endocardial delineation to avoid LV foreshortening during image acquisition[37] and that true superior–inferior axial alignment of LA from apical views may be overlooked. Indeed, dimension-based LAD/LADi showed better correlations with most diastolic indices than volume-based LA measures (with and without index) in current work.

We had previously reported that NT-proBNP, a clinical marker of LVH, DD, or HF,[38] may rise in the asymptomatic stage of structural heart disease from ethnic Asians.[39] However, data comparing LAD and NT-proBNP levels from a large Asian population remain unexplored. So far, high NT-proBNP value (≥125 pg/mL) based on current ESC guidelines accompanied by evident DD or structural anomalies has been proposed to be a recommended clinical cut-off for high HF probability. Our current work showed that LAD discriminated NT-proBNP levels with a cut-off of 125 pg/mL, before (31.1 vs. 33.6 mm) and after (31.2 vs. 32.7 mm, both $P < 0.001$) adjustment of key clinical covariates and LV mass. Further, our data showed that LAD set at 30.6 and 34 mm, a value far below 40 mm, could efficiently provide abnormal cut-off for subjects with high NT-proBNP (≥125 pg/mL) in both women and men in a preclinical stage, respectively.

Limitations

An important limitation of this study was its retrospective nature and cross-sectional design, and longitudinal follow-up data were lacking. Additional prospective studies are required to further characterize the parameters that affect the LAD. Further, LA measures using volume-based modality (such as Biplane Simpson's measures by 2D) can be more accurate in estimating true LA size, although LAD using M-mode may be more suitable for large population screens. Our data suggested that LAD as a clinical surrogate of DD or abnormally high NT-proBNP may start at a lower value, at which stage the concern about constrained LA remodelling from the anteroposterior dimension may not be relevant. Finally, it would be of interest to also assess or to integrate other cardiac function information, especially diastolic parameters,[13] as part of the echo-derived determinants in predicting LA remodelling, which may strengthen the mechanistic link between altered LV filling and LA adaptations.

Conclusions

Our data demonstrated the strong associations between guideline-based cut-offs for DD and high probability of clinical HF with LA structural remodelling by utilizing LAD in a large, preclinical stage of ethnic Asian population. The optimal LAD chosen for identifying guideline-based functional abnormality cut-offs was relatively low for both genders and yielded satisfactory discriminatory ability and high negative predictive accuracy. These data may have important implications for targeting specific populations at high risk of HF. Our data further provided useful threshold from a primary preventive standpoint by identifying modifiable clinical risks in subjects with high LAD in order to avoid progressive heart damage or incident AF in Asians.

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Conflict of interest

None declared.

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Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Figure S1. Paired comparisons of LAD and LADi between groups of guideline-based diastolic dysfunction and high probability for clinical HF.

Figure S2. Values and distribution of LAD across ASE-recommended DD scoring (A) (0, 1, 2, 3, and 4), sex-specific comparisons (B), together with sex-specified LAD by ASE-recommended DD categories (C, as “Normal”, “Inconclusive”, and “DD”) and ESC HF probability cutoff for abnormally high Nt-ProBNP level (≥125 pg/mL, D).

Table S1. Baseline demographic, clinical characteristics and echocardiography indices of all study participants stratified by sex.

Table S2. Sex-stratified prevalence and distribution of abnormal diastolic indices and diastolic dysfunction (DD) by ASE guideline.

Table S3. The associations of various LA measures, ASE recommended diastolic functional indices and Nt-ProBNP level.

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