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Exploring the impact of angiotensin-converting enzyme (*ACE*) gene polymorphism on early diastolic function in hypertension using four-dimensional echocardiography

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Abstract

Background This study explores the relationship between angiotensin-converting enzyme (*ACE*) gene polymorphisms and early diastolic dysfunction in patients with hypertension utilizing four-dimensional echocardiography and assesses the prognosis.

Methods This study consecutively selected 470 patients with hypertension who visited the Fourth Affiliated Hospital of Soochow University between September 2021 and August 2022, with 274 meeting the inclusion criteria. Hypertension gene testing was performed using polymerase chain reaction-restriction fragment length polymorphism (PCR–RFLP) techniques, and the Hardy–Weinberg equilibrium test was used to confirm genetic equilibrium. Patients were categorized into the D allele group ($n=163$) and the non-D allele group ($n=111$). Diastolic function was assessed using four-dimensional echocardiography, which included averaging the E/e' ratio over three cardiac cycles, measuring the left atrial (LA) maximum volume index (LA volume), tricuspid regurgitation velocity (TR velocity), LA strain, and left ventricular isovolumic relaxation time (IVRT). Patients were subsequently classified into the diastolic dysfunction group ($n=133$) and the normal diastolic function group ($n=141$). Chi-square tests were used to analyze differences in diastolic function indicators between the groups, Logistic regression was applied to control for potential confounding factors, and receiver operating characteristic (ROC) curves were plotted to assess the predictive value of different *ACE* alleles for diastolic dysfunction in patients with hypertension.

Results The genotype distribution in both the D allele group and the non-D allele group was consistent with Hardy–Weinberg equilibrium ($P>0.05$). Compared to the non-D allele group, echocardiographic indicators in the D allele group showed a decline in diastolic function: the average E/e' ratio over three cardiac cycles (14.67 [13.82, 15.80] *vs.* 9.30 [8.12, 12.00]), LA volume (32.76 [29.34, 34.61] *vs.* 25.61 [22.63, 29.64] ml/m^2), TR velocity (2.90 [2.40, 2.90] *vs.* 1.40 [1.10, 2.40] cm/s), LA strain (18.00 [14.00, 25.00] *vs.* 37.00 [24.00, 40.00] %), and IVRT (104.25 [95.87, 106.25] *vs.* 88.09 [80.99, 96.56] ms). Differences between each group were statistically significant (all $P<0.05$). The number of patients with diastolic dysfunction was higher in the D allele group ($n=102$; 62.6%) compared to the non-D allele group

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(*n* = 31; 27.9%). In the logistic regression model, the D allele was associated with an increased risk of early diastolic dysfunction in hypertension (OR = 4.32, 95% CI = 2.56–7.27, *P* < 0.01). In the adjusted model, the D allele remained associated with an elevated risk of early diastolic dysfunction in hypertension (OR = 3.83, 95% CI = 2.24–6.54, *P* < 0.01). ROC curve analysis indicated that the D allele has predictive value for early diastolic dysfunction in patients with hypertension (area under the curve [AUC], 0.667; 95% confidence interval [CI], 0.608–0.723; sensitivity, 76.7%; and specificity, 56.7%; *P* < *0.05*).

Conclusions The *ACE*-D allele is associated with early diastolic dysfunction in hypertension. *ACE* gene testing can enhance the predictive value for diastolic dysfunction in patients with hypertension.

Keywords Four-dimensional echocardiography, Hypertension, Diastolic dysfunction, *ACE* gene polymorphisms, Genetic equilibrium

Introduction

Hypertension is a widespread condition that poses a significant public health challenge globally. According to the World Health Organization (WHO), an estimated 1.3 billion people were living with hypertension in 2019, with over 150 million cases in Central and Eastern Europe alone [1]. In China, approximately 245 million, people are affected by hypertension, with an overall prevalence among adults ranging from 30 to 45% [2]. Diastolic dysfunction, an early indicator of hypertensive heart damage, often presents with non-specific clinical symptoms, making it difficult to diagnose [3]. Conventional echocardiography has limitations in accurately detecting diastolic dysfunction, leading to frequent underdiagnosis in its early stages [4]. If left untreated, diastolic dysfunction can progress to systolic dysfunction and eventually lead to heart failure, severely impacting the life expectancy and quality of life of the patients [5].Therefore, our study defined early diastolic dysfunction as the condition where a patient does not meet the diagnostic criteria for congestive heart failure and retains normal systolic function, yet exhibits abnormal findings in relevant auxiliary tests. Currently, the primary diagnostic method is echocardiography. An E/A ratio of 0.8 or lower indicates grade 1, a ratio of 2 or higher indicates grade 3, and a ratio between 0.8 and 2 is considered grade 2 (the diagnostic gray zone) [6, 7].

The pathogenesis of hypertension involves a complex interplay of genetic, environmental, and lifestyle factors, with genetics playing a pivotal role [8]. Certain individuals are genetically predisposed to hypertension, with various genetic mutations and polygenic inheritance patterns contributing to an increased risk of developing the condition [9]. Studies have shown a significant correlation between angiotensin-converting enzyme (*ACE*) gene polymorphisms and the development of cardiovascular diseases [10]. Among the widely studied *ACE* gene polymorphisms is the I/D polymorphism, which results from the insertion or deletion of a repetitive DNA sequence in the 16th intron. This polymorphism leads to three genotypes: insertion homozygote (I/I), deletion homozygote (D/D), and heterozygote (I/D) [11]. In China, studies indicate that the I/I genotype is the most common among healthy Han Chinese individuals [12]. Additionally, research has demonstrated that the D allele is more frequently associated with hypertensive heart disease and left ventricular changes compared to the non-D allele [13]. However, no studies have yet examined the relationship between *ACE* gene polymorphisms and early diastolic dysfunction in hypertension.

This study employs four-dimensional echocardiography to assess and compare diastolic function indicators among patients with different *ACE* gene alleles, aiming to explore the correlation between *ACE* gene polymorphisms and early diastolic dysfunction in hypertension. Additionally, it evaluates the predictive value of the D allele for identifying early diastolic dysfunction in patients with hypertension. The ultimate goal is to facilitate the early identification of individuals at risk of diastolic dysfunction, enabling targeted treatment strategies that could reduce the incidence of hypertensive heart disease and improve long-term patient outcomes.

Patients and methods

Study participants

The required sample size was calculated using the formula $n = \frac{Z^2_{\alpha/2} \cdot p(1-p)}{E^2}$, where n represents the sample size, Z represents the desired significance level ($Z = 1.96$), p is the expected incidence rate, and E is the allowable margin of error ($E = 0.05$). Based on existing epidemiological studies on diastolic dysfunction [14], an average value of $p = 0.24$ was used, resulting in a calculated sample size of $n = 280$.

This study included 470 patients with hypertension who visited the Fourth Affiliated Hospital of Soochow University between September 2021 and August 2022. Hypertension was defined according to guidelines as a systolic blood pressure (SBP) ≥ 140 mmHg or diastolic blood pressure (DBP) ≥ 90 mmHg [15]. The inclusion criteria were: (1) patients meeting the hypertension

diagnostic criteria and consenting to participate; (2) aged between 18 and 75 years; and (3) in sinus rhythm. The exclusion criteria were: (1) secondary hypertension; (2) poorly controlled blood pressure; (3) diagnosed hypertensive heart disease; (4) body mass index (BMI) ≥ 30 kg/m^2; (5) severe arrhythmias; (6) coronary artery disease, cardiomyopathy, myocarditis, pericarditis, valvular heart disease, or congenital heart disease; (7) severe infections, major trauma, severe pulmonary, liver, or kidney diseases, hematological disorders, cerebrovascular diseases, malignancies, or psychiatric disorders; and (8) poor echocardiographic image quality or inability to cooperate with the examination.

Ultimately, 274 patients met the inclusion criteria and were enrolled in the study. This group comprised 171 men (62.4%) and 101 women (37.6%), with a mean age of (51.97 ± 15.57) years. All participants provided written informed consent. The study was reviewed and approved by the Ethics Committee of the Fourth Affiliated Hospital of Soochow University (Dushu Lake Hospital).

Research methods

Collection of general clinical data

Comprehensive clinical data were collected from all patients, including age, gender, height, weight, medical history, personal history, and family history. Upon admission, each patient underwent a full set of diagnostic tests, including electrocardiograms (ECGs), complete blood counts, liver and kidney function tests, electrolyte assessments, lipid profiles, and blood glucose measurements.

Blood pressure assessment

Baseline blood pressure was recorded upon admission using a semi-automated device (Dinamap MPS; GE Healthcare, Wisconsin). Two readings were taken at two-minute intervals and averaged to determine the baseline value. Mean arterial pressure was calculated by adding one-third of the pulse pressure to the diastolic pressure. Additionally, 24-h ambulatory blood pressure monitoring was conducted to assess the average systolic and diastolic pressures and to evaluate the presence of a dipping pattern. Hypertension is classified into three grades based on the patient's highest recorded blood pressure. Grade 1 is defined by a blood pressure between 140–159/90–99 mmHg, Grade 2 by a range of 160–179/100–109 mmHg, and Grade 3 by a blood pressure of 180/110 mmHg or higher [16].

ACE genotype testing

A 5 mL sample of peripheral venous blood was collected from each patient. DNA was extracted using the QIAamp DNA Blood Mini Kit (Qiagen, Shanghai; catalog numbers 51104 or 51,106). The concentration and purity of the extracted DNA were measured with an ultraviolet spectrophotometer, with acceptable DNA OD260/OD280 values between 1.8 and 2.0 and concentrations ranging from 10 to 100 ng/μL. Samples failing to meet these quality standards were excluded from further testing. Specifically, samples with concentrations < 10 ng/μL were re-sampled for nucleic acid extraction, while those with > 100 ng/μL were diluted to a concentration of 50 ng/μL by adding 50 μL of purified water to 50 μL of extracted DNA. The DNA was tested immediately after extraction. The kit comprises three reaction systems. The B reaction tube, which utilizes the FAM channel, detects the *ACE* (I/D) polymorphism. Samples with two peaks identical to the positive control (with a Tm deviation of < 1.5 °C) were classified as I/D heterozygotes. Samples showing only a low Tm melting peak were classified as D/D homozygotes, while those with only a high Tm melting peak were classified as I/I homozygotes.

Cardiac diastolic function assessment

Patients were instructed to rest in a supine position for 10 min while their ECG was monitored. During this time, patient data such as height and weight were recorded. An experienced echocardiographer performed the assessment using the Vivid E95 (4Vc) machine from GE Healthcare, USA. The evaluation of diastolic function followed the 2024 guidelines provided by the British Society of Echocardiography [7], and included the following methods:

(1) Tricuspid regurgitation velocity (TR velocity): Transthoracic echocardiographic images were obtained from parasternal short-axis and apical four-chamber views. The tricuspid regurgitation spectrum was captured using continuous-wave Doppler in color Doppler flow mode. The maximum systolic velocity was then measured.

(2) Left atrial (LA) maximum volume index (LA volume): Apical four- and two-chamber views were captured. Images were frozen in one to two frames before mitral valve (MV) opening to ensure length and width measurements. LA volume was measured excluding the LA appendage and pulmonary veins. The system then corrected for body surface area to calculate the LA maximum diastolic volume and index (Fig. 1).

(3) Average E/e' ratio: This ratio was calculated by dividing the peak E-wave velocity of mitral inflow by the average early diastolic velocity (e') of the mitral annulus at the lateral and septal walls, measured over three cardiac cycles.

(4) LA strain: To assess LA strain, a clear apical four-chamber view was obtained and switched to 4D

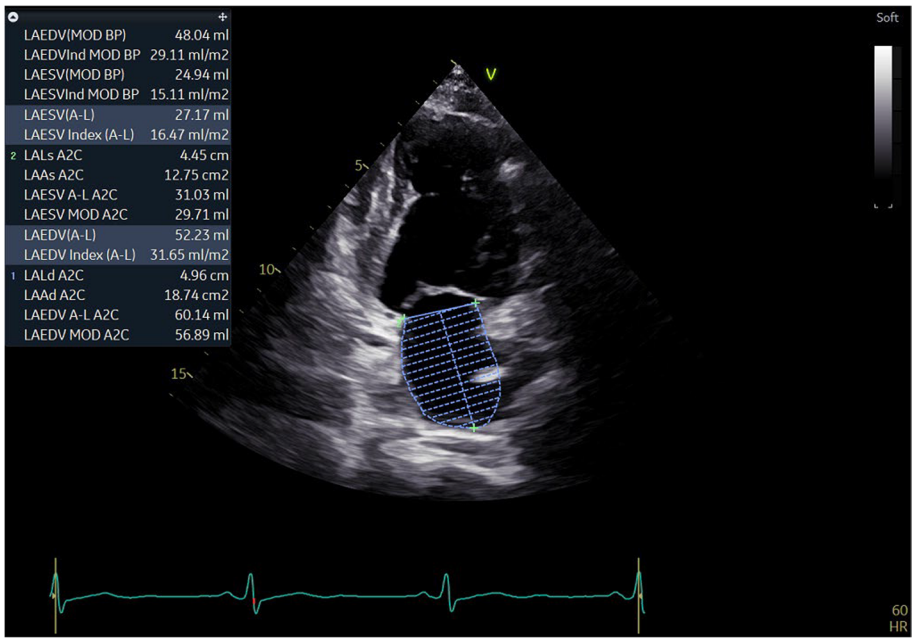

Fig. 1 LA volume measurement image

mode for real-time three-dimensional reconstruction of the LA. The 4D Auto LAQ menu was used to identify the MV center. The LA endocardial surface was automatically traced in the apical four-chamber, three-chamber, and two-chamber views within the same cardiac cycle, making necessary adjustments. The software then generated LA strain parameters. Reservoir strain (LASr) was measured from the end of ventricular diastole (MV closure) until the MV opened, encompassing left ventricular isovolumic contraction, ejection, and isovolumic relaxation (Fig. 2).

(5) Left ventricular isovolumic relaxation time (IVRT): The apical four-chamber view was obtained with the pulsed-wave (PW) Doppler sample volume positioned at the lateral side of the mitral annulus. IVRT was measured from the end of the s' wave to the beginning of the e' wave (Fig. 3; IVRT = 102.52 ms).

(6) Mitral annular plane systolic excursion (MAPSE): An apical four-chamber view was obtained in M-mode, with the sampling line placed on the lateral and septal sides of the mitral annulus. The displacement of the mitral annulus was tracked in M-mode to measure the distance of its movement from diastole to systole.

Diagnostic criteria for diastolic dysfunction: According to the British Society of Echocardiography, diastolic dysfunction is diagnosed based on the following criteria: (1) Primary criteria: an average E/e' ratio over three cardiac cycles > 1.4; LA volume > 34 ml/m^2; and TR velocity > 2.8 cm/s. (2) Secondary criteria: LA strain < 18%; prolonged Ar-A duration > 30 ms or presence of an L wave > 20 cm/s; and IVRT > 100 ms. Diastolic dysfunction is diagnosed if either all three primary criteria are met or one primary criterion along with two secondary criteria [17].

Statistical methods

The Hardy–Weinberg equilibrium test was employed to determine if the genetic variants were in equilibrium. Statistical analyses were performed using IBM SPSS Statistics for Windows (version 27.0.1; IBM Corp., Armonk, NY, USA), MedCalc, GraphPad Prism 9, and Origin 2023 software. Continuous variables with a normal distribution were expressed as mean ± standard deviation ($\bar{x} \pm s$) and compared between groups using an independent sample *t*-test. For continuous variables with a non-normal distribution, data were expressed as median (*M [Q1, Q3]*) and compared using the Mann–Whitney U test. Logistic regression was used to test the association between *ACE* genotype and early diastolic function in hypertension. Odds ratios (ORs) and 95% confidence intervals (CI) were documented. Categorical data were presented as conducted using receiver operating characteristic (ROC)

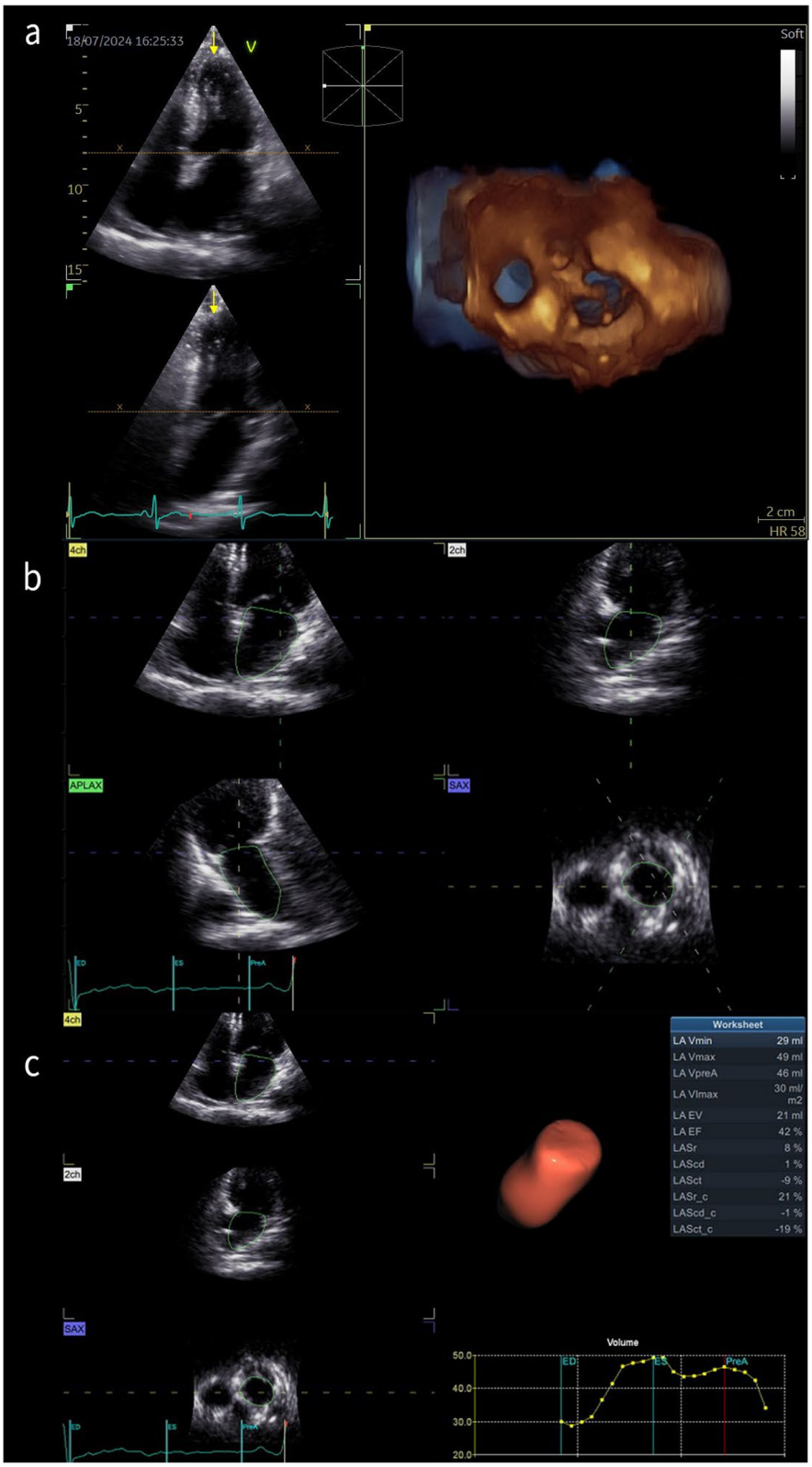

Fig. 2 LA strain measurement image

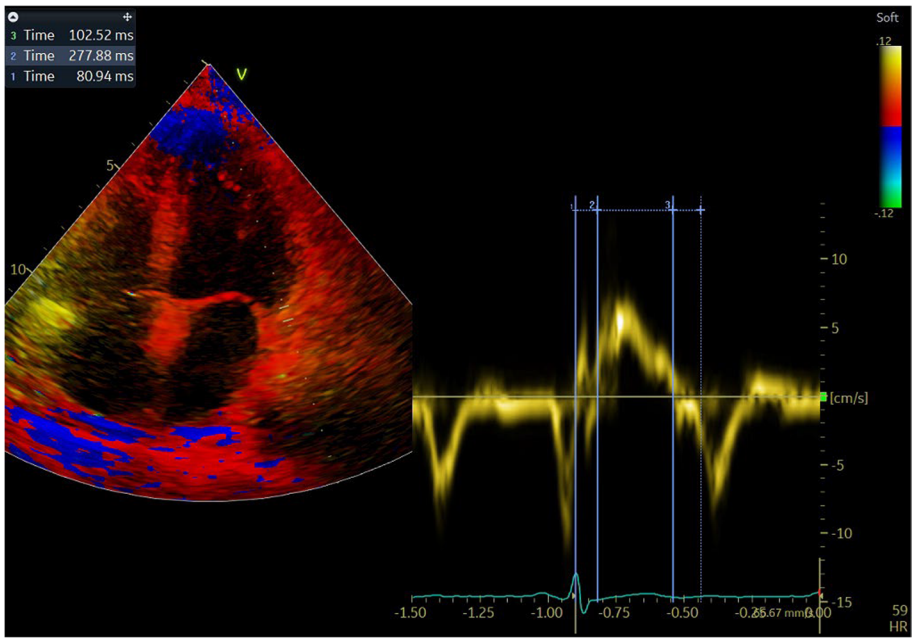

Fig. 3 Left ventricular isovolumic relaxation time measurement image

curves. A two-sided *P*-value of < 0.05 was considered statistically significant.

Results

Comparison of general clinical data between the two groups

The D allele group comprised 164 patients, while the non-D allele group included 111 patients. There were no statistically significant differences between the two groups regarding age, gender, height, weight, and BMI ($P > 0.05$). Additionally, no significant differences were observed in kidney function and levels of triglycerides (TG), total cholesterol (TC), high-density lipoprotein (HDL), low-density lipoprotein (LDL), or HbA1c ($P > 0.05$). The left ventricular voltage was also similar between the groups ($P > 0.05$; Table 1).

Table 1 Demographic characteristics analysis of groups with different D alleles

Variables	D($n = 163$)	Non-D($n = 111$)	$t/Z/\chi^2$	*P*
Age(years)	53.56 ± 15.60	49.64 ± 15.29	-2.05	0.041
Male(%)	101(62.00)	70(63.10)	0.03	0.854
High(cm)	166.00(160.00,174.00)	165.00(159.00,171.00)	-0.07	0.942
Weight(kg)	70.00(61.00,78.00)	71.00(62.00,80.00)	-1.13	0.109
BMI(kg/m^2)	25.40(23.83,25.76)	26.08(24.52,27.68)	0.81	0.152
Scr(umol/L)	73.20(58.05,86.03)	71.30(54.70,88.10)	0.07	0.938
Renal Dysfunction(%)	10(6.10)	7(6.30)	0.21	0.328
TG(mmol/L)	1.41(1.01,2.18)	1.46(1.04,2.09)	-0.75	0.132
TC(mmol/L)	4.28(3.55,5.13)	4.38(3.63,4.94)	-0.04	0.968
HDL-C(mmol/L)	1.09(0.89,1.34)	1.08(0.86,1.26)	1.41	0.288
LDL-C(mmol/L)	2.64(1.92,3.41)	2.59(1.96,3.35)	0.23	0.318
Dyslipidemia(%)	99(60.70)	73(65.70)	-1.24	0.215
HbA1c	6.10(5.60,6.50)	6.10(5.60,6.50)	0.02	0.898
RV5(mV)	2.46(2.08,3.26)	2.39(2.09,3.18)	-0.48	0.216
RV5 + SV1(mV)	3.41(2.91,3.67)	3.50(2.93,3.74)	0.35	0.297

Table 2 Baseline blood pressure characteristics analysis of groups with different D alleles

Variables	D(*n* = 163)	Non-D(*n* = 111)	*t*/*Z*/χ^2	*P*
SBP(mmHg)	130.00(120.00,137.00)	129.00(124.00,146.00)	-1.66	0.096
DBP(mmHg)	80.00(74.00,87.00)	82.00(75.00,91.00)	-1.52	0.128
Dipper(%)	28(17.20)	12(10.80)	3.47	0.116
Non-Dipper(%)	99(60.70)	79(71.20)		
Riser(%)	36(22.10)	20(18.00)		
NBPFR-A(%)	53(32.50)	30(27.00)	0.94	0.332

Table 3 Analysis of conventional echocardiographic parameters in groups with different D alleles

Variables	D(*n* = 163)	Non-D(*n* = 111)	*t*/*Z*/χ^2	*P*
LA(mm)	36.00(33.00,40.00)	35.00(33.00,39.00)	1.47	0.139
LV(mm)	9.00(8.00,10.00)	9.00(8.00,10.00)	0.03	0.973
IVS(mm)	9.00(8.00,10.00)	9.00(9.00,10.00)	-0.81	0.415
LVPW(mm)	10.00(8.00,11.00)	11.00(8.00,12.00)	0.28	0.777
LVEDD(mm)	50.00(46.00,52.00)	50.00(46.00,53.00)	-0.84	0.396
LVEF(%)	64.00(61.00,69.00)	63.00(59.00,70.00)	1.09	0.277
E(m/s)	60.00(48.00,69.00)	64.00(53.00,77.00)	-2.27	0.070
A(m/s)	80.00(68.00,94.00)	81.00(68.00,94.00)	0.01	0.990
E/A	0.80(0.60,1.00)	0.80(0.60,1.00)	-0.44	0.660
DT(ms)	208.00(179.00,236.00)	194.00(155.00,218.00)	2.75	0.060

Comparison of ambulatory blood pressure between the two groups

No statistically significant differences were observed between the two groups regarding average SBP and DBP ($P > 0.05$). The proportions of dipper and reverse dipper patterns also did not differ significantly between the groups ($P > 0.05$). Although the D allele group had a higher proportion of non-dipper patterns and greater abnormal nocturnal blood pressure variability compared to the non-D allele group, these differences were not statistically significant ($P > 0.05$; Table 2).

Comparison of conventional echocardiography between the two groups

There were no statistically significant differences between the two groups concerning LA and left ventricular diameters, interventricular septal thickness, left ventricular posterior wall thickness, E and A-waves, deceleration time (DT), E/A ratio, and left ventricular ejection fraction (LVEF) ($P > 0.05$; Table 3).

Comparison of diastolic function parameters by four-dimensional echocardiography between the two groups

In four-dimensional echocardiography, the D allele group exhibited higher average E/e' ratios (14.67 [13.82, 15.80] *vs.* 9.30 [8.12, 12.00]), LA volume (32.76 [29.34, 34.61] *vs.* 25.61 [22.63, 29.64] ml/m^2), TR velocity (2.90 [2.40, 2.90] *vs.* 1.40 [1.10, 2.40] cm/s), and IVRT (104.25 [95.87, 106.25] *vs.* 88.09 [80.99, 96.56] ms) compared to the non-D allele group, with these differences being statistically significant (all $P < 0.05$). Conversely, LA strain (18.00 [14.00, 25.00] *vs.* 37.00 [24.00, 40.00] cm/s), MAPSE in systole (MAPSE-s; 13.00 [11.80, 14.00] *vs.* 15.80 [14.60, 16.40] mm), and MAPSE in diastole (MAPSE-i; 14.90 [14.00, 15.90] *vs.* 17.70 [16.70, 18.50] mm) were significantly lower in the D allele group (all $P < 0.05$). No statistically significant differences were found between the two groups regarding the Ar-A duration or L-wave ($P > 0.05$; Fig. 4).

Correlation analysis of diastolic function parameters

Correlation analyses were performed on TR velocity, LA volume, average E/e', LA strain, IVRT, E-wave, MAPSE-s, and MAPSE-i. The results showed that IVRT was positively correlated with average E/e' ($r = 0.63$), LA volume ($r = 0.35$), and TR velocity ($r = 0.53$) ($P < 0.05$). It was negatively correlated with LA strain ($r = -0.43$) and the E-wave ($r = -0.57$) ($P < 0.05$). MAPSE-s and MAPSE-i were positively correlated with LA strain (MAPSE-s: $r = 0.45$, MAPSE-i: $r = 0.48$) and the E-wave (MAPSE-s: $r = 0.53$, MAPSE-i: $r = 0.53$) ($P < 0.05$), and negatively correlated with average E/e' (MAPSE-s: $r = -0.76$, MAPSE-i: $r = -0.77$), LA volume (MAPSE-s: $r = -0.36$, MAPSE-i: $r = -0.37$), and TR velocity (MAPSE-s: $r = -0.42$, MAPSE-i: $r = -0.45$) ($P < 0.05$; Fig. 5).

Examining the association between *ACE* genotype and early diastolic dysfunction in hypertension using logistic regression

In this study, the group with normal diastolic function and the group with impaired function differed significantly in the proportion of the D allele(61[43.26%]*vs.*102[76.69%]), as well as in age(50.97 ± 16.00*vs.*53.09 ± 14.86), left atrial diameter(36.00[33.00,38.00]*vs.*36.00[33.00,40.00]), and the prevalence of renal dysfunction(13[9.22%]*vs.*4[3.01%];$P < 0.05$). However, no significant differences were found in BMI(25.41[23.12,27.61]*vs.*25.00[23.88,27.55]), diabetes prevalence(5[3.60%]*vs.*8[6.10%]), hypertension classification(1:131[92.91%]*vs.*127[95.49%];2:8[5.67%]*vs.*6[4.51%];3:2[1.42%]*vs.*0[0.00%]), dyslipidemia prevalence(96[71.64%]*vs.*76[60.80%]), or medication(ACEI/ARB/ARNI:117[82.90%]*vs.*109[81.90%];β-Blocker:19[13.40%]*vs.*17[12.70%];CCB:5[3.70%]*vs.*7[5.40%];$P > 0.05$; Table 4). Logistic regression was used to test the association between *ACE* genotype and early diastolic function in hypertension. In the crude model, *ACE* genotype was associated with an increased risk of early diastolic

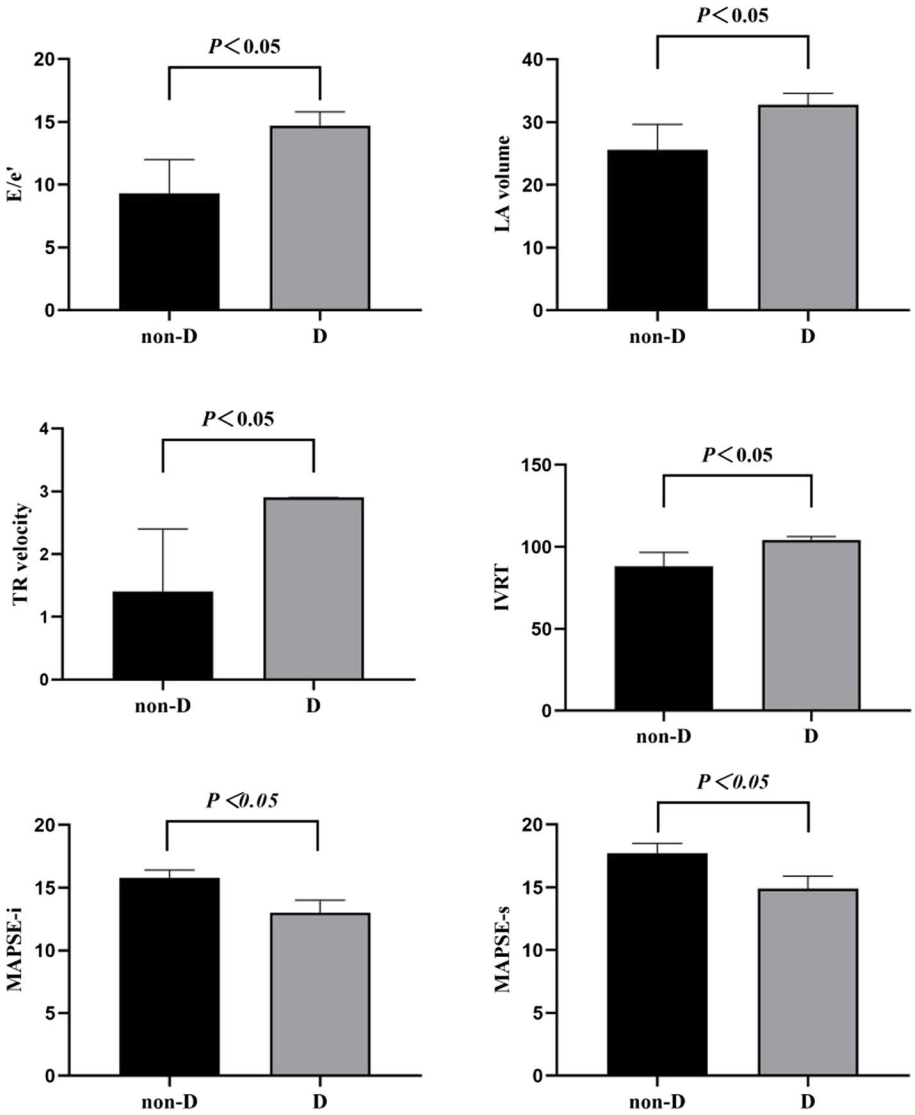

Fig. 4 Bar chart comparing diastolic function parameters by four-dimensional echocardiography between the two groups

dysfunction in hypertension (OR = 4.32, 95% CI = 2.56–7.27, $P < 0.01$). In the adjusted model, after adjusting for age, sex, the prevalence of renal dysfunction, and left atrial diameter, *ACE* genotype remained associated with an increased risk of early diastolic dysfunction in hypertension (OR = 3.83, 95% CI = 2.24–6.54, $P < 0.01$; Table 5).

ROC curve analysis of the D allele for predicting diastolic dysfunction in patients with hypertension

In the D allele group, 102 patients (62.6%) exhibited diastolic dysfunction, which was significantly higher compared to 31 patients (27.9%) in the non-D allele group ($P < 0.05$). ROC curve analysis indicated that the D allele has predictive value for diastolic dysfunction in patients with hypertension, with an area under the curve (AUC) of 0.667, 95% confidence interval (CI) = 0.608–0.723, a sensitivity of 76.7%, and a specificity of 56.7% ($P < 0.05$; Fig. 6).

Discussion

Hypertensive heart disease is a serious complications of hypertension characterized by both structural and functional changes in the heart resulting from prolonged high blood pressure. Early manifestations include ventricular wall thickening, ventricular enlargement, myocardial hypertrophy, and impaired diastolic function. As the disease progresses, it can lead to global heart enlargement, reduced systolic function, and in severe cases, recurrent heart failure hospitalizations, malignant arrhythmias, and life-threatening events such as sudden cardiac

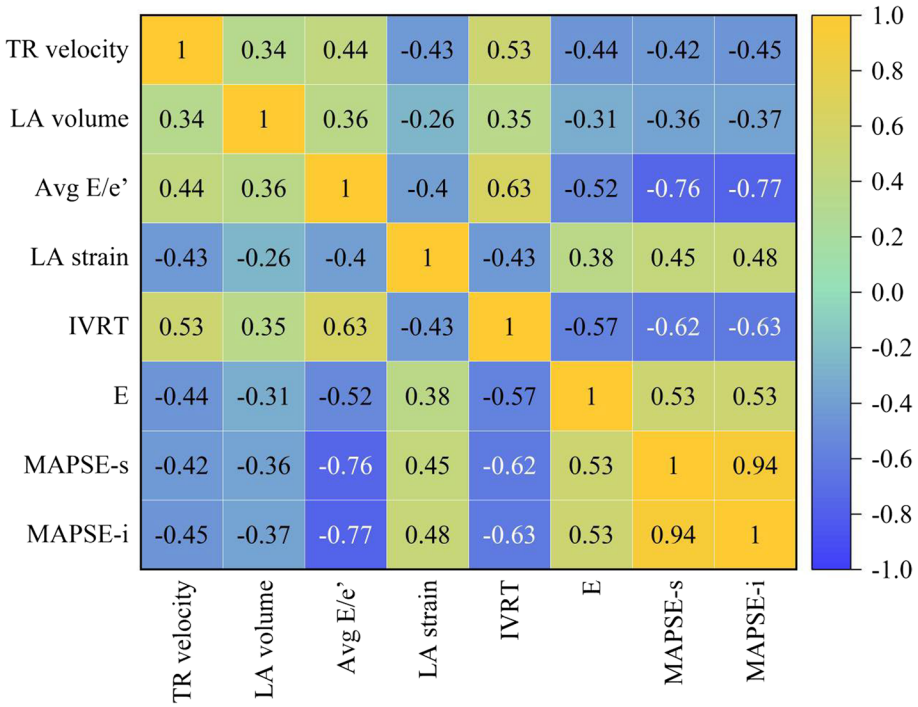

Fig. 5 Correlation analysis of diastolic function parameters by four-dimensional echocardiography between the two groups

death. Severe diastolic dysfunction can progress to diastolic heart failure with isolated diastolic heart failure or heart failure with preserved ejection fraction (HFpEF), accounting for nearly 50% of clinical heart failure cases. Hypertension is a major contributor to vascular disease-related HFpEF, with early indicators including left ventricular filling, expansion, and diastolic dysfunction. Therefore, early detection and intervention in patients with hypertension at high risk for diastolic dysfunction are crucial for preventing HFpEF, reducing the incidence of heart failure, and lowering cardiovascular mortality.

Hypertension is a complex cardiovascular syndrome influenced by a range of genetic and environmental factors. This heterogeneity leads to varied treatment approaches and differences in the underlying mechanisms of the disease. With advancements in precision medicine, the field of hypertension has rapidly developed personalized blood pressure management strategies tailored to individual clinical characteristics and phenotypes. Concurrently, research in hypertension pharmacogenomics has progressed significantly. Kato et al. identified the *ACE* gene D/D genotype as an independent risk factor for cardiovascular and cerebrovascular diseases, particularly noting its association with an increased incidence of left ventricular hypertrophy in a cohort study of patients with hypertension [18]. In this study, we classified patients with hypertension based on their *ACE* genotype and evaluated diastolic function using echocardiography. Our findings suggest that individuals carrying the D allele are at a higher risk of developing diastolic dysfunction compared to those without the D allele.

Patients with hypertension frequently have comorbid conditions such as hyperlipidemia, diabetes, and target organ damage. Research indicates a correlation between the D allele and the development of hyperlipidemia [19]. In our study, patients carrying the D allele exhibited higher levels of LDL cholesterol compared to those without the D allele.

Blood pressure typically follows a circadian rhythm, showing a "dipper" pattern during the day [20]. However, patients with a "non-dipper" pattern who do not exhibit this pattern are more likely to experience nocturnal hypertension, which is harder to control and often leads to progression of hypertensive heart disease, including diastolic dysfunction [21]. In this study, the proportion of non-dipper patterns and abnormal nocturnal blood pressure variability was higher among patients with the D allele compared to those without it.

Diastolic dysfunction in patients with hypertension can be identified through echocardiography, which may reveal left ventricular wall thickening, and electrocardiography, which can show increased left ventricular voltage(RV5 > 2.5 mV;RV5 + SV1 > F:3.5 mV/M:4.0 mV) [22–24]. Previous research has indicated that carriers of the D allele are more prone to developing left ventricular

Table 4 Analysis of demographic characteristics in different diastolic function groups

Variables	Total ($n=274$)	Normal ($n=141$)	Impaired ($n=133$)	$t/Z/\chi^2$	P
Age(years)	51.97 ± 15.57	50.97 ± 16.00	53.09 ± 14.86	-2.20	0.028
Male(%)	171 (62.41)	85 (60.28)	86 (64.66)	0.56	0.455
High(cm)	166.00 (160.00, 173.75)	166.00 (160.00, 175.00)	166.00 (160.00, 172.00)	-0.64	0.522
Weight(kg)	70.00 (62.00, 80.00)	70.00 (60.00, 80.00)	70.00 (63.00, 78.00)	-0.14	0.889
BMI(kg/m^2)	25.15 (23.40, 27.55)	25.41 (23.12, 27.61)	25.00 (23.88, 27.55)	-0.66	0.512
Scr(umol/L)	72.10 (57.00, 87.10)	72.90 (55.20, 88.70)	71.15 (57.60, 83.53)	-0.68	0.497
Renal Dysfunction(%)				4.54	0.033
NO	257 (93.80)	128 (90.78)	129 (96.99)		
YES	17 (6.20)	13 (9.22)	4 (3.01)		
TG(mmol/L)	1.44 (1.03, 2.19)	1.43 (1.04, 2.14)	1.47 (1.03, 2.19)	-0.32	0.746
TC(mmol/L)	4.35 (3.58, 5.04)	4.36 (3.52, 5.00)	4.28 (3.74, 5.13)	-0.13	0.894
HDL-C(mmol/L)	1.09 (0.89, 1.31)	1.06 (0.87, 1.26)	1.10 (0.91, 1.34)	-1.44	0.150
LDL-C(mmol/L)	2.62 (1.95, 3.38)	2.64 (1.89, 3.42)	2.60 (2.02, 3.28)	-0.09	0.927
Dyslipidemia(%)				3.41	0.065
NO	87 (33.59)	38 (28.36)	49 (39.20)		
YES	172 (66.41)	96 (71.64)	76 (60.80)		
HbA1c	6.10 (5.60, 6.50)	6.10 (5.60, 6.50)	6.10 (5.60, 6.50)	-0.17	0.862
RV5(mV)	2.42 (2.03, 3.11)	2.37 (1.96, 3.06)	2.45 (2.07, 3.25)	-0.59	0.553
RV5 + SV1(mV)	3.28(2.92,3.62)	3.26(2.79,3.54)	3.36(2.91,3.59)	1.24	0.207
SBP(mmHg)	130.00 (121.00, 137.00)	129.00 (123.00, 141.00)	130.00 (121.00, 135.00)	-1.18	0.239
DBP(mmHg)	81.00 (74.25, 88.00)	83.00 (75.00, 88.00)	79.00 (72.00, 87.00)	-1.64	0.100
LA(mm)	36.00 (33.00, 39.00)	36.00 (33.00, 38.00)	36.00 (33.00, 40.00)	-2.11	0.035
LV(mm)	9.00 (8.00, 10.00)	9.00 (8.00, 10.00)	9.00 (8.00, 10.00)	-0.62	0.538
IVS(mm)	9.00 (8.00, 10.00)	9.00 (8.00, 10.00)	9.00 (8.00, 10.00)	-0.25	0.802
LVPW(mm)	11.00 (8.00, 11.00)	11.00 (8.00, 12.00)	10.00 (8.00, 10.00)	-1.54	0.386
LVEDD(mm)	50.00 (46.00, 52.00)	49.00 (46.00, 52.00)	50.00 (46.00, 53.00)	-1.38	0.167
LVEF(%)	63.00(58.00,70.00)	64.00(59.00,69.00)	63.00(59.00,71.00)	-2.34	0.435
E(m/s)	65.00 (49.25, 72.00)	66.00 (57.00, 75.00)	65.00 (47.00, 71.00)	-1.25	0.098
A(m/s)	80.00 (68.00, 94.00)	80.00 (69.00, 93.00)	80.00 (67.00, 94.00)	-0.08	0.933
E/A	0.80(0.60,1.00)	0.80(0.60,1.00)	0.80(0.60,1.00)	-0.32	0.580
DT(ms)	203.00(163.00,225.00)	205.00(169.00,226.00)	198.00(157.00,220.00)	1.95	0.251
ACE-D(%)				31.74	< .001
0	111 (40.51)	80 (56.74)	31 (23.31)		
1	163 (59.49)	61 (43.26)	102 (76.69)		
Hypertension Classification				-	0.528
1	258 (94.16)	131 (92.91)	127 (95.49)		
2	14 (5.11)	8 (5.67)	6 (4.51)		
3	2 (0.73)	2 (1.42)	0 (0.00)		
Medication(%)				-	0.479
ACEI/ARB/ARNI	226(82.40)	117(82.90)	109(81.90)		
β-Blocker	36(13.10)	19(13.40)	17(12.70)		
CCB	12(4.50)	5(3.70)	7(5.40)		
DM(%)				1.21	0.185
0	261(95.20)	136(96.40)	125(93.90)		
1	13(4.80)	5(3.60)	8(6.10)		

t: t-test, Z: Mann–Whitney test, χ^2: Chi-square test, -: Fisher exact

SD standard deviation, *M* Median, Q_1 1st Quartile, Q_3 3st Quartile

Table 5 Association between ACE and early diastolic function in hypertension by logistic regression analysis

		Crude Model		Adjusted Model		
	OR	95% CI	P	OR	95% CI	*P*
ACE	4.32	2.56- 7.27	< .001	3.83	2.24–6.54	< .001
Crude Model						
Variables	β	S.E	Z	*P*	OR (95%CI)	
Intercept	-0.95	0.21	-4.48	< .001	0.39 (0.26 ~ 0.59)	
ACE-D						
0					1.00 (Reference)	
1	1.46	0.27	5.49	< .001	4.32 (2.56 ~ 7.27)	
Adjusted Model						
Variables	β	S.E	Z	*P*	OR (95%CI)	
Intercept	-3.52	1.07	-3.29	0.001	0.03 (0.00 ~ 0.24)	
ACE-D						
0					1.00 (Reference)	
1	1.34	0.27	4.92	< .001	3.83 (2.24 ~ 6.54)	
Sex						
Female					1.00 (Reference)	
Male	0.25	0.28	0.87	0.383	1.28 (0.73 ~ 2.23)	
Age	0.01	0.01	1.48	0.138	1.01 (1.00 ~ 1.03)	
Renal Dysfunction						
NO					1.00 (Reference)	
YES	-1.29	0.66	-1.94	0.052	0.28 (0.08 ~ 1.01)	
LA	0.05	0.03	1.75	0.080	1.05 (0.99 ~ 1.12)	

Crude model: Unadjusted model; Adjusted model: adjusted for age, sex, the prevalence of renal dysfunction, left atrial diameter. *OR* Odds ratios, *CI* confidence interval, *OR* Odds Ratio, *CI* Confidence Interval. *OR* Odds Ratio, *CI* Confidence Interval

thickening. This condition is associated with increased *ACE* activity, which leads to ventricular remodeling and, subsequently, left ventricular hypertrophy. Some studies have also found that carriers of the D allele are more likely to have an RV5 + SV1 value that exceeds the normal range on a standard ECG [25]. However, our study did not observe this finding, which may be attributed to the inclusion of patients with early-stage hypertension with well-controlled blood pressure. This discrepancy highlights the need for more precise methods to evaluate diastolic function.

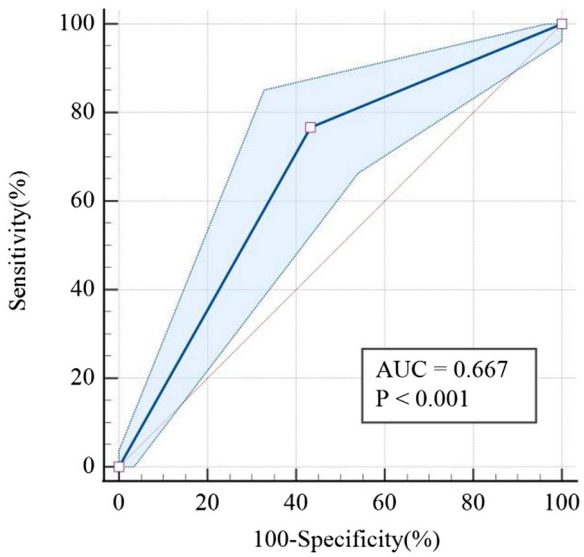

Fig. 6 ROC curve analysis of the D allele for predicting diastolic dysfunction in patients with hypertension

Echocardiography is the primary diagnostic tool for hypertensive heart disease, with the E/A ratio commonly used to assess diastolic function. However, its sensitivity in detecting early diastolic dysfunction is limited [26]. Recent guidelines have introduced additional parameters to enhance the assessment of diastolic dysfunction. Primary indicators include an E/e' ratio > 1.4, LA volume > 34 ml/m^2, and TR velocity > 2.8 cm/s. Secondary indicators include LA strain < 18%, Ar-A duration > 30 ms, and L-wave velocity > 20 cm/s. Four-dimensional echocardiography, combined with synchronized ECG, allows for comprehensive evaluation by capturing various cardiac chamber views within the same cycle and tracking phase-specific changes in chamber pressure, valve movements, blood flow, and chamber volume. This technique provides a precise assessment of diastolic function, with adjustments made for individual differences in height and weight. Our study found that carriers of the D allele are more likely to exhibit diastolic dysfunction based on these parameters. However,

there was no correlation between secondary indicators Ar-A duration and L-wave velocity, which may be due to the significant impact of factors such as respiration and heart rate. To better differentiate diastolic function between the two groups, we also measured IVRT and MAPSE in addition to the standard diagnostic criteria. Our findings revealed that the D allele group showed prolonged IVRT(IVRT > 100 ms) and increased MAPSE(MAPSE < 10 mm). Correlation analysis confirmed that these changes are indicative of diastolic dysfunction, aligning with findings from other studies [27, 28].

Previous studies have shown that age is a risk factor for diastolic dysfunction [6]. In this study, a significant difference in age was observed between the D allele group and the non-D allele group, as well as between the normal diastolic function group and the impaired diastolic function group. Additionally, differences in left atrial diameter and the prevalence of renal dysfunction were found between the normal and impaired diastolic function groups. To eliminate the influence of factors such as age, left atrial diameter, and the prevalence of renal dysfunction on the results, logistic regression analyses were performed using both the crude and adjusted models. After adjusting for confounding factors, the D allele remained associated with an increased risk of early diastolic dysfunction in hypertension. Therefore, the D allele can be considered an independent risk factor for early diastolic dysfunction in hypertension.

The *ACE* gene is located on chromosome 17 at position 17q23 and spans 44,769 base pairs, consisting of 26 exons and 25 introns. The enzyme encoded by the *ACE* gene has dipeptidyl carboxypeptidase activity, which hydrolyzes angiotensin I—a 10-amino acid peptide—by cleaving its C-terminal dipeptide to produce angiotensin II, an eight-amino acid peptide. Carriers of the D allele have higher levels of ACE compared to non-carriers, leading to increased levels of angiotensin II [29]. In patients with hypertension, elevated angiotensin II can raise blood pressure by activating angiotensin receptors and downstream signaling pathways. ACE inhibitors (ACEIs), such as captopril and enalapril, counteract the effects of angiotensin II by modulating the renin–angiotensin–aldosterone system (RAAS) and reducing aldosterone release. This helps alleviate the impact on diastolic function, making ACEIs a key treatment option in the clinical management of hypertension.

Research has demonstrated that in hypertensive animal models, angiotensin II interacts with the angiotensin II type 1 receptor, which enhances inflammatory and oxidative stress responses, promotes apoptosis, and ultimately leads to myocardial hypertrophy and fibrosis [30]. Additionally, mineralocorticoid receptors in myocardial cells can increase collagen synthesis, contributing to myocardial interstitial fibrosis. Prolonged exposure to these factors is associated with left ventricular hypertrophy and remodeling [31]. Furthermore, endothelial nitric oxide synthase (*NOS3*) gene polymorphisms have been associated with hypertension-induced left ventricular hypertrophy. *NOS3* deficiency can result in cardiac hypertrophy, congenital septal defects, and postpartum heart failure [32]. Therefore, monitoring *ACE* genotypes is vital for understanding the development of hypertensive heart disease. Patients with the D allele have higher levels of ACE, which increases their susceptibility to hypertension-related cardiac damage. In our study, carriers of the D allele also demonstrated a higher propensity for early diastolic dysfunction.

Conclusion

In summary, among individuals with hypertension, those carriers of the *ACE*-D allele are more likely to develop early diastolic dysfunction compared to non-carriers. Therefore, incorporating *ACE* gene testing to identify patients with hypertension with the D allele, followed by detailed diastolic function assessment using four-dimensional echocardiography, could facilitate the early detection of individuals at high risk for progressing to hypertensive heart disease. Implementing more rigorous blood pressure monitoring and stricter blood pressure control standards, early and targeted interventions based on this information could potentially enhance long-term outcomes for these patients.

However, this study has certain limitations: it is a single-center study with a relatively small sample size, and the duration of hypertension exposure was not strictly controlled. This lack of control may have introduced variability in the severity of hypertensive heart disease among patients with different disease durations [33]. Additionally, most participants did not exhibit significant abnormalities on echocardiography. To address these limitations, larger studies with more rigorous blood pressure management and extended follow-up periods are necessary.To further explore the relationship between *ACE* genotypes and the progression of diastolic dysfunction in hypertension, a broader range of patients with varying levels of hypertension and diastolic dysfunction could be included in the study. Such studies would help validate the predictive value of *ACE* genotyping for assessing the prognosis of patients with hypertension.

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Authors' contributions
Both authors had access to the data. XC wrote the paper. XM, YJ and YZ reviewed and edited the manuscript. ZZ provided valuable guidance on data analysis, while JS, HJ and HX offered numerous insightful suggestions for drafting and reviewing the response emails during the major revision of this manuscript.

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Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
This study was approved by the Ethics Committee of The Fourth Affiliated Hospital of Soochow University(Suzhou Dushu Lake Hospital) (approval No.210047) and the methods were carried out in accordance with the approved guidelines. All the patients have been informed and signed informed consent before the experiments. This research does not cause harm to participants and does not involve sensitive personal information. This study complies with the principles expressed in the Declaration of Helsinki. Moreover, this study complies with the ethical exemption requirements of the "Ethical Review Measures for Life Sciences and Medical Research Involving Humans" promulgated by China.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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