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RESEARCH ARTICLE

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Quantitative assessment of left atrial functions by speckle tracking echocardiography in hypertensive patients with and without retinopathy

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Abstract

Purpose: The association between hypertensive retinopathy and left atrial (LA) impairment is unknown. Accordingly, it was aimed to investigate the possible relationship between hypertensive retinopathy and LA phasic functions by means of two-dimensional speckle-tracking echocardiography (2D-STE).

Methods: A total of 124 hypertensive patients and 27 control subjects were included in the study. LA reservoir strain (LA_{S-S}), LA conduit strain (LA_{S-E}), and LA booster strain (LA_{S-A}) parameters were used to evaluate LA myocardial functions.

Results: Hypertensive patients (with and without retinopathy) displayed an obvious reduction in the LA reservoir strain (LA_{S-S}), and LA conduit strain (LA_{S-E}). Moreover, further impairment in LA reservoir and conduit strain was found in patients with hypertensive retinopathy than in the isolated hypertensive patients. There were no significant differences in LA booster strain (LA_{S-A}) among the three groups. Impaired LA_{S-S} (OR: 0.764, CI: 0.657–0.888, and $p < 0.001$), LA_{S-E} (OR: 0.754, CI: 0.634–0.897, and $p = 0.001$), and hypertension (HT) duration (OR: 2.345, CI: 1.568–3.507, and $p < 0.001$) were shown to be independent predictors of hypertensive retinopathy.

Conclusion: Impaired LA reservoir and conduit strain may be used to predict hypertensive patients at higher risk of developing hypertensive retinopathy, and to determine which patients should be followed more closely for hypertensive retinopathy.

KEYWORDS
hypertension, left atrium, retinopathy, strain

1 | INTRODUCTION

Hypertension (HT) is a devastating socioeconomic health problem empiercing large populations and is an essential determinant of cardiovascular adverse outcome.[1] Due to the silent progression of HT and its harmful effects on the vascular system, early diagnosis and more effective treatment strategies are needed. Target organ damage (TOD) is an early clinical manifestation of HT and usually exists in the most patients before the diagnosis.[2,3] The main sites of end-organ damage are the micro-and macrovascular systems and the heart.[1]High blood pressure (BP) can cause retinal vascular deterioration.[4] Moreover, retinopathy secondary to HT has been implicated as an individual predictor of cardiovascular disorder, irregardless of other hypertensive TOD.[5,6]The retinal microvascular network is the only

system that can be observed directly and is often used to identify HT-related microvascular injury.[1,3] The first reaction to increased luminal stress is vasoconstriction causing retinal arteriolar narrowing (vasoconstrictive phase). Following this stage, high BP causes endothelial damage resulting in intimal thickening and a reduction in the vessel lumen area (sclerotic phase). Prolonged exposure to HT damages the blood-retina barrier, causing the accumulation of blood particles in the retinal layers (exudative phase). Optic nerve damage can also develop in patients with long-standing HT or severe malignant HT which manifests as papillitis.[4]

Systemic HT also causes morphological and functional abnormalities in the left atrium. However, it remains unknown whether there is a relationship between hypertensive retinopathy and the degree of LA impairment. The left atrium serves as a dynamic apparatus by modulating left ventricular (LV) filling during LV systole, allowing blood flow from the pulmonary veins to the LV during early diastole, and augmenting LV filling during late diastole.[7] LA enlargement has been shown to predict hypertensive TOD and is associated with cardiovascular disease, including atrial fibrillation (AF), heart failure, and stroke.[8,9] However, in the early stages of HT subtle changes in LA function cannot be discerned by conventional echocardiography. Therefore, 2D-STE-based strain measurements have been recognized as a relatively new method superior to conventional echocardiography for detecting subclinical LA dysfunctions.[10,11]

Assessment of LA myocardial functions via 2D-STE imaging may evaluate better LA dysfunction and its association with hypertensive retinopathy. Accordingly, the present study was designed to investigate the possible relationship between hypertensive retinopathy and LA phasic functions by means of 2D-STE in hypertensive patients. Additionally, we aimed to determine whether the degree of deterioration in the LA strain predicts the presence of retinopathy.

2 | METHODS

2.1 | Study population

This cross-sectional prospective study was conducted in outpatient primary hypertensive patients that were being followed up by a tertiary hospital for at least 1 year. Among these, 24-h ambulatory blood pressure monitoring (ABPM), fundus examination, conventional and 2D-STE analyses were performed to the patients who presented to the outpatient clinic between September 2021 and January 2022. Echocardiographic analysis was performed on the day of admission to the outpatient clinic and fundus examinations were performed within 1 week after echocardiographic analysis. Demographic characteristics, medical histories, and drug use were obtained from patients or medical records, and detailed clinical examination, anthropometric measurements, and laboratory analysis done for all patients. Exclusion criteria were left ventricular systolic dysfunction [left ventricular ejection fraction (LVEF) < 50%], the evidence of coronary artery disease, moderate-to-severe valvular regurgitation or stenosis, previous cardiac surgery, congenital heart disease, history of AF or conduction disturbances, renal failure [glomerular filtration rate (GFR) <60 ml/min], the presence of secondary HT, systemic inflammatory disease, chronic lung disease, pregnancy, and inappropriate echocardiographic images. Secondary causes of HT were excluded based on the history, physical and laboratory examination results. In addition, patients with diabetes mellitus (DM) were excluded as DM may interfere with both retinal changes and LA function. Written informed consent was obtained from each participant. Ethical approval has been obtained from Istanbul Medeniyet University, Goztepe Training and Research Hospital ethics committee. The study was carried out per the Declaration of Helsinki.A total blood cholesterol level of greater than 220 mg/dl was categorized as hypercholesterolemia (HL), as was receiving lipid-lowering medication. DM was considered as fasting blood glucose level of ≥126, 2-h post-challenge blood glucose ≥200 mg/dl, or treatment with insulin or hypoglycemic drugs. Coronary heart disease was described as myocardial infarction or coronary revascularization histories or the presence of significant coronary artery stenosis (≥50%) in prior angiogram. Twenty-seven age-matched healthy volunteers who did not have any chronic disease were recruited as the normal control group. The control subjects had no abnormalities on routine physical examination, conventional echocardiographic study, and electrocardiogram, except age-related changes and were not regularly taking any medication. A 24-h ABPM, fundus examination, conventional and 2D-STE analyses were performed on all individuals.

2.2 | Diagnosis of arterial HT

A 24-h ABPM was completed in all patients followed up with HT, and in the control group. The ABPM (Custo medical Gmbh, Germany) was used to perform the 24-h ABPM on the non-dominant arm. All participants were instructed to execute their usual activities during the day, but to keep their arms still during measurements. Each patient's recordings [averaged over 24 h, daytime and overnight systolic BP (SBP) and diastolic BP (DBP)] were then evaluated. HT was defined as the average 24-h SBP/DBP greater than 130/80 mmHg, and/or daytime SBP/DBP greater than 135/85 mmHg, and nighttime SBP/DBP greater than 120/70 mmHg or clinical SBP≥140 or DBP≥90 mmHg or the use of antihypertensive medication.[1]

2.3 | Fundus evaluation

All subjects underwent retinal color photography of both eyes using a 45° digital retinal camera (Topcon TRC-NW8, Tokyo, Japan) 20 min later of the pupillary dilatation. Pupillary dilatation was achieved with one drop of tropicamide in each eye. Two standard retinal scans have been taken of both eyes, one centered on the optic disc and the other on the macula.

After that, each photograph was randomly assessed by two professional ophthalmologists who were unaware of the patient's clinical characteristics. Any inconsistency between the two ophthalmologists was resolved with consensus. Measurements of all arterioles and

veins were made in the area between half and one disc diameter from the margin of the optic disc.

Hypertensive retinopathy occurrence was assessed according to the Keith–Wagener–Barker classification, which includes; stage 0: patients with no visible retinal abnormalities; stage 1: mild generalized retinal arteriolar narrowing, but no focal constriction, decreased arteriolar/venular ratio; stage 2: definite arteriolar narrowing with focal constriction, arteriovenous nicking; stage 3: signs of stage 2 retinopathy with retinal hemorrhage, exudate, and cotton-wool spots; and stage 4: signs of stage 3 retinopathy with papilledema.[12]

2.4 | Echocardiographic examination

2.4.1 | Conventional echocardiography

Two-dimensional transthoracic echocardiography (TTE) was implemented using a Vivid 7 (GE Medical Systems, Milwaukee, WI) equipped with a 3.5 MHz transducer with digital storage software for offline analysis by experienced operators blinded to the patient's clinical characteristics.

All the images and measurements were performed during expiratory breath-hold from parasternal long-axis and LV apical two- and four-chambers with simultaneous electrocardiogram (ECG) recording and the images were digitally stored for offline analysis.[13] All measurements were obtained in three consecutive cycles and the mean value of three of these images was included in the analysis. Afterward, the analysis of the data was made by using EchoPAC (GE Vingmed Ultrasound AS).

LV end-diastolic (LVEDD) and end-systolic (LVESD) diameters, LV posterior, and interventricular wall thickness were measured in diastolic phase using M-mode echocardiography from parasternal long-axis view. LV mass (LVM), and relative wall thickness (RWT) were computed by following Devereux et al's description. Accordingly, left ventricular mass index (LVMI) was calculated by dividing LVM by BSA.[14] The modified Simpson's method was used to calculate LVEF in apical views.

Transmitral inflow peak E and A velocities in early diastole and late diastole, and the ratio of these velocities (E/A ratio) were measured from the apical 4-chamber view with pulsed-wave Doppler placed at the top of the mitral valve leaflets. LV longitudinal functions (peak systolic (S′), peak early diastolic (e'), and peak late diastolic (A') velocities were gained by tissue Doppler imaging from the septal and lateral regions of the mitral annulus. The mean values of septal and lateral positions were used for the analysis. The E/e' ratio was determined as a LV filling pressure index.[13]

2.4.2 | Assessment of LA volumes and function

LA volume was determined at the three distinct cardiac cycle phases by using the biplane Simpson's method from apical four and two chambers views, then the LA volume index (LAVI) was calculated through dividing LA volume by BSA. $LAVI_{max}$ was obtained at the end of ventricular systole, just before the mitral valve opening; $LAVI_{pre\text{-}A}$ (pre atrial contraction) was measured at the onset of the P wave on the ECG; $LAVI_{min}$ was measured at the end of diastole, just before mitral valve closure. LA phasic functions were calculated as follows: Left atrial total emptying fraction (LATEF) which represents LA reservoir function: $(LAVI_{max}\text{-}LAVI_{min)} / LAVI_{max} \times 100$.

Left atrial passive emptying fraction (LAPEF) which represents LA conduit function: $(LAVI_{max}\text{-}LAVI_{preA}) / LAVI_{max} \times 100$.

Left atrial active emptying fraction (LAAEF) which represents LA booster pump function: $(LAVI_{preA}\text{-}LAVI_{min)} / LAVI_{preA} \times 100$.

2.4.3 | Speckle tracking echocardiography

For 2D-STE analysis, we recorded standard two-dimensional grayscale images of apical 4- and 2-chamber views focused on the left atrium at a frame rate of 40–80 frames/sec (Figure 1). All recorded images, obtained during breath-hold from three consecutive cardiac cycles with a stable ECG recording, were analyzed offline using custom software (EchoPAC PC; GE Vingmed Ultrasound AS) by two experienced and independent operators blinded to the clinical data.[10,15] Recordings were carefully taken to ensure the proper scanning and avoiding foreshortening of the left atrium.The endocardial surface of the LA was manually outlined at end-systole in apical 4- and 2-chamber views by point-and-click approach. The software generated epicardial surface tracing automatically. The interested region was manually identified to cover the myocardial thickness of the left atrium, which provides an automatic segment tracking quality analysis. Each LA wall (lateral, interatrial, anterior, and inferior) was divided into 3 segments, resulting in a total of 12 segments for each patient. If there were segments with unsatisfactory tracking quality, then further manual adjustments were performed for these regions of interest. A cine loop preview was also used to validate that the region of interest's inner border matched the LA endocardial border appropriately throughout the cardiac cycle. Even after repeated manual adjustment, segments with inadequate tracking quality were excluded from the analysis, and patients with more than 3 segments with no adequate tracking quality among 12 segments were eliminated from the study.[16,17]

For each segment, LA longitudinal strain curves were created. Global LA strain parameters were determined as the average of the accepted segmental values obtained from apical 4- and 2- chamber views. Peak LA longitudinal strain ($LA_{S\text{-}S}$) which mostly reflects LA reservoir function was obtained just before mitral valve opening; late diastolic LA longitudinal strain ($LA_{S\text{-}A}$) which mostly reflects LA booster pump function was obtained at the precise onset of the P-wave; early diastolic LA longitudinal strain ($LA_{S\text{-}E}$) which mostly reflects LA conduit function was obtained as the difference between the $LA_{S\text{-}S}$ and $LA_{S\text{-}A}$.[16]

The LV endocardial surface was manually traced at the end-systole, and the LV wall was divided into six segments in both apical 4- and 2-chamber views and the systolic LV global longitudinal strain

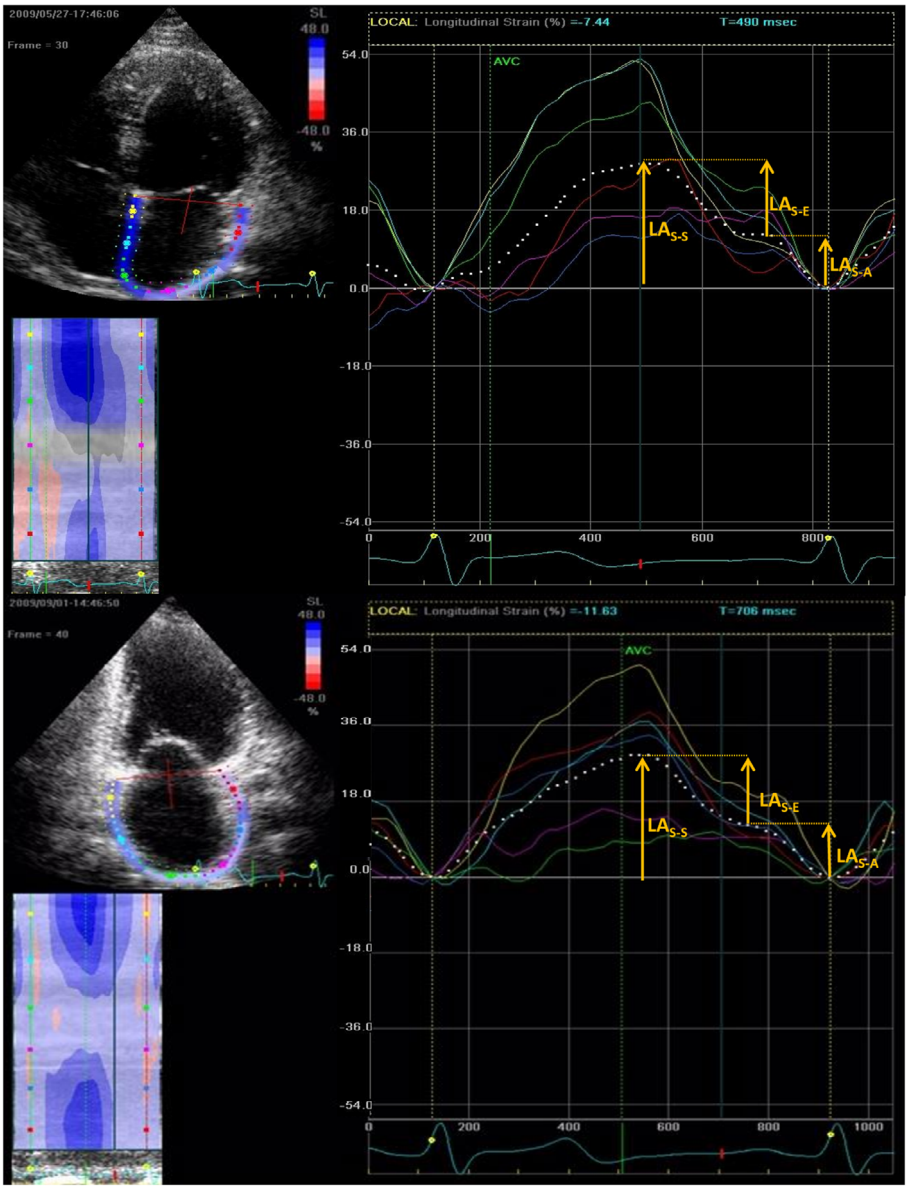

FIGURE 1 Two-dimensional strain curves acquired from the apical four-and two-chamber views. It shows the strain curves of the left atrium and the measurement method of the parameters in a patient with hypertensive retinopathy

(GLS) was determined as the average of the recognized segmental values.[18]

The reproducibility of LA strain measurements was assessed in the randomly selected subset of 25 hypertensive patients. These patients were reanalyzed by the same cardiologist or by two independent cardiologists to evaluate the variability of LA strain values. Inter-observer and intraobserver variability coefficients were as follows: $LA_{S\text{-}S}$, 5,7% and 4,8%; $LA_{S\text{-}E}$, 6,2% and 5,7%; and $LA_{S\text{-}A}$, 6,4% and 5,8%, respectively.

2.5 | Statistical analysis

SPSS version 21 was used for all of the analyses (SPSS, Inc., Chicago, Illinois). While percentage expression was used to represent the categorical variables, the continuous variables were given by way of mean values (standard deviation [SD]) or medians with interquartile ranges. For continuous variables that continuously distributed, a 2-tailed Student *t*-test was used, whereas non-normally distributed continuous variables were assessed by Mann–Whitney U test. In addition, the analysis of variance (ANOVA) procedure was used to compare the control group with the retinopathy (+) and (−) hypertensive groups. The Chi-square test was used to investigate the categorical variables. Univariate regression analysis was used to examine the influence of each variable on the progression of retinopathy. The variables with unadjusted $p < 0.1$ in univariate analysis and clinically retinopathy-related parameters were determined as confounding factors and involved in the multivariate regression analysis to reveal the independent predictors. The predictive values of $LA_{S\text{-}S}$ and $LA_{S\text{-}E}$ were estimated by the areas under the receiver operating characteristic (ROC) curve analysis. All the statistical tests were 2-tailed, and a $p < 0.05$ value was considered as significant.

TABLE 1 Clinical characteristics of the study population

Variables	Control ($n = 27$)	HT (+), RP (−) ($n = 68$)	HT(+) RP (+) ($n = 56$)	p-value
Age (years)	51.2 ± 9.4	50.8 ± 8.5	52.4 ± 8.3	0.589
Male gender, *n* (%)	15 (55.6%)	31 (45.6%)	25 (44.6%)	0.615
Smoking, *n* (%)	8 (29.6%)	23 (33.8%)	17 (30.4%)	0.887
Dyslipidemia, *n* (%)	6 (22.6%)	18 (26.5%)	14 (25%)	0.911
BSA (m^2)	1.9 ± 0.08	1.9 ± 0.07	1.89 ± 0.06	0.096
Creatinine (mg/dl)	0.85(0.82–0.93)	0.86(0.80–0.99)	0.86(0.82–0.99)	0.865
HT duration (years)		3(2–4)	5(4–7.7)	<0.001*
Day SBP (mmHg)	133.2 ± 4.1	139.5 ± 9.2	140.2 ± 9.9	0.792
Day DBP (mmHg)	82.5 ± 3.2	85.5 ± 4	86.5 ± 4.4	0.509
Night SBP (mmHg)	119.3 ± 4.6	124 ± 7.5	124.4 ± 6.7	0.260
Night DBP (mmHg)	70.1 ± 4.9	74.9 ± 4	73.4 ± 3.9	0.665
Mean SBP(mmHg)	128.6 ± 2.9	134.2 ± 8.4	134.9 ± 8	0.234
Mean DBP (mmHg)	78.4 ± 2.8	82.2 ± 3.7	82.4 ± 3.5	0.590
Medications, *n*(%)				
ACEIs/ARBs		57(83.8%)	48(85.7%)	0.808*
CCBs		24(35.3%)	18(32.1%)	0.849*
Alfa blockers		4(6%)	3(5.4%)	0.990*
Diuretics		31(45.6%)	27(48.2%)	0.857*
Beta blockers		11(16.2%)	10(17.9%)	0.815*

Abbreviations: ACEIs, angiotensin-converting enzyme inhibitors; ARBs, angiotensin II receptor blockers; BSA, body surface area; CCBs, calcium-channel blockers; HT, hypertension; RP, retinopathy; SBP:, systolic blood pressure.
Note: *p*-value represents the difference between hypertensive patients and control group.
*p-value represents difference between [HT(+),RP(+)] group and [HT(+),RP(−)] group.

3 | RESULTS

3.1 | Study population

In the overall study population, 12 subjects (11 patients and one control) were excluded during offline analysis due to the inability to adequately track more than three LA segments. The remaining 124 patients (patients with HT but not retinopathy, $n = 68$; patients with HT and retinopathy, $n = 56$), and 27 control subjects were included in the study. The rate of retinopathy was found as 45.1% in the hypertensive patient group. Of the patients with hypertensive retinopathy, 37.5% ($n = 21$) had grade 1 retinopathy, 48.2% ($n = 27$) had grade 2 retinopathy, and 14.2% ($n = 8$) had grade 3 retinopathy. There was no patient with grade 4 retinopathy.

The key clinical characteristics of the study population are shown in Table 1. Age, gender, and body surface area (BSA) were similar among the three groups ($p > 0.05$ for all). There was also no significant difference among the three groups in terms of smoking, dyslipidemia, and serum creatinine levels.

The hypertensive patient group had greater daytime and nighttime SBP and DBP than the control group, but the differences were not statistically significant.

Patients with hypertensive retinopathy appeared to suffer from HT for a longer time period (3 vs. 5 years) than patients without retinopathy ($p < 0.001$). Antihypertensive medication did not differ significantly between the two patient groups (Table 1).

3.2 | Conventional echocardiographic parameters

The comparison of echocardiographic parameters is presented in Table 2. There were no significant differences in terms of the LV diameters as well as LVEF among the three groups ($p > 0.05$).

Compared with the control group, LVMI, RWT, septal, and posterior wall thickness were significantly greater in both groups of hypertensive patients with and without retinopathy ($p < 0.005$). However, there were no significant differences between the two hypertensive groups ($P > 0.05$).

Peak systolic (S′) and early diastolic (E') LV longitudinal functions were significantly lower in the hypertensive group than in the control group but were not significantly different between the two hypertensive groups. Also, the peak late diastolic tissue velocity of LV (A') was similar among the three groups.

Conventional Doppler parameters—lower E/A ratio and longer deceleration time were able to demonstrate LV diastolic dysfunction in hypertensive patients. Also, higher E/E' ratio reflected increased LV filling pressure compared to the control group. However, there were no significant differences between the two hypertensive groups with or without retinopathy (Table 2).

TABLE 2 Echocardiographic Characteristics of the Study Population

Variables	Control ($n = 27$)	HT (+), RP (−) ($n = 68$)	HT(+) RP (+) ($n = 56$)	*p*-value
LVEF (%)	60.9 ± 2.7	60.5 ± 3	60.7 ± 3	0.779
LVEDD (mm)	48.7 ± 3.1	49.6 ± 2.2	49.9 ± 2.1	0.076
LVESD (mm)	30.6 ± 3.9	30.1 ± 2.6	29.1 ± 2.2	0.093
IVS thickness (mm)	9(8–10)	10(10–11)	10(10–11)	0.001
				0.773*
PW thickness (mm)	8(8–8)	10(10–11)	10(10–11)	0.001
				0.642*
LVMI (g/m^2)	76.1(65.8–87.6)	98.6(89.9–104.6)	95.9(90.5–113.6)	<0.001
				0.906*
RWT	0.33(0.29–0.35)	0.4(0.38–0.43)	0.4(0.39–0.42)	<0.001
				0.827*
E' (cm/sec)	11.9 ± 2.4	9.3 ± 1.4	9.2 ± 1.5	<0.001
				0.622*
A' (cm/sec)	10 ± 1.2	10.5 ± 1.1	10.3 ± 1.4	0.247
S′ (cm/sec)	9.7 ± 1.1	8.2 ± 1.2	8.2 ± 1.4	<0.001
				0.764*
E/E' ratio	7.3 ± 0.7	7.7 ± 1.2	8 ± 1	0.021
				0.191*
E/A ratio	1.1 ± 0.1	0.8 ± 0.1	0.8 ± 0.1	<0.001
				0.926*
Dec time (msec)	191 ± 18	214 ± 33	209 ± 30	0.003
				0.316*
LV GLS (%)	20.6 ± 1.2	18.9 ± 1.3	18.7 ± 1.1	<0.001
				0.414*
LAVI max (ml/m^2)	26.7 ± 3.6	31.3 ± 3.8	32 ± 4.5	<0.001
				0.363*
LAVI min (ml/m^2)	10.4 ± 2.2	14.7 ± 2.1	15 ± 3.1	<0.001
				0.405*
LAVI pre A (ml/m^2)	16.4 ± 3.3	22.4 ± 3	23.1 ± 3.9	<0.001
				0.270*
LATEF (%)	61 ± 3.7	53.24 ± 2.5	53.2 ± 3.9	<0.001
				<0.936*
LAPEF (%)	39 ± 5.4	28.59 ± 2.4	28 ± 4.3	<0.001
				0.376*
LAAEF (%)	36.1 ± 3	34.48 ± 3.6	35.1 ± 3.4	0.115
LA_{S-S} (%)	40.8 ± 4	34.2 ± 3.6	29.6 ± 4.5	<0.001
				<0.001*
LA_{S-E} (%)	22.8 ± 3.6	18.7 ± 3.1	15.3 ± 2.9	<0.001
				<0.001*
LA_{S-A} (%)	17 ± 3	17.7 ± 2.8	17.5 ± 3.2	0.586

Abbreviations: A', late diastolic annular velocity; E′, early diastolic annular velocity; HT, hypertension; IVS, interventricular septum; LAAEF, left atrial active emptying fraction; LAPEF, left atrial passive emptying fraction; LATEF, left atrial total emptying fraction; LA_{S-A}, late diastolic left atrial longitudinal strain; LA_{S-E}, early diastolic left atrial longitudinal strain; LA_{S-S} peak left atrial longitudinal strain; LAVI: left atrial volume index; LVEDD, left ventricular end diastolic diameter; LVEF, left ventricular ejection fraction; LVESD, left ventricular end systolic diameter; LV GLS: left ventricular global longitudinal strain; LVMI, left ventricular mass index; preA, preatrial contraction; PW, posterior wall; RP, retinopathy; RWT, relative wall thickness; S′, peak systolic annular velocity.

Note:*p*-value represents the difference between hypertensive patients and control group.

*p-value represents difference between [HT(+),RP(+)] group and [HT(+),RP(−)] group.

TABLE 3 Independent predictors of hypertensive retinopathy

Variables	Univariable OR (95% CI)	*p*-value	Multivariable OR (95% CI)	*p*-value
HT duration	1.980 (1.515–2.589)	<0.001	2.345 (1.568–3.507)	<0.001
Age	1.027 (0.971–1.086)	0.353		
Gender (male)	0.886 (0.349–2.250)	0.794		
SBP total	1.058 (0.960–1.166)	0.254		
DBP total	0.888 (0.349–1.097)	0.270		
LA_{S-E}	0.704 (0.611–0.810)	<0.001	0.754 (0.634–0.897)	0.001
LA_{S-S}	0.760 (0.680–0.848)	<0.001	0.764 (0.657–0.888)	<0.001
LA_{S-A}	0.977 (0.868–1.100)	0.699		
$LAVI_{max}$	1.041 (0.955–1.134)	0.361		
$LAVI_{min}$	1.220 (1.060–1.404)	0.006		
$LAVI_{preA}$	1.149 (1.034–1.278)	0.010		

Abbreviations: DBP, diastolic blood pressure; HT, hypertension; LA_{S-E}, early diastolic left atrial longitudinal strain; LA_{S-S}: peak left atrial longitudinal strain; LA_{S-A}, late diastolic left atrial longitudinal strain; LAVI, left atrial volume index; SBP, systolic blood pressure.

3.3 | Left atrial volumetric parameters

Maximum, minimum, and pre-A LAVIs were significantly higher in both hypertensive groups in comparison with the control group ($p < 0.001$). However, the differences in these volumetric parameters were not significant between the isolated HT and HT with the retinopathy group.

The hypertensive groups had significantly lower LATEF and LAPEF values than the control group but the difference between the retinopathy (+) and (−) groups did not reach statistical significance. Also, there was no significant difference in terms of LAAEF among the three groups.

3.4 | LA strain parameters

The LA reservoir strain (LA_{S-S}) was lower in the hypertensive group as compared to the control group, and it was furtherly decreased in the retinopathy (+) group ($p < 0.001$).

Similarly, The LA conduit strain (LA_{S-E}) was lower in the HT group than in the control group, and it was further depressed in the retinopathy (+) group ($p < 0.001$). On the other hand, the LA booster strain (LA_{S-A}) did not differ siginificantly among the three groups (ANOVA, $P = 0.586$).

The peak systolic LV-GLS was also lower in the HT group and the HT with retinopathy group compared with the control group (ANOVA, $p < 0.001$). However, the difference between the retinopathy (+) and (−) groups was not significant ($P = 0.414$) (Table 2).

We used logistic regression analysis to identify predictors associated with the presence of hypertensive retinopathy. Impaired LA_{S-S} (OR: 0.764, CI: 0.657–0.888, and $p < 0.001$), LA_{S-E} (OR: 0.754, CI: 0.634–0.897, and $p = 0.001$), and hypertension (HT) duration (OR: 2.345, CI: 1.568–3.507, and $p < 0.001$) were revealed to be independent predictors of hypertensive retinopathy in multivariate analysis (Table 3).

Receiver-operating characteristic (ROC) analysis was carried out to identify the role of both LA_{S-S} and LA_{S-E} in predicting retinopathy. LA_{S-S} less than 32.21% predicted retinopathy with 71.4% sensitivity and 69.1% specificity (area under the curve (AUC): 0.776 (95% confidence interval [CI]: 0.695–0.857, $p < 0.001$). Also, optimal cut-off value of LA_{S-E} in predicting retinopathy was 16.92% with 73.2% sensitivity and 70.6% specificity (AUC: 0.780, 95% CI: 0.700–0.860, and $p < 0.001$) (Figure 2).

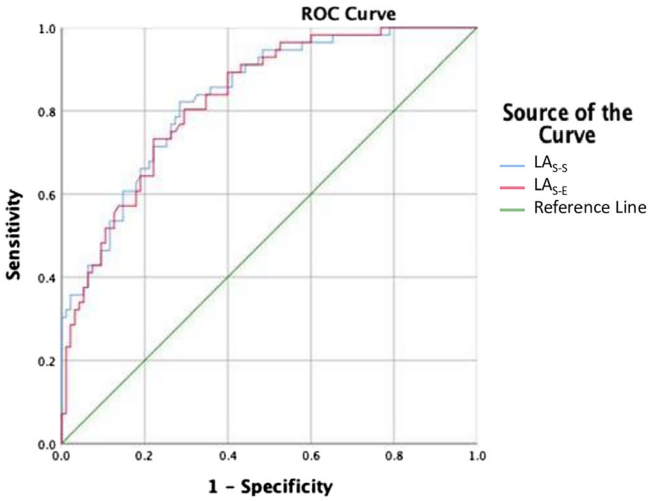

FIGURE 2 The curve analysis of receiver-operating characteristic for LA_{S-S} and LA_{S-E} for the prediction of hypertensive retinopathy. It shows the curve analysis of receiver-operating characteristic to predict hypertensive retinopathy. Optimal cut-off value of LA_{S-S} in predicting retinopathy is 32.21 with 71.4% sensitivity and 69.1% specificity (AUC: 0.776 95 CI% [0.695–857]; $p < 0.001$). Optimal cut-off value of LA_{S-E} in predicting retinopathy is 16.92 with 73.2% sensitivity and 70.6% specificity (AUC: 0.780 95 CI% [0.700–860]; $p < 0.001$)

4 | DISCUSSION

In the current study, we performed a comprehensive evaluation of LA functions in patients with HT and a control group of normal subjects.

Using 2D-STE, we have shown that hypertensive patients with or without retinopathy, had impaired LA reservoir (LA_{S-S}) and conduit strain (LA_{S-E}) compared with the age-and gender-matched controls; the magnitude of this impairment was further increased in patients with coexisting hypertensive retinopathy. The second important finding was that impaired LA_{S-S}, LA_{S-E}, and duration of HT were independent predictors of hypertensive retinopathy.

HT acts as a silent killer for many years until TOD becomes clinically evident. As a result, most patients with HT have TOD at the time of diagnosis.[2] The manifestations of TOD consist of micro and macro circulatory changes such as retinopathy, coronary artery disease, stroke, proteinuria, and arterial stiffness.[1] Previous studies have revealed alterations in cardiac structure caused by HT parallel structural changes in the great arteries, kidney, brain, and eye.[19–21] However, research findings to date on the relationship between hypertensive retinopathy and cardiac involvement are inconsistent.

The first study to associate retinal changes and cardiac impairment was conducted in the late 1980s by Dimmit et al. No association was found between these retinal changes and left ventricular hypertrophy (LVH).[22] In a study by Cuspidi et al., it was investigated the relationship between initial retinal microvascular changes and cardiac or extracardiac TOD (LVH, microalbuminuria, and carotid wall alterations) in patients who had never been treated for HT. They found no variation in the mass of LV, LVMI, LV wall thickness, or LV diameter between patients with and without retinopathy.[20] In line with these results, there was no difference in conventional echocardiographic parameters (LVMI, RWT, LVEF, septal, or posterior wall thickness) or Doppler parameters (S′, E', A', E/A, and E/E') between hypertensive patients with and without retinopathy in our study.

On the other hand, Dahlof et al. showed that several retinal features associated with HT correlate with LVH, in particular septal wall thickness.[23] Furthermore, in the study of Shigematsu et al. hypertensive retinopathy was highly correlated with LVH, particularly concentric LVH.[21]

In hypertensive disease, the prevalence of LVH is influenced by numerous demographic and clinical variables, including age, race, gender, the severity of HT and duration of HT, effective BP control, and possibly the type of antihypertensive therapy.[24] As shown in previous studies; although there is a close relationship between advanced hypertensive retinopathy (grades 3, 4) and cardiac involvement such as LVH and macrovascular indicators of TOD; the lack of association between low-grade retinopathy (grades 1, 2) and major cardiac involvement indicates that early retinal abnormalities are not associated with major structural cardiac damage. The fact that the majority of the hypertensive patients in our study had stages 1 and 2 hypertensive retinopathy and the BP was under control also explains the absence of major cardiac involvement such as LVH.

In HT, impaired LV diastolic compliance and increased LV filling pressure lead to higher LA afterload. Meanwhile, histological changes (e.g., increased fibrosis) in LA are also key factors causing LA dysfunction.[25] The LA myocardial architecture is complex and consists of two layers, which are longitudinal in the subendocardium and circumferential in the subepicardium.[26] Negative remodeling in the subendocardial layer of the LV secondary to HT may cause the same fibrotic changes in the subendocardial layer of the LA.[27,28] It is worth noting that HT impairs LV diastolic function before systolic function.[29] Similarly, HT causes impairment of LA diastolic functions first, but not contractile function. Consistent with this, in the present study, we found that LA reservoir strain (LA_{S-S}) and conduit strain (LA_{S-E}) was reduced, but LA booster strain (LA_{S-A}) was preserved or even slightly increased. Moreover, LATEF and LAPEF, which represent the reservoir and conduit functions of the left atrium, respectively, were also decreased. However, the LAAEF representing the booster pump function has not changed significantly. Similarly, Tsai et al. found that untreated hypertensive individuals had considerably decreased LA reservoir and conduit properties and yet no alteration in contractile performance.[30] In addition, Miyoshi et al. reported lower reservoir and conduit functions of LA in asymptomatic hypertensive subjects compared to the control group, but no difference in LA booster pump function.[31] No significant difference in booster pump function also supports the hypothesis of a lower effect of HT on LA booster pump function.

Furthermore, our study offers a new perspective in this field. The LA reservoir (LA_{S-S}) and conduit (LA_{S-E}) strain displayed a differential change between isolated hypertensive patients and patients with hypertensive retinopathy. We found that significantly lower LA_{S-S} and LA_{S-E} were observed in patients with hypertensive retinopathy in comparison with hypertensive patients without retinopathy. Taking these findings into consideration, further impairment in the reservoir and conduit strain of LA in hypertensive retinopathy patients may be attributable to greater subendocardial fibrosis or other mechanisms, resulting in further impairment of LA function. To the best of our knowledge, this is the first study to show that the reservoir and conduit strain of LA is further decreased in the coexistence of hypertensive retinopathy.

Previous studies have predominantly focused on LVH as the TOD in the heart in HT. However, LVH is not a sensitive marker to detect cardiac impairment, and recent research in the field of HT-associated TOD has focused on LA remodeling. HT causes LA structural changes earlier than LVH. Even before LA enlargement and onset of LVH, LA phasic function is impaired.[32] Similarly, in this study, there was a gradually decreasing trend in the reservoir (LA_{S-S}) and conduit (LA_{S-E}) strain from control subjects to the patients with isolated HT and patients with hypertensive retinopathy. More impressively, the LA_{S-S} and LA_{S-E} were independently related to retinopathy in HT. Therefore, in this study, we highlight the sensitive, sustained, and integrative role of the 2DSTE-based strain to detect LA functional remodeling in HT and its association with hypertensive retinopathy.

There is also evidence that the duration of HT was a significant risk factor for retinopathy.[33] Consistent with this, our study revealed that HT duration was significantly associated with hypertensive retinopathy. In a study by Eren et al. duration of HT, was found as a significant risk factor for retinopathy. In that study, the higher retinopathy frequency was explained by the longer average HT duration of 6 years.[34] Similarly, in our study patients with hypertensive retinopathy appeared to suffer from HT for a longer time (median duration 3 vs. 5 years) than patients without retinopathy. Moreover,

Kanar et al. found that patients with a higher grade of retinopathy exhibited a longer duration of HT. They also showed that a longer duration of HT was linked to increased LA volumes.[35]

The prevalence of hypertensive retinopathy in nondiabetic patients comes from hypertensive cohort studies demonstrating that this microvascular dysfunction is more common in hypertensive patients with uncontrolled BP than in normotensive individuals.[23] On the contrary, in our study, BP was only slightly increased with the exacerbation of hypertensive retinopathy. The reason for the relatively low BP in patients with hypertensive retinopathy in our study may be the use of antihypertensive drugs.

The current study has some limitations. The study's primary limitation was the study's tiny sample size. Also, there was no patient with grade 4 retinopathy, as it was encountered only in the emergency department. Lack of data on home and office BP measurements may have influenced the results. In addition, antihypertensive treatment may have affected BP level, LA function, and retinal microvascular changes. Finally, LA strain parameters assessed with 2D-STE were not compared with those obtained using 3D- echocardiography. However, earlier research has established that assessing LA function with 2D or 3D echocardiography is equally accurate.[36]

5 | CONCLUSION

Impaired LA reservoir and conduit functions obtained from 2D-STE-based strain may have clinical significance in predicting hypertensive retinopathy. Our findings support the hypothesis that LA strain analysis may be used to predict hypertensive patients at higher risk of developing hypertensive retinopathy, and to determine which patients should be followed more closely for hypertensive retinopathy.

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DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

ETHICS STATEMENT

Ethical approval for this study was given from Istanbul Medeniyet University Ethical Committee and the number is 2021/0548, oral and written informed consent was taken from all participants of the study.

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