Original Article

Interaction effect of type 2 diabetes mellitus and hypertension on left atrial function: a three-dimensional echocardiography study

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Background: Type 2 diabetes mellitus (T2DM) and hypertension (HT) often coexist and contribute to left atrial (LA) functional abnormalities. The aim of the present study was to explore whether there is a potential interaction effect between T2DM and HT on LA function.

Methods: A total of 135 patients (45 with T2DM only, 45 with HT only, and 45 with both T2DM and HT) were enrolled and compared to 45 age- and sex-matched controls. LA volume fraction, including LA ejection fraction (LAEF), LA expansion index (LAEI), LA passive emptying fraction (LAPEF), and LA active emptying fraction (LAAEF), and strain parameters, including LA reservoir longitudinal strain (LASr), LA conduit longitudinal strain (LAScd), and LA contraction longitudinal strain (LASct), were obtained using three-dimensional echocardiography (3DE).

Results: Patients with T2DM had significantly more impaired LA reservoir and conduit functions compared to those without T2DM (P<0.05), and patients with HT had a significantly more impaired LA reservoir function, conduit function, and booster pump function compared to those without HT (P<0.05). Two-way analysis of variance showed that there were significant additive interaction effects between T2DM and HT with respect to LASr ($P_{T2DM+HT}$ =0.002) and LAScd ($P_{T2DM+HT}$ =0.001). Generalized linear model demonstrated that T2DM + HT had a greater relative contribution than either T2DM or HT alone to the LA strain indexes, even after adjustment for other confounders (LASr, $\beta_{T2DM+HT}$ =−3.931, 95% CI: −6.237 to −1.624, P=0.001; LAScd, $\beta_{T2DM+HT}$=−3.781, 95% CI: −5.653 to −1.908, P<0.001).

Conclusions: Both T2DM and HT had an adverse effect on LA function. The coexistence of both conditions further impaired LA performance in an additive interaction fashion.

Keywords: Left atrial function (LA function); interaction; three-dimensional echocardiography (3DE); type 2 diabetes mellitus (T2DM); hypertension (HT)

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Introduction

The importance of left atrial (LA) enlargement for cardiac function has long been recognized (1). In recent years, LA dysfunction has also received considerable attention due to its increasingly important value in the diagnosis and prognosis of cardiovascular disease (2-4).

As two main risk factors of cardiovascular disease, type 2 diabetes mellitus (T2DM) and hypertension (HT) frequently coexist (5), and both are associated with LA morphological and functional abnormalities. Several studies have shown that patients with T2DM or HT had decreased LA emptying fractions (6,7). However, previous studies have mainly focused on their independent effect on LA function, with limited understanding of the interaction effect between the two conditions.

Traditionally, LA function has been assessed by two-dimensional echocardiography (2DE). However, it is often limited by several shortcomings: geometric assumptions, loss of some speckles that move out of the image plane (i.e., through-plane motion), and not easy to analyze (8,9). These limitations have been gradually overcome with the rapid development of three-dimensional echocardiography (3DE) in recent years. Four-dimensional automatic left atrial quantitation (4D Auto LAQ), a new tool for analyzing LA structure and function based on 3DE, has distinct advantages in the 'one-stop-shop' comprehensive evaluation of LA volume, emptying fraction, and strain, which can provide more valuable information for clinical diagnosis (10).

Thus, the aim of the present study was to explore whether there is a potential interaction effect between T2DM and HT on LA function using the 4D Auto LAQ.

Methods

Study population

This was a single-center cross-sectional study conducted at Fuwai Central China Cardiovascular Hospital. A total of 135 patients affected by T2DM and/or HT were prospectively enrolled between December 2020 and March 2022. Of these, 45 had T2DM only (T2DM group), 45 had HT only (HT group), and 45 had both T2DM and HT (T2DM + HT group). For comparison, 45 healthy volunteers without T2DM and HT (control group) of similar age and sex were included. They were defined as healthy volunteers with age >18 years, no history of cardiovascular or pulmonary disease, and with normal electrocardiogram and echocardiographic results. The diagnosis of T2DM was based on the current American Diabetes Association guideline recommendations (11). HT was defined as the use of antihypertensive therapy or more than two measurements of systolic blood pressure (SBP) of ≥140 mmHg and/or diastolic blood pressure (DBP) of ≥90 mmHg at rest (12). The exclusion criteria included left ventricular ejection fraction (LVEF) of <50%, heart failure, coronary artery disease, myocardial infarction, arrhythmia, any cardiomyopathy (primary or secondary), valvular heart disease, congenital heart disease, type 1 diabetes mellitus, secondary HT, estimated glomerular filtration rate (eGFR) of <30 mL/min/1.73 m^2, history of chronic obstructive pulmonary disease, abnormal thyroid function or other significant systemic chronic disease, malignant tumor, and poor imaging quality. *Figure 1* represents a flow chart detailing the identification of the study population. This study was conducted following the Declaration of Helsinki (as revised in 2013) and was approved by the ethics committee of Fuwai Central China Cardiovascular Hospital (No. 202136). All subjects signed the informed consent form.

Conventional echocardiographic measurements

Transthoracic echocardiography was performed on all subjects at rest using a Vivid E95 system (GE Vingmed Ultrasound AS, Horten, Norway) equipped with a 4Vc-D probe (1.4–5.2 MHz). All study participants were scanned in the left lateral position with continuous electrocardiogram monitoring. Left ventricular end-diastolic diameter (LVEDD), inter-ventricular septum thickness, and posterior wall thickness were measured at end-diastole in the parasternal long-axis view using M-mode. Left ventricular (LV) relative wall thickness and LV mass (LVM) were calculated using the formula recommended by the American Society of Echocardiography (9). LV end-diastolic and end-systolic volumes were measured using the biplane Simpson method and LVEF was then calculated. Mitral inflow early (E) and late (A) peak velocities were measured in the apical four-chamber view using pulsed-wave Doppler with the sample placed at the tip of the mitral valve leaflets. Early peak diastolic myocardial velocity (e') was measured in the same view with the pulsed tissue Doppler sample placed in the septal and lateral mitral annuli. Average mitral annular e'

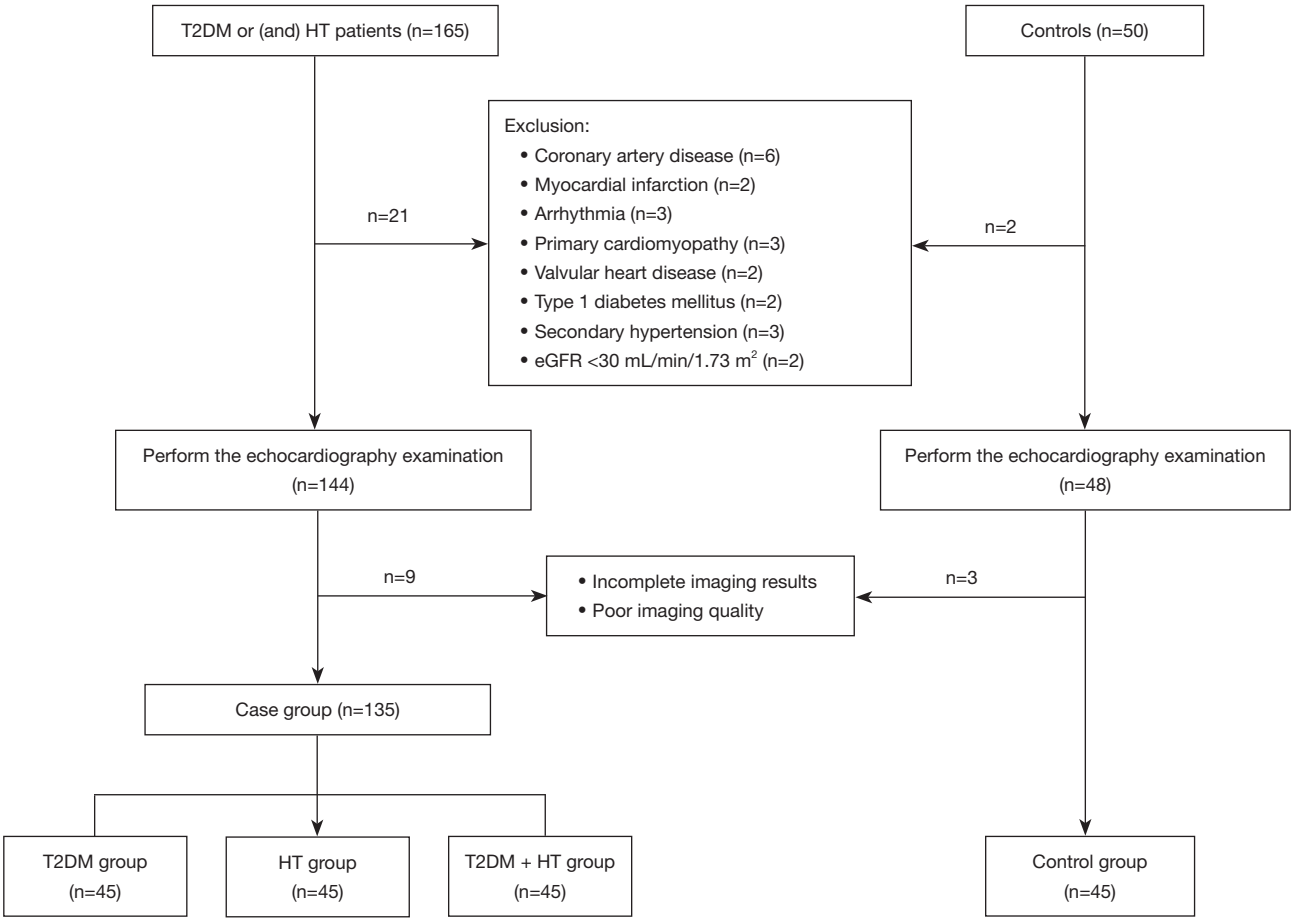

Figure 1 Flow chart of the study population. T2DM, type 2 diabetes mellitus; HT, hypertension; eGFR, estimated glomerular filtration rate.

velocity and average E/e' ratio was then calculated.

The 4D Auto LAQ analysis

The echocardiographic examination used a 3D model after 2DE with a clear image of the LA cavity in the apical four-chamber view (*Figure 2A*). Multi-beat (three or four beats) acquisition settings were used, and the frame rate was adjusted to a heart rate of ≥40% to obtain the 3D full dynamic volume images. The best-quality image was selected for online analysis, and all measurements were performed using the dedicated software package (4D Auto LAQ). When using the tool, the first step was to adjust the 2D gain and zoom, if needed. Then, in the Set Landmark stage, the frame control was adjusted until the mitral valve was closed, and the landmark was dragged to the center of the mitral annulus level. In addition, the image position and angle were adjusted so that the vertical line intersected the mitral valve center and the LA apex. In the next Review stage, endocardial LA boundaries were identified in each frame by an automated processing method and manually adjusted if necessary. The pulmonary vein mouth and LA appendage were excluded. In the Results stage, various parameters of LA volume and function were acquired automatically as follows (*Figure 2B*):

- Volumes and EF: LA minimal volume (LAVmin), LA maximal volume (LAVmax), LA presystolic volume (LAVpreA), LA ejection fraction (LAEF);
- Strain: especially LA longitudinal strain, defined as the average change of deformation for the whole LA in the longitudinal direction along the LA endocardial border (13). LA reservoir longitudinal strain (LASr), longitudinal strain during reservoir phase, measured as the difference of the strain value

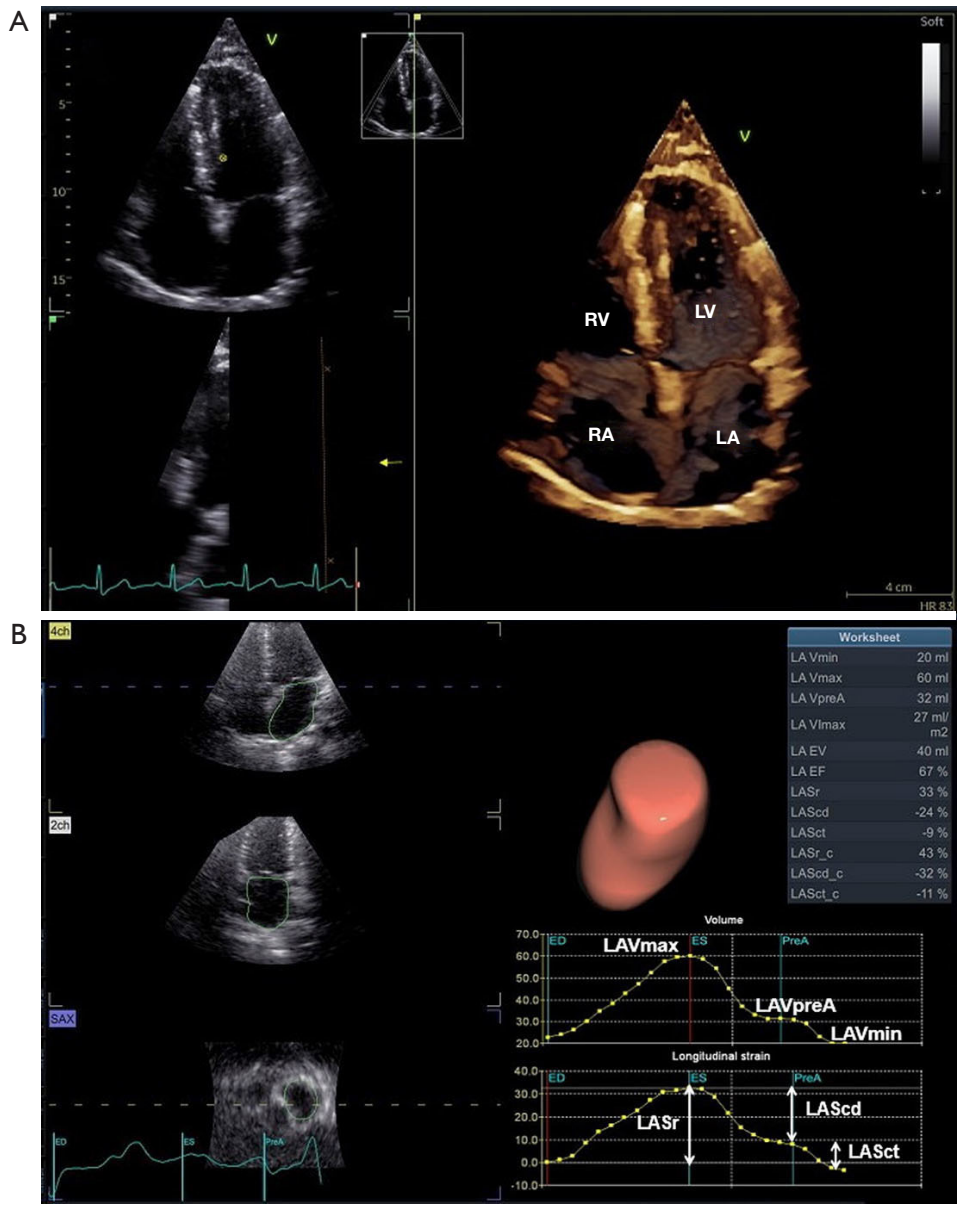

Figure 2 Measurement of LA geometry and function. (A) Volume rendering of a full-volume data set of the heart obtained using multibeat acquisition to reach a frame rate >40% of the heart rate. The yellow arrow indicates the observation spot. (B) Quantitative analysis of the LA geometry and function using 4D Auto LAQ. The upper right corner displays the LA parameters obtained from 4D Auto LAQ, and the lower right of the images are the LA volume curve and strain curve. V, ventricle; RV, right ventricle; LV, left ventricle; RA, right atrium; LA, left atrium; 4ch, four-chamber; 2ch, two-chamber; SAX, short-axis; ED, end-diastolic; ES, end-systolic; PreA, onset of atrial contraction; LAVmin, left atrial minimal volume; LAVmax, left atrial maximal volume; LAVpreA, left atrial presystolic volume; LAVImax, left atrial maximal volume index; LAEV, left atrial ejection volume; LAEF, left atrial emptying fraction; LASr, left atrial reservoir longitudinal strain; LAScd, left atrial conduit longitudinal strain; LASct, left atrial contraction longitudinal strain; LASr_c, left atrial reservoir circumferential strain; LAScd_c, left atrial conduit circumferential strain; LASct_c, left atrial contraction circumferential strain; 4D Auto LAQ, four-dimensional automatic left atrial quantitation.

at mitral valve opening minus ventricular end-diastole (positive value); LA conduit longitudinal strain (LAScd), longitudinal strain during conduit phase, measured as the difference of the strain value at the onset of atrial contraction minus mitral valve opening (negative value); LA contraction longitudinal strain (LASct), longitudinal strain during contraction phase, measured as difference of the strain value at ventricular end-diastole minus onset of atrial contraction only in patients in sinus rhythm (negative value). All LA strain parameters were expressed as absolute values.

The following indexes of LA function were then calculated:

$$LA\ expansion\ index(LAEI) = \frac{LAVmax - LAVmin}{LAVmin} \times 100\% \quad [1]$$

reflecting atrial reservoir function.

$$LA\ passive\ emptying\ fraction(LAPEF) = \frac{LAVmax - LAVpreA}{LAVmax} \times 100\% \quad [2]$$

reflecting atrial conduit function.

$$LA\ active\ emptying\ fraction(LAAEF) = \frac{LAVpreA - LAVmin}{LAVpreA} \times 100\% \quad [3]$$

reflecting atrial booster pump function.

Variability analysis

Intra- and inter-observer variabilities for the LA volume and strain were analyzed in 30 random cases, including 20 patients and 10 controls. To determine the intra-observer variability, one observer (Wang S) assessed the same subjects in two separate measurements one week apart. For the inter-observer variability assessments, a second investigator (Zhang R) who was blinded to the first observer's results and clinical data, reanalyzed the measurements.

Statistical analysis

Categorical variables were represented as numbers (percentage) and compared using the χ^2 or Fisher's exact test. The Shapiro-Wilk test was used to confirm the normality of continuous variables' distribution. Normally distributed continuous data were expressed as mean ± standard deviation (SD) and compared using the Student's *t*-test or one-way analysis of variance as appropriate, followed by the LSD-*t post-hoc* test. Non-normally distributed variables were expressed as the medians (interquartile ranges) and compared using the Mann-Whitney *U* test or Kruskal-Wallis *H* test as appropriate, followed by Bonferroni's *post-hoc* test. General linear modeling was employed for evaluation of the main effect of T2DM and HT, as well as the interaction effect between the two conditions on LA myocardial deformation in a 2×2 factorial design. Univariate correlations were determined using Pearson's coefficient for continuous variables or the Point-biserial coefficient for dichotomous variables. Generalized linear models were performed to explore the associations of T2DM and HT with LA strain indexes, which were presented as β values and 95% Wald confidence intervals. Adjustment for possible confounders, such as age, sex, body mass index (BMI) and average E/e' ratio, was also carried out. A two-tailed P value of <0.05 was considered to indicate statistical significance. All statistical analyses were performed using SPSS version 25 for Windows (IBM, Armonk, NY, USA).

The sample size for this study was estimated based on the preliminary results. LAScd was observed as the main indicator using factorial analysis of variance. The test level was set at α=0.05, the power was set at 1–β=0.85, a 20% dropout rate was assumed, and recruitment of at least 45 participants for each group was needed. The sample size and power analysis were calculated using PASS version 15 for Windows (NCSS, Kaysville, UT, USA).

Results

Baseline characteristics

The demographic, clinical, biochemical, and conventional echocardiographic characteristics of the study population are summarized in *Table 1*.

As expected, both SBP and DBP were significantly higher in the HT and T2DM + HT groups than in the T2DM and control groups. Glycated hemoglobin (HbA1c) levels were significantly higher in the T2DM and T2DM + HT groups than in the HT and control groups (all P<0.001). In addition, the four groups were also different in terms of plasma triglycerides (TG), high-density lipoprotein (HDL), and medication use (all P<0.05). The age, sex, body surface area (BSA), BMI, heart rate, current smoker status, diabetes duration, HT duration, total cholesterol (TC), low-density lipoprotein (LDL), and eGFR were not significantly different among the observed groups (all P>0.05).

Among the conventional echocardiographic parameters, the relative wall thickness and left ventricular mass index (LVMI) were significantly increased in the HT and T2DM + HT groups compared to the control group (all P<0.05). In addition, the E, E/A, and average mitral annular e' velocity

Table 1 Baseline characteristics of the study cohort

Variables	Controls (n=45)	T2DM (n=45)	HT (n=45)	T2DM + HT (n=45)	$F/Z/\chi^2$	P
Clinical						
Age (years)	46.07±11.03	46.11±8.94	46.58±8.30	49.09±9.26	1.044	0.374
Male	29 [64]	30 [66]	31 [68]	32 [71]	0.509	0.917
BSA (m^2)	1.81±0.19	1.81±0.17	1.85±0.20	1.88±0.19	1.418	0.239
BMI (kg/m^2)	24.89±2.84	25.04±2.92	26.37±3.57	26.03±3.12	2.472	0.063
SBP (mmHg)	129.58±9.57	123.82±9.54*	148.33±16.46*†	141.80±12.40*†‡	37.065	<0.001
DBP (mmHg)	84.93±6.01	80.60±7.98*	98.33±12.04*†	89.64±8.74*†‡	32.351	<0.001
Heart rate (beats/min)	70.58±7.38	71.44±7.70	74.04±9.93	74.87±9.45	2.502	0.061
Current smoker	13 [28]	15 [33]	13 [28]	14 [31]	0.288	0.962
Diabetes duration (years)	–	3.00 (1.00, 6.00)	–	5.00 (2.00, 10.50)	−1.834	0.067
Hypertension duration (years)	–	–	2.00 (1.00, 7.00)	2.00 (1.00, 4.50)	−0.224	0.822
Biochemical						
HbA1c (%)	5.30±0.34	8.71±2.09*	5.21±0.34†	8.21±1.76*‡	80.980	<0.001
TC (mmol/L)	4.19±0.75	4.43±1.02	4.49±0.96	4.82±1.60	2.388	0.071
TG (mmol/L)	1.46±0.80	1.93±1.81	1.65±0.84	2.99±2.96*†‡	6.286	<0.001
HDL (mmol/L)	1.14±0.34	1.05±0.23	1.27±0.42†	1.10±0.33‡	3.290	0.022
LDL (mmol/L)	2.56±0.74	2.90±0.94	3.02±0.95	2.72±1.19	1.965	0.121
eGFR ($mL/min/1.732\ m^2$)	105.34±10.34	106.57±13.54	101.41±13.11	100.92±19.35	1.708	0.167
Medications						
Oral	–	29 [64]	–	34 [75]	1.323	0.250
Insulin	–	10 [22]	–	10 [22]	0.000	>0.999
ACEI/ARB	–	–	14 [31]	7 [15]	3.043	0.081
Beta-blocker	–	–	10 [22]	3 [6] ‡	4.406	0.036
Calcium channel blocker	–	–	9 [20]	12 [26]	0.559	0.455
Diuretics	–	–	8 [17]	1 [2] ‡	6.049	0.014
Echocardiography						
LVEDD (mm)	44.87±3.39	44.20±2.87	45.16±2.37	45.13±3.03	1.037	0.378
Relative wall thickness	0.43±0.05	0.44±0.04	0.46±0.05*	0.47±0.05*†	6.022	0.001
LVMI (g/m^2)	79.63±9.31	80.55±16.04	88.13±17.48*†	88.86±15.11*†	4.878	0.003
LVEF (%)	65.13±3.56	64.38±3.28	64.76±3.05	64.16±3.20	0.774	0.510
E (cm/s)	0.81±0.13	0.73±0.12*	0.78±0.17	0.71±0.19*‡	3.596	0.015
A (cm/s)	0.62±0.14	0.66±0.12	0.77±0.13*†	0.77±0.15*†	14.393	<0.001
E/A ratio	1.35±0.31	1.13±0.26*	1.03±0.23*	0.94±0.26*†	19.286	<0.001
Average mitral annular e' velocity (cm/s)	0.12±0.03	0.10±0.02*	0.09±0.02*	0.08±0.02*†‡	22.452	<0.001
Average E/e' ratio	7.06±1.81	7.46±1.87	8.75±2.43*†	9.25±2.93*†	9.098	<0.001

Data are presented as mean ± standard deviation, numbers [percentage], or median (interquartile range). *, P<0.05 *vs.* controls; †, P<0.05 *vs.* T2DM group; ‡, P<0.05 *vs.* HT group. T2DM, type 2 diabetes mellitus; HT, hypertension; BSA, body surface area; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; HbA1c, glycated hemoglobin; TC, total cholesterol; TG, plasma triglycerides; HDL, high-density lipoprotein; LDL, low-density lipoprotein; eGFR, estimated glomerular filtration rate; ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blockers; LVEDD, left ventricular end-diastolic diameter; LVMI, left ventricular mass index; LVEF, left ventricular ejection fraction; E, peak value of early diastolic velocity of mitral inflow; A, peak value of late diastolic velocity of mitral inflow; e', peak value of early diastolic tissue Doppler velocity of septal and lateral walls of mitral annulus.

Table 2 4D Auto LAQ derived LA parameters of the study cohort

Variables	Controls (n=45)	T2DM (n=45)	HT (n=45)	T2DM + HT (n=45)	F_{T2DM}	P_{T2DM}	F_{HT}	P_{HT}	$F_{T2DM+HT}$	$P_{T2DM+HT}$
LAVImax (mL/m^2)	25.58±3.14	26.26±3.00	28.36±5.42	28.49±4.47	0.427	0.514	16.528	<0.001	0.202	0.654
LAVIpreA (mL/m^2)	16.22±2.37	18.16±2.49	19.50±4.45	20.50±4.20	7.874	0.006	28.876	<0.001	0.805	0.371
LAVImin (mL/m^2)	9.95±1.58	11.10±1.83	11.98±2.96	12.65±2.90	6.506	0.012	24.994	<0.001	0.450	0.503
LAEF (%)	61.19±3.24	57.82±4.12	57.92±5.47	55.92±5.25	15.260	<0.001	14.204	<0.001	0.983	0.323
LAEI (%)	159.45±22.23	139.28±23.04	141.48±30.69	130.02±27.69	16.469	<0.001	12.198	0.001	1.247	0.266
LAPEF (%)	36.56±5.56	30.79±6.14	31.46±6.51	28.46±6.58	22.434	<0.001	16.119	<0.001	2.245	0.136
LAAEF (%)	38.58±5.14	38.88±5.16	38.60±5.13	38.26±6.01	0.001	0.979	0.140	0.709	0.164	0.686
LASr (%)	31.18±3.88	25.44±3.46	24.60±4.06	22.71±4.61	40.367	<0.001	60.237	<0.001	10.269	0.002
LAScd (%)	19.04±4.06	13.38±2.94	13.64±3.47	11.51±3.15	58.194	<0.001	50.508	<0.001	11.941	0.001
LASct (%)	12.07±2.44	12.13±3.15	10.93±2.63	11.16±3.17	0.114	0.736	6.100	0.014	0.033	0.856

Data are presented as mean ± standard deviation. 4D Auto LAQ, four-dimensional automatic left atrial quantitation; LA, left atrial; T2DM, type 2 diabetes mellitus; HT, hypertension; LAVImax, left atrial maximal volume index; LAVIpreA, left atrial presystolic volume index; LAVImin, left atrial minimal volume index; LAEF, left atrial emptying fraction; LAEI, left atrial expansion index; LAPEF, left atrial passive emptying fraction; LAAEF, left atrial active emptying fraction; LASr, left atrial reservoir longitudinal strain; LAScd, left atrial conduit longitudinal strain; LASct, left atrial contraction longitudinal strain

were significantly decreased in the T2DM, HT, and T2DM + HT groups, while the A and average E/e' ratio were significantly increased compared to those in the control group (all P<0.05). Furthermore, there was no significant difference in the LVEDD and LVEF among the groups (all P>0.05).

Comparison of 4D Auto LAQ findings among groups

Main effect of T2DM on LA

Table 2 shows that patients with T2DM had significantly more impaired LA reservoir [LAEF: F_{T2DM} =15.260, P_{T2DM} <0.001; LA expansion index (LAEI): F_{T2DM} =16.469, P_{T2DM} <0.001; LASr: F_{T2DM} =40.367, P_{T2DM} <0.001] and conduit [LA passive emptying fraction (LAPEF): F_{T2DM} =22.434, P_{T2DM} <0.001; LAScd: F_{T2DM} =58.194, P_{T2DM} <0.001] functions compared to those without T2DM. Therefore, the T2DM group had significantly more impaired LA reservoir and conduit functions compared to those in the control group. The T2DM + HT group had significantly more impaired LA reservoir and conduit functions compared to those in the HT group. However, there was no significant difference in booster pump function [LA active emptying fraction (LAAEF): P_{T2DM} =0.979; LASct: P_{T2DM} =0.736] between patients with and without T2DM. In addition, patients with T2DM had greater LAVIpreA (F_{T2DM} =7.874, P_{T2DM} =0.006) and LAVImin (F_{T2DM} =6.506, P_{T2DM} =0.012) than those without T2DM, while there was no significant difference in LAVImax (P_{T2DM} =0.514).

Main effect of HT on LA

Table 2 shows that patients with HT had a significantly more impaired LA reservoir function (LAEF: F_{HT} =14.204, P_{HT} <0.001; LAEI: F_{HT} =12.198, P_{HT} =0.001; LASr: F_{HT} =60.237, P_{HT} <0.001), conduit function (LAPEF: F_{HT} =16.119, P_{HT} <0.001, LAScd: F_{HT} =50.508, P_{HT} <0.001), and booster pump function (LASct: F_{HT} =6.100, P_{HT} =0.014) compared to those without HT. Thus, the HT group had significantly more impaired LA reservoir, conduit, and booster pump functions compared to those in the control group. The T2DM + HT group had significantly more impaired LA reservoir, conduit, and booster pump function compared to those in the T2DM group. In addition, patients with HT had greater LAVImax (F_{HT} =16.528, P_{HT} <0.001), LAVIpreA (F_{HT} =28.876, P_{HT} <0.001), and LAVImin (F_{HT} =24.994, P_{HT} <0.001) than those without HT.

Interaction effect between T2DM and HT on LA

Table 2 shows that the interaction effects between T2DM and HT on LASr ($F_{T2DM+HT}$ =10.269, $P_{T2DM+HT}$ =0.002) and LAScd ($F_{T2DM+HT}$ =11.941, $P_{T2DM+HT}$ =0.001) were significant. Evaluation of *Figure 3* demonstrated the patients with both T2DM and HT had a greater decline in LASr and LAScd than either one alone. There were no significant

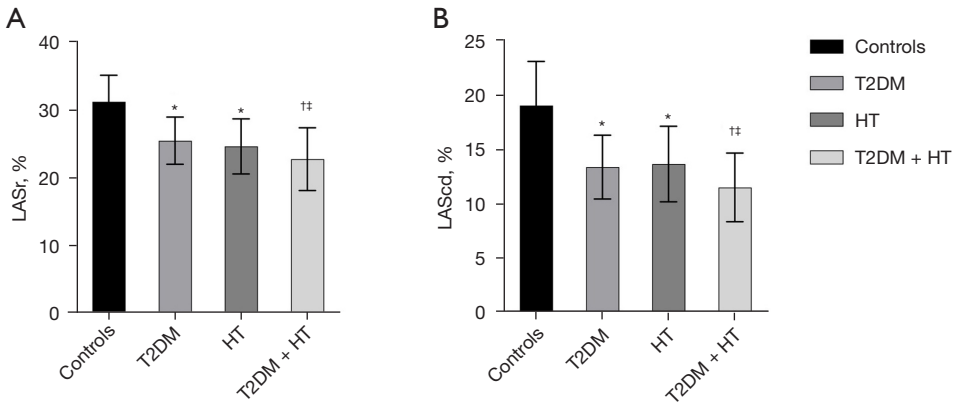

Figure 3 Comparisons of LASr (A) and LAScd (B) among the four study groups. *, P<0.05 *vs.* controls; †, P<0.05 *vs.* T2DM group; ‡, P<0.05 *vs.* HT group. LASr, left atrial reservoir longitudinal strain; T2DM, type 2 diabetes mellitus; HT, hypertension; LAScd, left atrial conduit longitudinal strain.

interactions between the two conditions on LAEF, LAEI, LAPEF, LAVIpreA and LAVImin (all $P_{T2DM+HT}$ >0.05).

Association of T2DM, HT and LA strain

Univariate correlations of LA strain indexes in the overall study population are listed in *Table 3*. T2DM and HT had a significant negative correlation with LASr (r=–0.364 and r=–0.465, respectively; P<0.001) and LAScd (r=–0.410 and r=–0.421, respectively; P<0.001). In addition, these LA strain indexes also showed significant relationships with SBP, DBP, HbA1c, relative wall thickness, LVMI, and indexes of diastolic function.

Table 4 shows the generalized linear model analysis for LASr and LAScd. This was shown by the standardized β coefficients demonstrating that the interaction term T2DM + HT had a greater relative contribution to the generalized linear model than either T2DM or HT alone, despite similar *P* values. Similar results were also obtained when adjusted for age, sex, BMI, and average E/e' ratio (LASr, $\beta_{T2DM+HT}$ =–3.931, 95% CI: –6.237 to –1.624, P=0.001; LAScd, $\beta_{T2DM+HT}$ =–3.781, 95% CI: –5.653 to –1.908, P<0.001).

Reproducibility test

Intra- and inter-observer variability values for LA parameters obtained from the 4D Auto LAQ are summarized in *Table 5*. There were excellent intra- and inter-observer agreements in the measurement of LA volume indexes [intraclass correlation coefficient (ICC) =0.991–0.996 and 0.988–0.996, respectively], LAEF (ICC =0.994 and 0.976, respectively), and LA strain indexes (ICC =0.941–0.991 and 0.845–0.964, respectively).

Discussion

The present study investigated the interaction effect betweenT2DM and HT on LA function using the 4D Auto LAQ. The main findings are as follows.

(I) LA reservoir and conduit functions were impaired in patients with T2DM, while there was no significant difference in booster pump function. LA reservoir, conduit, and booster pump functions were all impaired in patients with HT;

(II) There were significant additive interaction effects between T2DM and HT on LASr and LAScd, while no such significant additive effects were observed for other parameters;

(III) The interaction effects between T2DM and HT can result in greater impairment in LASr and LAScd than either one alone, which remained the same after adjusting for potential confounders.

LA phasic function

During LV systole and isovolumic relaxation, the LA serves as a reservoir receiving blood from the pulmonary veins and storing energy in the form of pressure. The reservoir function is mainly modulated by LV contraction through the descent of the LV base during systole and by LA properties (i.e., relaxation and stiffness) (14). During early

Table 3 Univariate correlations of LA strain indexes

Variables	LASr		LAScd	
	r	P	*r*	P
Diabetes mellitus	–0.364	<0.001	–0.410	<0.001
Hypertension	–0.465	<0.001	–0.421	<0.001
Age (years)	–0.115	0.124	–0.264	<0.001
Male	–0.007	0.923	–0.134	0.072
Body mass index (kg/m^2)	–0.121	0.105	0.016	0.835
SBP (mmHg)	–0.273	<0.001	–0.261	<0.001
DBP (mmHg)	–0.207	0.005	–0.171	0.022
Heart rate (beats/min)	–0.069	0.357	0.038	0.612
HbA1c (%)	–0.295	<0.001	–0.314	<0.001
TC (mmol/L)	–0.148	0.048	–0.131	0.080
TG (mmol/L)	–0.118	0.115	–0.097	0.194
HDL (mmol/L)	0.049	0.511	–0.019	0.801
LDL (mmol/L)	–0.109	0.146	–0.095	0.205
eGFR (mL/min/1.732 m^2)	0.121	0.105	0.173	0.020
LVEDD (mm)	0.001	0.985	0.061	0.420
Relative wall thickness	–0.247	0.001	–0.265	<0.001
LVMI (g/m^2)	–0.195	0.009	–0.237	0.001
E (cm/s)	0.209	0.005	0.215	0.004
A (cm/s)	–0.228	0.002	–0.313	<0.001
E/A ratio	0.355	<0.001	0.437	<0.001
Average E/e' ratio	–0.301	<0.001	–0.377	<0.001

LA, left atrial; LASr, left atrial reservoir longitudinal strain; LAScd, left atrial conduit longitudinal strain.; SBP, systolic blood pressure; DBP, diastolic blood pressure; HbA1c, glycated hemoglobin; TC, total cholesterol; TG, plasma triglycerides; HDL, high-density lipoprotein; LDL, low-density lipoprotein; eGFR, estimated glomerular filtration rate; LVEDD, left ventricular end-diastolic diameter; LVMI, left ventricular mass index; E, peak value of early diastolic velocity of mitral inflow; A, peak value of late diastolic velocity of mitral inflow; e', peak value of early diastolic tissue Doppler velocity of septal and lateral walls of mitral annulus.

LV diastole, the LA acts as a conduit and blood is effectively drawn into the LV via LV suction, which may be more appropriately viewed as a property of LV diastolic function rather than intrinsic LA function. The conduit function is especially modulated by LV diastolic properties (LV relaxation and early diastolic pressures) (15). During late LV diastole, the LA serves as a pump. It is a contractile chamber that actively empties immediately before the onset of LV systole and establishes the final LV end-diastolic volume. LA booster pump function is mostly dependent on intrinsic atrial contractility and becomes increasingly important for maintaining cardiac function in the presence of reduced LV compliance (1).

Effect of T2DM and HT on LA function

LA functional abnormalities have been described in T2DM patients via conventional two-dimensional speckle-tracking echocardiography (2D-STE) and 3DE (6,16,17). The present study extended those findings using 4D Auto LAQ. Consistent with previous studies, the results of the present study showed impaired LA reservoir and conduit functions in T2DM patients. Persistent hyperglycemia causes increased glucose metabolism in cardiomyocytes, which

Table 4 Generalized linear model analysis of LA strain indexes

Variables	Unadjusted†		Adjusted‡	
	β (95% CI)	P	*β* (95% CI)	P
LASr				
T2DM	−1.889 (−3.533 to −0.245)	0.024	−1.715 (−3.354 to −0.076)	0.040
HT	−2.733 (−4.377 to −1.089)	0.001	−2.265 (−3.971 to −0.559)	0.009
T2DM + HT	−3.844 (−6.170 to −1.519)	0.001	−3.931 (−6.237 to −1.624)	0.001
LAScd				
T2DM	−2.133 (−3.535 to −0.732)	0.003	−1.835 (−3.165 to −0.505)	0.007
HT	−1.867 (−3.268 to −0.465)	0.009	−1.445 (−2.830 to −0.060)	0.041
T2DM + HT	−3.533 (−5.515 to −1.552)	<0.001	−3.781 (−5.653 to −1.908)	<0.001

†, including T2DM and HT; ‡, adjusted for age, sex, BMI and average E/e' ratio. LA, left atrial; CI, confidence interval; LASr, left atrial reservoir longitudinal strain; T2DM, type 2 diabetes mellitus; HT, hypertension; LAScd, left atrial conduit longitudinal strain; BMI, body mass index; E, peak value of early diastolic velocity of mitral inflow; e', peak value of early diastolic tissue Doppler velocity of septal and lateral walls of mitral annulus.

Table 5 Intra- and inter-observer variability of LA parameters

Variables	Intra-observer		Inter-observer	
	ICC	95% CI	ICC	95% CI
LAVImax	0.991	0.981–0.996	0.992	0.983–0.996
LAVpreA	0.996	0.991–0.998	0.988	0.974–0.994
LAVmin	0.995	0.991–0.998	0.996	0.991–0.998
LAEF	0.994	0.987–0.997	0.976	0.950–0.988
LASr	0.991	0.980–0.995	0.964	0.926–0.983
LAScd	0.983	0.966–0.992	0.943	0.885–0.973
LASct	0.941	0.881–0.971	0.845	0.699–0.923

LA, left atrial; ICC, intraclass correlation coefficient; CI, confidence interval; LAVImax, left atrial maximal volume index; LAVpreA, left atrial presystolic volume; LAVmin, left atrial minimal volume; LAEF, left atrial emptying fraction; LASr, left atrial reservoir longitudinal strain; LAScd, left atrial conduit longitudinal strain; LASct, left atrial contraction longitudinal strain.

increases oxidative stress via the development of reactive oxygen species from the mitochondria, thereby provoking collagen synthesis by cardiac fibroblasts and eventually resulting in myocardial fibrosis (18). Fibrosis increases LA stiffness and leads to a decrease in LA compliance, which may be a crucial substrate for LA remodeling. In addition, LA conduit function is governed by LV diastolic properties and diabetes-related LV dysfunction has been well recognized in previous studies, which maybe another cause of impaired LA conduit function (19,20).

A negative impact of HT on LA function has been previously demonstrated by 3DE and 2D-STE evaluation of phasic LA volumes and strains (21,22). Similarly, in the present study, the LA reservoir and conduit functions were significantly impaired in patients with HT. In terms of hemodynamics in HT patients, the hypertrophic cardiomyocyte growth is the primary response by which the heart reduces the stress on the LV wall, leading to increased stiffness of the ventricular wall and LV dysfunction, thereby contributing to LA remodeling (23). In addition, the changes in humoral factors are also important factors. The increased secretion of catecholamine, angiotensin II, aldosterone, and other factors in HT patients can stimulate cardiomyocyte hypertrophy and interstitial fibrosis, leading

to the occurrence of inflammatory reactions and collagen fiber deposition, which may have a direct impact on LA mechanics (24).

Interaction effect between T2DM and HT on LA function

In general, physicians are more concerned with the association between risk factors and outcomes. As a result, interactions are often neglected. The term "interaction" refers to the fact that at different levels of a risk factor, another risk factor has different effects on the disease and vice versa (25). The present study found that there were significant interactions between T2DM and HT in terms of LASr and LAScd. The interaction effects between them can result in greater impairment in LASr and LAScd than either T2DM or HT alone. Previous studies have shown that there is an adverse positive feedback cycle between T2DM and HT due to many individual or common pathophysiological factors, such as myocardial hypertrophy, fatty degeneration, interstitial fibrosis, and myocardial energy loss (26,27). Although the interactions between various factors have not been fully elucidated, the final common pathway appears to be an increased interstitial fibrosis followed by LA myocardial dysfunction. It is well known that both T2DM and HT often share comorbidities and conditions, like obesity and LV diastolic dysfunction, which are associated with impaired LA function (28,29). The association remained valid even after the present study results were adjusted for age, sex, BMI, and average E/e' ratio, indicating that the interaction was independent of these possible confounders. In addition, the present results also showed that there were no significant interactions between the two conditions in terms of LA volume fractions, which may support previous evidence showing that volumetric parameters are indirect indices of LA function and are less sensitive for detecting changes in LA function (30,31).

Clinical implications

The assessment of LA function in physiological and pathological states is increasingly recognized as a biomarker of prognosis in various cardiovascular diseases (32). T2DM and HT commonly exist as comorbidities, and both significantly increase the risk of cardiovascular disease and death. Therefore, it is of great value to assess their combined effects on LA function. As a LA analysis technique based on 3DE, the 4D Auto LAQ is different from traditional 2DE, although both assess LA function by measuring myocardial deformation. Several studies have confirmed that 3DE measurements have higher accuracy and repeatability than 2DE because of the identification of the non-foreshortened imaging planes and the possibility of restoring the real anatomy (33,34). In addition, the 4D Auto LAQ is quick and easy to perform and may be considered a promising tool for evaluating LA function in the future.

Study limitations

First, this was a cross-sectional study that lacked clinical follow-up, further longitudinal studies are required to investigate the interaction effect of T2DM and HT on LA function and prognostic significance of this effect. Second, some of the T2DM and HT patients were receiving treatment, and the influence of long-term medication use on LA function measurements cannot be entirely excluded. Drug factors will be taken into account or untreated patients will be included in future studies. Finally, this was a single-center study with a relatively small sample size, and further multi-center studies with a larger population should be performed to validate these findings.

Conclusions

In conclusion, both T2DM and HT were associated with impaired LA functions. More importantly, there were significant additive interactions between them with respect to LASr and LAScd, which can result in greater impairment than either one alone. Preventive approaches to control risk of HT in patients with T2DM should be emphasized and vice versa.

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Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. This study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was reviewed and approved by the Ethics Committee of Fuwai Central China Cardiovascular Hospital (No. 202136). The participants provided their written informed consent to participate in this study.

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