Original Article

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Detection of Subclinical Left Ventricular Dysfunction in Hypertensive Men with Low Serum Levels of Testosterone using 2-D Speckle Tracking Echocardiography

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Abstract:

Objective: This study investigated whether hypertension and low testosterone exert synergistic detrimental effects on cardiac dysfunction, as assessed by 2-D speckle tracking echocardiography.

Material and Methods: Fifty-five adult men underwent clinical evaluation, blood sampling, and blood pressure measurement, and were classified into four groups: control, low testosterone (Low T), hypertension (HTN), and combined hypertension with low testosterone (HTN + Low T). Cardiac structure and function were assessed using 2-D echocardiography.

Results: Concentric remodeling and reduced LV global longitudinal strain (GLS) were observed in the Low T, HTN, and HTN + Low T groups with subclinical LV dysfunction most frequent in HTN + Low T. Low testosterone was associated with a markedly increased risk of subclinical LV dysfunction (OR=15.84, 95% CI: 1.31–192) in both normotensive and hypertensive men.

Conclusion: Hypertension and low testosterone showed interactive effects on cardiac dysfunction. Low testosterone may contribute to subclinical LV dysfunction.

Keywords: cardiovascular diseases, global longitudinal strain, hypertension, low testosterone, Speckle tracking echocardiography, subclinical left ventricular dysfunction

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Introduction

Cardiovascular diseases (CVDs) are a primary cause of death among the global population, and hypertension (HTN) is a leading risk factor for CVDs. Patients with HTN have been predicted to face a six-fold greater risk of myocardial infarction compared with normotensive subjects. This finding demonstrates an association between hypertension and heart failure[1]. HTN causes changes in cardiac structure and function. The progression from arterial hypertension to CHF includes an increase in afterload on the left ventricle (LV), leading to increased wall tension and more ATP consumption than required, which induce mechanical changes and result in adaptation of LV radius and wall thickness, according to the LaPlace relation. Subsequently, stress-induced LV remodelling and concentric LV hypertrophy are linked[1]. Changes in LV geometry lead to LV diastolic dysfunction and the consequent progression of heart failure with preserved ejection fraction (HFpEF).

Previous studies have reported a gender difference in the incidence of CVDs during youth, with the risk being higher in men than in women, suggesting that male sex hormones may have potentially precarious effects on heart function. However, the effects of testosterone on CVDs are controversial. Ruige et al. reported that endogenous testosterone was not associated with the risk for CVDs in middle-aged men[2], while an inverse association was found between testosterone and cardiac contraction in healthy men[3]. Since testosterone plays a role in promoting the antiatherogenic lipid profile, low testosterone leads to the accumulation of lipids in the endocardial layer of the artery[4], progressing to atherosclerosis[5] as a consequence and thereby increasing the risk of CVDs. The main interest of this study was in hypertensive patients and whether an interaction exists between hypertension and low testosterone levels on cardiac function.

Early detection of LV dysfunction in hypertensive patients is crucial in preventing the progression of heart failure. Recently, the detection of early subendocardial dysfunction using two-dimensional speckle tracking echocardiography (2-D STE) has been found to provide more accurate information, which is essential for identifying early LV dysfunction[6]. Global longitudinal strain (GLS) is an independent predictor of ejection fraction in heart failure with reduced ejection fraction (HFrEF)[7]. It is also able to identify LV systolic dysfunction in hypertensive patients with preserved ejection fraction[8].

We hypothesized that hypertensive men with low testosterone have greater impairment in myocardial strain than those with normal testosterone, and that hypertension and low testosterone interact to exacerbate cardiac dysfunction as assessed by two-dimensional speckle-tracking echocardiography.

Material and Methods

Study population and study design

All participants in this study were volunteers recruited from local hospitals. Some participants were aware of their hypertension, though none of them had been informed about their testosterone levels. Participants with a systolic blood pressure (SBP) of 140 mmHg, a diastolic blood pressure (DBP) of 90 mmHg or higher, or a prior diagnosis of hypertension were categorised as hypertensive. Participants were classified as hypogonadal if they met at least one of the following criteria: a total testosterone level ≤3 ng⁄mL in accordance with American Urological Association (AUA) guidelines, a documented prior diagnosis of testosterone deficiency, or self-reported symptoms consistent with hypogonadism.

This cross-sectional study enrolled a total of 276 men, aged 35-65 years, from Phitsanulok Province,

Thailand, in 2022. Following the approval of the study proposal by the Institutional Review Board of Naresuan University (COA No. 068/2021), all subjects voluntarily participated and provided their written informed consent. The participants underwent a demographic and clinical assessment, which included providing their medical history, blood tests, and measurement of height, weight, and blood pressure. Participants were excluded from the study if they had any of the following conditions: valvular heart disease, congenital heart disease, cardiomyopathies, coronary artery disease, congestive heart failure, diabetes mellitus, arrhythmia, kidney disease, obesity, use of anabolic steroids, or other steroids.

Laboratory blood tests

Blood samples were collected in the morning (08:00–08:30 a.m.) after an overnight fast at two local hospitals. Samples were obtained using a 4-mL lithium heparin vacutainer tube and a 2-mL sodium fluoride vacutainer tube. All specimens were kept chilled at 4 °C and transported to the Medical Device Research Laboratory, Naresuan University, for metabolic and hormonal analyses within 2 hours of collection (133 and 143 samples per collection, respectively). Serum testosterone and pro-B-type natriuretic peptide (proBNP) levels were measured using electrochemiluminescence assays (Roche Elecsys Testosterone II and Roche Elecsys proBNP II). Plasma glucose, total cholesterol, triglycerides, low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol, and creatinine levels were quantified using enzymatic assays, followed by calculation of the estimated glomerular filtration rate (eGFR).

According to the criteria of this study, the participants were categorised into four groups, including 1) normotension and normal testosterone group (control), 2) normotension and low testosterone group (Low T), 3) hypertension and normal testosterone (HTN) group, and 4) combined hypertension and low testosterone (HTN + Low T) group.

Sample size

The sample size was calculated using the Bonferroni t-test with a significance level (α) of 0.05 and a statistical power of 0.90, based on the study by D'Andrea et al. (2018) (*Left atrial myocardial dysfunction after chronic abuse of anabolic androgenic steroids: a speckle tracking echocardiography analysis*, *International Journal of Cardiovascular Imaging*). Assuming a mean difference (Δ) of 5.5 and a standard deviation (σ) of 3.5, the required sample size was 13 participants per group across four groups. To account for a 20% potential dropout rate, the final sample size was increased to 16 participants per group.

Due to the limited number of participants in the low testosterone groups and the withdrawal of four volunteers, a total of 60 participants underwent comprehensive two-dimensional transthoracic echocardiography using a Philips Affiniti 50 echocardiographic system equipped with an S5-1 transducer. Image analysis was performed using Philips Q-Station ultrasound workspace software.

Conventional two-dimensional and speckle-tracking echocardiography

Conventional 2-D echocardiographic measurements were performed according to guidelines from the American Society of Echocardiography[9]. Measurements of LV end-diastolic wall thickness (LVIVSd, LVPWd), end-diastolic chamber diameter (LVIDd), LV mass, aortic root, and left atrial (LA) dimensions were performed by a linear method in the parasternal long-axis view. LV mass index was obtained by normalising LV mass with body surface area. Relative wall thickness (RWT) was calculated as 2xLVPWd/LVIDd. LV ejection fraction (EF) and LA volume were measured by the biplane Simpson's method using apical four-chamber

(A4C) and two-chamber (A2C) views. LV diastolic function was measured by the mitral valve (MV) inflow method (E/A ratio) and tissue Doppler velocity of the septal and lateral mitral annulus (septal and lateral e' and a' velocities). Right ventricular (RV) basal cavity (RVD1) and mid cavity (RVD2) dimensions were measured in the A4C RV-focused view, and RV function (TAPSE) was assessed in the A4C view.

LV global longitudinal strain (GLS) was performed by 2-D STE in the A4C, A2C, and apical three-chamber (A3C) views. In the analysis processes, the Q-Station software program was used. To obtain LV GLS, after identification of the MV annulus and the LV apex, endocardial surface tracing was automatically generated by the program. The region of interest (ROI) was then adjusted to exclude the pericardium. The quality of myocardial tracking was evaluated until adequate tracking was achieved. Peak systolic strain values of each segment were automatically recorded by the program. Longitudinal strain values were obtained for a total of 18 segments, and the mean value was determined as the GLS[9]. According to the Journal of the American Society of Echocardiography[9], normal LV strain values from meta-analysis showed GLS mean±S.D., analysed using a Phillips echocardiographic device, and Q-Station software was 18.9±2.5 %. Therefore, -16.4% was used as a cut-off point for LV longitudinal strain dysfunction in this study.

Statistical analysis

The Statistical Package for Social Science (SPSS) version 17.0 was used in this study. Continuous variables were presented as means and standard deviation (mean±S.D.), while categorical variables were presented as frequency and percentages. Intergroup comparisons were performed using two-way Analysis of variance (ANOVA) followed by Tukey's multiple comparisons for continuous data and Fisher's Exact test for categorical data. The odds ratio and 95% confidence interval (CI) for GLS were calculated by multivariable logistic regression.

Results

A total of 276 participants were initially recruited for this study. Following laboratory blood test analysis, 64 individuals who met the predefined criteria for male sex hormone levels and blood pressure status were enrolled. After the withdrawal of four volunteers, 60 participants underwent echocardiographic assessment; five were subsequently excluded due to inadequate image quality. Consequently, 55 male participants were categorized into four groups, including 16 volunteers with normotension and normal testosterone (control), 12 volunteers with normotension and low testosterone (Low T), 16 patients with systemic hypertension and normal testosterone (HTN), and 11 patients with combined systemic hypertension and low testosterone (HTN + Low T).

The demographic and clinical characteristics of the participants are shown in Table 1. There was no significant difference in age, DBP, heart rate, or BMI amongst the four groups. In the group of HTN + Low T, the participants had significantly higher glucose than those in the Low T group. No significant differences in serum pro-BNP, lipid profiles (cholesterol, triglyceride, LDL, HDL), or renal function (creatinine and eGFR) were detected amongst the four groups, except SBP and testosterone levels. The hypertensive groups showed higher SBP compared with the normotensive groups at the same testosterone levels (139±15.6 vs. 123±9.35 mmHg in the normal testosterone groups, 145±17.7 vs. 130±9.01 mmHg in the low testosterone groups). The low testosterone groups showed reduced total testosterone in serum compared with the normal testosterone levels under the same blood pressure conditions (2.88±0.51 vs. 5.55±1.27 ng/ml in the normotensive groups, 2.55±0.75 vs. 5.83±1.76 ng/ml in the hypertensive groups).

Table 1 Demographic and clinical characteristics of participants

Parameters	Normotension		Hypertension	
	Norm T (n=16)	Low T (n=12)	Norm T (n=16)	Low T (n=11)
	Control	Low T	HTN	HTN + Low T
Age, year	49.6±8.3	53.5±11.9	56.0±6.4	52.2±7.6
SBP, mmHg	123±9	130±9	139±16†	145±18†
DBP, mmHg	78±9	77±7	77±14	83±13
HR, bpm	61.6±7.4	66.3±8.4	65.9±9.4	72±13.5
BMI, kg/m^2	23.0±2.4	25.6±3.8	24.7±2.8	25.8±5.6
Laboratory findings				
Testosterone level, ng/ml	5.5±1.3	2.9±0.5*	5.8±1.8	2.5±0.7*
Pro BNP, pg/ml	18.3±9.4	40.8±43.0	33.3±29.1	25.0±25.9
Glucose, mg/dl	90.7±18.8	100±42.4	97.8±16.8	145±103.5#
Cholesterol, mg/dl	192±40.5	193±31.2	194±44.7	202±49.4
Triglyceride, mg/dl	133±93.5	218±151	168±81.7	215±135
LDL, mg/dl	116±33.3	99.5±37.1	116±37.4	98±47.4
HDL, mg/dl	50.6±13.4	43.0±8.9	43.2±8.9	41.9±12.3
Creatinine, mg/dl	0.93±0.12	0.89±0.14	0.97±0.16	0.92±0.25
eGFR, ml/min/1.73m^2	96.4±16.4	101.3±19.7	87.3±19.0	102.7±30.3

Data are means±S.D. from N=11–16 subjects. *Significantly different (p–value<0.05) from the normal level of testosterone (Norm T) group within the same arterial tension condition, †Significantly different (p–value<0.05) from the corresponding group within the same level of testosterone, #Significantly different (p–value<0.05) from the control group. Data comparison was performed by using Two–way ANOVA with Tukey's multiple comparisons.

Conventional echocardiography

Conventional echocardiographic data are presented in Table 2. No significant differences were found in LA size, LA/Ao, LV, or RV sizes amongst the four groups. LVEF showed no significant difference and was subsequently classified within the normal range. TAPSE of the four groups was not different and within the normal values, indicating RV systolic function was not changed in the HTN + Low T group. According to LV diastolic function, there was higher A velocity in the Low T group compared to the Norm T group in the normotensive condition. The Tissue Doppler's imaging method showed decreased e' velocities with less than the cut–off value in both septal and lateral mitral annular velocities[10] (septal e' <7 cm/s, lateral e' <10 cm/s) in the HTN group compared to the control group. Consequently, the average E/e' ratio was significantly higher in the HTN group. Interestingly, a normal average E/e' ratio value (<8) was observed in the control group, whereas the average E/e' ratio from the three other groups fell within the grey zone (average E/e': 8–15), indicating indeterminate LV filling pressure.

Two–dimensional speckle tracking echocardiography (2–D STE)

Representative images of GLS, presented as a bull's eye derived from 2–D STE of all groups, are shown in Figure 2. Two–dimensional speckle tracking echocardiographic data are shown in Table 3. Two–way ANOVA followed by Tukey's multiple comparisons showed a significant leading effect of hypertension, such that the HTN participants had a significantly lower absolute LV GLS compared with the control participants (18.3±1.71 vs. 21.0±1.31 %). The main

effect of low testosterone was also significant, such that reduced absolute LV GLS was detected in the Low T groups compared to the Norm T groups (17.5±0.79 vs. 21.0±1.31 % in the normotensive groups, and 17.0±1.31 vs. 18.3±1.71 % in the hypertensive groups). Remarkably, two-way ANOVA demonstrated a significant interaction effect, suggesting that hypertension influences LV GLS differently according to testosterone status.

The control group (normotension and normal testosterone) was the only group to demonstrate LV GLS values exceeding the mean, while the remaining groups showed less negative GLS values. Clinical LV systolic dysfunction in this study is defined as GLS negative lower than −16.4 %. Consequently, the participants with subclinical LV systolic function were 12.5% in the HTN, 16.7 % in the Low T, and 27.3% in the HTN + Low T group (Table 3). A bar graph of LV GLS comparing the normotensive groups and the hypertensive groups is shown in Figure 3, which indicates that reduced myocardial strain is induced by low serum testosterone (Low T), hypertension (HTN), and the combined effects of hypertension and low testosterone (HTN + Low T).

Table 2 Conventional echocardiographic data of participants

Parameters	Normotension		Hypertension	
	Norm T (n=16)	Low T (n=12)	Norm T (n=16)	Low T (n=11)
	Control	Low T	HTN	HTN + Low T
IVSd, mm	1.01±0.22	1.05±0.14	1.13±0.21	1.13±0.17
LVPWd, mm	0.97±0.17	1.05±0.24	1.00±0.19	1.08±0.20
LVIDd, mm	4.73±0.42	4.70±0.56	4.85±0.54	4.80±0.63
Relative wall thickness	0.41±0.07	0.46±0.13	0.43±0.11	0.46±0.11
LVMI, g/m^2	94.5±23	96.7±24	103±21	107±22
LA dimension, mm	3.53±0.56	3.72±0.50	3.86±0.52	3.81±0.54
LA/Ao	1.20±0.21	1.35±0.73	1.24±0.25	1.25±0.22
LAVI, ml/m^2	22.1±4.5	20.6±4.1	23.2±4.7	21.6±3.6
RVD1, cm	3.42±0.76	3.33±0.50	3.35±0.59	3.28±0.55
RVD2, cm	3.14±0.51	3.03±0.38	3.25±0.51	3.11±0.47
Systolic function:				
LVEF, %	69.6±4.81	67.0±8.35	67.9±3.31	69.1±6.54
RV TAPSE, cm	2.31±0.25	2.25±0.28	2.25±0.25	2.11±0.22
Diastolic function:				
E, cm/s	66.8±12.8	79.1±17.8	69.1±14.2	69.3±15.8
A, cm/s	56.2±11.3	70.9±16.0*	65.1±9.8	66.0±16.9
DT, ms	207±51.4	198±60.9	205±35.4	191±30.4
E/A	1.26±0.32	1.19±0.42	1.08±0.30	1.11±0.33
septal e', cm/s	8.54±2.1	7.82±2.27	6.78±1.6†	7.35±1.15
lateral e', cm/s	12.2±3.4	10.4±2.77	8.84±2.62†	10.8±3.21
average E/e'	7.03±2.00	9.08±2.60	9.07±1.87†	8.23±2.06

Data are means±S.D. *Significantly different (p-value<0.05) from the normal level of testosterone (Norm T) group within the same arterial tension condition, †Significantly different (p-value<0.05) from the corresponding group within the same level of testosterone, #Significantly different (p-value<0.05) from the control group. Data comparison was performed by using Two-way ANOVA with Tukey's multiple comparisons. IVSd indicates interventricular septum during diastole; LVPWd=left ventricular posterior wall during diastole, LVIDd=left ventricular inner diameter during diastole, LVMI=left ventricular mass index, LAVI=left atrial volume index, EF=Ejection fraction, RV TAPSE=right ventricular tricuspid annular plane systolic excursion, E/A=ratio of mitral peak velocity of early filling (E) to mitral peak velocity of late filling (A) during diastole.

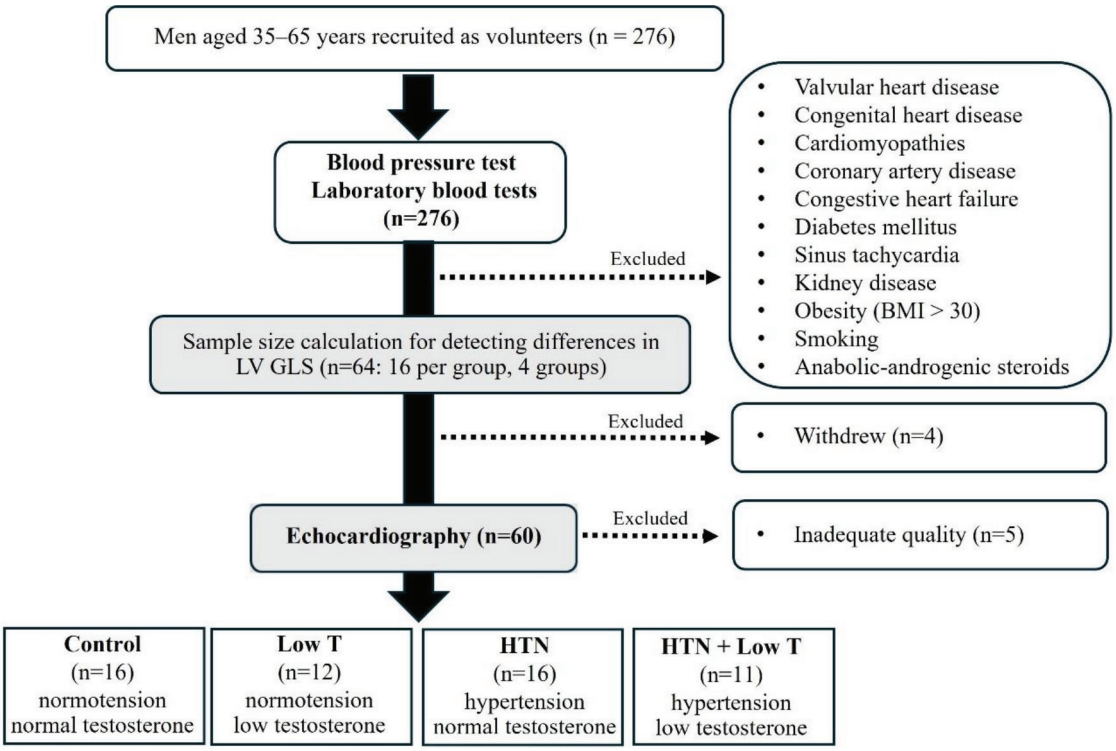

Figure 1 Flowchart of the study population. A total of 276 participants were initially recruited. Of the 60 participants who underwent transthoracic echocardiography, five were excluded due to inadequate image quality. Consequently, 55 volunteers were categorized into four study groups.

Table 3 Two-dimensional speckle tracking echocardiographic data of participants

Parameters	Normotension		Hypertension	
	Norm T (n=16)	Low T (n=12)	Norm T (n=16)	Low T (n= 11)
	Control	Low T	HTN	HTN+Low T
Myocardial strain:				
LV GLS, %	21.0±1.3	17.5±0.8*	18.3±1.7†	17.0±1.3#
Normal systolic function	16 (100%)	10 (83.3%)	14 (87.5%)	8 (72.7%)
Subclinical dysfunction	0 (0%)	2 (16.7%)	2 (12.5%)	3 (27.3%)

Quantitative data are means±S.D. Qualitative data are presented as frequency and percentage (%). *Significantly different (p-value<0.05) from the normal level of testosterone (Norm T) group within the same arterial tension condition, †Significantly different (p-value<0.05) from the corresponding group within the same level of testosterone, #Significantly different (p-value<0.05) from the control group. The comparisons of quantitative and qualitative data were performed by using Two-way ANOVA with Tukey's multiple comparisons and Fisher's Exact test, respectively. LV GLS indicates left ventricular global longitudinal strain.

Multivariable logistic regression analysis was performed to identify prognostic factors associated with abnormal LV GLS in patients with hypertension or low testosterone levels. The model was adjusted for age, body weight, body mass index (BMI), and proBNP levels, and the results are presented in Table 4. The multivariable odds ratio of hypertension for reduced LV GLS was 3.50 (95%CI; 0.35–35.39; p–value=0.288). The odds ratio of low testosterone for reduced LV GLS was 15.84 (95% CI; 1.31–192, p–value=0.030).

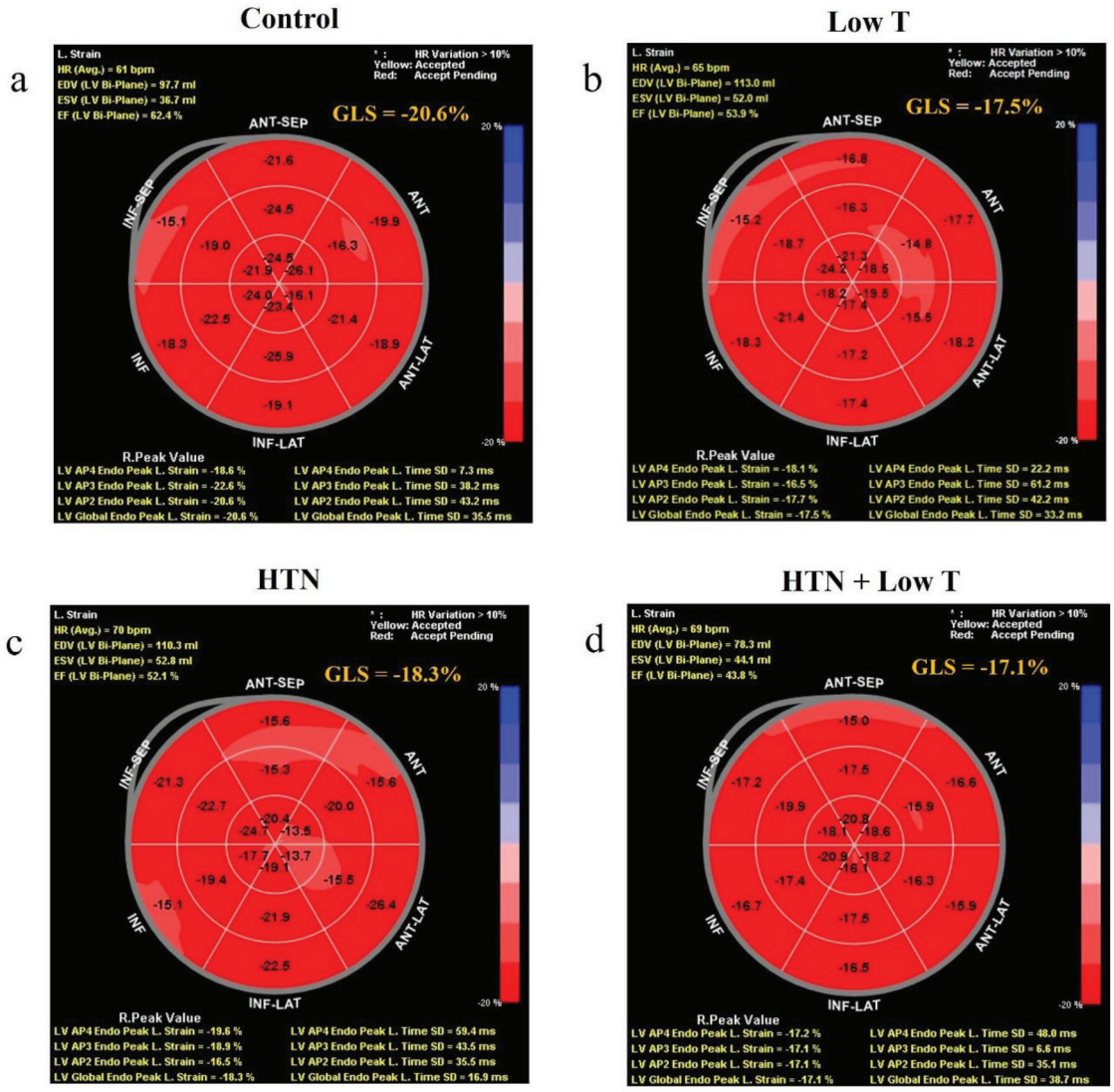

Figure 2 Bull's eye images of left ventricular global longitudinal strain (LV GLS) of participants with a) normotension and normal testosterone (Control), b) normotension and low testosterone (Low T), c) hypertension and normal testosterone (HTN), d) hypertension and low testosterone (HTN+ Low T)

Table 4 Univariable and Multivariable logistic regression analysis on risk factors associated with abnormal LV GLS (GLS > −16.4%)

Variables	Univariable			Multivariable		
	OR	95% CI	p-value	OR	95% CI	p-value
Low testosterone	8.61	0.93, 79.62	0.058	15.84	1.31, 192	0.030*
Hypertension	2.26	0.38, 13.51	0.371	3.50	0.35, 35.39	0.288
Age	1.03	0.93, 1.14	0.551	1.03	0.92, 1.14	0.646
Weight	0.98	0.91, 1.05	0.552	1.03	0.86, 1.24	0.729
BMI	0.87	0.67, 1.13	0.299	0.68	0.34, 1.34	0.265
Pro BNP	0.98	0.95, 1.02	0.494	0.96	0.91, 1.02	0.236

*Significantly different (p-value<0.05), OR=Odds ratios, CI=indicates confidence interval, GLS=global longitudinal strain, BMI=body mass index, BNP=B-type natriuretic peptide

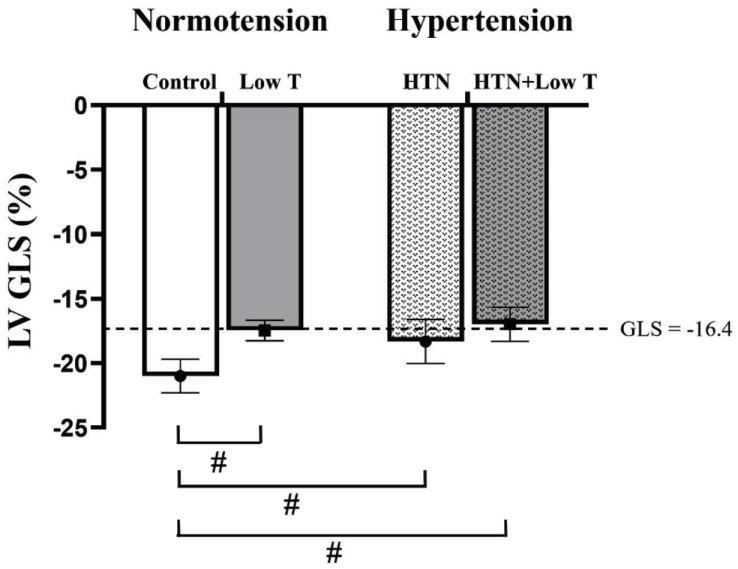

Figure 3 Comparison between the normotension group and the hypertensive group in LV global longitudinal strain (LV GLS). #Significantly different (p-value<0.05) from the control group. Data comparison was performed by using Two-way ANOVA with Tukey's multiple comparisons.

Discussion

This study demonstrated the impacts of systolic hypertension, low testosterone, and the combination of hypertension and low testosterone on cardiac structure and functions. The myocardial strain (LV GLS) was evaluated in the following groups: 1) normotension and normal testosterone (control), 2) normotension and low testosterone (Low T), 3) hypertension and normal testosterone (HTN), and 4) combined hypertension and low testosterone (HTN + Low T). The important findings of this study are as follows.

First, all three conditions of testing, including HTN, Low T, or HTN + Low T, induced LV concentric remodelling adaptations in LV geometry. Second, reduced LV GLS was found in the three conditions. Third, the effect of hypertension on LV GLS differs between individuals with low and normal testosterone levels. Finally, the results indicate a potential association between low testosterone levels and abnormal left ventricular global longitudinal strain; however, its role as an independent predictor remains uncertain. Given the relatively small sample size and the resulting wide confidence intervals for the odds ratios, the precision of the present findings is limited. Therefore, the predictive value of low testosterone for impaired myocardial strain should be interpreted with caution in broader clinical contexts.

Although no significant differences in LV mass index and RWT were observed between the groups, their LV geometry was classified into two different types: normal geometry and concentric remodelling. Normal geometry was found in the control group, whereas concentric remodelling was detected in the three other groups. The results of hypertensive participants in this study are in concordance with the findings of Lovic D et al., who showed that chronically increased systolic arterial pressure leads to left ventricle adaptation in various hypertrophic patterns, including concentric or eccentric remodelling, concentric or eccentric hypertrophy, or a combination of the two[11].

In the present study, conventional echocardiography demonstrated preserved ejection fraction in men with decreased testosterone levels. This finding contrasts with previous reports in middle-aged men with coronary artery disease, in whom significantly lower testosterone levels than in healthy controls were associated with reduced left ventricular ejection fraction, as well as with a documented association between total testosterone levels and left ventricular ejection fraction[12].

A study demonstrated that cardiovascular pathology contributed by physiological levels of testosterone and was found to involve the renin-angiotensin hormonal system. The interaction of testosterone and angiotensin II induced vascular dysfunction, hypertension, and cardiac hypertrophy in male rats via strengthened angiotensin II receptor-mediated signalling[13]. Moreover, evidence from a study suggests that angiotensin II may play a modulatory role in the effects of gonadotropins on Leydig cells, thereby influencing steroidogenesis and testosterone synthesis[14]. Testosterone production by Leydig cells is regulated by catecholamines, which act through both α- and β-adrenoceptors[15]. Therefore, it is possible that the impaired cardiac contractions in testosterone deficiency are partly due to disrupted regulation of the testicular renin-angiotensin system and altered testosterone-catecholamine levels.

To determine the abnormality of cardiac structure and function in patients with hypertension, low testosterone, or a combination of these two factors, pro-B-type natriuretic peptide (proBNP) was tested. Considerable evidence suggested that peptide was useful to detect left ventricular dysfunction, hypertrophy, and cardiac stress in hypertension[16]. However, this study found no differences in proBNP levels among the four groups, with all values remaining within the normal range (<125 pg/mL). These findings are consistent with conventional echocardiographic results, which demonstrated preserved global systolic function (ejection fraction) and no increase in left ventricular wall thickness. In contrast, previous studies have reported that borderline-low testosterone levels are associated with reduced left ventricular wall thickness in men[17]. LV relaxation impairment (abnormal septal and lateral e' velocity) was detected in the hypertensive group. While LV filling pressure, E/e' ratio, from the Low T, HTN, and HTN + Low T remained in the grey zone, which was indefinite.

Myocardial assessment by speckle-tracking echocardiography is more sensitive and superior to conventional echocardiography in differentiating patients with subclinical cardiac dysfunction[18,19]. In this study, LV systolic

dysfunction was detected when the global longitudinal strain was less negative than the cut-off value (GLS > -16.4%) in three conditions: Low T, HTN, and HTN + Low T.

The results of this study demonstrated that left ventricular (LV) systolic longitudinal dysfunction in the hypertensive group was consistent with previous findings, in which tissue deformation and motion abnormalities, assessed by LV global longitudinal strain (GLS), were detectable in patients with early-stage hypertension[8].

Therefore, speckle-tracking echocardiography (STE) represents a promising tool for the early detection of left ventricular dysfunction and myocardial fibrosis, offering advantages over conventional 2D echocardiographic parameters in patients with uncontrolled or resistant hypertension[20,21].

The reduced systolic function of the ventricular endocardial myocardium, as reflected by LV GLS, in participants with low testosterone is consistent with previous studies demonstrating impaired cardiac contractile function at the trabecular muscle level in testosterone-deficient rats[22].

In the low testosterone groups with both normotensive and hypertensive, subclinical LV dysfunction was detected, indicating that a normal testosterone level is essential for the protection of systolic function. This positive effect of testosterone on cardiomyocytes has also been presented in animal studies, which showed that testosterone plays an important role in regulating myocardial contractile function; a lack of testosterone leads to a decrease in the contraction of cardiomyocytes[22-24] and directly modifies heart structure and function, promoting maladaptive remodeling, diastolic dysfunction[25], and maladaptive electrical remodeling in ventricular myocytes[26] in the aging heart.

Epidemiological studies have also shown that testosterone deficiency in aging is associated with CVDs[27]. A decline in testosterone/estradiol ratio in aging males has been linked to reduced dehydroepiandrosterone sulphate, which may increase the risk and severity of CVDs[28]. The risk of CVDs increases in both aging men and women[29]. The strongest risk factors for coronary artery disease are advancing age and male gender[30]. Based on this evidence, aging was used as a confounding factor in the multivariable regression model for this study.

The multivariable logistic regression analysis of risk factors associated with abnormal left ventricular global longitudinal strain (LV GLS) revealed that low testosterone levels, in both normotensive and hypertensive individuals, were associated with approximately a 16-fold higher risk of subclinical LV dysfunction compared with participants exhibiting normal testosterone levels. These findings suggest a potential mechanistic link between reduced testosterone and early myocardial impairment, highlighting the possible role of hormonal imbalance in the pathogenesis of subclinical cardiac dysfunction.

Nevertheless, the relatively small sample size warrants caution in interpreting these results. Limited statistical power may have contributed to model instability, wide confidence intervals, and potential overfitting, thereby constraining the precision and generalizability of the regression estimates. Furthermore, as this study was cross-sectional in nature, causal inferences cannot be established.

Taken together, while low testosterone appears to be associated with impaired myocardial strain, this relationship should be interpreted within the context of these methodological limitations. Further large-scale, prospective studies are required to confirm these findings and to elucidate the underlying mechanisms linking testosterone deficiency to subclinical left ventricular dysfunction.

Cardiac function is strongly modulated by antihypertensive therapy. In this study, participants in both the HTN and HTN + Low T groups received medications from the major antihypertensive classes, including thiazide diuretics, calcium channel blockers, β-blockers, angiotensin receptor blockers, and ACE inhibitors. Thiazide diuretics reduce intravascular volume and cardiac preload, thereby

lowering heart failure risk[31], although the efficacy of hydrochlorothiazide relative to other thiazides, such as chlorthalidone, remains debated[32]. Amlodipine, β-blockers, and RAS inhibitors exert distinct but overlapping effects on afterload, heart rate, and ventricular remodeling[33-35], complicating efforts to isolate the impact of any single agent on cardiac performance.

Although both treatment groups included similar antihypertensive classes, variations in regimen composition may have influenced cardiac physiology. Greater vasodilator and RAS blockade exposure in the HTN group may favor ventricular remodeling, whereas higher β-blocker use in the HTN + Low T group may reduce myocardial oxygen demand but limit chronotropic reserve. Despite these differences, no significant variation in ejection fraction, diastolic function, or heart rate was observed, suggesting preserved cardiac function with adequate blood pressure control. Nonetheless, incomplete medication and clinical data in some participants may have introduced bias and limited interpretive accuracy.

The clinical implications of detecting subclinical left ventricular (LV) dysfunction in hypertensive men with low serum testosterone using two-dimensional speckle-tracking echocardiography (2D-STE) are considerable. This advanced imaging technique enables the early identification of myocardial dysfunction not detectable by conventional echocardiography, thus allowing for timely interventions to prevent progression to overt heart disease[6,36]. While the diagnostic utility of 2D-STE is well established, its integration into routine clinical practice should be considered within a broader cardiovascular risk management strategy. This includes comprehensive lifestyle modifications and pharmacologic interventions to control hypertension and potentially optimize testosterone levels.

According to the American Urological Association's 2024 guideline on the Evaluation and Management of Testosterone Deficiency[37], low testosterone levels are associated with an increased incidence of major adverse cardiac events and warrant a strong recommendation for evaluation and potential treatment, based on Grade B evidence. This indicates moderate certainty but a favorable balance of benefits and risks in recommending testosterone replacement therapy (TRT). Supporting evidence from prior studies suggests that TRT in hypogonadal men is generally cardiovascularly safe and does not significantly increase the risk of cardiac events[38,39].

Our findings suggest that hypertensive men with low testosterone levels may be associated with greater cardiac abnormalities compared to those with normal testosterone levels. Clinically, this underscores the potential value of including testosterone assessment as part of cardiovascular risk stratification in this population. Although our study does not establish a causal relationship or support specific treatment recommendations, it raises the possibility that identifying and managing testosterone deficiency could contribute to improved cardiac outcomes in hypertensive men.

Future interventional studies are necessary to evaluate whether testosterone replacement can mitigate myocardial dysfunction in this high-risk group. Additionally, further research should assess the cost-effectiveness and long-term impact of implementing 2D-STE as a routine diagnostic tool to guide clinical decisions in hypertensive patients with low testosterone.

Limitations

This work utilized a cross-sectional approach. Therefore, the correlation between outcome and exposure could not be fully determined.

The study has limitations, including a small sample size that may affect the applicability of the findings to a wider population. The relatively small sample size may limit the statistical power of the analysis and increase type II errors. The precision of the estimated odds ratios may be reduced with wide confidence intervals. Nonetheless, the consistent

results indicate a potential biological connection between testosterone levels, hypertensive condition, and cardiac function, highlighting the necessity for future research with larger cohorts.

An additional limitation of the present study is the absence of detailed information regarding antihypertensive medication use among participants. The lack of such data may have introduced residual confounding, as specific antihypertensive classes exert distinct hemodynamic and myocardial effects that could influence cardiac performance. Future investigations incorporating comprehensive pharmacologic data and standardized treatment documentation are warranted to more precisely characterize the differential cardiovascular impacts of individual antihypertensive regimens and to delineate the independent contributions of serum testosterone levels and hypertensive status to cardiac function.

Conclusion

Subclinical LV dysfunction can be detected by two-dimensional speckle tracking echocardiography in men with three conditions: hypertension, low testosterone, and a combination of hypertension and low testosterone. The interactive effects of hypertension and low testosterone on cardiac dysfunction were observed. Low testosterone may be linked to subclinical LV dysfunction, though its role as an independent predictor remains uncertain. Early detection of impaired LV dysfunction in men with low testosterone, especially in hypertensive patients, is crucial as it may enhance prevention strategies and the clinical management of cardiovascular diseases.

Availability of data:

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Ethical approval

The study was approved by Naresuan University Institutional Review Board (COA No.419/2021 IRB No. P10172/64). All subjects participated voluntarily and provided their written informed consent to participate in this study. The Declaration of Helsinki was adequately addressed.

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Conflict of interest

The authors have stated explicitly that there are no conflicts of interest in connection with this article.

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