ORIGINAL ARTICLE

T helper 17 cell responses induce cardiac hypertrophy and remodeling in essential hypertension

Liangjie Xu[1], Guanghua Chen[1], Yi Liang[1], Cuicui Zhou[1], Fen Zhang[1], Tingpan Fan[1], Xinxin Chen[1], Hong Zhou[2], Wei Yuan[1]

1 Department of Cardiology, Affiliated Hospital of Jiangsu University, Zhenjiang, Jiangsu Province, China
2 School of Medicine, Jiangsu University, Zhenjiang, Jiangsu Province, China

KEY WORDS

cardiac hypertrophy, cardiac remodeling, essential hypertension, inflammation, type 17 helper T cells

ABSTRACT

INTRODUCTION An increasing body of evidence has shown that type 17 helper T (T_H17) cell responses play an important role in the progression of cardiac remodeling stimulated by long-term pressure overload.

OBJECTIVES We aimed to investigate the relationship between T_H17 responses and cardiac remodeling, and the prognostic value of T_H17 responses in hypertensive patients.

PATIENTS AND METHODS A total of 187 adults with hypertension and 70 healthy controls were enrolled in the present study. T_H17 cell frequencies, matrix metallopeptidase 9, procollagen type I, and procollagen type III were studied at baseline. All adults underwent routine echocardiography to assess left ventricular diastolic function (LVDF) at baseline and after 24 months of follow-up.

RESULTS The percentage of T_H17 cells was increased in hypertensive patients, particularly in adults with left ventricular hypertrophy (LVH). Receiver operating characteristic (ROC) analysis revealed that the area under the curve (AUC) of T_H17 cells for predicting of LVH was 0.943 (95% CI, 0.914–0.971; $P < 0.001$) and the cutoff value was 2.3%. On logistic regression analysis, the percentage of T_H17 cells was an independent predictor of LVH (odds ratio, 1.47; 95% CI, 2.23–2.28; $P = 0.005$). The percentage of T_H17 cells significantly correlated with the levels of fibrotic parameters. According to the cutoff value of T_H17 cells, patients with a lower level of T_H17 cell differentiation had a better prognosis.

CONCLUSIONS The differentiation of T_H17 cells reflected the cardiac hypertrophy and remodeling response to hypertension-induced pressure overload, and it might be a potential inflammatory marker to predict the prognosis of hypertensive patients.

INTRODUCTION Pressure overload (PO) associated with essential hypertension induces various changes, including sarcomere rearrangement, cardiomyocyte enlargement, and cardiac fibrosis, leading to cardiac hypertrophy and remodeling.[1-3] Continuous PO in essential hypertension may be the driving force for recruitment of inflammatory cells and proinflammatory cytokines, which is indispensable for the development of cardiac hypertrophy and remodeling. Moreover, during chronic inflammatory response over long-term PO, a large number of cardiomyocytes are lost, leading to cardiac diastolic and systolic dysfunction with reduced ejection fraction, which is associated with adverse outcomes.

Recently, studies have suggested that type 17 helper T (T_H17) cells are involved in many inflammatory cardiovascular diseases and play a critical role in the pathogenesis of myocardial dysfunction.[4,5] In our previous studies, T_H17 responses amplified the inflammatory responses in the arterial wall and induced the endothelial dysfunction in atherosclerosis. T_H17-related cytokines greatly contribute to the accumulation of fibrillar extracellular matrix in atrial fibrillation, and can act as an independent predictor of a higher risk for atrial fibrillation recurrence after catheter ablation.[6,7] However, the role of T_H17 cells in hypertension-induced PO has not been well defined. We hypothesized that T_H17 responses

Correspondence to:
Wei Yuan, PhD,
Department of Cardiology,
Affiliated Hospital of Jiangsu University, 438 Jiefang Road,
Zhenjiang, Jiangsu Province, China,
phone: +86 0511 85026387,
email: dryuanwei123@163.com
Received: September 22, 2020.
Revision accepted: February 7, 2021.
Published online: February 11, 2021.
Pol Arch Intern Med. 2021;
131 (3): 257-265
doi:10.20452/pamw.15811

WHAT'S NEW?

In the present study, we demonstrated that type 17 helper T (T_H17) cell responses were indispensable for hypertension-induced pressure overload, which contributed to cardiac hypertrophy and remodeling, and high proportion of T_H17 cells could be used as a potential inflammatory marker to reflect myocardial fibrosis in hypertensive patients. Moreover, T_H17 responses could be used as an independent predictor of left ventricular diastolic function in the development of hypertensive structural heart disease.

contributed to myocardial fibrosis, elevated filling pressure, increased diastolic stiffness, and reduced distensibility, which could trigger left ventricular hypertrophy (LVH) and remodeling, and subsequently, left ventricular diastolic dysfunction (LVDD) appeared with further progression of heart disease.

In the present study, we aimed to investigate the relationship between T_H17 cell differentiation and cardiac remodeling in adults with hypertension. Moreover, we also identified the effect of T_H17 responses on the prognosis of hypertensive patients.

PATIENTS AND METHODS

Study population

A total of 187 consecutive patients who were diagnosed with essential hypertension and never received regular antihypertensive therapy, and 70 healthy adults (matched for age and sex) admitted to a health examination center at the same time were enrolled in the present study. All patients had preserved left ventricular ejection fraction (LVEF; >55%). The exclusion criteria were as follows: coronary artery disease, diabetes mellitus, valvular heart disease, hypertrophic cardiomyopathy, and renal disease.

Based on left ventricular mass index (LVMI),[8] hypertensive patients were assigned into 2 groups. Left ventricular hypertrophy (LVH) was defined as LVMI greater than 125 g/m^2 in men and LVMI greater than 110 g/m^2 in women. Those without LVH constituted the NLVH group. The images of echocardiography of the control, NLVH, and LVH groups are presented in Supplementary material, *Figure S1*.

Follow-up

Blood specimens were obtained from all participants at baseline. All patients underwent routine echocardiography at baseline and after 24 months of follow-up. Hypertensive patients were regularly followed-up at 3, 6, 9, 12, 18, and 24 months by both clinical visits and telephone calls for the occurrence of the primary endpoint (FIGURE 1). The primary endpoint included new-onset angina pectoris, new-onset arrhythmia, myocardial infarction, myocardial ischemia, new-onset heart failure, and all-cause mortality. As this was an observational study, the diagnostic procedures and treatment were not assessed.

Two-dimensional Doppler echocardiography

A routine echocardiographic evaluation was performed using a commercially available ultrasound device (Vivid E9; GE Healthcare, Horten, Norway) equipped with an M5S transducer. Images and parameters were obtained in 3 left ventricular short-axis views (basal, middle, and apical) and 3 left ventricular apical views (4-chamber, 2-chamber, and long-axis views). The following parameters were determined according to the recommendations of the American Society of Echocardiography and the European Association of Cardiovascular Imaging[9]: left ventricular end-diastolic diameter, left ventricular posterior wall diameter, interventricular septal thickness in end-diastolic period, LVEF, left atrial volume index, peak tricuspid regurgitation velocity (TR_{max}), tissue Doppler velocities in early diastole (e'), E wave deceleration time; change in E/A with Valsalva maneuver (val ΔE/A), duration of pulmonary vein flow and mitral inflow during atrial contraction (Ar–A duration), and stroke volume. The following LVDF parameters were also assessed: 1) LV relaxation; 2) average E/e' ratio; 3) mitral E/a ratio; left atrial pressure; 4) LA volume index; and 5) peak tricuspid regurgitation (TR) velocity. Different grades of LVDD were identified according to the 2016 American Society of Echocardiography and the European Association of Cardiovascular Imaging guidelines.[9]

Flow cytometric analysis

Cell suspensions from blood were stained with anti-CD4 mAbs (eBioscience, San Jose, California, United States) followed by permeabilization and incubation with intracellular anti-interleukin (IL)-17 mAbs (eBioscience). The stained cells were analyzed with a FACS Calibur instrument (Becton Dickinson, Shanghai, China).

Enzyme-linked immunosorbent assay (ELISA)

A blood sample (5 ml) was centrifuged at 2000 g for 15 min at 4 °C within 2 hours of collection. Subsequently, the obtained plasma was aliquoted into 500-µl straws and immediately stored at –80 °C prior to further analysis. Serum levels of IL-17, IL-6, IL-23, matrix metallopeptidase 9, procollagen type I , and procollagen type III were determined using a commercial biotin / avidin-based ELISA kits (eBiosciences).

Intra- and interobserver variability

A single observer analyzed all imaging data twice in random order separated by an interval of 1 month to test intraobserver variability. A second observer analyzed the data without knowledge of the results of the first observer to test interobserver variability. Inter- and intraobserver variability for LVDF parameters were described in Supplementary material, *Table S1*. The variability of all LVDF parameters was less than 7%.

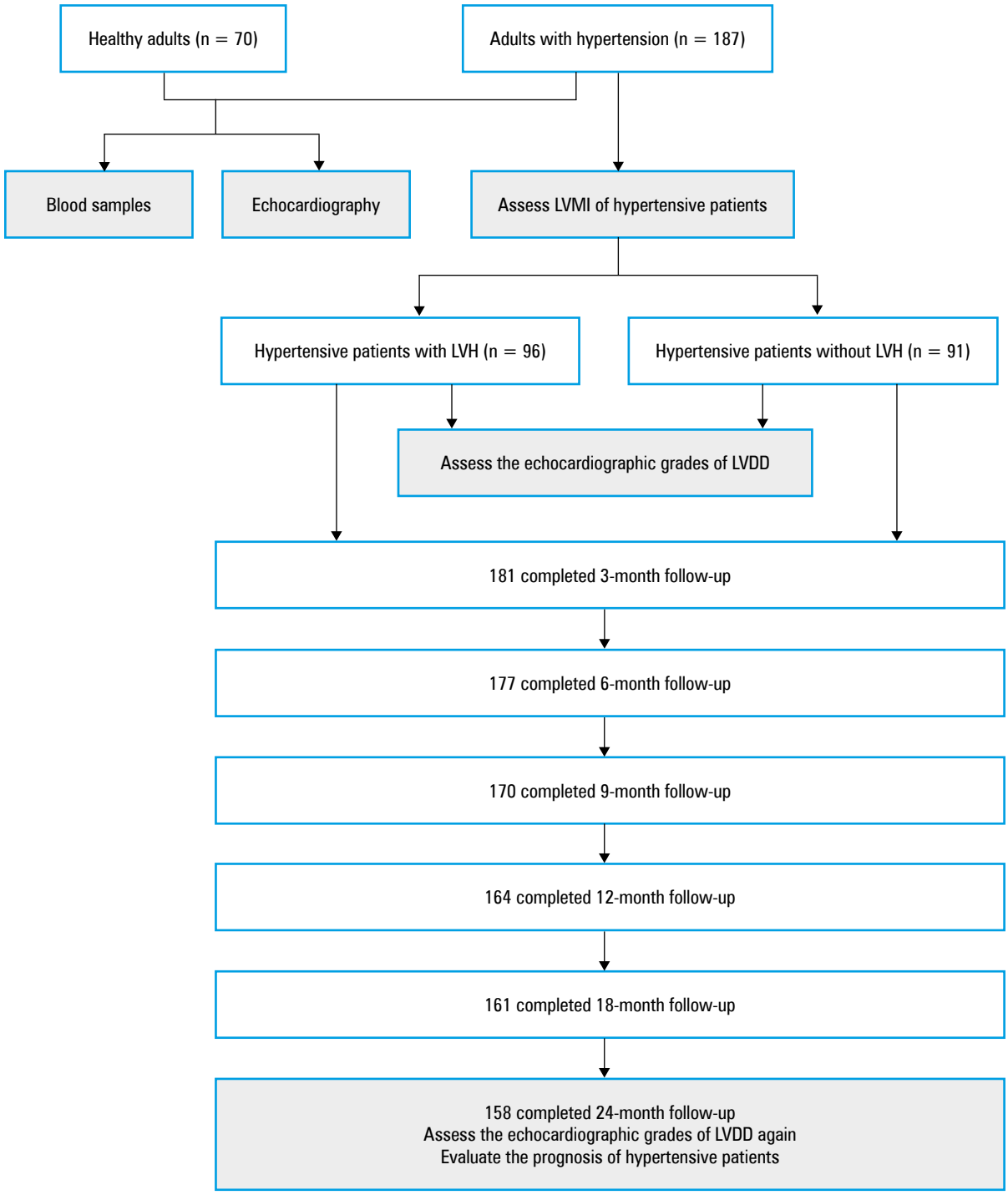


FIGURE 1 Flow chart showing the enrollment protocol
Abbreviations: LVDD, left ventricular diastolic dysfunction; LVH, left ventricular hypertrophy; LVMI, left ventricular mass index

Statistical analysis Descriptive data were expressed as means (SD) or as medians with interquartile ranges in case of skewed distribution. Categorical variables were expressed as numbers (percentages). Continuous variables were analyzed using analysis of variance (ANOVA) or the Mann–Whitney test as appropriate. When a significant difference was found in ANOVA, multiple comparisons were made using the Bonferroni procedure with type I error adjustment. The Pearson correlation test was adopted to investigate bivariate correlations. Moreover, the analysis of ROC curves was also conducted. The optimal prognostic cutoff (nonparametric method) of percentage of T_H17 was derived from the AUC assessed at baseline. We used the Youden index for best sensitivity and specificity values. The optimal cutoff was calculated as sensitivity + specificity – 1. The independent effect of T_H17 on LVH occurrence, after controlling for baseline clinical characteristics and echocardiographic parameters (adopted factors: sex, body surface area, body mass index, heart rate, hyperlipidemia, smoking, systolic blood

TABLE 1 Baseline characteristics of study patients

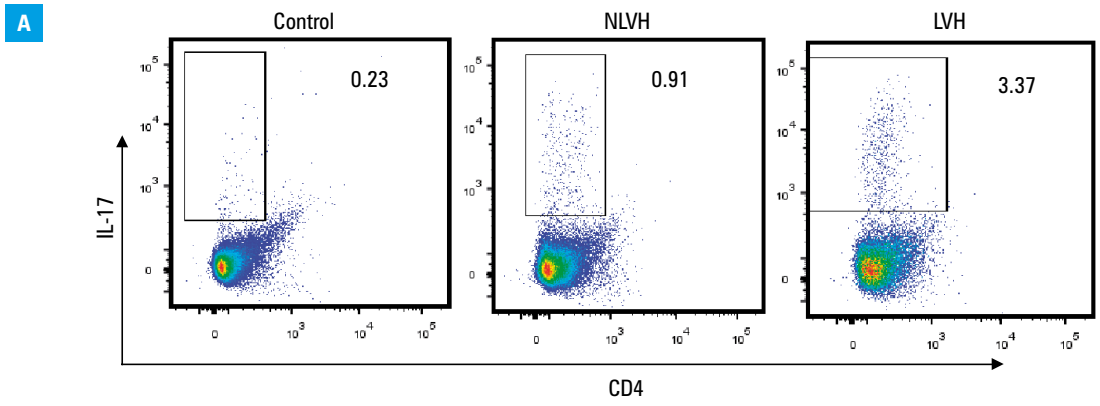
Characteristic	Control (n = 70)	NLVH (n = 96)	LVH (n = 91)
Male sex, n (%)	43 (61)	58 (60)	56 (62)
BSA, m^2, mean (SD)	1.79 (0.4)	1.81 (0.1)	1.76 (0.2)
BMI, kg/m^2, mean (SD)	22.5 (2.1)	22.3 (2.7)	22.1 (1.9)
Heart rate, bpm, mean (SD)	66 (13)	68 (12)	67 (13)
Hyperlipidemia, n (%)	11 (16)	19 (20)	15 (16)
Smoking, n (%)	16 (23)	23 (24)	19 (21)
SBP, mm Hg, mean (SD)	121 (13)	137 (17)	151 (14)
DBP, mm Hg, mean (SD)	76 (9)	77 (11)	80 (10)
LAD, mm, mean (SD)	34 (3)	38 (4)	41 (5)
IVSD, mm, mean (SD)	8.9 (1.1)	9.2 (0.4)	11.6 (1.4)
LVPWD, mm, mean (SD)	8.7 (0.8)	9.1 (0.6)	11.9 (1.6)
LVEDV, ml, mean (SD)	79 (16)	81 (11)	82 (14)
LVESV, ml, mean (SD)	31 (7)	32 (12)	32 (8)
LVEF, %, mean (SD)	66 (3)	65 (8)	66 (5)
LAVI, ml/m^2, mean (SD)	25 (5)	25 (7)	34 (8)
TR max, cm/s, mean (SD)	238 (27)	240 (33)	269 (35)
Average E/e', median (IQR)	10.3 (10–18.9)	11.2 (11–19.6)	15.9 (10.3–19.8)
DT, cm/s, mean (SD)	203 (32)	206 (37)	207 (42)
E, m/s, mean (SD)	0.82 (0.13)	0.84 (0.15)	0.76 (0.11)
A, m/s, mean (SD)	0.41 (0.04)	0.53 (0.07)	0.87 (0.08)
E/A, median (IQR)	2.13 (1.56–2.91)	1.76 (1.02–2.32)	1.31 (0.67–1.93)
val ΔE/A, median (IQR)	0.41 (0.3–0.65)	0.40 (0.32–0.61)	0.81 (0.46–1.02)
Ar-A duration, ms, median (IQR)	9 (6–19)	18 (11–31)	30 (18–43)

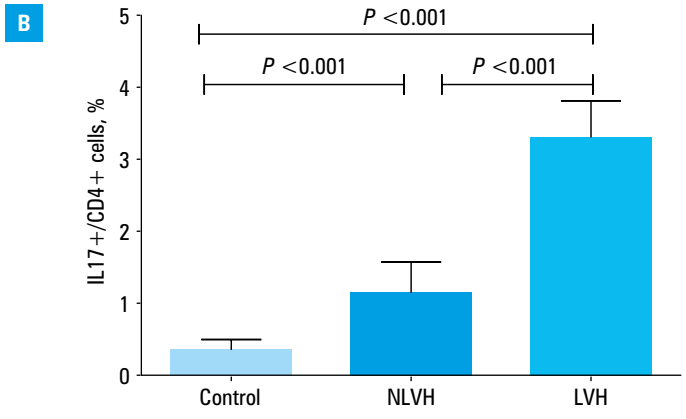
Abbreviations: A, peak velocity during late diastole of anterior mitral leaflet; Ar–A duration, duration of pulmonary vein flow and mitral inflow during atrial contraction; BSA, body surface area; BMI, body mass index; DBP, diastolic blood pressure; DT, E wave deceleration time; E, peak velocity during early diastole of anterior mitral leaflet; e', Tissue Doppler velocities in early diastole; IVSD, interventricular septal thickness in end-diastolic period; IQR, interquartile range; LAD, left atrial diameter; LAEF, left atrial emptying fraction; LAVI, left atrial volume index; LVEDV, left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction; LVESV, left ventricular end--systolic volume; LVPWD, left ventricular posterior wall thickness in end-diastolic period; NLVH, patients without left ventricular hypertrophy; SBP, systolic blood pressure; TR max, peak tricuspid regurgitation velocity; val ΔE/A, change in E/A with Valsalva maneuver; others, see **FIGURE 1**

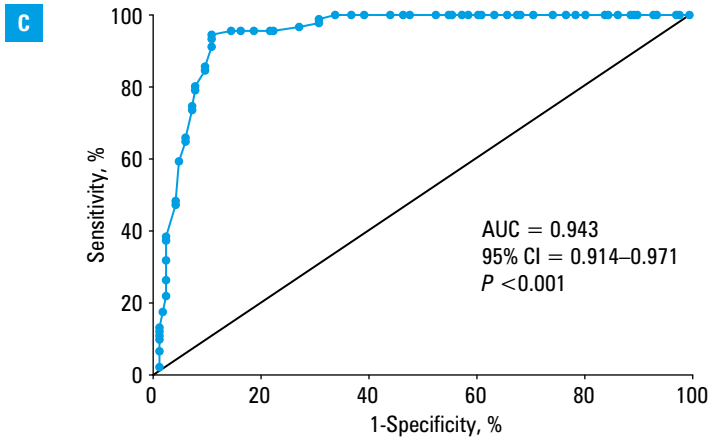
pressure [SBP], left ventricular end-diastolic volume, LVEF, TR_{max}, average E/E', E wave deceleration time, E, A, E/A, val ΔE/A, Ar–A duration, T_H17 cells) was assessed via logistic regression analysis. The χ^2 was used to compare frequencies of the normal LVDF between-groups comparisons. Survival curves for the primary endpoint as a function over time were obtained using the Kaplan–Meier method and compared using the log-rank statistic. Cox regression analysis was used to assess the correlations between T_H17 cells and the considered primary endpoint, baseline clinical and echocardiographic values were used as adjustment variables. All assays were conducted using the SPSS software, version 11.5 (Chicago, Illinois, United States). A *P* value of less than 0.05 was considered statistically significant.

Ethics Informed consent was obtained from every participant, and the study was approved by the Ethics Committee of Affiliated Hospital of Jiangsu University.

RESULTS Patient characteristics and echocardiographic variables The baseline clinical and echocardiographic characteristics of all participants are presented in **TABLE 1**. Hypertensive patients were assigned into 2 groups according to LVMI: LVH group (n = 96) and NLVH group (n = 91). The control group was compared with the NLVH group and LVH group, respectively. SBP, left atrial diameter, the interventricular septal thickness at the end of diastole, thickness of the posterior left ventricular wall at the end of diastole, Ar–A duration, A, and E/A of the NLVH and LVH groups were different from the control group. The pattern in SBP, left atrial diameter, Ar–A duration of the control, NLVH, and LVH groups could be ranked as follows: LVH group, NLVH group, control group. The E/A was the maximal, and the A value was the minimum in the control group. Left atrial volume index, TR_{max}, average E/e', val ΔE/A showed higher levels in the LVH group when compared with the NLVH group and the control group (Supplementary material, *Table S2*).







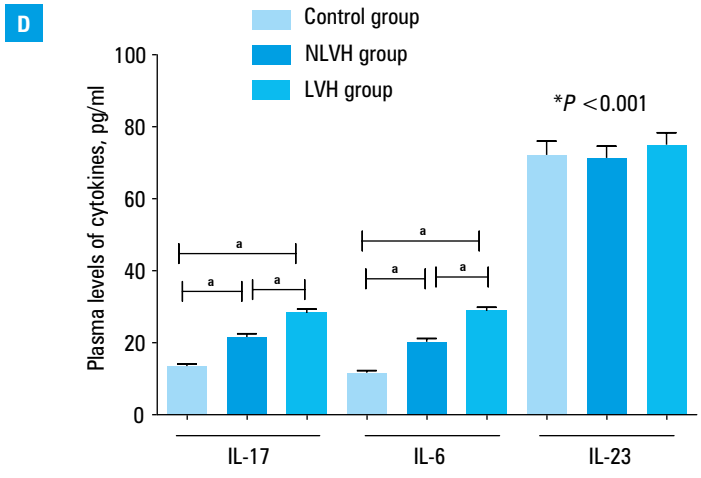


FIGURE 2 Type 17 helper T (T_H17) cell differentiation in the study groups. **A**, **B** – flow cytometric analysis of T_H17 cells; **C** – receiver operating characteristic curve for the prediction of left ventricular hypertrophy using T_H17 cell differentiation; **D** – expression of interleukin (IL) 17, IL-6, and IL-23 in the study groups.
a $P < 0.05$
Abbreviations: AUC, area under the receiver operating characteristic curve; others, see **FIGURE 1** and **TABLE 1**

Higher circulating T_H17 cell percentages in adults with hypertension We measured the percentage of T_H17 cells and serum T_H17-related cytokines (IL-17, IL-6, and IL-23) in patients at baseline. A higher T_H17 expression was observed in hypertensive patients when compared with the control group, and the percentage of T_H17 cells was significantly higher in the LVH group compared with the NLVH group (**FIGURE 2A** and **2B**). Using ROC curves, we observed that T_H17 differentiation (AUC, 0.943; 95% CI, 0.914–0.971; $P < 0.001$) showed a significant AUC (**FIGURE 2C**), and the cut-off value was 2.3%. On logistic regression analysis, the percentage of T_H17 cells was an independent predictor of LVH (odds ratio [OR], 1.47, 95% CI, 2.23–2.28; $P = 0.005$). Factors associated with LVH in hypertensive patients are depicted in Supplementary material, *Table S3*. Univariable logistic regression analysis showed that SBP, TR_{max}, average E/e', A, E/A, val ΔE/A, Ar–A duration, T_H17 cells were significantly associated with LVH. Multivariable logistic regression analysis showed that SBP and T_H17 cells were independent predictors of LVH in hypertensive patients, after adjusting for potential confounders.

We observed that the levels of IL-17 and IL-6 in the LVH group were higher in hypertensive patients compared with the control group, and the levels of IL-17 and IL-6 in the LVH group were significantly higher compared with the NLVH group ($P < 0.001$). There was no difference in the levels of IL-23 among the 3 groups (**FIGURE 2D**).

Relationship between T_H17 cells and fibrotic parameters We analyzed the correlations between T_H17 cells and fibrotic parameters in hypertensive patients at baseline. The proportion of T_H17 cells was positively associated with the levels of matrix

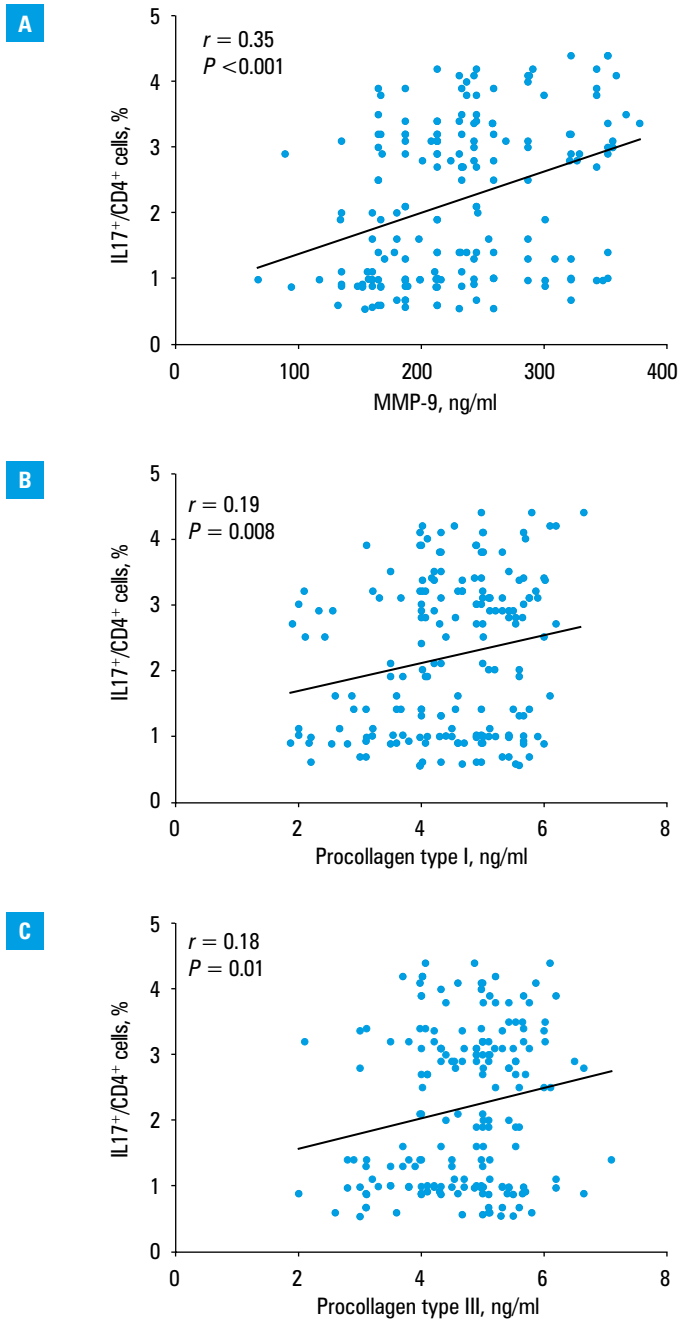


FIGURE 3 Association of helper T 17 (T_H17) cell differentiation with fibrosis parameters in adults. **A** – correlation between the proportion of T_H17 cells and matrix metallopeptidase 9 (MMP-9); **B** – correlation between the proportion of T_H17 cells and procollagen type I; **C** – correlation between the proportion of T_H17 cells and procollagen type III
Abbreviations: see **FIGURE 2**

metallopeptidase 9 (r = 0.35; P <0.001), procollagen type I (r = 0.19; P = 0.008), and procollagen type III (r = 0.18; P = 0.01) (**FIGURE 3**).

Assessment of the prognosis of hypertensive patients

According to the cutoff value of the percentage of T_H17 cells, hypertensive patients were divided into 2 groups: those with the cutoff of less than 2.3% (the <2.3% group; n = 101) and those with the cutoff of 2.3% and greater (the ≥2.3% group; n = 86). Based on the antihypertensive therapy, we reevaluated the LVDF at 24-month follow-up.

Even in asymptomatic patients, the 3-to-5-year mortality rate of patients with grade I LVDD is 5-fold higher than that of patients with normal diastolic function.[9] We compared the proportion of patients with normal LVDF in different groups at baseline and after 24-months of follow-up. We observed that the proportion of patients with normal LVDF in the <2.3% group was higher compared with the patients in the ≥2.3% group at baseline (P <0.001). At 24-month follow-up, the proportion of patients with normal LVDF changed from 49% to 64% (P = 0.03) in the <2.3% group, and when compared with the <2.3% group, the proportion gap was further widened (P <0.001). However, the proportion of patients with normal LVDF in the ≥2.3% group had no significant improvement at 24-month follow-up (**FIGURE 4A** and **4B**).

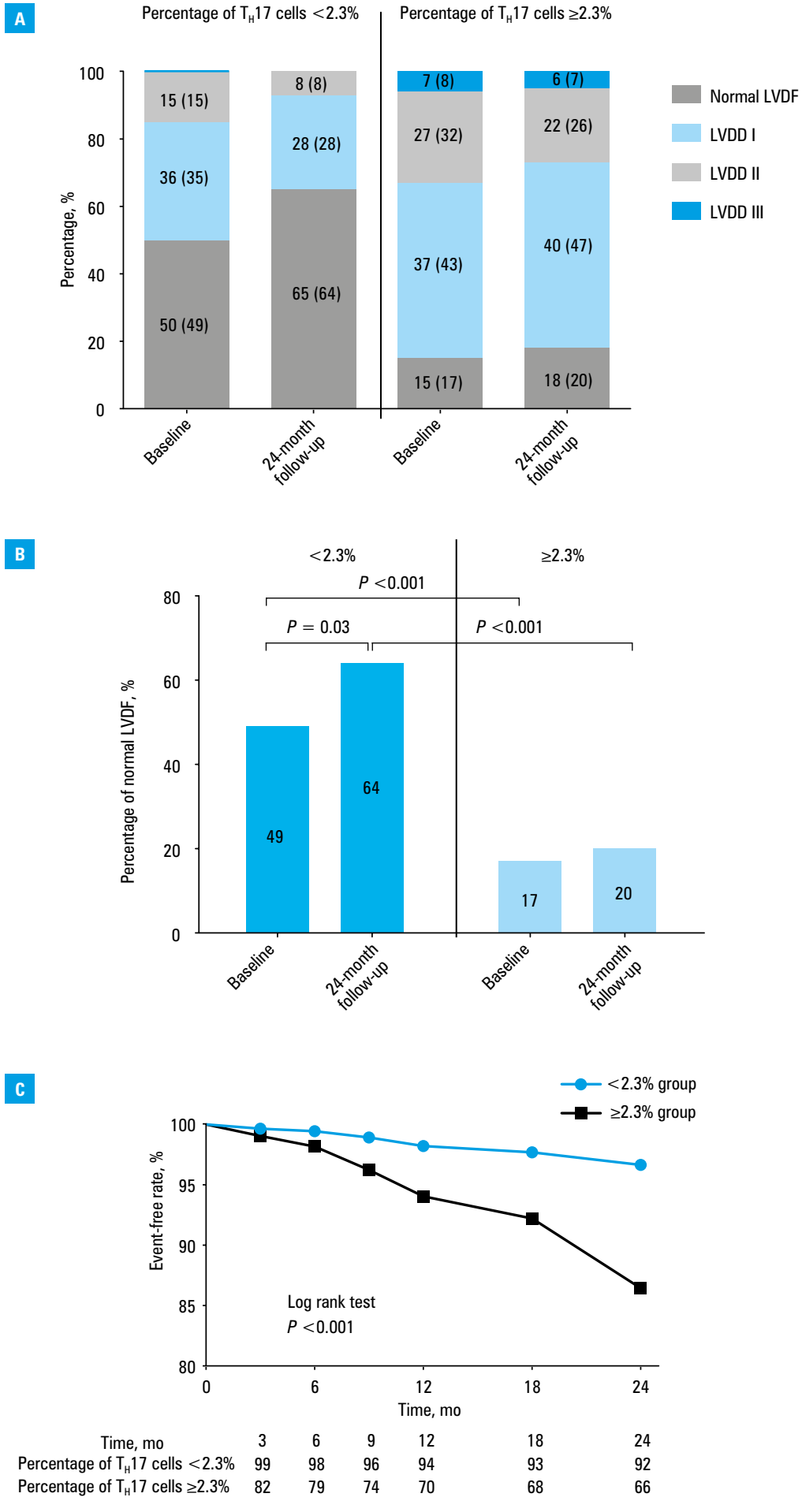
During the follow-up period of 24 months, 29 patients (15%) met the composite primary endpoint. The higher percentage of T_H17 cells (≥2.3%) was associated with a higher probability of the primary endpoint in unadjusted analysis (P <0.001). Importantly, the percentage of T_H17 cells was also significantly associated with an increased risk of the primary endpoint after multivariable adjustment for LVMI, LVH, and baseline clinical characteristics (P = 0.003, hazard ratio, 1.52; 95% CI, 1.02–1.87). The higher the percentage of T_H17 cells, the poorer the prognosis (**FIGURE 4C**).

DISCUSSION In the present study, we demonstrated that T_H17 responses were indispensable for hypertension-induced PO, which contributed to cardiac hypertrophy and remodeling, and a high percentage of T_H17 cells could be used as a potential inflammatory marker to reflect myocardial fibrosis in hypertensive patients. Moreover, T_H17 responses could be used as an independent predictor of LVDF in the development of hypertensive structural heart disease.

Hypertension-induced chronic inflammation activation and infiltration into LV negatively contributed to the progression of myocardial dysfunction through myocardial fibrosis, LVH, and remodeling. T_H17 responses have been identified as a new prognostic biomarker of cardiac abnormalities that can promote stiffness of arteries and fibrosis in the myocardium, playing a critical role in cardiac remodeling.[10-12] Consistent with previous studies, our results demonstrated that the percentage of T_H17 cells was significantly higher in patients with LVH, and strongly correlated with fibrotic parameters in hypertensive patients.

T_H17 responses trigger early-phase ventricular remodeling as demonstrated by higher expressions of fibrosis-related cytokines, interstitial fibrosis, and microvascular endothelial dysfunction. Then, T_H17 responses aggravate late-phase ventricular remodeling as presented by ventricular fibrosis and apoptosis, impair ventricular relaxation, and lead to cardiac dysfunction.[12,13] Increasing evidence has linked T_H17 responses with

FIGURE 4
The prognostic impact of T helper 17 (T_H17) cell differentiation in adults with hypertension.
A – left ventricular diastolic function at baseline and at last follow-up; **B** – normal left ventricular diastolic function at baseline and at last follow-up;
C – survival analysis according to the proportion of T_H17 cells. Kaplan–Meier event-free rates of the adverse cardiac events and all-cause mortality.
Abbreviations: LVDF, left ventricular diastolic function; others, see **FIGURE 1**



Time, mo	3	6	9	12	18	24
Percentage of T_H17 cells <2.3%	99	98	96	94	93	92
Percentage of T_H17 cells ≥2.3%	82	79	74	70	68	66

myocardial fibrosis in hypertensive structural heart disease,[14,15] and here, we showed that activation of T_H17 responses could promote the expression of fibrosis-related cytokines in the progression of ventricular remodeling. In this way, a malignant circle was created in hypertension-induced PO, which contributed to cardiac hypertrophy and remodeling. If we could intervene at the early-phase of ventricular remodeling, the cardiac abnormalities might be reversed. Otherwise, systolic and diastolic dysfunctions and adverse cardiovascular events would happen.

T_H17 responses induces hypertension in a rat model when the disease aggravates,[16] hypertension-induced PO causes several changes in hemodynamics, and the fluid shear stress stimulates a systemic inflammatory state in the circulation. Our study also showed coherent relationships between hypertension-induced PO, T_H17 responses, and T_H17-related cytokines in the immune systems. Therefore, systemic inflammation occurs before myocardial fibrosis, and the increased percentage of T_H17 cells is observed before a higher expression of fibrosis-related cytokines. In the initiation of cardiac disorder, diastolic dysfunction usually appears first, and it contributes to the adverse clinical outcome.[17-19] In this study, we found that the differentiation of T_H17 cells was strongly correlated with the levels of fibrosis-related cytokines in hypertensive patients, indicating that T_H17 responses played a profibrotic role in promoting myocardial fibrosis and LV remodeling, eventually leading to LVDD.

Left ventricular hyperthrophy and remodeling were identified as important contributors to high myocardial diastolic stiffness, especially in LVDD. Based on the above-mentioned data, we hypothesized that T_H17 responses induced LV remodeling, and thus regulated LVDF in hypertensive structural heart disease.

According to the cutoff value of the percentage of T_H17 cells, the higher percentage of T_H17 cells was dramatically associated with poor prognosis, suggesting its effect on the development of myocardial fibrosis, and irreversible ventricular remodeling. Therefore, T_H17 responses were a critical factor affecting cardiac hypertrophy and remodeling in hypertensive patients, and it could be used as a more reliable diagnostic indicator for prognosis of hypertension-induced PO.

However, this study is a single-center trail, and the sample size was relatively small. Therefore, it is necessary to carry out further studies with larger sample size and multicenter trails. Second, in the present study, we demonstrated that T_H17 responses induced cardiac hypertrophy and remodeling in essential hypertension. However, the underlying molecular mechanism remains largely unexplored. Further investigation on the molecular mechanisms is still ongoing.

Collectively, the differentiation of T_H17 cells reflected cardiac hypertrophy and remodeling response to hypertension-induced PO, and contributed to LVDD by chronic inflammation and myocardial fibrosis. Moreover, the differentiation of T_H17 cells could be a potential inflammatory marker to predict the prognosis of hypertensive patients.

SUPPLEMENTARY MATERIAL

Supplementary material is available at www.mp.pl/paim.

ARTICLE INFORMATION

ACKNOWLEDGMENTS This study was supported by the project of preventive medicine of Jiangsu Province (no. Y2018110; to LX), the medical research project of Jiangsu provincial health committee (no. H2019075; to LX), the project of Social Development of Zhenjiang (no. SH2019087; to TF), and the Zhenjiang Cardiovascular Clinical Research Center Project (no. SS2018008; to WY).

CONTRIBUTION STATEMENT WY and LX conceived the concept of the study. FZ, TP, and GC contributed to the design of the research and statistical analysis. HZ and XC were involved in data collection. LX and CZ analyzed the data. YL coordinated the project tasks. All authors edited, revised, and approved the final version of the manuscript.

CONFLICT OF INTEREST None declared.

HOW TO CITE Xu L, Chen G, Liang Y, et al. T helper 17 cell responses induce cardiac hypertrophy and remodeling in essential hypertension. Pol Arch Intern Med. 2021; 131: 257-265. doi:10.20452/pamw.15811

REFERENCES

1 Shenasa M, Shenasa H. Hypertension, left ventricular hypertrophy, and sudden cardiac death. Int J Cardiol. 2017; 237: 60-63.

2 Frangogiannis NG. Cardiac fibrosis: cell biological mechanisms, molecular pathways and therapeutic opportunities. Mol Aspects Med. 2019; 65: 70-99.

3 Liu Y, Lu H, Zhang C, et al. Recent advances in understanding the roles of T cells in pressure overload-induced cardiac hypertrophy and remodeling. J Mol Cell Cardiol. 2019; 129: 293-302.

4 Chang SL, Hsiao YW, Tsai YN, et al. Interleukin-17 enhances cardiac ventricular remodeling via activating MAPK pathway in ischemic heart failure. J Mol Cell Cardiol. 2018; 122: 69-79.

5 Liu Y, Zhu H, Su Z, et al. IL-17 contributes to cardiac fibrosis following experimental autoimmune myocarditis by a PKCβ/Erk1/2/NF-κB-dependent signaling pathway. Int Immunol. 2012; 24: 605-612.

6 Xu L, Geng T, Zang G, et al. Exosome derived from CD137-modified endothelial cells regulates the Th17 responses in atherosclerosis. J Cell Mol Med. 2020; 24: 4659-4667.

7 Xu L, Wang N, Liang Y, et al. Interleukin-17A contributes to atrial fibrillation recurrence and left atrial reservoir function after catheter ablation. Pol Arch Intern Med. 2019; 129: 432-435.

8 Roberto ML, Luigi PB, Victor M, et al. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. Eur Heart J Cardiovasc Imaging. 2015; 16: 233-270.

9 Nagueh SF, Smiseth OA, Appleton CP, et al. Recommendations for the evaluation of left ventricular diastolic function by echocardiography: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. Eur Heart J Cardiovasc Imaging. 2016; 17: 1321-1360.

10 Libby P, Hansson GK. Taming immune and inflammatory responses to treat atherosclerosis. J Am Coll Cardiol. 2018; 71: 173-176.

11 Taleb S, Tedgui A. IL-17 in atherosclerosis: the good and the bad. Cardiovasc Res. 2018; 114: 7-9.

12 Valente AJ, Yoshida T, Gardner JD, et al. Interleukin-17A stimulates cardiac fibroblast proliferation and migration via negative regulation of the dual-specificity phosphatase MKP-1/DUSP-1. Cell Signal. 2012; 24: 560-568.

13 Zhou SF, Yuan J, Liao MY, et al. IL-17A promotes ventricular remodeling after myocardial infarction. J Mol Med. 2014; 92: 1105-1116.

14 Ellims AH, Shaw JA, Stub D, et al. Diffuse myocardial fibrosis evaluated by post-contrast t1 mapping correlates with left ventricular stiffness. J Am Coll Cardiol. 2014; 63: 1112-1118.

15 Hamdani N, Paulus WJ. Myocardial titin and collagen in cardiac diastolic dysfunction: partners in crime. Circulation. 2013; 128: 5-8.

16 Lee E, Kim N, Kang J, et al. Activated pathogenic Th17 lymphocytes induce hypertension following high-fructose intake in Dahl salt-sensitive but not Dahl salt-resistant rats. Dis Model Mech. 2020; 13: dmm044107.

17 Aroor AR, Jia G, Sowers JR. Cellular mechanisms underlying obesity-induced arterial stiffness. Am J Physiol Reg I. 2018; 314: R387-R398.

18 Mohammed SF, Hussain S, Mirzoyev SA, et al. Coronary microvascular rarefaction and myocardial fibrosis in heart failure with preserved ejection fraction. Circulation. 2015; 131: 550-559.

19 Franssen C, Chen S, Unger A, et al. Myocardial microvascular inflammatory endothelial activation in heart failure with preserved ejection fraction. JACC Heart Fail. 2016; 4: 312-324.