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# Association Between Longitudinal Changes in Left Ventricular Structure and Function and 24-Hour Urinary Free Cortisol in Essential Hypertension

Gao-Zhen Cao[1,2] | Jia-Yi Huang[2,3] | Qing-Shan Lin[4] | Run Wang[2] | Cong Chen[2] | Jian-Cheng Xiu[1] | Kai-Hang Yiu[2,3]

[1]The First School of Clinical Medicine, Southern Medical University, Guangzhou, China | [2]Division of Cardiovascular Medicine, Cardiac and Vascular Center, The University of Hong Kong-Shenzhen Hospital, Shenzhen, China | [3]Division of Cardiology, Department of Medicine, The University of Hong Kong, Queen Mary Hospital, Hong Kong, China | [4]Division of Radiology, Department of Medicine, The University of Hong Kong-Shenzhen Hospital, Shenzhen, China

**Correspondence:** Kai-Hang Yiu (khkyiu@hku.hk) | Jian-Cheng Xiu (xiujch@163.com)

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## ABSTRACT

This study aimed to investigate the associations between 24-hour urinary cortisol levels (24 h-UFC) and alterations in left ventricular (LV) structure and function in patients with essential hypertension. A prospective cohort study was conducted, including 315 patients with essential hypertension who underwent baseline 24 h-UFC measurement and echocardiographic evaluation of left ventricular mass (LVM), left ventricular ejection fraction (LVEF), and the E/e′ ratio. Over a mean follow-up period of 28.54 ± 14.21 months, patients were grouped into tertiles based on baseline 24 h-UFC levels. Higher baseline 24 h-UFC levels were significantly associated with greater increases in LVM and E/e′, reflecting adverse LV remodeling and diastolic dysfunction. These associations persisted after adjusting for potential confounders, including age, gender, baseline blood pressure, and their changes during follow-up. Moreover, patients in the highest 24 h-UFC tertile showed an increased prevalence of LV hypertrophy, contrasting with a reduction observed in the lower tertiles. These findings underscore the independent role of elevated 24 h-UFC levels in driving adverse cardiac structural and functional changes in essential hypertension.

## 1 | Introduction

Left ventricular hypertrophy (LVH) is a well-established risk factor for cardiovascular events including heart failure [1], ischemic heart disease [2], atrial fibrillation [3], and sudden cardiac death [4] in hypertensive patients. Although robust evidence indicates that increased cardiac workload is fundamental in the development of LVH in hypertension, numerous additional non-hemodynamic factors may also be involved. These include gender, genotype, body mass, and multiple biochemical and hormonal mediators such as angiotensin II, catecholamines, steroid hormones, insulin, and some growth factors and cytokines [5]. Additionally, LVH often occurs in conjunction with changes in left ventricular (LV) filling characteristics that reflect LV diastolic dysfunction. LV diastolic dysfunction has been shown to be associated with development of heart failure and is predictive of all-cause mortality [6, 7]. Therefore, timely identification of factors that contribute to the development of LVH and LV diastolic dysfunction is crucial to preventing functional cardiac deterioration leading to heart failure.

Hypertension is a prominent feature among patients with abnormal increases in circulating glucocorticoid levels, and cardiovascular events are a leading cause of morbidity and

mortality in these patients. Previous studies conducted on patients with Cushing's syndrome consistently demonstrate that chronic hypercortisolism results in adverse cardiac structural and functional changes that cannot be explained solely by blood pressure elevation [8–10]. Recent research found that midnight and dexamethasone suppression test (DST) plasma cortisol levels are independent predictors of LV mass and geometry in patients with essential hypertension [11]. However, no studies have yet established a clear relationship between cortisol levels and changes in LV structure and function in patients with essential hypertension. This study aimed to examine the relationships between 24-hour urinary cortisol levels (24 h-UFC) levels and alterations in LV structure and function in patients with essential hypertension through a prospective cohort study.

## 2 | Methods

### 2.1 | Study Design and Study Population

This prospective cohort study was conducted at the Hypertension Center of the University of Hong Kong—Shenzhen Hospital. A total of 414 patients diagnosed with essential hypertension at the hypertension center between July 2018 and December 2021 were included. Blood pressure measurements and hypertension diagnosis were conducted following current guidelines [12]. The inclusion criteria for the study population were as follows: (1) age ≥18 years; (2) a diagnosis of any grade of hypertension; and (3) no use of antihypertensive medications or glucocorticoids within 4 weeks prior to study enrollment. All patients were excluded from having secondary causes of hypertension. Cushing's syndrome was excluded based on the measurements of plasma cortisol levels (8 a.m., 4 p.m., 12 a.m.), 24 h-UFC, and plasma cortisol level after an overnight DST with 1 mg dexamethasone, according to the guidelines [13]. Adrenal magnetic resonance or computed tomography imaging excluded the presence of adrenal incidentalomas. Patients with a history of ischemic heart disease ($n$ = 25), cardiac valve disease ($n$ = 11), stroke ($n$ = 11), estimated glomerular filtration rate (eGFR) <30 mL/(min 1.73 $m^2$) ($n$ = 14), alcohol abuse ($n$ = 2), or acute infection ($n$ = 2), were excluded. A total of 349 patients were initially recruited for baseline evaluation. Patients were subsequently excluded if they developed a history of myocardial infarction ($n$ = 2), underwent percutaneous coronary intervention ($n$ = 6), or died ($n$ = 1) during follow-up. Additionally, 25 patients were excluded due to loss to follow-up. Ultimately, 315 patients were included in the final analysis (Figure 1). The study was conducted in accordance with the principles of the Declaration of Helsinki and received approval from the local Institutional Review Board. Informed consent was obtained from all participants.

### 2.2 | Blood Pressure Measurement

Blood pressure was measured in accordance with the European Society of Hypertension and the European Society of Cardiology (ESH/ESC) guidelines [12] using a validated device (Omron HEM-7130; Omron Health Care, Kyoto, Japan). Patients were seated comfortably in a quiet setting for at least 5 min, with their arm positioned at heart level. Initial measurements were taken from both arms, followed by two additional measurements from the arm with the highest initial reading, at 2-min intervals. The average of the final two measurements was recorded for analysis.

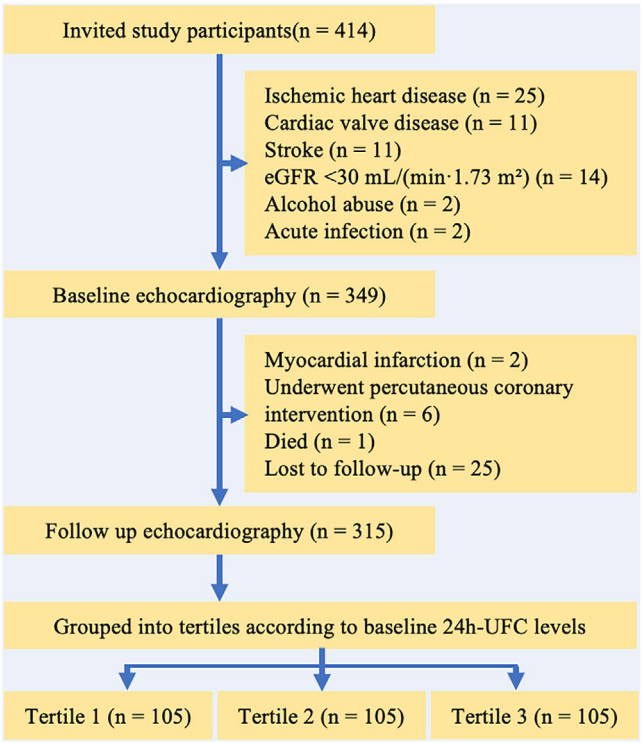


**FIGURE 1** | The flowchart for participants in this study. eGFR indicates estimated glomerular filtration rate; 24 h-UFC, 24-hour urinary cortisol levels.

### 2.3 | Laboratory Measurements

24 h-UFC levels were measured using the UniCel DxI 800 Access Immunoassay System (Beckman Coulter Inc., Brea, CA, USA). Morning blood samples, collected after a minimum of 12 h of fasting, were analyzed for various biochemical parameters including glycosylated hemoglobin (HbA1c), triglycerides (TGs), total cholesterol (TC), low-density lipoprotein cholesterol (LDL), high-density lipoprotein cholesterol (HDL), serum creatinine (SCr), and adrenocorticotropic hormone (ACTH) using the Roche COBAS 8000 platform (Roche Diagnostic, Basel, Switzerland). The estimated glomerular filtration rate (eGFR) was calculated using the modification of diet in renal disease (MDRD) equation [14].

### 2.4 | Echocardiography

Standard 2D echocardiography and tissue Doppler imaging were performed using a VingmedE9 echocardiography system (General Electric Vingmed Ultrasound, Horten, Norway) by experienced operators who were blinded to the patients' clinical and biochemical data. Images were captured in the lateral decubitus position with a 3.5-MHz transducer and stored digitally in cine-loop format. Left ventricular ejection fraction (LVEF) was calculated using the modified Simpson's biplane method from apical 4- and 2-chamber views. Measurements of

left ventricular end-diastolic diameter (LVEDd), left ventricular end-systolic diameter (LVESd), interventricular septal thickness (IVSd), and posterior wall thickness (PWTd) were obtained from 2D-guided M-mode tracings in the parasternal long-axis view, using the leading-edge method [15]. Left ventricular mass index (LVMi) was estimated using the corrected American Society of Echocardiography (ASE) formula [15] ($0.8 \times (1.04 \times ((IVSd + LVEDd + PWTd)^3 - (LVEDd)^3)) + 0.6$) and normalized to body surface area (BSA). LVH was defined as increased LVMi ($\geq 95$ g/m$^2$ in females; $\geq 115$ g/m$^2$ in males). Relative wall thickness (RWT) was calculated by the ASE formula: $RWT = 2 \times PWTd/LVEDd$, with increased RWT defined as >0.42 [15]. LV structural patterns were classified as normal (normal LVMi and RWT), concentric remodeling (normal LVMi, increased RWT), eccentric hypertrophy (LVH, normal RWT), and concentric hypertrophy (LVH, increased RWT). Left atrial volume (LAV) was quantified by tracing the endocardial borders in both the apical four- and two-chamber views, and the LAV index (LAVi) was calculated by normalizing to body surface area. In patients with atrial fibrillation (AF), echocardiographic measurements, including LAV, were averaged over three consecutive cardiac cycles to account for beat-to-beat variability, in accordance with current echocardiographic guidelines. LV diastolic function was evaluated through pulsed-wave Doppler of mitral valve inflow, measuring peak velocities during early diastole (E-wave) and late diastole (A-wave), which were used to calculate the E/A ratio. Tissue Doppler imaging measured peak early diastolic mitral annular velocity (e′) at the septal and lateral annuli, and the E/e′ ratio was calculated. Diastolic dysfunction was graded according to the 2016 ASE/EACVI guidelines using a two-step process [16]. The first step involved assessing septal or lateral e′ velocity, E/e′ ratio, LAVi, and peak tricuspid regurgitation (TR) velocity to diagnose diastolic dysfunction. In the second step, patients with diastolic dysfunction were further graded based on the E/A ratio and E velocity followed by LAVi, E/e′ ratio, and peak TR velocity. The median follow-up period was 26 months (range 15–41 months).

## 2.5 | Statistical Analysis

Patients were categorized into three groups according to their 24 h-UFC tertile at enrollment, with demographic and clinical characteristics analyzed separately. The Kolmogorov–Smirnov test was used to assess the distribution of continuous variables. Normally distributed variables are presented as means ± standard deviations (SDs), while non-normally distributed variables are presented as medians (interquartile ranges) and log-transformed for normal distribution before statistical analysis. Categorical data are presented as absolute numbers (percentages). Intergroup differences were evaluated using Student's *t*-test or the Mann–Whitney test for continuous variables and the $\chi^2$ test for categorical variables. Group comparisons were performed using ANOVA or the Bonferroni test for multiple comparisons. Stepwise linear regression was applied to explore the relationship between changes in echocardiographic parameters and baseline echocardiographic values, alongside various baseline clinical risk factors such as age, gender, hypertension duration, BMI, blood pressure, heart rate, smoking status, LDL-C, HbA1c, SCr, ACTH, 24 h-UFC, medication type and quantity, and changes in BMI, blood pressure, and heart rate. Furthermore, we conducted collinearity diagnostics for all variables included in the stepwise regression analysis by calculating the Variance Inflation Factor (VIF). The results confirmed that the VIF for all variables was below 10, ensuring that collinearity issues were minimized in the final model. We also performed an Analysis of Covariance (ANCOVA), adjusting for sex, age, BMI, blood pressure, and heart rate, to compare echocardiographic parameters among the three patient groups. All statistical analyses were conducted using SPSS for Windows (Version 23.0), with a two-sided $p$ value <0.05 considered statistically significant.

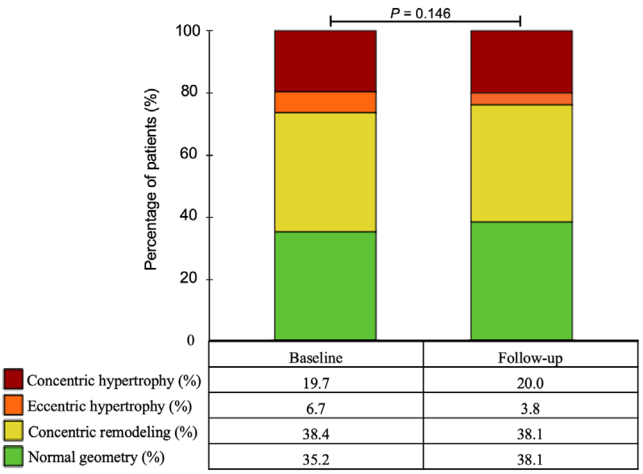


**FIGURE 2** | Longitudinal changes in the proportion of LVH types in the entire cohort. LVH indicates left ventricular hypertrophy.

## 3 | Results

### 3.1 | Clinical Characteristics of the Entire Cohort

The clinical characteristics and echocardiographic parameters at baseline and follow-up, along with their longitudinal changes, are summarized in Table 1. The mean age of the cohort was 44.68 ± 12.20 years, with 29.8% being female. The mean follow-up period was 28.54 ± 14.21 months. During this period, significant reductions were observed in BMI, systolic and diastolic blood pressure, and heart rate. The proportions of antihypertensive drug usage, including ACEI/ARB, ARNI, CCB, diuretics, spironolactone, beta-blockers, and alpha-blockers, remained consistent from baseline to the end of the study.

### 3.2 | Echocardiographic Parameters of the Entire Cohort

The cohort demonstrated a significant reduction in LV structure parameters, including LVMi, LVESV, and LVEDV at follow-up, while RWT and LAVi remained similar. The prevalence of LVH decreased from 26.4% at baseline to 23.8% at follow-up, though this reduction was not statistically significant (Figure 2). Additionally, the mean LVEF significantly increased from 64.91% ± 6.69% to 66.11% ± 6.29% ($p = 0.002$). However, there was no significant change in the proportion of patients with diastolic dysfunction during the follow-up period (Figure 3).

**TABLE 1** | Clinical characteristics and echocardiography parameters of patients at baseline and follow-up.

| | Baseline | Follow up | Absolute change | *p* value |
|---|---|---|---|---|
| Demographic characteristics | | | | |
| Female, *n* (%) | 94 (29.8) | 94 (29.8) | 0 (0) | |
| Smoking, *n* (%) | 76 (24.1) | 74 (23.5) | −2 (0.63) | 0.158 |
| BMI (kg/m$^2$) | 26.70 ± 4.48 | 26.53 ± 4.18 | −0.17 ± 0.57 | 0.060 |
| SBP (mmHg) | 161.77 ± 24.82 | 133.22 ± 13.56 | −28.56 ± 25.34 | 0.000 |
| DBP (mmHg) | 102.37 ± 18.65 | 84.00 ± 11.63 | −18.38 ± 18.82 | 0.000 |
| HR (bpm) | 83.79 ± 13.86 | 74.97 ± 9.90 | −8.69 ± 13.78 | 0.000 |
| Medications | | | | |
| ACEI/ARB, *n* (%) | 222 (70.5) | 226 (71.7) | 6 (1.9) | 0.434 |
| ARNI, *n* (%) | 9 (2.9) | 11 (3.5) | 2 (0.6) | 0.158 |
| CCB, *n* (%) | 244 (77.5) | 249 (79.0) | 5 (1.6) | 0.166 |
| Diuretics, *n* (%) | 42 (13.3) | 43 (13.7) | 1 (0.3) | 0.565 |
| Spironolactone, *n* (%) | 18 (5.7) | 18 (5.7) | 0 (0) | 1.000 |
| Beta-blockers, *n* (%) | 137 (43.5) | 141 (44.8) | 4 (1.3) | 0.206 |
| $\alpha$-Blockers, *n* (%) | 15 (4.8) | 16 (5.1) | 1 (0.3) | 0.318 |
| Laboratory variables | | | | |
| 24 h-UFC (ug/24 h) | 212.00 (142.00∼304.00) | | | |
| ACTH (pg/mL) | 24.10 ± 22.26 | | | |
| SCr (umol/L) | 86.57 ± 60.85 | | | |
| eGFR (mL/min/1.73 m2) | 94.33 ± 33.07 | | | |
| TC (mmol/L) | 4.65 ± 1.19 | | | |
| TGs (mmol/L) | 1.70 (1.11∼2.51) | | | |
| LDL-C (mmol/L) | 2.94 ± 0.99 | | | |
| HDL-C (mmol/L) | 1.18 ± 0.36 | | | |
| HbA1c (%) | 5.97 ± 1.14 | | | |
| Echocardiography variables | | | | |
| LVM (g) | 185.42 ± 70.67 | 176.72 ± 67.66 | −8.70 ± 41.51 | 0.000 |
| LVMi (g/m$^2$) | 98.37 ± 29.62 | 94.71 ± 28.00 | −3.66 ± 22.24 | 0.004 |
| RWT | 0.44 ± 0.74 | 0.44 ± 0.73 | 0.00 ± 0.08 | 0.775 |
| LVEDV (mL) | 107.94 ± 31.47 | 103.30 ± 29.86 | −4.64 ± 21.85 | 0.000 |
| LVESV (mL) | 38.82 ± 20.74 | 36.00 ± 18.60 | −2.82 ± 12.32 | 0.000 |
| LVEF (%) | 64.91 ± 6.69 | 66.11 ± 6.29 | 1.20 ± 6.78 | 0.002 |
| LAV (mL) | 27.66 ± 14.62 | 28.18 ± 16.07 | 0.52 ± 12.93 | 0.477 |
| LAVi (mL/m$^2$) | 14.32 ± 7.10 | 15.13 ± 7.91 | 0.82 ± 6.96 | 0.038 |
| E/e′ | 10.59 ± 3.49 | 10.37 ± 3.13 | −0.22 ± 3.05 | 0.251 |
| E/A | 1.06 ± 0.36 | 1.04 ± 0.36 | −0.02 ± 0.38 | 0.409 |
| E (cm/s) | 76.20 ± 19.10 | 75.70 ± 18.94 | −0.50 ± 19.46 | 0.650 |
| A (cm/s) | 75.76 ± 18.99 | 76.26 ± 18.65 | 0.51 ± 16.26 | 0.580 |
| *e′* septal (cm/s) | 7.71 ± 2.40 | 7.72 ± 2.45 | 0.01 ± 2.42 | 0.946 |
| *e′* lateral (cm/s) | 10.63 ± 2.94 | 10.94 ± 3.25 | 0.25 ± 2.51 | 0.661 |

Abbreviations: A, trans-mitral late diastolic peak velocity; ACEI, angiotensin-converting enzyme inhibitor; ACTH, adrenocorticotropic hormone; ARB, angiotensin II receptor blocker; ARN, angiotensin receptor-neprilysin inhibitor; BMI, body mass index; CCB, calcium channel blocker; DBP, diastolic blood pressure; *e′* lateral, peak early diastolic lateral mitral annular velocity; *e′* septal, peak early diastolic septal mitral annular velocity; E, trans-mitral early diastolic peak velocity; eGFR, estimated glomerular filtration rate; HbA1c, glycosylated hemoglobin; HDL-C, high-density lipoprotein cholesterol; HR, heart rate; LAV, left atrial volume; LAVi, left atrial volume index; LDL-C, low-density lipoprotein cholesterol; LVEDV, left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction; LVESV, left ventricular end-systolic volume; LVM, left ventricular mass; LVMi, left ventricular mass index; *n*, number; RWT, relative wall thickness; SBP, systolic blood pressure; SCr, serum creatinine; TC, total cholesterol; TGs, triglycerides; UFC, urinary free cortisol.

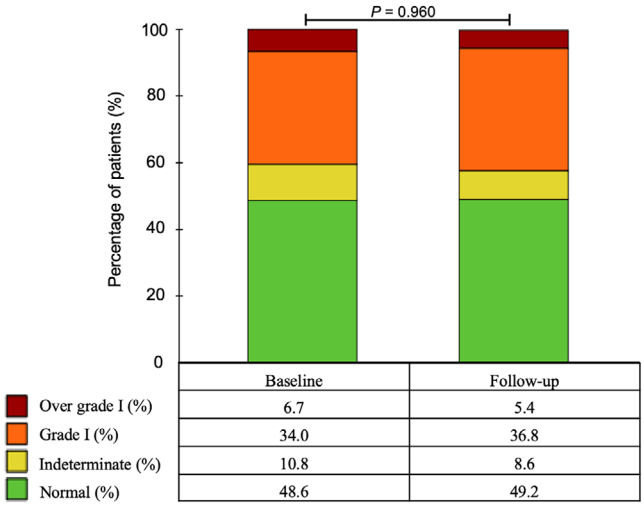


**FIGURE 3** | Longitudinal changes in the proportion of LV diastolic dysfunction in the entire cohort. LV indicates left ventricular.

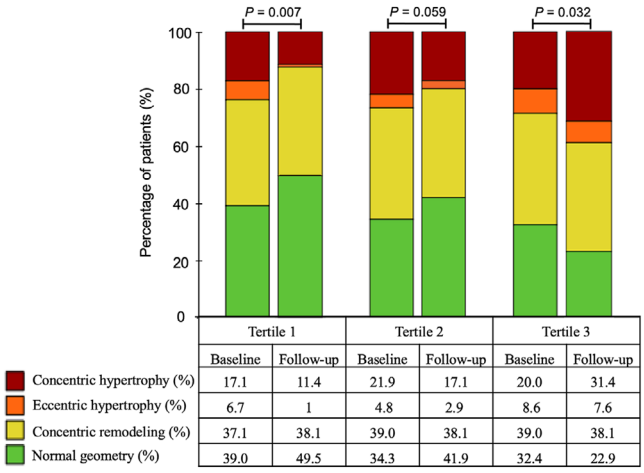


**FIGURE 4** | Longitudinal changes in the proportion of LVH types of patients grouped according to tertiles of 24 h-UFC. LVH indicates left ventricular hypertrophy; 24 h-UFC, 24-hour urinary cortisol levels.

### 3.3 | Factors Associated With Changes in LV Structure and Function

Baseline cardiac parameters were negatively correlated with changes in cardiac structure and function during follow-up (Table 2). After adjusting for multiple variables, higher 24 h-UFC levels, analyzed as a continuous variable, were associated with greater increases in left ventricular mass (LVM), LVMi, and the E/e′ ratio, but not with changes in LVEF. For further analysis, patients were divided into three tertiles based on their 24 h-UFC levels (Table 3). At baseline, patients in Tertile 3 had the highest LVM compared to those in Tertiles 1 and 2. During follow-up, the increase in LVM, LVMI, RWT, and E/e′ were significantly greater in Tertile 3 than in the other tertiles. While the prevalence of LVH decreased in Tertiles 1 and 2, it increased notably in Tertile 3 (Figure 4). No significant changes in the prevalence of LV diastolic dysfunction were observed across the tertiles from baseline to follow-up (Figure 5).

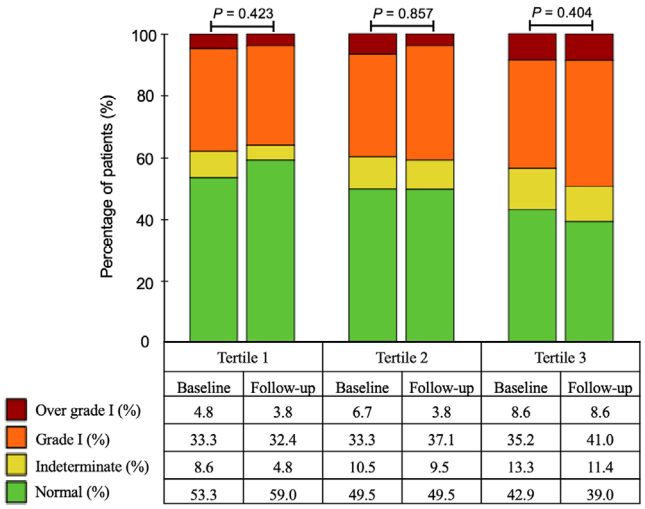


**FIGURE 5** | Longitudinal changes in the proportion of LV diastolic dysfunction of patients grouped according to tertiles of 24 h-UFC. LV indicates left ventricular; 24 h-UFC, 24-hour urinary cortisol levels.

## 4 | Discussion

To the best of our knowledge, this is the first prospective cohort study to examine the relationship between longitudinal changes in cardiac structure/function and 24 h-UFC in essential hypertension. The most significant finding of our study is that baseline 24 h-UFC levels are significantly associated with adverse LV remodeling in these patients, even after adjusting for various confounding factors.

Previous studies in patients with Cushing's syndrome have shown that excessive cortisol levels can independently induce abnormalities in LV structure and function, irrespective of blood pressure changes [17–19]. Similar findings have been reported in small-sample cross-sectional studies in patients with essential hypertension [11, 20]. However, the cross-sectional nature of these studies does not allow for definitive conclusions regarding a causal relationship between cortisol levels and LV changes. Consequently, we designed the current prospective cohort study to examine the relationship between baseline cortisol levels and longitudinal changes in LV structure and function. In this study, we used 24 h-UFC as a measure of circulating free cortisol levels. This method provides a direct assessment of free cortisol in circulation, independent of corticosteroid-binding globulin (CBG), and minimizes the impact of cortisol's circadian rhythm, thus offering a more accurate reflection of tissue and organ exposure to active cortisol [21, 22]. Our analysis revealed that changes in LVM (ΔLVM) were independently associated with baseline 24 h-UFC levels. We further investigated changes in LV geometry from baseline to the end of follow-up among patients with different 24 h-UFC levels. Notably, patients in the highest 24 h-UFC tertile exhibited a higher proportion of LVH at baseline and a further increase during follow-up, particularly in concentric hypertrophy, even after antihypertensive treatment. In contrast, patients with lower and moderate cortisol levels showed a reduction in the proportion of LVH following antihypertensive treatment. This difference cannot be fully explained by blood pressure control, as there were no significant differences in changes in systolic and diastolic blood pressure (ΔSBP and ΔDBP)

**TABLE 2** | Factors related to changes in cardiac structure and function parameters.

| Variables | △LVM, g | | △LVMi, g/m$^2$ | | △LVEF, % | | △*E*/*A* | | △Average *E*/*e*′ | | △LAVi, mL/m$^2$ | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | *β* | *p* value | *β* | *p* value | *β* | *p* value | *β* | *p* value | *β* | *p* value | *β* | *p* value |
| Baseline cardiac parameters | −0.430 | 0.000 | −0.461 | 0.000 | −0.635 | 0.000 | −0.729 | 0.000 | −0.518 | 0.000 | −0.422 | 0.000 |
| Average follow-up duration | | | | | | | | | | | | |
| Baseline risk factors | | | | | | | | | | | | |
| Age (years) | | | | | | | −0.010 | 0.000 | 0.049 | 0.000 | 0.100 | 0.001 |
| Sex | | | | | | | | | | | | |
| Hypertension duration | | | | | | | | | | | | |
| BMI | 2.081 | 0.001 | | | −0.166 | 0.014 | −0.010 | 0.010 | | | | |
| SBP | | | | | 0.049 | 0.000 | | | | | | |
| DBP | | | | | | | | | | | | |
| HR | | | | | −0.048 | 0.033 | −0.003 | 0.009 | | | | |
| Smoking status | | | | | | | | | | | | |
| LDL-C | | | | | | | | | | | | |
| HbA1c | | | | | | | | | | | 0.693 | 0.029 |
| SCr | 0.075 | 0.025 | | | | | | | 0.005 | 0.043 | | |
| ACTH | | | | | | | | | | | | |
| Log 24 h-UFC | 54.579 | 0.000 | 26.842 | 0.000 | | | | | 2.321 | 0.000 | | |
| Medications | | | | | | | | | | | | |
| Number of medications | | | | | | | | | | | | |
| ACEI/ARB | | | | | | | | | | | | |
| ARNI | | | | | | | | | | | | |
| CCB | | | | | | | | | | | | |
| Diuretics | | | | | | | | | | | | |
| Spironolactone | | | | | | | | | | | | |
| *β*-blocker | | | | | | | | | | | | |
| *α*-blocker | | | | | | | | | | | | |
| Change in risk factors | | | | | | | | | | | | |
| △BMI | | | −6.229 | 0.001 | | | | | | | | |
| △SBP | 0.159 | 0.020 | | | | | | | | | | |
| △DBP | | | | | | | | | | | | |
| △HR | | | | | | | | | | | | |

Baseline cardiac parameters indicate baseline LVM (for change in LVM), baseline LVMi (for change in LVMi), baseline LVEF (for change in LVEF), baseline E/A (for change in E/A), baseline average E/e′ (for change in average E/e′), and baseline LAVi (for change in LAVi), respectively. Stepwise linear regression was used to assess the independent correlations between the change of cardiac parameters and baseline cardiac parameters, Average follow-up duration, baseline risk factors (age, sex, Hypertension duration, BMI, SBP, DBP, HR, smoking status, LDL-C, Hba1c, SCr, ACTH, and 24-UFC), the change in risk factors, and medication at baseline (ACEI/ARB, ARNI, CCB, diuretics, Spironolactone, *β*-blocker, and *α*-blocker).

Abbreviations: A, trans-mitral late diastolic peak velocity; ACEI, angiotensin-converting enzyme inhibitor; ACTH, adrenocorticotropic hormone; ARB, angiotensin II receptor blocker; ARNI, angiotensin receptor-neprilysin inhibitor; BMI, body mass index; CCB, calcium channel blocker; DBP, diastolic blood pressure; *e′*, peak early diastolic mitral annular velocity; E, trans-mitral early diastolic peak velocity; HbA1c, glycosylated hemoglobin; HR, heart rate; LAVi, left atrial volume index; LDL-C, low-density lipoprotein cholesterol; LVEF, left ventricular ejection fraction; LVM, left ventricular mass; LVMi, left ventricular mass index; SBP, systolic blood pressure; SCr, serum creatinine; UFC, urinary free cortisol.

**TABLE 3** | Echocardiographic parameters of patients grouped by 24 h-UFC tertiles, analyzed using ANCOVA with sex, age, BMI, SBP, DBP, and HR as covariates.

| | Tertile 1 ($n = 105$) | Tertile 2 ($n = 105$) | Tertile 3 ($n = 105$) | Total ($n = 315$) | $F$ | $p$ value | Partial $\eta^2$ |
|---|---|---|---|---|---|---|---|
| LVM (g) | | | | | | | |
| Baseline | 167.05 ± 53.27 | 187.51 ± 63.04 | 201.70 ± 87.49 | 185.42 ± 70.67 | 3.049 | 0.049[c] | 0.020 |
| Follow-up | 149.46 ± 39.50 | 171.76 ± 55.31 | 208.94 ± 85.89 | 176.72 ± 67.66 | 11.891 | 0.000[a,b,c] | 0.072 |
| Change | −21.61 ± 4.02 | −14.61 ± 3.86 | 10.13 ± 3.93 | −8.70 ± 2.21 | 16.503 | 0.000[b,c] | 0.097 |
| LVMI (g/m$^2$) | | | | | | | |
| Baseline | 92.82 ± 24.00 | 100.00 ± 29.84 | 102.31 ± 33.67 | 98.37 ± 29.62 | 0.741 | 0.477 | 0.005 |
| Follow-up | 84.43 ± 19.05 | 92.31 ± 25.74 | 107.40 ± 32.65 | 94.71 ± 28.00 | 11.909 | 0.000[b,c] | 0.072 |
| Change | −10.33 ± 2.16 | −7.06 ± 2.07 | 6.40 ± 2.11 | −3.66 ± 1.18 | 16.277 | 0.000[b,c] | 0.096 |
| RWT | | | | | | | |
| Baseline | 0.44 ± 0.08 | 0.45 ± 0.07 | 0.44 ± 0.07 | 0.44 ± 0.07 | 1.111 | 0.331 | 0.007 |
| Follow-up | 0.43 ± 0.07 | 0.44 ± 0.07 | 0.46 ± 0.07 | 0.44 ± 0.07 | 1.040 | 0.355 | 0.007 |
| Change | −0.01 ± 0.01 | −0.01 ± 0.01 | 0.02 ± 0.01 | 0.00 ± 0.01 | 3.249 | 0.040[b,c] | 0.021 |
| LVEDV (mL) | | | | | | | |
| Baseline | 100.08 ± 24.15 | 105.96 ± 20.26 | 117.79 ± 42.80 | 107.94 ± 31.47 | 1.954 | 0.143 | 0.013 |
| Follow-up | 93.98 ± 20.61 | 102.20 ± 21.84 | 113.72 ± 39.89 | 103.30 ± 29.86 | 5.619 | 0.004[b,c] | 0.035 |
| Change | −8.98 ± 2.24 | −3.13 ± 2.14 | −2.60 ± 2.18 | −4.91 ± 1.22 | 2.374 | 0.095 | 0.015 |
| LVESV (mL) | | | | | | | |
| Baseline | 35.04 ± 12.01 | 37.62 ± 12.21 | 43.80 ± 31.06 | 38.82 ± 20.74 | 0.776 | 0.461 | 0.005 |
| Follow-up | 32.16 ± 10.41 | 34.74 ± 11.73 | 41.09 ± 27.50 | 36.00 ± 18.60 | 2.645 | 0.073 | 0.017 |
| Change | −4.36 ± 1.23 | −2.70 ± 1.18 | −1.72 ± 1.2 | −2.93 ± 0.67 | 1.106 | 0.332 | 0.007 |
| LVEF (%) | | | | | | | |
| Baseline | 65.22 ± 5.68 | 65.08 ± 6.21 | 64.43 ± 8.00 | 64.91 ± 6.69 | 0.072 | 0.930 | 0.000 |
| Follow-up | 66.56 ± 5.84 | 66.65 ± 6.01 | 65.11 ± 6.92 | 66.11 ± 6.29 | 0.986 | 0.374 | 0.006 |
| Change | 1.55 ± 0.69 | 1.65 ± 0.66 | 0.40 ± 0.67 | 1.20 ± 0.38 | 1.063 | 0.347 | 0.007 |
| $E/e'$ | | | | | | | |
| Baseline | 10.38 ± 3.18 | 10.72 ± 3.60 | 10.67 ± 3.70 | 10.59 ± 3.49 | 0.476 | 0.622 | 0.003 |
| Follow-up | 9.80 ± 2.48 | 10.16 ± 3.10 | 11.16 ± 3.57 | 10.37 ± 3.13 | 5.080 | 0.007[c] | 0.032 |
| Change | −0.52 ± 0.31 | −0.64 ± 0.30 | 0.50 ± 0.30 | −0.22 ± 0.17 | 4.228 | 0.015[b,c] | 0.027 |
| $E/A$ | | | | | | | |
| Baseline | 1.01 ± 0.32 | 1.08 ± 0.37 | 1.08 ± 0.38 | 1.06 ± 0.36 | 0.974 | 0.379 | 0.006 |
| Follow-up | 1.03 ± 0.32 | 1.00 ± 0.33 | 1.09 ± 0.35 | 1.04 ± 0.36 | 2.847 | 0.060 | 0.018 |
| Change | 0.00 ± 0.04 | −0.08 ± 0.04 | 0.03 ± 0.04 | −0.02 ± 0.02 | 2.43 | 0.090 | 0.016 |
| $E$ (cm/s) | | | | | | | |
| Baseline | 75.79 ± 17.78 | 77.83 ± 18.10 | 74.97 ± 21.28 | 76.20 ± 19.10 | 0.654 | 0.521 | 0.004 |
| Follow-up | 75.77 ± 18.20 | 73.88 ± 18.39 | 77.45 ± 20.18 | 75.70 ± 18.94 | 2.311 | 0.101 | 0.015 |
| Change | −0.54 ± 2.00 | −3.84 ± 1.92 | 2.88 ± 1.95 | −0.50 ± 1.10 | 2.648 | 0.073 | 0.027 |
| $A$ (cm/s) | | | | | | | |
| Baseline | 77.28 ± 16.76 | 76.74 ± 22.57 | 73.25 ± 17.01 | 75.76 ± 18.99 | 1.207 | 0.301 | 0.008 |
| Follow-up | 76.87 ± 17.50 | 78.19 ± 21.50 | 73.73 ± 16.44 | 76.26 ± 18.65 | 1.799 | 0.167 | 0.012 |
| Change | −0.57 ± 1.68 | 1.46 ± 1.61 | 0.63 ± 1.64 | 0.51 ± 0.92 | 0.366 | 0.694 | 0.002 |

(Continues)

**TABLE 3** | (Continued)

| | Tertile 1 ($n = 105$) | Tertile 2 ($n = 105$) | Tertile 3 ($n = 105$) | Total ($n = 315$) | $F$ | $p$ value | Partial $\eta^2$ |
|---|---|---|---|---|---|---|---|
| LAV (mL) | | | | | | | |
| Baseline | 25.49 ± 14.24 | 26.76 ± 12.04 | 30.74 ± 16.81 | 27.66 ± 14.62 | 0.654 | 0.520 | 0.004 |
| Follow-up | 27.13 ± 17.08 | 25.00 ± 11.61 | 32.42 ± 17.99 | 28.18 ± 16.07 | 3.992 | 0.019[b,c] | 0.025 |
| Change | 1.11 ± 1.32 | −1.49 ± 1.26 | 1.93 ± 1.28 | 0.52 ± 0.72 | 2.017 | 0.135 | 0.013 |
| LAVi (mL/m$^2$) | | | | | | | |
| Baseline | 13.74 ± 7.59 | 14.02 ± 6.45 | 15.20 ± 7.16 | 14.32 ± 7.09 | 0.327 | 0.721 | 0.002 |
| Follow-up | 15.29 ± 9.23 | 13.47 ± 6.12 | 16.63 ± 7.83 | 15.13 ± 7.91 | 3.738 | 0.025[b,c] | 0.024 |
| Change | 1.28 ± 0.71 | −0.41 ± 0.68 | 1.59 ± 0.69 | 0.82 ± 0.72 | 2.52 | 0.082 | 0.016 |

Baseline and follow-up values are presented as mean ± standard deviation (SD). Changes from baseline to follow-up are expressed as least square mean (LSM) ± standard error of the mean (SEM) based on ANCOVA. The ANCOVA model was adjusted for sex, age, BMI, SBP, DBP, and HR.

Abbreviations: A, trans-mitral late diastolic peak velocity; BMI, body mass index; DBP, diastolic blood pressure; *e′*, peak early diastolic mitral annular velocity; E, trans-mitral early diastolic peak velocity; HR, heart rate; LAV, left atrial volume; LAVi, left atrial volume index.; LVEDV, left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction; LVESV, left ventricular end-systolic volume; LVM, left ventricular mass; LVMI, left ventricular mass index; *n*, number; RWT, relative wall thickness; SBP, systolic blood pressure.

[a]Significant difference between tertiles 1 and 2.

[b]Significant difference between tertiles 2 and 3.

[c]Significant difference between tertiles 1 and 3.

among the three groups. Previous studies in Cushing's syndrome patients have also demonstrated that the reversibility of LV structural changes is not related to post-treatment blood pressure changes [9, 18]. Beyond hypertension, chronic exposure to high cortisol levels is associated with other metabolic abnormalities, including central obesity, insulin resistance, hyperglycemia, and dyslipidemia, all of which may contribute to LV hypertrophy, fibrosis, and fat deposition [23]. In addition to these metabolic factors, the direct effects of cortisol on the cardiovascular system must be considered. The cardiovascular system is a primary target of cortisol, but the pathophysiological mechanisms underlying its direct effects remain complex and not fully elucidated [24]. Cortisol exerts its biological effects primarily through binding to glucocorticoid receptors (GR) and mineralocorticoid receptors (MR), with these effects modulated by 11$\beta$-hydroxysteroid dehydrogenase type 1 (HSD1) and type 2 (HSD2) [25, 26]. 11$\beta$-HSD1 converts inactive cortisone to active cortisol, increasing both circulating and local active cortisol concentrations, while 11$\beta$-HSD2 inactivates cortisol [27–29]. Therefore, the effects of cortisol on target cells are closely linked to the balance between 11$\beta$-HSD1 and 11$\beta$-HSD2 both in circulation and within cells. At physiological levels, cortisol helps maintain cardiac performance by regulating the life cycle of cardiomyocytes, including growth, differentiation, metabolism, and apoptosis [30]. However, excessive levels of glucocorticoids can lead to overactivation of GR, promoting cardiomyocyte hypertrophy [31]. Studies have shown that exposure of rat cardiomyocytes to dexamethasone results in significant increases in cell size and elevated expression levels of hypertrophy markers such as atrial natriuretic factor (ANF), $\beta$-myosin heavy chain ($\beta$-MHC), and skeletal muscle $\alpha$-actin ($\alpha$-SKA), effects that were mitigated by GR antagonists or GR knockdown [32]. Additionally, cortisol can directly activate MR in cardiomyocytes, producing aldosterone-like effects and promoting the progression of LVH [33, 34]. Under physiological conditions, circulating cortisol levels are over 100 times higher than aldosterone levels, with greater affinity for MRs than aldosterone [35]. Furthermore, cortisol has been shown to enhance the effects of noradrenaline and Angiotensin II, thereby promoting LVH by enhancing the sympathetic nervous system and the renin-angiotensin-aldosterone system (RAAS). In addition to its actions on circulating RAAS, cortisol can also activate myocardial tissue RAAS via paracrine pathways, leading to cardiomyocyte proliferation and hypertrophy [36].

Our study also demonstrates that baseline 24 h-UFC levels are independently positively correlated with changes in the E/e′ ratio (ΔE/e′). We, therefore, further investigated alterations in LV diastolic function from baseline to follow-up among patients with varying 24 h-UFC levels. The results indicated no significant changes in the proportion of patients with LV diastolic dysfunction across the three groups from baseline to follow-up. However, in contrast to the groups with lower and moderate cortisol levels, the group with the highest cortisol levels exhibited a trend toward a further increase in the proportion of patients with LV diastolic dysfunction, despite effective blood pressure control. The lack of significant improvement in diastolic function, despite improvements in LVMI and LVEF, may reflect the inherent complexity of diastolic dysfunction. Unlike LV hypertrophy or systolic dysfunction, diastolic dysfunction is often influenced by myocardial stiffness and fibrosis, which are less reversible and may require a longer duration to improve. Previous research has shown that patients with Cushing's syndrome, characterized by excessive cortisol secretion, have a higher prevalence of LV diastolic dysfunction compared to those with essential hypertension [37]. Furthermore, a cross-sectional study in patients with essential hypertension revealed that the prevalence of LV diastolic dysfunction increases with higher DST cortisol levels [11]. Recent studies in patients with type 2 diabetes have also demonstrated a significant positive correlation between plasma cortisol concentration and the E/e′ ratio [38]. The relationship between cortisol levels and LV diastolic dysfunction is not entirely attributable to LVH. Research has indicated that, compared to

healthy subjects and patients with essential hypertension, untreated patients with Cushing's syndrome exhibit significantly increased myocardial fibrosis and more severe LV diastolic dysfunction [8]. Following treatment for Cushing's syndrome, both myocardial fibrosis and LV diastolic function can improve, suggesting that excessive cortisol may promote myocardial fibrosis, thereby contributing to the development of LV diastolic dysfunction. The absence of statistically significant changes in the proportion of patients with LV diastolic dysfunction at the end of follow-up in our study may be due to the relatively small sample size and the insufficient duration of follow-up. Further studies with larger cohorts and longer follow-up periods are warranted to explore these mechanisms in greater depth.

## 5 | Limitations

The limitations of this study should be acknowledged. The relatively small sample size and the considerable variability in the intervals between ultrasound follow-ups among individuals somewhat weaken the strength of the study's conclusions. Moreover, assessing cortisol exposure based on a single 24 h-UFC measurement may not be fully reliable due to daily fluctuations in 24 h-UFC levels [39]. The lack of plasma cortisol measurements limits our ability to further validate cortisol exposure and compare its effects with 24 h-UFC. Furthermore, the study measured only baseline 24 h-UFC levels, without tracking dynamic changes over time. Future larger-scale studies, incorporating both plasma cortisol and dynamic 24 h-UFC measurements, are needed to clarify the independent effects of cortisol levels on changes in LV structure and function in patients with essential hypertension.

## 6 | Clinical Implications

In patients with essential hypertension, a subset experiences further progression of LV remodeling and diastolic dysfunction despite antihypertensive treatment. Identifying factors beyond elevated blood pressure that contribute to LV remodeling is crucial for developing therapies that effectively prevent or reverse this remodeling. Our study suggests an independent association between 24 h-UFC levels and the progression of LV remodeling in hypertensive patients. Even with equally effective blood pressure control, patients with higher 24 h-UFC levels exhibit more pronounced progression of LV remodeling. These findings highlight new potential avenues for the prevention and treatment of LV remodeling in hypertensive patients. Future studies should explore methods to reduce excess cortisol to prevent the development of LV remodeling.

## 7 | Conclusions

Elevated 24 h-UFC levels are independently associated with adverse changes in LV structure and diastolic function in patients with essential hypertension. These findings suggest that cortisol plays a significant role in promoting LV hypertrophy and diastolic dysfunction, beyond the effects of blood pressure. Future research should explore interventions targeting cortisol reduction to prevent or reverse cardiac remodeling in hypertensive patients with elevated cortisol levels.

### Author Contributions

All authors critically reviewed and contributed to the manuscript's intellectual content. Kai-Hang Yiu and Jian-Cheng Xiu were responsible for the study's conception. Gao-Zhen Cao carried out the initial data preparation. Statistical analyses were conducted by Gao-Zhen Cao, with support from Kai-Hang Yiu and Jian-Cheng Xiu, and additional input from Jia-Yi Huang, Run Wang, Cong Chen, and Qing-Shan Lin. Gao-Zhen Cao and Kai-Hang Yiu drafted multiple versions of the manuscript. Kai-Hang Yiu and Jian-Cheng Xiu served as the guarantors of this work, having full access to all the data and assuming responsibility for the integrity of the data and the accuracy of the analysis. All authors have reviewed and approved the final version of the manuscript.

### Ethics Statement

The study was conducted according to the principles of the Declaration of Helsinki and was approved by the ethics committee of the University of Hong Kong-Shenzhen Hospital (Approval No. [2019]309).

### Consent

Written informed consent was obtained from all participants.

### Conflicts of Interest

No potential conflicts of interest relevant to this article were reported.

### Data Availability Statement

The data used in this study are available upon request from the corresponding author Kai-Hang Yiu.

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