Cellular and Molecular Biology

Zhou *et al. Cell. Mol. Biol.*2016, 62 (6): 1-7
ISSN: 1165-158X
doi: 10.14715/cmb/2016.62.6.1

Original Research

Epicardial adipose tissue volume a diagnostic study for independent predicting disorder of circadian rhythm of blood pressure in patients with essential hypertension

L. Zhou[1,2#], Y. Deng[1#], J. Gong[2], X. Chen[2], Q. Zhang[2], J. Wang[2*]

[1] Department of Critical Care Unit, Yancheng First Peoples' Hospital, China
[2] Department of cardiology, Jinling Hospital, Clinical school of medical college, Nanjing University, China

Abstract: The aim of the study was to determine whether epicardial adipose tissue volume (EATV), a new cardiometabolic risk factor, is associated with circadian changes of blood pressure (BP) in patients with newly diagnosed essential hypertension. Ninety patients with newly diagnosed essential hypertension underwent ambulatory blood pressure monitoring for 24 h. EATV was measured using cardiac computed tomography. These patients were categorized into three groups according to their BP patterns (group 1, n=46, dipper hypertension, also called normal pattern; group 2, n=24, non-dipper hypertension; group 3, n=20, anti-dipper hypertension; group 2 and 3 are also called abnormal pattern). Data were collected retrospectively and compared between hypertensive patients with normal pattern and abnormal pattern. The normal pattern hypertensive patient had significant lower mean EATV and BP ((EATV, 91.3±29.4 cm^3) than those of abnormal pattern patients including group 2 (EATV, 116.2±31.06cm^3, P<0.01) and group 3 (EATV, 124.8±28.5cm^3, P<0.01). Mean systolic BP over 24 h (BP_s24) and mean diastolic BP over 24 h (BP_d24) of group 1 (BP_s24, 135.7 ± 12.6 mmHg; BP_d24, 83.6 ± 10.6 mmHg) were significantly lower than those of group 2 (BP_s24, 150.1± 17.6 mmHg, P<0.01; BP_d24, 93.2 ± 16.5 mmHg, P<0.01) and group 3 (BP_s24, 154.1 ± 16.6mmHg, P<0.01; BP_d24, 93.8 ± 17.5 mmHg; P<0.01). Bivariate correlation analysis showed that correlation coefficient of EATV with abnormal blood pressure mode was 0.500 (p< 0.001), partial correlation coefficient after adjustment for waist circumference and body mass index was 0.469 (p< 0.001). When multivariate backward logistic regression analysis was performed to assess the correlation of BP pattern with EAT volume, it showed that the prevalence of abnormal BP pattern (non-dipper and anti-dipper BP pattern) increased by 1.54 times after adjusting for age and gender per additional 10 cm^3 of EAT volume. Receiver operating characteristic curve for EAT alone indicated that the cutoff value of 95.17cm^3 had the best performance in predicting abnormal BP pattern with a sensitivity of 75.0% and a specificity of 72.7%. EATV was elevated in newly diagnosed and untreated patients with non-dipper hypertension and anti-dipper hypertension. EATV measured by cardiac computed tomography can be used to indicate the increased risk of circadian rhythm of blood pressure.

Key words: Epicardial adipose tissue, computed tomography, hypertension, blood pressure monitoring, ambulatory.

Introduction

Ambulatory blood pressure monitoring (ABPM) can provide description in continuous change of blood pressure (BP) more accurately than office BP measurements. The device is worn continuously for 24 h to record both daytime and nighttime blood pressure data. BP has a physiological circadian rhythm (dipper pattern), normallyit is generally lower during the nighttime than the daytime. However, studies by ABPM have demonstrated that normal physiological process of nocturnal reduction in BP is diminished in some patinets (1,2). Blood pressure circadian rhythm disorders were characterized by non-dipper and anti-dipper. Average nocturnal BP falling off less than 10% is defined as a non-dipper BP pattern and average nocturnal BP increasing than daytime is defined as an anti-dipper BP pattern (3). Compared with the dipper BP pattern, the non-dipper and anti-dipper BP pattern are associated with a higher prevalence of adverse cardiovascular events and a poorer prognosis (4,5). Sedentary lifestyle, poor sleep quality, impaired renal function, endocrine disorders and salt-sensitive hypertension are also associated with the non-dipper or anti-dipper BP pattern (6,7).

The prevalence of hypertension is associated with ectopic adipose accumulation in the intrathoracic and epicardial areas (8-10). Epicardial adipose tissue is a new marker of metabolic syndrome and cardiometabolic risk (11-13). Patients with abdominal obesity have altered circadian BP and increased prevalence of non-dipper BP pattern (11,14). Epicardial fat tissue, another form of visceral adiposity, has been proposed as a new cardiometabolic risk factor and the possible association of epicardial fat with hypertension has been shown in some recent studies. It is also suggested that excessive epicardial adipose tissue may be associated with prevalence of hypertension (14), but it remains unclear whether increased EATV alters circadian BP and increases the prevalence of non-dipper or anti-dipper BP pattern. Therefore, the purpose of this study is to investigate the association between EATV and circadian BP changes in patients with newly diagnosed or untreated essential hypertension.

Received November 11, 2015; **Accepted** April 30, 2016; **Published** May 30, 2016

*** Corresponding author:** Jing Wang, Department of cardiology, Jinling Hospital, clinical school of medical college, Nanjing university, Nanjing, 210002, China. Email: wangjing_wj2015@sina.com

[#] Equal contributors

Materials and Methods

Study Population

This study was approved by Yancheng First Peoples' Hospital and written informed consent was obtained from all participants. A total of 90 consecutive patients, who underwent both dual-source computed tomography coronary angiography and ambulatory blood pressure monitoring (ABPM) between October 2011 and June 2014 were enrolled in this study. All patients were older than 18. Patient's medical histories were recorded through a questionnaire. All patients underwent anthropometric measurements and routine laboratory tests, including blood fat and cholesterol, complete blood cell counts, dual-source cardiac CT and 24 h ABPM. These patients were divided into three groups: 24 patients whose mean nighttime BP fall <10% compared with their mean daytime BP were categorized in group 2 (non-dippers) and 20 patients whose mean nighttime BP increased were categorized in group 3 (anti-dipper), and 46 patients whose mean nighttime BP fell ≥10% were categorized in group 1 (dippers). Exclusion criteria were as follows: Patients who had a left ventricular ejection fraction (LVEF) of less than 50%, moderate or severe valvular regurgitation or stenosis, liver disease, cancer, nephropathy (serum creatinine >1.3 mg/dL in women and >1.5 mg/dL in men), thyroid disorders, Obstructive sleep apnea hypopnea syndrome. In addition, none of the patients received BP medication before this study.

Anthropometry and Laboratory Tests

Body mass index (BMI) was defined as weight (in kilograms) divided by the square of height (in meters). Body surface area (BSA), following formula below:
$S(male)=0.0057\times height(cm)+0.0121\times weight(Kg)+0.0882$,
$S(female)=0.0073\times height(cm)+0.0127\times weight(Kg)-0.2106$.

Waist circumference (WC; cm) was recorded as the average of two measurements at the lowest rib and at the iliaccrest, with the subject standing at midpoint. Total cholesterol (TC), triglycerides (TG), low-density lipoprotein cholesterol (LDL-c), and high-density lipoprotein cholesterol (HDL-c), glucose, and hemoglobin levels were assayed by using routine laboratory techniques. Metabolic syndrome was defined according to the adult treatment panel III criteria. The patients were diagnosed with metabolic syndrome (MS) if they met three or more of the following five items (15,16): (i) waist circumference (WC) >90 cm in men or >80 cm in women; (ii) triglycerides >150 mg/dL; (iii) HDL <40 mg/dL in men or <50 mg/dL in women; (iv) BP >130/85 mm Hg or had been diagnosed as hypertesion; and (v) fasting blood glucose (FG) >110 mg/dL. The coefficients of variation were less than 5% for every measurement.

CT angiography and image analysis

CT examinations were performed using a 64-slice dual-source Cardiac CT scanner (Somatom Denition, Siemens Medical Solutions, Forchheim, Germany) using two X-ray sources for image generation. With two tubes and two detectors mounted at the orthogonal orientation in the gantry, the transmission data required for reconstruction of one slab can be acquired in half the time needed by a conventional multislice computed tomography (MSCT) system. The scanning volume was defined as the area from the carina to the diaphragm. A gantry rotation time of 0.33 s, therefore resulted in a temporal resolution of 83 ms. The tube voltage for CT-angiography was 120 kV for both tubes, with the current of 350 mAs, gantry rotation time of 0.33 s and pitch of 0.20-0.43 adapted to the heart rate, and collimation of 64 × 0.6 mm. Contrast agent (80 ml, 370 mg I/ml, Ultravist, Schering, Berlin, Germany) was injected at a constant rate of 5 ml/s, followed by flushing with 40 ml of normal saline. The CT value of the area of interest at the root of ascending aorta was monitored since the beginning of contrast injection. The radiation dose for scan in this study was 2.7 mSv on average. Image reconstruction was performed using the CardIQ image analysis software program (Siemens Healthcare) on a dedicated computer workstation (Advantage Workstation Ver.4.2, Siemens Healthcare).

Epicardial adipose tissue quantification

The amount of EAT volume was measured by two independent observers using a commercially available software tool (Volume, Siemens Healthcare) based on attenuation dependent segmentation methods (Fig. 1). For preventing recall bias, the quantification of EAT was performed on different days in random order by each observer who was blinded to the results. Observers manually traced the epicaridium from its superior extent (lower surface of left pulmonary artery origin) to the end of the ventricular apex interpolating slices of 5-10mm thickness which defined the extent of the epicaridial volume, and all extra epicardial tissues were excluded (17,18). The software automatically interpolated between the user-defined traces. Automatically traced contours were manually adjusted to the epicaridium if needed. The EATV was defined as any adipose tissue

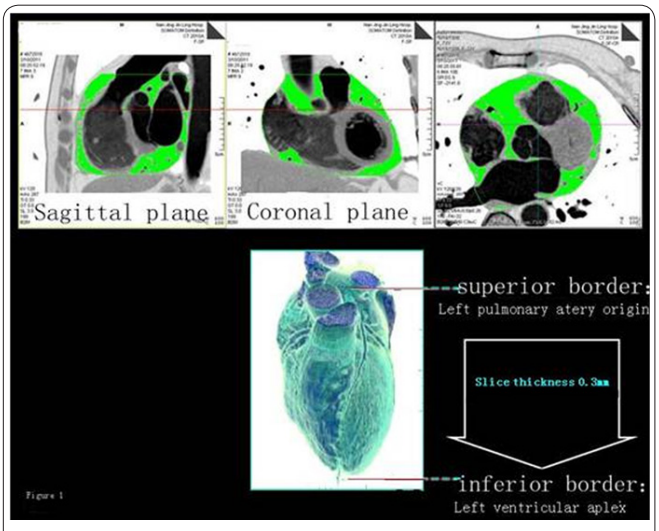

Figure 1. Total epicardial adipose tissue volume(EATV) measurements on 64-slice Dual-CT. A region of interest (ROI) is manually placed along the visceral pericardium and EAT was extracted on an axial image (blue). 3D image: EAT area is measured on each axial image from the lower surface of left pulmonary artery origin to the left ventricular apex and total EAT volume is obtained from Volume Analysis software at a dedicated workstation(Syngo MMWP, Siemens, Germany).

located within the pericaridial sac (13,19). A predefined threshold of -250HU to -30HU was used to identify voxels corresponding to fat (20).

Ambulatory Blood Pressure Monitoring (ABPM)

Ambulatory blood pressure monitoring was performed with a non-invasive recorder, the Tracker NIBP2 (Ambulatory Blood Pressure Monitor TM-2430, Japan) for 24 h typical daily activity. Blood pressure readings were obtained automatically at 15 min intervals from 6 am to 11 pm and at 30 min intervals from 11 pm to 6 am. Mean systolic and diastolic BPs over 24 h (BPs 24 and BPd 24), mean systolic and diastolic BPs during the daytime (BPs daytime and BPd daytime), and mean systolic and diastolic BPs during the nighttime (BPs nighttime and BPd nighttime) were recorded. Awake and asleep periods were determined from the patient's diaries (Most patients match the definition based on fixed day and night intervals (e.g. daytime defined as 0600-2200 h and night-time as 2200-0600 h),). Essential hypertension was considered present if the mean daytime BP was higher than 135/85 mm Hg and the mean nighttime BP was above 120/75mm Hg, according to criteria stated in The Seventh Report of the Joint National Committee (21). A 24 h mean BPs >125 mm Hg or a 24 h mean BPd >80 mm Hg was used to exclude white coat hypertension (22). Daytime, nighttime, and 24 h average heart rates (HRs) (HR daytime, HR nighttime, and HR 24h) were also recorded.

Statistical Analysis

Statistical analysis was performed with commercially available statistical software (SPSS for Windows version 19.0 SPSS Inc., Chicago, IL, USA). Continuous quantitative variables were expressed as mean ± standard deviation (SD). Comparison between two groups (eg.,dipper vs non or antifipper) been done using t-test .$\chi 2$ test was used for categorical variables. Multiple comparison was carried out using one-way analysis of variance (ANOVA), followed by SNK test among groups. Two factors correlation and partial correlation analysis was used for correlation analysis, diagnosis consistency used kappa test. Multivariate stepwise logistic regression analysis was performed to assess the parameters that are associated with a non-dipper BP pattern. The presence of abdominal obesity (male> 90cm, female> 80cm defined 1; otherwise defined 0), LDL-cholesterol, EATV (with per additional 10 cm^3 of EAT volume, increased prevalence of abnormal BP pattern) and BMI etc, were included as the covariates in the multivariate regression model. The sensitivity and specificity of the cut-off value of EATV to detect the abnormal BP pattern were estimated by receiver operating characteristic (ROC) curve analysis. A P value < 0.05 was considered as statistically significant.

Results

Baseline demographic properties of the study subjects are listed in Table 1. The mean age of the study population was 48.7 ± 5.8 years and the mean BMI was 24.7± 3.7kg/m^2. Patients in each group were similar with regard to age, gender, smoking status, BMI, FG level, and fasting lipid profile and left ventricular ejection fraction. In addition, the incidences of MS were similar among three groups (P =0.13). Non-dipper and anti-dipper were grouped as abnormal pattern because there was no significant difference between them.

The ambulatory blood pressure monitoring parameters and left ventricular ejection fraction (LVEF) are shown in Table 2. The normal pattern hypertensive patient had significant lower mean EATV and BP ((EATV, 91.3±29.4 cm^3) than those of abnormal pattern patients including group 2 (EATV, 116.2±31.06cm^3, P<0.01) and group 3 (EATV, 124.8±28.5cm^3, P<0.01). The mean Waist of abnormal BP groups (group 2 and 3) were significantly greater than that of group 1(93.1±8.21cm vs 89.1± 5.4cm, P=0.01). The mean BMI of abnormal BP groups was similar with group 1(24.9±3.1Kg/m2 vs. 24.5±3.7 Kg/m2, P =0.60). The BPs24 (group1 vs abnormal BP groups, 135.7 ±12.6mmHg vs 152.0 ±16.4mmHg, P<0.001) and the BPd24 (group1 vs abnor-

Table 1. Baseline demographic characteristics of the study population.

Characteristics	Dippers (n = 46)	Non-dippers (n = 24)	anti-dippers (n=20)	abnormal pattern(n=44)	a*P*	aa*P*	*P*-value
Age (y)	46.9 ± 6.0	50.1 ± 5.8 a	51.3 ± 3.4 a	50.3±4.9 a	0.1	0.01	0.02
Gender (% male)	56.5	62.5	55.0	59.1	0.31	0.56	0.48
Smoking (%)	54.3	53.8	60.0	59.1	0.68	0.40	0.59
BMI (kg/m^2)	24.5±3.7	24.6±4.0	25.7±3.5	24.9±3.1	0.74	0.46	0.60
WC (cm)	89 .1± 5.4	94.5 ± 8.23 a	91.5 ± 8.31	93.1±8.21 a	0.001	0.1	0.01
MS ATP-III (%)	54.3	66.6	70.0	68.2	0.20	0.08	0.13
BSA	1.86±0.42	1.92±0.33a	1.95±0.47a	1.94±0.51a	0.001	0.002	0.001
CHD(%)	58.7	62.5	65.0	63.6	0.55	0.42	0.39
Total cholesterol (mmol/L)	5.5 ± 1.0	5.7± 1.0	5.41 ± 1.1	5.5±1.10	0.46	0.88	0.50
LDL-cholesterol (mmol/L)	3.5± 0.9	3.6 ± 0.8	3.7 ± 0.8	3.7±0.8	0.48	0.72	0.59
HDL-cholesterol (mmol/L)	1.3 ± 0.4	1.2 ± 0.3	1.2 ± 0.3	1.2±0.3	0.36	0.41	0.20
Triglyceride (mmol/L)	1.5 ± 0.6	1.6 ± 0.8	1.6 ± 0.8	1.6±0.8	0.74	0.68	0.46
FG (mmol/L)	5.2 ± 0.3	5.3 ± 0.3	5.2 ± 0.3	5.2±0.3	0.77	0.81	0.36

Abbreviations: BMI: body mass index; BSA:body surface area .WC: waist circumference; MS ATP-III: metabolic syndrome according to adult treat-ment panel; LDL: low-density lipoprotein; HDL: high-density lipoprotein; FG: fasting glucose; a P<0.05, compared to Dippers; aa P<0.05, anti-dippers compared to Dippers; b P<0.05.

Table 1. Echocardiographic characteristics and ambulatory blood pressure measurements of the study population.

Characteristics	Dippers (n = 46)	Non-dippers (n= 24)	anti-dipper (n=20)	abnormal pattern	*P*-value
EATV (cm^3)	91.3±29.4	116.2±31.06a	124.8±28.5a	120.6±27.4a	<0.001
EATVI(cm^3/m^2)	57.9±16.7	74.6±17.7 a	78.6±15.7 a	76.4±18.1 a	<0.001
LVEF (%)	64 .0± 2.1	66.0 ± 2.8	63.0 ± 2.7	65.0±3.8	0.38
HR daytime	85.3 ± 11.3	86.7 ± 11.1	87.5 ± 13.1	87.0±12.1	0.47
BPs daytime (mm Hg)	143.7 ± 13.1	151.5 ± 16.9	152.5 ± 15.9	152.0±16.5	0.06
BPd daytime (mm Hg)	90.2 ± 11.2	95.5 ± 16.3	93.5 ± 15.3	94.5±15.8	0.10
HR nighttime	74.9 ± 12.2	75.1 ± 12.7	76.1 ± 12.7	75.5±12.8	0.12
BPs nighttime(mm Hg)	124 .1± 10.8	149.2± 6.3a	155.9±12.4a	$152.0±15.3_a$	<0.001
BP_d nighttime(mm Hg)	75.8 ± 9.8	92.4 ± 17.8a	94.4 ± 15.8a	93.4±16.8a	<0.001
24 h mean HR	81 .2± 10.9	81.6± 11.5	82.8 ± 12.5	82.3±12.0	0.77
24h mean BPs (mmHg)	135.7 ± 12.6	150.1 ± 17.6a	154.1 ± 16.6a	152.0 ±16.4a	<0.001
24h mean BP_d(mmHg)	83.6 ± 10.6	93.2 ± 16.5a	93.8 ± 17.5a	93.5± 17.2a	0.012
NBPDR(%)	13.71±2.31	7.26±1.93 a	-3.71±2.16 ab	----------	<0.001

Abbreviations: EATV: epicardial adipose tissue volume; EATV: EATV/BSA;LVEF: ejection fraction; HR: heart rate; BPs: systolic blood pressure; BPd: diastolic blood pressure;NBPDR: nocturnal blood pressure drop rate. a*P*<0.05, compared to Dippers; b*P*<0.05, compared to Non-dippers.

mal BP groups, 83.6 ± 10.6mmHg vs 93.5±17.2mmHg, P=0.012) of abnormal BP groups were significantly higher compared with group 1. Meanwhile, the abnormal BP groups also had significantly higher BPs nighttime (152±15.3mmHg vs. 124.1± 10.81mmHg, P<0.001) and BPd nighttime (93.4±16.8 mmHg vs. 75.8 ± 9.8 mmHg, P<0.001). Besides, thenighttime blood pressure decrease rate had statistically significant differences in three groups. BPs daytime and Bpd daytime were higher in abnormal BP groups than those of group 1, but there is no statistically significant differences. 24h heart rate, HR daytime, and HR nighttime were also similar between group 1 and abnormal BP groups.

Results of multivariate analyses were shown in Table 3. Bivariate correlation analysis showed that correlation coefficient of EATV with abnormal blood pressure mode was 0.500 (p < 0.001), partial correlation coefficient after adjustment for waist circumference and body mass index was 0.469 (p < 0.001). Multivariate logistic regression analysis was applied to evaluate the association of anthropometric data, BMI and metabolic syndrome with increased prevalence of abnormal BP pattern (non-dipper and anti-dipper BP pattern). Age for 1 year, EATV for 10 ml. Model and variable according to the following method, Model 1 : X (explenatory variables) =Age, Gender, MS (NCEPATP3); Model 2 : Age, gender, BMI (>25); Model 3 : Age, gender, WC male>90cm and female>80cm defined 1;otherwise defined 0).; Model 4 : Age, gender, EAT (for 10 cm^3 increase), prevalence of abnormal BP pattern (non-dipper and anti-dipper BP pattern) increased by 1.54 times after adjusting for age, gender.

Table 3. Multivariate logistic regression analysis.

	OR(95%CI)	P
Model 1		
Age	0.99(0.90-1.08)	0.77
Gender	1.07(0.43-2.69)	0.88
MS	1.77(0.70-4.48)	0.23
Model 2		
Age	0.96(0.89-1.03)	0.27
Gender	1.17(0.48-2.86)	0.74
BMI	1.68(0.69-4.09)	0.25
Model 3		
Age	0.96(0.89-1.04)	0.31
Gender	1.47(0.55-3.90)	0.44
WC	1.60(0.59-4.36)	0.36
Model 4		
Age	0.98(0.90-1.06)	0.60
Gender	1.10(0.39-3.10)	0.86
EATV	1.54(1.25-1.89)	<0.01

OR refers to 1unit variation of covariates; CI, confidence interval; Abbreviations: EATV: epicardial adipose tissue volume; BMI: body mass index; WC: waist circumference; MS ATP-III: metabolic syndrome according to adult treatment panel; LDL: low-density lipoprotein.

Figure 2 showed ROC curves of logistic regression analysis for BMI, MS and EATV in predicting abnormal BP pattern (non-dipper hypertension and anti-dipper

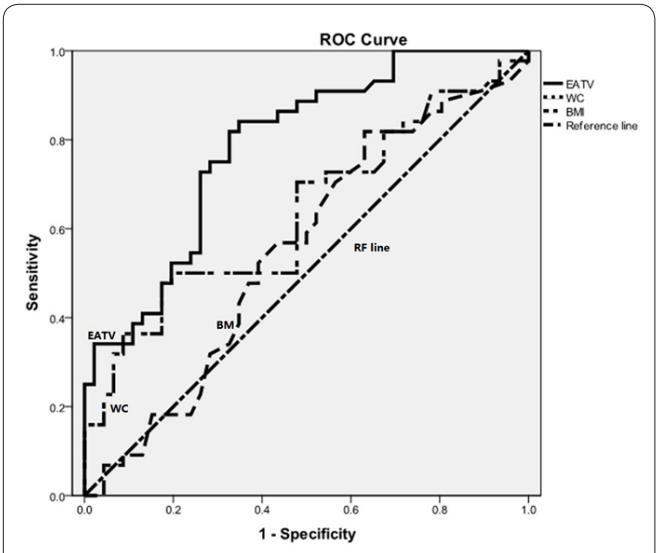

Figure 2. Receiver operating characteristic curves of body mass index(BMI), Waist circumference(WC) and epicardial adipose tissue Volume(EATV) in predicting abnormal BP pattern.

hypertension). The area under the curve for BMI was 0.56 (0.45–0.69), P = 0.28. The area under the curve for WC was 0.64 (0.60–0.81), P =0.02. The area under the curve for EATV was 0.78 (0.69–0.88), P < 0.01. According to the ROC curve for EATV alone, the cutoff value of 95.17 cm^3 had the best performance in predicting abnormal BP pattern (non-dippers hypertension and anti-dipper hypertension), with a sensitivity of 75.0% and a specificity of 72.7%. The diagnosis of abnormal blood pressure patterns for threshold value of 95.17 cm^3, the kappa value was 0.467, positive predictive value was 0.75, and negative predictive value was 0.717.

Discussion

To our knowledge, we first reported EATV was significantly higher in hypertensive patients with abnormal BP pattern than in those with normal BP pattern. It was found that EATV was independently associated with abnormal BP pattern (non-dipper hypertension and anti-dipper hypertension), indicating an increased risk of non-dipper or anti-dipper hypertension-related target organ damage and adverse cardiovascular events. The relationship between hypertension and excess body weight had long been recognized in several studies (23,24). Individuals with abdominal obesity had an increased risk for hypertension, however, excess adipose has traditionally been found in intra-abdominal organs such as the liver and in subcutaneous tissue (16,25,26). Based upon our findings, patients with increased EATV measured by Dual-CT may be in higher risk of an abnormal BP pattern (non-dipper hypertension and anti-dipper hypertension). These individuals we presumed may also represent an increased target organ damage and cardiovascular risk (27,28).

There are growing evidences that adipocyte-derived factors originating outside of the heart are capable of affecting vascular homeostasis (29,30). It stores triglyceride to supply free fatty acids for myocardial energy production and produce adipokines. Epicardial adipose tissue and myocardium share the same microcirculation (30). In addition, epicardial adipose is an active organ that produces several proinflammatory and proatherogenic cytokines such as angiotensinogen, angiotensin and Neuropeptide Y(NPY) (31,32). Sympathetic nervous excitement at night increased blood pressure mainly through the following channels: (1) To excite α receptor, the small artery contraction, increase peripheral resistance; shrink vein, increase the backflow of blood volume; (2) Excited heart β receptor, increased heart rate, increased cardiac output; (2) Activation of the RAS system directly or indirectly, Promoted Ang II generation and aldosterone secretion. Therefore, epicardial adipose tissue and other visceral fat may play a role in the pathogenesis of hypertension (33). An animal study reported that the maximum rate of fatty acid release was significantly higher in epicardial adipose tissue than that in the pericardial, perirenal and popliteal depots (34). As we all know, sympathetic nerve goes through and immerses in the epicardial adipose. Sensory nerves innervating the arterial wall are predominantly found in the adventitial layer (35). These nerves have been shown to be associated with unique microvasculature in the adventitia. Manzella et al (34,36) found that the rate of fatty acid released by epicardial adipose tissue was approximately twice that of the pericardial and perirenal depots, and toxic levels of free fatty acids may stimulate the activity of cardiac autonomic nervous system through an increased catecholamine concentration in plasma. Furthermore, Bambace et al (37) reported that adiponectin mRNA expression was lower in epicardial adipose than that in peritoneal and subcutaneous fat. Kremen et al (29) also found the expression of adiponectin was lower in epicardial adipose than omental fat, but mRNA expressions of resistin and other adipocytokines were higher than that in omental fat. The production of epicardial adipose tissue-derived adiponectin was also decreased in patients with hypertension (38). Besides, the data from Della Mea's lab (39) proved that non-dipper essential hypertensive patients had more prominent insulin resistance and lower adiponectin compared to dippers, suggesting epicardial adipose may be more closely related to obesity related hypertension. Given all these observation, high levels of free adiposety acid and reduced adiponectin may be related to non-dipping hypertension because they may cause autonomic dysfunction and sympathetic overactivity. It has been known that many patients with hypertension are associated with MS, so insulin resistance may also play a driving role in the formation of abnormal BP pattern to some extent. All of the above were well-known mechanisms of the abnormal BP pattern (non-dipper and anti-dipper) (40).

Epicardial accumulation of excessive adipose is a metabolic marker for cardiac risk. Fallo et al (41) reported that high prevalence of visceral adipose was associated with insulin resistance and low adiponectin levels in essential hypertensive patients with a non-dipper profile. Furthermore, recently reported that epicardial adipose tissue correlated with endothelial dysfunction (42,43) independent of traditional risk factor. Our patients in three groups did not significantly differ in MS and BMI. However, the mean EATV of the abnormal BP pattern group was greater than that of the dipper group. In the multivariate logistic regression analysis, EATV was the variable significantly associated with the abnormal BP pattern. Adipocytokines (such as leptin) can activate sympathetic nerve system in the brain (44). The demonstration of EATV as a novel risk factor/indicator of the non-dipper BP pattern may be clinically promising.

So far, the mechanism of the abnormal BP pattern still remains unclear. Endocrine system dysfunction, increased sympathetic tone, lack of exercises, and salt-sensitive hypertension are involved in the pathogenesis of the non-dipper BP pattern. Patients with obesity, diabetes mellitus and insulin resistance have an increased prevalence of the non-dipper BP pattern (33). Tartan et al (45) also reported a higher frequency of the MS in non-dippers than in dippers. In our study, the frequency of MS, BMI and fasting serum lipid levels was similar among three groups. However, due to the small sample size, larger sample size was required for the next step research. Many studies have demonstrated that the non-dipper BP pattern was associated with target organ damage whether the individual was hypertensive or normotensive. Cuspidi et al (46) studied never-treated hypertensive patients who had been diagnosed for less

than 1 year and found that the prevalence of left ventricular hypertrophy was highest among individuals with the non-dipper BP pattern. Therefore, the early detection of a non-dipper and anti-dipper BP pattern through detection of above-average EATV may help to identify high-risk individuals for target organ damage of hypertension.

Study Limitations

We acknowledge that there are limitations in our study. Firstly, this was a cross-sectional, pivotal study that included a small number of patients; therefore, our findings should be replicated in a larger population before they are translated into clinical practice. The non-dipper BP pattern can also be caused by daytime inactivity and poor sleep quality; however, these variables were not examined in our study. In addition, clinical parameter of left Ventricular diastolic function failed to be collected and these patients were not followed up. It may be very interesting to further investigate if patients would benefit from good control of BP and/or lipid-lowering therapy. Lastly, our results were merely statistical corrrelated, we cannot rule out that higher epicardial fat is the consequence rather than the cause of non-dipper status, causal inference needs support of inflammatory factor data from epicardial adipose tissue.

In summary, we found that larger EATV had a higher prevalence of the abnormal BP pattern in newly diagnosed untreated hypertensive patients; For confirmation, a larger, prospective, epidemiological study may be conducted to further demonstrate the use of EATV to assess the prevalence of abnormal (non-dipper and anti-dipper) BP pattern and the target organ damage related to the abnormal BP pattern.

Acknowledgements

This study was supported by the "Six Peaks of The Talented in Jiangsu Province".

References

1. Verdecchia P, Schillaci G, Porcellati C, Dippers versus non-dippers. J Hypertens Supplement: official journal of the International Society of Hypertension. 1991, 9: 42-44.

2. Mahabala C, Kamath P, Bhaskaran U, Pai N D, Pai A U. Antihypertensive therapy: nocturnal dippers and nondippers. Do we treat them differently? Vascular health and risk management. 2013, 9: 125-33.

3. Cuspidi C, Sala C, Valerio C, Negri F, Mancia G, Nocturnal hypertension and organ damage in dippers and nondippers. Am J Hypertens. 2012, 25: 869-875.

4. Pickering T. The clinical significance of diurnal blood pressure variations. Dippers and nondippers. Circulation. 1990, 81: 700-702.

5. Coleman C T, Stowasser M, Jenkins C, Marwick T H, Sharman J E, Central hemodynamics and cardiovascular risk in nondippers. J Clin Hypertens. 2011, 13: 557-562.

6. Huang Y, Mai W, Hu Y, Wu Y, Song Y, et al. Poor sleep quality, stress status, and sympathetic nervous system activation in nondipping hypertension. Blood Press Monit. 2011, 16: 117-123.

7. Javaheri S, Redline S, Sleep Slow-Wave Sleep, and Blood Pressure. Curr Hypertens Rep. 2012, 14: 442-448.

8. Sacks H S, Fain J N, Human epicardial adipose tissue: a review. Am Heart J 2007, 153: 907-917.

9. Ding J, Hsu F C., Harris T B., Liu Y, Kritchevsky S B, et al. The association of pericardial fat with incident coronary heart disease: the Multi-Ethnic Study of Atherosclerosis (MESA). Am J Clin Nutr. 2009, 90: 499-504.

10. Wang J, Wang L, Peng Y, Zhang L, Jiang S, et al. Association of pericardial adipose tissue volume with presence and severity of coronary atherosclerosis. Clinical and investigative medicine Medecine clinique et experimentale. 2012, 36: E143-E143.

11. Sironi A M, Pingitore A, Ghione S De, Marchi D, Scattini B, et al. Early hypertension is associated with reduced regional cardiac function, insulin resistance, epicardial, and visceral fat. Hypertension. 2008, 51: 282-288.

12. Iacobellis G, Ribaudo M C, Assael F, Vecci E, Tiberti C, et al. Echocardiographic epicardial adipose tissue is related to anthropometric and clinical parameters of metabolic syndrome: a new indicator of cardiovascular risk. J Clin Endocr Metab. 2003, 88: 5163-5168.

13. Wang C P, Hsu H L, Hung W C, Yu T H, Chen Y H, et al. Increased epicardial adipose tissue (EAT) volume in type 2 diabetes mellitus and association with metabolic syndrome and severity of coronary atherosclerosis. Clin Endocrinol. 2009, 70: 876-882.

14. Sengul C, Cevik C, Ozveren O, Duman D, Eroglu E, et al. Epicardial fat thickness is associated with non-dipper blood pressure pattern in patients with essential hypertension. Clin Exp Hypertens. 2012, 34: 165-170.

15. Eckel R H, Grundy S M, Zimmet P Z, The metabolic syndrome. The Lancet. 2005, 365: 1415-1428.

16. Hall J E, Hildebrandt D A, Kuo J, Obesity hypertension: role of leptin and sympathetic nervous system&ast. Am J Hypertens. 2001, 14: 103-115.

17. Gorter P M, van Lindert A S, de Vos A M, Meijs M F, van der Graaf Y, et al. Quantification of epicardial and peri-coronary fat using cardiac computed tomography; reproducibility and relation with obesity and metabolic syndrome in patients suspected of coronary artery disease. Atherosclerosis. 2008, 197: 896-903.

18. Nichols J H, Samy B, Nasir K, Fox C S, Schulze P C, et al. Volumetric measurement of pericardial adipose tissue from contrast-enhanced coronary computed tomography angiography: a reproducibility study. J Cardiovasc Comput. 2008, 2: 288-295.

19. Sarin S, Wenger C, Marwaha A, Qureshi A, Go B D, et al. Clinical significance of epicardial fat measured using cardiac multislice computed tomography. Am J Cardiol. 2008, 102: 767-771.

20. Alexopoulos N, McLean D S, Janik M, Arepalli C D, Stillman A E, et al. Epicardial adipose tissue and coronary artery plaque characteristics. Atherosclerosis. 2010, 210: 150-154.

21. Chobanian A V, Bakris G L, Black H, R, Cushman W C, Green L A, et al. Seventh report of the joint national committee on prevention, detection, evaluation, and treatment of high blood pressure. Hypertension. 2003, 42: 1206-1252.

22. O'Brien E, Asmar R, Beilin L, Imai Y, Mallion J M, et al. European Society of Hypertension recommendations for conventional, ambulatory and home blood pressure measurement. J Hypertens. 2003, 21: 821-848.

23. KANNEL W B, BRAND N, SKINNER J J, DAWBER T R, MCNAMARA P M, The relation of adiposity to blood pressure and development of hypertension The Framingham Study. Ann Intern Med. 1967, 67: 48-59.

24. Chiang B N, Perlman L V, Epstein F H, Overweight and Hypertension A Review. Circulation. 1969, 39: 403-421.

25. Goodfriend T L, Calhoun D A, Resistant hypertension, obesity, sleep apnea, and aldosterone theory and therapy. Hypertension. 2004, 43: 518-524.

26. Murakami K, Wada J, Ogawa D, Horiguchi C S, Miyoshi T, et al. The effects of telmisartan treatment on the abdominal fat depot in patients with metabolic syndrome and essential hypertension:

Abdominal fat Depot Intervention Program of Okayama (ADIPO). Diabetes Vasc Dis Re. 2013, 10: 93-96.
27. Parati G, Pomidossi G, Albini F, Malaspina D, Mancia G, Relationship of 24-hour blood pressure mean and variability to severity of target-organ damage in hypertension. 1987, J Hypertens. 5: 93-98.
28. Julius S, Jamerson K, Mejia A, Krause L, Schork N, et al. The association of borderline hypertension with target organ changes and higher coronary risk. JAMA-J Am Med Assoc. 1990, 264: 354-358.
29. Mazurek T, Zhang L, Zalewski A, Mannion J D, Diehl J T, et al. Human epicardial adipose tissue is a source of inflammatory mediators. Circulation. 2003, 108: 2460-2466.
30. Iacobellis G, Corradi D, Sharma A M, Epicardial adipose tissue: anatomic, biomolecular and clinical relationships with the heart. Nat Clin Pract Card. 2005, 2: 536-543.
31. Wu F Z, Huang Y L, Wang Y C, Lin H S, Chen C S., et al. Impact of Location of Epicardial Adipose Tissue, Measured by Coronary Artery Calcium-Scoring Computed Tomography on Obstructive Coronary Artery Disease. Am J Cardiol. 2013, 112(7): 943-949.
32. Raggi P, Epicardial Adipose Tissue as a Marker of Coronary Artery Disease Risk. J Am Coll Cardiol. 2013, 61: 1396-1397.
33. Kotsis V, Stabouli S, Bouldin M, Low A, Toumanidis S, et al. Impact of obesity on 24-hour ambulatory blood pressure and hypertension. Hypertension. 2005, 45: 602-607.
34. Marchington J M, Mattacks C A, Pond C M. Adipose tissue in the mammalian heart and pericardium: structure, foetal development and biochemical properties. Comparative Biochemistry and Physiology Part B: Comparative Biochemistry. 1989, 94: 225-232.
35. Jansen O I, Gulbenkian S, Valenca A, Antunes J, Wharton J, et al. The peptidergic innervation of the human superficial temporal artery: immunohistochemistry, ultrastructure, and vasomotility. Peptides. 1995, 16: 275-287.
36. Manzella D, Barbieri M, Rizzo M R, Ragno E, Passariello N, et al. Role of free fatty acids on cardiac autonomic nervous system in noninsulin-dependent diabetic patients: effects of metabolic control. J Clin Endocr Metab. 2001, 86: 2769-2774.
37. Bambace C, Telesca M, Zoico E, Sepe A, Olioso D, et al. Adiponectin gene expression and adipocyte diameter: a comparison between epicardial and subcutaneous adipose tissue in men. Cardiovasc Pathol. 2011, 20: 153-156.
38. Teijeira F E, Eiras S, Grigorian S L, Fernandez A, Adrio B, et al. Epicardial adipose tissue expression of adiponectin is lower in patients with hypertension. J hum hypertens. 2008, 22: 856-863.
39. Della M P, Lupia M, Bandolin V, Guzzon S, Sonino N, et al. Adiponectin, insulin resistance, and left ventricular structure in dipper and nondipper essential hypertensive patients. Am J Hypertens. 2005, 18: 30-35.
40. Kanbay M, Turgut F, Erkmen U M, Akcay A, Covic A, Causes and mechanisms of nondipping hypertension. Clin Exp Hypertens. 2008, 30: 585-597.
41. Fallo F, Dalla P A, Sonino N, Federspil G, Ermani M, et al. Nonalcoholic fatty liver disease, adiponectin and insulin resistance in dipper and nondipper essential hypertensive patients. J Hypertens. 2008, 26: 2191-2197.
42. Girerd N, Scridon A, Bessière F, Chauveau S, Geloen A, et al. Periatrial Epicardial Fat Is Associated with Markers of Endothelial Dysfunction in Patients with Atrial Fibrillation. PloS one. 2013, 8: 271-272.
43. Gaborit B, Kober F, Jacquier A, Moro P J, Flavian A, et al. Epicardial fat volume is associated with coronary microvascular response in healthy subjects: a pilot study. Obesity. 2012, 20: 1200-1205.
44. Gu P, Xu A, Interplay between adipose tissue and blood vessels in obesity and vascular dysfunction. Rev in Endocr Metab Dis. 2013, 14:49-58.
45. Tartan Z, Uyarel H, Kasikcioglu H, Alper A T, Ozay B, et al. Metabolic syndrome as a predictor of non-dipping hypertension. Tohoku J Exp Med. 2006, 210: 57-66.
46. Cuspidi C, Meani S, Salerno M, Valerio C, Fusi V, et al. Cardiovascular target organ damage in essential hypertensives with or without reproducible nocturnal fall in blood pressure. J Hypertens. 2004, 22: 273-280.