Medicine®

OBSERVATIONAL STUDY

OPEN

Association of Increased Epicardial Adipose Tissue Thickness With Adverse Cardiovascular Outcomes in Patients With Atrial Fibrillation

Chun-Yuan Chu, MD, Wen-Hsien Lee, MD, Po-Chao Hsu, MD, PhD, Meng-Kuang Lee, MD, Hung-Hao Lee, MD, Cheng-An Chiu, MD, Tsung-Hsien Lin, MD, PhD, Chee-Siong Lee, MD, Hsueh-Wei Yen, MD, Wen-Chol Voon, MD, Wen-Ter Lai, MD, Sheng-Hsiung Sheu, MD, and Ho-Ming Su, MD

Abstract: The thickness of epicardial adipose tissue (EAT) was reported to be highly associated with the incidence and severity of atrial fibrillation (AF). This study was conducted to analyze the ability of EAT thickness in predicting adverse cardiovascular (CV) events in AF.

In 190 persistent AF patients, we performed a comprehensive transthoracic echocardiographic examination with assessment of EAT thickness. The definition of CV events included CV mortality, hospitalization for heart failure, myocardial infarction, and stroke.

There were 69 CV events including 19 CV deaths, 32 hospitalizations for heart failure, 3 myocardial infarctions, and 15 strokes during a mean follow-up of 29 (25th–75th percentile: 17–36) months. The multivariable analysis demonstrates that chronic heart failure, increased left ventricular (LV) mass index and the ratio of transmitral E-wave velocity to early diastolic mitral annulus velocity, decreased body mass index, and increased EAT thickness (per 1-mm increase, odds ratio 1.224, 95% confidence interval [CI] 1.096–1.368, $P < 0.001$) were associated with adverse CV events. Additionally, the addition of EAT thickness to a model containing CHA_2DS_2-VASc score, left atrial volume index, and LV systolic and diastolic function significantly improved the values in predicting CV events (global χ^2 increase 14.65, $P < 0.001$ and integrated discrimination improvement 0.10, 95% CI 0.04–0.16, $P < 0.001$).

In AF, EAT thickness was useful in predicting adverse CV events. Additionally, EAT thickness could provide incremental value for CV outcome prediction over traditional clinical and echocardiographic parameters in AF.

Editor: Leonardo Roever.
Received: August 10, 2015; revised: November 16, 2015; accepted: January 28, 2016.
From the Faculty of Medicine, College of Medicine (C-YC, W-HL, P-CH, T-HL, C-SL, H-WY, W-CV, W-TL, S-HS, H-MS); Division of Cardiology, Department of Internal Medicine, Kaohsiung Medical University Hospital (C-YC, W-HL, P-CH, M-KL, H-HL, C-AC, T-HL, C-SL, H-WY, W-CV, W-TL, S-HS, H-MS); and Department of Internal Medicine, Kaohsiung Municipal Hsiao-Kang Hospital, Kaohsiung Medical University (W-HL, M-KL, H-MS), Kaohsiung, Taiwan.
Correspondence: Ho-Ming Su, MD, Department of Internal Medicine, Kaohsiung Municipal Hsiao-Kang Hospital, Kaohsiung Medical University, No. 482, Shanming Rd, Hsiaogang Dist., Kaohsiung City 812, Taiwan (e-mail: cobeshm@seed.net.tw).
Our study is supported by the grant from Kaohsiung Municipal Hsiao-Kang Hospital (kmhk-104–025), Kaohsiung Medical University, Kaohsiung, Taiwan.
The authors report no conflicts of interest.

ISSN: 0025-7974
DOI: 10.1097/MD.0000000000002874

(*Medicine* 95(11):e2874)

Abbreviations: AF = atrial fibrillation, BMI = body mass index, CI = confidence interval, CV = cardiovascular, E = early mitral inflow velocity, E/E′ = the ratio of transmitral E-wave velocity to early diastolic mitral annulus velocity, E′ = early diastolic mitral annulus velocity, EAT = epicardial adipose tissue, ECG = eletrocardiography, eGFR = estimated glomerular filtration rate, IDI = integrated discrimination improvement, LAVI = left atrial volume index, LVEF = left ventricular ejection fraction, LVMI = left ventricular mass index, ROC = receiver-operating characteristic.

INTRODUCTION

Atrial fibrillation (AF) is the most common arrhythmia in the elderly with evidence of an increasing prevalence and incidence worldwide.[1–3] AF is associated with an increased risk of ischemic stroke, incident myocardial infarction, all-cause mortality, and heart failure.[4]

Epicardial adipose tissue (EAT) represents a real and unique visceral fat deposit of the heart as indicated by the size of its adipocytes, metabolic activity, and biochemical composition. EAT has significantly higher rates of lipolysis and lipogenesis than visceral fat depots of other sites. Because no definite barrier exists between the EAT and the contiguous myocardium, EAT influences the myocardium and adjacent coronary arteries via a paracrine or vasocrine mechanism. Increased EAT thickness is strongly associated with diabetes mellitus, cardiovascular (CV) disease, visceral obesity, subclinical atherosclerosis at multiple locations, and the metabolic syndrome.[5–9] EAT is also increased in subjects with AF[10] and is associated with AF severity and the recurrence of AF after catheter ablation.[11,12] In non-AF patients, increased EAT thickness is shown to be positively associated with the severity of coronary artery disease and left ventricular diastolic dysfunction[5,13] and is a useful parameter in predicting adverse CV events.[14,15] However, there was no study to analyze the ability of EAT thickness in prediction of adverse CV events in AF patients. Hence, this study was conducted to evaluate whether EAT thickness was a useful parameter in prediction of adverse CV events in patients with AF. Besides, we also evaluated the major correlates of EAT thickness in these patients.

METHODS

Study Patients

From April 2010 to June 2012, this prospective observational study consecutively enrolled patients diagnosed with persistent AF and referred for transthoracic echocardiography.

The definition of persistent AF was sustained arrhythmia beyond 7 days, which was confirmed by 12-lead eletrocardiography (ECG), ECG recording during transthoracic echocardiography, or 24-hour Holter ECG. Our strategy in treating patients with persistent AF was rate control. A total of 225 patients were initially enrolled but those with inadequate echocardiographic visualization (n = 11) were excluded first. Then patients with moderate-to-severe valvular heart disease were also excluded (n = 14). Ten patients were lost to follow-up. Finally, 190 AF patients were enrolled for further evaluation. The protocol of this study was reviewed and approved by the Institutional Review Board and all enrolled patients signed informed consent forms.

Echocardiographic Evaluation

The transthoracic echocardiography was performed using VIVID 7 (General Electric Medical Systems, Horten, Norway) by one independent cardiologist that blind to original patient characteristics according to the standardized protocol, which was also described in our previous studies.[16–19] The cardiologist was blinded to the clinical data. Patients stayed in the left decubitus position to acquire the anatomic M-mode and 2-dimensional echocardiographic images. The gain was minimized and the wall filter settings were well adapted to eliminate the high-frequency signal. From the apical 4-chamber view, the Doppler sample volume was positioned at the tips of the mitral leaflets to acquire the left ventricular inflow waveforms and at the septal and lateral corners of the mitral annulus to acquire the pulsed tissue Doppler imaging. Early diastolic mitral annulus velocity (E′) was averaged from septal and lateral ones. The modified Simpson method, the Devereux-modified method, and the biplane area-length method were used to calculate left ventricular ejection fraction (LVEF), left ventricular mass, and left atrial volume respectively.[20,21] Left ventricular mass index (LVMI) was defined as left ventricular

TABLE 1. Comparison of Traditional Clinical and Echocardiographic Characteristics According to the Value of EAT Thickness (6.0 mm)

Characteristics	EAT Thickness ≦6.0 mm (n = 97)	EAT thickness >6.0 mm (n = 93)	*P*	All patients (n = 190)
Age, y	68 ± 10	73 ± 10	<0.001	70 ± 10
Male sex (%)	67	68	0.914	67
Diabetes mellitus (%)	26	29	0.614	27
Hypertension (%)	62	70	0.243	66
CAD (%)	5	16	0.014	11
CHF (%)	21	37	0.015	29
Stroke (%)	15	19	0.479	17
Smoking (%)	18	9	0.069	13
SBP, mmHg	130 ± 20	135 ± 20	0.093	133 ± 20
DBP, mmHg	78 ± 12	77 ± 12	0.493	77 ± 12
Heart rate, min^{-1}	85 ± 21	82 ± 19	0.403	83 ± 20
BMI, kg/m^2	25.6 ± 3.9	26.8 ± 4.3	0.039	26.3 ± 4.1
CHA_2DS_2-VASc score	2.9 ± 1.8	3.9 ± 1.7	<0.001	3.4 ± 1.8
eGFR	56 ± 17	51 ± 17	0.046	53 ± 17
Medications				
Antiplatelet use (%)	63	55	0.260	59
Anticoagulant use (%)	24	34	0.104	29
ACEI and/or ARB use (%)	54	56	0.750	54
β-blocker use (%)	48	39	0.176	44
CCB use (%)	30	39	0.201	34
Diuretics use (%)	40	44	0.588	42
Echocardiographic data				
LVEDD, mm	52 ± 7	52 ± 9	0.754	137 ± 40
LVESD, mm	36 ± 9	36 ± 10	0.711	36 ± 9
LVEF (%)	54 ± 14	55 ± 15	0.416	55 ± 14
LVMI, g/m^2	134 ± 44	140 ± 36	0.331	137 ± 40
LAVI, mL/m^2	48 ± 20	48 ± 19	0.901	36 ± 9
E, cm/s	94 ± 20	99 ± 26	0.169	96 ± 23
EDT, ms	139 ± 29	160 ± 61	0.002	149 ± 49
E′, cm/s	9.5 ± 2.3	8.2 ± 2.2	<0.001	8.9 ± 2.4
E/E′	10.4 ± 3.1	13.0 ± 5.2	<0.001	11.7 ± 4.5
EAT thickness, mm	4.4 ± 0.9	8.1 ± 1.6	<0.001	6.2 ± 2.3

ACEI = angiotensin-converting enzyme inhibitor, ARB = angiotensin II receptor blocker, BMI = body mass index, CAD = coronary artery disease, CCB = calcium channel blocker, CHF = chronic heart failure, DBP = diastolic blood pressure, E = early mitral inflow velocity, E′ = early diastolic mitral annulus velocity, E/E′ = the ratio of transmitral E-wave velocity to early diastolic mitral annulus velocity, EAT = epicardial adipose tissue, EDT = E wave deceleration time, eGFR = estimated glomerular filtration rate, LAVI = left atrial volume index, LVEDD = left ventricular end-diastolic dimension, LVEF = left ventricular ejection fraction, LVESD = left ventricular end-systolic dimension, LVMI = left ventricular mass index, SBP = systolic blood pressure.

mass divided by body surface area. Left atrial volume index (LAVI) was defined as left atrial volume divided by body surface area.

Measurement of EAT Thickness

EAT thickness was measured on the free wall of right ventricle from the parasternal long-axis views by one independent cardiologist. EAT was identified as an echo-free space located between the visceral pericardium and the outer wall of myocardium on the 2-dimensional echocardiography, and EAT thickness was calculated perpendicularly on the free wall of the right ventricle at end-diastole for 3 cardiac cycles.[8,22] The mean value from 3 cardiac cycles was calculated for the later analysis. The aortic annulus was used as anatomical reference of standardized measurement, which was performed at one location on the free wall of the right ventricle along the midline of the ultrasound beam, perpendicular to the aortic annulus. The raw data of echocardiography were stored for off-line analysis using the EchoPAC software (EchoPAC version 08; GE-Vingmed Ultrasound AS GE Medical Systems, Horten, Norway).

Left ventricular dimensions, LVMI, LVEF, and LAVI were measured using the index beat method.[23–25] As their measurements were rapid and easy, the early mitral inflow velocity (E), E-wave deceleration time, and E′ were averaged from 3 beats. However, a heartbeat was avoided if the duration of a cardiac cycle was too short to finish the diastolic process. Therefore, the measurement of E, E-wave deceleration time, and E′ was not consecutive every time.

Collection of Clinical Data

Clinical data of AF patients comprising sex, age and history of diabetes mellitus, hypertension, coronary artery disease (CAD), chronic heart failure (CHF), stroke, and smoking were acquired from interviews with patients or medical records. The following definitions were also described in our previous studies.[16,18] The readings of systolic and diastolic blood pressures were obtained using a mercury sphygmomanometer. The definition of hypertension was based on a systolic blood pressure >140 mmHg or a diastolic blood pressure >90 mmHg or antihypertensive drugs prescribed for blood pressure control. The definition of diabetes mellitus was based on antidiabetic agents prescribed to control blood glucose, a fasting blood glucose level >126 mg/dL, or a postprandial blood glucose level >200 mg/dL obtained 2 hours after meals. The definition of body mass index (BMI) was a person's weight in kilograms divided by the square of height in meters. The definition of stroke was based on a history of cerebrovascular accident including infarction or cerebral bleeding. The definition of CAD was based on any documented coronary angiography, any positive stress test in patients with a history of typical angina, a history of old myocardial infarction, or a history of percutaneous coronary intervention or bypass surgery. Heart failure was defined according to the Framingham criteria.[26] Myocardial infarction was defined according to the universal definition.[27] Estimated glomerular filtration rate (eGFR) was obtained by using the 4-item Modification of Diet in Renal Disease Study equation.[28]

The prescribed medications comprising antiplatelets, anticoagulants, angiotensin II receptor blockers, angiotensin-converting enzyme inhibitors, β-blockers, calcium channel blockers, and diuretics were surveyed form the formal medical records in the study period.

Definition of CV Events

In AF patients, CV events were defined as CV mortality, myocardial infarction, stroke, and hospitalization for heart failure, which resulted from dyspnea with concurrent intravenous diuretics and with pulmonary congestion confirmed radiographically. The diagnosis of stroke was confirmed by clinical assessment of a neurologist combined with computed tomographic or magnetic resonance imaging findings.

Two cardiologists were selected to determine and judge CV events. If any disagreement was encountered, a third cardiologist was assigned for final judgement after reviewing all clinical data and medical records. If patients had several CV events, only the first event was coded. If patients died after

TABLE 2. Univariable and Multivariable Correlates of EAT Thickness in Study Patients

	Univariable Analysis		Multivariable Analysis	
	r	*P*	β	*P*
Age, y	0.367	<0.001	0.343	<0.001
Male sex	−0.037	0.617		
Diabetes mellitus	0.077	0.289		
Hypertension	0.062	0.398		
CAD	0.174	0.016		
CHF	0.122	0.095		
Stroke	0.061	0.405		
Smoking	0.134	0.065		
SBP, mmHg	0.133	0.091		
DBP, mmHg	−0.078	0.340		
Heart rate, min^{-1}	0.013	0.862		
BMI, kg/m^2	0.128	0.086		
CHA_2DS_2-VASc score	0.304	<0.001		
eGFR	−0.184	0.013		
Medications				
Antiplatelet use (%)	−0.026	0.719		
Anticoagulant use (%)	0.119	0.101		
ACEI and/or ARB use (%)	0.047	0.520		
β-Blocker use (%)	−0.057	0.436		
CCB use (%)	0.173	0.017	0.161	0.020
Diuretics use (%)	0.005	0.945		
Echocardiographic data				
LVEDD, mm	0.022	0.763		
LVESD, mm	0.045	0.534		
LVEF (%)	0.039	0.594		
LVMI, g/m^2	0.161	0.031		
LAVI, mL/m^2	−0.024	0.745		
E, cm/s	0.064	0.382		
EDT, ms	0.157	0.031		
E′, cm/s	−0.276	<0.001		
E/E′	0.263	<0.001	0.164	0.023

ACEI = angiotensin-converting enzyme inhibitor, ARB = angiotensin II receptor blocker, BMI = body mass index, CAD = coronary artery disease, CCB = calcium channel blocker, CHF = chronic heart failure, DBP = diastolic blood pressure, E = early mitral inflow velocity, E′ = early diastolic mitral annulus velocity, E/E′ = the ratio of transmitral E-wave velocity to early diastolic mitral annulus velocity, EAT = epicardial adipose tissue, EDT = E wave deceleration time, eGFR = estimated glomerular filtration rate, LAVI = left atrial volume index, LVEDD = left ventricular end-diastolic dimension, LVEF = left ventricular ejection fraction, LVESD = left ventricular end-systolic dimension, LVMI = left ventricular mass index, SBP = systolic blood pressure.

episodes of heart failure, myocardial infarction, or stroke during the same admission, they were coded as CV deaths. In patients reaching the study end points, they were followed until the first episode of adverse events, whereas the other patients received follow-up until March 2014.

Reproducibility

To investigate the interobserver variability of measurement of EAT thickness, 30 patients were randomly chosen by 2 independent observers. Then identical measurement of echocardiographic parameters was repeated 1 week later to investigate the intraobsever variability. The mean percent error was obtained by dividing the absolute difference by an average of above 2 observations.

Statistical Analysis of Clinical Data

We used the SPSS 18.0 software (SPSS Inc, Chicago, IL) for further statistical analysis. Clinical data were listed as mean ± standard deviation, percentage, or median values (25th–75th percentile) for the follow-up period. We compared categorical and continuous variables between 2 groups by using the χ^2 test and independent samples *t* test, respectively, and investigated any relationship between 2 continuous variables by using the bivariate correlation method. Significant variables in the univariable analysis were chosen for further multivariable analysis. Cox proportional hazards model with forward selection was used to identify the predictors of adverse CV events. To define the best cut-off of EAT thickness, we calculated the Youden index (sensitivity + specificity − 1) by using the receiver-operating

TABLE 3. Predictors of Cardiovascular Events Using Cox Proportional Hazards Model

	Univariate		Multivariate (Forward)	
	HR (95% CI)	***P***	**HR (95% CI)**	***P***
Age, y	1.048 (1.022–1.075)	<0.001		
Male sex	0.831 (0.494–1.398)	0.485		
Diabetes mellitus	1.190 (0.706–2.005)	0.513		
Hypertension	0.788 (0.486–1.278)	0.335		
CAD	1.910 (1.002–3.642)	0.049		
CHF	3.025 (1.883–4.858)	<0.001	2.508 (1.455–4.323)	0.001
Stroke	0.969 (0.508–1.848)	0.923		
Smoking	0.357 (0.130–0.981)	0.046		
SBP, mmHg	1.004 (0.991–1.018)	0.531		
DBP, mmHg	1.005 (0.983–1.027)	0.661		
Heart rate, min^{-1}	1.002 (0.990–1.014)	0.748		
BMI, kg/m^2	0.900 (0.841–0.962)	0.002	0.909 (0.844–0.979)	0.011
CHA_2DS_2-VASc score	1.271 (1.118–1.446)	<0.001		
eGFR	0.971 (0.956–0.987)	<0.001	0.974 (0.959–0.990)	0.001
Medications				
Antiplatelet use (%)	1.064 (0.656–1.726)	0.803		
Anticoagulant use (%)	0.975 (0.574–1.654)	0.924		
ACEI and/or ARB use (%)	1.126 (0.698–1.817)	0.626		
β-Blocker use (%)	1.015 (0.631–1.632)	0.950		
CCB use (%)	1.125 (0.685–1.850)	0.642		
Diuretics use (%)	1.902 (1.184–3.058)	0.008		
Echocardiographic data				
LVEDD, mm	1.031 (0.999–1.064)	0.056		
LVESD, mm	1.039 (1.013–1.067)	0.004		
LVEF (%)	0.968 (0.953–0.984)	<0.001		
LVMI, g/m^2	1.013 (1.007–1.019)	<0.001	1.011 (1.005–1.017)	<0.001
LAVI, mL/m^2	1.012 (0.999–1.024)	0.065		
E, cm/s	1.008 (0.998–1.018)	0.117		
EDT, ms	1.004 (1.000–1.009)	0.066		
E′, cm/s	0.771 (0.690–0.862)	<0.001		
E/E′	1.100 (1.059–1.143)	<0.001		
EAT thickness, mm	1.286 (1.168–1.417)	<0.001	1.211 (1.084–1.351)	0.001

ACEI = angiotensin-converting enzyme inhibitor, ARB = angiotensin II receptor blocker, BMI = body mass index, CAD = coronary artery disease, CCB = calcium channel blocker, CHF = chronic heart failure, CI = confidence interval, DBP = diastolic blood pressure, E = early mitral inflow velocity, E′ = early diastolic mitral annulus velocity, E/E′ = the ratio of transmitral E-wave velocity to early diastolic mitral annulus velocity, EAT = epicardial adipose tissue, EDT = E wave deceleration time, eGFR = estimated glomerular filtration rate, HR = hazard ratio, LAVI = left atrial volume index, LVEDD = left ventricular end-diastolic dimension, LVEF = left ventricular ejection fraction, LVESD = left ventricular end-systolic dimension, LVMI = left ventricular mass index, SBP = systolic blood pressure. Covariates in this multivariate model included the significant variables in univariable analysis (age, smoking, CAD, CHF, BMI, CHA_2DS_2-VASc score, eGFR, diuretic use, LVESD, LVMI, LVEF, E′, E/E′, and EAT thickness).

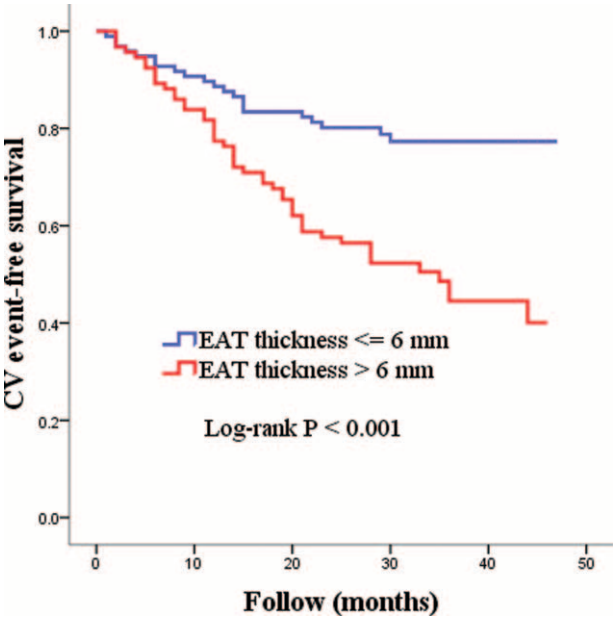

FIGURE 1. Kaplan–Meier analysis of cardiovascular (CV) event-free survival according to epicardial adipose tissue (EAT) thickness ≦6.0 mm and >6.0 mm (log-rank $P < 0.001$).

characteristic (ROC) curve. We also evaluated incremental model performance by calculating sequential change of the χ^2 value and performed the Kaplan–Meier survival analysis of CV events. Besides, we performed stepwise multiple linear regression analysis to identify the correlates of EAT thickness. Finally, incremental model performance was also assessed by Integrated Discrimination Improvement (IDI) using SAS 9.3 (SAS Institute, Cary, NC). Statistical significance was recognized if $P < 0.05$ in 2-sided tests.

RESULTS

Our final study population included 190 persistent AF patients (128 male and 62 female) with a mean age of 70 ± 10 years. In ROC curve analysis, we found that 6.0 mm was the best cutoff value of EAT thickness in the prediction of CV events. Table 1 demonstrates the comparison of traditional clinical and echocardiographic characteristics according to EAT thickness (6.0 mm). We found that age, the prevalence of CAD, the presence of CHF, BMI, CHA_2DS_2-VASc score, eGFR, E-wave deceleration time, E′, the ratio of transmitral E-wave velocity to early diastolic mitral annulus velocity (E/E′), and EAT thickness were significantly different between patients with EAT thickness ≦6.0 mm and >6.0 mm.

Table 2 demonstrates univariable and multivariable correlates of EAT thickness in AF patients. We found that older age, the existence of CAD, higher CHA_2DS_2-VASc score, lower eGFR, the prescription of calcium channel blockers, higher LVMI, longer E-wave deceleration time, lower E′, and higher E/E′ were correlated with higher EAT thickness in the univariable analysis. After performing the multivariable analysis, older age, the prescription of calcium channel blockers, and higher E/E′ were still correlated with higher EAT thickness.

The follow-up duration of AF patients experiencing CV events was 29 (25th–75th percentile: 17–36) months. Sixty-nine CV events, including CV death (n = 19), hospitalization for heart failure (n = 32), myocardial infarction (n = 3), and stroke (n = 15) were recognized during the follow-up period. The total amount of person-years was 459 and incidence rate of CV events was 15.0% per year during follow-up. Table 3 shows predictors of CV events using the Cox proportional hazards regression analysis. We found that older age, the existence of CAD and CHF, non-smoking status, lower BMI, higher CHA_2DS_2-VASc score, lower eGFR, diuretic use, larger left ventricular end-systolic dimension, lower LVEF, higher LVMI, lower E′, higher E/E′, and higher EAT thickness were associated with adverse CV events in the univariable analysis. After performing the multivariable analysis, the existence of CHF, lower BMI and eGFR, and higher LVMI and EAT thickness (hazard ratio, 1.211; 95% confidence interval [CI], 1.084–1.351; $P < 0.001$) were still independent predictors of adverse CV events in AF patients.

Figure 1 demonstrates the Kaplan–Meier curves for CV event-free survival in study patients subdivided according to EAT thickness ≦6.0 mm and >6.0 mm (log-rank $P < 0.001$).

Table 4 shows incremental values of EAT thickness in the prediction of adverse CV events. Adding EAT thickness to a Cox model containing CHA_2DS_2-VASc score, LAVI, LVEF, and E/E′ demonstrated significant improvement in the prediction of future CV events (difference in χ^2 value: 14.65, $P < 0.001$ and IDI 0.10, 95% CI 0.04–0.16, $P < 0.001$). Subgroup analysis, which focused only on patients with a CHA_2DS_2-VASc score of 0 for males (n = 19) and 1 for females (n = 6), was performed and EAT thickness could further identify CV events in males with a CHA_2DS_2-VASc score of 0 (IDI 0.13, 95% CI 0.05–0.21, $P = 0.002$) and showed a trend in further identifying CV events in females with a CHA_2DS_2-VASc score of 1 (IDI 0.10, 95% CI -0.01–0.20, $P = 0.056$), when compared with a Cox model containing CHA_2DS_2-VASc score, LAVI, LVEF, and E/E′.

For measurement of EAT thickness, our result demonstrated that the intraobserver mean percent error was

TABLE 4. Incremental Values of EAT Thickness in Relation to CV Events

CV Events	Difference in χ^2 Value	*P*	IDI	*P*
Model 1: CHA_2DS_2-VASc score	Reference			
Model 2: model 1 + LAVI, LVEF, E/E′	28.21	<0.001	Reference	
Model 3: model 2 + EAT thickness	14.65	<0.001	0.10	<0.001

P value based on the difference in χ^2 value was compared with the previous model. *P* value based on IDI was compared with the model 2. CV = cardiovascular, E/E′ = the ratio of transmitral E-wave velocity to early diastolic mitral annulus velocity, EAT = epicardial adipose tissue, IDI = integrated discrimination improvement, LAVI = left atrial volume index, LVEF = left ventricular ejection fraction.

7.1% ± 10.1%, whereas the interobserver mean percent error was 8.3% ± 12.1%.

DISCUSSION

Our study estimated the association of EAT thickness with adverse CV events in patients with documented AF. We found that higher EAT thickness was associated independently with further risks of adverse CV events in AF patients. Additionally, the EAT thickness could add significant incremental values beyond the conventional clinical and echocardiographic parameters in prediction of adverse CV events.

EAT represents a type of visceral adipose tissue adjacent the heart and has a unique character in terms of the biochemical composition, the size of its adipocytes, and metabolic activity. EAT has been proposed to influence the development of coronary atherosclerosis owing to its endocrine and paracrine activity by secreting anti-inflammatory and proinflammatory cytokines and chemokines.[29–31] Jeong et al found that in patients with documented CAD, EAT thickness was correlated significantly with its severity of atherosclerosis.[5] Several studies showed age and BMI were associated significantly with EAT thickness.[5,7,14,32] In patients diagnosed with metabolic syndrome, Park et al[13] also found that E/E′ was associated significantly with EAT thickness. In the present study, we similarly demonstrated that compared to AF patients with EAT thickness ≦6.0 mm, those with EAT thickness >6.0 mm had an older age, more prevalent CAD, and higher BMI and E/E′.

In the general population, Mahabadi et al[14] found an association between EAT and incident myocardial infarction and CV risk factors. In the cross-section study by Akil et al,[33] the EAT thickness in patients diagnosed with ischemic stroke was found to be higher than those in healthy controls. Several studies have showed EAT thickness is associated significantly with left ventricular diastolic dysfunction.[13,34] Left ventricular diastolic dysfunction was correlated to poor CV prognosis.[35–37] In our study, the multivariable analysis consistently revealed that increased E/E′ and old age were independently associated with increased EAT thickness. Old age is a well-recognized risk factor of adverse CV events.[38] E/E' was also a strong predictor of adverse CV events in various population including patients with type 2 diabetes mellitus, chronic kidney disease, and dialysis.[39–41] Our present results found EAT thickness as a useful predictor for adverse CV events even after adjustment for many important clinical and echocardiographic parameters might be partially explained by the older age and higher E/E′ in our patients with higher EAT thickness. Besides, adding EAT thickness to a Cox model containing CHA_2DS_2-VASc score, LAVI, LVEF, and E/E′ demonstrated significant improvement in the prediction of future CV events. Hence, EAT thickness may be a useful indicator of poor CV outcomes in AF patients.

STUDY LIMITATIONS

Several limitations existed in our study. First, EAT thickness was measured by echocardiography and by one independent cardiologist, but not by computed tomography scan. Hence, we could not analyze the relationship between periatrial fat and adverse CV events in AF patients. Second, we did not withdraw antihypertensive, antiplatelet, or anticoagulant medications for ethical reasons. Hence, pharmacological influence on the present findings could not be excluded. However, we have taken the use of medicine into consideration in the multivariable analysis. Third, the using rate of anticoagulation medication was low in our study, but it was similar to our national survey for AF.[30] Fouth, because AF patients were selected from those who received transthoracic echocardiographic examination, it was predisposed to selection bias and resulted in findings potentially less generalized. Finally, the limited power and the possibility of chance findings should be considered owing to the large amount of variables in the analysis but with only 69 outcomes.

CONCLUSIONS

In AF, EAT thickness was useful in predicting future CV events. Additionally, EAT thickness could provide incremental value for CV outcome prediction over traditional clinical and echocardiographic parameters in AF.

ACKNOWLEDGMENTS

We are grateful to the assistance from the Statistical Analysis Laboratory, Department of Medical Research, Kaohsiung Medical University Hospital, Kaohsiung Medical University.

REFERENCES

1. Camm AJ, Lip GY, De Caterina R, et al. 2012 focused update of the ESC Guidelines for the management of atrial fibrillation: an update of the 2010 ESC Guidelines for the management of atrial fibrillation. Developed with the special contribution of the European Heart Rhythm Association. *Eur Heart J.* 2012;33:2719–2747.
2. Chugh SS, Havmoeller R, Narayanan K, et al. Worldwide epidemiology of atrial fibrillation: a Global Burden of Disease 2010 Study. *Circulation.* 2014;129:837–847.
3. Mozaffarian D, Benjamin EJ, Go AS, et al. Heart disease and stroke statistics – 2015 update: a report from the American Heart Association. *Circulation.* 2015;131:e29–322.
4. January CT, Wann LS, Alpert JS, et al. 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the Heart Rhythm Society. *J Am Coll Cardiol.* 2014;64:e1–76.
5. Jeong JW, Jeong MH, Yun KH, et al. Echocardiographic epicardial fat thickness and coronary artery disease. *Circ J.* 2007;71:536–539.
6. Karastergiou K, Fried SK. Multiple adipose depots increase cardiovascular risk via local and systemic effects. *Curr Atheroscler Rep.* 2013;15:361.
7. Natale F, Tedesco MA, Mocerino R, et al. Visceral adiposity and arterial stiffness: echocardiographic epicardial fat thickness reflects, better than waist circumference, carotid arterial stiffness in a large population of hypertensives. *Eur J Echocardiogr.* 2009;10:549–555.
8. Iacobellis G, Ribaudo MC, Assael F, et al. Echocardiographic epicardial adipose tissue is related to anthropometric and clinical parameters of metabolic syndrome: a new indicator of cardiovascular risk. *J Clin Endocrinol Metab.* 2003;88:5163–5168.
9. Bos D, Shahzad R, van Walsum T, et al. Epicardial fat volume is related to atherosclerotic calcification in multiple vessel beds. *Eur Heart J Cardiovasc Imag.* 2015;16:1264–1269.
10. Al Chekakie MO, Welles CC, Metoyer R, et al. Pericardial fat is independently associated with human atrial fibrillation. *J Am Coll Cardiol.* 2010;56:784–788.
11. Tsao HM, Hu WC, Wu MH, et al. Quantitative analysis of quantity and distribution of epicardial adipose tissue surrounding the left

atrium in patients with atrial fibrillation and effect of recurrence after ablation. *Am J Cardiol.* 2011;107:1498–1503.

12. Chao TF, Hung CL, Tsao HM, et al. Epicardial adipose tissue thickness and ablation outcome of atrial fibrillation. *PLoS One.* 2013;8:e74926.
13. Park HE, Choi SY, Kim M. Association of epicardial fat with left ventricular diastolic function in subjects with metabolic syndrome: assessment using 2-dimensional echocardiography. *BMC Cardiovasc Disord.* 2014;14:3.
14. Mahabadi AA, Berg MH, Lehmann N, et al. Association of epicardial fat with cardiovascular risk factors and incident myocardial infarction in the general population: the Heinz Nixdorf Recall Study. *J Am Coll Cardiol.* 2013;61:1388–1395.
15. Ulucan S, Kaya Z, Efe D, et al. Epicardial fat tissue predicts increased long-term major adverse cardiac event in patients with moderate cardiovascular risk. *Angiology.* 2015;66:619–624.
16. Chen SC, Chang JM, Liu WC, et al. Echocardiographic parameters are independently associated with increased cardiovascular events in patients with chronic kidney disease. *Nephrol Dial Transplant.* 2012;27:1064–1070.
17. Hsu PC, Tsai WC, Lin TH, et al. Association of arterial stiffness and electrocardiography-determined left ventricular hypertrophy with left ventricular diastolic dysfunction. *PLoS One.* 2012;7:e49100.
18. Lee WH, Hsu PC, Chu CY, et al. Anemia as an independent predictor of adverse cardiac outcomes in patients with atrial fibrillation. *Int J Med Sci.* 2015;12:618–624.
19. Chen SC, Lee WH, Hsu PC, et al. Association of brachial-ankle pulse wave velocity with cardiovascular events in atrial fibrillation. *Am J Hypertens.* 2016;29:348–356.
20. Devereux RB, Alonso DR, Lutas EM, et al. Echocardiographic assessment of left ventricular hypertrophy: comparison to necropsy findings. *Am J Cardiol.* 1986;57:450–458.
21. Lang RM, Bierig M, Devereux RB, et al. Recommendations for chamber quantification: a report from the American Society of Echocardiography's Guidelines and Standards Committee and the Chamber Quantification Writing Group, developed in conjunction with the European Association of Echocardiography, a branch of the European Society of Cardiology. *J Am Soc Echocardiogr.* 2005;18:1440–1463.
22. Iacobellis G, Assael F, Ribaudo MC, et al. Epicardial fat from echocardiography: a new method for visceral adipose tissue prediction. *Obes Res.* 2003;11:304–310.
23. Govindan M, Kiotsekoglou A, Saha SK, et al. Validation of echocardiographic left atrial parameters in atrial fibrillation using the index beat of preceding cardiac cycles of equal duration. *J Am Soc Echocardiogr.* 2011;24:1141–1147.
24. Lee CS, Lin TH, Hsu PC, et al. Measuring left ventricular peak longitudinal systolic strain from a single beat in atrial fibrillation: validation of the index beat method. *J Am Soc Echocardiogr.* 2012;25:945–952.
25. Kusunose K, Yamada H, Nishio S, et al. Index-beat assessment of left ventricular systolic and diastolic function during atrial fibrillation using myocardial strain and strain rate. *J Am Soc Echocardiogr.* 2012;25:953–959.
26. Ho KK, Anderson KM, Kannel WB, et al. Survival after the onset of congestive heart failure in Framingham Heart Study subjects. *Circulation.* 1993;88:107–115.
27. Thygesen K, Alpert JS, White HD, et al., Joint ESCAAHAWHFTFf-tRoMI. Universal definition of myocardial infarction. *Circulation.* 2007;116:2634–2653.
28. Levey AS, Coresh J, Greene T, et al. Using standardized serum creatinine values in the modification of diet in renal disease study equation for estimating glomerular filtration rate. *Ann Intern Med.* 2006;145:247–254.
29. Mazurek T, Zhang L, Zalewski A, et al. Human epicardial adipose tissue is a source of inflammatory mediators. *Circulation.* 2003;108:2460–2466.
30. Laine P, Kaartinen M, Penttila A, et al. Association between myocardial infarction and the mast cells in the adventitia of the infarct-related coronary artery. *Circulation.* 1999;99:361–369.
31. Hirata Y, Tabata M, Kurobe H, et al. Coronary atherosclerosis is associated with macrophage polarization in epicardial adipose tissue. *J Am Coll Cardiol.* 2011;58:248–255.
32. Park JS, Ahn SG, Hwang JW, et al. Impact of body mass index on the relationship of epicardial adipose tissue to metabolic syndrome and coronary artery disease in an Asian population. *Cardiovasc Diabetol.* 2010;9:29.
33. Akil E, Akil MA, Varol S, et al. Echocardiographic epicardial fat thickness and neutrophil to lymphocyte ratio are novel inflammatory predictors of cerebral ischemic stroke. *J Stroke Cerebrovasc Dis.* 2014;23:2328–2334.
34. Lin HH, Lee JK, Yang CY, et al. Accumulation of epicardial fat rather than visceral fat is an independent risk factor for left ventricular diastolic dysfunction in patients undergoing peritoneal dialysis. *Cardiovasc Diabetol.* 2013;12:127.
35. Park SJ, Lee SC, Jang SY, et al. E/e' ratio is a strong prognostic predictor of mortality in patients with non-valvular atrial fibrillation with preserved left ventricular systolic function. *Circ J.* 2011;75:2350–2356.
36. Hillis GS, Moller JE, Pellikka PA, et al. Noninvasive estimation of left ventricular filling pressure by E/e' is a powerful predictor of survival after acute myocardial infarction. *J Am Coll Cardiol.* 2004;43:360–367.
37. Gharacholou SM, Scott CG, Takahashi PY, et al. Left ventricular diastolic function and long-term outcomes in patients with normal exercise echocardiographic findings. *Am J Cardiol.* 2013;112:200–207.
38. Go AS, Mozaffarian D, Roger VL, et al. Heart disease and stroke statistics – 2013 update: a report from the American Heart Association. *Circulation.* 2013;127:e6–e245.
39. Blomstrand P, Engvall M, Festin K, et al. Left ventricular diastolic function, assessed by echocardiography and tissue Doppler imaging, is a strong predictor of cardiovascular events, superior to global left ventricular longitudinal strain, in patients with type 2 diabetes. *Eur Heart J Cardiovasc Imag.* 2015;16:1000–1007.
40. Han JH, Han JS, Kim EJ, et al. Diastolic dysfunction is an independent predictor of cardiovascular events in incident dialysis patients with preserved systolic function. *PLoS One.* 2015;10:e0118694.
41. Chen SC, Chang JM, Tsai YC, et al. Ratio of transmitral E-wave velocity to early diastole mitral annulus velocity with cardiovascular and renal outcomes in chronic kidney disease. *Nephron Clin Pract.* 2013;123:52–60.