Am J Cardiovasc Dis 2021;11(1):29-38
www.AJCD.us /ISSN:2160-200X/AJCD0126275

Original Article

The relationship between coronary microvascular dysfunction, atrial fibrillation and heart failure with preserved ejection fraction

Cevher Ozcan[1,2], Tess Allan[3], Stephanie A Besser[1,2], Anthony de la Pena[1], John Blair[1,2]

[1]Department of Medicine, University of Chicago, 5841 S. Maryland Avenue, MC 6080, Chicago, IL 60637, USA; [2]Section of Cardiology, Department of Medicine, University of Chicago, 5841 S. Maryland Avenue, MC 6080, Chicago, IL 60637, USA; [3]Pritzker School of Medicine, University of Chicago, 5841 S. Maryland Avenue, MC 6080, Chicago, IL 60637, USA

Received November 14, 2020; Accepted December 21, 2020; Epub February 15, 2021; Published February 28, 2021

Abstract: Objective: Coronary microvascular dysfunction (CMD) is a new frontier in cardiovascular disease and an important contributor to myocardial ischemia. A high prevalence of CMD is shown in heart failure, however, the cause-and-effect relationship between CMD and atrial fibrillation (AF) is unknown. We hypothesize that CMD is associated with AF and increases susceptibility to the co-existence of AF and heart failure with preserved ejection fraction (HFpEF). Methods: Our study examined the relationship between CMD, AF, and HFpEF in all patients who underwent invasive coronary physiology studies for assessment of chest pain or dyspnea. CMD was defined as impaired coronary flow reserve (CFR) without obstructive coronary disease. Results: A total of 80 patients (mean age 60±12 years, 68.8% female, median follow up of 2.2 years) were studied. Patients with AF (61%) or HFpEF (62%), or both (71%) were more likely to have CMD than those patients without these conditions. Of the patients with AF and abnormal CFR, 91% had HFpEF. CMD was a predictor of AF with concomitant HFpEF (OR 4.38, P=0.02). Our clinical outcome analysis demonstrated that patients with CMD, AF or HFpEF had lower survival free of HF hospitalization than those patients without (P<0.05). AF (OR 5.5, P=0.02), diabetes, older age, female gender, and higher heart rate were predictors of CMD. Conclusion: CMD is highly prevalent in patients with AF with or without HFpEF. CMD is associated with poor clinical outcomes and the co-existence of AF and HFpEF. Understanding of the association between CMD and AF is important for developing an effective treatment strategy and the risk stratification for the prevention of AF in patients with CMD and vice versa.

Keywords: Atrial fibrillation, microvascular dysfunction, heart failure, coronary flow reserve

Introduction

Coronary microvascular dysfunction (CMD) is a new frontier in cardiovascular disease involving myocardial injury, nonobstructive and obstructive coronary artery disease (CAD), and heart failure with preserved ejection fraction (HFpEF) [1-4]. A growing body of literature indicates that CMD contributes substantially to the pathophysiology of ischemic heart disease and the increased risk of adverse events [5, 6]. Recent non-invasive studies demonstrated a high prevalence of CMD in HFpEF patients and proposed possible association with atrial fibrillation (AF) [3, 7]. Yet, the cause-and-effect relationship between CMD and AF with or without HFpEF is not known.

CMD is associated with attenuation of coronary flow augmentation in response to stress leading to demand-supply mismatch, and myocardial ischemia [1-3]. The coronary microcirculation embodies a complex series of compartments and receptive to dynamic changes in myocardium. CMD is linked to sympathetic innervation, neuro-hormonal activation, and myocardial fibrosis which are known to have role in pathogenesis of AF and heart failure (HF) [1, 8-15]. Yet, it is unclear whether CMD causes AF or vice versa. AF and CMD are complex disease processes with multiple contributing clinical and molecular factors. AF and CMD are associated with HF individually [1-4, 10-17]. AF and HF are dual epidemics with increasing incidence and prevalence [15-18]. AF is the most

common sustained arrhythmia in clinical practice by affecting 9% of those ≥65 years of age [10, 18]. Patients with both AF and HFpEF have disproportionately poor cardiovascular outcomes [10, 14, 15, 18]. Although there is a high prevalence of AF in HFpEF patients. The impact of CMD on AF or co-existence of AF and HFpEF has not been characterized. Also, there is no published data evaluating tripartite intricate relationship between CMD, AF and HFpEF. We propose that impaired myocardial perfusion with CMD can facilitate atrial remodeling and electrical instability to cause AF. Understanding of the pathogenic relation between CMD and AF in the presence and absence of HFpEF is important for risk stratification and management of patients. Previous studies have demonstrated high prevalence of CMD in HFpEF patients, as assessed by positron emission tomography, or Doppler echocardiography. However, obstructive CAD was not ruled out as a cause of the measured flow abnormalities, and measurements of microvascular resistance was not performed in these studies [1-3, 6, 15].

Here, we hypothesize that CMD is associated with AF and increases susceptibility to the co-existence of AF with HFpEF. To test this hypothesis, we examined the relationship between CMD and AF with or without HFpEF by using invasive coronary physiology studies (ICPS) to diagnose CMD. ICPS with the assessment of coronary flow reserve (CFR) is a gold standard diagnostic test for CMD [1-3, 5, 6, 19-21]. Our study was performed in a registry of patients at our institution who have undergone an ICPS to assess CMD [2, 19]. To our knowledge, this is the first study investigating the link between CMD, AF and HFpEF by using ICPS and invasive measurement of CFR. We also studied the effect of CMD on clinical outcomes in patients with AF, HFpEF or both compared to control patients without AF or HFpEF.

Materials and methods

All consecutive patients who underwent -ICPS and had no obstructive CAD at the University of Chicago Medical Center (UCMC) between December 2014 and April 2019 were included in this study. The study was approved by the UCMC Institutional Review Board (#IRB14-0927). A written informed consent was obtained from all patients. We excluded patients who did not consent to participate in the registry. All patients met indications for diagnostic catheterization by practice guidelines, with the indication of either angina or dyspnea. We analyzed the data on a prospectively-collected registry of all patients who underwent ICPS with a focus on the clinical outcomes including mortality, HF hospitalization, clinical AF and HFpEF. In order to eliminate selection biases, all consecutive patients were included in this study. Patients with prior MI, prior CABG, severe valvular disease determined by baseline echocardiogram, obstructive CAD, prior cardiac transplantation, previous history of reduced left ventricular EF (≤35%) that has subsequently normalized, and HFpEF due to infiltrative disorders such as amyloidosis and genetic cardiomyopathies were excluded. Obstructive CAD was defined as a stenosis >50% in the left main coronary artery, >70% in a non-left main coronary artery, or any stenosis with a fractional flow reserve of ≤0.80, and patients with hemodynamically significant myocardial bridges.

Data collection

Data were abstracted from the electronic medical record containing complete records of all patients treated and followed at the UCMC. Demographic data, comorbidities, medications, and electrocardiograms were abstracted from the database and/or electronic medical record. Left ventricular ejection fraction (LVEF) and the presence of valve disease were determined by echocardiography within 90 days of the procedure. Incidence of AF during follow-up was determined by review of all ECGs, ambulatory event monitors and inpatient telemetry recordings. Using the standard definition, paroxysmal or non-paroxysmal AF including persistent, long-standing persistent, and permanent AF were all included [10, 22, 23]. HFpEF was diagnosed if the patient had a LVEF ≥50%, had less than moderate valvular heart disease, and met Framingham criteria for HF and had a pulmonary capillary wedge pressure of >15 mmHg or a left ventricular end diastolic pressure of >18 mmHg [24]. Outcome data were collected via phone call, office visits, and/or abstraction of the medical record quarterly for one year after the cardiac catheterization date. Survival was determined by obtaining the most recent date of contact between the patient and the

hospital. If no contact had occurred, the patient was contacted via phone. If the patient was no longer living at the time of follow-up, the date and cause of death was recorded. For a hospitalization to be considered a HF hospitalization, the patient had to meet Framingham Criteria for HF and HF had to be the primary reason for the hospitalization.

Coronary physiology study

Coronary angiography and ICPS were performed by using a standardized protocol as described previously [2, 28]. Briefly, left ventricular end-diastolic pressure was measured using either a pigtail or Judkins right catheter with standard calibrated pressure transducers. A guide catheter was placed in the left main coronary artery and heparin was administered for a target activated clotting time of 250 seconds or greater. Intracoronary nitroglycerin (100-200 μg) was injected through the guide catheter and a 0.014-inch Pressure X wire (Abbott) was calibrated and equalized to the guide catheter pressure and advanced to the distal two-thirds of the left anterior descending coronary artery. CFR and IMR were measured using commercially available software (RADI analyzer, Abbott) using the thermodilution technique with intravenous adenosine (140 μg/kg/min) as the vasodilator. CFR was calculated using the ratio of hyperemic blood flow (1/Tmn, hyperemia) to resting blood flow (1/Tmn, resting), or simply Tmn, resting/Tmn, hyperemia. IMR was calculated using the ratio of hyperemic mean distal coronary artery pressure to hyperemic flow, or simply mean distal coronary artery pressure x Tmn, hyperemia. Abnormal values were defined as <2.0 for CFR and >23 units for IMR [2, 5]. CMD was defined as abnormal CFR in the absence of obstructive CAD [1, 2, 21].

Cardiac electrophysiology and imaging

All patients had a supine 12 lead ECG which was stored on a digital recording and archiving system (Cardiolab, GE Healthcare). ECGs were used to determine underlying rhythm and conduction intervals including P wave duration, PR interval, QRS duration and corrected QT interval (QTc). P-wave duration and PR interval were measured in leads II and V1. A PR interval >200 ms was considered prolonged. The measurements were made by two physicians who were blinded to the patients' characteristics. If there was inter-observer variation (>10 ms) in measurements, an electrophysiologist who was also blind to the patients, measured the intervals. Conduction disease, AF and other arrhythmias were detected by review of all available cardiac recordings including ECGs, ambulatory event monitors and telemetry [22, 23]. Cardiac function and structure was evaluated by transthoracic, Doppler, and tissue Doppler echocardiography by using the American Society of Echocardiography guidelines [25]. Two-dimensional chamber quantification and Doppler parameters were obtained, measured, and analyzed using Intellispace (Phillips Healthcare) using the echocardiography guidelines for chamber quantification and diastolic dysfunction [26].

Statistical analysis

Continuous characteristics were expressed as means ± standard deviations or medians with interquartile ranges and compared with either Student's t-tests or Mann-Whitney U (Wilcoxon) tests as determined by Shapiro-Wilk tests of normality. Categorical characteristics were expressed as relative counts and percentages and compared with Chi-square tests of association or Fisher's exact tests. Univariable and multivariable logistic regressions determined baseline clinical characteristics were associated with CMD, AF, HFpEF, and both HFpEF and AF. Kaplan Meier time-to-event analysis with the log-rank test for statistical significance was used to determine time to death or HF hospitalization for patients with and without abnormal CFR, and for patients with and without either HFpEF or AF. Tests were two-tailed and considered statistically significant with a p-value <0.05. All statistical analyses were conducted using STATA MP version 15 (College Station, TX).

Results

Overall study population

A total of 80 consecutive patients (mean age 60±12 years and median age 60 years (interquartile range 53-68) who underwent ICPS were included in this study. The study population included a majority of women (69%) and African Americans (AA) (73%). There were 22.5% patients with AF and 50% patients with

Table 1. Baseline characteristics among patients with and without coronary microvascular disease

Characteristics	All Patients (n=80)	Abnormal CFR (n=34)	Normal CFR (n=46)	*P* Value
Age, years + SD	60±12	60±12	60±12	0.98
Women, %	68	74	64	0.39
African-American, %	73	68	78	0.31
Hypertension, %	80	79	80	0.95
CKD, %	29	38	22	0.12
Dyslipidemia, %	71	71	71	0.96
COPD, %	37	35	38	0.82
Diabetes, %	43	56	33	0.045
Angina, %	66	53	76	0.04
AF, %	23	32	15	0.07
HFpEF, %	50	62	41	0.07
NYHA class ≥III, %	16	24	11	0.14
BMI, kg/m^2	33	37	31	0.049
BMI >30.0, %	66	73	61	0.27
BNP, pg/dL	130	173	77	0.10
LVEF, %	63±7	62±7	63±7	0.32
LVEDP, mmHg	13±6	15±6	12±5	0.05
MAP, mmHg	91	91	93	0.16
LAVI, mL/m^2	26±9	27±12	25±6	0.53
Non-obstructive CAD, %	17	21	15	0.54
CFR (median (IQR))	2.5 (1.6-3.7)	1.6 (1.3-1.7)	3.4 (2.6-5.2)	--
AV Block, %	13	12	14	1
PAC, %	6	6	7	1
PR interval, ms	164	166	160	0.81
P wave duration, ms	116	121	112	0.30
LA Duration, ms	62±17	64±17	61±16	0.40
QRS interval, ms	86	86	86	0.28
QTc interval, ms	440	448	433	0.03
Heart rate, bpm	70	78	67	0.008

Abbreviations: CFR, indicates coronary flow reserve; CKD, chronic kidney disease; COPD, chronic obstructive lung disease; AF, atrial fibrillation; HFpEF, heart failure with preserved ejection fraction; NYHA, New York Heart Association; BMI, body mass index; BNP, B-natriuretic peptide; LVEF, left ventricular ejection fraction; LVEDP, left ventricular end diastolic pressure; MAP, mean arterial pressure; LAVI, left atrial volume index; CAD, coronary artery disease; AV, atrio ventricular; PAC, premature atrial contraction; LA, left atria.

HFpEF. Abnormal CFR, a marker of CMD, was found in 34 patients (42.5%) in study group. There was nof those AA). In the HFpEF subgroup, 73% were female (63% of tho o gender (64% versus 74% women, P=0.39) or race (78% versus 68% AA, P=0.31) difference regarding the incidence of CMD in our study. In patients with AF, 61% were female (64% se AA). In patients with both AF and HFpEF, 64% were females (50% were AA females). Detailed baseline characteristics of the overall study population grouped by abnormal CFR are provided in **Table 1**. Underlying clinical conditions and demographic data were comparable between patients with normal CFR and those with abnormal CFR. Diabetes and angina were more common in patients with abnormal CFR. The average BMI was higher in patients with abnormal CFR, but there was no difference in prevalence of obesity between the two groups. Abnormal index of microvascular resistance (IMR) was more common in patients with abnormal CFR. The average QTc interval was longer and the average heart rate higher in patients with abnormal CFR.

Relationship between AF, HFpEF and CMD

Detailed baseline characteristics of the study groups based on AF and HFpEF are displayed in **Table 2**. There was significant AF and HFpEF association as HFpEF was present in 78% of patients with AF versus 42% without AF (P=0.007). Patients with AF were older (65.7±12.6 versus 58.3± 11.1; P=0.02), had a higher average B-type natriuretic peptide (BNP), and had a higher prevalence of chronic kidney disease (CKD) and chronic obstructive pulmonary disease (COPD) than those patients without AF. Prevalence of atrioventricular block (AVB), and premature atrial contractions (PAC) were more common in AF patients, and PR interval and P wave duration were longer in AF patients. A trend was observed with AF patients having a higher prevalence of abnormal CFR than patients without AF (61% versus 37%, P=0.07;

Table 2. Comparisons of Groups According to AF or HFpEF

Characteristics	AF (n=18)	No AF (n=62)	*P* Value	HFpEF (n=40)	No HFpEF (n=40)	*P* Value
Age, years + SD	66±13	58±11	0.02	64±10	56±12	0.001
Women, %	61	70	0.45	73	64	0.42
AA, %	61	77	0.23	78	69	0.41
Hypertension, %	89	77	0.34	93	67	0.004
CKD, %	50	23	0.03	45	13	0.002
Dyslipidemia, %	72	70	0.89	85	56	0.005
COPD, %	67	28	0.003	48	26	0.04
Diabetes, %	39	44	0.69	58	28	0.009
Angina, %	50	70	0.11	50	82	0.003
HFpEF, %	78	42	0.007	35	10	0.007
NYHA class ≥III, %	28	13	0.16	30	3	0.001
BMI, kg/m^2	36	32	0.08	37	30	0.002
BMI >30.0, %	78	62	0.22	82	50	0.003
BNP (pg/dL)	1221	114	0.001	161	33	0.003
LVEF, %	62±7	63±6	0.62	62±6	63±8	0.73
LVEDP, mmHg	15±4	13±6	0.13	16±5	10±5	<0.001
MAP, mmHg	91	92	0.43	91	92	0.51
LAVI, mL/m^2	30±14	25±7	0.055	27±11	24±6	0.18
Non-obstructive CAD, %	18	17	1	14	21	0.42
Abnormal CFR, %	61	37	0.07	53	33	0.07
CFR (median)	1.7 (1.4-3.8)	2.5 (1.7-3.7)	0.13	1.8 (1.5-3.3)	2.6 (1.8-4.3)	0.051
AV Block, %	33	7	0.009	13	14	1
PAC, %	22	2	0.01	10	3	0.36
PR interval, ms	182	159	0.01	164	154	0.41
P wave, ms	132	112	0.01	116	112	0.09
LA Duration, ms	69±22	60±15	0.10	66±19	58±14	0.04
QRS interval, ms	88	86	0.32	86	86	0.91
QTc interval, ms	451	437	0.57	449	428	0.01
Heart rate, bpm	68	70	0.48	73	68	0.04

Abbreviations: CFR indicates coronary flow reserve; CKD, chronic kidney disease; COPD, chronic obstructive lung disease; AA, African American; AF, atrial fibrillation; HFpEF, heart failure with preserved ejection fraction; NYHA, New York Heart Association; BMI, body mass index; BNP, B-natriuretic peptide; LVEF, left ventricular ejection fraction; LVEDP, left ventricular end diastolic pressure; MAP, mean arterial pressure; LAVI, left atrial volume index; CAD, coronary artery disease; AV, atrio ventricular; PAC, premature atrial contraction; LA, left atria.

Table 2). Also, there was a trend towards patients with abnormal CFR having higher rates of AF than those patients with normal CFR (32% versus 15%, P=0.07; **Table 1**). Similarly, patients with HFpEF were older (64.2±10.1 versus 55.7±11.9; P=0.001), had higher average BNP, and had a higher prevalence of HTN, CKD, dyslipidemia, COPD, diabetes, angina and obesity than those patients without HFpEF (**Table 2**). AF was documented in 35% of patients with HFpEF versus 10% without HFpEF (P=0.007). Average LVEDP (P<0.001) and heart rate (P=0.04) were higher in HFpEF patients. ECG showed longer left atrial (LA) duration and QTc interval in HFpEF patients than in those patients without. Patients with AF (61%) and patients with HFpEF (62%) or both (71%) were more likely to have abnormal CFR than those patients without these conditions. Of the patients with AF and abnormal CFR, 91% had HFpEF.

Clinical predictors of the associations between AF, CMD and HFpEF, and overall outcome

A univariate logistic regression model demonstrated that older age, HFpEF, CKD, COPD, elevated BNP, AVB, PAC, prolonged P wave duration and PR interval are predictors of AF in this

Table 3. Logistic regression model for atrial fibrillation and/or heart failure

A. AF		
Characteristics	OR (95% CI)	*P* value
Age	1.06 (1.0-1.1)	0.02
CKD	3.36 (1.1-10.0)	0.03
COPD	5.18 (1.6-16)	0.004
HFpEF	4.85 (1.4-16.4)	0.01
BNP	1.00 (1.0-1.0)	0.03
AV Block	6.88 (1.6-28)	0.007
PAC	2.49 (1.05-5.9)	0.04
PR interval	1.03 (1.0-1.05)	0.005
P wave	1.06 (1.0-1.1)	0.009
B. HFpEF		
Characteristics	OR (95% CI)	*P* value
Age	1.07 (1.02-1.1)	0.003
HTN	6.17 (1.6-23.8)	0.008
CKD	3.36 (1.1-10.1)	0.03
Dyslipidemia	4.38 (1.5-12.8)	0.007
COPD	2.62 (1.02-6.7)	0.046
Diabetes	3.44 (1.35-8.8)	0.01
Angina	0.22 (0.08-0.6)	0.004
NYHA class ≥III	16.3 (2.0-132)	0.009
BNP	1.01 (1.0-1.0)	0.04
BMI	1.09 (1.0-1.1)	0.004
P wave	1.03 (1.0-1.07)	0.054
LA duration	1.03 (1.0-1.07)	0.05
C. Concurrent AF and HFpEF		
Characteristics	OR (95% CI)	*P* value
Age	1.07 (1.01-1.14)	0.02
CKD	6.56 (1.89-22.73)	0.003
COPD	4.05 (1.20-13.63)	0.02
Angina	0.21 (0.06-0.72)	0.01
NYHA class ≥III	3.96 (1.06-14.8)	0.04
BNP	1.00 (1.0-1.0)	0.03
LAVI	1.10 (1.01-1.19)	0.03
Abnormal CFR	4.38 (1.24-15.48)	0.02
PAC	2.07 (1.01-4.25)	0.046
P wave	1.05 (1.00-1.10)	0.04
LA duration	1.06 (1.01-1.10)	0.02

Abbreviations: AF indicates atrial fibrillation; HFpEF, heart failure with preserved ejection fraction; OR, odds ratio; CI, confidence interval; CKD, chronic kidney disease; COPD, chronic obstructive lung disease; NYHA, New York Heart Association; BNP, B-natriuretic peptide; LAVI, left atrial volume index; CFR, coronary flow reserve; AV, atrio ventricular; PAC, premature atrial contraction; LA, left atria.

population (P<0.05, **Table 3A**). HFpEF was associated with older age, HTN, CKD, hyperlipidemia, COPD, diabetes, absence of angina, high NYHA class, BNP, P wave duration, and LA duration (P<0.05, **Table 3B**). There were several univariate predictors of AF in HFpEF patients including older age, CKD, COPD, angina, NYHA Class ≥III, abnormal CFR, enlarged LA, elevated BNP, PAC, prolonged P wave duration and LA conduction delay (P<0.05, **Table 3C**). Abnormal CFR was a predictor of HFpEF with concomitant AF (HR 4.38, P=0.02). Multivariate logistic regression analysis demonstrated predictors of CMD include abnormal IMR (OR=8.78, p=0.001), AF (OR=5.50, P=0.02), diabetes (OR=3.77, P=0.035), higher heart rate (OR=1.05, P=0.02), female gender (OR=0.25, P=0.053), and older age (OR=0.96, P=0.16). The long-term survival and HF hospitalization were evaluated in our study population. Patients with abnormal CFR were associated with lower survival free of HF hospitalization at one-year compared to those with normal CFR during a median of 2.2 years follow up (70.8% versus. 92.8% in 1-year, P=0.01) (**Figure 1**). Also, patients with either HFpEF or AF had lower survival free of HF hospitalization at one-year compared to patients with neither HFpEF nor AF (71.9% versus 100% in 1-year, P=0.001).

Discussion

Our unique study presents several original findings. 1) There is significant association between CMD and AF with or without HFpEF. 2) CMD is highly prevalent in patients with AF. 3) CMD is a predictor of concomitant AF and HFpEF. 4) CMD and AF or HFpEF are associated with higher risk of mortality and HF hospitalization. 5) There was no significant sex- and race-based difference in the relationship between CMD, AF and HFpEF. 6) AF, diabetes, older age, female gender, and higher heart rate were predictors of CMD.

Recent studies showed high prevalence of CMD in HFpEF patients without excluding underlying obstructive CAD [1-3, 6, 15]. In PROMIS HFpEF study CFR was measured indirectly with adenosine stress echocardiography [3] and the study was unable to exclude coronary artery atherosclerosis as potential reason for impaired CFR (<2.5) in the HFpEF patients. Authors stated that systematic coronary angiography in all patients to exclude epicardial CAD and invasive coronary assessment of the index of microvascular resistance would have been difficult in a

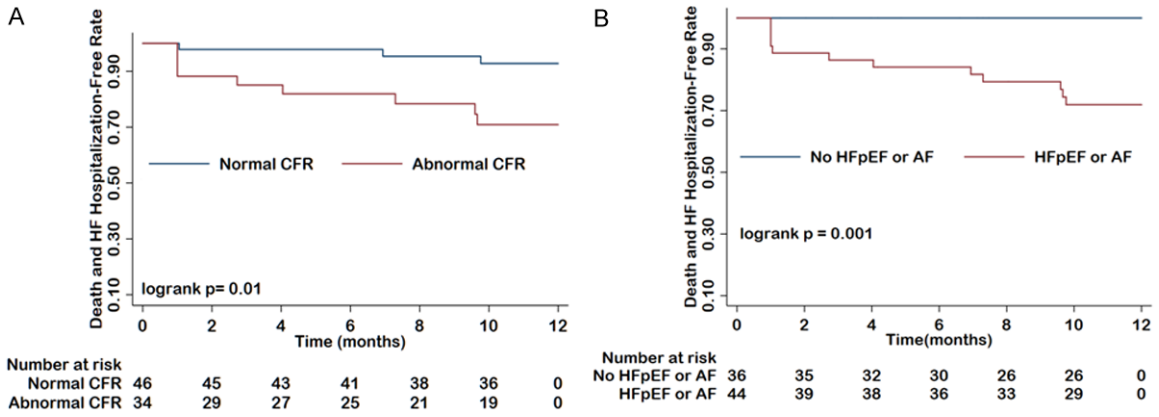

Figure 1. Kaplan-Meier curves demonstrate the time to survival and hospitalization based on coronary flow reserve (CFR) (A) and atrial fibrillation (AF) with heart failure with preserved ejection fraction (HFpEF) (B).

study the size of PROMIS, but both could have added an additional dimension to the evaluation of CMD in HFpEF. In our study, all of our patients underwent coronary angiography and ICPS. We measured CFR and IMR directly with ICPS for diagnosis of CMD and also exclusion of macrovascular CAD in our patients. Indeed, CMD diagnosis with CFR measurement by using ICPS is the gold-standard. All of our patients underwent ICPS with the measurements of CFR and IMR in addition to coronary angiogram for CAD and left ventricular end diastolic pressure measurement. Importantly, obstructive CAD was ruled out in our study, whereas non-invasive determination of CFR does not rule this out. We defined CMD with abnormal CFR (<2.0) in the absence of obstructive CAD [1, 2, 5].

Here we provide evidence of the clinical association between AF and CMD in the presence or absence of HFpEF. This has a major clinical implication for cardiovascular health. Our findings can guide novel strategies for the prevention AF and/or CMD. By using invasive CFR measurements, our study shows significant association of CMD and AF in a population in which women and minority patients are well-represented. The majority of our patients with AF (85%) had CMD and one third of the patients with CMD were found to have AF. Almost all patients with AF and CMD (91%) had HFpEF. Thus, there was a strong association between CMD and AF with concomitant HFpEF. We also found that CMD is associated with higher risk of mortality and HF hospitalization compared to those without CMD. Similarly, patients with AF or HFpEF showed lower survival free of HF hospitalization. AF with and without HFpEF was associated with older age, CKD, COPD, elevated BNP, angina, NYHA Class ≥III, enlarged LA, AVB, PAC and prolonged P wave duration. Abnormal CFR was a predictor of AF with concomitant HFpEF in our study population. These clinical predictors are useful for the risk stratification and management of the patients.

Recent studies indicated that CMD contributes to HFpEF pathophysiology directly through cardiomyocyte stiffening and diffuse interstitial fibrosis, as well as indirectly through exercise-induced myocardial ischemia and LV systolic and diastolic dysfunction [1, 27]. However, the effect of CMD in AF pathogenesis and its molecular mechanism are unclear. Myocardial fibrosis is a potential common pathway for AF, CMD and HFpEF [1, 8-17, 27-34]. We and others proposed that CMD may cause atrial myocardial disease with possible fibrosis and inflammation that may facilitate atrial substrate for AF [22, 23, 27-34]. A small clinical study showed impaired myocardial hyperemic perfusion reserve in persistent lone AF by using positron emission tomography which was partially reversible with restoring sinus rhythm [7]. The authors suggested that CMD in these patients was linked to the arrhythmia, sympathetic innervation, neurohormonal activation, endothelial dysfunction, or myocardial remodeling. Here, our study demonstrates that CMD is associated with AF. Mechanisms of the association between CMD, AF and HFpEF are not known. Arrhythmogenic atrial electro-anatomical remodeling is critical in development of AF which is triggered by multiple clinical or molec-

ular factors including stretch, neurohormonal activation, and oxidative stress. Myocardial perfusion is essential to contractility and electrical stability. As a result, CMD may have a role in facilitating atrial remodeling and electrical instability. Atrial electro-anatomical remodeling with AF and HFpEF is associated with metabolic dysregulation, energy depletion, oxidative stress, inflammation and fibrosis [28-34]. A recent study of evaluating epicardial fat volume, a surrogate for microvascular inflammation, in patients with HFpEF demonstrated that fat volume correlates to presence of AF and diabetes, supporting the hypothesis that CMD can be a pathogenic link between HFpEF and AF [34]. Whether CMD causes AF is not known. However, it is known that AF occurs in up to one-half of patients with HFpEF and effects the clinical outcome [15, 18, 35, 36]. Our recent studies in both mouse and human atria demonstrated progressive atrial remodeling in the coexistence of AF and HF that included atrial enlargement, cardiomyocyte loss, fibrosis and heterogeneous conduction [22, 23, 29-31]. CMD can provide insight into the mechanism of atrial remodeling in relation to AF and HFpEF.

The strengths of our study include 1) evaluating complex relationships between AF, CMD and HFpEF, 2) using the gold-standard diagnostic test for CMD with CFR measurement by using ICPS and excluding obstructive CAD, 3) A low cutoff for CFR (<2.0) improved specificity for the diagnosis of CMD and 4) representation of women and minorities in the study population including AA women. Diagnostic accuracy of CMD in our study is an important aspect for the evaluation of the association between CMD in AF and HFpEF. We ruled out obstructive CAD, which could potentially confound non-invasive assessment for CMD. In other studies, CFR was measured indirectly by using positron emission tomography or cardiac magnetic resonance imaging or Doppler [3, 6, 7]. Although the sample size and low event rate are limitations of this study, given the nature of CMD diagnosis with invasive coronary study, sample size is equitable for the analysis. Minor insufficiencies or variation may have occurred in the data collection. Prevalence of subclinical AF before the ICPS may have been higher.

In conclusion, our study reveals that there is significant association between CMD and AF, especially with concomitant HFpEF. CMD is highly prevalent in patients with AF and HFpEF, and affects clinical outcomes. Evaluation of CMD in patients with AF and vice versa is a reasonable strategy for early detection and treatment patients these disease processes, particularly in patients with HFpEF. Thus, our study has significant clinical implication for risk stratification and management of patients with AF and/or CMD in addition to scientific advancement in the field. Ultimately, our findings will help to improve AF- and CMD-related morbidity and mortality by facilitating early diagnosis and prevention of AF and CMD.

Disclosure of conflict of interest

None.

Address correspondence to: Dr. Cevher Ozcan, Center for Arrhythmia Care, Heart and Vascular Center, University of Chicago Medicine, Section of Cardiology, 5841 S. Maryland Avenue, MC 6080, Chicago, IL 60637, USA. Tel: 773-702-2559; Fax: 773-702-8875; E-mail: cozcan@uchicago.edu

References

[1] Taqueti VR and Di Carli MF. Coronary microvascular disease pathogenic mechanisms and therapeutic options: JACC State-of-the-Art Review. J Am Coll of Cardiol 2018; 72: 2625-2641.

[2] Dryer K, Gajjar M, Narang N, Lee M, Paul J, Shah AP, Nathan S, Butler J, Davidson CJ, Fearon WF, Shah SJ and Blair JEA. Coronary microvascular dysfunction in patients with heart failure with preserved ejection fraction. Am J Physiol Heart Circ Physiol 2018; 314: H1033-1042.

[3] Shah SJ, Lam CSP, Svedlund S, Saraste A, Hage C, Tan RS, Beussink-Nelson L, Ljung Faxén U, Fermer ML, Broberg MA, Gan LM and Lund LH. Prevalence and correlates of coronary microvascular dysfunction in heart failure with preserved ejection fraction: PROMIS-HFpEF. Eur Heart J 2018; 39: 3439-3450.

[4] Patel AR and Blair JA. Heart failure with preserved ejection fraction: have we finally found the perfect noninvasive biomarker? Circ Cardiovas Imaging 2016; 9: e005905-005907.

[5] Lee JM, Jung JH, Hwang D, Park J, Fan Y, Na SH, Doh JH, Nam CW, Shin ES and Koo BK. Coronary flow reserve and microcirculatory resistance in patients with intermediate coronary stenosis. J Am Coll Cardiol 2016; 67: 1158-1169.

[6] Taqueti VR, Solomon SD, Shah AM, Desai AS, Groarke JD, Osborne MT, Hainer J, Bibbo CF,

Dorbala S, Blankstein R and Di Carli MF. Coronary microvascular dysfunction and future risk of heart failure with preserved ejection fraction. Eur Heart J 2018; 39: 840-849.

[7] Range FT, Schäfers M, Acil T, Schäfers KP, Kies P, Paul M, Hermann S, Brisse B, Breithardt G, Schober O and Wichter T. Impaired myocardial perfusion and perfusion reserve associated with increased coronary resistance in persistent idiopathic atrial fibrillation. Eur Heart J 2007; 28: 2223-2230.

[8] Estes MN, Sacco RL, Al-Khatib SM, Ellinor PT, Bezanson J, Alonso A, Antzelevitch C, Brockman RG, Chen PS, Chugh SS, Curtis AB, DiMarco JP, Ellenbogen KA, Epstein AE, Ezekowitz MD, Fayad P, Gage BF, Go AS, Hlatky MA, Hylek EM, Jerosch-Herold M, Konstam MA, Lee R, Packer DL, Po SS, Prystowsky EN, Redline S, Rosenberg Y, Van Wagoner DR, Wood KA, Yue L and Benjamin EJ. American Heart Association atrial fibrillation research summit: a conference report from the American Heart Association. Circulation 2011; 124: 363-372.

[9] Burstein B and Nattel S. Atrial fibrosis: mechanisms and clinical relevance in atrial fibrillation. J Am Coll Cardiol 2008; 51: 802-809.

[10] January CT, Wann LS, Alpert JS, Calkins H, Cigarroa JE, Cleveland JC Jr, Conti JB, Ellinor PT, Ezekowitz MD, Field ME, Murray KT, Sacco RL, Stevenson WG, Tchou PJ, Tracy CM and Yancy CW. 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation. J Am Coll Cardiol 2014; 64: e1-76.

[11] Lam CS, Rienstra M, Tay WT, Liu LC, Hummel YM, van der Meer P, de Boer RA, Van Gelder IC, van Veldhuisen DJ, Voors AA and Hoendermis ES. Atrial fibrillation in heart failure with preserved ejection fraction: association with exercise capacity, left ventricular filling pressures, natriuretic peptides, and left atrial volume. JACC Heart Fail 2017; 5: 92-98.

[12] Santema BT, Kloosterman M, Van Gelder IC, Mordi I, Lang CC, Lam CSP, Anker SD, Cleland JG, Dickstein K, Filippatos G, Van der Harst P, Hillege HL, Ter Maaten JM, Metra M, Ng LL, Ponikowski P, Samani NJ, Van Veldhuisen DJ, Zwinderman AH, Zannad F, Damman K, Van der Meer P, Rienstra M and Voors AA. Comparing biomarker profiles of patients with heart failure: atrial fibrillation vs. sinus rhythm and reduced vs. preserved ejection fraction. Eur Heart J 2018; 39: 3867-3875.

[13] Shantsila E, Shantsila A, Blann AD and Lip GY. Left ventricular fibrosis in atrial fibrillation. Am J Cardiol 2013; 111: 996-1001.

[14] Yancy CW, Jessup M, Bozkurt B, Butler J, Casey DE Jr, Drazner MH, Fonarow GC, Geraci SA, Horwich T, Januzzi JL, Johnson MR, Kasper EK, Levy WC, Masoudi FA, McBride PE, McMurray JJ, Mitchell JE, Peterson PN, Riegel B, Sam F, Stevenson LW, Tang WH, Tsai EJ and Wilkoff BL. ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol 2013; 62: e147-239.

[15] Santhanakrishnan R, Wang N, Larson MG, Magnani JW, McManus DD, Lubitz SA, Ellinor PT, Cheng S, Vasan RS, Lee DS, Wang TJ, Levy D, Benjamin EJ and Ho JE. Atrial fibrillation begets heart failure and vice versa: temporal associations and differences in preserved versus reduced ejection fraction. Circulation 2016; 133: 484-492.

[16] Braunwald E. Shattuck lecture--cardiovascular medicine at the turn of the millennium: triumphs, concerns, and opportunities. N Engl J Med 1997; 337: 1360-1369.

[17] Anter E, Jessup M and Callans DJ. Atrial fibrillation and heart failure: treatment considerations for a dual epidemic. Circulation 2009; 119: 2516-2525.

[18] Benjamin EJ, Muntner P, Alonso A, Bittencourt MS, Callaway CW, Carson AP, Chamberlain AM, Chang AR, Cheng S, Das SR, Delling FN, Djousse L, Elkind MSV, Ferguson JF, Fornage M, Jordan LC, Khan SS, Kissela BM, Knutson KL, Kwan TW, Lackland DT, Lewis TT, Lichtman JH, Longenecker CT, Loop MS, Lutsey PL, Martin SS, Matsushita K, Moran AE, Mussolino ME, O'Flaherty M, Pandey A, Perak AM, Rosamond WD, Roth GA, Sampson UKA, Satou GM, Schroeder EB, Shah SH, Spartano NL, Stokes A, Tirschwell DL, Tsao CW, Turakhia MP, VanWagner LB, Wilkins JT, Wong SS and Virani SS; American Heart Association Council on Epidemiology and Prevention Statistics Committee and Stroke Statistics Subcommittee. Heart Disease and Stroke Statistics-2019 update: a report from the American Heart Association. Circulation 2019; 139: e56-528.

[19] Allan T, Dryer K, Fearon WF, Shah SJ and Blair JEA. Coronary microvascular dysfunction and clinical outcomes in patients with heart failure with preserved ejection fraction. J Card Fail 2019; 25: 843-845.

[20] Kern M. Coronary physiology revisited: practical insights from the cardiac catheterization laboratory. Circulation 2000; 101: 1344-1351.

[21] Fearon WF, Balsam LB, Farouque HMO, Farouque HM, Caffarelli AD, Robbins RC, Fitzgerald PJ, Yock PG and Yeung AC. Novel index for invasively assessing the coronary microcirculation. Circulation 2003; 107: 3129-3132.

[22] Ozcan C, Strom JB, Newell JB, Mansour MC and Ruskin JN. Incidence and predictors of atrial fibrillation and its impact on long-term

survival in patients with supraventricular arrhythmias. Europace 2014; 16: 1508-1514.
[23] Deshmukh A, Kim G, Burke M, Anyanwu E, Jeevanandam V, Uriel N, Tung R and Ozcan C. Atrial arrhythmias and electroanatomical remodeling in patients with left ventricular assist devices. J Am Heart Assoc 2017; 6: e005340-005349.
[24] McKee P, Castelli W, McNamara P and Kannel W. The natural history of congestive heart failure: the Framingham study. N Engl J Med 1971; 285: 1441-1446.
[25] Picard MH, Adams D, Bierig SM, Dent JM, Douglas PS, Gillam LD, Keller AM, Malenka DJ, Masoudi FA, McCulloch M, Pellikka PA, Peters PJ, Stainback RF, Strachan GM and Zoghbi WA. American Society of Echocardiography recommendations for quality echocardiography laboratory operations. J Am Soc Echocardiogr 2011; 24: 1-10.
[26] Nagueh SF, Smiseth OA, Appleton CP, Byrd BF 3rd, Dokainish H, Edvardsen T, Flachskampf FA, Gillebert TC, Klein AL, Lancellotti P, Marino P, Oh JK, Alexandru Popescu B and Waggoner AD. Recommendations for the evaluation of left ventricular diastolic function by echocardiography: an update from the American society of echocardiography and the European association of cardiovascular imaging. J Am Soc Echocardiogr 2016; 29: 277-314.
[27] Paulus WJ and Tschöpe C. A novel paradigm for heart failure with preserved ejection fraction: comorbidities drive myocardial dysfunction and remodeling through coronary microvascular endothelial inflammation. J Am Coll of Cardiol 2013; 62: 263-271.
[28] Heijman J, Algalarrondo V, Voigt N, Melka J, Wehrens XH, Dobrev D and Nattel S. The value of basic research insights into atrial fibrillation mechanisms as a guide to therapeutic innovation: a critical analysis. Cardiovasc Res 2016; 109: 467-479.
[29] Weil BR and Ozcan C. Cardiomyocyte remodeling in atrial fibrillation and hibernating myocardium: shared pathophysiologic traits identify novel treatment strategies? BioMed Res Int 2015; 2015: 587361-587368.
[30] Ozcan C, Battaglia E, Young R and Suzuki G. LKB1 knockout mouse develops spontaneous atrial fibrillation and provides mechanistic insights into human disease process. J Am Heart Assoc 2015; 4: e001733-001746.
[31] Ozcan C, Li Z, Kim G, Jeevanandam V and Uriel N. Molecular mechanism of the association between atrial fibrillation and heart failure includes energy metabolic dysregulation due to mitochondrial dysfunction. J Card Fail 2019; 25: 911-920.
[32] Goette A, Kalman JM, Aguinaga L, Akar J, Cabrera JA, Chen SA, Chugh SS, Corradi D, D'Avila A, Dobrev D, Fenelon G, Gonzalez M, Hatem SN, Helm R, Hindricks G, Ho SY, Hoit B, Jalife J, Kim YH, Lip GY, Ma CS, Marcus GM, Murray K, Nogami A, Sanders P, Uribe W, Van Wagoner DR and Nattel S. EHRA/HRS/APHRS/SOLAECE expert consensus on atrial cardiomyopathies: definition, characterization, and clinical implication. Europace 2016; 18: 1455-1490.
[33] Alex L, Russo I, Holoborodko V and Frangogiannis NG. Characterization of a mouse model of obesity-related fibrotic cardiomyopathy that recapitulates features of human heart failure with preserved ejection fraction. Am J Physiol Heart Circ Physiol 2018; 315: H934-949.
[34] van Woerden G, Gorter TM, Westenbrink BD, Willems TP, van Veldhuisen DJ and Rienstra M. Epicardial fat in heart failure patients with mid-range and preserved ejection fraction. Eur J Heart Fail 2018; 20: 1559-1566.
[35] Zafrir B, Lund LH, Laroche C, Ruschitzka F, Crespo-Leiro MG, Coats AJS, Anker SD, Filippatos G, Seferovic PM, Maggioni AP, De Mora Martin M, Polonski L, Silva-Cardoso J and Amir O. Prognostic implications of atrial fibrillation in heart failure with reduced, mid-range, and preserved ejection fraction: a report from 14 964 patients in the European society of cardiology heart failure long-term registry. Eur Heart J 2018; 39: 4277-4284.
[36] Sartipy U, Dahlström U, Fu M and Lund LH. Atrial fibrillation in heart failure with preserved, mid-range, and reduced ejection fraction. JACC Heart Fail 2017; 5: 565-574.