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Measures of Ventricular-Arterial Coupling and Incident Heart Failure Preserved Ejection Fraction (HFpEF): A Matched Case-Control Analysis

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2) STRUCTURED ABSTRACT

Objectives—This study was designed to detect differences in markers associated with incident heart failure preserved ejection fraction (HFpEF) when comparing matched case-control groups.

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Background—Evidence continues to demonstrate increasing prevalence, cost and mortality implications of HFpEF, but clearly defined parameters that distinguish between controls and HFpEF have not been established.

Methods—A study cohort of case (incident patients with HFpEF, n=155) and matched control (patients with no prior HF, n=155) groups was retrospectively identified. Matching criteria included race, sex, age and date of echocardiogram (within 1 year). Physiologic and echocardiographic markers were collected from previously acquired transthoracic echocardiograms. These echocardiogram images were re-analyzed and measures of ventricular-arterial coupling were calculated. Using conditional logistic regression and controlling for covariates, models were fit to detect differences in HFpEF markers between cases and controls.

Results—Statistically significant differences in markers that reflect ventricular elastance (Ees) ($p=0.007$) and left atrial diameter (LAdiam) ($p=0.04$) were detected when comparing the case and control groups. Conditional logistic regression analyses suggested a 40% higher odds of being in the case group with every 1 unit increase in Ees, OR 1.40 (1.10, 1.79) and a 2.92 times higher odds of being in the case group for every 1 cm increase in LAdiam, OR 2.92 (1.064, 7.994).

Conclusions—Ees and LAdiam are easily measurable echocardiographic markers which may have a role in identifying and tracking the progression toward incident HFpEF without increasing cost or risk to the patient. Prospective studies are indicated to explore the use of Ees and LAdiam as predictors of impending HFpEF.

Keywords

Heart Failure Preserved Ejection Fraction (HFpEF); Diastolic Heart Failure; Matched case-control; Ventricular-arterial coupling

Introduction

Heart failure preserved ejection fraction (HFpEF) accounts for at least 50% of all hospital admissions for heart failure (HF) in the United States (U.S.) yet measures that predict risk of diagnosis and onset of HFpEF are lacking.^{1,2} HFpEF is a heterogeneous syndrome likely affected by multiple comorbidities with inflammatory precursors.^{3,4} The pathophysiology of HFpEF is complex reflected by left ventricular (LV) hypertrophy, increased pro-inflammatory markers, slow LV relaxation, LV diastolic stiffness, decreased LV systolic performance, left atrial remodeling, increased peripheral vascular resistance, impaired endothelial function, increased pulmonary arterial and venous resistance, neurohormonal activation and mismatched ventricular-arterial coupling.^{2,3}

Clinical diagnosis of HFpEF is typically based on patient history and physical examination; however, epidemiologic studies suggest that asymptomatic patients may have pre-clinical evidence of echocardiographic abnormalities such as LV diastolic dysfunction (DD).^{5,6} A normal ejection fraction (EF) does not preclude abnormalities in vascular load, contractility and ventricular-arterial stiffening.⁷ Accordingly, echocardiographic measurements of left ventricular hypertrophy (LVH), estimates of left ventricular filling (E/e'), left atrial (LA) size, global longitudinal strain (GLS), arterial elastance (Ea), ventricular elastance (Ees) and ventricular-arterial coupling^{7–10} have been proposed as markers of risk in HFpEF.

Most studies predicting risk or outcomes in patients with HFpEF compared patients with HFpEF to those with heart failure reduced ejection fraction (HFrEF)⁷⁻⁹ while only a few have evaluated the impact of age, sex and race on incident HFpEF which suggests multiple phenotypes.^{11,12} Although some studies suggest higher relative mortality and earlier age of onset in Black patients with HFpEF compared to White patients,^{11,13} none of the studies included race as a matching factor. Therefore, studies that include samples stratified by age, race and sex to identify markers that predict impending HFpEF may help establish informed approaches for HFpEF prevention.

Although LV ejection fraction (EF) is the most commonly used method for assessing LV function,¹⁴ EF does not account for vascular load, contractility and the interaction of ventricular-arterial stiffening.⁷ Ees(mmHg/ml), a measure of ventricular elastance, and Ea (mmHg/ml) a measure of atrial elastance, may be more robust measures than EF alone in reflecting the dynamic interaction of ventricular arterial coupling on the risk of developing early HFpEF. Ees is calculated from end-systolic pressure volume relationship (ESPVR) which is a vascular load-independent measure of contractile function and by including chamber volumes takes into account LV chamber size and remodeling, and Ea(mmHg/ml), a measure of arterial elastance, incorporates end-systolic pressure (ESP) and end-diastolic volume to incorporate stroke volume (SV) reflected in the formula $Ea=ESP/SV$.¹⁵⁻¹⁷ Through normal aging, ventricular stiffening increases out of proportion to vascular load,¹⁶ however, studies are lacking and novel approaches are needed to improve HFpEF risk stratification in representative and diverse populations.

Methods

Design

The study was observational with a retrospective matched case-control design. This study was approved by the University of North Carolina at Chapel Hill and Duke University institutional review boards and all data processing was completed with strict adherence to the Health Insurance Portability and Accountability Act (HIPAA).

Study Patients

Case and control groups included residents of Durham County to facilitate enrollment of patients with similar socioeconomic, racial and access to medical care.

Case Group—The case group consists of inpatients discharged from Duke University Hosptial in Durham, North Carolina from January 1, 2007 thru January 1, 2014 with a primary discharge diagnosis of incident HFpEF based on coding of the International Classification of Diseases, 9th revision, Clinical Modification (ICD-9_CM) code book with codes for 428.30 (diastolic heart failure, unspecified), 428.31 (acute diastolic heart failure), 428.32 (chronic diastolic heart failure), 428.33 (acute on chronic diastolic heart failure). This time period was selected because echocardiogram institutional protocols and methods were updated in 2007. Incident HFpEF diagnosis was verified by the study investigator based on the European Society of Cardiology (ESC) diagnostic criteria for HFpEF.¹⁸ Patients were required to have at least 1 echocardiogram completed within one month prior to

hospitalization. The ESC diagnostic criteria for HFpEF, described as heart failure normal ejection fraction (HFNEF) is one of four published criteria; however, the ESC guide is the only document that incorporates clinical symptoms and echocardiogram markers into the diagnostic guideline without using invasive measures. Specifically, the ESC diagnostic criteria require clinical signs and symptoms of HF (dyspnea, fluid overload or congestion), LVEF>50%, evidence of DD, elevated left ventricular end diastolic pressure (LVEDP)>16mmHg, pulmonary capillary wedge pressure (PCWP)>12mmHg, $E/e' > 15$, mitral flow velocity Doppler signal showing early ventricular filling (E)/late diastolic filling (A) ratio<0.5+deceleration time (DT) >280ms, LA size>40mL/m², or LV mass>149g/m²-men or >122g/m²-women.¹⁸

Control Group—Using medical records, patients eligible for the control group were those presenting either through the emergency department or to an outpatient clinic for evaluation and management of shortness of breath, based on ICD-9 codes for shortness of breath (786.05) to Duke University from January 1, 2007-January 1, 2014 and required normal echocardiograms for inclusion. Both emergency department and outpatient clinics were used to obtain an adequate sample size to match to the case group. Patients were matched one to one to the case group based on age (3 years or less), race, sex and a record of at least 1 echocardiogram completed within 1 year of the matched case. See Table I.

Inclusion/Exclusion Criteria—All included patients were age 18years with an address in a Durham County zip code. Patients were excluded if medical record review indicated prior HF hospitalization for either HFpEF or HFrEF, prior EF<50%, presence of moderate/severe mitral valve disease, history of aortic or mitral valve surgery or vegetation, heart transplantation, hypertrophic obstructive cardiomyopathy, atrial fibrillation at the time of echocardiogram, congenital heart disease, severe pulmonary arterial hypertension (not due to diastolic dysfunction), connective tissue disorders such as rheumatoid arthritis, shock or advanced malignancy. See Table II.

Data Collection

All study data were extracted from pre-existing electronic sources (medical records, echocardiogram data/imaging databases).

Echocardiogram

Data from previously obtained two-dimensional (2D), M (motion)-mode Doppler transthoracic echocardiograms within the Duke University Health System were used for study analysis. All previously obtained echocardiograms were acquired using standardized techniques recommended by the ASE.¹⁹ All echocardiogram image measurements used by the investigator for the following formulas were obtained by certified cardiac sonographers. The following measurements are incorporated into a calculation that estimates ventricular-arterial elastance.

Ea, the measure of arterial elastance, was calculated as the ratio of end-systolic pressure volume to stroke volume ($Ea = ESP/SV$). ESP was estimated as 0.90 multiplied times systolic blood pressure (SBP) by manual cuff at the time of echocardiogram as recommended²⁰.

Stroke volume (SV, cm³) was measured from the left ventricular outflow tract (LVOT) diameter at the pulse wave (PW) Doppler signal.²⁰

Ees (ventricular elastance) was calculated using the single-beat method outlined by Chen and colleagues²⁰ as described in the following equations:

$$\text{Ees}(\text{sb}) = (\text{DBP} - (\text{Endest} * \text{ESP})) / (\text{SV} * \text{Endest})$$

$$\text{Endest} = 0.0275 - (0.165 * \text{EF}) + 0.3656 * (\text{DBP} / \text{ESP}) + (0.515 * \text{Endavg})$$

$$\text{Endavg} = 0.35695 + (-7.2266 * \text{tn}) + (74.249 * \text{tn}^2) + (-307.39 * \text{tn}^3) + (684.54 * \text{tn}^4) + (-856.92 * \text{tn}^5) + (571.95 * \text{tn}^6) + (-15$$

tn (ms) = R wave to flow onset time / R wave to flow end time; determined noninvasively from the echo Doppler signal in the LV outflow tract by pulse wave.

Statistical Methods

All variables with approximately symmetric distributions are described by their mean and standard deviation, and variables with skew are described by the median and interquartile range. Bivariate associations between case status and markers (SBP DBP, HR, BMI, Ea, Ees, Ea/Ees, LAdiam) were assessed using paired t-tests. Markers with $p < 0.1$ in the bivariate analysis were included in a single multivariable conditional logistic regression model for case status. Collinearity diagnostics using measures of tolerance (collinear if < 0.40) and variance inflation factors (VIF) (collinear if > 2.50), were calculated for each variable in the regression model to assess for multicollinearity. To assess the validity of pooling the two sources of controls (ED and outpatient), we examined whether the effect differed by source by testing the interaction between each biomarker and an indicator of source.

Statistical significance was defined as $p < 0.05$. Statistical analyses were performed using SAS, Inc., 9.4, statistical software (SAS Institute Inc., Cary, North Carolina) and JMP, version 11.2.0 (SAS Institute Inc., Cary, North Carolina).

Results

Study Population

Of the 876 potential case patients (incident HFpEF) identified, 624 were excluded leaving a case group of 252 incident patients with HFpEF eligible for matching. The most common reasons for exclusion included: a) evidence of EF $< 50\%$ on prior echocardiogram ($n = 296$, 49%), b) no incident HFpEF ($n = 188$, 30%) defined by the HFNEF diagnostic criteria outlined by the ESC¹⁸, c) severe mitral or aortic valve disease ($n = 89$, 14%). See Figure I.

Of the potential 1035 control patients who had previously presented to the emergency department, 720 were excluded due to death within 1 year of visit due to comorbid conditions such as advanced malignancy or acute pulmonary embolism (67%) or echocardiogram evidence of EF $< 50\%$ (20%), leaving 315 eligible for the control group. Of the potential 1175 patients identified electronically who had presented to outpatient clinics, 1007 were excluded mostly due echocardiogram evidence of EF $< 50\%$ (67%), leaving 168 patients eligible for the control group. Of the 483 total controls identified, after matching, 155 pairs were included in the analysis. See Figure II.

The study included 155 matched pairs for a total sample of 310 patients. The mean age for the entire cohort was 69 years (SD 12.56), 74% are female and 60% are Black. Though the groups were matched on age (within 3 years), the control group was slightly older than the case group (mean of 70 versus 67 years). In comparing the means of markers between the case and control groups, there were statistically significant differences in SBP, HR, BMI, Ees, LAdiam and Ees/Ea. See Table III.

Case-Control Biomarker Analysis Results

All effects with a bivariate $p < 0.1$ were considered and included in the single conditional logistic regression model, including SBP, DBP, HR, BMI, EF, LAdiam, Ea, Ees, Ea/Ees. Collinearity diagnostics suggested multicollinearity with SBP, DBP and Ees/Ea results (tolerance 0.11, 0.13, 0.14, respectively), (VIF 7.57, 7.69, 7.10, respectively) and therefore were eliminated from the final conditional logistic regression model. Therefore, in the final conditional logistic regression model the predictor variables included LAdiam, Ees, HR and BMI. The results of the conditional logistic regression comparing the case-control suggest statistically significant effects of Ees (0.007) and LAdiam (0.040). After controlling for covariates, a 1 unit increase in Ees was associated with a 40% higher odds, (OR=1.40; 95% CI 1.09, 1.79) of being in the case group. For LAdiam, every unit increase was associated with a 2.92 times increase (95% CI 1.064, 7.994) in odds of being in the case group. See Table IV.

The interactions between control source and Ees and LAdiam were included to assess whether the controls from the emergency department had an effect different from the controls of the outpatient clinics, and both were found to be non-significant ($p=0.76$, 0.51 , respectively).

Discussion

The primary objective of this study was to detect differences in clinical markers between the case and control groups. To preserve the comparability between groups, key methodologic principles²¹ were used to guide selection of the control group and consisted of three principles that included: a) study base, b) deconfounding and c) comparative accuracy.²² To preserve comparability of the study base, the case and control groups only included residents of one county which reduced the variability in patient population given that patients from regional, national and international locations were referred to the Health System. To further control the study base only previously completed 2D (dimensional) M (motion) mode Doppler echocardiograms were eligible for this study if they were a) ordered with the Health System, b) read at a certified and regulated core laboratory and c) adhered to standards set by the American Society of Echocardiography (ASE) on patients that met the inclusion and exclusion criteria.

In addition, the study successfully achieved the goal of an age, race and sex diverse sample with patients ranging from ages 33 to 99 years, 59% Black patients and 72% women. Based on 2012 U.S. Census Data, in Durham County, the general population is 38% White, 41% Black and 14% Hispanic.²³ By attaining this goal, measures that reflect risk were identified

regardless of diverse phenotype thus detecting markers that may represent early risk of HFpEF.

In comparing characteristics of the matched pairs, the case group had significantly higher SBP, HR, BMI, Ees LAdiam and Ees/Ea, regardless of age, race or sex. These findings are consistent with other studies evaluating HFpEF in which age and sex were controlled for although none of prior studies were case-control designs and none controlled for race.^{3,10,24} Within the case group, the mean value for Ees was higher (6.13 mmHg/ml) than published by Chen²⁰ (normal Ees usually 2 to 4), however to validate this finding, echocardiogram images were re-measured and re-calculated and echocardiogram reports were re-analyzed to insure that conditions such as hypertrophic cardiomyopathy and/or high output failure patients were not included within the case cohort. As to the reason for higher mean Ees than reported by Chen,²⁰ elevated SBP and underlying pathophysiology of the incident HFpEF group may be factors. It is noteworthy that in a published manuscript by Desai et al, in which Ees was measured with normal, hypertensive and patients with HFpEF, the mean Ees measures were 3.7 mmHg/ml, 8.1 mmHg/ml and 6.5 mmHg/ml, respectively²⁵. Consistent with the Desai paper, our findings demonstrated a mean Ees of 6.13 mmHg/ml. Further study in prospective longitudinal studies that include measures of ventricular elastance may clarify this finding. In addition, conditional logistic regression showed that increased Ees and LAdiam were associated with higher odds of membership in the case group. For each unit increase in Ees and/or LAdiam, there is a substantial increase in HFpEF risk. In this rigorously matched group of incident HFpEF to non HF patients, we found significant differences in readily available and clinically relevant measures that may represent composite markers of impending HFpEF risk. The markers within this study are not novel, but the study design, diverse study sample and integration of arterial and ventricular coupling suggest a novel approach to studying this phenomenon without increasing risk or cost to the patient.

Previous studies have demonstrated increases in Ees and LAdiam with age in women suggesting that this is due to age related LV stiffening.²⁶ However, in this study, increases in Ees and LAdiam were associated with higher odds of membership in the case group regardless of age, race or sex. This study suggests that future studies with a prospective design and evaluation of Ees and LAdiam may provide an opportunity for risk assessment. Although multiple physiologic mechanisms affect the pathogenesis of HFpEF, most would agree that clinical endpoints such as ventricular elastance and LAdiam may reflect progression of this disease if measured longitudinally.

In addition to Ees and LAdiam, the current literature supports use of global longitudinal strain (GLS) and E/e' , to track risk.^{27,28} GLS measured by echocardiogram has been shown to be an accurate measure of systolic function superior to EF and provides important prognostic information when predicting all-cause mortality and hospitalization for HF.²⁷ In addition, Donal et al. evaluated E/e' in 538 patients with HFpEF as a predictor of re-hospitalization and mortality and found when comparing E/e' to BNP, EF, right ventricular fractional shortening, and after adjusting for age and sex, only E/e' was the only statistically significant predictor (HR 1.49, $p=0.0012$).²⁸ In addition to E/e' as a predictor of LV filling, increased LA size has also been used as an indicator of increased LV filling pressures.^{29,30}

Paulus and Tschope provide a new model into the pathophysiology of HFpEF that includes a sequence of events that result in myocardial remodeling.³ Although new insights are emerging into HFpEF pathophysiology, the current literature lacks risk stratification of early markers that predicts impending HFpEF, especially when considering subgroups that are affected by incident HFpEF, such as Black patients.¹¹ More focused study is required to identify relevant markers that enable clinicians to mitigate risk and modify the progression to disease.

In addition, this study documented that 70% of patients identified with HFpEF solely based on ICD-9 codes did not meet criteria for incident HFpEF. The most common reasons for exclusion was evidence of prior echocardiograms with EF <50% (305 patients) and not meeting ESC diagnostic criteria (187 patients) for 'incident' HFpEF. For example, many of the patients with ICD-9 for HFpEF also included prior admissions for HFpEF thus not meeting criteria for this study. Given the substantial percent of patients excluded as a result of chart review, this finding has very important implications for retrospective and/or epidemiological research evaluating incident HFpEF using only ICD9 codes.

Limitations

One limitation of this study is related to the importance of associated co-morbidities and inflammatory markers in relationship to HFpEF. This study does not include an exhaustive list of clinical markers associated with incident HFpEF. The focus of this study was primarily on physiologic and echocardiographic markers of HFpEF available on conventional echocardiogram reports and images and did not specifically incorporate co-morbidities or pro-inflammatory markers into the matched case-control analysis. As suggested by Paulus and Tschope, the unique characteristics of HFpEF may be caused by inflammation more so than increases in LV load.³ Future studies that combine markers of inflammation and physiologic performance such as LA volume, GLS, E/e' and Ees, within a longitudinal design would likely contribute to the current science of early identification of markers that predict incident HFpEF.

Another limitation is that the validity of the study design is based on some assumptions. Medical record review was within a single health care system which requires the assumption that complete medical history (including inclusion/exclusion criteria) for each patient was available in that health system. Additionally, as with any case-control study, we assumed that control patients would have been admitted to the selected hospital, and thus been in the "case" group, had they developed HFpEF. Selecting locally-residing patients minimized both of these potential biases. In addition, unavailable pulse wave images from the LV outflow tract required for Ees and LAdiam led to missing Ees and LAdiam calculations, but still met necessary minimums for statistical analysis.

Conclusions

This matched case-control cohort revealed significant differences in readily available clinical markers such as SBP, HR, BMI, Ees and LAdiam. Changes in LAdiam and Ees were associated with higher odds of HFpEF development and thus may have predictive clinical utility. Translating into clinical practice, this study highlights the importance of shortness of

breath as a clinically relevant symptom in identifying patients with HFpEF. In addition, this study demonstrated feasibility in calculating Ees and LA diam from routinely obtained echocardiogram reports and images without increasing cost or risk to the patient while also revealing important epidemiologic implications and subsequent limitations of retrospective designs based solely on identifying subjects only by ICD-9 codes. Further exploration of the predictive value of tracking these markers in longitudinal designs suggests promise in identifying those at risk for incident HFpEF.

3) ABBREVIATIONS LIST

ACC	American College of Cardiology
ACCF	American College of Cardiology Foundation
AHA	American Heart Association
ASE	American Society of Echocardiography
ARB	Angiotensin Receptor Blockers
Ea(mmHg/ml)	Arterial Elastance
Ea/Ees(ratio)	Arterial/Ventricular Elastance
AF	Atrial Fibrillation
BMI(kg/m²)	Body Mass Index
BNP(pg/mL)	Brain Natriuretic Peptide
cMRI	Cardiac Magnetic Resonance Imaging
CO(L/min)	Cardiac Output
CAD	Coronary Artery Disease
CrCl(ml/min)	Creatinine Clearance
DM	Diabetes
DD(grade)	Diastolic Dysfunction
DBP(mmHg)	Diastolic Blood Pressure
E/A ratio	Early (E) and late (A) diastolic filling
(e')(cm/s)	Early Mitral Valve Annular Velocity
E(cm/s)	Early Ventricular Filling
EF(%)	Ejection Fraction
ESP	End Systolic Pressure Volume
ESC	European Society of Cardiology

GLS(%)	Global Longitudinal Strain
HIPAA	Health Insurance Portability and Accountability Act
HF	Heart Failure
HFNEF	Heart Failure Normal Ejection Fraction
HFrEF	Heart Failure Reduced Ejection Fraction
HFpEF	Heart Failure Preserved Ejection Fraction
HR(bpm)	Heart Rate
Hct(%)	Hematocrit
Hgb(g/dL)	Hemoglobin
HgbA1C(%)	Hemoglobin A1C
Hs-CRP (mg/L)	High Sensitivity C Reactive Protein
(μmol/L)	Homocysteine
HTN	Hypertension
IRB	Institutional Review Board
ICD-9	International Classification of Diseases, 9 th revision
IVRT (ms)	Isovolumetric Relaxation Time
A(cm/s)	Late Diastolic Filling
LAdiam(cm)	Left Atrial Diameter
LAE	Left Atrial Enlargement
LV	Left Ventricle
LA	Left Atrial
LVEDP(mmHg)	Left Ventricular End Diastolic Pressure
E/e' (ratio)	Left Ventricular Filling Pressure
LVH(grade)	Left Ventricular Hypertrophy
LVOT(cm)	Left Ventricular Outflow Track
Ees(mmHg/ml)	Left Ventricular Systolic Elastance
NHANES	National Health and Nutrition Examination Survey
PCWP (mmHg)	Pulmonary Capillary Wedge Pressure
RAAS	Renin-Angiotensin-Aldosterone System

SV(cm³)	Stroke Volume
SBP(mmHg)	Systolic Blood Pressure
TOPCAT	Treatment of Preserved Cardiac Function in Heart Failure with an Aldosterone Antagonist
U.S.	United States
WT(lbs)	Weight

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Highlights

- Measures of ventricular elastance and left atrial diameter may provide an opportunity for early risk assessment for incident HFpEF
- Identifying incident HFpEF solely by ICD9 diagnosis codes may be misleading.
- Increases in Ees and LAdiam were associated with membership in the case group regardless of age, race or sex

Figure I.
Process for identifying the Case Group

Figure II.
Process for identifying the Control Group

Table I

Case-Control Matching Criterion

Matching Control to Case	1:1
Age	within 3 years
Race	1:1
Sex	1:1
Echocardiogram	Within 1 year of match Case

Table II

Case-Control Inclusion/Exclusion Criterion

Inclusion Criteria	Exclusion Criteria
Age ≥18 years	Prior hospitalization for HFpEF or HFrEF
Durham County zip codes	Prior EF<50%
Echocardiogram within 1 month of HFpEF hospitalization (Case group)	Moderate/severe mitral valve disease
ESC diagnostic criteria for HFpEF	History of mitral or aortic valve surgery or vegetation
	Heart transplantation
	Hypertrophic obstructive cardiomyopathy
	Persistent tachycardia due to atrial fibrillation
	Congenital heart disease
	Severe pulmonary hypertension
	Connective tissue disorders
	Shock or advanced malignancy

Table III

Comparison of markers for the matched case-control

Matched case n=155		Characteristics, matched case-control				
Matched control n=155		Paired t-tests				
Parameter	Matched Group	N	Mean	SD	t	p
SBP(mmHg)	Case	154	144	25	4.42	
	Control	154	133	18		
DBP(mmHg)	Case	154	74	13	0.19	0.85
	Control	154	74	12		
HR(bpm)	Case	154	77	13.4	1.96	
	Control	154	74	12.4		
BMI(kg/m ²)	Case	154	36	10	5.24	
	Control	154	31	7		
EF(%)	Case	152	54.95	0.43	-1.05	0.30
	Control	152	55.11	2.03		
LAdiam(cm)	Case	124	4.25	0.61	8.35	
	Control	124	3.65	0.67		
Ea(mmHg/ml)	Case	59	1.96	0.57	1.12	0.26
	Control	59	1.83	0.59		
Ees(mmHg/ml)	Case	59	6.13	2.51	3.79	
	Control	59	4.47	1.93		
Ees/Ea	Case	59	3.06	0.82	4.56	0.0001
	Control	59	2.40	0.85		

Table IV

Conditional logistic regression results, combined matched case-control

Conditional logistic regression results, combined matched case-control					
Parameter	Parameter Estimate	Standard Error	Odds Ratio	CI	P value
Ees	0.3374	0.1251	1.40	(1.097, 1.791)	
LAdiam	1.0704	0.5144	2.92	(1.064, 7.994)	
HR	-0.0032	0.0243	0.997	(0.950, 1.045)	
BMI	0.0761	0.0422	1.079	(0.993, 1.172)	