ESC European Society of Cardiology

European Journal of Heart Failure (2021) **23**, 765–772
doi:10.1002/ejhf.2010

RESEARCH ARTICLE

Coronary microvascular dysfunction is associated with exertional haemodynamic abnormalities in patients with heart failure with preserved ejection fraction

Ali Ahmad[1], Michel T. Corban[1], Takumi Toya[1,2], Frederik H. Verbrugge[1,3], Jaskanwal D. Sara[1], Lilach O. Lerman[4], Barry A. Borlaug[1], and Amir Lerman[1]*

[1]Department of Cardiovascular Medicine, Mayo Clinic, Rochester, MN, USA; [2]Division of Cardiology, National Defense Medical College, Tokorozawa, Japan; [3]Biomedical Research Institute, Faculty of Medicine and Life Sciences, Hasselt University, Hasselt, Belgium; and [4]Division of Nephrology and Hypertension, Mayo Clinic, Rochester, MN, USA

Received 28 July 2020; revised 4 September 2020; accepted 16 September 2020; online publish-ahead-of-print 7 October 2020

Aims This study uniquely explored the relationship between coronary microvascular function and exercise haemodynamics using concurrent invasive testing.

Methods and results Fifty-one consecutive patients with unexplained cardiac exertion symptoms, non-obstructive coronary artery disease and normal left ventricular ejection fraction (>50%) underwent haemodynamic exercise assessment and concurrent coronary reactivity testing. Heart failure with preserved ejection fraction (HFpEF) was defined as a pulmonary arterial wedge pressure (PAWP) ≥15 mmHg at rest and/or ≥25 mmHg at peak exercise. Endothelium-independent coronary microvascular dysfunction (CMD) was defined as a coronary flow reserve (CFR) ≤2.5, while endothelium-dependent CMD was defined as ≤50% increase in coronary blood flow (CBF) in response to intracoronary acetylcholine infusions. Patients with HFpEF ($n = 22$) had significantly lower CFR (2.5 ± 0.6 vs. 3.2 ± 0.7; $P = 0.0003$) and median %CBF increase in response to intracoronary acetylcholine [1 (−35; 34) vs. 64 (−4; 133); $P = 0.002$] compared to patients without HFpEF ($n = 29$). PAWP was significantly higher in patients with endothelium-independent CMD compared to controls during both rest and exercise. This significant elevation was only present during exercise in patients with endothelium-dependent CMD compared to controls. CFR had significant inverse correlations with PAWP at rest ($r = -0.31$; $P = 0.03$) and peak exercise ($r = -0.47$, $P = 0.001$). CFR also had positive correlations with maximal exercise capacity (in W/kg) ($r = 0.33$, $P = 0.02$).

Conclusions Coronary microvascular function is inversely associated with filling pressures, particularly during exercise. Both types of CMD are associated with higher filling pressures at peak exercise. These findings underscore the potential mechanism and therapeutic target for CMD and HFpEF.

Keywords Heart failure with preserved ejection fraction • Microvascular dysfunction • Exercise haemodynamics

Introduction

Heart failure with preserved ejection fraction (HFpEF) accounts for approximately one-half of heart failure cases worldwide. While this condition is increasingly recognized and has a rising prevalence because of an ageing population, its pathophysiology remains poorly understood and no effective treatment strategy has been developed.[1] Several observations have shown that coronary microvascular dysfunction (CMD) may play an important role in HFpEF,[2–6] possibly because impaired myocardial perfusion

*Corresponding author. Department of Cardiovascular Medicine, Mayo Clinic, 200 First Street SW, Rochester, MN 55905, USA. Tel: +1 507 255-4152, Fax: +1 507 255-7798, Email: lerman.amir@mayo.edu

causes ischaemia,[7,8] angina, and cardiomyocyte injury, leading to a depressed cardiac functional reserve[9,10] and myocardial fibrosis.[3]

In the absence of significant epicardial coronary artery disease (CAD), CMD is mainly determined by a deficient vasodilatory response to demand through endothelium-dependent and/or -independent processes.[11] Despite compelling evidence in support of the presence of CMD in HFpEF, most studies have relied on non-invasive assessment of both CMD and HFpEF which might not be accurate. To avoid misclassification,[12,13] the reference standard method for making a HFpEF diagnosis requires invasive haemodynamic assessment during exercise, yet no studies using this modality have also directly evaluated coronary microvascular function. This study addresses this gap by undertaking a comprehensive and concurrent assessment of coronary reactivity and intracardiac filling pressures at rest and during exercise in a patient population with unexplained cardiac exertion symptoms referred to the cardiac catheterization laboratory for clinically indicated evaluation of CMD and HFpEF.

Methods

Patient population

This study included consecutive subjects with unexplained cardiac exertion symptoms (like dyspnoea), and non-obstructive CAD at coronary angiography (<50% stenosis), who underwent both clinically indicated invasive coronary reactivity testing (CRT) for the evaluation of CMD, as well as haemodynamic exercise right heart catheterization for the evaluation of HFpEF between 2010 and 2019. Exclusion criteria were: (i) any history of left ventricular ejection fraction <50%; (ii) intermediate or significant epicardial CAD (angiographic stenosis ≥50% in a major vessel); (iii) significant valvular heart disease (more than moderate regurgitation and/or stenosis); (iv) primary cardiomyopathies (hypertrophic, infiltrative, or restrictive); (v) constrictive pericarditis; (vi) severe myocardial bridging; (vii) stiff left atrial syndrome; or (viii) pulmonary disease (pulmonary arterial hyptertension, chronic obstructive pulmonary disease).

Study protocol

This study was conducted in accordance with the guidelines of the Declaration of Helsinki and was approved by the Mayo Clinic Institutional Review Board. All patients provided written informed consent for participation in the study. Clinical, laboratory, and echocardiography data, as well as microvascular function parameters and haemodynamic measurements, were abstracted from the medical records through detailed chart review.

The catheterization protocol is depicted in *Figure 1*. Patients discontinued vasodilatory medications (calcium channel blockers, beta-blockers, and long-acting nitrates) at least 48 h before the study. They were only allowed to take sublingual nitroglycerin tablets or spray for angina up to 6 h prior to the catheterization procedure. The Mayo Clinic protocol of CRT has been described previously in detail.[14,15] In brief, patients underwent diagnostic coronary angiography using standard clinical protocols. Those with no significant epicardial CAD (no or mild angiographic stenosis <50% in any major vessel) went on to receive 5000 U of heparin intravenously, after which a Doppler guidewire (FloWire, Philips/Volcano Corp., San Diego, CA, USA) was positioned in the mid-left anterior descending coronary artery (LAD). First, to assess endothelium-independent vasodilatation, intracoronary bolus injections of incremental doses (18 to 72 μg) of adenosine were administered through the guiding catheter until maximal hyperaemia was achieved. Coronary flow reserve (CFR) was calculated as the ratio of hyperaemic over baseline blood velocities. Endothelium-independent CMD was subsequently defined as CFR ≤2.5 in response to adenosine.[15] Next, coronary microvascular endothelial function was assessed using infusions of increasing concentrations of intracoronary acetylcholine (10^{-6}, 10^{-5}, and 10^{-4} mol/L for 3 min each). Doppler measurements of peak velocity were performed after each acetylcholine infusion, followed by repeat coronary angiography. Mid-LAD diameter was measured in the segment 5 mm distal to the tip of the Doppler wire, using a quantitative coronary angiography programme (QAngio, Medis Corp, Leiden, The Netherlands). Coronary blood flow (CBF) was then calculated using the formula: $\text{CBF} = \pi \times (\text{peak velocity}/2) \times (\text{coronary artery diameter}/2)^2$, as previously described.[15] The maximal percent change in CBF in response to acetylcholine compared to baseline (%ΔCBF) was then calculated, and endothelium-dependent CMD was defined as %ΔCBF ≤50%.[15,16]

Right heart catheterization was performed through a 9F sheath via the right internal jugular vein.[12] Right atrial pressure, right ventricular pressures, pulmonary arterial pressures, and the pulmonary arterial wedge pressure (PAWP) were measured at end-expiration (mean of ≥3 beats) using 2F high-fidelity micromanometer-tipped catheters (Millar Instruments, Houston, TX, USA) advanced through the lumen of a 7F fluid-filled catheter (Balloon wedge, Arrow, Wayne, PA, USA). Mean micromanometer pressures were calibrated to mean fluid-filled pressures at the beginning and throughout each procedure to avoid baseline drift. Transducers were zeroed at mid-axilla, measured by laser calipers in each patient. Mean PAWP was taken at mid-a wave. PAWP position was verified by typical waveforms, appearance on fluoroscopy, and direct oximetry (PAWP blood saturation ≥94%). Arterial blood pressure was measured through a 4F to 6F radial arterial cannula throughout the tests. After obtaining resting haemodynamics, each subject performed a symptom-limited exercise test on a supine bicycle while on the catheterization table. The first stage of exercise (20 W) was performed for 5 min and followed by graded 20 W increments in workload every 2 min until exhaustion. HFpEF was defined as PAWP ≥15 mmHg at rest and/or ≥25 mmHg at peak exercise, as recommended by current guidelines.[12,17]

Statistical analysis

Normally distributed data are presented as mean ± standard deviation (SD), and skewed data as median and interquartile range (Q25; Q75). Comparisons for continuous variables are made using the independent-samples *t*-test, Wilcoxon rank-sum test and one-way ANOVA. Categorical data were compared using the chi-square test or Fisher's exact test (when appropriate). Linear regression was used to assess the relationship between haemodynamic parameters and indexes of CMD. Age- and sex-adjusted regression was also done. Correlations are reported using Pearson's r correlation coefficients. Statistical analyses were performed using JMP v.13 software (SAS Institute, Cary, NC, USA). All tests are two-tailed, and $P < 0.05$ was considered to be statistically significant.

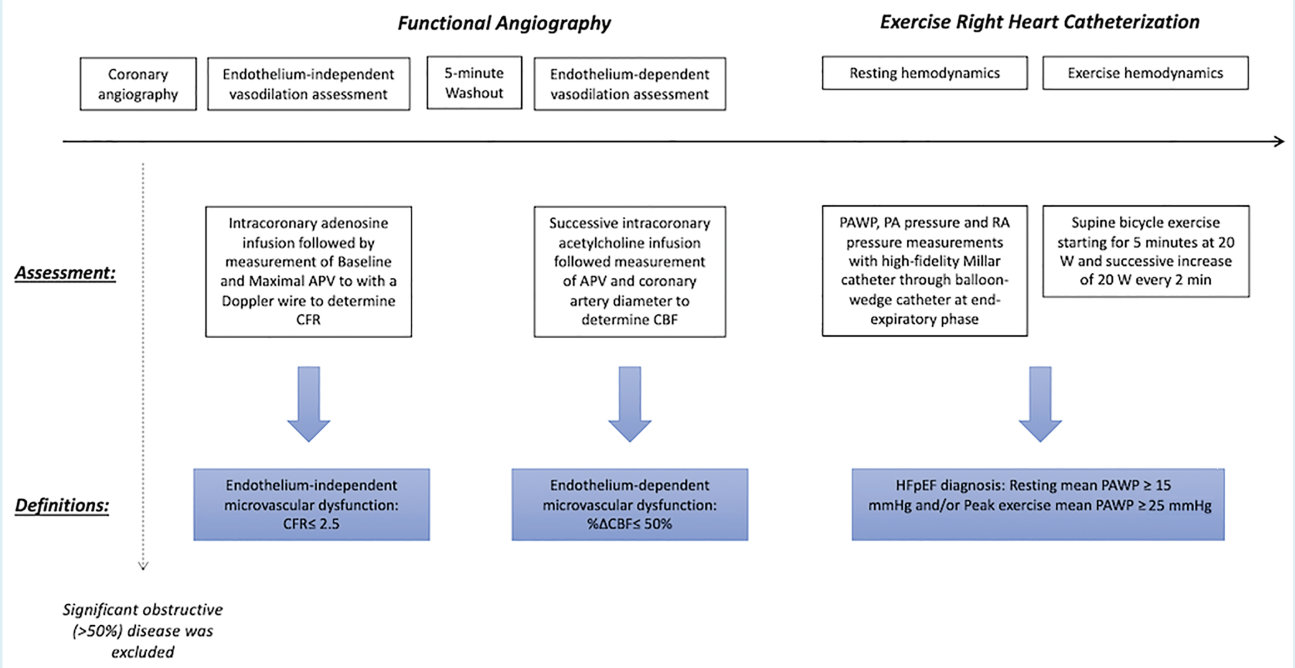

Figure 1 Protocol of the catheterization study. APV, average peak velocity; CBF, coronary blood flow; CFR, coronary flow reserve; HFpEF, heart failure with preserved ejection fraction; PA, pulmonary artery; PAWP, pulmonary arterial wedge pressure; RA, right atrial.

Results

Study population

From 65 consecutive subjects undergoing both CRT and invasive haemodynamic evaluation during exercise, 51 fulfilled criteria for inclusion and constitute the study population (online supplementary *Figure S1*). From this group, 22 (43%) were found to have HFpEF by invasive diagnosis. Patients with HFpEF had higher levels of invasively diagnosed endothelium-independent CMD (46% vs. 21%; $P = 0.06$), and endothelium-dependent CMD (86% vs. 35%; $P = 0.0002$) as compared to non-HFpEF group (*Table 1*). Patients with HFpEF had early stage disease, with relatively few comorbidities, and displayed similar baseline characteristics, laboratory values, and echocardiography parameters to those without HFpEF, with the exception of a higher medial E/e′ by echocardiography [11.4 (8.5; 15.0) vs. 7.5 (6.7; 10.7); $P = 0.01$] (*Table 1*). CFR in response to adenosine and %ΔCBF in response to acetylcholine were significantly lower in patients with HFpEF as compared to non-HFpEF group [CFR: 2.5 ± 0.6 vs. 3.2 ± 0.7, $P = 0.0003$; %ΔCBF: 1% (−35; 34) vs. 64% (−4; 133), $P = 0.002$] (*Table 1*). Comparisons between patients with CMD and controls are presented in online supplementary *Table S1*. Patients with endothelium-independent CMD and endothelium-dependent CMD had significantly higher levels of N-terminal pro B-type natriuretic peptide as compared to controls [128 (66; 307) vs. 47 (25; 77); $P = 0.001$; and 83 (39; 137) vs. 43 (25; 69), respectively; $P = 0.04$] (online supplementary *Table S1*).

Microvascular function indices and exercise haemodynamics

There was a significant inverse linear correlation between CFR and mean PAWP at rest which became stronger during peak exercise, with Pearson's r of −0.31 at rest and −0.47 at exercise (*Figure 2A*). In addition, the slope of the CFR–PAWP relationship became steeper at peak exercise compared to rest as indicated by the significant correlation between ΔPAWP (peak exercise PAWP − PAWP at rest) and CFR (Pearson's r = −0.38; $P = 0.01$; *Figure 2B*). The %ΔCBF response to acetylcholine was inversely related to PAWP at peak exercise (Pearson's r = −0.36; $P = 0.01$; *Figure 2C*). There was a positive correlation between CFR and peak ergometric work exercise capacity, as represented by the maximum W/kg attained by every patient (r = 0.33, $P = 0.02$; *Figure 3A*), this relationship was not observed with %ΔCBF (r = 0.19; $P = 0.18$; *Figure 3B*). On age- and sex-adjusted regression analyses, the relationship between CFR and %ΔCBF with resting PAWP became stronger (Pearson's r = −0.45; $P = 0.007$ and r = −0.29; $P = 0.058$, respectively). The relationship between CFR and %ΔCBF with peak exercise PAWP remained significant ($P = 0.005$ and $P = 0.048$, respectively). The other adjusted regression analyses are shown in *Table 2*.

Coronary microvascular dysfunction and exercise haemodynamics

In patients with vs. without endothelium-independent CMD, PAWP was significantly higher, both at rest (12.3 ± 2.4 mmHg vs.

Table 1 Baseline characteristics of patients with vs. those without heart failure with preserved ejection fraction

	HFpEF diagnosis		*P*-value
	No ($n = 29$)	Yes ($n = 22$)	
Baseline characteristics			
Age, years	54.3 ± 10.4	59.6 ± 10.1	0.08
Female sex, *n* (%)	22 (76)	15 (68)	0.54
Body mass index, kg/m^2	28.2 ± 6.3	31.1 ± 5.7	0.10
Atrial fibrillation, *n* (%)	1 (4)	2 (9)	0.57
Hypertension, *n* (%)	15 (52)	12 (55)	0.84
Diabetes mellitus type II, *n* (%)	2 (7)	6 (27)	0.06
Hyperlipidaemia, *n* (%)	16 (55)	17 (77)	0.10
Smoking exposure, *n* (%)	11 (38)	7 (32)	0.65
Prior HF hospitalization	1 (4)	2 (9)	0.57
eGFR, mL/min/1.73 m^2	79.4 ± 19.9	73.6 ± 20.0	0.31
Medications, *n* (%)			
ACEI or ARB	4 (14)	4 (18)	0.71
Beta-blockers	10 (35)	12 (55)	0.15
CCB	5 (17)	6 (27)	0.39
Statins	16 (55)	14 (64)	0.54
Diuretics	3 (10)	2 (9)	0.88
Labs			
Haemoglobin, g/dL	13.8 ± 1.2	13.6 ± 1.3	0.59
Creatinine, mg/dL	0.9 [0.7; 1.0]	1.0 [0.8; 1.0]	0.31
Total cholesterol, mg/dL	178 [155; 216]	155 [147; 207]	0.29
LDL-cholesterol, mg/dL	106 [81; 138]	85 [58; 119]	0.21
HDL-cholesterol, mg/dL	58 [46; 64]	54 [45; 81]	0.86
Triglycerides, mg/dL	85 [56; 135]	105 [63; 128]	0.61
NT-proBNP, ng/dL	64 [33; 83]	75 [25; 224]	0.46
Echocardiography parameters			
LVEF, %	64 [62; 66]	63 [59; 66]	0.4
LAVI, mL/m^2	26 [21; 29]	27 [22; 34]	0.36
Mitral E, m/s	0.7 [0.6; 0.8]	0.7 [0.6; 0.8]	0.86
Medial e′, m/s	8.2 [7.1; 10.9]	6.0 [5.0; 7.0]	0.002
Lateral e′, m/s	10.0 [9.0; 11.6]	8.0 [6.5; 10.0]	0.07
Mitral E/A	1.0 [0.86; 1.33]	1.0 [0.73; 1.18]	0.19
Average E/e′	7.1 [6.4; 9.2]	9.2 [7.3; 12.4]	0.05
TR velocity max, m/s	2.4 [2.2; 2.5]	2.4 [2.3; 2.5]	0.76
Invasive parameters			
QCA (%)	0 [0; 30]	0 [0; 20]	0.58
Coronary flow reserve	3.2 ± 0.7	2.5 ± 0.6	0.0003
%Δ Coronary blood flow	64 [−4; 133]	1 [−35; 34]	0.002
%Δ Coronary artery diameter	−6 [−21; 4]	−21 [−29; −9]	0.01
Resting RVEDP, mmHg	8.8 ± 3.0	10.1 ± 2.8	0.12
Resting mean PAWP, mmHg	9.9 ± 2.6	12.5 ± 2.7	0.001
Peak exercise mean PAWP, mmHg	18.0 ± 4.4	28.4 ± 3.6	<0.0001
Endothelial-independent CMD, *n* (%)	6 (21)	10 (46)	0.06
Endothelial-dependent CMD, *n* (%)	10 (35)	19 (86)	0.0002

ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CCB, calcium channel blocker; CMD, coronary microvascular dysfunction; eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein; HF, heart failure; HFpEF, heart failure with preserved ejection fraction; LAVI, left atrial volume index; LDL, low-density lipoprotein; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal pro B-type natriuretic peptide; PAWP, pulmonary arterial wedge pressure; QCA, quantitative coronary angiography; RVEDP, right ventricular end-diastolic pressure; TR, tricuspid regurgitation.

Mitral E, medial e′, and mitral E/A were missing for 6 (12%) of the patients. LAVI, lateral e′, and average E/e′ were missing for 10 (20%) of patients. TR maximum velocity was missing for 23 (45%) of the patients. Six patients out of the 51 did not undergo echocardiography at our institution. To make sure they never had an ejection fraction <50%, their ejection fraction was abstracted from other imaging modalities or from clinical notes. All other data are complete.

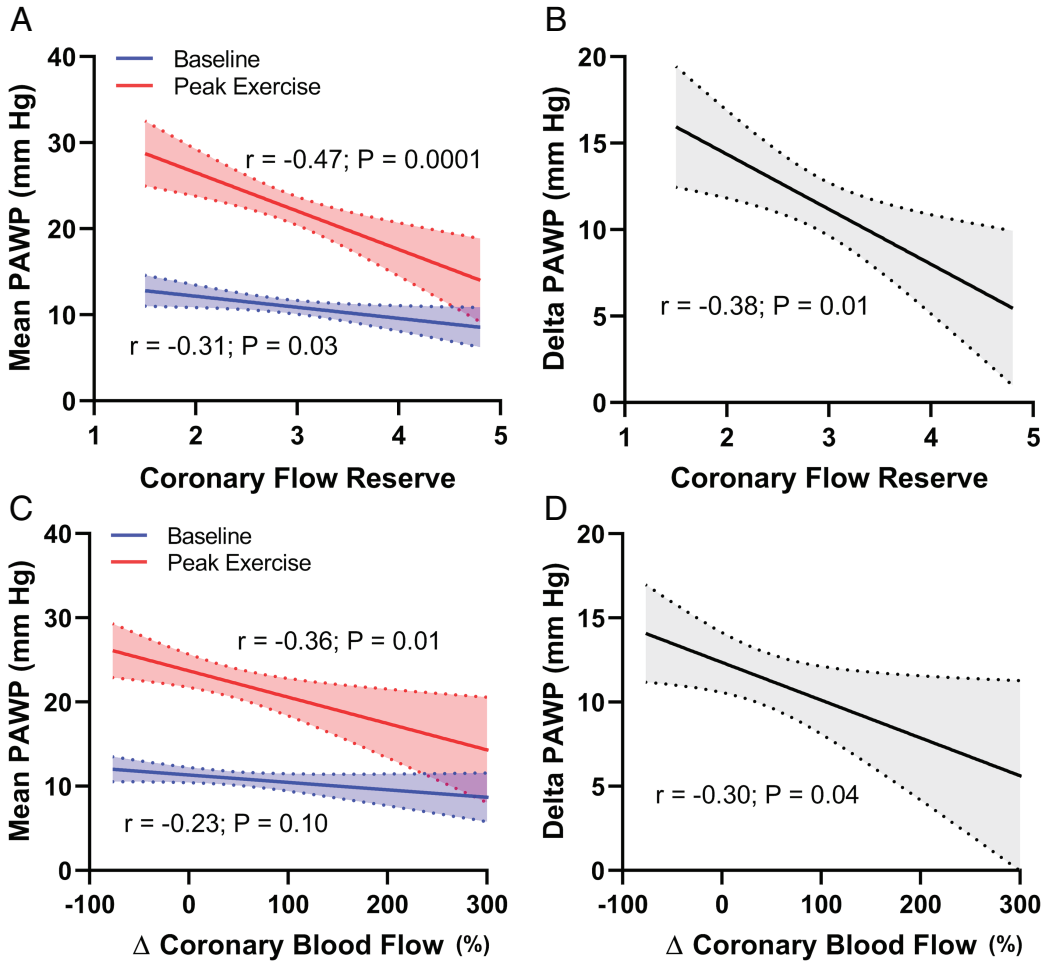

Figure 2 (*A*,*C*) Correlation between coronary flow reserve (CFR) (*A*) or %Δ coronary blood flow (CBF) (*C*) and mean pulmonary arterial wedge pressure (PAWP), both at rest and during peak exercise. (*B*,*D*) Correlation of CFR (*B*) or %ΔCBF (*D*) and delta PAWP (peak exercise PAWP − PAWP at rest).

10.4 ± 3.0 mmHg; $P = 0.02$) and at peak exercise (25.8 ± 5.9 mmHg vs. 20.9 ± 6.6 mmHg; $P = 0.01$). In contrast, PAWP was only higher at peak exercise in patients with vs. without endothelium-dependent CMD (24.9 ± 6.2 vs. 19.3 ± 5.7; $P = 0.002$) (*Figure 4*).

Discussion

The present study demonstrates the important relationship between CMD and exercise haemodynamics in HFpEF. The HFpEF cohort examined includes patients with earlier disease stage, with younger age and fewer comorbidities, but invasively proven HFpEF. The major findings are that: (i) endothelium-independent function correlates inversely with rest and exercise left-sided cardiac filling pressures; endothelium-dependent function correlates inversely with peak exercise left-sided cardiac filling pressures; (ii) endothelium-independent function has a positive correlation with peak exercise capacity; (iii) patients with HFpEF have significantly lower coronary microvascular function (as measured by CFR in response to adenosine and %ΔCBF in response to acetylcholine) compared to those without HFpEF; (iv) 46% of HFpEF patients have endothelium-independent CMD, 86% have endothelium-dependent CMD. Thus, the current results demonstrate a potential role and therapeutic target for the coronary microvasculature in the pathophysiology of HFpEF in humans.

Microvascular function and exercise haemodynamics

Results of the current study suggest a direct link between coronary microvascular function assessed by CFR and peak exercise capacity, represented by peak external ergometric work (W/kg), which reflects a reduced cardiac reserve. The current study extends previous studies. Echocardiography-derived CFR was shown to be inversely correlated to treadmill exercise capacity, while another

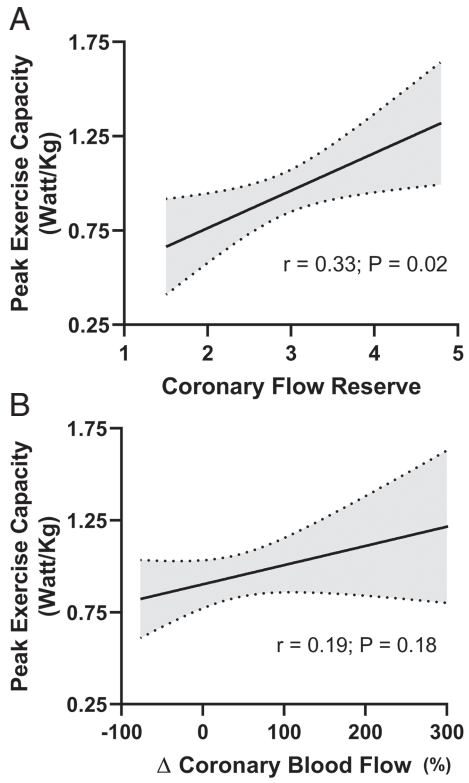

Figure 3 Correlation of peak exercise capacity (W/kg) and (*A*) coronary flow reserve and (*B*) %Δ coronary blood flow.

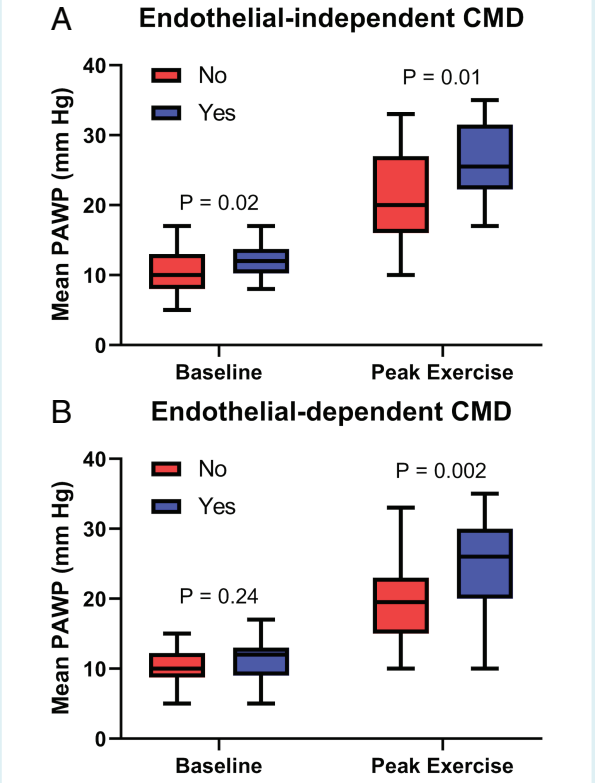

Figure 4 Baseline mean pulmonary arterial wedge pressure (PAWP) and peak exercise mean PAWP in patients with coronary microvascular dysfunction (CMD) vs. controls.

Table 2 Age- and sex-adjusted regression analysis between microvascular indices (coronary flow reserve and %Δ coronary blood flow) and haemodynamic parameters at baseline and at peak exercise

	Resting PAWP (mmHg)	Peak exercise PAWP (mmHg)	Δ PAWP (mmHg)	Exercise capacity (W/kg)
CFR				
Pearson's r	−0.45	−0.46	−0.29	0.14
P-value	0.007	0.005	0.07	0.38
%Δ CBF (%)				
Pearson's r	−0.29	−0.29	−0.18	0.07
P-value	0.059	0.048	0.20	0.64

CBF, coronary blood flow; CFR, coronary flow reserve; PAWP, pulmonary arterial wedge pressure.

study showed a reduced exercise capacity in women with CMD.[18] Ventricular relaxation during diastole is an active process that consumes adenosine triphosphate and hence requires adequate oxygen delivery for oxidative phosphorylation.[19] Several studies have demonstrated that detectable levels of cardiac troponins, signifying cardiomyocyte injury, are found in patients with HFpEF without significant epicardial CAD.[5,20] Obokata *et al.*[9] reported that compared with subjects with HFpEF with normal troponin T at rest, those with elevated troponin T displayed impaired systolic reserve during peak exercise, and that peak exercise oxygen consumption was inversely correlated with detectable levels of troponin in blood. Moreover, in patients with stable CAD and preserved left ventricular ejection fraction, chronic circulating levels of high-sensitivity troponins have been associated with increased incidence of cardiovascular death and heart failure.[20] It may be postulated that over time, repetitive cardiomyocyte injury might increase myocardial fibrosis leading to a more pronounced rise in cardiac filling pressures not only with exercise but also at rest.

Furthermore, in normal circumstances lusitropy increases during exercise to keep cardiac filling pressures low.[21] Ischaemia caused by CMD[7,8] may therefore be associated with a loss of lusitropy and higher filling pressures for a similar stroke volume, which can be exacerbated by exercise.

Coronary microvascular dysfunction and heart failure with preserved ejection fraction

In this study, CMD was associated with higher left-sided cardiac filling pressures at rest, with this relationship being even more

pronounced during an increased myocardial demand such exercise. Several pre-clinical studies have demonstrated an association between CMD and HFpEF. Paulus and Tschope[22] hypothesized that comorbidities common to HFpEF (e.g. diabetes, obesity, chronic kidney disease) lead to systemic inflammation including coronary endothelial inflammation leading to CMD, which subsequently reduces endothelial nitric oxide bioavailability and cyclic guanosine monophosphate (cGMP) production by adjacent cardiomyocytes. These processes result in downstream titin hypophosphorylation and increased cardiomyocyte stiffening and hypertrophy leading to increased left ventricular diastolic stiffening, a known hallmark of HFpEF.[22] An autopsy study has demonstrated that patients with HFpEF have more coronary microvascular rarefaction and myocardial fibrosis compared to age-matched controls.[3]

Coronary microvascular dysfunction might be caused by endothelium-dependent as well as endothelium-independent mechanisms, or a combination of both. Endothelium-dependent dysfunction occurs with the loss of balance between endothelium-derived relaxing factors (e.g. nitric oxide) and vasoconstrictors (e.g. endothelin), while endothelium-independent dysfunction mainly occurs due to an impaired myocyte tone.[23] In a multicentre study using adenosine stress echocardiographic imaging, Shah and colleagues found that CMD was present in 75% of recruited HFpEF patients, and was associated with the presence of atrial fibrillation, albuminuria and poorer right ventricular function.[4] Yang and colleagues first reported on the separate contributions of endothelium-dependent and independent CMD in HFpEF, with each present in approximately 30% of patients with HFpEF, and at least some type of CMD was identifiable in 72%.[6] The present study importantly confirms and extends upon these earlier studies, again showing that CMD is very common in patients with less advanced HFpEF. Importantly, this is the first study to evaluate the relationships of both endothelium-independent and endothelium-dependent CMD on resting and exercise haemodynamics in HFpEF. It is notable that impaired microvascular relaxation was associated with elevated filling pressures during exercise, regardless of the type of CMD. This common outcome underscores the difference in the roles that the endothelium and myocytes may have during resting and exercise perfusion.

Coronary microvascular response to increased demand is comprised of an endothelium-dependent paracrine release of molecules such as nitric oxide and endothelium-derived relaxing factor along with endothelium-independent microvascular vascular smooth muscle cell relaxation.[23] Despite most clinical studies regarding CMD and HFpEF focusing on endothelium-independent function,[2,4,5] as measured by CFR, pre-clinical studies linking CMD and HFpEF have mostly focused on the role of nitric oxide and cGMP in the pathophysiology of HFpEF.[24] There is no established treatment for HFpEF that reduces mortality, and while several trials have been done, most have been negative when assessing the same therapies used in HFrEF. Furthermore, few treatments that have been looked at for the treatment of HFpEF were also studied as a possible treatment for CMD, such as inorganic nitrite and phosphodiesterase inhibitors,[25–28] but these studies were also largely negative and provided no benefit. All this indicates that there is a possible confounding effect of CMD in patients with HFpEF that should be taken into account in future studies of HFpEF treatment. It is possible that patients with endothelium-dependent and endothelium-independent CMD represent specific phenotypes in HFpEF that should be evaluated separately in clinical trials testing interventions targeted to these specific pathophysiologies.

Strengths and limitations

First of all, the current study must be interpreted in the context of its retrospective single-centre design and limited population size. Second, due to the exclusion criteria applied in the design of the study, further limiting the population size included in the analysis, selection bias could not have been avoided and might affect generalizability of our results. Furthermore, the cross-sectional design of the study prevents from establishing causation. Also, duration of treatment, doses and titrations were not available for analysis and would have provided additional insight into the baseline characteristics of our population. Furthermore, additional lab values, such as high-sensitivity troponin after exercise, would have contributed to the evidence in the current study. Finally, cardiac magnetic resonance imaging has an emerging role in assessing diastology and the cause of HFpEF, and would have helped in further assessing the HFpEF population in this study. On the other hand, a major strength was that both HFpEF and CMD diagnoses were confirmed by gold-standard invasive measurements, which greatly enhances accuracy of diagnosis as compared to non-invasive diagnostic modalities.[13,29] The patients with HFpEF in the present study displayed earlier disease stage, with younger age and lower comorbidity burden than in other series, and these baseline differences must be considered in applying the current results to the broader spectrum of patients with HFpEF. Longitudinal studies with pre-defined target populations and interventions are needed to further establish the role of CMD in the pathophysiology, diagnosis and treatment of HFpEF, as well as phenotyping of patients to guide therapeutic decision making.

Conclusion

In patients with non-obstructive epicardial stenosis and with a preserved ejection fraction presenting for unexplained cardiac exertion symptoms, the presence of invasively defined CMD correlates with higher intracardiac filling pressures at peak exercise, and is strongly associated with invasive gold standard HFpEF diagnosis. Further studies are needed to explore the potential diagnostic and prognostic value of CMD in patients with HFpEF, as well as its potential role as a therapeutic target.

Supplementary Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Funding

This work was supported by Mayo institutional funding. F.H.V. is supported by a Fellowship of the Belgian American Educational

Foundation (B.A.E.F.) and by the Special Research Fund (BOF) of Hasselt University (BOF19PD04). B.A.B. is supported by RO1 HL128526.

Conflict of interest: A.L declares consulting honoraria from Philips Volcano. All other authors have nothing to disclose.

References

1. Redfield MM. Heart failure with preserved ejection fraction. *N Engl J Med* 2016;**375**:1868–1877.
2. Kato S, Saito N, Kirigaya H, Gyotoku D, Iinuma N, Kusakawa Y, Iguchi K, Nakachi T, Fukui K, Futaki M, Iwasawa T, Kimura K, Umemura S. Impairment of coronary flow reserve evaluated by phase contrast cine-magnetic resonance imaging in patients with heart failure with preserved ejection fraction. *J Am Heart Assoc* 2016;**5**:e002649.
3. Mohammed SF, Hussain S, Mirzoyev SA, Edwards WD, Maleszewski JJ, Redfield MM. Coronary microvascular rarefaction and myocardial fibrosis in heart failure with preserved ejection fraction. *Circulation* 2015;**131**:550–559.
4. Shah SJ, Lam CS, Svedlund S, Saraste A, Hage C, Tan RS, Beussink-Nelson L, Ljung Faxen U, Fermer ML, Broberg MA, Gan LM, 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.
5. Taqueti VR, Solomon SD, Shah AM, Desai AS, Groarke JD, Osborne MT, Hainer J, Bibbo CF, Dorbala S, Blankstein R, Di Carli MF. Coronary microvascular dysfunction and future risk of heart failure with preserved ejection fraction. *Eur Heart J* 2018;**39**:840–849.
6. Yang JH, Obokata M, Reddy YN, Redfield MM, Lerman A, Borlaug BA. Endothelium-dependent and independent coronary microvascular dysfunction in patients with heart failure with preserved ejection fraction. *Eur J Heart Fail* 2020;**22**:432–441.
7. Hasdai D, Gibbons RJ, Holmes DR Jr, Higano ST, Lerman A. Coronary endothelial dysfunction in humans is associated with myocardial perfusion defects. *Circulation* 1997;**96**:3390–3395.
8. Summers MR, Lerman A, Lennon RJ, Rihal CS, Prasad A. Myocardial ischaemia in patients with coronary endothelial dysfunction: insights from body surface ECG mapping and implications for invasive evaluation of chronic chest pain. *Eur Heart J* 2011;**32**:2758–2765.
9. Obokata M, Reddy YN, Melenovsky V, Kane GC, Olson TP, Jarolim P, Borlaug BA. Myocardial injury and cardiac reserve in patients with heart failure and preserved ejection fraction. *J Am Coll Cardiol* 2018;**72**:29–40.
10. Borlaug BA, Olson TP, Lam CS, Flood KS, Lerman A, Johnson BD, Redfield MM. Global cardiovascular reserve dysfunction in heart failure with preserved ejection fraction. *J Am Coll Cardiol* 2010;**56**:845–854.
11. Lerman A, Zeiher AM. Endothelial function: cardiac events. *Circulation* 2005;**111**:363–368.
12. Borlaug BA, Nishimura RA, Sorajja P, Lam CS, Redfield MM. Exercise hemodynamics enhance diagnosis of early heart failure with preserved ejection fraction. *Circ Heart Fail* 2010;**3**:588–595.
13. Obokata M, Kane GC, Reddy YN, Olson TP, Melenovsky V, Borlaug BA. Role of diastolic stress testing in the evaluation for heart failure with preserved ejection fraction: a simultaneous invasive-echocardiographic study. *Circulation* 2017;**135**:825–838.
14. Widmer RJ, Samuels B, Samady H, Price MJ, Jeremias A, Anderson RD, Jaffer FA, Escaned J, Davies J, Prasad M, Grines C, Lerman A. The functional assessment of patients with non-obstructive coronary artery disease: expert review from an international microcirculation working group. *EuroIntervention* 2019;**14**:1694–1702.
15. Sara JD, Widmer RJ, Matsuzawa Y, Lennon RJ, Lerman LO, Lerman A. Prevalence of coronary microvascular dysfunction among patients with chest pain and nonobstructive coronary artery disease. *JACC Cardiovasc Interv* 2015;**8**:1445–1453.
16. Widmer RJ, Flammer AJ, Herrmann J, Rodriguez-Porcel M, Wan J, Cohen P, Lerman LO, Lerman A. Circulating humanin levels are associated with preserved coronary endothelial function. *Am J Physiol Heart Circ Physiol* 2013;**304**:H393–397.
17. Pieske B, Tschope C, de Boer RA, Fraser AG, Anker SD, Donal E, Edelmann F, Fu M, Guazzi M, Lam CS, Lancellotti P, Melenovsky V, Morris DA, Nagel E, Pieske-Kraigher E, Ponikowski P, Solomon SD, Vasan RS, Rutten FH, Voors AA, Ruschitzka F, Paulus WJ, Seferovic P, Filippatos G. How to diagnose heart failure with preserved ejection fraction: the HFA-PEFF diagnostic algorithm: a consensus recommendation from the Heart Failure Association (HFA) of the European Society of Cardiology (ESC). *Eur Heart J* 2019;**40**:3297–3317.
18. Eroglu S, Sade LE, Polat E, Bozbas H, Muderrisoglu H. Association between coronary flow reserve and exercise capacity. *Hellenic J Cardiol* 2015;**56**:201–207.
19. Varma N, Eberli FR, Apstein CS. Increased diastolic chamber stiffness during demand ischemia: response to quick length change differentiates rigor-activated from calcium-activated tension. *Circulation* 2000;**101**:2185–2192.
20. Omland T, Pfeffer MA, Solomon SD, de Lemos JA, Rosjo H, Saltyte Benth J, Maggioni A, Domanski MJ, Rouleau JL, Sabatine MS, Braunwald E; PEACE Investigators. Prognostic value of cardiac troponin I measured with a highly sensitive assay in patients with stable coronary artery disease. *J Am Coll Cardiol* 2013;**61**:1240–1249.
21. Cheng CP, Igarashi Y, Little WC. Mechanism of augmented rate of left ventricular filling during exercise. *Circ Res* 1992;**70**:9–19.
22. Paulus WJ, Tschope 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 Cardiol* 2013;**62**:263–271.
23. Gutterman DD, Chabowski DS, Kadlec AO, Durand MJ, Freed JK, Ait-Aissa K, Beyer AM. The human microcirculation: regulation of flow and beyond. *Circ Res* 2016;**118**:157–172.
24. Franssen C, Chen S, Unger A, Korkmaz HI, De Keulenaer GW, Tschope C, Leite-Moreira AF, Musters R, Niessen HW, Linke WA, Paulus WJ, Hamdani N. Myocardial microvascular inflammatory endothelial activation in heart failure with preserved ejection fraction. *JACC Heart Fail* 2016;**4**:312–324.
25. Bock JM, Treichler DP, Norton SL, Ueda K, Hughes WE, Casey DP. Inorganic nitrate supplementation enhances functional capacity and lower-limb microvascular reactivity in patients with peripheral artery disease. *Nitric Oxide* 2018;**80**:45–51.
26. Borlaug BA, Anstrom KJ, Lewis GD, Shah SJ, Levine JA, Koepp GA, Givertz MM, Felker GM, LeWinter MM, Mann DL, Margulies KB, Smith AL, Tang WH, Whellan DJ, Chen HH, Davila-Roman VG, McNulty S, Desvigne-Nickens P, Hernandez AF, Braunwald E, Redfield MM; National Heart, Lung, and Blood Institute Heart Failure Clinical Research Network. Effect of inorganic nitrite vs placebo on exercise capacity among patients with heart failure with preserved ejection fraction: the INDIE-HFpEF randomized clinical trial. *JAMA* 2018;**320**:1764–1773.
27. Hoendermis ES, Liu LC, Hummel YM, van der Meer P, de Boer RA, Berger RM, van Veldhuisen DJ, Voors AA. Effects of sildenafil on invasive haemodynamics and exercise capacity in heart failure patients with preserved ejection fraction and pulmonary hypertension: a randomized controlled trial. *Eur Heart J* 2015;**36**:2565–2573.
28. McLaughlin K, Lytvyn Y, Luca MC, Liuni A, Gori T, Parker JD. Repeated daily dosing with sildenafil provides sustained protection from endothelial dysfunction caused by ischemia and reperfusion: a human in vivo study. *Am J Physiol Heart Circ Physiol* 2014;**307**:H888–894.
29. Cassar A, Chareonthaitawee P, Rihal CS, Prasad A, Lennon RJ, Lerman LO, Lerman A. Lack of correlation between noninvasive stress tests and invasive coronary vasomotor dysfunction in patients with nonobstructive coronary artery disease. *Circ Cardiovasc Interv* 2009;**2**:237–244.