

Microvascular dysfunction in heart failure with preserved ejection fraction (HFpEF): Evidence from PROMIS-HFpEF

Carolyn S. P. Lam, Sanjiv J. Shah, Sara Svedlund, Antti Saraste, Camilla Hage, Ru San Tan, Maria Lagerström Fermer, Malin A. Broberg, Li-Ming Gan, Lars H. Lund

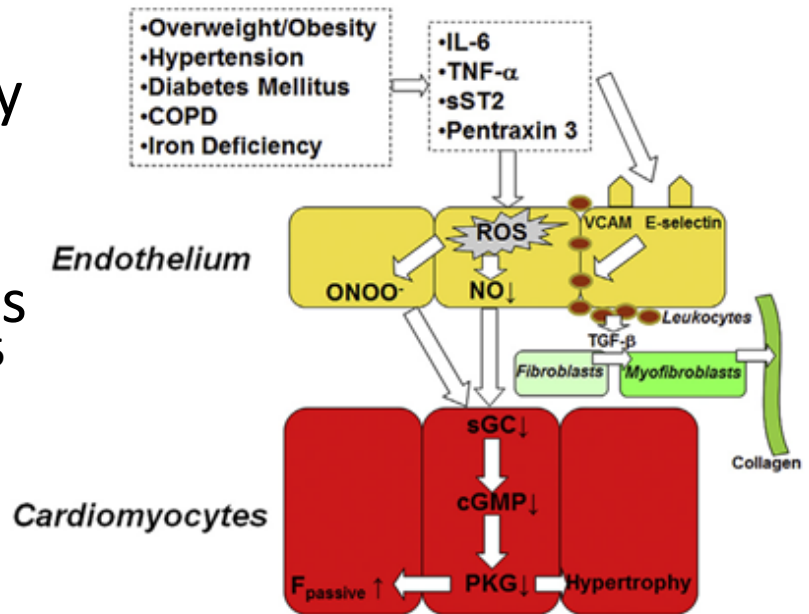
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Disclosures

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- Consulted for Astra Zeneca, Bayer, Novartis, Amgen, Merck, Janssen Research & Development LLC, Menarini, Boehringer Ingelheim, Abbott Diagnostics, Corvia, Stealth BioTherapeutics, and Takeda
- PROMIS-HFpEF is an AstraZeneca initiated and sponsored study

Background

- No treatment yet shown to reduce morbidity and mortality in HFpEF¹
- Coronary microvascular dysfunction (CMD) proposed as a novel mechanism in HFpEF²⁻⁵
- Clinical evidence of CMD in HFpEF limited to selected referral samples⁶⁻¹⁰



Aims

Prospective multicenter PRevalence Of Microvascular dySfunction in HFpEF (PROMIS-HFpEF) study

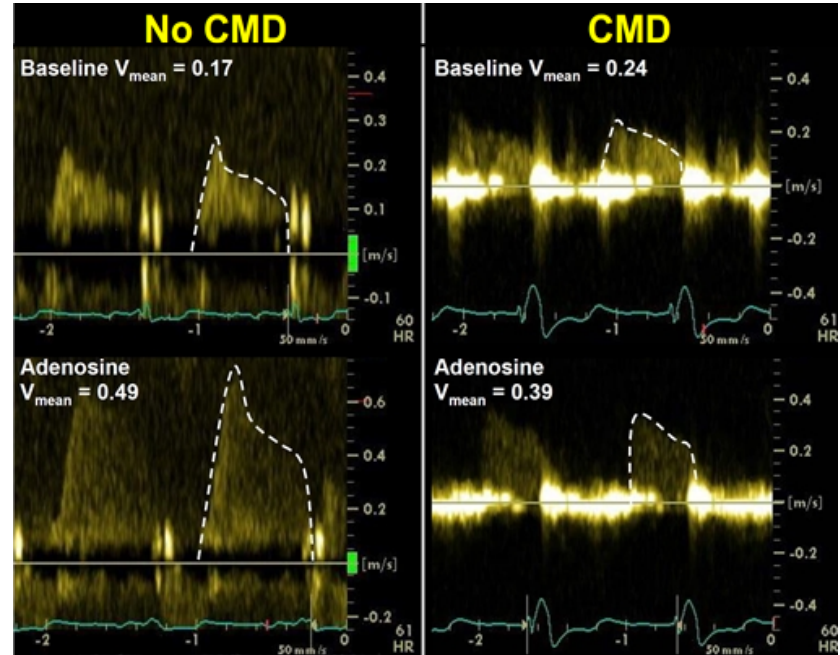
- To investigate the prevalence of CMD and its association with systemic endothelial dysfunction, HF severity, and myocardial dysfunction in a well-defined, prospective HFpEF population using a comprehensive functional imaging approach

Methods

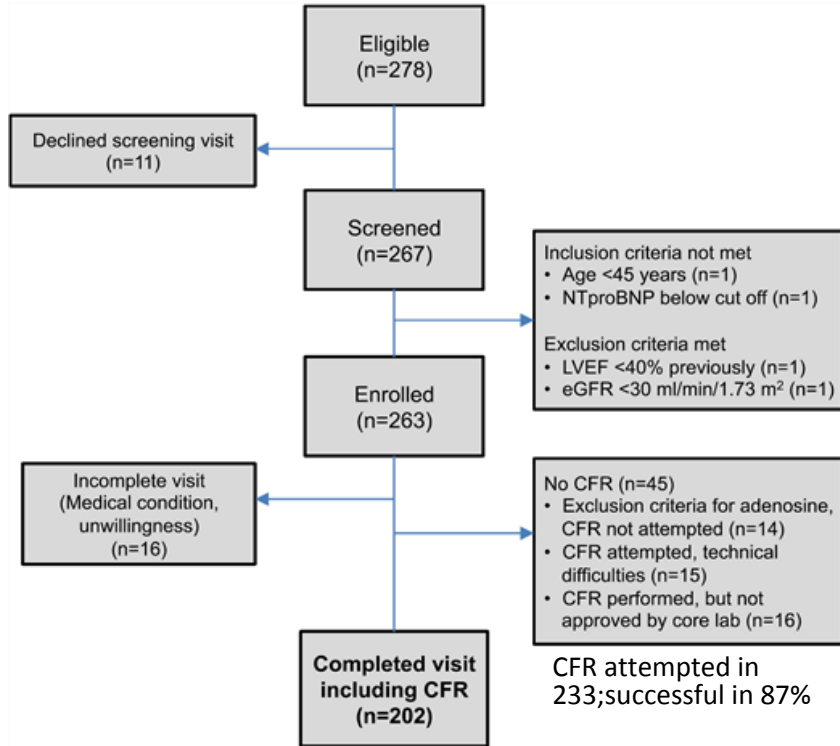
- Prospective patients with confirmed chronic HFpEF from Sweden, US, Finland and Singapore
- Major inclusion criteria:
 - Signs & symptoms of HF; stable NYHA II-IV
 - EF \geq 40%
 - At least one of (1) \uparrow natriuretic peptides;¹ (2) HF hospitalization in last 12 months with LVH/LAE; (3) PCWP $>$ 15 mmHg (rest) or $>$ 25 mmHg (exercise); or (4) E/e' $>$ 15
- Major exclusion criteria:
 - Significant unrevascularized epicardial CAD
 - Primary cardiomyopathy
 - Hemodynamically significant valve disease
 - Any history of EF $<$ 40%

Methods

- Coronary flow reserve (CFR) by transthoracic Doppler echo coronary flow velocity at rest and with adenosine
 - Read by core lab
 - CMD defined as $CFR < 2.5$
- Systemic microvascular function by peripheral arterial tonometry (EndoPAT) reactive hyperemia index (RHI)
- Myocardial function by echo tissue Doppler and speckle-tracking



Results



Prevalence of CMD among 202 HFpEF with CFR = 75% (95% CI 69-81%)

- Mean (SD) CFR = 2.13 (0.51)
- Median (IQR) CFR = 2.08 (1.78-2.50)

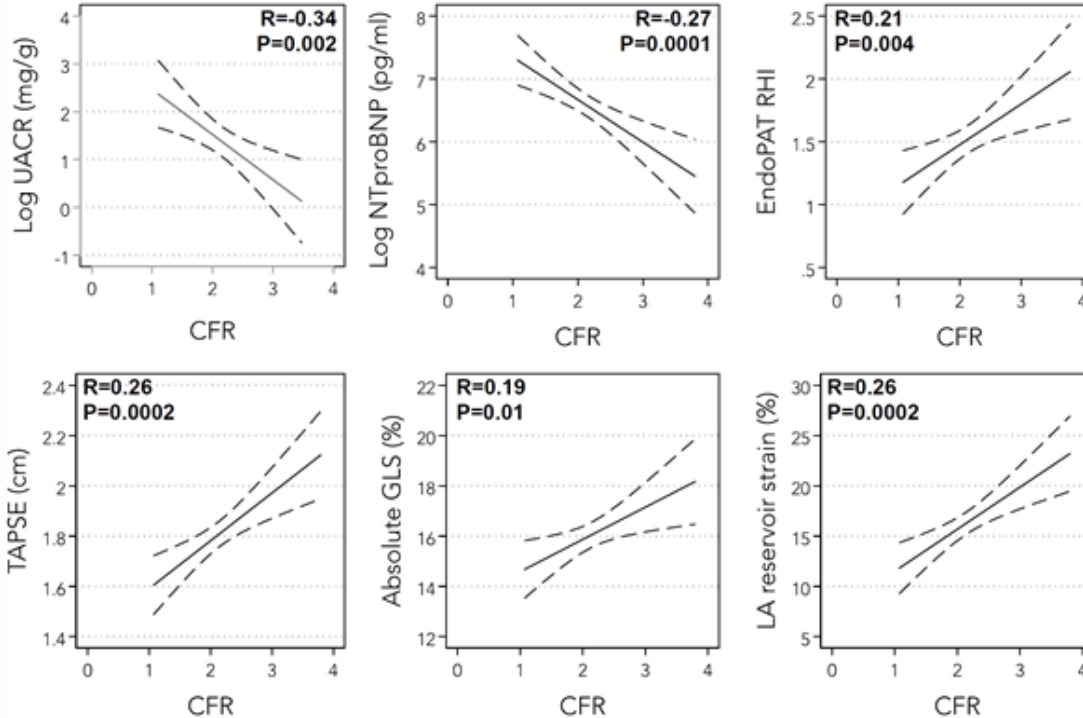
Results

Characteristic	CMD absent (N=51)	CMD present (N=151)	P-value
Age, years	72.4±9.0	74.7±8.7	0.11
Female, n(%)	32(63)	79(52)	0.20
<i>Comorbidities, n(%)</i>			
• Hypertension	47(92)	123(81)	0.07
• Previously revascularized CAD	8(16)	31(21)	0.45
• Atrial fibrillation	18(35)	88(58)	0.004
• Diabetes	13(25)	45(30)	0.56
• Obesity	22(43)	49(32)	0.17
• Chronic kidney disease	25(49)	80(53)	0.63
• Current or prior cigarette smoker	22(43)	106(70)	<0.001

Characteristic	CMD absent	CMD present	P-value
• eGFR, mL/min/1.73 m ²	63±20	59±19	0.16
• UACR, mg/g	2.4 (1.1-3.7)	4.3 (1.4-18.8)	0.036
• NT-proBNP, pg/mL	597 (190-1410)	1050 (396-1930)	0.004
<i>Doppler echo</i>			
• LV mass index, g/m ²	102.1±26.1	110.3±36.6	0.14
• LV E/e' ratio	12.4±4.7	13.5±6.2	0.24
• RV wall thickness, cm	4.7±0.6	4.9±0.7	0.016
• TAPSE, mm	19.7±3.6	17.5±3.7	<0.001
• PASP, mmHg	40.5±10.8	45.6±15.3	0.05

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<i>Speckle-tracking echocardiography</i>			
• LV global longitudinal strain, %	17.0±3.5	15.7±3.5	0.023
• RV free wall strain, %	23.3±5.1	21.6±5.2	0.05
• LA reservoir strain, %	19.8±8.3	15.0±7.7	<0.001

Results



After multivariable adjustment¹ worse CFR was related to:

- higher UACR & NT-proBNP
- lower RHI, TAPSE, RV strain

PROMIS-HFpEF: Conclusions

- Largest prospective multicenter study of CMD in HFpEF
- High (75%) prevalence of CMD in HFpEF in the absence of unrevascularized macrovascular CAD
- CMD is associated with HF severity (\uparrow NT-proBNP), systemic endothelial dysfunction (\downarrow EndoPAT RHI, \uparrow UACR), and cardiac dysfunction (\downarrow LV, LA, RV strain)
- Microvascular dysfunction may be a promising composite risk marker and therapeutic target in HFpEF

Prevalence and correlates of coronary microvascular dysfunction in heart failure with preserved ejection fraction: PROMIS-HFpEF

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FAST TRACK CLINICAL RESEARCH
Heart failure/cardiomyopathy

Prevalence and correlates of coronary microvascular dysfunction in heart failure with preserved ejection fraction: PROMIS-HFpEF

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Aims To date, clinical evidence of microvascular dysfunction in patients with heart failure (HF) with preserved ejection fraction (HFpEF) has been limited. We aimed to investigate the prevalence of coronary microvascular dysfunction (CMD) and its association with systemic endothelial dysfunction, HF severity, and myocardial dysfunction in a well-defined, multi-centre HFpEF population.

Methods and results This prospective, multinational, multi-centre observational study enrolled patients fulfilling strict criteria for HFpEF according to current guidelines. Those with known unrevascularized macrovascular coronary artery disease (CAD) were excluded. Coronary flow reserve (CFR) was measured with adenosine stress echocardiography. Diastolic echocardiography, systemic endothelial function [reactive hyperemia index (RHI)] was measured by peripheral arterial occlusion. Among 332 patients with HFpEF, 131 (39%) (95% confidence interval 36–41%) had CMD (defined as CFR <1.5). Patients with CMD had a higher prevalence of current or prior smoking (70% vs. 43%, $P=0.006$) and atrial fibrillation (AF) (28% vs. 20%, $P=0.004$) compared with those without CMD. HFpEF was associated with higher coronary artery atherosclerotic mass (CAC), and HFpEF and lower RHI, excepted atrial fibrillation, systemic aortic atherosclerosis, and right ventricular (RV) free wall strain after adjustment for age, sex, body mass index, atrial fibrillation, diabetes, myocardial CAD, smoking, left ventricular mass, and study site ($P<0.05$ for all associations).

Conclusions PROMIS-HFpEF is the first prospective multi-centre, multinational study to demonstrate a high prevalence of CMD in HFpEF in the absence of unrevascularized macrovascular CAD, and to show its association with systemic endothelial dysfunction (RHI, CAC) as well as markers of HF severity (RV dysfunction and RV dysfunction). Microvascular dysfunction may be a promising therapeutic target in HFpEF.

Keywords Heart failure with preserved ejection fraction • Coronary microvascular dysfunction • Coronary flow reserve • Endothelial dysfunction • Echocardiography • Biomarkers

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