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SHORT COMMUNICATION

Regional differences and coronary microvascular dysfunction in heart failure with preserved ejection fraction

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Abstract

Aims In heart failure with preserved ejection fraction (HFpEF), regional heterogeneity of clinical phenotypes is increasingly recognized, with coronary microvascular dysfunction (CMD) potentially being a common shared feature. We sought to determine the regional differences in clinical characteristics and prevalence of CMD in HFpEF.

Methods and results We analysed clinical characteristics and CMD in 202 patients with stable HFpEF (left ventricular ejection fraction ≥40%) in Finland, Singapore, Sweden, and United States in the multicentre PROMIS-HFpEF study. Patients with unrevascularized macrovascular coronary artery disease were excluded. CMD was assessed using Doppler echocardiography and defined as coronary flow reserve (adenosine-induced vs. resting flow) < 2.5. Patients from Singapore had the lowest body mass index yet highest prevalence of hypertension, dyslipidaemia, and diabetes; patients from Finland and Sweden were oldest, with the most atrial fibrillation, chronic kidney disease, and high smoking rates; and those from United States were youngest and most obese. The prevalence of CMD was 88% in Finland, 80% in Singapore, 77% in Sweden, and 59% in the United States; however, non-significant after adjustment for age, sex, N-terminal pro-brain natriuretic peptide, smoking, left atrial reservoir strain, and atrial fibrillation. Associations between CMD and clinical characteristics did not differ based on region (interaction analysis).

Conclusions Despite regional differences in clinical characteristics, CMD was present in the majority of patients with HFpEF across different regions of the world with the lowest prevalence in the United States. This difference was explained by differences in patient characteristics. CMD could be a common therapeutic target across regions.

Keywords Coronary flow reserve; Coronary microvascular dysfunction; HFpEF; Region

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Introduction

Heart failure (HF) with preserved ejection fraction (HFpEF) is associated with multiple common co-morbidities suggested to drive systemic inflammation and endothelial dysfunction, leading to coronary microvascular dysfunction (CMD).[1] CMD is present in 75% of patients with HFpEF and associated with an increased risk of HF hospitalization and mortality.[2,3] Even though a single treatment strategy to reduce mortality and morbidity in HFpEF exits in sodium glucose co-transporter-2

(SGLT-2) inhibitors,[4,5] the effectiveness may differ in different phenotypes due to disease heterogeneity. Exploration and subgroup characterization may reveal phenotype-specific treatment targets.[6]

While geographical influences on HFpEF phenotypes have been previously suggested, regional differences in CMD have not been explored. Data from the PARAGON-HF trial indicate that patients with HFpEF in North America are more obese

Table 1 Clinical characteristics of HFpEF patients by country

	Finland (n = 40)	Singapore (n = 20)	Sweden (n = 91)	United States (n = 51)	P-overall
Age (years)	75 (70;81)	74 (69;80)	78 (72;82)	69 (62;75)	**<0.001**
Sex (female)	24 (60)	8 (40)	43 (47)	36 (71)	**0.024**
HR (b.p.m)	72 (61;79)	66 (59;70)	67 (60;79)	69 (64;78)	0.498
SBP (mmHg)	139 (129;152)	161 (139;172)	140 (130;157)	126 (113;135)	**<0.001**
DBP (mmHg)	78 (73;88)	80 (71;93)	80 (70;85)	66 (59;75)	**<0.001**
BMI (kg/m^2)	29 (25;33)	26 (23;30)	27 (24;29)	32 (27;45)	**<0.001**
JVD	0 (0)	4 (20)	0 (0)	47 (92)	**<0.001**
Oedema	4 (10)	11 (55)	25 (28)	43 (84)	**<0.001**
Orthopnoea	0 (0)	9 (53)	7 (12)	29 (58)	**<0.001**
KCCQ	53 (44;68)	75 (58;86)	80 (58;88)	61 (39;78)	**<0.001**
6MWT (m)	400 (306;448)	265 (186;361)	331 (240;416)	345 (285;400)	**0.038**
RHI	0.69 (0.47;0.83)	1.77 (1.56;1.98)	1.85 (1.54;2.18)	1.29 (0.78;2.0)	**<0.001**
Ethnicity					**<0.001**
White	40 (100)	0 (0)	91 (100)	43 (84)	
Asian	0 (0)	20 (100)	0 (0)	1 (2)	
Black	0 (0)	0 (0)	0 (0)	7 (14)	
NYHA[a]					**<0.001**
I	0 (0)	0 (0)	3 (3)	0 (0)	
II	25 (63)	18 (90)	76 (84)	30 (59)	
III	15 (38)	1 (5)	12 (13)	21 (41)	
IV	0 (0)	1 (5)	0 (0)	0 (0)	
Co-morbidities					
AF	28 (70)	6 (30)	61 (67)	11 (22)	**<0.001**
Anaemia	8 (21)	8 (40)	34 (38)	25 (49)	0.052
CAD	3 (8)	7 (35)	24 (26)	5 (10)	**0.007**
CKD	28 (72)	5 (25)	49 (54)	23 (45)	**0.004**
DM	9 (23)	10 (50)	25 (28)	14 (28)	0.792
Hyperlipidaemia	19 (48)	17 (85)	45 (50)	30 (59)	**0.022**
Hypertension	35 (88)	20 (100)	72 (79)	43 (84)	0.120
Obesity	16 (40)	5 (25)	20 (22)	32 (63)	**<0.001**
Smoking	19 (48)	8 (40)	73 (80)	28 (55)	**<0.001**
Treatments					
ACE-inhibitor	11 (28)	10 (50)	36 (40)	8 (16)	**0.008**
ARB	18 (45)	8 (40)	41 (45)	18 (35)	0.689
Beta-blocker	37 (93)	16 (80)	70 (77)	26 (51)	**<0.001**
Diuretics	34 (85)	17 (85)	68 (75)	36 (71)	0.313
MRA	11 (28)	0 (0)	15 (17)	26 (51)	**<0.001**
Laboratory					
eGFR (mL/min/1.73 m^2)	54 (44;63)	73 (49;85)	58 (49;68)	62 (44;79)	**0.032**
Haemoglobin (g/L)	133 (123;146)	130 (115;142)	132 (121;140)	121 (112;131)	**0.001**
LDL (mmol/L)	2.0 (1.5;3.1)	2.4 (1.9;2.7)	2.4 (1.8;3.1)	1.9 (1.7;2.6)	0.133
NT-proBNP (pg/mL)	1220 (742;2040)	386 (130;1301)	1260 (812;1943)	198 (93;440)	**<0.001**
Troponin (ng/mL)	16 (10;28)	18 (14;25)	16 (11;25)	10 (10;10)	**<0.001**
Echocardiography					
LVEF (%)	58 (54;61)	64 (57;69)	58 (54;63)	64 (59;66)	**<0.001**
LAVI (mL/m^2)	40 (32;49)	36 (25;40)	41 (35;47)	29 (22;33)	**<0.001**
E/e′	13 (8.4;16)	13 (11;16)	12 (9;16)	12 (9.4;16)	0.570
LVMI (g/m^2)	105 (85.9;128)	111 (87.1;134)	111 (85;130)	94 (76;112)	0.112
Left atrial reservoir strain (%)	11 (9;20)	18 (12;25)	12 (8;18)	24 (16;28)	**<0.001**

Categorical variables are presented as number (n) and percentage (%) and continuous variables as median and upper and lower quartiles (Q1;Q3), P-value for overall comparisons.

6MWT, 6 minute walk test; ACE-inhibitor, angiotensin converting enzyme inhibitor; AF, atrial fibrillation/flutter; ARB, angiotensin receptor blocker; BMI, body mass index; CAD, coronary artery disease; CKD, chronic kidney disease; CMD, coronary microvascular dysfunction; DBP, diastolic blood pressure; E/e′, early mitral diastolic velocity/early annular diastolic velocity; eGFR, estimated glomerular filtration (creatinine) rate; HR, heart rate; JVD, jugular vein distension; KCCQ, Kansas city cardiomyopathy questionnaire; LAVI, left atrial volume index; LDL, low density lipoprotein; LVEF, left ventricular ejection fraction; LVMI, left ventricular mass index; MRA, mineral corticoid receptor antagonist; NT-proBNP, N-terminal pro-brain natriuretic peptide; NYHA, New York Heart Association; RHI, reactive hyperemia index; SBP, systolic blood pressure.

[a]NYHA class I on the day of enrolment into the study.

with diabetes mellitus (DM), whereas in Asia, they suffer from DM too, but obesity is less common, and in Europe, atrial fibrillation (AF) is more common.[7] Prevalence and correlates of CMD in HFpEF (PROMIS-HFpEF) was a study with comprehensive characterization of HFpEF patients from North America, Asia, and Europe with the primary aim to study prevalence of CMD.[2]

Aims

In the present analysis, we explore the regional differences in CMD and clinical characteristics and the influence of region on the associations between clinical characteristics and CMD in patients from Finland, Singapore, Sweden, and United States.

Methods

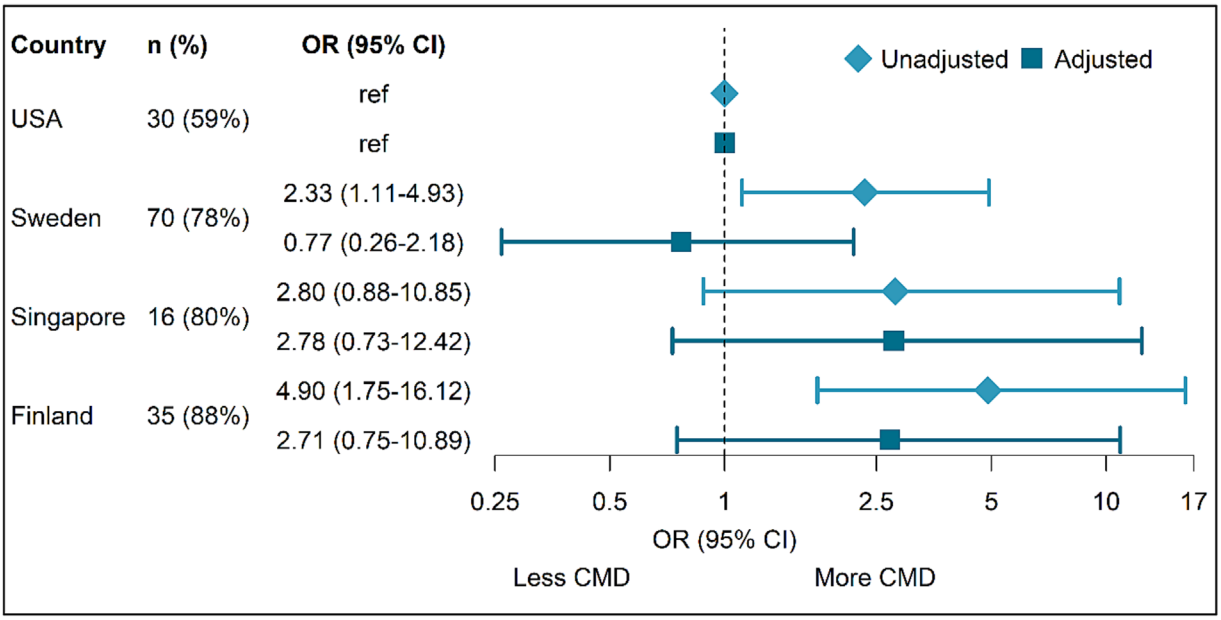
Study design

We performed a retrospective analysis of patients enrolled in the prospective, multinational, multicentre, observational PROMIS-HFpEF study. Sites participated from four countries: Stockholm and Gothenburg (Sweden); Turku (Finland); Chicago (United States); and Singapore. A thorough description of inclusion and exclusion criteria is available in supplementary materials of a previous publication.[2] In short, patients were required to have New York Heart Association II–IV, a left ventricular ejection fraction (LVEF) $\geq$ 40%, and one or more of the following: (i) prior hospitalization with evidence of left ventricular hypertrophy or left atrial dilatation; (ii) elevated natriuretic peptides; (iii) E/e' ratio $\geq$15; and (iv) elevated invasive capillary wedge pressures. Most important exclusion criteria were unknown unrevascularized macrovascular coronary artery disease and a recorded LVEF ever $<$40%. CMD was defined as coronary flow reserve $<$2.5 assessed by adenosine-induced versus basal coronary flow measured by transthoracic Doppler echocardiography, as previously described in PROMIS-HFpEF.[2]

Demographic, clinical, laboratory, echocardiographic, functional (6 min walk test; 6MWT), patient-reported quality of life data (Kansas City Cardiomyopathy Questionnaire; KCCQ) and peripheral endothelial dysfunction expressed as reactive hyperaemia index (RHI) measured through EndoPAT® were collected. Definitions are available in supplementary materials of a previous publication.[2]

All study participants provided written informed consent, and the institutional review board at each of the participating sites approved the study. The study complied with the Declaration of Helsinki.

Figure 1 Showing association between CMD and country. Prevalence of CMD presented as numbers and percentages n (%) for each country. Crude and adjusted odds ratios (OR) [95% confidence interval (CI)], for the associations between CMD and country. Point of reference USA at 1.0 (grey vertical line). Adjusted for age, sex, NT-proBNP, smoking, left atrial reservoir strain, and atrial fibrillation.



Statistical analysis

Descriptive data are presented as median and interquartile range (Q1;Q3) and numbers (*n*) and percentages (%). Comparisons between all countries were analysed using Kruskal–Wallis and Pearson's chi-square test as appropriate and presented as '*P*-overall' (*Table 1*). To assess whether the regional prevalence of CMD differed based on differences in clinical characteristics, a logistic regression analysis was performed with CMD as the dependent variable adjusting for age, sex, N-terminal pro-brain natriuretic peptide (NT-proBNP), smoking, left atrial reservoir strain, and AF (*Figure 1*). The covariates were chosen from a univariable logistic regression analysis on CMD and baseline characteristics based on *P*-value <0.01 and if of clinical relevance. These univariable and multivariable analyses are presented as odds ratio, 95% confidence interval, and *P*-value and are available in *Table S1*.

The effect modification of country on the association between CMD and clinical characteristics was explored through a multivariable interaction analysis, adjusted with the same covariates above, presented as *P* for interaction (country*covariate) with CMD as the dependent variable. A *P*-value of <0.05 was set as significance level (*Table 2*). All analyses were performed using R 4.2.1.

Table 2 Interaction region on association between patient characteristics and CMD

Variables	*P*-value interaction (*n* = 202)
Age (years)	0.070
Sex (female)	0.688
SBP (mmHg)	0.445
DBP (mmHg)	0.979
BMI (kg/m^2)	0.664
JVD	0.835
Oedema	0.513
Co-morbidities	
AF	0.937
Anaemia	0.295
CAD	0.536
CKD	0.926
DM	0.886
Hyperlipidaemia	0.065
Hypertension	0.492
Obesity	0.928
Smoking	0.814
Treatments	
ACE-inhibitor	0.888
ARB	0.087
Beta-blocker	0.788
Diuretics	0.923
Laboratory	
eGFR (mL/min/1.73 m^2)	0.580
Heamoglobin (g/L)	0.288
LDL (mmol/L)	0.083
NT-proBNP (pg/mL)	0.679
Troponin (ng/mL)	0.143
Echocardiography	
LVEF (%)	0.507
LAVI (mL/m^2)	0.350
LVMI (g/m^2)	0.161
Left atrial strain (%)	0.426

P for interaction denotes *p*-value for effect modification by country.
ACE-inhibitor, angiotensin converting enzyme inhibitor; AF, atrial fibrillation/flutter; ARB, angiotensin receptor blocker; BMI, body mass index; CAD, coronary artery disease; CKD, chronic kidney disease; DBP, diastolic blood pressure; DM, diabetes mellitus; eGFR, estimated glomerular filtration (creatinine) rate; JVD, jugular vein distension; LAVI, left atrial volume index; LDL, low density lipoprotein; LVEF, left ventricular ejection fraction; LVMI, left ventricular mass index; NT-proBNP, N-terminal pro-brain natriuretic peptide; SBP, systolic blood pressure.

Results

In total, 202 patients from Sweden (*n* = 91), United States (*n* = 51), Finland (*n* = 40), and Singapore (*n* = 20) had CMD assessed. Clinical characteristics are summarized in *Table 1*. Patients in the United States were the youngest (69 years) and in Sweden the oldest (78 years; *P*-overall <0.001). In Finland and Sweden, AF (70% and 67%) and CKD (72% and 54%) were common (*P*-overall <0.001 and *P*-overall = 0.004). Obesity was present in the majority of the patients in the United States (63%; *P*-overall <0.001). Both hyperlipidaemia (85%) and coronary artery disease (35%) were most prevalent in Singapore (*P*-overall = 0.022 and *P*-overall = 0.007). NT-proBNP levels were higher in Sweden (1260 pg/mL) and Finland (1220 pg/mL) compared with Singapore (386 pg/mL) and United States (198 pg/mL; *P*-overall <0.001). Left atrial volume index was the lowest in the United States (29 mL/m^2) and the highest in Sweden (41 mL/m^2; *P*-overall<0.001). Finland displayed the lowest RHI and KCCQ (*P*-overall <0.001 for both), and the highest 6MWT (*P*-overall = 0.038).

The prevalence of CMD varied and was the highest in Finland (88%) and the lowest in the United States (59%) (*Figure 1*). There was no difference in prevalence of CMD between countries after adjusting for age, sex, NT-proBNP, smoking, left atrial reservoir strain, and AF (*Figure 1*). There was no effect modification of country (interaction analysis) (*Table 2*).

Conclusions

CMD was common in all regions but varied in prevalence with differences in patient characteristics. Associations between clinical characteristics and CMD were similar across regions.

We confirm previous findings that regional phenotypes exist in HFpEF.[7] In HFpEF patients, CMD was present in the majority regardless of country. Patients in Scandinavia were

older, with AF and impaired atrial function and high NT-proBNP that may contribute to a high prevalence of CMD.[8] Peripheral endothelial dysfunction, expressed as a low RHI, was most common in Finland, possibly relating to CKD and CMD.[9]

The highest prevalence of CMD was in Finland and the lowest in the United States despite the more obese American HFpEF phenotype. Obesity is suggested as a driver of CMD and HFpEF[1] and the lower prevalence in the United States may be explained by younger age and lower prevalence of AF.[8] Indeed, after adjusting for age, sex, NT-proBNP, smoking, left atrial reservoir strain, and AF, the prevalence of CMD was similar across regions. Patients in Singapore were hypertensive and, despite being leaner, had higher prevalence of DM, consistent with previous findings.[7] Still, prevalence of CMD was high, possibly associated with a more peturbed metabolic phenotype with hyperlipidaemia and DM. The lack of effect modification of region for any of the associations between clinical characteristics and CMD suggests that potential 'drivers' of CMD are uniform across regions.

PROMIS-HFpEF was not designed primarily to investigate regional differences, which is reflected by the uneven population distribution across countries limited to patients from White and Asian populations represented. The LVEF cut-off was set at ≥40%, which includes patients with mildly reduced LVEF. However, only 20 patients (10%) displayed an LVEF <50%. Data on SGLT-2 inhibitors were not collected as they were not indicated for HF at the time.

CMD was present in the majority of patients with HFpEF, with the lowest prevalence in the United States. The association between countries and CMD disappeared after multivariable adjustment. Clinical characteristics associated with CMD were similar in all countries. CMD could be a therapeutic target for HFpEF regardless of regional phenotype.

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Conflict of interest

Dr. Faxén has received consulting fees from Orion Pharma and Anacardio. Dr. Sanjiv Shah has received consulting fees from Abbott, Actelion, AstraZeneca, Amgen, Aria CV, Axon Therapies, Bayer, Boehringer-Ingelheim, Boston Scientific, Bristol-Myers Squibb, Cardiora, Coridea, CVRx, Cyclerion, Cytokinetics, Edwards Lifesciences, Eidos, Eisai, Imara, Impulse Dynamics, Intellia, Ionis, Ironwood, Lilly, Merck, MyoKardia, Novartis, Novo Nordisk, Pfizer, Prothena, Regeneron, Rivus, Sanofi, Shifamed, Tenax, Tenaya, and United Therapeutics. Dr. Carolyn S.P. Lam has received research support from Bayer and Roche Diagnostics; has served as consultant or on the Advisory Board/Steering Committee/Executive Committee for Abbott, Actelion, Alleviant Medical, Allysta Pharma, Amgen, AnaCardio AB, Applied Therapeutics, AstraZeneca, Bayer, Boehringer Ingelheim, Boston Scientific, Cytokinetics, Darma Inc., EchoNous Inc, Impulse Dynamics, Ionis Pharmaceutical, Janssen Research & Development LLC, Medscape/WebMD Global LLC, Merck, Novartis, Novo Nordisk, Prosciento Inc, Radcliffe Group Ltd., Roche Diagnostics, Sanofi, Siemens Healthcare Diagnostics and Us2.ai; and serves as co-founder & non-executive director of Us2.ai. Patent pending: PCT/SG2016/050217 Method for diagnosis and prognosis of chronic heart failure. US Patent No. 10,702, 247. Automated clinical workflow that recognizes and analyses 2-dimensional and Doppler echo images for cardiac measurements and the diagnosis, prediction, and prognosis of heart disease. Dr. Antti Saraste has received research grants from Academy of Finland and Finnish Foundation for Cardiovascular Research during the conduct of the study; and consulting fees from GE healthcare, Novartis, Abbot, Astra Zeneca. Dr. Camilla Hage has received consulting fees from Novartis, Roche Diagnostics and AnaCardio, research grants from Bayer and speaker and honoraria from MSD and Novartis. Supported by the Swedish Research Council [grant 20,180,899]. Dr. Lars H. Lund has received research grants from Novartis, Boehringer-Ingelheim, Vifor Pharma, AstraZeneca, Mundipharma and Relypsa and consulting fees from Novartis, Merck, Boehringer-Ingelheim, Sanofi, Bayer, Pharmacosmos, Myokardia, Medscape and AstraZeneca. Stock owner in Anacardio. Dr Jasper Tromp has received consulting or speaker fees from Daiichi-Sankyo, Boehringer Ingelheim, Roche diagnostics and Us2.ai, owns patent

US-10702247-B2 unrelated to the present work. All other authors have no disclosures to report.

Table S1. Associations between patient characteristics and coronary microvascular dysfunction.

Supporting information

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

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