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Original Article

Pathophysiological and Prognostic Importance of an ExtraCardiac Comorbidity Burden in Patients with Heart Failure with Preserved Ejection Fraction

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ABSTRACT

Background: Extracardiac comorbidities are highly prevalent in patients with heart failure with preserved ejection fraction (HFpEF). We investigated the pathophysiological contribution of an extracardiac comorbidity burden to cardiac function, exercise capacity, and prognosis in patients with HFpEF.

Methods: A total of 775 patients (372 HFpEF patients and 403 control subjects) underwent exercise echocardiography, with simultaneous expired gas analysis. We separated the previously validated Meta-Analysis Global Group in Chronic Heart Failure (MAGGIC) risk score into cardiac, extracardiac, and demographic categories. An Extracardiac burden was defined as an extracardiac domain score ≥ 5 (median value).

Results: Compared to control subjects (n = 403) and patients with HFpEF without an extracardiac burden (n = 185), patients with HFpEF with an extracardiac burden (n = 187) had higher natriuretic peptide levels and worse exercise capacity. They also had worse ventilatory efficiency and worse peripheral O_2 extraction during exercise. Kaplan–Meier analysis revealed that HFpEF patients with an extracardiac burden had a significantly higher risk of the composite outcome of all-cause mortality and worsening HF events than did those without this

RÉSUMÉ

Contexte : Les maladies concomitantes extracardiaques sont très fréquentes chez les patients atteints d'insuffisance cardiaque à fraction d'éjection préservée (ICFEP). Nous avons étudié la contribution physiopathologique du fardeau des maladies concomitantes extracardiaques à la fonction cardiaque, à la capacité d'effort et au pronostic chez les patients atteints d'ICFEP.

Méthodologie : Au total, 775 patients (372 patients atteints d'ICFEP et 403 sujets témoins) ont été soumis à une échocardiographie à l'effort accompagnée d'une analyse simultanée des gaz expirés. Nous avons séparé le score du risque MAGGIC (Meta-Analysis Global Group in Chronic Heart Failure) auparavant validé en trois catégories : cardiaque, extracardiaque et démographique. Un fardeau extracardiaque était défini comme un score du domaine extracardiaque ≥ 5 (valeur médiane).

Résultats : Comparativement aux sujets témoins (n = 403) et aux patients atteints d'ICFEP sans fardeau extracardiaque (n = 185), les patients atteints d'ICFEP avec fardeau extracardiaque (n = 187) affichaient des taux de peptides natriurétiques plus élevés et une moins bonne capacité d'effort. Leur efficacité ventilatoire était moindre tout comme l'extraction en O_2 périphérique à l'effort. Une analyse de

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See page 410 for disclosure information.

Heart failure (HF) with preserved ejection fraction (HFpEF) accounts for more than half of all HF cases, and its prevalence has been increasing, posing a substantial global public health challenge.[1-3] The primary manifestation of HFpEF is exercise intolerance, which is associated with severe symptoms of dyspnea, reduced quality of life, and even worse clinical

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burden (log-rank $P < 0.0001$). Cox regression analysis showed that the extracardiac domain score was significantly associated with a higher risk of the composite events ($P < 0.0001$). In contrast, an extracardiac comorbidity burden was not associated with impaired exercise capacity, worse ventilatory efficiency, impaired peripheral O_2 extraction, or worse clinical outcomes in control subjects.

Conclusions: An extracardiac comorbidity burden in patients with HFpEF is associated with relevant pathophysiological features characterized by impaired exercise capacity, worse ventilatory efficiency, impaired O_2 extraction and utilization in the periphery, and poor clinical outcomes.

Kaplan−Meier a révélé que les patients atteints d'ICFEP avec fardeau extracardiaque présentaient un risque significativement plus élevé pour le critère combiné de décès toutes causes confondues et d'aggravation des épisodes d'insuffisance cardiaque que les patients sans fardeau extracardiaque (log-rank $p < 0{,}0001$). Une analyse de régression de Cox a démontré que le score du domaine extracardiaque était significativement corrélé à un risque accru d'événements combinés ($p < 0{,}0001$). Par contre, un fardeau de maladie concomitante extracardiaque n'était pas associé à une capacité d'effort réduite, à une réduction de l'efficacité ventilatoire, à une altération de l'extraction en O_2 ou à une dégradation des issues cliniques chez les sujets témoins.

Conclusions : Un fardeau de maladie concomitante extracardiaque chez les patients atteints d'ICFEP est associé à des facteurs physiopathologiques pertinents caractérisés par une capacité d'effort réduite, par une efficacité ventilatoire diminuée, par une altération de l'extraction et de l'utilisation de l'O_2 en périphérie et par des issues cliniques défavorables.

outcomes.[4,5] HFpEF is a pathophysiologically complex and heterogeneous syndrome associated with multiple cardiac and extracardiac abnormalities.[6,7] Accumulating data suggest that extracardiac comorbidities, such as obesity, chronic kidney disease, and chronic pulmonary disease, are prevalent in patients with HFpEF, and the burden of extracardiac comorbidities is associated with the pathophysiological complexity of HFpEF.[8,9] Of note, recent research suggests that the benefit of medical therapy may be influenced by the severity of the extracardiac comorbidity burden in patients with HFpEF.[10] Thus, an improved understanding of the pathophysiological contribution of extracardiac comorbidity may lead to better therapeutic strategies in patients with HFpEF.

We hypothesized that, rather than individual components of extracardiac comorbidities, the accumulation of these comorbidities would be more relevant to the pathophysiology and clinical outcomes of in patients with HFpEF. Accordingly, the aim of the present study was to investigate the association of the cumulative burden of extracardiac comorbidities with exercise capacity, cardiac and ventilatory function during exercise, and clinical outcomes in patients with HFpEF.

Methods

Study population

We retrospectively identified consecutive patients referred to exercise stress echocardiography for the evaluation of exertional dyspnea at the Gunma University Hospital, Maebashi, Japan between October 2019 and May 2024. The diagnosis of HFpEF was defined using the **H**eart **F**ailure **A**ssociation **P**re-test assessment, **E**chocardiography and Natriuretic Peptide, **F**unctional Testing, **F**inal Etiology (HFA-PEFF) algorithm, steps 1-3.[11] In brief, the HFA-PEFF score was calculated as the sum of echocardiographic functional (age-specific cutoffs for early diastolic mitral annular velocity [e'] velocity, early transmitral flow velocity [E]/e' ratio, tricuspid regurgitation [TR] velocity, and longitudinal strain: maximum, 2 points), morphologic (rhythm-specific left atrial [LA] volume, relative wall thickness, and sex-specific measures of left ventricular [LV] mass: maximum, 2 points), and natriuretic peptide (maximum, 2 points) domains. Subsequently, 2 or 3 points were added based on the E/e' ratio and TR velocity during exercise stress echocardiography. The diagnosis of HFpEF was confirmed if the combined score from steps 2 and 3 was ≥ 5 points. If patients had high LV filling pressures on exercise right heart catheterization (pulmonary capillary wedge pressure of > 15 mm Hg at rest and/or ≥ 25 mm Hg during exercise), they were classified as having HFpEF.[12-14] Patients were excluded if they had any of the following: an ejection fraction (EF) of $< 50\%$; significant left-sided valvular heart disease ($>$ moderate regurgitation, $>$ mild stenosis); infiltrative, restrictive, or hypertrophic cardiomyopathy; nongroup II pulmonary arterial hypertension; insufficient exercise testing; or age < 20 years. Duplicate cases also were excluded (Supplemental Fig. S1).

Patients who did not meet either the HFA-PEFF algorithm or the invasive criteria were classified as having noncardiac dyspnea (control subjects). The study was conducted in accordance with the Declaration of Helsinki and the ethical guidelines for medical and biological research involving human subjects in Japan. The study was approved by our institutional review board (Gunma University Hospital, Clinical Research Review Board), with a waiver of consent because of the retrospective design. Participants were given the opportunity to refuse to participate in the study, via use of an opt-out approach.

Exercise stress echocardiography with simultaneous expired gas test

Transthoracic echocardiography was performed by experienced sonographers using a commercially available ultrasound system (Vivid E95; GE Healthcare, Horten, Norway). The EF and systolic mitral annular tissue velocity at the septal annulus (mitral s') were measured at rest and during exercise to assess LV systolic function and reserve. LV volumes and EF at rest and during exercise were determined using apical 4-chamber views. The septal E/e' ratio was determined to estimate LV filling pressure. Stroke volume was determined from the LV outflow

dimension and a pulse Doppler profile. Cardiac output was calculated from the product of the heart rate and stroke volume. The systolic tissue velocity at the lateral tricuspid annulus (TV s') and the tricuspid annular plane systolic excursion (TAPSE) at rest and during exercise were measured to assess right ventricular systolic function and reserve. Pulmonary artery systolic pressure (PASP) was calculated as 4 × (peak TR velocity)^2 + estimated right atrial pressure (RAP). The RAP was estimated from the diameter of the inferior vena cava and its respiratory change at rest and during exercise, coded as 3 mm Hg, 8 mm Hg, or 15 mm Hg.[15]

All participants underwent symptom-limited supine bicycle exercise, starting at 20 W for 5 minutes, with increments of 20 W in 3-minute stages to participant-reported exhaustion, as previously described (Angio imaging, Lode B.V., Groningen, The Netherlands).[16-18] Echocardiographic images were obtained at baseline and during all stages of exercise. All Doppler measurements represent the mean of ≥ 3 beats. Expired gas analysis was performed simultaneously with echocardiography, at rest and during exercise, in most of the participants (n = 672; 87%) to measure breath-by-breath oxygen consumption (volume of inspired oxygen [VO_2]), volume of carbon dioxide production (VCO_2), tidal volume (V_T), respiratory rate, and minute ventilation ($V_E = V_T$ x respiratory rate; all measured using the AE-100i, MINATO Medical Science, Osaka, Japan).[4,5,19] Peripheral oxygen (O_2) extraction was assessed as the arteriovenous O_2 content difference (AVO_2 difference: $VO_2 \div CO$ [in mL/dL]).[20,21]

Calculation of the cumulative burden of cardiac and extracardiac comorbidities

We utilized the Meta-Analysis Global Group in Chronic Heart Failure (MAGGIC) risk score, a validated total risk score in patients with HF, to estimate and quantify each risk component—demographic, cardiac, and extracardiac comorbid burden.[22] The MAGGIC score derived an optimal model for predicting death in patients with both HFrEF and HFpEF, with 13 variables identified as being highly significant. In the present study, we classified the 13 variables into 3 subcategories as follows: demographic burden (age and sex); cardiac burden (lower LVEF, New York Heart Association [NYHA] class, lower systolic blood pressure, HF duration, no β-blocker use, no angiotensin-converting enzyme inhibitor [ACE-I] or angiotensin-receptor blocker [ARB] use); and extracardiac disease burden (lower body mass index [BMI], diabetes, chronic obstructive pulmonary disease [COPD], creatinine levels, current smoking), as previously reported.[8,10] A total score of 52 points was possible (demographic domain, 0-16; cardiac domain, 0-16; and extracardiac domain, 0-20; Supplemental Fig. S2).

Outcome assessment

Patients were followed from the day of the exercise stress echocardiographic examinations. The primary endpoint was a composite of all-cause mortality and worsening HF events. Worsening HF was defined as hospitalization for HF, unplanned visits requiring intravenous diuretic treatment, or intensification of oral diuretics (initiated or increased for worsening HF after 1 month of exercise testing).[5] Follow-up data were obtained from medical records, death certificates, and telephone interviews.

Statistical analysis

Data are presented as mean (standard deviation), median (interquartile range [IQR]), or number (%), unless otherwise specified. Differences between groups were compared using 1-way analysis of variance, the Kruskal–Wallis test, or the χ^2 test, as appropriate. Tukey's honestly significant difference test or the Steel–Dwass test was used to adjust for multiple tests. A trend test was used to assess the relationship between the extracardiac domain score and exercise parameters. Elevated natriuretic peptide levels were defined as a B-type natriuretic peptide (BNP) > 80 pg/mL or N-terminal pro B-type natriuretic peptide (NT-proBNP) > 220 pg/mL in sinus rhythm, or BNP > 240 pg/mL or NT-proBNP > 660 pg/mL in atrial fibrillation. The clinical endpoint was evaluated using the Kaplan–Meier analysis and compared with the log-rank test. Univariable Cox proportional hazards regression analysis was used to assess the association of cardiac, and extracardiac domain scores and the risk of primary endpoints, and to calculate the hazard ratio (HR) and a 95% confidence interval (CI) for the endpoint. All tests were 2-sided, with statistical significance set at $P < 0.05$. All statistical analyses were performed with JMP 16.2.0 software (SAS Institute, Cary, NC).

Results

Baseline clinical characteristics

The final study cohort included 372 patients with HFpEF and 403 control subjects (Supplemental Fig. S1). The median MAGGIC scores in HFpEF and control subjects were 22 (IQR 18-28) and 18 (IQR 13-22), respectively ($P < 0.0001$). The median demographic, cardiac, and extracardiac domain scores of HFpEF patients were 12 (IQR 9-15), 6 (IQR 4-9), and 5 (IQR 3-6), respectively. Then, patients with HFpEF were classified into 2 groups according to the median value of the extracardiac domain score of 5 points, as follows: HFpEF with an extracardiac burden (extracardiac domain score ≥ 5; n = 187); and HFpEF without an extracardiac burden (extracardiac domain score ≤ 4; n = 185). Per definition, the extracardiac domain score was the greatest in HFpEF patients with an extracardiac burden, whereas the cardiac domain score was similar across groups (Fig. 1). Compared to control subjects, patients with HFpEF were older, had a greater NYHA functional class, and had a higher prevalence of coronary artery disease, systemic hypertension, and atrial fibrillation (Table 1). The use of an ACE-I or ARB and beta-blockers was higher in patients with HFpEF than it was in control subjects, and the use of mineralocorticoid receptor antagonists, diuretics, and sodium-glucose cotransporter 2 inhibitors was the highest in patients with an extracardiac burden. Sex and vital signs were similar among groups. As expected, in HFpEF patients with an extracardiac burden, BMI was the lowest, renal function was the most impaired, and the prevalence of diabetes and COPD was the highest. Patients with an extracardiac burden had higher natriuretic peptide levels and lower hemoglobin and albumin levels than did other groups (Fig. 2). As expected, patients with HFpEF displayed typical cardiac structural and functional abnormalities, with higher LV mass index and LA volume index, lower mitral e' and s' velocities, higher E/e' ratio and PASP, and lower TV s' and TAPSE than did control

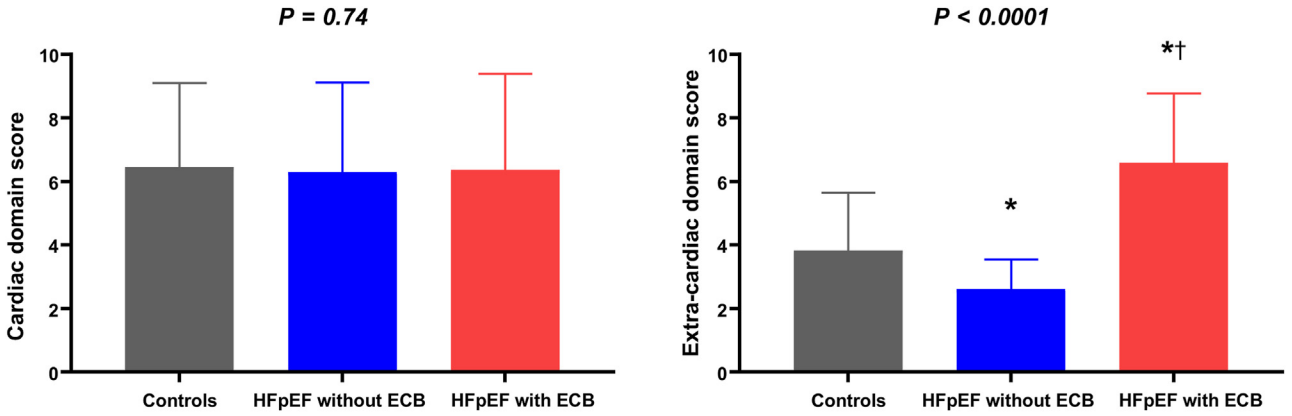

Figure 1. Comparison of cardiac and extracardiac domain scores among the 3 patient groups (control subjects, patients with heart failure with preserved ejection fraction [HFpEF], with and without extracardiac burden [ECB]). *$P < 0.05$ vs control subjects. †$P < 0.05$ vs HFpEF without extracardiac burden.

subjects, but no differences were observed between the HFpEF groups (Table 1).

Echocardiography and expired gas data during peak exercise

All participants underwent supine ergometry exercise stress echocardiography. Compared to the other groups, exercise capacity was more impaired in those with HFpEF with an extracardiac burden, as evidenced by a lower peak exercise workload achieved and a shorter exercise duration (Fig. 3A; Supplemental Fig. S3A; Table 2). The exercise workload relative to the peak VO_2 was also lower in the patients with an extracardiac burden than in other groups, suggesting that the former had poorer mechanistic efficiency (Fig. 3B). During peak exercise, LV systolic and diastolic function was impaired in patients with HFpEF, compared to that in control subjects, as evidenced by the following: a lower mitral e' velocity; a higher E/e' ratio, PASP, and RAP; and lower TV s' and TAPSE. But no differences occurred between the HFpEF groups (Table 2).

The presence of an extracardiac burden in patients with HFpEF was associated with remarkable ventilation and peripheral abnormalities. Compared to the other groups, patients with an extracardiac burden had lower V_E and V_T, and a worse V_E vs VCO_2 slope (Fig. 3C). A greater extracardiac burden was associated with a lower AVO_2 difference during exercise, suggesting that patients with an extracardiac burden exhibited the poorest O_2 extraction in the periphery (Fig. 3D; Supplemental Fig. S3B).

Extracardiac burden and clinical outcomes

Of the 775 participants, follow-up data were available for 541 patients (259 control subjects, 141 HFpEF patients without an extracardiac burden, and 141 HFpEF patients with an extracardiac burden). During a median follow-up duration of 401 days (IQR 181-745), 71 clinical endpoints occurred (11.3%), including 20 deaths (7 cardiac, 13 noncardiac) and 51 worsening HF events. Kaplan–Meier analysis showed that HFpEF patients with an extracardiac burden had significantly higher rates of adverse events than did control subjects and those without this burden (log-rank $P < 0.0001$; Fig. 4). The presence of an extracardiac burden in HFpEF patients was associated with a 2.7-fold increased risk of the composite outcomes, compared to the risk in those without an extracardiac burden (hazard ratio [HR] 2.66, 95% confidence interval [CI], 1.46-4.85; $P = 0.001$), and a 4.3-fold increased risk compared to that among control subjects (HR 4.26, 95% CI, 1.46-4.82). In a univariable Cox proportional hazards model, the extracardiac domain score was associated with an increased risk of the primary endpoint (HR 1.25 per 1-point increase; 95% CI, 1.14-1.36; $P < 0.0001$). Multivariable Cox proportional hazard models showed that the extracardiac domain score remained significantly associated with the outcomes, even after adjusting for age, sex, baseline E/e', left atrial volume index, and elevated natriuretic peptide levels (HR 1.17 per 1-point increase; 95% CI, 1.06-1.29; $P = 0.002$). In contrast, the cardiac domain score was not associated with the composite outcome (HR 1.06 per 1-point increase, 95% CI 0.96-1.17; $P = 0.25$).

Sex-specific analyses

Of the 372 patients with HFpEF, 150 were men, and 222 were women. Men with HFpEF had significantly higher extracardiac burden domain scores than those of HFpEF women (5 [IQR 3-7]) vs 3 [IQR 3-5]; $P < 0.0001$). The analysis of male patients with HFpEF showed that peak workload (50 ± 23 vs 64 ± 23 W; $P = 0.0004$), peak workload relative to peak VO_2 (4.4 ± 1.4 vs 5.1 ± 1.3 W*min*kg/mL; $P = 0.006$), and the AVO_2 difference (11.9 ± 4.1 vs 15.1 ± 6.4 mL/dL; $P = 0.002$) were lower, and the V_E vs VCO_2 slope was higher (38.2 ± 10.0 vs 34.3 ± 6.0; $P = 0.04$) in patients with an extracardiac burden (n = 86) than they were in those without this burden (n = 64). Similar results were obtained in female HFpEF patients; female HFpEF patients with an extracardiac burden (n =101) demonstrated a lower peak workload (38 ± 27 vs 48 ± 19 W; $P = 0.0001$), a lower peak workload relative to peak VO_2 (3.5 ± 1.3 vs 4.4 ± 1.4 W*min*kg/mL; $P < 0.0001$), and a lower AVO_2 difference (9.9 ± 2.9 vs 11.9 ± 4.6 mL/dL; $P = 0.004$) than did those without this burden. The extracardiac burden score was significantly associated with increased risk of the primary endpoints occurring in

Table 1. Baseline characteristics

Characteristic	Control subjects (n = 403)	Patients with HFpEF without extracardiac burden (n = 185)	Patients with HFpEF with extracardiac burden (n = 187)	*P*
Age, y	65 ± 14	75 ± 8*	77 ± 7*	< 0.0001
Female	241 (60)	121 (65)	101 (54)	0.08
Body mass index, kg/m^2	23.8 ± 5.1	25.6 ± 4.6*	21.8 ± 4.2*,†	< 0.0001
MAGGIC score	18 (13, 22)	21 (17, 24)*	24 (21, 28)*,†	< 0.0001
Demographic domain	8 (3, 12)	12 (9, 15)*	12 (9, 15)*	< 0.0001
Cardiac domain	6 (5, 8)	6 (4, 9)	6 (4, 9)	0.74
Extracardiac domain	3 (3, 5)	3 (2, 3)*,†	6 (5, 8)*,†	< 0.0001
NYHA	2.0 ± 0.7	2.2 ± 0.7*	2.2 ± 0.8*	0.001
Comorbidities				
Coronary disease	17 (4)	20 (11)*	27 (15)*	< 0.0001
Diabetes mellitus	58 (14)	9 (5)*	92 (50)*,†	< 0.0001
Hypertension	255 (63)	154 (83)*	154 (82)*	< 0.0001
Atrial fibrillation	54 (13)	66 (36)*	59 (32)*	< 0.0001
Chronic obstructive pulmonary disease	29 (7)	2 (1)*	22 (12)*,†	< 0.0001
Medications				
ACEIs or ARBs	112 (28)	81 (44)*	76 (41)*	0.0001
ARNI	4 (1.6)	10 (9.5)*	7 (6.0)	0.003
Beta-blocker	40 (10)	59 (32)*	60 (32)*	< 0.0001
MRA	11 (3)	20 (11)*	40 (22)*,†	< 0.0001
Loop diuretics	35 (9)	44 (24)*	67 (36)*,†	< 0.0001
SGLT2i	16 (4)	14 (8)	30 (16)*,†	< 0.0001
Laboratories				
BNP, pg/mL, n = 311	27 (13, 52)	90 (38, 156)*	120 (55, 223)*	< 0.0001
NT-pro BNP, pg/mL, n = 529	86 (48, 149)	306 (148, 681)*	449 (214, 902)*,†	< 0.0001
Hemoglobin, g/dL	13.4 ± 1.5	12.9 ± 1.5*	12.2 ± 1.9*,†	< 0.0001
eGFR, mL/min per 1.73 m^2	68.6 ± 20.6	61.6 ± 13.6*	53.3 ± 23.5*,†	< 0.0001
Albumin, g/dL	4.2 ± 0.4	4.0 ± 0.4*	3.9 ± 0.4*,†	< 0.0001
C-reactive protein, mg/dL	0.2 ± 0.6	0.3 ± 0.6	0.5 ± 1.7*,†	0.01
Vital signs				
Heart rate, bpm	74 ± 13	72 ± 13*	72 ± 14*	0.03
Systolic BP, mm Hg	128 ± 20	127 ± 17	127 ± 19	0.95
Saturation, %	97 ± 2	97 ± 2	97 ± 2	0.80
LV structure and function				
LV diastolic dimension, mm	43 ± 5	44 ± 6	43 ± 6	0.27
LV mass index, g/m^2	75 ± 19	89 ± 23*	90 ± 24*	< 0.0001
LV ejection fraction, %	64 ± 7	63 ± 7	62 ± 7*	0.007
LA volume index, mL/m^2	23 (19, 29)	37 (29, 47)*	38 (29, 50)*	< 0.0001
E-wave, cm/s	66 ± 17	75 ± 24*	75 ± 27*	< 0.0001
Septal mitral e', cm/s	7.1 ± 2.0	5.7 ± 1.6*	5.9 ± 1.7*	< 0.0001
Septal mitral s', cm/s	8.0 ± 1.7	6.8 ± 2.0*	6.8 ± 1.9*	< 0.0001
E/e' ratio (septal)	9.7 ± 2.8	13.7 ± 4.5*	13.7 ± 6.5*	< 0.0001
TV s', cm/s	12.3 ± 2.8	11.9 ± 3.2	11.5 ± 3.0*	0.03
TAPSE, mm	20.0 ± 4.6	18.2 ± 4.7*	18.6 ± 4.9*	< 0.0001
PASP, mm Hg	20 ± 6	22 ± 8*	24 ± 9*	< 0.0001
Maximal IVC diameter, mm	12 ± 4	13 ± 4*	13 ± 5*	< 0.0001
RAP, mm Hg	3 ± 2	4 ± 3	4 ± 3*	< 0.0001

Values are n (%), mean ± standard deviation, or median (interquartile range), unless otherwise indicated. The final column reflects overall group differences.

ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin-receptor blocker; ARNI, angiotensin-receptor neprilysin inhibitor; BNP, B-type natriuretic peptide; BP, blood pressure; E/e' ratio, the ratio of early diastolic mitral inflow to mitral annular tissue velocities; eGFR, estimated glomerular filtration rate; HFpEF, heart failure with preserved ejection fraction; IVC, inferior vena cava; LA, left atrial; LV, left ventricular; MAGGIC, Meta-Analysis Global Group in Chronic Heart Failure; MRA, mineralocorticoid receptor antagonist; NCD, noncardiac dyspnea; NT-pro BNP, N-terminal pro B-type natriuretic peptide; NYHA, New York Heart Association; PASP, pulmonary artery systolic pressure; RAP, right atrial pressure; SGLT2i, sodium-glucose co-transporter 2 inhibitor; TAPSE, tricuspid annular plane systolic excursion; TV, tricuspid valvular.

* $P < 0.05$ vs control subjects.

† $P < 0.05$ vs HFpEF without extracardiac burden.

men (HR 1.33 per 1-point increase, 95% CI 1.17-1.50; $P < 0.0001$) and women (HR 1.17 per 1-point increase, 95% CI 1.01-1.33; $P = 0.04$).

Extracardiac burden in control subjects

We also investigated the impact of extracardiac comorbidities in control subjects. We divided the control subjects into 2 groups based on the extracardiac domain score of 5 points, as follows: control subjects without an extracardiac burden (n = 249); and control subjects with an extracardiac burden (n = 154). Control subjects with an extracardiac burden were older and had a lower BMI, compared to subjects without this burden (Supplemental Table S1). However, exercise gas exchange data during peak exercise revealed that peak VO_2, V_E, V_T, V_E vs VCO_2 slope, and AVO_2 difference during exercise did not differ between the 2 groups (Supplemental Table S2). Furthermore, the extracardiac domain score was not associated with an increased risk of the primary endpoints in control subjects (HR 0.97 per 1-point increase, 95% CI 0.76-1.25; $P = 0.85$).

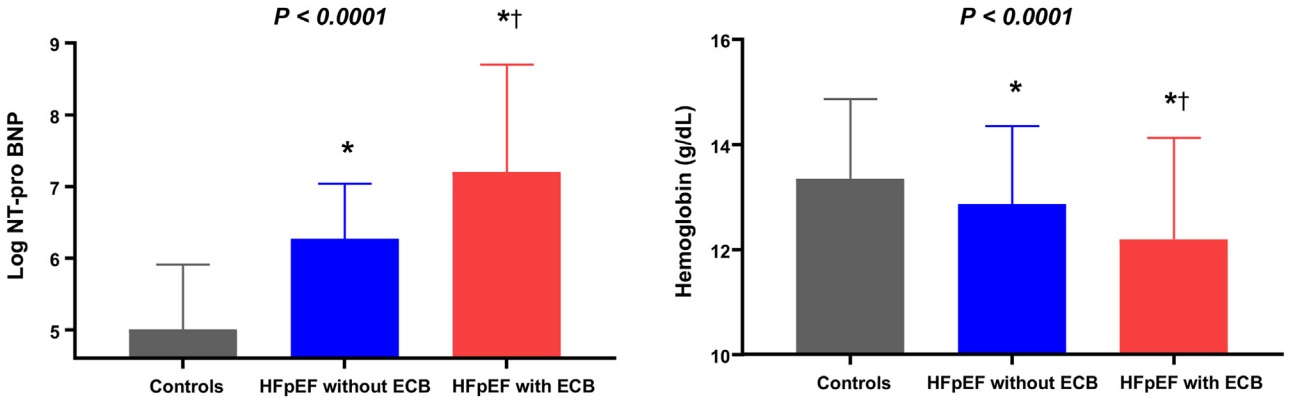

Figure 2. Comparison of Log N-terminal pro B-type natriuretic peptide (NT-pro BNP; n = 529) and hemoglobin levels among the 3 patient groups (control subjects, patients with heart failure with preserved ejection fraction [HFpEF], with and without extracardiac burden). ECB, extracardiac burden. *$P < 0.05$ vs controls. †$P < 0.05$ vs patients with HFpEF without extracardiac burden.

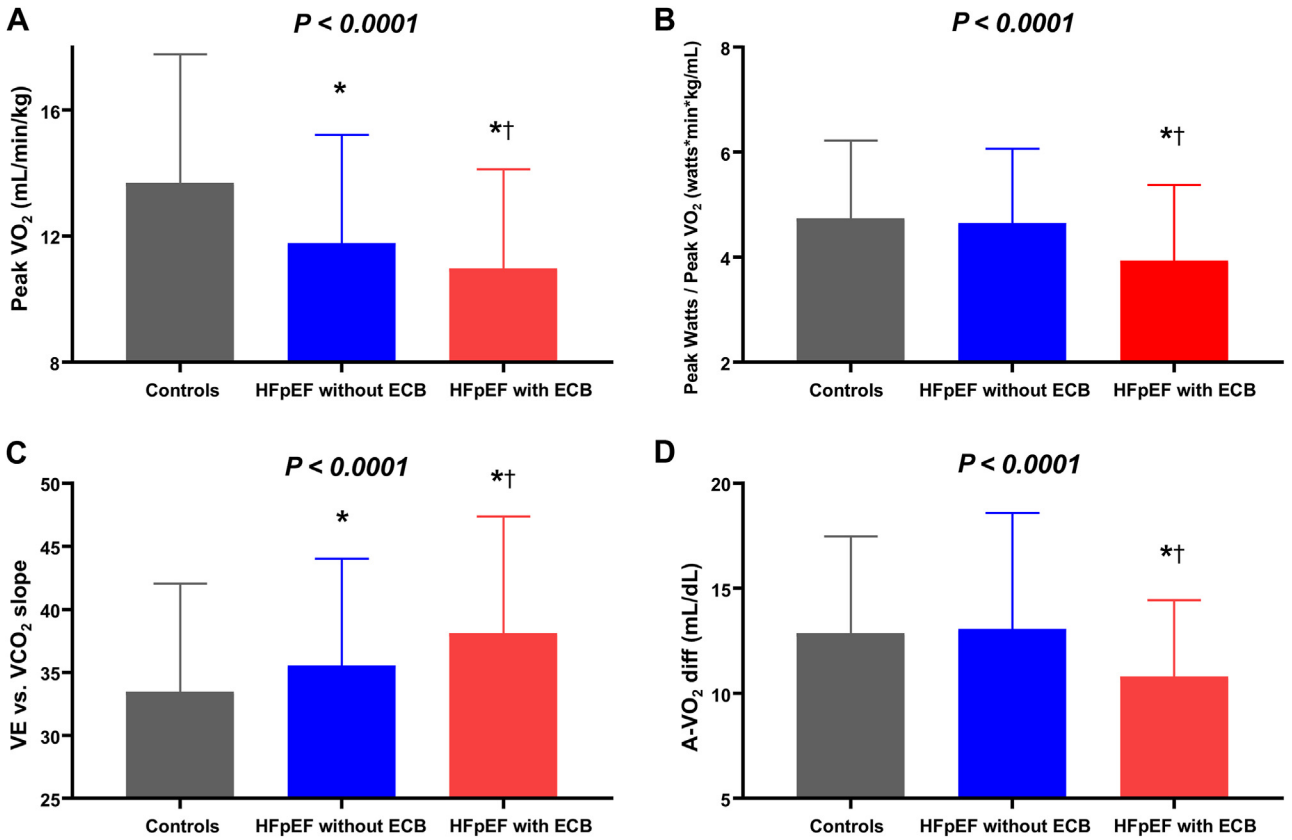

Figure 3. Comparison of peak oxygen consumption (VO_2), exercise workload relative to peak VO_2, minute ventilation (V_E) vs. carbon dioxide volume (VCO_2) slope, and arterial-venous oxygen content difference (AVO_2) difference among the 3 patient groups (control subjects, patients with heart failure with preserved ejection fraction [HFpEF], with and without extracardiac burden). ECB, extracardiac burden.; VCO_2,; *$P < 0.05$ vs control subjects. †$P < 0.05$ vs HFpEF without extracardiac burden.

Table 2. Echocardiographic measures and expired gas data during peak exercise

Measure	Control subjects (n = 403)	Patients with HFpEF without extracardiac burden (n = 185)	Patients with HFpEF with extracardiac burden (n = 187)	*P*
Peak W, W	65 ± 25	53 ± 21*	43 ± 21*,†	< 0.0001
Exercise time, min	10.3 ± 3.6	8.1 ± 3.2*	7.0 ± 3.0*,†	< 0.0001
Vital signs				
Heart rate, bpm	116 ± 21	107 ± 22*	102 ± 21*	< 0.0001
Systolic BP, mm Hg	168 ± 30	161 ± 29	158 ± 31*	0.0008
Saturation, %	95 ± 3	96 ± 3	95 ± 4	0.27
Echocardiographic measures				
LV ejection fraction, %	71 ± 7	70 ± 9	67 ± 8*,†	< 0.0001
E-wave, cm/s	108 ± 23	118 ± 28*	116 ± 30*	< 0.0001
Septal mitral e', cm/s	10.2 ± 2.5	7.7 ± 2.0*	7.5 ± 2.0*	< 0.0001
Septal mitral s', cm/s	9.1 ± 2.1	7.6 ± 2.0*	7.0 ± 1.8*,†	< 0.0001
E/e' ratio (septal)	10.9 ± 2.6	16.1 ± 5.2*	16.6 ± 6.9*	< 0.0001
Cardiac output, L/min	6.9 ± 2.1	6.2 ± 2.2	5.8 ± 1.9*	< 0.0001
Stroke volume, mL	60 ± 17	59 ± 20	57 ± 17	0.14
TV s', cm/s	14.7 ± 3.0	13.3 ± 3.5*	12.6 ± 3.2*	< 0.0001
TAPSE, mm	23.1 ± 5.1	20.3 ± 5.0*	20.2 ± 5.6*	< 0.0001
PASP, mm Hg	39 ± 12	44 ± 14*	43 ± 12*	< 0.0001
Maximal IVC diameter, mm	15 ± 4	17 ± 5*	18 ± 9*	< 0.0001
RAP, mm Hg	5 ± 3	6 ± 4*	7 ± 4*	< 0.0001
Expired gas data				
VO_2, mL/min/kg	13.6 ± 4.1	11.7 ± 3.4*	11.0 ± 3.1*,†	< 0.0001
RER	1.13 ± 0.15	1.10 ± 0.15	1.09 ± 0.13*	0.01
Respiratory rate, /min	32 ± 9	31 ± 7	30 ± 7	0.28
$V_{E,}$ L/min	33.6 ± 11.5	30.7 ± 10.4*	26.9 ± 9.7*,†	< 0.0001
$V_{T,}$ mL	1113 ± 353	1024 ± 397*	905 ± 283*,†	< 0.0001
V_E vs VCO_2 slope	33.5 ± 8.6	35.5 ± 8.5*	38.1 ± 9.3*,†	< 0.0001
AVO_2 diff, mL/dL	12.9 ± 4.6	13.1 ± 5.5	10.8 ± 3.6*,†	< 0.0001

Data are mean ± standard deviation or median (interquartile range), unless otherwise indicated. The final column reflects overall group differences.

AVO_2 diff, arterial−venous oxygen difference; BP, blood pressure; bpm, beats per minute; E/e' ratio, the ratio of early diastolic mitral inflow to mitral annular tissue velocities; HFpEF, heart failure with preserved ejection fraction; IVC, inferior vena cava; LV, left ventricular; PASP, pulmonary artery systolic pressure; RAP, right atrial pressure; RER, respiratory exchange ratio; TAPSE, tricuspid annular plane systolic excursion; TV, tricuspid valvular; VCO_2, carbon dioxide volume; $V_{E,}$ minute ventilation; VO_2, oxygen consumption; $V_{T,}$ tidal volume.

* $P < 0.05$ vs control subjects.

† $P < 0.05$ vs HFpEF without extracardiac burden.

Discussion

In the present study, we assessed the pathophysiological and prognostic impact of the cumulative burden of extracardiac comorbidities in patients with HFpEF. The major findings are as follows: (i) despite similar abnormalities in cardiac structure and function, HFpEF patients with an extracardiac burden based on the MAGGIC risk score had higher levels of natriuretic peptide levels than did those without this burden; (ii) exercise capacity was more impaired in the patients with an extracardiac burden than in those without this burden, possibly owing to worse O_2 extraction in the periphery; and (iii) the severity of an extracardiac burden was independently associated with worse clinical outcomes, whereas the severity of cardiac burden was not. These data suggest that the cumulative burden of extracardiac comorbidities is a pathophysiological driver of the HFpEF syndrome.

Extracardiac comorbid burden in HFpEF

Extracardiac comorbidities, such as diabetes, renal dysfunction, chronic lung disease, anemia, chronic liver disease, and cancer, are highly prevalent in patients with HF, especially those with HFpEF.[9,23] This fact suggests that extracardiac comorbidities are not just a comorbid condition, but rather are pathologic drivers contributing to HFpEF syndrome. Concordant with these previous reports, our results demonstrated a higher prevalence of diabetes, hypertension, COPD, and renal dysfunction in patients with HFpEF than that in control subjects. A growing body of evidence suggests that each of these comorbidities has adverse effects on the pathophysiology in patients with HFpEF. For example, the presence of chronic kidney disease may worsen HF conditions, through sodium and fluid retention, renal anemia, activated renin-angiotensin-aldosterone system and sympathetic activation, hypertension, inflammation, and uremic toxins. However, few studies have examined the impact of the cumulative burden of extracardiac comorbidities on the pathophysiology, exercise capacity, and clinical outcomes in patients with HFpEF. The MAGGIC score, a validated risk score in HF, may provide an opportunity to estimate the cumulative burden of cardiac and extracardiac comorbidities.[8,10]

Association of an extracardiac burden with cardiovascular responses and exercise capacity in patients with HFpEF

In the current study, we applied the MAGGIC score to a cohort undergoing exercise stress echocardiography for the evaluation of dyspnea. We found that the total MAGGIC score and the extracardiac domain score were higher in HFpEF patients with an extracardiac burden (by definition) than they were in those without this burden and in control subjects, whereas the cardiac domain score did not differ between HFpEF patients and control subjects. This finding suggests that the presence of HFpEF may not be explained by

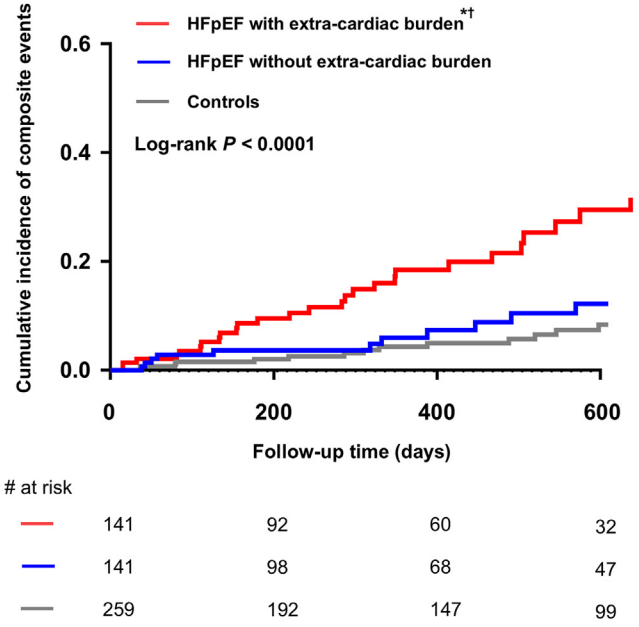

Figure 4. Kaplan–Meier curves for incidence of composite events (all-cause mortality or heart failure events) among 3 patient groups (control subjects, and patients with heart failure with preserved ejection fraction [HFpEF], with and without an extracardiac burden). *$P < 0.05$ vs control subjects. †$P < 0.05$ vs patients with HFpEF without an extracardiac burden.

the cardiac burden domain (lower LVEF, NYHA class, lower systolic blood pressure, HF duration, no β-blocker use, no ACE-I or ARB use). Despite their having similar abnormalities in cardiac structure and function, as well as NYHA class, patients with an extracardiac burden had higher NT-proBNP levels than did those without this burden. This finding suggests that an accumulating extracardiac burden would worsen the severity of HF.

We found that exercise capacity and mechanistic efficiency (exercise workload relative to peak VO_2) were more impaired in patients with an extracardiac burden than in those without this burden. Notably, cardiac responses to exercise were similar between HFpEF patients with vs without an extracardiac burden, except for LV systolic function (peak EF and mitral s'). In striking contrast, the AVO_2 difference during peak exercise was more impaired in patients with an extracardiac burden than it was in those without this burden, suggesting that exercise intolerance in the patients was related to impairment in O_2 extraction and utilization in the periphery. Poor ventilatory efficiency and anemia also were likely to adversely affect exercise capacity in patients with an extracardiac burden.

Extracardiac burden in control subjects

In contrast to the HFpEF population, in control subjects, an extracardiac comorbidity burden was not associated with exercise capacity, ventilatory efficiency, peripheral O_2 extraction, or clinical outcomes. In the current study, the extracardiac burden was calculated based on BMI, presence of diabetes, presence of COPD, creatinine levels, and current smoking. One might speculate that the accumulation of extracardiac disease in control subjects would affect exercise capacity and outcomes in a manner similar to that in HFpEF patients. Although the underlying mechanisms remain unknown, these findings suggest that the burden of extracardiac comorbidities may be specific to patients with HFpEF. Further studies on this issue are needed.

Prognostic relevance of extracardiac burden in HFpEF

Beyond its aforementioned pathophysiological importance, we found that the severity of an extracardiac burden was independently associated with adverse clinical outcomes in patients with HFpEF. In contrast, cardiac burden was not associated with the risk of composite outcomes. These findings are consistent with results of a previous study showing that an extracardiac burden is a greater contributor to adverse outcomes than is the cardiac burden in patients with HFpEF.[8] We also investigated a sex difference in extracardiac comorbidities in patients with HFpEF. Although the severity of an extracardiac burden was greater in men with HFpEF than it was in women with HFpEF, the extracardiac burden was associated with reduced exercise capacity, lower peripheral O_2 utilization, and worse clinical outcomes in both sexes. These data suggest that the cumulative burden of extracardiac comorbidities in patients with HFpEF, regardless of sex, has pathophysiologic and prognostic importance.

Our results have the following 2 important clinical implications: (i) they emphasize the utility of the MAGGIC score in estimating the relative contribution of cardiac and extracardiac burden in individual patients and identifying patients at high risk for clinical outcomes; and (ii) they suggest that therapies targeting components of an extracardiac comorbid burden might improve exercise capacity, and eventually clinical outcomes, in patients with HFpEF. Beyond reducing the incidence of HF hospitalization,[24,25] sodium-glucose cotransporter 2 inhibitors may have multiple beneficial effects on extracardiac comorbidities, including diabetes, renal dysfunction, anemia, and obesity.[26-28] Given

that exercise intolerance in patients with an extracardiac burden was associated with abnormal peripheral O_2 utilization in the current study, exercise training may be an optimal therapeutic option in this population.[29] Other candidate approaches include use of glucagon-like peptide-1 agonists for obesity, intravenous iron administration for iron deficiency, and use of bronchodilators for COPD.[30-32]

Limitations

This study was retrospective, and it was conducted at a single tertiary referral centre, which may have led to significant bias. The sample size and event rates were modest. Although the HFpEF patients were identified carefully, we cannot exclude the possibility that some patients were missed. In addition, the MAGGIC score, although it is widely accepted and validated, includes only 13 clinical variables, which may have oversimplified the impact of a cardiac and extracardiac burden in patients with HFpEF. In particular, potentially important extracardiac comorbidities in HFpEF patients include mental health, neurologic disorders, and gastrointestinal diseases, and data on these factors were not available. Finally, this study could not determine whether interventions targeting an extracardiac burden could improve clinical outcomes in patients with HFpEF. Further large-scale multicentre studies with long-term follow-up are needed to confirm the present results.

Conclusions

We demonstrated that the cumulative burden of extracardiac comorbidities is associated with impaired exercise capacity, poor mechanistic efficiency during exercise, worse ventilatory efficiency, impaired peripheral O_2 extraction, and increased risk of clinical outcomes in patients with HFpEF. In contrast, an extracardiac comorbidity burden was not associated with impaired exercise capacity, worse ventilatory efficiency, impaired peripheral O_2 extraction, or worse clinical outcomes in control subjects. These findings suggest that the extracardiac burden in HFpEF patients has pathophysiological and prognostic significance.

Ethics Statement

The study was conducted in accordance with the Declaration of Helsinki and the ethical guidelines for medical and biological research involving human subjects in Japan. The study was approved by our institutional review board (Gunma University Hospital, Clinical Research Review Board), with a waiver of consent because of its retrospective design. Participants were given the opportunity to refuse to participate in the study, via use of an opt-out approach.

Patient Consent

The authors confirm that patient consent is not applicable to this article.

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Supplementary Material

To access the supplementary material accompanying this article, visit *CJC Open* at https://www.cjcopen.ca/ and at https://doi.org/10.1016/j.cjco.2025.01.004.