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Original Article

Better Respiratory Function in Heart Failure Patients With Use of Central-Acting Therapeutics

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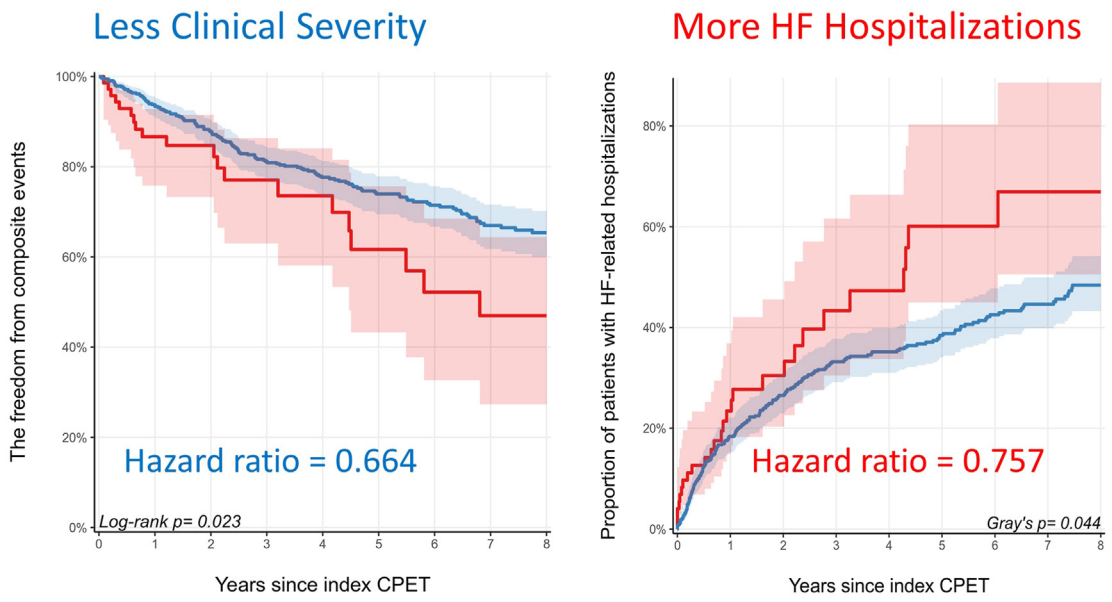

Central Drugs & Outcomes			Peripheral Drugs & Outcomes
Ramipril	32	Peak VE/VCO_2	37 Enalapril
Candesartan	2.56	FEV1 (L/s)	2.24 Valsartan
Carvedilol	35	PETCO2 (mmHg)	32 Bisoprolol
	13.5	Peak VO2 (mL/kg/min)	12.4

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ABSTRACT

Background: Diaphragm atrophy can contribute to dyspnea in patients with heart failure (HF) with its link to central neurohormonal overactivation. HF medications that cross the blood-brain barrier could act centrally and improve respiratory function, potentially alleviating diaphragmatic atrophy. Therefore, we compared the benefit of central- vs peripheral-acting HF drugs on respiratory function, as assessed by a single cardiopulmonary exercise test (CPET) and outcomes in HF patients.

Methods: A retrospective study was conducted of 624 ambulatory adult HF patients (80% male) with reduced left ventricular ejection fraction $\leq$ 40% and a complete CPET, followed at a single institution between 2001 and 2017. CPET parameters, and the outcomes all-cause death, a composite endpoint (all-cause death, need for left ventricular assist device, heart transplantation), and all-cause and/or HF hospitalizations, were compared in patients receiving central-acting (n = 550) vs peripheral-acting (n = 74) drugs.

Results: Compared to patients who receive peripheral-acting drugs, patients who receive central-acting drugs had better respiratory function (peak breath-by breath oxygen uptake [VO_2], $P = 0.020$; forced expiratory volume in 1 second [FEV1], $P = 0.007$), and ventilatory efficiency (minute ventilation / carbon dioxide production [VE/VCO_2], $P < 0.001$; end-tidal carbon dioxide tension [$PETCO_2$], $P = 0.015$; and trend for forced vital capacity [FVC], $P = 0.056$). Many of the associations between the CPET parameters and drug type remained significant after multivariate adjustment. Moreover, patients receiving central-acting drugs had fewer composite events ($P = 0.023$), and HF hospitalizations ($P = 0.044$), although significance after multivariant correction was not achieved, despite the hazard ratio being 0.664 and 0.757, respectively.

Conclusions: Central-acting drugs were associated with better respiratory function as measured by CPET parameters in HF patients. This could extend to clinically meaningful composite outcomes and hospitalizations but required more power to be definitive in linking to drug effect. Central-acting HF drugs show a role in mitigating diaphragm weakness.

RÉSUMÉ

Contexte : L'atrophie du diaphragme peut contribuer à la dyspnée chez les personnes atteintes d'insuffisance cardiaque (IC), compte tenu de son lien avec la suractivation neuro-hormonale centrale. Or, les médicaments contre l'IC qui franchissent la barrière hématoencéphalique pourraient exercer une action centrale, améliorer la respiration et ainsi éventuellement atténuer l'atrophie du diaphragme. C'est pourquoi nous avons voulu comparer, au moyen d'une seule épreuve d'effort cardiopulmonaire (EECP), les effets bénéfiques exercés par des médicaments à action périphérique et des médicaments à action centrale sur la fonction respiratoire, de même que l'issue des patients atteints d'IC auxquels ils ont été administrés.

Méthodologie : Nous avons réalisé une étude rétrospective auprès de 624 adultes ambulatoires atteints d'IC (80 % d'hommes) dont la fraction d'éjection ventriculaire gauche était réduite ($\leq$ 40 %), qui se sont prêtés à une EECP complète et qui ont été suivis dans le même établissement entre 2001 et 2017. Les paramètres de l'EECP et la mortalité toutes causes confondues, un critère d'évaluation composé (décès toutes causes confondues, nécessité de recourir à un dispositif d'assistance ventriculaire gauche, transplantation cardiaque), et les hospitalisations toutes causes confondues et/ou liées à l'IC ont été comparés entre les patients qui recevaient des médicaments à action centrale (n = 550) et ceux qui recevaient des médicaments à action périphérique (n = 74).

Résultats : Comparativement aux patients ayant reçu des médicaments à action périphérique, ceux qui ont reçu des médicaments à action centrale ont bénéficié d'une meilleure fonction respiratoire (consommation maximale d'oxygène [VO_2], $p = 0{,}020$; volume expiratoire maximal par seconde [VEMS], $p = 0{,}007$) et d'une meilleure efficacité ventilatoire (ventilation minute/production de dioxyde de carbone [VE/VCO_2], $p < 0{,}001$; pression partielle de dioxyde de carbone en fin d'expiration [$PETCO_2$], $p = 0{,}015$; et tendance de la capacité vitale forcée [CVF], $p = 0{,}056$). De plus, bon nombre des associations entre les paramètres de l'EECP et le type de médicament sont demeurées significatives après ajustement multivarié. Les patients qui ont reçu des médicaments à action centrale ont également présenté moins d'événements faisant partie du critère d'évaluation composé ($p = 0{,}023$) et moins d'hospitalisations liées à l'IC ($p = 0{,}044$), même si la différence après correction multivariée n'a pas été significative et que les rapports de risques étaient respectivement de 0,664 et de 0,757.

Conclusions : Les médicaments à action centrale ont été associés à une meilleure fonction respiratoire, mesurée à l'aide des paramètres d'une EECP, chez les patients atteints d'IC. Ce résultat pourrait également s'appliquer au critère d'évaluation composé et aux hospitalisations, mais une étude plus puissante est nécessaire pour établir un lien cliniquement significatif avec l'effet des médicaments. Les médicaments à action centrale contre l'IC ont donc un rôle à jouer dans la correction de la faiblesse du diaphragme.

Heart failure (HF) is a growing medical and economic problem affecting at least 26 million people worldwide.[1] The lifetime risk of developing HF remains 1 in 5 with a 5-year mortality rate of 50%.[1-3] Dyspnea, a cardinal symptom of HF,[4] significantly impacts both the functional capacity and quality of life of patients living with HF.[5] Dyspnea can be attributed to an elevated ventilatory drive,[6-8] and impaired diaphragmatic structure and function.[9-11]

Weakness of the diaphragm, known as diaphragmatic atrophy, is a salient, yet poorly recognized symptom of HF patients.[9-11] Diaphragmatic atrophy contributes to both dyspnea and exercise intolerance[10,11]; however, the pathophysiology of diaphragmatic atrophy is not well understood. The impaired cardiorespiratory fitness and ventilatory efficiency seen in the cardiopulmonary exercise test (CPET)—the gold-

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See page 753 for disclosure information.

standard evaluation of cardiovascular, pulmonary, and metabolic adaptations to exercise in cardiac patients[6]—of HF patients could be explained, in part, by diaphragm weakness.[12] Some have theorized that diaphragmatic atrophy is associated with pulmonary edema or interstitial lung fibrosis that develop over time, and cause mechanical stress, which leads to diaphragmatic remodelling.[13,14] But an alternate mechanism has been suggested recently by preclinical studies[15] that uncovered a novel functional codependence between angiotensin II and β-adrenergic signalling leading to increased ventilatory drive. In HF, independent of lung loading conditions, this central neurohormonal pathway is overactivated, leading to increased ventilatory drive that promotes diaphragm atrophy, mediated by elevated endoplasmic reticulum stress and inhibition of protein synthesis.[15] These mechanisms are blocked with drugs capable of penetrating the blood-brain barrier. Consequently, the use of HF drugs that cross the blood-brain barrier could potentially alleviate diaphragmatic issues in HF patients.[15,16]

Central-acting HF drugs (ie, carvedilol, metoprolol; beta-blockers or candesartan, telmisartan; angiotensin receptor blockers) could help mitigate diaphragmatic weakness by sympatho-adrenergic inhibition,[15] which is thought to be involved in inadequate ventilatory response and therefore relative hypoventilation, and this would be reflected in the various measures of the CPET (ie, minute ventilation [VE] / carbon dioxide production [VCO_2], forced vital capacity [FVC], and end-tidal carbon dioxide tension [$PETCO_2$]). Evaluating potential new solutions with immediate actionability to address symptoms of dyspnea and exercise intolerance is critical given the large number of patients with HF. Therefore, the aim of the present proof-of-concept study was to compare the effect of central- vs peripheral-acting HF medications on various measures of respiratory function as reflected by a single CPET study; we also added a secondary more explorative aim, which was to define any association to outcomes in patients with HF.

Methods

Study population

We conducted a retrospective observational study of adult ambulatory HF patients evaluated between December 2001 and 2017, at a single centre. The study was approved by the institutional ethics board (#18-6190), and it included adults aged $\geq$ 18 years with HF and a reduced left ventricular ejection fraction (LVEF) of $\leq$ 40%, who had had a complete CPET during the study period, and who were not supported with a left ventricular assist device (LVAD) or listed for heart transplantation (HTx). Patients were excluded if they had a missing value for LVEF (n = 308), were diagnosed with congenital heart disease (n = 794), were not on any HF drugs (n = 45), or were taking both central- and peripheral-acting HF drugs (n = 277).

Clinical variables were extracted from the electronic patient records at or around the time of the CPET study (corresponding clinical visit or ± 3 months for laboratory and echocardiogram findings). Complete exercise data were obtained from the MGC Diagnostics Ultima CPX system (St. Paul, MN) used at the tertiary institution.

CPET protocol

Cardiopulmonary exercise testing was performed using 2 standardized protocols: a cycler ergometer with a ramp protocol of 10 watts per minute (10 W/min); or a treadmill standardized Bruce protocol. Patients were instructed to continue taking their regular medications. Once patients were connected to the calibrated metabolic cart (Lode Corival, Canadian Hospital Specialties Limited, Canada), breath-by breath oxygen uptake (VO_2), VCO_2, and VE were measured. All measurements were recorded for 1 minute at rest, for a 2-minute unloaded warmup period (0 W), throughout exercise, and during 5 minutes of recovery. During the exercise protocol, patients were actively encouraged to exercise to their maximal capacity, aiming for a test duration of 8-12 minutes. All cardiorespiratory data were recorded using the MGC Diagnostics Ultima Series system (St-Paul, MN). Volitional effort was considered maximal if a respiratory exchange ratio greater than 1.1 was achieved. Normative data derived from the Wasserman-Hansen equation,[17] and continuous heart rate and rhythm, were monitored; a 12-lead electrocardiographic and blood pressure data were measured every 2 minutes with a mercury sphygmomanometer.

Central- and peripheral-acting HF drugs

The following were defined as central-acting HF drugs as based on their lipophilic properties or evidence of crossing the blood-brain barrier: (i) angiotensin-converting enzyme inhibitors—fosinopril, lisinopril, perindopril, ramipril, and trandolapril; (ii) angiotensin receptor blockers—candesartan and telmisartan; and (iii) beta-blockers—carvedilol and metoprolol tartrate.

The following were defined as peripheral-acting HF drugs, based on their hydrophilic properties or an absence of evidence that they cross the blood-brain barrier: (i) angiotensin-converting enzyme inhibitors—enalapril; (ii) angiotensin receptor blockers— irbesartan, losartan, valsartan, and sacubitril/valsartan; (iii) beta-blockers—atenolol and bisoprolol. Patients who received only any of the central-acting HF drugs were classified as the "central-acting drugs group," and patients who received only peripheral-acting HF drugs were classified as the "peripheral-acting drugs group."

Outcome

In patients with multiple complete CPET studies, the data from the first CPET (index CPET) were included. The primary outcome of the study was the respiratory efficiency at the index CPET study. Secondary outcomes included the following: (i) all-cause death; (ii) a composite of all-cause death, the receipt of LVAD, or HTx; (iii) all-cause hospitalization; and (iv) HF-related hospitalization, defined as a hospital admission resulting directly from cardiac dysfunction requiring inpatient care. The follow-up time started at the time of the index CPET study. Patients were followed until an event (ie, death, hospitalization). Follow-up was at the last clinic visit in patients who did not experience an event.

Statistical analyses

Clinical characteristics at the index CPET study were characterized. Continuous variables were summarized by the median, and the 25th and 75th percentiles; dichotomous and

polytomous categorical variables were summarized by frequencies. Between-group differences in continuous and categorical variables were evaluated using Wilcoxon rank-sum tests and Fisher's exact tests, respectively.

For the measures of respiratory function, multivariable linear regression was applied separately to assess and quantify the association of central- vs peripheral-acting drugs with each measure, adjusted for demographics, body mass index, HF etiology, New York Heart Association (NYHA) class, comorbidities, and other HF-related medication uses. For each measure of respiratory function, the effect of the central- vs peripheral-acting drug was quantified as the incremental change of the measure. The corresponding 95% confidence intervals (CIs) and *P*-values were calculated using *t* statistics.

The Kaplan-Meier survival method was applied to describe the freedom from death or the composite of death, LVAD, and HTx, overall and by group. Between-group difference in the freedom was evaluated using log-rank tests. HF-related hospitalizations were characterized using competing risk models, in terms of the cumulative incidence functions, overall and by group. Between-group difference in cumulative incidence functions was evaluated using Gray's tests. Administrative censoring at 8 years was applied in all time-to-event analyses.

Multivariable Cox proportional hazard regression was applied to quantify the association of central- vs peripheral-acting drugs on the outcome event in terms of hazard ratios. The corresponding 95% CIs and *P*-values were evaluated using Wald's statistics. Only a limited number of patients died or experienced the composite event; therefore, based on clinical expertise, we included clinically relevant covariates (eg, demographics, body mass index, HF etiology, NYHA class, the presence of diabetes mellitus, arrhythmias, and chronic renal disease) in the regression models. We also modeled continuous covariates (ie, age and body mass index) using natural cubic splines to account for possible nonlinear associations. For hospitalizations, cause-specific hazard regression was applied to quantify the effect of central- vs peripheral-acting drugs, adjusted for the same covariates. Missing values were imputed using multiple imputation by chain equations, and the imputed regression results were pooled using Rubin's rule.

All analyses assumed a significance level of $P < 0.05$ and were performed using R version 4.0.3, with the packages of survival, cmprsk, tidyverse, and splines (R Foundation, Vienna, Austria).

Results

General characteristics

The study population comprised 624 adult ambulatory HF patients (80% males; Table 1). Most patients were in NYHA class II (45%) or III (31%), with a median LVEF of 26% (20%-32%); 550 (88%) were on the central-acting drugs, and 74 (12%) were on peripheral-acting drugs. No significant differences were present in NYHA class, LVEF, or device therapy between the 2 groups. However, patients on the central-acting drugs were younger (57.1 years [range: 47.7-63.8] vs 59.9 years [range: 53.6-66.9]), and a greater proportion had idiopathic (51% vs 39%) or ischemic (35% vs 23%) cardiomyopathy, as well as a lower burden of comorbidities with improved kidney function, compared to the peripheral-acting drugs group (Table 1).

CPET parameters

The CPET parameters and their distribution according to drug group are shown in Table 2 and Supplemental Figure S1, respectively. In 98% of the cases, the cycle ergometer protocol was used. Patients receiving central-acting drugs, compared to those receiving peripheral-acting drugs (median [25th to 75th percentile]), were more likely to have better respiratory function as indicated by a higher forced expiratory volume in 1 second (FEV1) (2.56 L/s [1.95-3.15] vs 2.24 L/s [1.91-2.88], $P = 0.007$), and higher levels of resting partial pressure of end-tidal carbon dioxide ($PETCO_2$) (35 mm Hg [31-37] vs 32 mm Hg [30-35], $P = 0.015$) and oxygen saturation ($P < 0.05$), as well as a tendency for a higher FVC (3.26 L [2.61-3.99] vs 3.02 L [2.68-3.42], $P = 0.056$) (Table 2). In addition, patients in the central-acting drugs group also had a higher peak VO_2 (13.5 mL/kg per minute (11.1-16.6) vs 12.4 mL/kg per minute (10.0-15.3), $P = 0.020$), peak VO_2 predicted (28.8 mL/kg per minute (25.3-31.7) vs 27.4 mL/kg per minute (23.9-29.6), $P = 0.001$), lower peak VE/VCO_2 (32 mm Hg (28-37) vs 37 mm Hg (32-45), $P < 0.001$), and anaerobic threshold VE/VCO_2 (32 mm Hg (28-36) vs 36 mm Hg (31-41), $P < 0.001$), all indicators of better respiratory function (Table 2). The adjusted regression analysis (Supplemental Table S1) showed that, compared to use of the peripheral-acting drugs, the use of central-acting drugs was associated with higher oxygen saturation, peak VO_2 predicted, and a lower VE/VCO_2 slope at peak.

Secondary outcome analysis

The median follow-up was 3.7 years (25th-75th percentiles of 1.5-6.9). During the first 8 years of the follow-up, 83 patients (13%) died, 154 (25%) had a composite event, and 288 (46%) were hospitalized, of which 270 (43%) hospitalizations were HF-related. The 8-year survival rate was similar among groups ($P = 0.470$; Fig. 1A), whereas those in the central-acting drugs group were less likely to experience a composite adverse outcome ($P = 0.023$; Fig. 1B). No difference occurred between the groups with respect to the number of any hospitalizations ($P = 0.056$; Fig. 1C), whereas HF-related hospitalizations were reduced in the central-acting drugs group ($P = 0.044$; Fig. 1D). By multivariable analysis, the risk of events was not statistically significant among groups (Supplemental Table S2).

We repeated the analyses after exclusion of patients undergoing the CPET study using the treadmill, and the results remained largely consistent.

Discussion

In this retrospective single-centre proof-of-concept study on ambulatory HF patients with LVEF $\leq 40\%$, we found an association between the use of central-acting HF medications and improved respiratory function and higher efficiency, as reflected in the CPET parameters. Moreover, our data suggest that patients on central-acting drugs were less likely to experience a secondary outcome, such as a composite event, or a

Table 1. Overall patient demographic and clinical characteristics, for the total population and by drug group

Variable	Total population		Central-acting drugs		Peripheral-acting drugs		*P*
	N	Stats	N	Stats	N	Stats	
Number of patients	624		550	550 (88.1)	74	74 (11.9)	
Age at CPET, y	624	57.2 (49.0–64.2)	550	57.1 (47.7–63.8)	74	59.9 (53.6–66.9)	0.035
Male sex	624	497 (79.6)	550	439 (79.8)	74	58 (78.4)	0.760
Prior HF hospitalizations within 1 y of CPET	624	159 (25.5)	550	141 (25.6)	74	18 (24.3)	0.890
Type of cardiomyopathy	624		550		74		< 0.001
Idiopathic		311 (49.8)		282 (51.3)		29 (39.2)	
Ischemic		207 (33.2)		190 (34.5)		17 (23.0)	
Hypertrophic		19 (3.0)		8 (1.5)		11 (14.9)	
Valvular disease		12 (1.9)		10 (1.8)		2 (2.7)	
Metabolic		8 (1.3)		5 (0.9)		3 (4.1)	
Myocarditis		11 (1.8)		10 (1.8)		1 (1.4)	
Chemotherapy/drug		17 (2.7)		13 (2.4)		4 (5.4)	
Postpartum		10 (1.6)		8 (1.5)		2 (2.7)	
Combined etiology		12 (1.9)		8 (1.5)		4 (5.4)	
Other		17 (2.7)		16 (2.9)		1 (1.4)	
Comorbidities							
Peripheral vascular disease	623	18 (2.9)	550	12 (2.2)	73	6 (8.2)	0.012
Hypertension	622	249 (40.0)	549	211 (38.4)	73	38 (52.1)	0.030
Diabetes mellitus	623	150 (24.1)	550	130 (23.6)	73	20 (27.4)	0.470
Current smoker	622	82 (13.1)	550	72 (13.1)	74	10 (13.5)	0.860
Atrial fibrillation	623	163 (26.2)	550	134 (24.4)	73	29 (39.7)	0.007
Chronic obstructive lung disease	622	23 (3.7)	549	19 (3.5)	73	4 (5.5)	0.330
Chronic renal dysfunction	623	89 (14.3)	550	71 (12.9)	73	18 (24.7)	0.012
Malignancy	623	34 (5.5)	550	25 (4.5)	73	9 (12.3)	0.012
Device	624		550		74		0.330
Pacemaker		8 (1.3)		7 (1.3)		1 (1.4)	
Implantable cardioverter-defibrillator		224 (35.9)		194 (35.3)		30 (40.5)	
Cardiac resynchronization therapy		118 (18.9)		101 (18.4)		17 (23.0)	
None		274 (43.9)		248 (45.1)		26 (35.1)	
Pacing	624	127 (20.4)	550	109 (19.8)		18 (24.3)	0.360
New York Heart Association class	459		406		53		0.590
I		80 (17.4)		72 (17.7)		8 (15.1)	
II		218 (47.5)		195 (48.0)		23 (43.4)	
III		143 (31.2)		122 (30.0)		21 (39.6)	
IV		18 (3.9)		17 (4.2)		1 (1.9)	
Echocardiography							
Left ventricular ejection fraction, %	624	26.0 (20.0–32.0)	550	25.0 (20.0–30.9)	74	27.8 (21.2–35.8)	0.093
Laboratory values							
Hemoglobin, mmol/L	544	141 (132–152)	480	142 (132–152)	64	137 (126–151)	0.172
Platelets, 10^9 cells/L	544	209 (171–252)	480	211 (173–254)	64	184 (155–223)	0.010
Creatinine, μmol/L	550	95 (77–118)	487	93 (76–114)	63	110 (88–152)	< 0.001
Estimated glomerular filtration rate, mL/min per 1.73 m^2	549	70 (53–86)	487	71 (54–87)	63	60 (41–74)	< 0.001
Sodium, mmol/L	555	139 (137–140)	489	138 (137–140)	66	140 (137–141)	0.011
Potassium, mmol/L	553	4.2 (4.0–4.5)	487	4.2 (4.0–4.5)	66	4.2 (3.9–4.5)	0.240
Urea, mmol/L	386	7.5 (6.0–10.4)	336	7.4 (5.9–9.7)	50	9.2 (6.7–14.0)	0.004
B-type natriuretic peptide, ng/L	538	202.4 (74.9–594.9)	473	180.5 (71.6–555.5)	65	410.0 (178.2–1,116.8)	< 0.001
Medication							
Diuretics	624	441 (70.7)	550	383 (69.6)	74	58 (78.4)	0.136
Loop diuretics	623	434 (69.7)	549	377 (68.7)	74	57 (77.0)	0.178
Thiazides	623	37 (5.9)	549	31 (5.6)	74	6 (8.1)	0.430
Angiotensin-converting enzyme inhibitors	624	444 (71.2)	550	434 (78.9)	74	10 (13.5)	< 0.001
Angiotensin-converting enzyme inhibitor	444	434 (97.7)	434		10		< 0.001
Central-acting				434 (100)		0	
Fosinopril		6 (1.4)		6 (1.4)		0	
Lisinopril		30 (6.8)		30 (6.9)		0	
Perindopril		56 (12.6)		56 (12.9)		0	
Ramipril		340 (76.6)		340 (78.3)		0	
Trandolapril		2 (0.5)		2 (0.5)		0	
Peripheral acting		10 (2.3)		0		10 (100)	
Enalapril		10 (2.3)		0		10 (100)	
Angiotensin receptor blockers	624	125 (20.0)	550	84 (15.3)	74	41 (55.4)	< 0.001
Angiotensin receptor blocker	125		84		41		< 0.001
Central-acting		84 (67.2)		84 (100)		0	
Candesartan		79 (63.2)		79 (94.0)		0	
Telmisartan		5 (4.0)		5 (6.0)		0	

Continued

Table 1. Continued.

Variable	Total population N	Total population Stats	Central-acting drugs N	Central-acting drugs Stats	Peripheral-acting drugs N	Peripheral-acting drugs Stats	*P*
Peripheral-acting		41 (32.8)		0		41 (100)	
Irbesartan		9 (7.2)		0		9 (22.0)	
Losartan		3 (2.4)		0		3 (7.3)	
Valsartan		12 (9.6)		0		12 (29.3)	
Entresto		17 (13.6%)		0		17 (41.5)	
Beta-blockers	624	589 (94.4)	550	523 (95.1)	74	66 (89.2)	0.054
Beta-blocker	589		523		66	0	< 0.001
Central-acting		523 (88.8)		523 (100)		0	
Metoprolol		132 (22.4)		132 (25.2)		0	
Carvedilol		391 (66.4)		391 (74.8)		0	
Peripheral-acting		66 (11.2)		0		66 (100)	
Atenolol		1 (0.2)		0		1 (1.5)	
Bisoprolol		65 (11.0)		0		65 (98.5)	
Other medications							
Mineralocorticoid	623	360 (57.8)	549	316 (57.6)	74	44 (59.5)	0.800
Hydralazine	624	37 (5.9)	550	23 (4.2)	74	14 (18.9)	< 0.001
Nitrates	624	54 (8.7)	550	43 (7.8)	74	11 (14.9)	0.074
Ivabradine	624	2 (0.3)	550	0	74	2 (2.7)	0.014
Calcium antagonists	624	17 (2.7)	550	16 (2.9)	74	1 (1.4)	0.710
Lipid-lowering	624	339 (54.3)	550	308 (56.0)	74	31 (41.9)	0.025
Anti-arrhythmics	624	277 (44.4)	550	250 (45.5)	74	27 (36.5)	0.170
Digoxin	624	199 (31.9)	550	182 (33.1)	74	17 (23.0)	0.085
Anticoagulants	624	279 (44.7)	550	242 (44)	74	37 (50)	0.380
Platelet inhibitors	624	275 (44.1)	550	251 (45.6)	74	24 (32.4)	0.034

Values are expressed as median (25−75th percentile), or as frequencies and proportions (n or n [%]), unless otherwise indicated.
CPET, cardiopulmonary exercise test; HF, heart failure; Stats, statistics.

hospitalization, due to any cause or due to HF. However, in fully adjusted regression models, the associations between secondary outcomes and type of drug did not reach significance.

Diaphragmatic weakness is a common feature among HF patients, occurring in 23%-44%,[12,18-20] and it is associated with impaired functional capacity and a worse survival rate.[12,19] Despite the impact of diaphragm dysfunction in HF, it is still poorly recognized in clinical practice. A preclinical experimental study showed that diaphragm weakness occurs early in the disease course and that diaphragmatic atrophy happens in the presence of normal peripheral skeletal muscle, suggesting that its pathogenesis has a specific link with HF.[15] The mechanisms by which HF patients develop diaphragm weakness are still poorly understood, but changes in the oxidative metabolism and calcium handling are associated with diaphragmatic weakness and atrophy.[15,21] Also, extensive pulmonary remodelling and/or edema increases airway resistance, promoting stress to the respiratory muscles,[15] although most patients have a low burden of chronic lung edema to account for the diaphragmatic weakness.[22] This hypothesis is supported by the observation that pulmonary fibrosis occurred later in the disease progression, after the diaphragm atrophy.[15] Recently, the idea was proposed that central angiotensin II and β-adrenergic signalling could lead to ventilatory overdrive, independent of chemical drive (ie, arterial carbon dioxide).[15] The activation of extracellular signal-regulated kinase and phosphorylation of eukaryotic initiation factor 2α are suggested as the mechanisms underlying these findings. In diaphragm biopsies of HF patients supported by ventricular assist devices, several intracellular abnormalities were found, such as oxidative stress, mitochondrial dysfunction, impaired calcium homeostasis, and elevated proteasome-dependent proteolysis.[23] Although the mechanisms of diaphragm weakness are being revealed, new approaches to mitigate these effects are needed.

A new treatment paradigm was suggested by a study showing that HF drugs that cross the blood-brain barrier were able to mitigate the ventilatory overdrive and prevent diaphragm atrophy.[15] Interestingly, our study showed that patients who received central-acting HF drugs had better indices of respiratory function (peak VO_2 and FEV1), and improved ventilatory efficiency (VE/VCO_2, $PETCO_2$, and a trend for FVC). Centrally-acting HF drugs were also associated with peak VO_2 predicted and peak VE/VCO_2, 2 important prognostic parameters in HF.[24] Reduced diaphragm atrophy and/or weakness could explain these results, although the underlying mechanisms that could explain the increase in the peak VO_2 and the reduced VE/VCO_2 are not fully understood.

The concept of respiratory weakness in HF is not new.[12,20,25] Previous work has shown that HF patients with diaphragmatic weakness had a shorter 6-minute walk distance.[18] Our study did not assess diaphragm function directly, but a tendency toward a higher FVC in the central-acting drugs group could be interpreted potentially as a weak surrogate outcome for better diaphragm function.[12,20] However, for oxygenation saturation, although it was higher in the central-acting drugs group, whether it is a surrogate outcome for better diaphragm function is less clear, as it is associated with many confounders in this patient population. Also, in patients with unilateral or bilateral diaphragm paresis assessed by CPET, the peak VO2 and the breathing reserve were shown to be reduced, highlighting that the diaphragm weakness directly affects the ventilatory efficiency contributing to the dyspnea of HF patients.[26] Angiotensin-converting enzyme inhibitors are associated with improvement in skeletal muscle repair and fibrosis.[27,28] Perindopril, a

Table 2. Cardiopulmonary exercise testing (CPET) parameters, for the total population and by drug group

	Total population		Central-acting drugs		Peripheral-acting drugs		
Variable	N	Stats	N	Stats	N	Stats	*P*
Number of patients	624			550 (88.1)		74 (11.9)	
Physical examination							
Height, cm	624	173 (167–180)	550	174 (167–180)	74	172 (170–177)	0.510
Weight, kg	623	81.6 (70.0–96.0)	549	81.0 (69.0–96.8)	74	84.0 (70.5–92.9)	0.690
Body mass index, kg/m^2	623	27.10 (23.89–31.06)	549	27.1 (23.7–31.2)	74	27.5 (24.5–30.7)	0.550
CPET parameters							
Test duration, sec	624	494 (371–622)	550	498 (371–625)	74	466 (368–600)	0.740
Peak power output, Watts	610	80 (60–100)	539	80 (60–100)	71	70 (50–90)	0.099
Peak power output, % predicted	609	52 (41–66)	538	53 (42–66)	71	46 (35–67)	0.124
At baseline (rest)							
Systolic BP, mm Hg	623	110 (100–120)	549	110 (100–120)	74	110 (100–124)	0.280
Diastolic BP, mm Hg	624	70 (64–76)	550	70 (64–76)	74	70 (64–78)	0.360
Heart rate, bpm	624	70 (60–76)	550	70 (60–77)	74	65 (60–73)	0.068
Oxygen saturation, %	624	98 (98–99)	550	99 (98–99)	74	98 (97–99)	0.039
FVC, L	619	3.19 (2.62–3.95)	546	3.26 (2.61–3.99)	73	3.02 (2.68–3.42)	0.056
FVC, % predicted	619	74 (61–85)	546	75 (61–85)	73	70 (60–84)	0.149
FEV1, L/s	619	2.51 (1.93–3.10)	546	2.56 (1.95–3.15)	73	2.24 (1.91–2.88)	0.007
FEV1, % predicted	619	76 (62–87)	546	77 (63–88)	73	70 (59–87)	0.056
During exercise							
Systolic BP, mm Hg	622	130 (119–146)	549	130 (118–146)	73	133 (120–150)	0.380
Diastolic BP, mm Hg	624	74 (70–80)	550	74 (70–80)	74	70 (68–80)	0.480
Heart rate, bpm	624	107 (92–125)	550	108 (92–125)	74	103 (87–120)	0.059
Heart rate 1 min post exercise, bpm	623	90 (78–103)	549	90 (78–103)	74	84 (75–98)	0.083
Heart rate recovery, bpm	624	16 (9–24)	550	16 (9–24)	74	16 (9–22)	0.330
Oxygen saturation, %	624	98 (98–99)	550	98 (98–99)	74	98 (97–99)	0.007
Peak VO_2, L/min	622	1.12 (0.85–1.44)	548	1.13 (0.86–1.44)	74	1.00 (0.81–1.41)	0.098
Peak VO_2 predicted, L/min	624	2.17 (1.77–2.58)	550	2.18 (1.77–2.59)	74	2.10 (1.78–2.42)	0.370
Peak VO_2, % predicted, L/min	624	54 (43–64)	550	55 (44–64)	74	51 (39–64)	0.125
Peak VO_2, mL/kg per min	624	13.4 (11.1–16.5)	550	13.5 (11.1–16.6)	74	12.4 (10.0–15.3)	0.020
Peak VO_2 predicted, mL/kg per min	624	28.6 (25.0–31.5)	550	28.8 (25.3–31.7)	74	27.4 (23.9–29.6)	0.005
Peak VO_2, % predicted, mL/kg per min	617	50 (39–59)	545	50 (40–59)	72	46 (39–60)	0.540
Peak VE, L/min	624	39.8 (31.4–49.7)	550	39.7 (31.2–49.9)	74	41.0 (33.4–48.8)	0.380
Peak VCO_2, L/min	622	1.22 (0.91–1.58)	548	1.23 (0.91–1.58)	74	1.12 (0.83–1.54)	0.115
Anaerobic threshold, mL/kg per min	594	8.8 (7.4–10.7)	525	8.8 (7.4–10.7)	69	8.6 (7.6–10.7)	0.530
Peak VO_2, % predicted	594	32 (26–39)	525	32 (26–38)	69	32 (27–39)	0.410
Peak respiratory exchange ratio	623	1.08 (1.01–1.14)	549	1.08 (1.02–1.14)	74	1.05 (0.98–1.14)	0.158
Oxygen uptake efficiency slope	127	1.26 (0.93–1.68)	91	1.31 (0.92–1.68)	36	1.11 (0.97–1.59)	0.530
Resting $PETCO_2$, mm Hg	128	34 (31–37)	92	35 (31–37)	36	32 (30–35)	0.015
VE/VCO_2 slope (at peak)	594	32 (28–38)	537	32 (28–37)	57	37 (32–45)	< 0.001
VE/VCO_2 slope (at anaerobic threshold)	600	32 (29–37)	531	32 (28–36)	69	36 (31–41)	< 0.001
CPET risk score[38]	127	7 (3–13)	91	6 (3–12)	36	10 (3–13)	0.600

Values are expressed as median (25th–75th percentile), or as frequencies or proportions (n or n [%]), unless otherwise indicated.

BP, blood pressure; bpm, beats per minute; FEV1, forced expiratory volume in 1 second; FVC, forced vital capacity; HF, heart failure; $PETCO_2$, end-tidal carbon dioxide tension; Stats, statistics; VCO_2, carbon dioxide production; VE, minute ventilation; VO_2, oxygen uptake.

centrally-acting angiotensin-converting enzyme inhibitor, was able to improve maximum inspiratory and expiratory pressures after 6 months of therapy in an open-label trial,[25] but the class effect has yet to be evaluated. Beta-blockers are known to reduce the respiratory drive, such that a lower peak VO_2 threshold is used for HTx candidacy.[29] However, to our knowledge, no trials have compared the effect of different types of beta-blockers in cardio-respiratory pathophysiology.

The presence of respiratory muscle weakness among HF patients is associated with an over 2-fold increase in mortality, when adjusted for confounding factors.[20] In our study, patients treated with central-acting HF drugs received a protective effect for the composite outcome and for hospitalization. However, the adjusted analysis, which included variables related to prognosis, as well as clinically important variables with significant differences between the 2 groups at baseline, failed to show a benefit. The highly unbalanced number of patients in each group and the limited number of patients with events in the smaller (peripheral-acting drugs) group may have limited our results. For example, the multivariable Cox proportional hazard regression suggests that patients in the central-acting drugs group were 33.6% (hazard ratio [95% CI] = 0.664 [0.397, 1.111], $P = 0.118$) less likely to die or to receive LVAD/HTx than those in the peripheral-acting drugs group. Although the reduction in the risk may be considerable and clinically meaningful, we still do not have sufficient evidence to suggest that use of central-acting drugs reduces the risk of death, LVAD, or HTx, as only 20 patients died or had an LVAD and/or HTx in the peripheral-acting drugs group.

A previous network meta-analysis suggested that the mortality reduction associated with use of beta-blocker in HF was not driven by a specific or beta-selective receptor drug.[30] In fact, despite the benefits of metoprolol and bisoprolol in reducing mortality of HF patients, drugs such as bucindolol

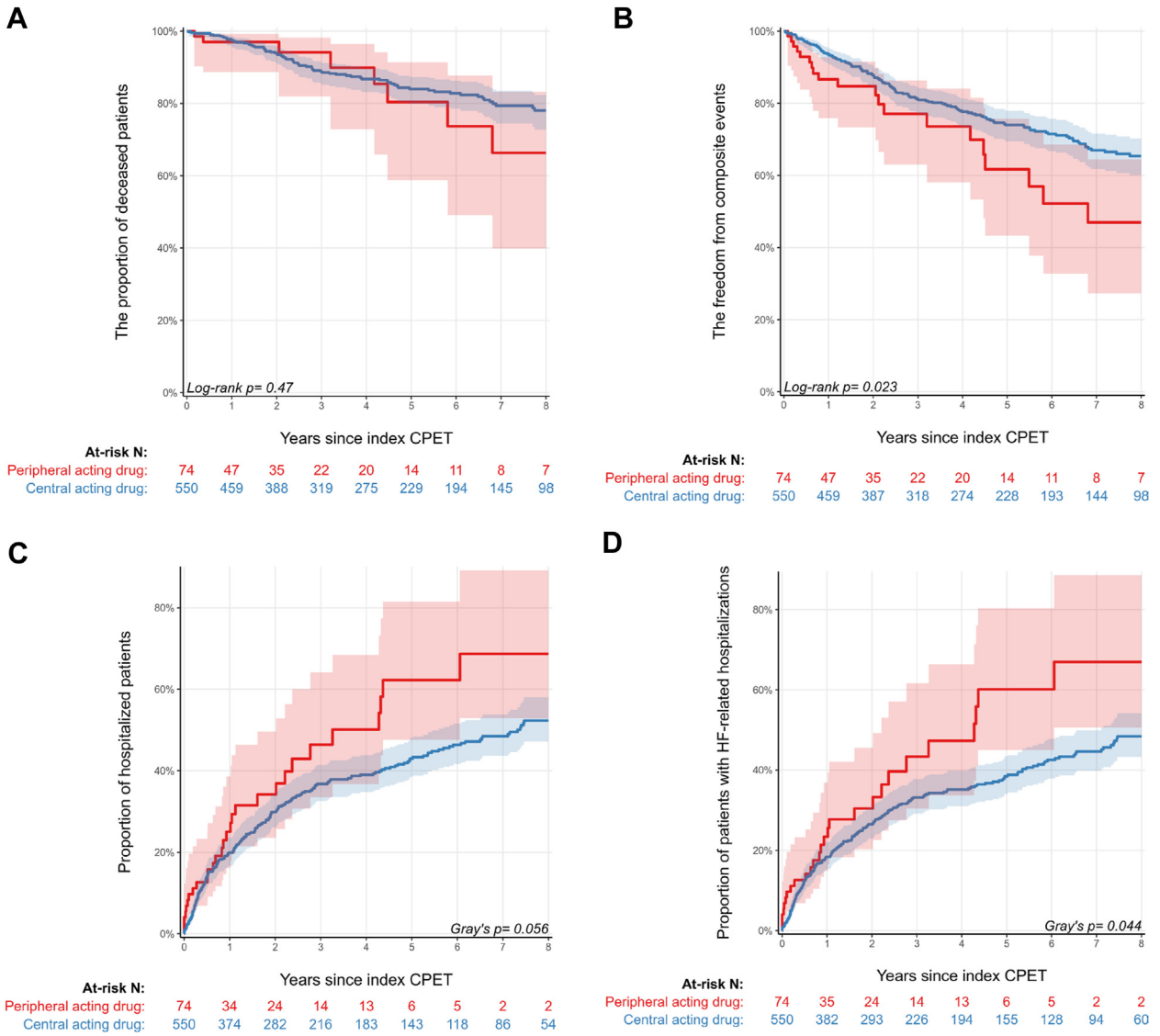

Figure 1. Kaplan-Meier curve for (**A**) all-cause death and (**B**) a composite event consisting of all-cause death, the receipt of a left ventricular assist device, or heart transplantation; and a Fine-Gray model for the proportion of patients with (**C**) any hospitalization, and (**D**) heart failure (HF)-related hospitalization, over 8 years of follow-up from the index cardiopulmonary exercise test (CPET). Central-acting drugs are indicated in **blue**, and peripheral-acting drugs are indicated in **red**. FEV1, forced expiratory volume in 1 second; $PETCO_2$, end-tidal carbon dioxide tension; VCO_2, carbon dioxide production; VE, minute ventilation; VO_2, oxygen uptake.

did not achieve mortality reduction.[31] However, whether such differences in the beta-blockers could be driven by mechanisms such as improvement of diaphragm weakness is unknown. Ramipril, a central-acting drug, showed the lowest incidence of all-cause mortality in a network meta-analysis comparing the efficacy and safety of different angiotensin-converting enzyme inhibitors.[32] Because we included patients with both central angiotensin II and β-adrenergic blockage vs peripheral, whether one of the central drugs could have a greater effect on its own or whether both central drugs would need to be used to create a benefit is unknown. We also do not yet have a companion diagnostic for ventilatory drive to establish the pharmacodynamics relating to outcomes.

Achieving better diaphragmatic function could be of interest to improve symptoms, with a potential impact on prognosis. Diaphragmatic stimulation with an electrode in patients who underwent cardiac resynchronization therapy was shown to improve symptoms and LVEF, but the small sample size and short follow-up limited the results.[33,34] However, these results highlight the fact that new treatments targeting diaphragmatic dysfunction in HF patients could improve outcomes. Our results highlight that a different choice—one that is elective and fully compliant with current guidelines—from the currently available HF drugs could be applied, based on central vs peripheral action mechanisms. New randomized clinical trials are warranted to test whether central-acting HF drugs are superior to peripheral-acting HF drugs.

Limitations

This is a single-centre, retrospective, nonrandomized study elucidating central- vs peripheral-acting HF drug efficacy, and

consequently, the results are limited to association. Other limitations of our study include the older age and higher burden of comorbidities in the peripheral-acting drugs group, which may introduce a bias toward sicker patients. Yet, these same patients could have progressed due to the lack of benefit from central-acting drugs. In addition, the large difference in sample size between the central-acting (n = 550) and peripheral-acting (n = 74) drug groups could confound the observed differences between the 2 drug groups. However, one of the main reasons for applying multivariable regression in our analyses was to quantify the effect of central-acting vs peripheral-acting drugs on CPET parameters, adjusted for confounding by the limited number of patients receiving peripheral-acting drugs. Although the validity of the results does not depend on the sample size, the effect estimates can be less precise (ie, have wider Cis). Although our study considers patients who were exclusively on central-acting or peripheral-acting drugs across all different classes of HF medications, some patients used a mix of central-acting and peripheral-acting medications. To what extent cardiopulmonary function was affected by the mixed uses of central-acting and peripheral-acting HF drugs remains unclear. Moreover, prior drug use, duration of drug exposure, and CPET and/or pulmonary function test performance were unknown. Another limitation relates to the population of patients studied, in that these are primarily patients with reduced ejection fraction and who have poor exercise tolerance, with a VE/VCO2 peak similar to the nadir.[35] In addition, the duration of the HF diagnosis was also unknown, and therefore, we could not take into account that a longer duration of HF already may have induced irreversible diaphragm remodelling. Also, HF patients are well known to have drug-induced alteration in chemosensitivity, which contributes to increased ventilation during exercise.[36,37] However, we were not able to take chemosensitivity into account in our analyses. Furthermore, whether patients had pulmonary hypertension was unknown. To what extent beta-blockers adversely affected the right ventricular function, resulting in right HF in those patients with pulmonary hypertension, remains unclear. Finally, the generalizability of the results to women with HF is limited, as the present study had a predominantly male population.

Conclusion

We showed that, in comparison to patients receiving peripheral-acting drugs, central-acting drugs were associated with better respiratory (diaphragmatic) function and higher ventilatory efficiency, as evidenced by improved CPET parameters. However, the impacts of central- vs peripheral-acting drugs on the composite outcome and hospitalizations remain unclear. Central-acting HF drugs could have a role in mitigating diaphragm weakness and may offer a novel therapeutic treatment strategy that addresses both cardiac and respiratory dysfunction within current HF management guidelines.

Ethics Statement

The study was approved by the institutional ethics board (#18-6190). The research reported has adhere to the institutional ethical guidelines. Patient had provided consent to have data collected for future studies.

Patient Consent

The authors confirm that patient consent is not applicable to this article. Individual consent was not sought as this was a retrospective study on patients who had already consented for their data to be used for studies.

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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.2024.01.003.