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Determinants of exercise intolerance in heart failure with preserved ejection fraction: A systematic review and meta-analysis

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ABSTRACT

Background: Severe exercise intolerance (EI), demonstrated by impaired peak oxygen consumption, intrinsically characterizes heart failure with preserved ejection fraction (HFpEF). Controversy exists on the determinants of EI in patients with HFpEF according to case-control studies. The purpose of this study is to systematically review and clarify the main (Fick) determinants of EI in HFpEF.

Methods: We conducted a systematic search of MEDLINE, Scopus and Web of Science since their inceptions until January 2017 for articles assessing peak cardiac output and/or arteriovenous oxygen difference ($a\text{-}vO_{2diffpeak}$) with incremental exercise in patients diagnosed with HFpEF and age-matched control individuals. Meta-analyses were performed to determine the standardized mean difference (SMD) in peak cardiac index (CI_{peak}) and $a\text{-}vO_{2diffpeak}$ between HFpEF and control groups. Subgroup and meta-regression analyses were used to evaluate potential moderating factors.

Results: Ten studies were included after systematic review, comprising a total of 213 HFpEF patients and 179 age-matched control individuals (mean age = 51–73 years). After data pooling, CI_{peak} ($n = 392$, SMD = −1.42; $P < 0.001$) and $a\text{-}vO_{2diffpeak}$ ($n = 228$, SMD = −0.52; $P = 0.002$) were impaired in HFpEF patients. In subgroup analyses, $a\text{-}vO_{2diffpeak}$ was reduced in HFpEF versus healthy individuals ($n = 114$, SMD = −0.85; $P < 0.001$) but not compared with control patients without heart failure ($n = 92$, SMD = −0.12; $P = 0.57$). The SMD in $a\text{-}vO_{2diffpeak}$ was negatively associated with age ($B = -0.05$, $P = 0.046$), difference in % females ($B = -0.01$, $P = 0.026$) and prevalence of hypertension ($B = -0.01$, $P = 0.015$) between HFpEF and control groups.

Conclusions: HFpEF is associated with a predominant impairment of CI_{peak}, accompanied by sex- and comorbidity-dependent reduced oxygen extraction at peak exercise.

1. Introduction

Heart failure (HF) affects >23 million individuals worldwide with staggering 5-year mortality rates around 50% [1,2]. Approximately half of patients diagnosed with HF have apparently normal systolic function, thus termed 'heart failure with preserved ejection fraction' (HFpEF) [3]. This condition is primarily associated with severe exercise intolerance (EI) barely reaching minimum functional capacity levels, as evidenced by up to 60% decrements in peak oxygen consumption (VO_{2peak}) [4–12]. Importantly, no effective therapy is currently available for HFpEF patients. Understanding the determinants of EI in HFpEF constitutes a fundamental step towards the advent of novel therapeutic strategies.

VO_{2peak}, a hallmark of exercise capacity, is a function of peak cardiac output (Q_{peak}) and arteriovenous oxygen difference ($a\text{-}vO_{2diffpeak}$), conforming to the Fick principle ($VO_{2peak} = Q_{peak} \times a\text{-}vO_{2diffpeak}$) [13]. The Fick determinants of VO_{2peak}, Q_{peak} and $a\text{-}vO_{2diffpeak}$ are mainly considered to reflect convective oxygen (O_2) delivery and O_2 extraction, respectively. In HFpEF patients, Q_{peak} is commonly reduced compared with age-matched control individuals [7,11,12], also when indexed to body surface area (BSA) [8–10]. This finding is however disputed by recent evidence suggesting that the status of Q_{peak} in HFpEF patients depends on exercise testing and Q_{peak} assessment methods [4]. A further point of contention is whether $a\text{-}vO_{2diffpeak}$ is altered in HFpEF [14]. Case-control studies have found preserved [8,9,11,12] or impaired [4,7] $a\text{-}vO_{2diffpeak}$ in HFpEF patients versus age-matched individuals, collectively leading to great uncertainty regarding the underlying basis of EI in HFpEF. Efforts to synthesize previous studies are likely compounded by their relatively small sample size, varied methodology and health/clinical status of the study population [4–12]. A meta-analytical approach may help to clarify the issue, but to our knowledge, this has not yet been performed.

Therefore, the primary aim of this study was to perform a systematic review and meta-analyze of studies comparing Q_{peak} (normalized by BSA) and/or $a\text{-}vO_{2diffpeak}$ in HFpEF patients versus age-matched control individuals, as well as to determine the influence of potential moderating factors. Among all potential contributing factors to EI, we focus on

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the Fick determinants of VO_{2peak} as its prognostic ability is well established in patients with HF [15,16].

2. Methods

The review is reported according to the Meta-analysis Of Observational Studies in Epidemiology (MOOSE) Group guidelines [17].

2.1. Data sources and searches

Our systematic search included MEDLINE, Scopus and Web of Science, since their inceptions until January 2017. We used combinations of the subject headings 'heart failure with preserved ejection fraction', 'VO_{2max}', 'maximal', 'peak', 'oxygen', 'aerobic', 'cardiac output', 'arteriovenous' and 'extraction'; the search strategy for MEDLINE is shown in Supplemental Fig. 1. We also performed hand searching in reference citations of identified reviews, articles included in meta-analysis and related citations in MEDLINE.

2.2. Article selection

To be included in the analysis, an original research article had to (i) assess Q_{peak} and/or whole-body a-$vO_{2diffpeak}$ with incremental (cycle ergometer or treadmill) exercise in patients diagnosed with HFpEF (LVEF ≥ 50%) and (ii) include a group of age-matched control individuals without HF. In addition, the article had to present Q_{peak} data scaled to BSA (CI_{peak}) or comprise HFpEF and control groups matched for BSA. In the event of multiple publications pertaining to the same research, the most comprehensive report was included. The selection of articles was not limited by language or publication status.

2.3. Data extraction and quality assessment

The following variables were summarized in a pre-formatted spreadsheet: authors, year of publication, inclusion/exclusion criteria, characteristics of study participants (*n*, age, gender, height, weight, body composition, BSA, body mass index (BMI), hemoglobin concentration, haematocrit, comorbities, smoking status, medication), cardiovascular/respiratory variables (heart rate, left ventricular end-diastolic volume, ejection fraction, stroke volume, cardiac output/index, blood pressure, total peripheral resistance, O_2 consumption, respiratory exchange ratio (RER)) and methodological characteristics of the assessment of exercise capacity, cardiac function and a-$vO_{2diffpeak}$. When CI_{peak} was not explicitly reported in a given article [7,12], CI_{peak} was determined by the quotient of mean Q_{peak} and BSA. A systematic appraisal of quality for observational research (SAQOR) [18] previously applied in meta-analysis of studies evaluating cardiovascular function [13,19–21] was performed to provide assessment of study quality. The SAQOR was adjusted to assess 1) the study sample, 2) the control sample, 3) quality of cardiac output assessment, 4) quality of a-vO_{2diff} assessment, 5) confounding variables and 6) data. Overall, the SAQOR was scored out of 16, quality deemed better with a greater score.

2.4. Data synthesis and analysis

The meta-analysis and related analyses were performed using Review Manager software (RevMan 5.3, Cochrane Collaboration, Oxford, UK) and Comprehensive Meta-analysis software (Biostat, Englewood, New Jersey, USA). The primary outcomes were the standardized mean difference (SMD) in CI_{peak} and the SMD in a-$vO_{2diffpeak}$ between HFpEF and control groups. Each SMD was weighted by the inverse variance and they were pooled with a random-effects model [22,23]. Publication and/or other biases were evaluated by the Begg and Mazumdar's rank correlation test and Egger's regression test [24].

Heterogeneity among studies was assessed using the chi-squared test for heterogeneity and I^2 statistics. Potential moderating factors influencing the SMD in CI_{peak} and SMD in a-$vO_{2diffpeak}$ were evaluated by subgroup analysis comparing studies grouped by qualitative variables (inclusion/exclusion criteria, methodology of exercise testing, CI_{peak} and a-$vO_{2diffpeak}$ assessment). In addition, meta-regression analyses were performed to determine the associations among the SMD in CI_{peak}, SMD in a-$vO_{2diffpeak}$ and potential moderating quantitative variables (sample size, age, % females, BMI, prevalence of comorbidities/medication, hemoglobin concentration, heart rate, stroke volume, blood pressure, RER at peak exercise, methodological quality score). In all meta-regression models, studies were weighted by the inverse variance of the dependent variable. Potential moderating factors were entered as independent variables in regressions models with the SMD in CI_{peak} or SMD in a-$vO_{2diffpeak}$ as the dependent variable. Publication and/or other biases were evaluated by the Begg and Mazumdar's rank correlation test and Egger's regression test [24]. A *P* value of <0.05 was considered statistically significant.

3. Results

3.1. Study selection and characteristics

The flow diagram of the process of article selection is shown in Supplemental Fig. 2, which resulted in the inclusion of 9 articles. One of the articles presented 2 separate study groups [6], each of which was evaluated as an individual study. Table 1 illustrates the main characteristics of the resulting 10 studies, comprising a total of 213 HFpEF patients and 179 age-matched control individuals (mean age ranging from 51 to 73 years). All studies included females and males within HFpEF and control groups (% females ranging from 7 to 94). Five studies included patients without HF as controls [5,6,10–12], 4 studies involved healthy control individuals [4,6–8], while 1 study did not plainly describe the comorbidities and medication of control individuals [9]. The mean quality of the studies was moderate-to-high. The average score was 11.5 ± 0.8 out of a possible 16 points (Supplemental Table 1). As for the evaluation of potential biases for the SMD in CI_{peak}, the funnel

Table 1
Main characteristics of studies included in the meta-analysis.

	n		Age (years)		% Females		BMI ($m^2 \cdot kg^{-1}$)		Hb ($g \cdot dl^{-1}$)		Health/clinical status[a]	
Reference	Ctrl	HFpEF	Crtl	HFpEF	Ctrl	HFpEF	Ctrl	HFpEF	Ctrl	HFpEF	Ctrl	HFpEF
Malhotra et al.,[10] 2016	30	48	58 ± 15	63 ± 12	37	60	28 ± 4	34 ± 8*	13.3 ± 1.3	13.2 ± 1.5	patients	LVEF ≥ 50%, VO_{2peak} < 80% pred. PWP_{peak} > 20 mmHg
Shimiaie et al.,[12] 2015	14	16	51 ± 4	57 ± 4	40	7	27 ± 1	27 ± 1	13.9 ± 0.4	13.1 ± 0.4	patients	LVEF ≥ 50%, VO_{2peak} < 80% pred. Rich HF criteria [50]
Santos et al.,[11] 2015	31	31	65 ± 12	65 ± 12	26	26	29 ± 6	33 ± 6*	14.4 ± 1.8	14.4 ± 1.7	patients	LVEF ≥ 50%, VO_{2peak} < 80% pred. PWP_{peak} ≥ 20 mmHg
Bhella et al.,[4] 2011	13	11	70 ± 4	73 ± 7	46	64	26 ± 2	34 ± 7*	N/A	N/A	healthy	LVEF ≥ 50%, VO_{2peak} < 80% pred. Framingham HF criteria
Haykowsky et al.,[7] 2011	25	48	68 ± 5	69 ± 6	52	85*	25 ± 4	31 ± 6*	N/A	N/A	healthy	LVEF ≥ 50%, VO_{2peak} < 80% pred. Rich HF criteria [50]
Maeder et al.,[9] 2010	8	14	61 ± 12	69 ± 10	37	36	25 ± 5	30 ± 5*	14.6 ± 1.4	13.7 ± 1.0	healthy/patients	LVEF ≥ 50%, VO_{2peak} < 80% pred. PWP_{peak} > 20 mmHg
Borlaug et al. A,[6] 2010	19	11	65 ± 11	67 ± 11	74	76	28 ± 3	34 ± 7*	14.2 ± 1.5	13.0 ± 1.3*	patients	LVEF ≥ 50%, VO_{2peak} < 80% pred. Framingham HF criteria
Borlaug et al. B,[6] 2010	10	10	62 ± 7	67 ± 11	70	76	31 ± 8	34 ± 7	13.0 ± 2.2	13.0 ± 1.3	healthy	LVEF ≥ 50%, VO_{2peak} < 80% pred. Framingham HF criteria
Borlaug et al.,[5] 2006	19	17	65 ± 9	65 ± 9	83	94	31 ± 6	37 ± 8*	12.5 ± 1.8	11.9 ± 1.4	patients	LVEF ≥ 50%, VO_{2peak} < 80% pred. Framingham HF criteria
Kitzman et al.,[8] 1991	10	7	61 ± 8	65 ± 12	40	57	26	27	N/A	N/A	healthy	LVEF ≥ 50%, VO_{2peak} < 80% pred. PWP_{peak} > 20 mmHg

Data are *n*, prevalence (%), mean or mean ± SD. * Significant difference from control group at $P < 0.05$.
One article presented a single HFpEF group independently compared with 2 separate control groups (herein distinguished by A and B).[6] In order to preserve meta-analytic accuracy, the sample size of the HFpEF group was divided into 2 parts so that the total numbers added up to the original size of the HFpEF group.
[a]Detailed information on comorbities and medication are described in Supplemental Table 3.
BMI, body mass index; Ctrl, control individuals; Hb, hemoglobin concentration; HF, heart failure; HFpEF, heart failure with preserved ejection fraction patients; LVEF, left ventricular ejection fraction; N/A, data not available; pred., predicted; PWP_{peak}, peak pulmonary wedge pressure; VO_{2peak}, peak oxygen consumption.