Abstract

Background: Heart failure with preserved ejection fraction (HFpEF) is a complex disease underlined by impaired ventricular-vascular coupling (VVC).

Objectives: To evaluate the VVC ratio in HFpEF patients at rest and during exercise and compare it to the healthy and heart failure with reduced ejection fraction (HFrEF) controls.

Methods: PubMed and EMBASE databases were searched for trials that matched the inclusion criteria. Random-effects models were used to estimate the pooled mean difference with 95% confidence interval using Open Meta[Analyst] software.

Results: A total of 13 trials met the inclusion criteria. Although VVC ratio was comparable between HFpEF and healthy controls at rest, it was significantly lower in HFrEF compared to HFpEF. During exercise, there was a significant decline in VVC ratio in HFpEF (-0.119, 95% CI (-0.183 to -0.055), $p<0.001$).

Conclusion: VVC ratio, although 'preserved' at rest in HFpEF patients, was overtly impaired during exercise highlighting the importance of dynamic testing.

Keywords:

Ventricular-vascular coupling (VVC)

Heart failure with preserved ejection fraction (HFpEF)

Systematic review

Introduction

Heart failure with preserved ejection fraction (HFpEF) is a challenging and significant public health problem [1]. It has now been reported to be the most common type of heart failure [1,2], with the prevalence relative to heart failure with reduced ejection fraction (HFrEF), increasing at an alarming rate of 1% per year [1]. Epidemiological studies [2–4] support a heterogeneous group of HFpEF patients who generally tend to be older women with multiple co-morbidities such as chronic hypertension, obesity, atrial fibrillation and diabetes mellitus. The heterogeneity of patients is mirrored by the complex, deranged physiological mechanisms underlying HFpEF, one of which is believed to be deranged ventricular-vascular coupling (VVC) [5–9].

The cardiovascular system is required to provide adequate pressure and flow to the body at rest and during periods of stress[10,11]. To accompany the changes in cardiac output and to prevent broad fluctuations in blood pressure, which can inevitably lead to vascular and end-organ damage, there needs to be a compliant relationship between the left ventricle and the arterial system[10]. This interaction, termed as ventricular-vascular coupling (VVC), is a fundamental marker of the cardiovascular performance [10,12]. It is estimated as a ratio of arterial elastance (E_a) to end-systolic elastance (E_{es}). E_a is an integrative index of the arterial load [13] whereas E_{es} is a coupled measure of left ventricular contractile function and systolic stiffening [5,14] estimated using validated non-invasive single-beat methods. One of these methods, described by by Chen et al [14] which relies on measurement of non-invasive systolic

and diastolic arterial blood pressures, estimated normalised ventricular elastance at the onset of ejection and stroke volume derived from Doppler echocardiogram.

Although VVC has been studied extensively [5–7,15,16], there is no systematic review examining the VVC ratio in patients with HFpEF compared to the controls and HFrEF patients. We therefore provide the first systematic review and meta-analysis for the evaluation of VVC and its components in the patients, which may provide a novel perspective into the pathogenesis of HFpEF and facilitate a focused approach towards the diagnosis of the patients. Thus, the aim of this review is to assess the ventricular-vascular coupling ratio and its components in patients with HFpEF compared to controls and HFrEF.

Methods

Our systematic review was conducted and reported in accordance to the Preferred Reporting Items for Systematic Reviews and Meta- Analyses (PRISMA) guidelines. We created a search strategy based around the concepts of heart failure and ventricular vascular coupling. A search of PubMed and EMBASE was performed from inception until February 2018 using the key terms: “Heart failure”, “preserved ejection fraction”, “normal ejection fraction”, “diastolic heart failure”, “HFpEF”, “ventriculovascular coupling” and “ventriculovascular interaction”. There were no restrictions imposed on language. The full search strategy is included in Appendix A**.**

Two authors (RB and BL) reviewed the articles independently. Any disagreements were resolved by discussion with a third author (VV). The search results from the databases were merged into a document and duplicates were removed. All the

articles identified in our search were screened using the titles and the abstracts. Any article identified as having a potential of fulfilling our inclusion criteria underwent full-text evaluation. Multiple reports from the same study were carefully searched for and removed.

European Society of Cardiology (ESC) [17] guidelines for the diagnosis of HFpEF and HFrEF were used. The diagnosis for HFpEF includes three main criteria: (1) Clinical signs and symptoms of heart failure (2) Left ventricular (LV) Ejection Fraction by echocardiography > 50% (3) Raised natriuretic peptides (Brain Natriuretic peptides (BNP) > 35pg/mL or N-terminal pro-B-type natriuretic peptide (NT-proBNP) >125 pg/mL) and at least one of the following criteria: relevant structural heart disease or diastolic dysfunction. Studies that defined HFpEF as heart failure symptoms with normal ejection fraction was also accepted. HFmrEF (Heart failure with mid-range Ejection Fraction), a new category for patients with EF (40-49%) was excluded from the meta-analysis.

Any study design which measured E_a, E_{es} and VVC ratio in adult HFpEF ($\geq$ 18 years) was included, except for narrative reviews or editorials, including any opinion-based publications. Studies published in languages other than English were excluded. Trials reporting on the same population were entered as a single study, considering the manuscript with the largest patient numbers.

After the eligible studies were identified, data were collected using data extraction forms. The following data were extracted from each included study: (1) General information: Author names, article title, trial registration, year of publication, type of

study, sources of funding (2) Characteristics of the participants: number of participants and sample size, mean/median age, gender distribution, heart rate, pulse pressure, prevalence of co-morbidities (atrial fibrillation, hypertension) (3) Methods: recruitment and diagnostic criteria, assessment of blinding (4) Interventions (if any) type and level of exercise (5) Outcomes: adjusted and non-adjusted effect size for outcomes and measurement tool.

The Newcastle-Ottawa Scale (NOS) was used to assess the quality of the included trials. Although it is specifically used for cohort and case control studies, it has been used previously for cross-sectional studies due to lack of interventions in these types of studies [18,19]. The scale comprises of three main components for which any study can obtain a maximum of four, two and three stars respectively. Trials with a total score of 7 or higher are considered to be high-quality studies.

We compared the mean values and standard deviation for both HFpEF patients and controls, as well as sample size. The data was analysed using Open Meta[Analyst] Software version 10.12 (developed by the Centre for Evidence Synthesis, Brown University, School of Public Health, Rhode Island State, USA) [20]. Statistical heterogeneity between the studies was evaluated by calculating I^2 statistics. This describes the percentage of the variability in effect estimates that is due to heterogeneity rather than sampling error, with a value less than 25% indicating low, 25% to 75% medium and higher than 75% indicates high heterogeneity [21]. Mean VVC ± 95% confidence interval (CI) in HFpEF and controls were compared using random effects models in case of high heterogeneity; otherwise, the fixed effects model was employed. The statistical significance was defined as $p<0.05$. Funnel

plots were used to assess publication bias using Review Manager (RevMan) software (Version 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014).

Results

Our search yielded 2172 studies from the database searches **(Figure 1)**. We rejected 2132 trials after duplication check and title-abstract screening. A total of 40 trials underwent full-text evaluation, out of which 26 studies were excluded: Thirteen did not have VVC data for HFpEF patients, 4 used same population, 5 had no healthy or HFrEF control group and exercise data, and 1 reported data in median value. Furthermore, 3 studies that used EF>45% as a threshold for HFpEF patients and 4 studies with no control group and exercise data were excluded to keep a comparable pool of patients. One study compared VVC ratio in HFpEF patients to significantly younger healthy controls. As VVC ratio and its components change with age [22,23], this study was excluded.

Thirteen studies were included in the analysis, providing a total of 814 HFpEF patients and 367 healthy age-matched controls and 284 HFrEF controls **(Supplemental file, Table 1).** The studies were predominantly non-invasive, one study reported invasive data as well, but for the purposes of this meta-analysis only the non-invasive data for ease of comparison. Out of 13 studies, 7 trials reported rest vs exercise data for HFpEF patients, and 4 studies analysed HFpEF vs HFrEF data. Two studies [24,25] categorised HFpEF patients, both of which were used in the analysis as study1, study2. All included trials scored >6 (moderate to high) in the

Newcastle Ottawa Scale (NOS) (**Supplemental file, Table 2)**. Funnel plot to assess publication bias was performed **(Supplemental file, Figure 1).**

The mean difference in pooled E_a and E_{es} between HFpEF and healthy age-matched controls was estimated as 0.021, 95% CI (-0.105 to 0.147), p= 0.746, I^2= 43%, **Figure 2A** and 0.529, 95% CI (-0.182 to 1.241), p= 0.145 I^2= 94%, **Figure 2B** respectively. Six out of nine trials reported ventricular-vascular coupling ratio as E_a/E_{es}. The mean difference between HFpEF and controls in E_a/E_{es} was 0.001, 95% CI (-0.101 to 0.103), p=0.983, I^2 = 85% **(Figure 2C)**. One study [26], excluded from the meta-analysis, reported VVC as E_{es}/E_a. Sensitivity analysis of E_a, E_{es} and E_a/E_{es} for HFpEF vs controls was performed by removing each study individually. This did not significantly change the overall results with the exception of E_{es} when Abramov study was excluded (**Supplemental file, Figure 2).**

During exercise, there was a significant increase in E_a (0.361, 95% CI (0.031 to 0.692), p=0.03, I^2= 92% **(Figure 3A)**) and indexed E_a (E_aI) (0.873, 95% CI (0.228 to 1.518), p=0.008, I^2= 98% **(Figure 3B)**) in HFpEF patients. A significant difference was also noted in E_{es} (1.650, 95% CI (0.640 to 2.659), p=0.001, I^2 = 94% (**Figure 3C)** and E_{es}I (5.989, 95% CI (1.061 to 10.917), p=0.017, I^2= 99% **(Figure 3D)** during exercise. As a consequence, VVC ratio (E_a/E_{es}) and indexed VVC ratio (E_aI/E_{es}I) decreased significantly during exercise (-0.119, 95% CI (-0.183 to -0.055), p<0.001, I^2 = 31% **(Figure 4A)** and -0.104, 95% CI (-0.197 to -0.010), p=0.03, I^2 = 95% **(Figure 4B)** respectively).

Four studies estimated VVC ratio and its components in HFpEF and HFrEF patients. There was no significant mean difference in pooled E_a (-0.103, 95% CI (-0.369 to 0.164), p=0.450, I^2 = 69% **(Figure 5A))**. Pooled E_{es}, however, was significantly raised in HFpEF patients (2.099, 95% CI (1.065 to 3.133), p< 0.001, I^2 = 96% **(Figure 5B)**. VVC, consequently, was significantly lower in HFpEF patients (-1.270, 95% CI (-0.910 to -0.631), p< 0.001, I^2 = 96% **(Figure 5C)**.

Discussion

This is the first systematic review and meta-analysis to assess the arterial elastance, end-systolic elastance and ventricular-vascular coupling ratio in HFpEF patients compared to age-matched healthy and HFrEF controls.

Pooled E_a, measured non-invasively using cuff pressures, was estimated to be similar between HFpEF patients and healthy controls. It is important to highlight that the studies with invasive data and statistically younger controls were excluded in this meta-analysis, which helped to compare E_a in the age-matched controls. Nevertheless, there is evidence of increased arterial stiffening and hence, raised E_a in a healthy ageing community [11,27] which is likely to be responsible for the comparable E_a in the pooled analysis. Besides, hypertension is a recognised risk factor which is known to affect E_a [13,27]. More than half of the HFpEF patients had a history of hypertension (73% Phan, 100% Desai, 80% Tan, 86% Borlaug), and subsequently, a significant number of patients were on antihypertensives [6,25,28,29]. It is likely that their enhanced blood pressure and arterial stiffness, had been neutralised by adequate treatment [23].

In addition, E_{es} assessed using non-invasive ‘single-beat’ method, was raised but not to a significant amount in HFpEF patients at rest compared to the healthy controls. Subsequently, VVC remained comparable in HFpEF and healthy controls at rest. Nevertheless, pooled estimates reflect a near-optimal ventricular-arterial coupling ratio at the expense of E_{es} and E_a [6], consequently leading to ‘preserved’ ejection fraction.

VVC in HFpEF patients, although preserved at rest, displayed an overt impairment during exercise, mainly due to an increase in exercise-induced vascular stiffening and impaired LV contractile reserve [10,13]. Despite a small number of studies with dynamic test data, there is compelling evidence that points towards the significance of dynamic examination as a diagnostic investigation of HFpEF.

ESC follows strict criteria for HFpEF diagnosis as outlined above. It also recommends invasive measurements of filling pressures or stress tests in cases of uncertainty. As our study has shown assessing the cardiac function of patients with exercise intolerance exclusively at rest risks concealing various haemodynamic impairments, and perhaps, under-diagnosing HFpEF. There is also evidence to support the hypothesis that the initial stage of HFpEF is characterised by normal resting but abnormal exercise haemodynamic parameters [30]. Multiple studies have shown evidence for the prognostic value of cardiopulmonary exercise testing in HFpEF [31,32]. The present review also advocates the utility of haemodynamic exercise testing to identify the population of patients with less advanced HFpEF.

The pathogenesis of HFpEF and HFrEF has been a debated topic mainly because the therapies that work effectively in HFrEF have not been improving outcomes in HFpEF [33]. Our study demonstrated a comparable E_a in both heart failure patients, despite HFpEF commonly associated with systolic hypertension, but only one trial [34] reported significantly higher patients on anti-hypertensive therapy in HFrEF than HFpEF. Additionally, our study showed a significantly raised end-systolic elastance in HFpEF and subsequently reduced VVC but a similar E_a compared to HFrEF at rest. Whether the increased E_{es} exclusively reflects higher contractility is less clear, as concentric hypertrophy and passive ventricular stiffening, processes commonly observed in HFpEF [35,36], contributes to increased E_{es} [10]. Even though it is vital to exhibit additional caution while interpreting the significance of elevated E_{es} in HFpEF participants [16], It begs to suggest that the contractility and the stiffness of the chamber perhaps play a significant role in the distinction between HFpEF and HFrEF.

This disproportionate rise in E_{es} compared to E_a has various clinical implications. A rise in E_{es} accompanies an increase in the systolic pressure, which is believed to be the culprit for the enhanced sensitivity to circulating volume in HFpEF patients [14]. This effect worsens the hypertensive stress responses [5,14,15], characterised by an inappropriate rise in systolic BP during exercise [37]. Any adjustment in LV end-diastolic volume, causes a dramatic change in arterial pressures, inducing blood pressure lability [14]. It explains the rapid-onset pulmonary oedema [5] commonly seen in the elderly and even HFpEF patients, on diuretics therapy [14], which is well tolerated by HFrEF patients. Future clinical trials should focus on drugs that act on ventricular stiffness and afterload [38].One such trial (PRESERVED-HF trial, NCT03030235) aims to evaluate the effects of dapagliflozin, a primarily anti-diabetic

drug, on exercise capacity in HFpEF patients. Dapagliflozin not only inhibits sodium-glucose cotransporter-2 and enhances glucose excretion but also improves myocardial energetics by reducing afterload and LV load [39].

The present study is the first systematic review and meta-analysis to outline the VVC ratio and its components in HFpEF compared to age-matched healthy and HFrEF controls. Nevertheless, there are a few limitations to the review. The meta-analysis included very few studies owing to strict inclusion criteria in an attempt to include comparable group of patients. Multiple studies lacked a control group, limiting our analysis to a relatively smaller number of studies, and the studies were non-randomised which introduces bias. Similarly, there was insufficient data to conduct further analyses such as changes in VVC ratio and diastolic response in controls during exercise which would have been significant. E_a and E_{es} were inconsistently adjusted, so the multivariate adjustments could not be produced across the studies. In addition, heterogeneity, despite our best endeavour, persisted among the studies. Despite undertaking random-effects analysis to account for heterogeneity, the variable diagnostic criteria for HFpEF disrupted the homogeneity even further. Whilst most studies used ESC guidelines to define HFpEF, other studies simplified their criteria by combining patients with heart failure symptoms and normal systolic function, endangering the uniformity of the patients. Future research should steer clear from exclusively LVEF-based HFpEF patients and emphasise on a uniform, well-defined cohorts.

In conclusion, impaired ventricular-vascular coupling, one of the distinctive mechanisms underlying HFpEF, is mainly apparent on exercise. This calls for a

change in the diagnostic guidelines to signify the contribution of dynamic testing, data for which are quite in scarce. Further studies are warranted to examine these components during exercise on well-defined HFpEF patients.

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Figure legends:

Figure 1: Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram of the trial selection process.
VVC, ventricular-vascular coupling; HFpEF, Heart failure with preserved ejection fraction; HFrEF, Heart failure with reduced ejection fraction.

Figure 2: Pooled mean difference in E_a (A), E_{es} (B) and VVC ratio (C) between HFpEF and age-matched healthy controls at rest using random-effect model.
CI, confidence interval; HFpEF, heart failure with preserved ejection fraction; E_a, arterial elastance; E_{es}, end-systolic elastance; VVC, ventricular-vascular coupling.

Figure 3: Pooled mean difference in E_a (A), E_aI (B), E_{es} (C) and $E_{es}I$ (D) during exercise in HFpEF using random-effect model.
CI, confidence interval; HFpEF, heart failure with preserved ejection fraction; E_a, arterial elastance; E_{es}, end-systolic elastance; E_aI, indexed arterial elastance; $E_{es}I$, indexed end-systolic elastance.

Figure 4: Pooled mean difference in E_a/E_{es} (A) and $E_aI/E_{es}I$ (B) and during exercise in HFpEF using random-effect model.
CI, confidence interval; HFpEF, heart failure with preserved ejection fraction; E_a, arterial elastance; E_{es}, end-systolic elastance; E_aI, indexed arterial elastance; $E_{es}I$, indexed end-systolic elastance.

Figure 5: Pooled mean difference in E_a (A), E_{es} (B) and VVC ratio (C) between HFpEF and HFrEF at rest using random-effect model.

CI, confidence interval; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; E_a, arterial elastance; E_{es}, end-systolic elastance; VVC, ventricular-vascular coupling.