The effect of parity on exercise physiology in women with heart failure with preserved ejection fraction

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Abstract

Aims Women are overrepresented amongst patients with heart failure with preserved ejection fraction (HFpEF); however, the underpinning mechanism for this asymmetric distribution is unclear. Pregnancy represents a potential gender-specific risk factor for HFpEF. It leads to significant physiological adaption, and increasing parity has been associated with some cardiovascular risk. We sought to examine the relationship between prior parity with the rest and exercise haemodynamic and echocardiographic profile of women with HFpEF.

Methods and results Patients referred for assessment of exertional dyspnoea and confirmed to have a haemodynamic and clinical profile consistent with HFpEF were included. Detailed evaluation consisted of rest and exercise right heart catheterization and echocardiography. A socio-economic and obstetric history was also documented. Fifty-eight women were assessed and categorized as having either ≥ 0 births or ≥ 3 births, dividing the cohort equally. Women with ≥ 3 births achieved a lower symptom-limited workload than those with 0–2 births [38 (24–51) vs. 46 (31–68) W, P = 0.04]. Women with ≥ 3 births had a greater rise in pulmonary capillary wedge pressure indexed to workload with exercise [0.5 (0.3–0.8) vs. 0.3 (0.2–0.5) mmHg/W, P = 0.03], paralleled by a greater rise in right atrial pressure [10 (8–12) vs. 7 (3–11), P = 0.01]. Pulmonary vascular resistance was also higher in women with ≥ 3 births [1.9 (1.6–2.4) vs. 1.6 (1.4–1.9) mmHg/L/min rest, P = 0.046, and 1.9 (2.4–2.4) vs. 1.4 (1–1.8) mmHg/L/min exercise, P = 0.024]. Left ventricular ejection fraction was lower at rest [60 (57–61) vs. 63 (60–66), P = 0.008] and during exercise [65 (62–67) vs. 68 (66–70), P = 0.038] in women with higher parity.

Conclusions Higher parity is associated with greater impairments in multiple physiologic parameters of HFpEF severity in women, including diastolic reserve, pulmonary vascular resistance, and systolic dysfunction.

Keywords Pregnancy; Parity; Heart failure with preserved ejection fraction; Sex characteristics; Haemodynamics

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Introduction

Heart failure with preserved ejection fraction (HFpEF) is rapidly becoming the most common form of heart failure. Whilst a key element of its diagnosis includes a left ventricular ejection fraction (LVEF) >50%, the pathophysiology is complex.¹ Key features include abnormal left ventricular diastolic performance, abnormal left atrial stiffness, and reduced systemic and pulmonary vascular compliance, although considerable phenotypic variation is recognized. Advancing age, hypertension, obesity, and diabetes are common features.² Notably, all large clinical trials of HFpEF have consistently demonstrated overrepresentation of women³,⁴ who are conversely far less likely to develop heart failure with reduced ejection fraction.⁵ To date, HFpEF clinical trials have been largely neutral; however, it is possible that specific sub-phenotypes, including female and male genders, might respond differentially to specific therapies.⁶ As such, understanding the mechanism that accounts for the gender imbalance in HFpEF is potentially of major clinical and therapeutic importance.

Women face unique haemodynamic challenges with pregnancy, which can lead to adverse cardiac remodelling and...
diastolic dysfunction, particularly in the context of repeated pregnancies.\textsuperscript{7} Pregnancy is associated with alterations to the cardiovascular system that place significant load on the maternal heart,\textsuperscript{9} in particular a significant increase in cardiac output. Accordingly, parity has been associated with increased long-term cardiovascular disease risk,\textsuperscript{9–11} specifically coronary artery disease\textsuperscript{12}; however, no study to date has examined the long-term haemodynamic consequences of multiparity in women with HfPEF.

On the basis of the cardiac remodelling impact of pregnancy, we hypothesized that women with higher numbers of pregnancies might be more likely to develop more advanced features of HfPEF if exposed to relevant risk factors. Accordingly, we compared the echocardiographic and invasive haemodynamic profiles of women with HfPEF according to their obstetric history.

**Methods**

**Study population**

The study cohort comprised women undergoing clinically indicated exercise right heart catheterization (RHC) to further investigate exertional dyspnoea after inconclusive non-invasive investigations for HfPEF. A cohort of men with HfPEF ($n = 51$) was also incorporated for a comparison of change in pulmonary capillary wedge pressure (PCWP) between genders and parity category. Patients were defined as having HfPEF if they had an LVEF $\geq 50\%$ together with a resting PCWP $\geq 15$ mmHg or an exercise PCWP $\geq 25$ mmHg, according to established definitions.\textsuperscript{13} Exclusion criteria were as follows: more than mild valvular stenosis or regurgitation; evidence of significant pulmonary disease on lung function testing or pulmonary imaging; chronic pulmonary emboli, hypertrophic cardiomyopathy; or previous heart transplantation.

**Right heart catheterization protocol**

Exercise RHC was performed using supine cycle ergometry as previously reported by us.\textsuperscript{14} All measurements and exercise were performed in the un-fasted state together with regular medications. Natriuretic peptide levels were taken at rest immediately prior to RHC. A 7F Swan-Ganz catheter was inserted via the brachial or internal jugular vein under local anaesthesia. End-expiratory measurements were taken from the right atrium, right ventricle, pulmonary artery, and pulmonary capillary wedge position. Wedge position was confirmed by identification of the appropriate pressure waveform, with oximetric confirmation when required. Cardiac output was calculated using thermodilution, and the average of three measures taken for patients in sinus rhythm or five in atrial fibrillation. Measurements recorded non-invasively included heart rate, systemic blood pressure, and arterial oxygen saturation via pulse oximetry. Non-invasive and invasive measurements were taken at rest and at 3 min intervals during exercise until the patient reached their peak tolerated workload. An important feature of this approach is the application of a weight corrected workload protocol, comprising an initial workload of 0.3 W/kg, incrementing every 3 min until symptom limitation. Subjects were instructed to maintain a cycle cadence of 60 rpm during exercise.

**Echocardiography**

Transthoracic echocardiography was performed with the patient in the supine position, using a commercially available ultrasound machine (IE33, Phillips, Andover, MA) to obtain apical two-chamber and four-chamber views, together with transmitral flow and tissue Doppler measurements. The majority of patients had resting echocardiography performed immediately prior to RHC. Peak exercise images were obtained immediately prior to cessation of symptom-limited exercise, simultaneous with RHC measures.

Invasive haemodynamic and echocardiographic data are presented as raw values or indexed to body surface area as appropriate. In accordance with similar studies,\textsuperscript{15} PCWP was indexed to workload. Pulmonary and systemic vascular compliance were calculated as the ratio of thermodilution-derived stroke volume to the pulmonary and systemic arterial pulse pressure, respectively.\textsuperscript{16} Arterial elastance (Ea) was calculated as $0.9 \times $ systemic systolic blood pressure divided by stroke volume.\textsuperscript{17} End-systolic elastance (Ees) was estimated as $0.9 \times $ systemic blood pressure divided by the left ventricular end-systolic volume. End-diastolic elastance (Ed) was estimated as the PCWP, used to estimate left ventricular end-diastolic pressure, divided by the left ventricular end-diastolic volume. The ratio of Ea to Ees was used to assess ventricular–vascular coupling.\textsuperscript{18}

**Obstetric history**

Obstetric history was compiled using a questionnaire incorporating menarche and menopause, pregnancies and live births, breastfeeding, oral contraceptive, and hormone replacement therapy. A detailed socio-economic history was also obtained.

**Ethics**

This study was completed following approval of the Alfred Human Research Ethics Committee.
Statistical methods

Data are presented as mean ± standard deviation if normally distributed and median (interquartile range) if non-parametric. Student’s t-test was used for comparisons of normally distributed data and Wilcoxon signed-rank test for non-parametric data. Categorical variables were compared using the chi-square test for independence. A two-tailed P-value <0.05 was considered statistically significant. A multivariate linear regression analysis was used to ascertain whether the effect of parity on haemodynamics was independent of age. All statistical analyses were performed using R (Version 3.4.1; R Foundation for Statistical Computing, Vienna, Austria).

Results

The study comprised 58 women with HfPEF. The median number of births was three, and the cohort was divided into those women with zero to two births and those with three or more births. Baseline characteristics of these two groups are identified in Table 1. There were no significant differences in co-morbidities or medications. Age and body mass index (BMI) were similar between the two groups. With regard to socio-economic status, there were no differences between parity groups in level of education, income bracket, or frequency of work during childbearing years.

Rest and exercise haemodynamics are detailed in Table 2. Women with ≥3 births achieved a lower symptom-limited workload than those with 0–2 births [38 (24–51) vs. 46 (31–68) W, P = 0.04]. Rest and exercise heart rate and blood pressure did not differ between groups. Right atrial (RA) pressure rose to a greater degree in women with ≥3 births [10 (8–12) vs. 7 (3–11), P = 0.01]. Similarly, PCWP indexed to workload was higher at exercise [0.9 (0.6–1.2) vs. 0.7 (0.4–1.1), P = 0.05] and rose to a greater degree in women with ≥3 births than those with 0–2 births [0.5 (0.3–0.8) vs. 0.3 (0.2–0.5), P = 0.03]. These findings are depicted in
Table 2: Invasive haemodynamics at rest and exercise according to parity category

|                      | 0–2 births<sup>19</sup> | ≥3 births<sup>19</sup> | P-value |
|----------------------|--------------------------|------------------------|---------|
| Peak workload (W)    | 46 (31–68)               | 38 (24–51)             | 0.04    |
| Rest HR (b.p.m.)     | 67 ± 14                  | 71 ± 15                | 0.29    |
| Exercise HR (b.p.m.) | 103 ± 24                 | 100 ± 21               | 0.58    |
| Rest SBP (mmHg)      | 147 ± 25                 | 151 ± 23               | 0.48    |
| Exercise SBP (mmHg)  | 177 ± 25                 | 174 ± 28               | 0.64    |
| Rest RAP (mmHg)      | 7 (5–9)                  | 6 (4–8)                | 0.3     |
| Exercise RAP (mmHg)  | 14 (12–17)               | 16 (13–21)             | 0.11    |
| Rest mean PAP (mmHg) | 20 (18–25)               | 21 (18–27)             | 0.65    |
| Exercise mean PAP (mmHg) | 43 (38–46)       | 45 (41–49)             | 0.14    |
| PCWP at rest (mmHg)  | 13 (10–15)               | 13 (10–14)             | 0.53    |
| Exercise PCWP indexed to workload (mmHg/W) | 0.7 (0.4–1.1) | 0.9 (0.6–1.2) | 0.05 |
| ΔPCWP indexed to cardiac output (mmHg/L/min) | 4.6 (3.2–7.7) | 6.9 (4.5–11) | 0.03 |
| Rest CI (L/min/m<sup>2</sup>) | 2.8 ± 0.6 | 2.7 ± 0.6 | 0.44 |
| Exercise CI (L/min/m<sup>2</sup>) | 4.7 ± 1.2 | 4.3 ± 1.2 | 0.25 |

CI, cardiac index; HR, heart rate; PAP, pulmonary artery pressure; PCWP, pulmonary capillary wedge pressure; RAP, right atrial pressure; SBP, systolic blood pressure.

Figure 1, with Figure 2 incorporating men to demonstrate the effect of sex and parity category on PCWP indexed to workload. The rise in PCWP with exercise indexed to the rise in cardiac output was also significantly higher in women with ≥3 births [6.9 (4.5–11) vs. 4.6 (3.2–7.7) mmHg/L/min, P = 0.03]. Un-indexed PCWP with exercise was not different between parity groups [30 (28–33) vs. 29 (26–33) mmHg, P = 0.53]. In multivariate linear regression analyses, parity category was a predictor of exercise and PCWP indexed to workload (P = 0.045 and 0.034, respectively), along with RA pressure (P = 0.016), independent of age. Cardiac index did not differ between the groups.

Echocardiographic data were available in 95% of patients, and 60% had simultaneous RHC together with rest and exercise echocardiography. For those without simultaneous studies, the interval between RHC and echocardiography was 82 (1–275) days. Table 3 highlights echocardiographic variables according to parity category. Women with three or more births had a lower LVEF at both rest [60 (57–61) vs. 63 (60–66), P = 0.008] and exercise [65 (62–67) vs. 68 (66–70), P = 0.038], pictured in Figure 3. Parity category was a significant predictor of LVEF at rest (P = 0.017), independent of age; however, this could not be confirmed during exercise. Left ventricular, right ventricular and left atrial strain were not different between groups; however, strain measurements were only available for 24 (41%) of the cohort. All strain measurements were performed on echocardiograms simultaneous with RHC. Otherwise, there were no significant differences between groups in left ventricular wall thickness and endsystolic and end-diastolic diameter.

As shown in Table 4, greater parity was also associated with features of impaired pulmonary vascular function, in the absence of clear differences in systemic vascular properties. Pulmonary vascular resistance (PVR) was higher both at rest and exercise in women with three or more births [1.9 (1.6–2.4) vs. 1.6 (1.4–1.9) mmHg/L/min rest, P = 0.046, and 1.9 (2.4–2.4) vs. 1.4 (1–1.8) mmHg/L/min exercise, P = 0.024]; however, neither finding was independent of age. This was further reflected in a lower pulmonary compliance in women with three or more births, but only at rest [3.2 (2.8–3.8) vs. 4.1 (3.2–5.2) mL/mmHg, P = 0.009, and after adjusting for age, P = 0.049]. The ratio of mean pulmonary artery pressure to cardiac output at exercise, also reflecting pulmonary vascular abnormality, was higher in women with three or more births [5.9 (5.2–7.2) vs. 5.1 (4.1–6.2) mmHg/L/min, P = 0.02]. Arterial elastance rose to a greater degree, and end-systolic elastance rose to a lesser degree, with exercise in women with three or more births; however, this did not translate to significant differences in ventricular–vascular coupling (Table 5).

Other variables included in the obstetric history questionnaire including years between menopause and menarche,
total duration of breastfeeding, weight at the time of the first pregnancy, and age at the time of first pregnancy were not independent predictors of haemodynamic variables.

**Discussion**

This study examined women with HFpEF with well-characterized invasive haemodynamics, echocardiography, and natriuretic peptides in the context of obstetric history. We identified several key impairments in both myocardial performance and pulmonary vascular function that related to higher parity, which could contribute to exercise intolerance in the context of a diagnosis of HFpEF. Women with an obstetric history of three or more births had a higher exercise PCWP indexed to workload along with a greater rise in PCWP indexed to workload and cardiac output with exercise, indicative of poorer diastolic reserve. This was

**Table 3** Echocardiography at rest and exercise according to parity category

|                      | 0–2 births[^20] | ≥3 births[^21] | P-value |
|----------------------|-----------------|----------------|---------|
| LVEF at rest (%)     | 63 (60–66)      | 60 (57–61)     | 0.008   |
| LVEF at exercise (%)^a| 68 (66–70)     | 65 (62–67)     | 0.038   |
| LVMi (g/m²)          | 84 (72–97)      | 79 (67–92)     | 0.31    |
| End-diastolic septal wall thickness (mm) | 10 (10–11) | 10 (9–12) | 0.8 |
| End-diastolic posterior wall thickness (mm) | 10 (9–10) | 9 (9–10) | 0.32 |
| LV end-diastolic diameter | 46 (43–48) | 45 (43–50) | 0.92 |
| LV end-systolic diameter | 29 (26–33) | 31 (27–35) | 0.31 |
| LAVI                 | 36 (30–44)      | 43 (32–51)     | 0.19    |
| LV global strain[^b] | –19 (–21 to –18) | –18 (–19 to –17) | 0.2 |
| RV global strain[^b] | –19 (–24 to –19) | –19 (–21 to –15) | 0.21 |
| LA global strain[^b] | 24 (20–26)      | 22 (17–31)     | 0.89    |
| RVSP at rest         | 28 (23–42)      | 34 (30–42)     | 0.16    |
| TAPSE                | 2.3 (2.1–2.8)   | 2.2 (1.9–2.4)  | 0.36    |
| E/e’ lateral at rest | 11.6 (10–13.3)  | 10.3 (8.7–12.2)| 0.12   |
| E/e’ septal at rest  | 14.4 (12.3–17)  | 13.2 (11.2–19.2)| 0.68 |
| E/e’ mean at rest    | 12.4 (11.6–15.6)| 11.3 (10.2–15.2)| 0.34 |
| E/e’ lateral at exercise[^a] | 12.9 (10.9–15.1) | 12 (10–13.4) | 0.47 |
| E/e’ septal at exercise[^a] | 14.4 (12.1–15.6) | 14.5 (11.9–17.2) | 0.93 |
| E/e’ mean at exercise[^a] | 13.7 (11.8–14.9) | 13.5 (10.9–14.8) | 0.68 |

[^20]: Exercise variables reported for 35 women with exercise echocardiography.
[^21]: Strain measurements were available for 24 (41%) of the cohort.

[^b]: LA, left atrial; LAVI, left atrial volume index; LV, left ventricular; LVEF, left ventricular ejection fraction; LVMi, left ventricular mass index; RV, right ventricular; RVSP, right ventricular systolic pressure; TAPSE, tricuspid annular plane systolic excursion.
accompanied by a greater rise in RA pressure with exercise and higher PVR at both rest and exercise. Women in the higher parity category also had a lower LVEF at both rest and exercise. These findings highlight a relationship between parity and greater left ventricular stiffness, pulmonary vascular and possibly right ventricular dysfunction, and impairments in systolic function (Figure 4).

Increased PCWP with exercise, and particularly a greater rise in PCWP with exercise, is an established feature of severity of HFpEF, which is closely linked to mortality. A key component of PCWP, which reflects left ventricular end-diastolic pressure, is diastolic relaxation, impairment of which is a central feature of HFpEF. The prominent explanation for the

### Table 4 Vascular resistance, compliance, and elastance according to parity category

| Invasively derived values                  | 0–2 births | ≥3 births | P-value |
|-------------------------------------------|------------|-----------|---------|
| Rest SVR (mmHg/L/min)                     | 18.4 ± 6.9 | 20.3 ± 5.4 | 0.24    |
| Exercise SVR (mmHg/L/min)                 | 11.4 (9.4–15.8) | 11.5 (9.8–16.1) | 0.93    |
| Rest PVR (mmHg/L/min)                     | 1.6 (1.4–1.9)  | 1.9 (1.6–2.4)  | 0.046   |
| Exercise PVR (mmHg/L/min)                 | 1.4 (1–1.8)   | 1.9 (2.4–2.4)  | 0.024   |
| Systemic compliance at rest (mL/mmHg)     | 1.1 (0.9–1.3) | 1 (0.8–1.2)   | 0.21    |
| Systemic compliance at exercise (mL/mmHg) | 1 (0.9–1.3)  | 1 (0.8–1.2)   | 0.91    |
| Pulmonary compliance at rest (mL/mmHg)    | 4.1 (3.2–5.2) | 3.2 (2.8–3.8) | 0.009   |
| Pulmonary compliance at exercise (mL/mmHg)| 2.5 (2.2–3.2) | 2.3 (1.8–2.8) | 0.15    |
| Pulmonary compliance (mL/mmHg)            | 1.5 (0.8–2.1) | 1 (0.3–1.5)   | 0.16    |
| Ea at rest (mmHg/mL/m²)                    | 1.8 (1.4–2)  | 2 (1.7–2.2)   | 0.059   |
| Ea at exercise (mmHg/mL/m²)               | 1.8 ± 0.4    | 1.9 ± 0.6    | 0.5     |
| Ea (mmHg/mL)                              | −0.09 (−0.4 to 0.09) | 0.1 (−0.2 to 0.4) | 0.041   |

Ea, arterial elastance; PVR, pulmonary vascular resistance; SVR, systemic vascular resistance.

### Table 5 Ventricular elastance and ventricular–vascular coupling according to parity category

|                  | 0–2 births | ≥3 births | P-value |
|------------------|------------|-----------|---------|
| Ees at rest      | 3.6 (2.8–4.5) | 3.4 (2.7–4.2) | 0.63    |
| Ees at exercise  | 4.8 (4.1–7.3) | 4 (3.6–5)   | 0.2     |
| Ees              | 1.7 (1.1–2.7) | 0.8 (0.4–1.3) | 0.046   |
| Ed at rest       | 0.1 (0.09–0.2) | 0.1 (0.1–0.14) | 0.63    |
| Ed at exercise   | 0.3 (0.3–0.4) | 0.3 (0.2–0.3) | 0.63    |
| Ed               | 0.2 (0.1–0.2) | 0.2 (0.1–0.2) | 0.89    |
| Ea/Ees at rest   | 0.5 (0.4–0.6) | 0.6 (0.5–0.8) | 0.35    |
| Ea/Ees at exercise| 0.4 (0.3–0.4) | 0.5 (0.4–0.6) | 0.06    |
| Ea/Ees           | 0.1 (0.09–0.19) | 0.09 (0.06–0.2) | 0.88    |

Ea, arterial elastance; Ed, end-diastolic elastance; Ees, end-systolic elastance.

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Figure 3 Rest and exercise left ventricular ejection fraction (LVEF) according to parity category.
development of diastolic dysfunction in HFP EF is that co-

morbidity, such as obesity, diabetes mellitus, chronic

obstructive pulmonary disease, and hypertension, lead to mi-

crovascular endothelial inflammation. This, in turn, leads to

both increased interstitial fi

brosis and hypophosphorylation

of titin, with the end result of increased ventricular stiff-

ness. It is conceivable that pregnancies could contribute

to this process, with possible mechanisms including adverse

lipid profiles in parous women,9 and up-regulation of the

renin–angiotensin–aldosterone system26 and increased insu-

lin resistance27 in pregnancy. Furthermore, the greater risk

of coronary atherosclerosis with increasing parity,12,28 even

after controlling for risk factors such as obesity and hyperten-
sion, suggests that pregnancy may have direct and lasting

effects on the vasculature. This is relevant to ventricular stiff-

ening given the role of coronary artery disease, and particu-

larly coronary microvascular disease,29 in the development

of HFP EF.

The PCWP is determined by a composite of diastolic relax-

ation, compliance, and extrinsic forces.13 Thus in conjunction

with myocardial stiffness and remodelling, the PCWP also in-

corporates pulmonary capillary and vascular remodelling,21

left atrial structure and function,20 and factors external to

the left ventricle including right heart–left heart interaction

and pericardial restraint.19 Similar invasive haemodynamic

studies have noted a rise in RA pressure in concert with the

rise in PCWP,13,30 consistent with our findings of a greater

rise in PCWP and RA pressure in women with higher parity.

This supports the contribution of external factors to PCWP

with exercise. Recent work has highlighted a particular

‘obese’ phenotype of HFP EF where those with a BMI ≥35

kg/m² had greater circulating volume, more concentric left

ventricular remodelling, greater right ventricular dilatation

dysfunction, and increased epicardial fat thickness and

greater total epicardial heart volume.31 There were no differ-

ences between parity groups in BMI, and there is no clear

mechanism for increased epicardial fat volume as a result of

a higher number of births in the absence of differences in

BMI; however, the haemodynamic changes and increased

blood volume with repeated pregnancies could lead to similar

right and left ventricular remodelling as the morbidly obese.

Thus, right ventricular dysfunction and ventricular interde-

pendence could be a key contributor to our finding of

increased workload indexed PCWP in women with higher par-

ty number.

Other haemodynamic findings in our study may lend sup-

port to a contribution of right ventricular dysfunction to exer-

cise limitation in women with ≥3 births. Women with greater

parity had higher PVR at both rest and exercise than those

with zero to two births. Pulmonary compliance was lower in

women with higher parity at rest and trended lower at exer-

cise, although this was not statistically significant. Pulmonary

hypertension is associated with poor prognosis in HFP EF and

generally reflects duration and severity of HFP EF.32,33 This is

particularly true when the post-capillary pulmonary hyperten-
sion is combined with pre-capillary changes.34 Women with

≥3 births had a number of haemodynamic characteristics sim-

ilar to HFP EF patients with combined pre-capillary and post-

capillary pulmonary hypertension, including increased PVR

and a greater rise in RA pressure with exercise.34 This could
反映心室的重构和更高水平的PCWP在较高 parity的女性中可能表明，重复妊娠可能直接影响肺循环。肺血管功能的变化，即使在三尖瓣环收缩和右心室后，趋势更为明显。右心室功能异常显著影响部分HFpEF患者的PCWP，且与较差的预后相关。35

右心室-动脉功能障碍，尤其是由于妊娠，也可能对PCWP的异常增高有所贡献。14 相对较少研究非侵入性心功能的可能原因。在本研究中，我们未发现直接证据支持妊娠对右心室功能的独立影响。36 这可能表明，我们研究中观察到的右心室功能的变化可能与妊娠关联度相对较低。

在临床上，妊娠对心功能的影响可能有别于妊娠前的情况。

**Clinical implications**

本研究有多个潜在的临床意义。首先，获得妊娠史的资料可能为理解妊娠相关的因素提供额外的洞察。虽然妊娠次数的平均值目前为1.7，41 但妊娠数和妊娠并发症之间存在U形关系。42-44 从我们数据推测，妊娠的影响可能具有更为持久的作用。妊娠后的心脏可能需要更长的时间来恢复，这可能对妊娠期间的孕妇及后续的长期心血管健康有重要的影响。

**Conclusion**

在本侵入性心功能分析中，妊娠次数为3或更多次的HFpEF患者可能有更高的PCWP和左心室收缩功能障碍，可能反映了组合的重构、肺血管重塑和左心室收缩功能异常。这可能在HFpEF中更为严重，妊娠次数为3或更多次的患者可能有更高的PCWP和左心室收缩功能障碍。这与已有的研究发现一致，妊娠可以对心功能产生长期的影响。因此，妊娠对心功能的影响可能需要更长的时间来恢复，这可能对妊娠期间的孕妇及后续的长期心血管健康有重要的影响。

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