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Research paper

Risk factors for heart failure in women with ischemia and no obstructive coronary artery disease

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ABSTRACT

Study objective: Women with ischemia and no obstructive coronary artery disease (INOCA) are at increased risk for heart failure (HF) hospitalizations, which is predominantly HF with preserved ejection fraction (HFpEF). We aimed to identify predictors for the development of heart failure HF in a deeply phenotyped cohort of women with INOCA and long-term prospective follow-up.

Design, setting and participants: Women enrolled in the NHLBI-sponsored Women's Ischemia Syndrome Evaluation (WISE) were evaluated for baseline characteristics including clinical history, medications, physical exam, laboratory data and angiographic data. Using a multivariate Cox analysis, we assessed the association between baseline characteristics and the occurrence of HF hospitalizations in 493 women with evidence of ischemia but no obstructive coronary disease, no prior history of HF, and available follow-up data.

Results: During a median follow-up of 6-years, 18 (3.7%) women were hospitalized for HF. Diabetes mellitus and tobacco use were associated with HF hospitalization. In a multivariate analysis adjusting for known HFpEF predictors including age, diabetes, hypertension, tobacco use, and statin use, novel predictive variables included higher resting heart rate, parity and IL-6 levels and lower coronary flow reserve (CFR) and poor functional status.

Conclusions: There is a considerable incidence of HF hospitalization at longer term follow-up in women with INOCA. In addition to traditional risk factors, novel risk variables that independently predict HF hospitalization include multi-parity, high IL-6, low CFR, and poor functional status. These novel risk factors may be useful to understand mechanistic pathways and future treatment targets for prevention of HFpEF.

1. Introduction

Heart failure (HF) currently impacts 5.1 million people in the United States, with a 5-year mortality rate ranging from 50% to 70% [1,2]. Approximately half of all patients with HF have heart failure with preserved ejection fraction (HFpEF) and this has been shown to be more prevalent in women than men [3,4]. Prior studies have identified multiple risk factors for HF in both genders including hypertension,

Abbreviations: HF, heart failure; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; CAD, coronary artery disease; AF, atrial fibrillation; BMI, body max index; CKD, chronic kidney disease; INOCA, ischemia with no obstructive coronary disease; CMD, coronary microvascular dysfunction; WISE, Women's Ischemia Syndrome Evaluation; MACE, major adverse cardiovascular events; HTN, hypertension; DM, diabetes mellitus; CFR, coronary flow reserve.

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diabetes, tobacco use, and coronary artery disease [5]. However, within the past two decades, HFpEF has emerged as a distinct clinical entity from heart failure with reduced ejection fraction (HFrEF) with increasing incidence, prevalence and unique risk factors [6].

Unlike HFrEF, current therapies for HFpEF are limited and largely directed towards the treatment of symptoms and the prevention of associated conditions [7]. The difficulty in establishing guideline-directed therapies likely stems from the heterogeneity and wide phenotypic spectrum seen in HFpEF [8]. Various cohort studies have identified multiple risk factors, but at present, the underlying mechanisms for the higher prevalence of HFpEF in females are poorly understood [3,4]. Data from the Women's Health Initiative noted that obesity and history of coronary artery disease (CAD) *without* myocardial infarction as HFpEF-specific risk factors [9]. The Prevention of Renal and Vascular End-stage Disease (PREVEND) study found a strong association with female gender, atrial fibrillation (AF), and age with the development of HFpEF [10]. Similarly, the SCREEN-HF study identified body mass index (BMI), hypertension (HTN), diabetes, chronic kidney disease (CKD), anemia, and statin use as risk factors for HFpEF [11]. Within the Framingham Heart Study [4,12], higher BMI, tobacco use, AF, and female gender predicted HFpEF.

Evidence of ischemia with no obstructive coronary disease (INOCA) is increasingly recognized [13] and one-half to two-thirds of women with symptoms of angina who undergo coronary angiography for suspected ischemic heart disease have no obstructive coronary disease [14,15]. Coronary microvascular dysfunction (CMD), or the abnormal dilation and constriction of the small vessels of the heart, is one such cause of INOCA. Studies have suggested that the endothelial dysfunction, decreased nitric oxide bioavailability, and cardiomyocyte injury caused by coronary microvascular dysfunction may contribute to inflammation and myocardial stiffness in patients with HFpEF [16–18].

The National Heart, Lung, and Blood Institute (NHLBI)-sponsored Women's Ischemia Syndrome Evaluation (WISE) study investigated the mechanisms and outcomes of ischemic heart disease in women [19]. One of the key findings of WISE is that women with signs and symptoms of INOCA often have CMD [20] and are at an increased risk for major adverse cardiovascular events (MACE), the most prevalent of which is HF hospitalization [21] confirmed to be predominately HFpEF [22]. A prior WISE analysis found that of 223 women with signs and symptoms of ischemia undergoing coronary angiography, 25 (11%) reported HF hospitalizations. Medical records were available for 13/25 of these patients. Left ventricular ejection fraction (LVEF) was measured in these verified cases and found to be preserved in 12/13 (92%) of these patients [22].

The purpose of this study was to investigate traditional and novel baseline clinical factors prospectively in a cohort of deeply phenotyped women with INOCA followed prospectively long-term for HF hospitalization. Our goal is to better understand potential mechanistic pathways to identify future treatment targets for prevention of HFpEF in women.

2. Materials and methods

The 4-center NHLBI sponsored WISE study enrolled 936 women with signs and symptoms of ischemia undergoing clinically indicated coronary angiography. Protocol details including selection criteria have been previously published [23]. In brief, all women underwent coronary angiography, completed a wide set of testing including blood tests and medical questionnaires, and had annual follow- up for outcomes. Baseline evaluation included collection of demographic information, reproductive history, and history of other medical conditions from 1998 to 2002, as previously detailed [23]. Functional status as assessed by the Duke Activity Status Index (DASI) [24] was obtained per previously published protocols. Institutional review board approval was obtained at all study sites and all patients were provided written informed consent.

Within the WISE cohort, 493 women had no (<20% stenosis) or non-obstructive CAD (<50% stenosis), no prior history of HF, and at least 1-year follow-up data available. A subgroup of 189 women underwent clinically indicated coronary reactivity testing to determine coronary flow reserve (CFR) [20] as previously described [25]. We analyzed baseline characteristics, including clinical history, medications, physical exam, laboratory data, and angiographic data to prospective outcomes with regards to women who developed HF hospitalization during follow-up versus those who did not. Formal records were not available to adjudicate all events, however the large majority of HF hospitalizations were presumed to represent HFpEF as existing HF was an entry exclusion criteria, and analysis from a single WISE site previously validated prospective HF hospitalization in this cohort to be HFpEF (92%) [22].

2.1. Statistical analysis

Demographic and clinical characteristics were summarized using mean ± standard deviation for continuous variables or percentages for categorical variables. Differences between categorical and continuous baseline variables in women who had HF hospitalization and those who did not were analyzed using log rank tests. Log transformations were made for several biomarkers where the distributions were skewed. Univariate and multivariate analyses assessing the hazard ratio for time-to- HF hospitalization were performed using Cox proportional hazard models. Multivariable Cox proportional hazards regressions were adjusted based on univariate analyses for age, HTN, DM, tobacco use, and statin use given the statistically significant differences seen between groups for these variables.

The proportional hazards assumption was evaluated using Schoenfeld residuals for rank transformed event times. Statistical tests were performed using a significance level of 0.05. All analyses were done using SAS version 9.4 (SAS Institute, Cary, NC).

3. Results

During a median follow-up of 6-years, 18 out of the 493 (3.7%) women were hospitalized for HF. Baseline demographics pertinent to our study are summarized in Table 1. Women with HF had a significantly higher rate of diabetes mellitus (DM) and tobacco use as assessed by number of cigarettes per day. The presence of AF at baseline was not

Table 1
Baseline characteristics.

	No HF (n = 475)	HF (n = 18)	Log rank p-value
Age	55 ± 11	57 ± 8	0.63
Caucasian	83%	83%	0.84
Total Cholesterol (mg/dL)	212 ± 49	206 ± 44	0.61
HDL-C (mg/dL)	53.4 ± 14.5	51.5 ± 21.2	0.43
SBP (mmHg)	135 ± 22	145 ± 19	0.06
DBP (mmHg)	77 ± 12	82 ± 9	0.11
HTN	53%	50%	0.79
DM	14%	33%	**0.02**
Cigarettes per day	18 ± 14	29 ± 18	**0.02**
BMI	30 ± 7	33 ± 8	0.07
CKD	2%	11%	0.02
Non-obstructive CAD	40%	61%	0.08
Statin Use	18%	22%	0.56
Atrial Fibrillation	0.42%	0%	0.81
HRT Use	44%	33%	0.18
Postmenopausal	69%	100%	**0.01**
DHEA-S (log μg/dL)	64.1 ± 59.8	43.7 ± 35.7	0.24
Estradiol (log pg/mL)	42.6 ± 49.8	26.3 ± 25.9	0.12
Progesterone (log ng/mL)	0.83 ± 2.44	0.19 ± 0.08	**0.02**
Testosterone (log ng/dL)	26.1 ± 14.5	23.9 ± 14.1	0.32
Number of Pregnancies	3.5 ± 2	4.8 ± 2.1	**0.01**

BMI = body mass index; CAD = coronary artery disease; CKD = chronic kidney disease; DBP = diastolic blood pressure; DM = diabetes mellitus; HDL-C = high density lipoprotein cholesterol; HF = heart failure; HTN = hypertension; SBP = systolic blood pressure.
Statistically significant; p<0.05

associated with the development of HF. Univariate analysis of clinical variables using an unadjusted Cox proportional hazard model for time-to-HF hospitalization is summarized in Table 2. Higher number of pregnancies, baseline heart rate, IL-6, and high sensitivity C-reactive protein levels, in addition to CKD and lower serum progesterone levels, predicted HF hospitalization. Similarly, women with low CFR and functional status as measured by DASI were at higher risk for developing HF.

After controlling for traditional HF risk factors including age, DM, HTN, tobacco use, and lack of statin use, factors including higher parity, resting HR and IL-6 levels as well as low CFR, progesterone and functional status remained statistically significant (Central Illustration; Table 3). However, given that progesterone levels decrease after menopause, we compared progesterone levels specifically in menopausal women without HF versus women who developed HF and found that it was no longer a statistically significant predictor ($p = 0.06$).

Among these novel risk factors, a low CFR was the strongest independent factor (HR 3.51, CI: 1.22–10.2, $p = 0.02$). Notably, further evaluation of pregnancy history demonstrated that in multivariable analyses adjusted for baseline differences, women with ≥5 pregnancies comprised a majority of patients who went on to develop HF, as demonstrated in Fig. 1. After controlling for socioeconomic factors such as annual household income (<$35,000 versus ≥$35,000) and education (high school diploma or above), this remained statistically significant (HR: 1.234, CI: 1.014–1.503, $p = 0.036$).

4. Discussion

We report that in women with INOCA, traditional risk factors including diabetes and tobacco use were associated with the development of HF. Additionally, we identified novel independent risk factors including higher parity and IL-6 levels, plus low CFR and poor functional status as unique predictors of HF within our cohort. Notably, a low CFR consistent with CMD was the strongest independent predictor of HF hospitalization.

HFpEF continues to disproportionately impact more women than men, and the mechanism(s) behind this disparity remains to be fully elucidated [4]. There is a growing body of evidence that implicates CMD in the pathogenesis of HFpEF via low-grade inflammation and endothelial dysfunction [18,26]. In our study of only women, traditional risk factors of DM and tobacco use were associated with the development of HF, similar to prior publications [4,9,11,12]. These conditions have been previously implicated in causing a pro-inflammatory state [27–29]. Additionally, elevated levels of inflammatory marker IL-6 was identified as a risk factor, also consistent with prior studies [30,31].

In contrast, atrial fibrillation was not prevalent in our cohort and was not associated with HF development. A prior study that evaluated the temporal relationship of AF and HFpEF found that risk factors for both prevalent and incident AF after HFpEF diagnosis were the presence of diastolic dysfunction, left atrial dilation, and older age [32], suggesting that the adverse cardiac remodeling that occurs in HFpEF may contribute to AF development. While AF and HFpEF share many similar risk factors, the lack of AF in our study may likely due to the fact that the mean age in our cohort is much younger than prior studies [4] and were studied at an earlier disease stage.

Table 2
Univariate analysis of risk factors for predicting HF.

	Hazard ratio	95% Confidence interval	Chi-squared p-value
Age	1.12	0.70–1.79	0.63
Caucasian	0.88	0.26–3.05	0.84
Total Cholesterol	1.00	0.99–1.01	0.61
HDL-C	0.99	0.95–1.02	0.43
SBP	1.23	1.00–1.53	0.06
DBP	1.37	0.93–2.03	0.11
HTN	0.88	0.35–2.23	0.79
DM	3.19	1.19–8.50	**0.02**
Cigarettes per day	1.42	1.05–1.91	**0.02**
BMI	1.05	0.99–1.12	0.08
CKD	5.55	1.26–24.40	**0.02**
Non-obstructive CAD	2.35	0.91–6.06	0.08
Statin Use	1.39	0.46–4.24	0.56
Low CFR	2.86	1.43–7.14	**0.02**
IL-6 (log pg/mL)	2.25	1.11–4.60	**0.03**
hsCRP	1.34	1.03–1.73	**0.03**
HRT Use	0.52	0.20–1.39	0.19
DHEA-S (log μg/dL)	0.87	0.50–1.51	0.62
Estradiol (log pg/mL)	0.69	0.43–1.10	0.12
Progesterone (log ng/dL)	0.35	0.15–0.77	**0.01**
Testosterone (log ng/dL)	0.61	0.23–1.62	0.32
Number of Pregnancies	1.26	1.06–1.49	**0.01**
Resting HR	1.05	1.01–1.08	**0.01**
DASI	1.71	1.10–2.60	**0.02**

Age (HR per 10-years); BMI = body mass index; CAD = coronary artery disease; CFR = coronary flow reserve (HR per 1-unit); CKD = chronic kidney disease; HSCRP = High-sensitivity C-reactive protein (log transformed); DASI = Duke activity status index (HR per 10-decrease); DBP = diastolic blood pressure; DM = diabetes mellitus; HDL-C = high density lipoprotein cholesterol; HR = heart rate; HRT = hormone replacement therapy; HTN = hypertension; IL-6 = Interleukin-6 (log transformed); Pregnancy (HR per pregnancy); SBP = systolic blood pressure.
Statistically significant; p<0.05

Table 3
Multivariate analysis controlling for age, HTN, DM, cigarettes per day and Statin use.

	Hazard ratio	95% Confidence interval	p-Value
CKD	2.16	0.606–7.696	0.23
Low CFR	3.509	1.215–10.204	**0.020**
IL-6	2.624	1.222–5.632	**0.013**
HSCRP	1.414	0.877–2.281	0.155
Progesterone	0.307	0.127–0.744	**0.009**
Number of pregnancies	1.274	1.058–1.534	**0.011**
Resting HR	1.046	1.01–1.082	**0.011**
DASI	1.706	1.071–2.716	**0.025**

CFR: = coronary flow reserve (HR per 1-unit); CKD = chronic kidney disease; HSCRP = C-reactive protein (log transformed); DASI = Duke activity status index (HR per 10-decrease); DM = diabetes mellitus; HR = heart rate; HTN = hypertension; IL-6 = Interleukin-6 (log transformed); Pregnancy (HR per pregnancy); Progesterone (HR per log ng/dL decrease).
Statistically significant; p<0.05

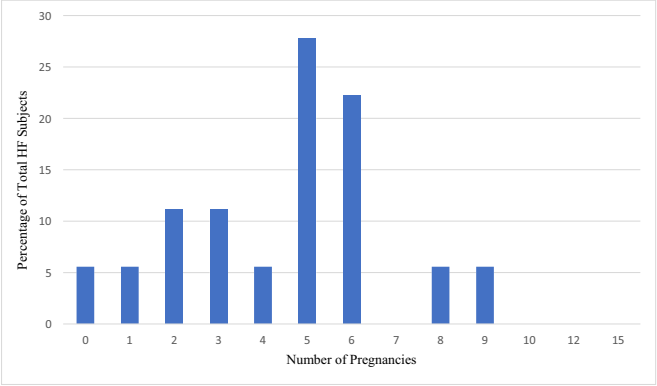

Fig. 1. Women with HF hospitalization stratified by number of pregnancies. Higher parity predicts heart failure in women with signs and symptoms of ischemia and no obstructive coronary artery disease. In multivariate analyses, women with ≥5 pregnancies comprised a majority of patients who went on to develop heart failure ($p = 0.011$).

Interestingly, BMI was not found to be an independent risk predictor, although we observed a trend in the univariate analysis (BMI HR 1.05 [0.99–1.12], $p = 0.08$) in contrast to prior reports [11,12]. There is currently conflicting evidence with regards to the sex-specific effects of BMI and HFpEF, with one study showing that obesity was far more prevalent among men than women with HFpEF [33], and another suggesting the opposite [34]. One study comparing obese and non-obese HFpEF patients found significant physiologic differences including increased plasma volume, greater biventricular remodeling, more right ventricular dysfunction, and impaired pulmonary vasodilation [35], suggesting that obesity- related HFpEF is a separate phenotype, possibly indicative of a more advanced stage than our subjects.

More importantly, within our study, women with decreased functional status at baseline as assessed by DASI were at risk for HF hospitalization. We have previously published data indicating that functional status, rather than BMI or abdominal obesity, was associated with adverse cardiovascular events in women with suspected ischemia [36]. These data suggest that lower levels of physical activity which predict lower functional capacity [37] may contribute to development of HF. Alternatively, given that physical inactivity has been associated with elevated diastolic filling pressures [38], it may be an indicator of preclinical HFpEF, and therefore assessment of functional status may be important for risk prediction and prevention.

Assessment of CMD involves the measurement of coronary flow reserve. Prior studies have demonstrated a relationship between low CFR and HFpEF severity [39,40]. Indeed, in our cohort of women with INOCA, a low CFR was the strongest independent predictor of HF hospitalization. Notably, our prior work observed that less than 20% of observed variability in CFR was explained by traditional and novel cardiac risk factors [41], suggesting that contributors to a low CFR is relatively unknown. A recent prospective study demonstrated CMD diagnosed by CFR was highly prevalent in HFpEF patients [42], and our data further support the hypothesis that CMD may play an important role in the pathophysiology of HF.

Finally, with respect to sex-specific characteristics, we observe for the first time that higher parity independently predicts HF hospitalization in our INOCA women. The mechanism(s) behind this finding is likely multifactorial. Higher parity has been previously associated with the development of metabolic syndrome and cardiovascular disease [43–45]. With specific regard to HFpEF, higher parity is associated with diastolic dysfunction [46], suggesting the hypothesis that repeated pregnancy-related ventricular remodeling of hypertrophy and regression may contribute to increased ventricular fibrosis and stiffness. Animal models have further demonstrated that higher parity appears to facilitate the formation of reactive oxygen species thereby inducing endothelial dysfunction [47]. These data suggest novel sex-specific mechanistic hypotheses for female-specific HF and HFpEF investigation.

4.1. Limitations

Our study included only women with suspected INOCA, and therefore may not be relevant to other populations. Our cohort was free of HF with normal left ventricular ejection fraction at baseline, and thus our prospective HF hospitalization cases likely represent relatively early stage HFpEF and may not be generalizable for more advanced HFpEF. Despite our relatively large deeply phenotyped cohort of women followed for longer-term, the number of HF hospitalizations is relatively small, and thus our analyses may be underpowered for specific risk predictors. Although we could not adjudicate each HF hospitalization in the full cohort, our prior work in a single WISE site confirmed the HF hospitalizations to be new onset HFpEF [22].

5. Conclusions

Our study of deeply phenotyped women with INOCA followed prospectively longer-term identifies both traditional and novel risk factors for HF hospitalization. While further studies are needed to confirm these findings, these traditional and novel risk factors support a pro-inflammatory environment and CMD contributing to progression to HFpEF. A female-specific factor of higher parity suggests the hypothesis that structural pregnancy-related recurrent ventricular remodeling may also contribute. Future studies should aim to elucidate the mechanisms by which low CFR and HFpEF occurs, and whether both invasive and non-invasive CFR could be utilized successfully as a surrogate disease marker for HFpEF. The combination of traditional, novel, and sex-specific risk factors identified in our study provides an initial platform for development of risk predictor tools for identifying high-risk women as well as treatment targets for possible interventions to slow or prevent the development of HFpEF.

Declaration of competing interest

Dr. C. Noel Bairey Merz serves as Board of Director for iRhythm, fees paid through CSMC from Abbott Diagnostics and Sanofi. Dr. Janet Wei reports honoraria paid to CSMC from Abbott Diagnostics. Dr. Vera Bittner serves on the Advisory Board for Pfizer, is senior guest editor for Circulation and Editor in Chief of ACCSAP. Dr. Bittner also reports fees paid to UAB from Sanofi, Astra Zeneca, Dalcor, Esperion, Novartis and Amgen.

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