International Journal of Cardiology 402 (2024) 131832

Contents lists available at ScienceDirect

International Journal of Cardiology

journal homepage: www.elsevier.com/locate/ijcard

Impact of sex on the assessment of the microvascular resistance reserve

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ARTICLE INFO

Keywords:
CMD
Sex differences
MRR
CFR
Chronic coronary syndromes

ABSTRACT

Background: The microvascular resistance reserve (MRR) is an innovative index to assess the vasodilatory capacity of the coronary circulation while accounting for the presence of concomitant epicardial disease. The MRR has shown to be a valuable diagnostic and prognostic tool in the general coronary artery disease (CAD) population. However, considering the fundamental aspects of its assessment and the unique hemodynamic characteristics of women, it is crucial to provide additional considerations for evaluating the MRR specifically in women.

Aim: The aim of this study was to assess the diagnostic and prognostic applicability of the MRR in women and assess the potential differences across different sexes.

Methods: From the ILIAS Registry, we enrolled all patients with a stable indication for invasive coronary angiography, ensuring complete physiological and follow-up data. We analyzed the diagnostic value by comparing

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https://doi.org/10.1016/j.ijcard.2024.131832
Received 15 September 2023; Received in revised form 29 December 2023; Accepted 1 February 2024
Available online 3 February 2024

differences between sexes and evaluated the prognostic value of the MRR specifically in women, comparing it to that in men.
Results: A total of 1494 patients were included of which 26% were women. The correlation between MRR and CFR was good and similar between women ($r = 0.80$, $p < 0.005$) and men ($r = 0.81$, $p < 0.005$). The MRR was an independent and important predictor of MACE in both women (HR 0.67, 0.47–0.96, $p = 0.027$) and men (HR 0.84, 0.74–0.95, $p = 0.007$). The optimal cut-off value for MRR in women was 2.8 and 3.2 in men. An abnormal MRR similarly predicted MACE at 5-year follow-up in both women and men.
Conclusion: The MRR seems to be equally applicable in both women and men with stable coronary artery disease.

1. Introduction

The vasodilator capacity of the coronary circulation plays a crucial role in the development of myocardial ischemia and its clinical sequelae [1]. It is increasingly recognized that an abnormal vasodilator capacity portends important clinical and prognostic value in patients with chronic coronary syndromes (CCS), even in the absence of epicardial coronary stenosis [2]. Consequently, the diagnostic work-up of these patients is more frequently geared towards the assessment of the vasodilator capacity as part of comprehensive evaluation of chest pain syndromes.

Recently, the microvascular resistance reserve (MRR) was introduced as a novel index to assess the vasodilator capacity of the coronary circulation [3]. The MRR corrects the traditional index of coronary flow reserve (CFR) for the presence of concomitant epicardial disease and the hemodynamic effects of the administration of potent vasodilators. By this capacity, MRR allows assessment of microvascular vasodilator function in the presence of epicardial coronary stenosis, and addresses intrinsic limitations of CFR while providing an index that can be derived by either the bolus or continuous thermodilution and Doppler-flow technique.

Following these theoretical advantages, MRR was documented to add diagnostic and prognostic value over CFR for the assessment of microvascular vasodilator dysfunction [4]. However, the hemodynamic characteristics of women merit specific consideration. In women, the fractional flow reserve (FFR) is generally higher, and the vasodilatory capacity (CFR) is generally lower [5]. As such, correcting the CFR for FFR might affect the applicability of MRR specifically in women. Unfortunately, limited data on the sex-specific considerations in the assessment of the MRR exists.

The aim of this study was to assess the diagnostic and prognostic applicability of the MRR in women and assess the potential differences across different sexes.

2. Methods

2.1. Study population

The ILIAS (Inclusive Invasive Physiological Assessment in Angina Syndromes) registry is a retrospective global, multi-center initiative pooling vessel-level coronary pressure and flow data, as well as vessel-level clinical outcome data. All studies included were approved by local medical ethics committees. The registry is composed of 20 expert medical institutes from the Netherlands, Korea, Japan, Spain, Denmark, Italy, and the United States of America. All data were gathered in local study protocols between 1998 and 2018. Patients who underwent clinically indicated invasive coronary angiography and comprehensive invasive physiological assessment of at least one native coronary artery were enrolled in the registry. Patients with hemodynamic instability, significant valvular pathology and prior coronary artery bypass graft surgery, as well as patients with a clinical presentation of acute coronary syndromes upon the index procedure, were excluded. Individual vessel-level data for pooled analysis were collected using standardized spreadsheets and a fully compliant cloud-based clinical data platform (Castor EDC, Amsterdam, The Netherlands). Standardized definitions were used for all variables. ILIAS Registry was registered at Clinicaltrials.gov (ClinicalTrials.gov Identifier: NCT04485234).

2.2. Coronary angiography and physiological assessment

Coronary angiography and intracoronary physiological assessments were performed in all institutions using standard techniques. After diagnostic coronary angiography, invasive physiological indices were measured using either separate pressure- (PressureWire, RADI medical – now Abbott Vascular, St Paul, MN) and Doppler velocity sensor-equipped coronary guidewires (FloWire, Endosonics – now Philips-Volcano, San Diego, CA), dual pressure- and Doppler flow velocity-equipped guide wire (ComboWire, Volcano Corp. – now Philips-Volcano, San Diego, CA), or a temperature-sensitive pressure sensor-equipped guide wire (PressureWire, St Jude Medical- now Abbott Vascular, St. Paul, MN) using routine techniques. Intracoronary nitrate (100 or 200 μg) was administered before physiologic measurements. Using the Doppler velocity technique, baseline (bAPV) and hyperemic average peak flow velocities (hAPV) were labelled baseline and hyperemic flow, respectively. Using the bolus coronary thermodilution technique, resting and hyperemic thermodilution curves were obtained in triplicate using three injections (4 mL each) of room-temperature saline, and the inverse of the average basal (bTmn) and hyperemic mean transit times (hTmn) was labelled baseline and hyperemic flow, respectively. Hyperemia was induced by intravenous infusion of adenosine (140 μg/kg per min) or adenosine triphosphate (ATP) (150 μg/kg per min) through a peripheral or central vein, intracoronary bolus injection of adenosine (20-200μg), or intracoronary bolus injection of nicorandil (3 mg), according to local standards [6].

2.3. Derivation of MRR

MRR was derived based on the theoretical framework by De Bruyne et al. [3] The formula used in this study is a product of CFR and FFR with correction for the impact of changes in hemodynamics from non-hyperemic to hyperemic conditions, as follows:

$$MRR = (CFR/FFR) \times \left(Pa_{rest}/Pa_{hyper}\right)$$

Where CFR indicates coronary flow reserve, the ratio of coronary flow (velocity) at maximal hyperemia to coronary flow (velocity) at non-hyperemic conditions, FFR indicates fractional flow reserve (calculated as the ratio of distal coronary pressure to aortic pressure at maximal hyperemia) and Pa, rest and Pa, hyper indicate aortic pressure during non-hyperemic conditions and maximal hyperemia, respectively. Herewith, MRR corrects the vasodilator reserve capacity of the coronary circulation (expressed by CFR) for the impact of epicardial coronary artery disease severity (expressed by FFR), and the impact of pharmacological vasodilatation on perfusion pressure (expressed by the ratio of resting to hyperemic aortic pressure).

2.4. Treatment and clinical follow-up

PCI was performed according to clinical practice guidelines at the time of the procedure. However, final decisions regarding revascularization were at the discretion of the operator. Clinical follow-up was

obtained at outpatient clinic visits or by telephone contact to ascertain the occurrence of major adverse cardiac events (MACE). MACE was defined as the composite of all-cause death, acute myocardial infarction of the target vessel, and clinically driven (urgent) revascularization by means of coronary artery bypass or percutaneous coronary intervention (PCI) [7]. All patient-reported events were verified by evaluating hospital records or contacting the treating cardiologist or general practitioner.

2.5. Statistical analysis

Data were analyzed on a per-patient basis. Normality and homogeneity of the variances were tested using Shapiro-Wilk and Levene tests. Continuous variables are presented as mean ± SD or median (first, third quartile [Q1, Q3]) and were compared with the student *t*-test or Mann-Whitney *U* test. Categorical variables are presented as counts and percentages and were compared using Fisher exact test. Receiver operating characteristic (ROC) curve analysis was performed to determine the diagnostic accuracy of the MRR in women. For this analysis, the presence of reversible perfusion abnormalities during non-invasive stress testing prior to coronary angiography was used as the standard of reference. Additionally, time-dependent ROC analysis was performed to derive the optimal MRR cut-off value for MACE in women and men. The optimal cut-off value was determined using the Liu method [8].

We subsequently evaluated the association of MRR as a continuous variable with MACE at 5-year follow-up. Survival analyses were performed based on time-to-first-event analyses. The hazard ratio for MACE per unit increase of MRR and CFR was calculated with the use of a Cox proportional hazards model. All models were adjusted for the effect of relevant clinical and angiographic characteristics ($P < 0.1$ for inclusion). All clinical and angiographic characteristics (Table 1) were considered as covariates. A *p*-value <0.05 (2-sided) was considered statistically significant. Stata version 14.0 (StataCorp, College Station, Texas) software package was used for calculations.

3. Results

3.1. Baseline characteristics

A total of 1836 patients with chronic coronary syndrome and a clinical indication for invasive coronary angiography in whom complete physiological and follow-up data were available, were included from the ILIAS registry. The key baseline characteristics of the whole study population and according to sex are depicted in Table 1. A total of 477 (26%) women were included in the final study population. Women were generally older (65 ± 10 vs 63 ± 10 years, $p < 0.005$) and had a higher prevalence of a positive family predisposition for cardiovascular disease (39 ± 5% vs 30 ± 3%, $p < 0.005$). Male patients more frequently were active smokers, or presented with a history of previous myocardial infarction or PCI.

Table 1
Baseline characteristics according to sex.

Patients	Total (*N* = 1836)	Women (*N* = 477)	Men (*N* = 1359)	P-value
Age, y	64 (63–64)	65 (64–66)	63 (62–64)	<0.005
Hypertension, %	59 (56–63)	62 (57–67)	58 (55–61)	0.152
Diabetes, %	28 (25–31)	25 (21–29)	29 (27–32)	0.090
Hyperlypidemia, %	66 (63–69)	64 (59–68)	67 (64–69)	0.373
Positive family history, %	32 (29–36)	39 (35–44)	30 (27–32)	<0.005
Current smoker, %	21 (19–24)	16 (13–19)	24 (21–26)	<0.005
Previous MI, %	19 (17–22)	13 (10–16)	22 (20–25)	<0.005
Previous PCI, %	28 (25–31)	18 (15–22)	31 (29–34)	<0.005

3.2. Characteristic of MRR and CFR according to sex

Baseline angiographic and physiological data according to sex are depicted in Table 2. The LAD was the most frequently evaluated vessel (59%). The percent diameter stenosis was slightly, albeit statistically significant, lower in women compared to men (49 ± 2% vs 52 ± 1%, $p = 0.009$). Mean FFR was higher in women compared to men (0.83 ± 0.11 vs 0.81 ± 0.13%, $p = 0.030$) and both MRR and CFR were lower in women compared to men (3.2 ± 1.1 vs 3.5 ± 1.4, $p < 0.005$ for MRR, 2.5 ± 1.2 vs 2.7 ± 1.0, $p < 0.005$ for CFR). Fig. 1 shows the correlation between CFR and MRR and its relationship with FFR. There was a strong correlation between MRR and CFR in both women ($r = 0.80$, $p < 0.005$) and men ($r = 0.81$, $p < 0.005$). The difference in CFR and MRR was equally related to decreasing FFR values in women compared to men (Correlation coefficient of −2.57 for women vs −2.93 for men, $p = 0.155$).

Univariate regression analysis indicated that age and minimal lumen diameter were significantly associated with MRR in women. In men, also BMI, the presence of hypertension or diabetes, and the percent diameter stenosis were found to be associated with MRR. Multivariate analysis including these confounders showed that only age and the minimal lumen diameter were significantly correlated with the MRR in both women and men. There was no statistical difference between the two prediction models stratified by sex ($p = 0.675$).

3.3. MRR threshold analysis

Time dependent ROC-analysis were performed to assess the discriminative characteristics of MRR for the occurrence of MACE during 5-year follow-up period (Fig. 2). The AUC showed a limited discriminative value of MRR for the occurrence of MACE and was similar between women and men (AUC 0.64 vs 0.59, $p = 0.06$ for the

Table 2
Angiographic and physiological characteristics.

Interrogated vessel	Total	Women	Men	P-value
LAD, %	59 (57–62)	64 (61–68)	57 (56–60)	<0.005
LCX, %	18 (16–20)	16 (13–19)	19 (17–21)	0.079
RCA, %	22 (20–24)	20 (17–23)	23 (22–25)	0.039
QCA Analysis				
Diameter stenosis, %	51 (50–53)	49 (48–51)	52 (51–53)	0.009
Minimal Lumen Diameter,	1.59 (1.54–1.64)	1.62 (1.55–1.70)	1.57 (1.53–1.61)	0.293
Lesion Length, mm	15.1 (14.1–16.1)	14.1 (12.7–15.5)	15.5 (14.7–16.3)	0.098
Physiological Assessment				
Baseline				
Aortic Pressure	98 (96–99)	101 (99–102)	96 (95–97)	<0.005
Distal Pressure	90 (89–91)	93 (92–95)	89 (88–90)	<0.005
Tmn	0.74 (0.71–0.78)	0.64 (0.59–0.69)	0.78 (0.75–0.82)	<0.005
APV	17 (16–18)	17 (17–18)	17 (16–18)	0.780
Hyperemic				
Aortic Pressure	90 (89–91)	93 (91–95)	89 (88–90)	<0.005
Distal Pressure	74 (73–76)	78 (76–79)	73 (72–74)	<0.005
Tmn	0.29 (0.27–0.31)	0.27 (0.25–0.29)	0.30 (0.29–0.32)	0.005
APV	38 (36–39)	37 (35–39)	38 (37–39)	0.488
Physiological indices				
Resting Pd/Pa	0.92 (0.91–0.93)	0.92 (0.91–0.93)	0.92 (0.92–0.93)	0.819
FFR	0.82 (0.81–0.83)	0.83 (0.82–0.84)	0.81 (0.81–0.82)	0.030
HMR	2.3 (2.2–2.4)	2.4 (2.2–2.5)	2.2 (2.1–2.3)	0.135
IMR	21 (19–22)	20 (19–22)	21 (20–22)	0.811
CFR	2.6 (2.5–2.7)	2.5 (2.4–2.6)	2.7 (2.6–2.7)	<0.005
MRR	3.4 (3.3–3.5)	3.2 (3.1–3.3)	3.5 (3.3–3.5)	<0.005

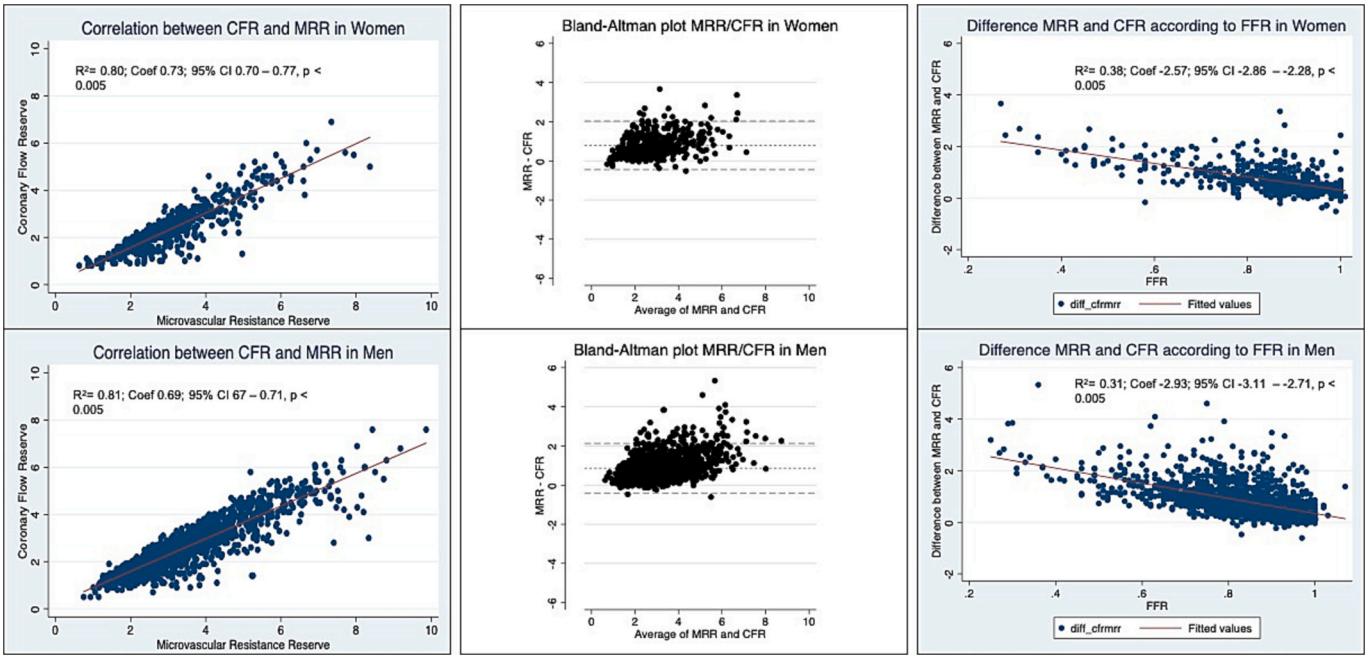


Fig. 1. Relationship between Coronary Flow Reserve (CFR) and Microvascular Resistance Reserve (MRR) in women (above) and men (below). The relationship is described by a scatterplot of the correlation between CFR and MRR (left panel), the corresponding bland-altman plot (middle panel) and an adjusted bland-altman plot for the difference between CFR and MRR according to the fractional flow reserve (FFR) (right panel).

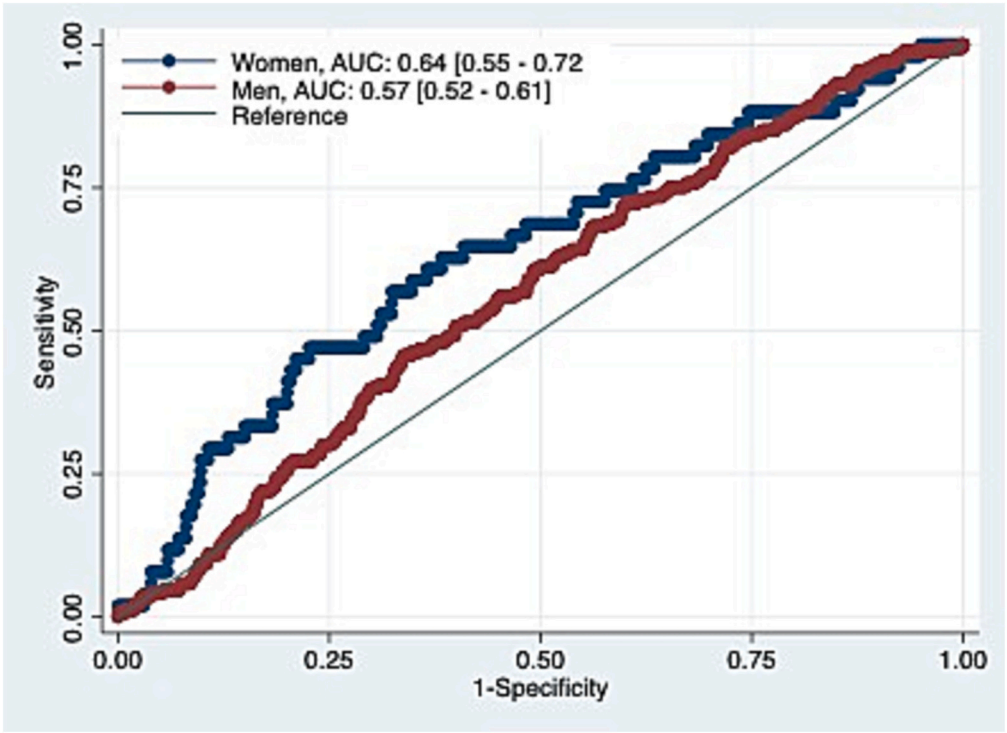


Fig. 2. Time dependent Receiver Operating Characteristics (ROC) curve for association of the MRR and the occurence of MACE among men (red line) and women (blue line).

difference). The optimal cut-off value for the occurrence of MACE in women was 2.8 and in men 3.2.

3.4. Prognostic value of MRR in women and comparison with men

The median follow-up period was 3.7 years (Q1,Q3; 2.0,5.1) for women, and 2.9 years (Q1,Q3; 1.9, 5.1) for men. A total of 9.2% women experienced at least one MACE, versus 11.7% of men. Univariate Cox regression analysis indicated that in women, age, diabetes mellitus, hypertension, a family predisposition for cardiovascular disease, previous myocardial infarction were significant confounders for MACE. After correction for these confounders, the MRR as a continuous variable was

significantly associated with MACE at 5-year follow-up (HR 0.67, 0.47–0.96, $p = 0.027$). The same analysis showed that in men the MRR as a continuous variable was also independently and significantly associated with MACE at 5-year follow-up (HR 0.84, 0.74–0.95, $p = 0.007$).

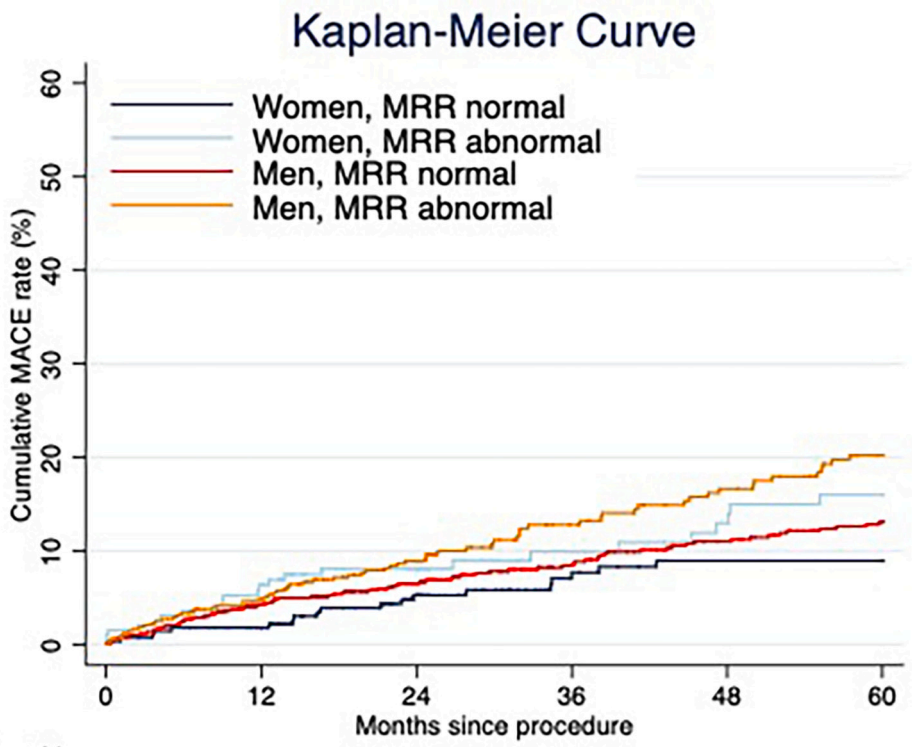
Using a cut-off value of 3.0 and after the correction of significant confounders, abnormal MRR was unequivocally associated with an increased risk for MACE at 5-year follow-up in women (HR 1.9, 95% CI 1.1–3.4, $p = 0.023$). A sensitivity analysis with the optimal cut-off value for women did not alter the conclusions significantly (data not shown). Similarly, for men an abnormal MRR based on a cut-off value of 3.0 showed an increased risk for MACE at 5-year follow-up (HR 2.3, 95% CI 1.3–3.7, $p = 0.002$) and applying the optimal cut-value for men did not alter the conclusions. Fig. 3 shows the cumulative incidence of MACE according to normal and abnormal MRR, based on the cut-off value of 3.0 and according to sex. There was no significant difference in the risk of MACE between sexes ($p = 0.430$).

4. Discussion

To our knowledge, this study is the first to assess the applicability of MRR specifically in female patients with stable angina, and to assess the impact of sex on its diagnostic and prognostic value. The most important findings were: (1) there was no considerable difference in the diagnostic characteristics of MRR between women and men, (2) MRR portends important prognostic value in both men and women. As such, this study underlines the potential of the MRR as an index of the vasodilator capacity of the coronary microcirculation, despite its theoretical limitations in women.

4.1. Coronary hemodynamics and sex differences: implications for the MRR

Sex differences in the assessment of the coronary hemodynamics in patients with anginal symptoms are increasingly recognized. Women presenting with anginal symptoms present at older age, have smaller



Number at risk						
Women, MRR normal	283	256	198	149	142	134
Women, MRR abnormal	194	168	131	92	86	83
Men, MRR normal	876	765	581	437	395	349
Men, MRR abnormal	483	431	316	209	192	171

Group	HR	95% CI	P-value	P-value*
Women, MRR normal	Ref.	Ref.	Ref.	
Women, MRR abnormal	1.9	1.1 – 3.4	0.047	Ref.
Men, MRR normal	Ref.	Ref.	Ref.	
Men, MRR abnormal	2.3	1.3 – 3.7	0.002	0.430

Fig. 3. Kaplan-Meier Curve for the occurence of major adverse cardiac events (MACE) among men and women with normal or abnormal microvascular resistance reserve (MRR) values (cut-off: 3.0) during a 5-year follow-up period. Hazard ratios (HR) derived by multivariate cox regression analysis. *P-value for the difference between men with abnormal MRR versus women with abnormal MRR.

vessel size and a generally lower vasodilator capacity expressed by lower CFR values, all of which impact the physiological assessment of the coronary circulation [9]. Consequently, for comparable angiographic stenosis severity, women have higher FFR values compared to men [10]. Hence, using the MRR, basically correcting the CFR for FFR, could theoretically impact the identification of coronary microvascular dysfunction in women compared to men. In addition, we found that age and minimal lumen diameter significantly impact the MRR value in both women and men.

Despite these considerations, we document that the diagnostic characteristics of MRR are similar between women and men. MRR, although generally lower in women, showed a similar agreement with CFR in both sexes ($r = 0.80$ for women, $r = 0.81$ for men) and comparable with the previously reported agreement in the overall CCS population [4]. The time dependent ROC-analysis showed a similar, but limited discriminative function for MACE at 5-year follow-up. The optimal cut-off value for MACE at 5-year follow-up was 2.8 in women and 3.2 in men. These findings are in line with previously reported cut-off value analysis in the general population (3.0), and with a recent publication by de Vos et al. whom reported that an MRR above 2.7 rules out microvascular dysfunction defined by concordant normal CFR and IMR in an ANOCA population dominated by women [11]. Additional prospective studies are warranted to confirm these findings.

4.2. Prognostic value of MRR in female patients

While the exact threshold defining abnormal vasodilatory capacity remains debated, the clinical and prognostic value of a reduced vasodilatory capacity is undisputed. The traditional indices of an abnormal vasodilatory capacity, CFR and indices of minimal microvascular resistance, have shown to portend prognostic value. However, both indices are susceptible of their own limitations. The MRR, theoretically addressing these limitations, was found to be a robust and prognostically valuable index in the general CCS population [4]. The current study addresses the theoretical concerns of the MRR in women and affirms its applicability in both women and men. The MRR as a continuous variable was independently and significantly associated with an increased risk of MACE in female patients (HR 0.67, 0.47–0.96, $p = 0.027$). An abnormal MRR in women based on the general cut-off value of 3.0 had a similar increased risk of MACE as it did in men (HR 1.9 vs 2.3, $p = 0.430$). Using the optimal cut-off value of 2.8 for women and 3.2 for men did not alter the conclusions. As such, based on the prognostic value, it can be assumed that the MRR is equally applicable in both women and men.

4.3. Limitations

First, despite the length of follow-up and the large number of included patients, the results should be interpreted considering the basic limitations of a retrospective registry. Second, the number of female patients is the current study is limited compared to the number of male patients. Although this an observational study and thereby a presentation of the contemporary clinical practice, these results should be interpreted with the historical underrepresentation of female patients diagnosed with coronary artery disease. Third, although the MRR is an index that can be derived by any robust flow-measuring technique, uniform application of continuous flow, as used in the initial derivation of MRR, may further enhance its diagnostic and prognostic value considering the operator-independent nature of this absolute flow measurements.

5. Conclusion

This study is the first to specifically assess the diagnostic and prognostic characteristics of the MRR in female patients. Despite the theoretical limitations of the MRR in female patients, there was no considerable difference in the diagnostic characteristics and the prognostic value of the MRR across sexes. As such, the MRR seems to be equally applicable in both women and men with CCS and could enhance the diagnostic yield of CMD interrogation in contemporary clinical practice. Future studies are warranted to address the potential of sex-specific decision-making thresholds using MRR.

CRediT authorship contribution statement

Coen K.M. Boerhout: Conceptualization, Data curation, Formal analysis, Project administration, Writing – original draft, Writing – review & editing. **C.E.M. Vink:** Writing – review & editing. **Joo Myung Lee:** Writing – review & editing. **Guus A. de Waard:** Writing – review & editing. **Hernan Mejia-Renteria:** Writing – review & editing. **Seung Hun Lee:** Writing – review & editing. **Ji-Hyun Jung:** Writing – review & editing. **Masahiro Hoshino:** Writing – review & editing. **Mauro Echavarria-Pinto:** Writing – review & editing. **Martijn Meuwissen:** Writing – review & editing. **Hitoshi Matsuo:** Writing – review & editing. **Maribel Madera-Cambero:** Writing – review & editing. **Ashkan Eftekhari:** Writing – review & editing. **Mohamed A. Effat:** Writing – review & editing. **Tadashi Murai:** Writing – review & editing. **Koen Marques:** Writing – review & editing. **Joon-Hyung Doh:** Writing – review & editing. **Evald H. Christiansen:** Writing – review & editing. **Rupak Banerjee:** Writing – review & editing. **Chang-Wook Nam:** Writing – review & editing. **Giampaolo Niccoli:** Writing – review & editing. **Masafumi Nakayama:** Writing – review & editing. **Nobuhiro Tanaka:** Writing – review & editing. **Eun-Seok Shin:** Writing – review & editing. **Yolande Appelman:** Writing – review & editing. **Marcel A.M. Beijk:** Writing – review & editing. **Niels van Royen:** Writing – review & editing. **Steven A.J. Chamuleau:** Writing – review & editing. **Paul Knaapen:** Writing – review & editing. **Javier Escaned:** Writing – review & editing. **Tsunekazu Kakuta:** Writing – review & editing. **Bon Kwon Koo:** Writing – review & editing. **Jan J. Piek:** Writing – review & editing. **Tim P. van de Hoef:** Writing – review & editing.

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