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Chest pain in the absence of obstructive coronary artery disease☆ A critical review of current concepts focusing on sex specificity, microcirculatory function, and clinical implications

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ABSTRACT

Patients presenting with chest pain suggestive of coronary artery disease (CAD) who at coronary arteriography appear to be free of obstructive disease have presented a diagnostic and therapeutic challenge since the 1970's. Studies in female patient populations have suggested that this is predominantly a women's syndrome usually caused by microvascular endothelial dependent and independent dysfunction. A critical review of the literature focusing on studies including both women and men revealed that apart from a higher incidence of this syndrome in women there are no clinical relevant differences between both sexes. In women a lower coronary flow reserve has been reported but this appears to be mainly due to a higher basal flow. Important questions with regard to the clinical implications of microvascular dysfunction have yet to be resolved in studies involving women as well as men in which a distinction is made between patients with normal coronary arteries and those with nonobstructive disease.

1. Introduction

Towards the end of the 20th century several health studies in women were started. In some studies, such as the Women's Health Initiative and the Nurses' Health Studies, the long underrated subject of cardiovascular diseases in women were part of a broader spectrum of female health issues. Other studies were specifically designed to gain more insight in gender related aspects of cardiovascular disease in women, such as the Heart and Estrogen/progestin Replacement Study (HERS) [1] and the Women's Ischemia Syndrome Evaluation Study (WISE) [2]. These studies have generated a host of data that have greatly enhanced our understanding of cardiovascular disease in women, however, since these studies included no men they allow no conclusions about the influence of sex in topics that are not inherently of a female nature.

A subject that has practical consequences concerns the large group of female patients with chest pain and normal or near normal coronary arteriogram (CAG). This was recognized in the WISE study which included as one of three major objectives: "to explore mechanisms for symptoms and myocardial ischemia in the absence of epicardial coronary artery stenoses" [2]. The results of WISE have contributed to the currently widespread perception that women with chest pain and angiographically normal or near normal coronary arteries, in contrast with men, frequently have microvascular or endothelial dysfunction. However, without questioning the existence of these disorders, it may be doubted whether they are predominantly 'women's diseases' and a frequent cause of chest pain associated with adverse prognostic consequences. There is a risk that women with chest pain in the absence of coronary artery obstructions are too easily supposed to have microvascular dysfunction. This could falsely confirm their fear of having a serious cardiac condition which may cause anxiety and lead to repeated hospitalizations and catheterizations.

To contribute to a balanced assessment of the clinical implications of this syndrome we critically reviewed the literature, focusing on the reported higher incidence and more serious consequences in women compared to men.

Abbreviations: Ach, acetylcholine; CAC, coronary artery calcium; CBF, coronary blood flow; CFR, coronary flow reserve; CMD, coronary microvascular dysfunction; CVR, coronary vascular resistance; FFR, fractional flow reserve; ICA, invasive coronary angiography; IMR, index of microcirculatory resistance; LA, luminal area; MBF, myocardial blood flow; Pd, mean distal coronary pressure; QCA, quantitative coronary angiography; RPP, rate pressure product; Tmn, mean transit time.

☆ All authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

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2. Evolution of insights into the syndrome of chest pain in the absence of obstructive coronary artery disease

Soon after the introduction of coronary arteriography in the early 1960's [3] it became apparent that a considerable proportion of patients with typical or atypical angina pectoris or other evidence or cardiac ischemia had angiographically normal or near normal coronary arteries [4,5]. Because of its unknown origin this 'syndrome' became known as 'syndrome X'. Patients with proven spasm of the epicardial coronary arteries or myocardial bridging and patients with aortic stenosis were generally excluded but some investigators used the term 'syndrome X' to classify all other patients with chest pain in the absence of obstructive coronary artery disease (CAD) whereas others included only patients with typical angina pectoris plus objective evidence of myocardial ischemia. Later most investigators required in addition a positive exercise test and various exclusion criteria, such as the presence of diabetes mellitus or renal failure, were used by different investigators [6].

Several causes of syndrome X have been postulated but eventually it has become generally accepted that the symptoms, if they are due to cardiac ischemia, must be related to impairment of the coronary microcirculation. Therefore, in lieu of 'syndrome X' Cannon and Epstein in 1988 introduced the term 'microvascular angina' [7]. At present many physicians use the latter term although the definitions still vary and it has not been proven that all cases have the same underlying mechanism [8,9].

3. Physiology and diagnosis of microvascular and endothelial dysfunction

In the last decade several excellent reviews on the coronary microcirculation and the role of the endothelium have been published [8,10–15]. In this paragraph we briefly review mechanisms involved in microvascular dysfunction and commonly used diagnostic parameters to allow a better understanding of the merits and limitations of published studies.

To adjust for changes in perfusion pressure and to comply with changing metabolic demands the coronary flow must be regulated. Since the epicardial coronary arteries are mainly conduits with very low resistance, the microcirculation is responsible for regulating coronary flow which is achieved by constriction and dilatation of 'resistance vessels' consisting of pre-arterioles ('small resistance arteries') and arterioles. The large and medium sized arterioles mainly respond to flow and pressure, a process that is in part endothelium dependent. The small arterioles are modulated by metabolic demand [12]. Therefore, to achieve maximal coronary flow in clinical investigations administration of a vasodilator of endothelium dependent vessels (such as nitroglycerin) and a vasodilator of endothelium independent vessels (such as adenosine or dipyramidol) is required.

Since the diameter of the vessels of the microcirculation is <400 μm the microcirculation cannot be imaged and its integrity can only be assessed by examining its function [16]. A frequently used functional parameter is the coronary flow reserve (CFR) which is the quotient of maximal (hyperemic) coronary flow divided by basal coronary flow. To account for inter-individual differences in metabolic demand basal flow is often corrected for the rate-pressure product [17,18]. At catheterization CFR can be assessed by either volumetric determination of coronary flow with thermodilution or flow velocity measurement using a Doppler catheter [17–21]. Flow velocity measurements have also been made noninvasively by transthoracic echo-Doppler of the left anterior descending artery [22].

A significant limitation of CFR is that it does not reveal whether a low CFR, usually defined as <2.5, is due to a low hyperemic flow or a high basal flow. Furthermore, CFR is in part dependent on the perfusion (aortic) pressure (Fig. 1 in online Supplementary material).

The index of microcirculatory resistance (IMR) introduced by Fearon et al. does account for perfusion pressure and is defined as the mean distal coronary pressure (P_d) minus venous pressure divided by flow [19,20]. The index reportedly has superior reproducibility and is less influenced by hemodynamic perturbations than CFR in the evaluation of microvascular angina [20,23–25].

Coronary flow may non-invasively be determined by positron emission tomography (PET). This appears to be the most accurate method to quantitate coronary flow volumes per unit of mass [10,26,27] but this modality is not widely available and entails a significant amount of radiation. Cardiac resonance imaging is a non-invasive technique that appears to have promise in the diagnosis of microvascular coronary disease and additionally has the potential to distinguish sub-endocardial from sub-epicardial perfusion [28,29].

To assess coronary endothelial function at catheterization at present mostly intracoronary infusion of acetylcholine (Ach) is used. Ach releases NO from an intact endothelium which causes vasodilation but it also has a vasoconstrictor effect on the smooth muscle cells of the vessel wall. In the presence of an intact endothelium the net effect is vasodilation of epicardial vessels as well as endothelium dependent vessels of the microcirculation whereas in the presence of a dysfunctional endothelium no dilatation or vasoconstriction results. The effect is measurable by hemodynamic parameters but also the occurrence of angina pectoris and ischemic ECG shifts in the absence of spasm of the epicardial arteries has been considered evidence of microvascular involvement [30].

4. Etiology of microvascular and endothelial dysfunction

Microvascular dysfunction may be caused by structural anatomical changes of the arterioles, formerly called 'small vessel disease', or endothelial dysfunction. It has also been suggested that microvascular spasm and not just reduced vasodilator capacity may cause microvascular angina pectoris [33,34] which also explains the occurrence of signs of ischemia at Ach tests [30].

Probably the most frequent cause of structural changes is systemic hypertension which for a long time has been shown to induce thickening of the media of coronary arterioles and to reduce the microcirculatory vasodilator capacity [35–37]. Another common cause that is held responsible for structural and functional changes of the coronary microcirculation is diabetes mellitus, but it has been argued that the reduced CFR which is often present in these patients is mainly due to an increased basal flow and not to a reduced maximal flow [38]. Structural changes of the microcirculation may also be associated with various less common disorders such as systemic immune diseases, hypertrophic cardiomyopathy and fibromuscular dysplasia [10,12,39,40] and may constitute a major problem in heart transplant patients [41].

Ingestion of toxic substances may affect the coronary microcirculation [42] and the microcirculatory toxicity of agents used in the treatment of cancer is being recognized as a serious risk factor to be considered in the choice of therapeutic options and cardioprotective measures [43].

Furthermore, iatrogenic damage to the microcirculation may occur during and after percutaneous and surgical interventions due to coronary artery embolization [44,45] and in patients undergoing revascularization procedures for acute coronary syndromes the occurrence of 'no reflow' and 'reperfusion injury' is in part related to obstruction of the microcirculation [46].

Endothelial dependent dysfunction of the microcirculation may be associated with structural changes but is usually associated with cardiovascular risk factors such as smoking and advanced age and often occurs in the course of developing coronary atherosclerosis [11,13].

5. The angiographic diagnosis of normal coronary arteries and non-obstructive disease

To obtain more accurate and objective assessments of coronary arteriograms than achievable by visual interpretation in an early stage

measuring devices were introduced, first hand held calipers and later also electronic caliper based systems [3] as were used in the WISE study [2,47]. The most objective and accurate assessments, however, may be obtained by computer assisted systems with automated edge detection, so-called 'quantitative coronary angiography (QCA)', which has become the standard in current clinical investigations [48].

Compared with state of the art QCA systems visual assessments and caliper measurements tend to overestimate lesions causing <70% lumen diameter reduction [49–51]. Since usually a cutoff of 50% diameter reduction is used to separate obstructive from non-obstructive lesions it is unlikely that visual or caliper assessments have led to a significant number of false classifications as non-obstructive disease. Furthermore, vessel wall irregularities causing <20% narrowing may be better perceived in motion studies than in still images as are employed in quantitative assessments because in motion studies random noise, such as quantum noise and graininess of cine film, is to a large extent smoothened [16] and in digital recordings the limiting size of pixels is less disturbing. This may in part explain why in the analyses in the WISE study vessel lumen reductions <20% were regularly observed in still images of otherwise normal looking arteries [52].

Comparing the outcome of visual interpretation with QCA in the PROMISE (Prospective Multicenter Imaging Study for the Evaluation of Chest Pain) trial Shah et al. recently found that patients with lumen reductions <50% according to QCA but >50% according to visual assessment had a poorer prognosis than patients in whom both methods agreed on the absence of >50% diameter reductions (1 year event rate 3.1 vs 0.9%) [51]. This suggests that 50% lumen diameter reduction per QCA may not be an optimal cutoff to predict clinical outcome. Furthermore, significant disagreement between angiographic and physiologic assessment of stenosis severity has been demonstrated [53].

Considering all limitations, it appears that the angiographic diagnosis of no or non-obstructive CAD is not as straightforward as it may seem. Nonetheless, at present expert visual or caliper aided interpretation, including motion studies and using 50% diameter reduction as cutoff, may still be considered a reasonable method to separate obstructive from non-obstructive CAD. In future studies, however, it may be advantageous to use more often state of the art QCA (with newly defined cutoff levels) in combination with functional parameters.

6. Incidence of typical or atypical angina pectoris in the absence of obstructive CAD

The incidence of angina pectoris or angina pectoris like chest pains in the absence of obstructive CAD has always been substantial, particularly in women. In 1986 Kemp et al. reported that in the CASS registry of 21,483 patients 4304 patients (20%) had normal or near normal coronary arteries [54]. In 2012 Jespersen et al. reported that of 11,223 patients referred for CAG because of stable angina pectoris 65% of the women and 32% of the men had no obstructive CAD [55]. In 2014 Patel et al. reported that of 661,063 patients undergoing elective CAG, mainly for atypical chest pain or stable angina pectoris, 58.4% had either normal coronary arteries or non-obstructive (<50% diameter obstruction) disease [56]. Young age, female sex and atypical symptoms were among the predictors of non-obstructive disease but noninvasive test findings had minimal incremental value. Similar results had been reported earlier in investigations based on other large data registries [57,58].

7. Incidence of microvascular or endothelial dysfunction in the absence of obstructive CAD

Judging by the literature there are very few centers in which testing for microvascular or endothelial dysfunction is standard procedure. Data on the incidence in patients with chest pain in the absence of obstructive CAD are therefore scarce and subject to considerable selection bias. Furthermore, differences in methodology to assess and criteria to define dysfunction inhibit reliable comparisons between published studies. In this study we reviewed the literature to examine the differences in microvascular function between women and men, focusing on stable patients with symptoms of ischemic heart disease in the absence of obstructive CAD. For details of our search strategy see online Supplementary material.

Table 1 summarizes studies that compare female and male patients with angiographically proven absence of obstructive CAD [20,30,59–62]. In the vast majority of the patients microvascular and endothelial function was assessed to reveal a potential alternative cause of angina pectoris or similar symptoms. In 5 of the 6 studies adenosine or dipyridamole was used to determine endothelium independent vasodilation, in 2 of these in combination with Ach to assess endothelium dependent vasomotion. In the 2 studies with PET [59,61] women had a higher basal and hyperemic blood flow than men and in multivariate analysis Danad et al. found that male gender, together with age and BMI, had a negative impact on hyperemic blood flow. These findings are in agreement with a study of Sara et al. who found in a series in a series of 1439 patients a higher baseline as well as peak flow velocity in women than in men [62]. With adenosine and Ach tests there was some sort of microvascular dysfunction in two thirds of their patients but age, and not sex, was in multivariate analysis the only variable that independently predicted abnormal microvascular function. In contrast, Aziz et al., extending a study previously published by Ong et al., observed with Ach provocation in patients with <50% luminal diameter reduction clinical evidence of what was considered microvascular spasm (occurrence of symptoms and ischemic ECG changes) in 42.4% of the women versus 20.2% of the men [30,63]. Remarkably, in 22.6% of women and 28.2% of the men the test result was classified as 'unspecific reaction'. Unfortunately, neither in the study by Aziz et al. nor in other studies were the patients stratified according to the presence or absence of non-obstructive CAD but in the previous study by Ong et al. patients with <20% narrowing were selected who showed similar reactions compared to patients with <50% narrowing [63].

Table 2 summarizes the results of studies in which no angiographic data are available but obstructive CAD was considered unlikely on clinical grounds [17,18,64–68]. Four of the 7 studies were executed with PET in healthy volunteers with mean ages ranging from 29 [67] to 65 [17] years. In the volunteers basal coronary flow correlated positively with age [17] and in two studies with volunteers [18,65] as well as in hyperlipidemic patients [64] basal flow was significantly higher in women than in men. In another study [67] baseline and maximal flow were non-significantly higher in women than in men but the resulting lower CFR in women reached borderline statistical significance.

Insofar as a comparison between the patients of Table 1 and the patients of Table 2 is meaningful it appears that in patients as well as healthy volunteers women have on average a higher basal coronary flow than men and consequently with identical maximal flow a lower CFR.

8. Prognosis based on angiographic findings

In 1973 Bruschke et al. in a minimal 5-year follow-up study were the first to report that the prognosis of patients examined for chest pain who appeared to have angiographically normal coronary arteries was excellent but that the prognosis of patients with vessel wall irregularities causing ≤50% diameter reduction, lesions generally considered 'non-obstructive', was significantly less favorable [69]. The prognostic difference between normal arteries and non-obstructive disease has been confirmed in almost all studies based on invasive coronary angiography (ICA) as summarized in Table 3 [5,22,31,54,55,69–75] and more recently in studies based on computed tomography coronary angiography (CTCA) [76,77]. In a comprehensive meta-analysis including CAG and CTCA results Wang et al. calculated for patients with stable angina the following annualized hard cardiac event rates: patients with normal coronary arteries 0.3% (95% CI 0.1%–0.4%), patients with non-obstructive

Table 1
Microvascular dysfunction in women versus men without angiographically obstructive coronary artery disease.

Year, first author	Demographic details	Coronary artery disease	Microvascular dysfunction	CFR	MBF	Other
1994, Rosen [59]	29 patients with 'syndrome X' and 20 matched controls 17 W: age 56 ± 6.6 12 M: age 51.6 ± 10.3	CAG without even minimal luminal irregularities	H2(15)O-PET (dipyridamole)		Baseline W > M ($p < 0.001$) 1.18 ± 0.20 vs 0.88 ± 0.19 Corrected for RPP W > M ($p = 0.01$) 1.35 ± 0.32 vs 1.02 ± 0.25 Stress W > M (p = NS)	W = M (p = NS) coronary vasodilator reserve No difference between patients and controls.
2008, Han [60]	142 patients 'referred for CAG' 89 W, 53 M age 49.3 ± 11.7	CAG <30% stenosis	Intracoronary Doppler (adenosine, acetylcholine)	W < M ($p < 0.001$) 2.80 (2.40–3.20) vs 3.30 (2.90–4.00)		W < M diffuse epicardial endothelial dysfunction
2011, Danad [61]	128 patients 89% with chest pain 78 W: age 55 ± 10 50 M: age 52 ± 10	CTCA <50% stenosis CAG <30% stenosis or FFR > 0.8	H2(15)O-PET/CT (adenosine)		Baseline W > M ($p < 0.01$) 1.09 ± 0.30 vs 0.91 ± 0.34 Corrected for RPP W = M (p = NS) Stress W > M ($p < 0.001$) 3.78 ± 1.27 vs 2.90 ± 0.85 also in multivariate analysis	
2015, Sara [62]	1439 patients angina pectoris, vasospasm (27.9%), history of m.i. (14.9%) 937 W, 502 M age 51.1 (17–81)	CAG < 40% stenosis	Intracoronary Doppler (adenosine, acetylcholine)			Peak flow velocity Baseline W > M ($p < 0.001$) 26.0 (21.0–33.0) vs 22.0 (17.0–27.0) Maximal flow W > M ($p < 0.001$) 49.0 (36.0–66.0) vs 45.0 (30.0–63.0)
2015, Kobayashi [20]	157 patients with angina 117 W: age 53.5 ± 13.5 40 M: age 53.7 ± 11.3	CAG <50% stenosis	Intracoronary thermodilution (adenosine)	W < M ($p = 0.004$) 3.8 ± 1.6 vs 4.8 ± 1.9 Baseline T_{mn} W < M ($p = 0.005$) 1.05 ± 0.46 vs 1.31 ± 0.51 Stress T_{mn} W = M (p = NS)		IMR W = M (p = NS)
2017, Aziz [30]	1379 patients with angina 806 W: 63.9 ± 11.1 573 M: 59.0 ± 11.6	CAG <50% stenosis	CAG (acetylcholine) symptoms and ischemic ECG changes			W > M abnormal coronary vasomotion 70.2% vs 43.1% ($p < 0.001$) W > M CMD 42.4% vs 20.2% ($p < 0.001$) In multivariate analysis OR 4.3 (3.1–5.5) ($p < 0.001$)

Abbreviations: CAG = coronary angiography, CFR = coronary flow reserve, CMD = coronary microvascular dysfunction, CTCA = computed tomography coronary angiography, FFR = fractional flow reserve, IMR = index of microcirculatory resistance, M = men, MBF = myocardial blood flow, NS = not significant ($p > 0.05$), OR = odds ratio, PET = positron emission tomography, RPP = rate pressure product, T_{mn} = mean transit time, W = women.

Table 2
Microvascular dysfunction in women versus men without clinical evidence of obstructive coronary artery disease.

Year, first author	Demographic details	Microvascular dysfunction	CFR	MBF	Other
1993, Czernin [17]	40 healthy volunteers, women only postmenopausal 12 W: age 62 ± 9 28 M: age 66 ± 9	(13)N ammonia PET (dipyridamole)	<50 years 4.08 ≥50 years 3.01	W = M (p = NS) Baseline 0.94 ± 0.25 vs 0.91 ± 0.25 Stress 2.61 ± 0.54 vs 2.73 ± 0.63	
1999, Duvernoy [64]	30 hyperlipidemic patients 15 W: age 53 ± 4 15 M: age 50 ± 8	H2(15)O-PET (adenosine)		W > M (p = 0.001) Baseline 94 ± 22 vs 72 ± 23 Stress 296 ± 56 vs 226 ± 47 In multivariate analysis (p = 0.02)	
2001, Chareonthaitawee [65]	169 healthy volunteers 38 W, 131 M age 46 ± 12	H2(15)O-PET (dipyridamole)		Corrected for RPP Baseline W > M (p < 0.001) - septum 1.52 ± 0.31 vs 1.28 ± 0.32 - anterior 1.74 ± 0.41 vs 1.36 ± 0.38 - lateral 1.72 ± 0.43 vs 1.31 ± 0.27 - inferior 1.40 ± 0.28 vs 1.18 ± 0.32 Stress W = M	
2010, Cortigiani [66]	1660 patients with chest pain syndrome, no wall motion abnormality on echocardiogram at rest and stress 906 W: age 65 ± 11 754 M: age 61 ± 12	Echo Doppler LAD (dipyridamole)	W < M (p = 0.04) 2.52 ± 0.62 vs 2.57 ± 0.66		
2011, Sdringola [67]	125 healthy volunteers 30 W, 95 M age 29 ± 5	Rb-82 PET (dipyridamole)	W < M (p = 0.049) 3.85 ± 0.59 vs 4.08 ± 0.90	Baseline W = M (p = NS) 0.76 ± 0.15 vs 0.69 ± 0.15 Stress W = M (p = NS) 2.83 ± 0.4 vs 2.72 ± 0.61	
2014, Murthy [68]	1218 patients 813 W: age 62.3 (54.1–71.6) 405 M: age 61.2 (52.8–69.8) Subgroup with no CAC on CT: 307 W, 97 M	Rest/stress PET CT no visual evidence of CAD	PET CT (dipyridamole, adenosine, regadenoson, dobutamine)	W = M (p = NS)	Baseline W > M (p < 0.0001) 1.2 (0.95–1.53) vs 0.92 (0.75–1.17) Stress W > M (p < 0.0001) 2.38 (1.82–3.14) vs 1.85 (1.3–2.51)
2016, Range [18]	26 healthy volunteers 16 W: age 34 ± 7 10 M: age 34 ± 3	H2(15)O-PET (adenosine, cold-pressor)	W: 3.07 ± 1.12 M: 3.44 ± 0.92 W = M (p = NS)	Baseline W > M (p = 0.003) 1.10 ± 0.18 vs 0.85 ± 0.20 Baseline corrected for RPP W > M 1.41 ± 0.33 vs 1.16 ± 0.19 ml/min/ml; p = 0.024). Cold-pressor W > M (p = 0.026) 1.39 ± 0.38 vs 1.06 ± 0.28 Adenosine W = M (p = NS)	Coronary vascular resistance Baseline W < M 81 ± 14 vs 107 ± 22 (p = 0.006) Cold-pressor W < M 71 ± 17 vs 91 ± 20 (p = 0.013) Adenosine W = M (p = NS)

Abbreviations: CAC = coronary artery calcium, CAD = coronary artery disease, CFR = coronary flow reserve, M = men, MBF = myocardial blood flow, NS = not significant (p > 0.05), PET = positron emission tomography, RPP = rate pressure product, W = women.

Table 3
Invasive coronary angiography studies comparing MACE in women versus men.

Year, first author	Number of patients		Endpoints	Difference in event rate (W vs M)	
	Women	Men			
1973, Bruschke [69]	196	304	Myocardial infarction Cardiac death	W > M	>5 year follow-up; extended by Proudfit et al. to 10 year follow-up [75]
1973, Kemp [5]	99	101	All cause death	W = M	Difference W vs M extracted from data
1986, Kemp [54]	2102	1949	All cause death Cardiac death	W = M	Data from Coronary Artery Surgery (CASS) registry
1986, Papanicolaou [70]	865	626	Myocardial infarction Cardiac death	W = M	Difference W vs M extracted from data
1994, Sullivan [71]	83	55	Myocardial infarction All cause death Readmissions	W = M	
1995, Lichtlen [72]	61	115	Myocardial infarction Cardiac death	W = M	
2009, Sicari [22]	223	394	Myocardial infarction Death	W = M	
2012, Jespersen [55]	3073	2110	Cardiovascular death Myocardial infarction Heart failure Stroke	W = M	
2013, Sedlak [31]	1757	1330	All cause death Myocardial infarction Coronary revascularization Stroke	W > M	W with nonobstructive CAD at higher risk of cardiac event only in first year of follow-up
2015, Johnston [73]	6610	4517	All cause death Myocardial infarction Coronary revascularization Stroke	W < M	Concerns group with stable chest pain
2016, Sinning [74]	158	212	All cause death Myocardial infarction	W = M	Only patients with 30–50% luminal diameter reduction included

Abbreviations: CAD = coronary artery disease, M = men, MACE = major adverse cardiovascular events, W = women.

(1–≤50%) disease 0.7% (95% CI 0.5–1.0%), patients with obstructive disease 2.7% (95% CI 1.7%–3.7%) [77]. Thus the prognosis in patients with non-obstructive disease is still markedly better than in patients with obstructive CAD.

In part due to the small numbers of adverse events only a few CAG studies have tried to subdivide the prognosis in non-obstructive CAD according to extent and severity of the arterial involvement. A large retrospective cohort study of US veterans comprising 8391 patients with normal coronary arteries and 8384 patients with non-obstructive CAD was reported by Maddox et al. [78]. The results are difficult to compare with the results of other studies because the definition of non-obstructive disease is slightly different from commonly used definitions and 95.5% of the patients were men. Nonetheless it is interesting that an increasing 1-year myocardial infarction rate was noted in patients with 1 to 3 vessel non-obstructive CAD.

In 2013 Sharaf et al. reported on adverse outcomes in women without obstructive coronary artery disease who participated in the WISE study [52]. The CAG revealed normal coronary arteries in 339 patients and non-obstructive CAD in 228 patients. Cardiovascular death or myocardial infarction at 10 years occurred in 6.7% of the women with normal arteries and in 12.8% of the women with non-obstructive disease. It should be noted that the patients with non-obstructive disease as compared with their 'normal' counterparts were older and more often postmenopausal, had in a higher percentage prior myocardial infarction and prior PTCA, and were more often current smokers or had diabetes. The WISE investigators suggested that their findings specifically related to women [79], however, as shown in Table 3 CAG studies including both sexes contradict this suggestion.

CTCA studies are comparable with invasive CAG studies in that both methods depict the anatomical status of the epicardial coronary arteries. However, the resolution of CT scanners, particularly of the older <64-slice scanners is lower than what is obtainable by invasive CAG with motion studies. The PICTURE study demonstrated that current 64-row CTCA compared with QCA as reference has a high sensitivity but still somewhat lower specificity (88.9%) in classifying CAD [80]. Nonetheless the results of CTCA are interesting among others because the use of this technique rapidly increases and in a growing number of cases is used to replace ICA.

In 2012 Abdulla et al. assessed the prognostic value of 64-slice CTCA in a meta-analysis including 2045 patients with normal CTA and 2068 patients with non-obstructive CAD. The cumulative major adverse cardiovascular event (MACE) rate over 21 months was 0.5% in the normal and 3.5% in the non-obstructive group [81]. In 2014 Jiang et al. published a meta-analysis of CTCA studies and concluded that the event rate for a normal CTCA was comparable with the event rate among healthy low-risk individuals and that the presence of non-obstructive CAD and obstructive CAD incrementally increased the risk of adverse events [76]. In these prognostic aspects the results of CTCA studies corroborate the findings in invasive CAG studies. Furthermore, several CTCA studies have demonstrated an increasing occurrence of MACE with increasing extent of non-obstructive disease [82–85].

Only a few CTCA studies have assessed the significance of sex but two CONFIRM (Coronary CT angiography for clinical outcomes) studies by respectively Leipsic et al. [83] and Schulman-Marcus et al. [85] have specifically addressed this issue. Leipsic et al. did a propensity analysis comprising 5731 women and 5731 men and after matching found that women and men experienced identical annualized rates of myocardial infarction, death, and MACE. In multivariate analysis non-obstructive CAD was associated with similarly increased MACE, for both women and men [83]. Schulman-Marcus et al., using the long-term CONFIRM registry, followed 5632 patients for 5 years and found that there were no distinct sex-specific differences in the risk of MACE defined as death or myocardial infarction [85].

Unfortunately, in spite of the relatively benign prognosis with regard to the occurrence of cardiovascular events, symptoms may persist for many years [70,72,86] which may lead to repeated hospitalizations and recatheterizations which seems to occur more often in women than in men.

9. Prognostic significance of microvascular or endothelial dysfunction

The role of endothelial dysfunction in atherogenesis is well established [11,13] but only a few studies have assessed its prognostic significance in patients with angina pectoris or angina-like chest pain in the absence of obstructive CAD. Table 4 lists prognostic studies that included both women and men with normal coronary arteries or non-obstructive disease demonstrated by ICA in whom microvascular and/or endothelial dysfunction was examined by direct investigation of the coronary circulation [22,32,87–89]. In three studies Ach was used to determine endothelial function of epicardial coronary arteries and endothelial dependent microvascular vessels [87–89]. These studies demonstrated that endothelial dysfunction of epicardial as well as of microvascular vessels is associated with more cardiovascular events. Studies by Schindler et al. [32] and Sicari et al. [22] were restricted to the effect of Ach on epicardial coronary arteries and both studies concluded that abnormal vasomotion was associated with increased cardiovascular risk. Halcox et al. reported that endothelium independent responses were not predictive of outcome [88] but the other studies allow no conclusions in this regard.

Except Reriani [89], who did not report on differences between sexes, all investigators reported similar results in women and men. Likewise Schäginger et al. found that sex was not associated with different outcome in patients with endothelial dysfunction but they did not clearly differentiate between patients with and those without coronary atherosclerosis [90]. Taqueti et al., however, found in a median 3-year follow-up study of 329 patients, 43% of whom were female, that only women with severely impaired CFR (<1.6) had a significant increased cardiovascular risk but it is unclear to what extent this concerned the 77 patients with no or non-obstructive coronary atherosclerosis (according to the definition of the investigators including patients with 50–74% obstruction in one artery [91,92].

Studies restricted to women have confirmed the prognostic significance of microvascular or endothelial dysfunction. In a 48 months (median) follow-up of 163 women of the WISE study, 75% of whom had normal coronary arteries or non-obstructive disease, von Mering et al. found that the response of epicardial coronary arteries to Ach, characterized by percentage change of cross-sectional area, and degree of CAD in multivariate regression analysis were the only variables that predicted cardiovascular events [93].

In 2010 Pepine et al. published the results of a WISE substudy designed to investigate whether microvascular dysfunction predicts major adverse outcomes among women with signs and symptoms of ischemia [21]. The study included 189 women, 152 of whom were free of obstructive CAD. Endothelium-independent function of the microcirculation was assessed by determining CFR with adenosine and using a cut-off of 2.32 because this appeared the value best predictive of MACE. The investigators concluded that coronary microvascular reactivity to adenosine significantly improves prediction of MACE over angiographic CAD severity and CAD risk factors. It must be noted, however, that of the 25 first major events 8 were cases of stroke, which makes a direct causal effect of cardiac microvascular dysfunction unlikely, 6 events were cases of congestive heart failure which is unusual in this category of patients, and that cause of death (n = 8) in most cases could not be ascertained.

Bugiardini et al. focused on endothelial function in relation to duration of symptoms and future development of coronary atherosclerosis [94]. They selected 42 women with de novo angina pectoris and angiographically normal coronary arteries without irregularities. With intracoronary Ach vasoconstriction was seen in 22 patients, 13 of them still had angina pectoris at the end of follow-up. Vasodilation was seen in 20 patients who all experienced complete resolution of chest pain. At the end of a ≥10 year follow-up coronary angiography was repeated in 37 patients which showed variable degrees of coronary lumen stenosis in all symptomatic patients and normal-appearing coronary arteries in the others. The authors conclude that endothelial dysfunction in a setting of normal appearing coronary arteries is often associated with persistence of chest pain and development of coronary atherosclerosis.

10. Discussion

In spite of the development of sophisticated noninvasive tests that are frequently used in the selection of patients for ICA the percentage of patients undergoing ICA for chest pain who appear to be free of obstructive CAD has not diminished since the publication of the Coronary Artery Surgery Study (CASS) results in 1986 [54,56]. In publications this 'syndrome' is consistently more prevalent in women than in men but the reported women/men prevalence ratios vary considerably. The difference between sexes may in part be due to a selection bias. Women more often than men may have atypical symptoms [95] which may contribute to more noninvasive tests being performed in women and in cases of positive test results to more referrals for ICA. In a meta-analysis of studies using different noninvasive myocardial perfusion modalities Takx et al. concluded that PET, CT, and MRI can accurately rule out hemodynamically significant CAD but that SPECT and echocardiography are clearly less accurate for this purpose [96]. Patel et al. found that the results of noninvasive tests, in most cases SPECT, only weakly correlated with the likelihood of obstructive CAD [56]. These studies indicate that reliance on functional tests in the selection of patients for ICA may contribute to a high percentage of patients who are found to be free of obstructive CAD, which could affect more women than men.

It has been suggested that women more often than men have microvascular dysfunction that may cause symptoms of ischemic heart disease [21,79]. However, this concept is not substantiated by studies that include both sexes. It is true that in some studies women have lower CFR than men but quantitative PET studies in patients as well as healthy volunteers have demonstrated that the difference is mainly due to a higher basal coronary flow in women and not to a lower maximal flow. A common cause of microvascular disease is hypertension which may lead to symptoms of cardiac ischemia by a combination of factors, that is: maximal coronary flow is reduced whereas a higher workload increases oxygen demand, and myocardial vascular rarefaction may occur because the vasculature does not develop in proportion

Table 4
Prognostic significance of endothelial and microvascular function in women versus men without obstructive coronary artery disease.

Year, first author	Number of patients		Main parameter	Median/mean follow-up (months)	Difference in event rate (W vs M)
	Women	Men			
2000, Al Suwaidi [87]	104	53	ΔCBF (acetylcholine, adenosine)	28	W = M
2002, Halcox [88]	42	134	ΔCVR (acetylcholine, adenosine)	46	W < M, but in multivariate analysis W = M
2003, Schindler [32]	39	91	ΔLA (cold pressor test)	45	W = M
2009, Sicari [22]	223	171	CFR (echo-Doppler of LAD)	51	W = M
2016, Reriani [89]	320	150	ΔCBF (acetylcholine, nitroglycerin)	116	Not reported

Abbreviations: CBF = coronary blood flow, CFR = coronary flow reserve, CVR = coronary vascular resistance, LA = luminal area, LAD = left anterior descending artery, M = men, W = women.

with the increasing myocardial mass associated with left ventricular hypertrophy. [35,36]. In animal models and in patients it has been demonstrated that reverse coronary microvascular remodeling may be achieved by antihypertensive treatment but in this respect not all classes of drugs appear to be equally effective [97,98].

The role of endothelium dependent microvascular vasodilation and microvascular spasm is still uncertain and merits further investigations. Provocation tests with intracoronary Ach, especially in high doses [30], have generated evidence of epicardial and microvascular endothelial dysfunction in a considerable proportion of patients which in one study concerned more women than men (70% vs 43%) [30]. However, it remains to be proven that in physiologic conditions coronary epicardial or endothelium dependent microvascular dysfunction is a common cause of chest pains considered compatible with cardiac ischemia. Furthermore, since endothelial dysfunction is closely associated with the initiation and progression of atherosclerosis [11,13] it is difficult to ascertain which of these two processes is responsible for the prognostic consequences. The link with atherosclerosis especially in the presence of hypertension may also explain the relatively high incidence of non-cardiac vascular events such as stroke in patients with endothelial dysfunction.

Regrettably, in the literature rarely a separation is made between patients with normal coronary arteries and patients with nonobstructive disease. There is overwhelming evidence that patients with suspicious chest pain and normal CAG irrespective of sex have a cardiovascular prognosis that is as least as good as the prognosis in the population at large. Therefore, if these patients frequently have endothelium dependent or endothelium independent microvascular dysfunction that either is a benign condition or occurs just as often in the population at large. In patients with nonobstructive disease, which may be interpreted as an early stage of coronary atherosclerosis, the prognosis is less favorable, albeit still better than in patients with obstructive disease, and it is conceivable that in these patients endothelium dependent and endothelium independent microvascular dysfunction play a greater role. Hopefully, in future studies and in clinical practice this aspect will be given more consideration and we recommend that undiscriminative terms like 'no significant CAD' be avoided.

11. Concluding remarks

Apart from a higher prevalence in women we found in the literature no convincing evidence of essential differences between women and men referred for ICA because of stable symptoms compatible with ischemic heart disease who are found to be free of obstructive CAD.

In the past the significance of microvascular and endothelial dysfunction probably has been underestimated but the full clinical significance of these disorders has yet to be clarified. In the meantime there is no justification to assume without objective proof that particularly in female patients angina-like symptoms in the absence of obstructive CAD are probably due to microvascular dysfunction. The Coronary Vasomotion Disorders International Study Group (COVADIS) recently published a scheme for standardization of diagnostic criteria for microvascular angina [99]. According to this a diagnosis or 'definitive microvascular angina' requires evidence of impaired coronary microvascular function which at present can only reliably be obtained by invasive investigations or PET. Obviously there is a need for widely available harmless non-invasive methods to assess microvascular function. In this respect studies with MR stress tests have shown promising results [28,29].

Given the favorable prognosis in patients, women as well as men, with normal CAG additional tests to assess microvascular or endothelial function may not always be required but these tests may provide useful information about the cause of the patient's symptoms. However, even with proven microvascular or endothelial dysfunction it may remain uncertain if there is a causal relationship with the patient's symptoms. Physicians should therefore be careful not to cause unnecessary anxiety when they inform patients about these disorders that may be mainly risk factors; it also should not withhold them to search for alternative causes of angina or angina-like chest pains such as aortic stenosis, myocardial bridging [23] and non-cardiac causes.

Remaining questions, particularly about the role of the microvasculature should be addressed in future studies that include men as well as women and if there are sex related differences we should try to analyze these and thus enhance our understanding of the mechanisms involved in the syndrome of angina pectoris in the absence of obstructive CAD. Perhaps also more emphasis should be placed on gender, defined as non-biological aspects of being male or female (e.g. social roles, personality traits), than on sex alone [100].

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