UNMASKING ISCHEMIA: PREVALENCE AND CLINICAL IMPLICATIONS OF CORONARY MICROVASCULAR DYSFUNCTION AND VASOSPASM IN NON-OBSTRUCTIVE CORONARY ARTERY DISEASE

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Abstract

Background: Ischemic heart disease remains a leading global cause of morbidity and mortality. A significant proportion of patients presenting with chest pain undergo coronary angiography that reveals no obstructive coronary artery disease (CAD). Despite the absence of obstructive lesions, these patients often experience myocardial ischemia, which can be attributed to coronary microvascular dysfunction (CMD) or coronary vasospasm. However, the true prevalence of CMD and coronary vasospasm among this population remains unclear.

Methods: A systematic review was conducted to assess the prevalence of CMD and coronary vasospasm in patients with non-obstructive CAD. PubMed and Scopus were systematically searched from inception until August 2024. Studies were included if they assessed patients with suspected CAD who had undergone diagnostic testing for CMD or coronary vasospasm and reported the proportion of positive cases. Data were extracted on patient demographics, clinical characteristics, diagnostic methods, and prevalence rates. A random-effects model was used to estimate pooled prevalence rates with 95% confidence intervals (CIs), and heterogeneity was assessed using the I^2 statistic.

Results: Nearly half of the patients with non-obstructive CAD exhibited CMD or coronary vasospasm. CMD was more frequently observed in women, though men were also significantly affected. Findings underscore the need for increased awareness, standardized diagnostic approaches, and improved management strategies to optimize care for patients with myocardial ischemia without obstructive CAD.

Conclusion: The high prevalence of CMD and coronary vasospasm in patients with non-obstructive CAD highlights the need for better diagnostic tools and clinical guidelines. Increased physician awareness and targeted management strategies can improve patient outcomes and reduce unnecessary invasive procedures. Future research should focus on refining diagnostic criteria and developing effective therapeutic interventions for this patient population.

Keywords: Ischemic heart disease, non-obstructive CAD, coronary microvascular dysfunction, coronary vasospasm, prevalence.

Introduction

Ischemic heart disease remains the leading cause of death and disability across the globe, posing a significant burden on healthcare systems (1). While coronary artery disease (CAD) is often characterized by the presence of obstructive atherosclerotic lesions, a considerable proportion of patients with suspected CAD undergo invasive coronary angiography only to reveal normal or minimally obstructed coronary arteries (2). These findings challenge the traditional understanding of ischemia, as many of these patients continue to experience symptoms and an increased cardiovascular risk (3). In fact, ischemia in the absence of obstructive CAD has been linked to higher rates of adverse cardiovascular events and a greater likelihood of repeat coronary angiography, underscoring the need for a broader perspective on its underlying causes (4,5).

Modern clinical guidelines recognize the complexity of ischemic heart disease, highlighting that chronic coronary syndromes may arise from mechanisms beyond simple atherosclerotic obstruction (6). While coronary artery narrowing due to plaque buildup is a well-established contributor, disorders affecting the microcirculation and vascular reactivity also play a crucial role in the pathogenesis of myocardial ischemia (7). These microvascular abnormalities may impair blood flow regulation, leading to ischemic symptoms even in the absence of significant epicardial stenosis (8). As a result, patients with persistent chest pain despite normal angiographic findings should not be dismissed as having a benign condition but rather assessed for alternative causes of myocardial ischemia (9).

Coronary microvascular disease (CMD) has emerged as a key contributor to ischemic heart disease in patients with no obstructive CAD (3). CMD is characterized by functional and structural abnormalities of the coronary microvasculature, which result in inadequate myocardial perfusion despite the absence of large vessel obstruction (5). This condition can be diagnosed using invasive methods such as cardiac catheterization with coronary flow reserve (CFR) assessment or non-invasive imaging techniques that evaluate microvascular function (7). The recognition of CMD as a significant factor in ischemic heart disease has led to a growing emphasis on refining diagnostic approaches to better identify affected patients and tailor appropriate management strategies (6).

In addition to CMD, epicardial coronary spasm represents another important mechanism leading to myocardial ischemia in patients without obstructive CAD (2). This condition is characterized by transient constriction of the coronary arteries, which can cause chest pain, ischemia, and even myocardial infarction (8). Provocation tests performed during invasive coronary angiography are considered the gold standard for diagnosing coronary spasm, as they allow direct observation of vascular reactivity under controlled conditions (9). However, the diagnosis of coronary spasm remains challenging in routine clinical practice, given its episodic nature and the lack of widespread availability of provocation testing (4).

Despite advances in understanding these no obstructive forms of ischemia, the true prevalence of CMD and coronary spasm in patients with normal or mildly diseased coronary arteries remains unclear (1). Many individuals experiencing persistent angina and ischemic symptoms undergo extensive cardiac evaluations, yet their underlying pathophysiology often goes unrecognized (3). Further research is needed to establish the epidemiology of these conditions, improve diagnostic accuracy, and develop targeted therapeutic approaches to reduce the burden of ischemic heart disease in this patient population (5,7). As awareness grows regarding the diverse mechanisms of myocardial ischemia, a more comprehensive diagnostic and treatment framework is essential to optimize care for patients with no obstructive CAD (6,9).

The aim of the present systematic review was to determine the prevalence of CMD and coronary spasm assessed by invasive and non-invasive methods in patients with no obstructive CAD.

Methods

A comprehensive review was conducted on studies that examined the prevalence of coronary microvascular disease (CMD) and coronary vasospasm in patients without obstructive coronary artery disease (CAD). Two independent reviewers (N.M. and G.M.) systematically searched PubMed and Scopus to identify relevant literature. The search was performed in August 2021, covering all available studies from their inception, and was conducted

separately for CMD and coronary vasospasm. No language restrictions were applied to maximize the scope of the review. Additionally, reference lists of selected studies and recent systematic reviews were examined to identify additional relevant publications. When multiple studies reported data from the same patient cohort, only the most recent publication was included.

Studies were eligible for inclusion if they met the following criteria: (1) enrolled patients with suspected CAD, (2) confirmed the absence of obstructive coronary disease, and (3) conducted a diagnostic assessment for CMD, coronary spasm, or both, while reporting the number of positive cases relative to the total number of evaluated patients. Based on the mechanism of ischemia investigated, studies were categorized into two groups: CMD and coronary vasospasm. Definitions of no obstructive CAD and the diagnostic thresholds for CMD were adopted as specified in each individual study. (10).

The primary objective of this study was to determine the prevalence of CMD and/or coronary vasospasm in individuals diagnosed with no obstructive CAD. Data extracted included patient demographics, clinical characteristics, diagnostic techniques used, and the number of patients testing positive for CMD or vasospasm.

Statistical Analysis

Categorical variables are presented as percentages, while continuous variables are expressed as mean ± standard deviation. Given the variability between studies, a random-effects model based on the Der Simonian-Laird method was applied to account for heterogeneity (12).

Results

A total of 150 articles underwent a full review, and A total of 37 studies focused on the prevalence of CMD among individuals without obstructive coronary artery disease, encompassing 7,212 participants. The mean age was 59±5 years, with 61% being female, 66% diagnosed with hypertension, 22% having diabetes, and 19% identified as smokers. Of these studies, 24 employed invasive diagnostic techniques, while 14 relied on non-invasive methods. Coronary flow reserve (CFR) evaluation via Doppler or thermodilution was the most commonly used invasive method (45%), followed by positron emission tomography (32%). The baseline characteristics of patients undergoing CMD assessment are presented in Table 1.

The pooled CMD prevalence was estimated at 41% (95% CI: 36–47%) (I^2=94%) (4). Among the 18 studies that reported CMD prevalence separately for men and women, analysis indicated no correlation between the percentage of female participants and CMD prevalence. However, women were 1.45 times more likely to test positive for CMD compared to men (5). The prevalence of CMD remained consistent across invasive and non-invasive diagnostic approaches, with invasive techniques reporting 43%and non-invasive methods showing 42%. Among non-invasive procedures, positron emission tomography revealed a higher CMD prevalence (46%) compared to alternative non-invasive modalities (40%).

Twenty-four studies explored the occurrence of coronary vasospasm, with a combined sample of 6,553 individuals. The mean age was 60.5±8.0 years, with 39% being female, 21% diagnosed with diabetes, and 32% identified as smokers. Baseline clinical characteristics of those evaluated for coronary spasm are outlined in Table 2. Among these studies, 21 focused exclusively on epicardial spasm, while 13 also reported on microvascular spasm. The overall prevalence of epicardial and microvascular spasm combined was estimated at 49% (6). Epicardial spasm alone had a prevalence of 40%, whereas microvascular spasm was present in 24% (7).

Acetylcholine was the primary agent used for the provocation test in 98% of cases (14–23, 31, 63, 66, 68), while ergon ovine was utilized in two studies (30, 34). No significant difference in spasm prevalence was observed between the two tests: 49% for acetylcholine versus 48% (95%) for ergon ovine. In 12 studies, coronary spasm prevalence was examined separately by sex, revealing similar rates: 28% in women versus 25% %) in men (8).

Subgroup analyses considering different definitions of epicardial spasm (≥90% vs. ≥70% coronary vasoconstriction) found no significant difference: 47% for ≥90% constriction compared to 49% for ≥70% constriction.

Three studies (33, 36, 63) assessed both CMD and coronary vasospasm in 541 participants, with a mean age of 58±10.2 years, 63% of whom were female. The prevalence of CMD alone was 23% while coronary vasospasm (either epicardial or microvascular) alone was found in 19%. Additionally, 23% of patients exhibited both CMD and vasospasm (Table 1, Table 2).

Table 1. Number of Positive Patients and Baseline Clinical Characteristics of the Patients Included in the Studies Investigating the Prevalence of Coronary Microvascular Disease.

Study	Patients included	No. positive, n (%)	Age, y	Women, n (%)	Hypertension, n (%)	Diabetes, n (%)	Dyslipidemia, n (%)
Cassar, 2009 [13]	376	170 (45%)	49±11	254 (68%)	157 (42%)	36 (10%)	208 (55%)
Godo, 2020 [32]	148	91 (62%)	44±9	111 (75%)	79 (53%)	11 (7%)	91 (62%)
Ford, 2018 [33]	151	78 (52%)	61±10	111 (74%)	125 (81%)	29 (19.2%)	120 (79.5%)
Graf, 2006 [35]	58	42 (72%)	58±10	39 (67%)	NA	8 (18%)	NA
Hasdai, 1998 [36]	203	118 (58%)	51 (17–78)	158 (78%)	59 (29%)	8 (4%)	88 (43.3%)
Kobayashi, 2015 [39]	157	39 (25%)	64±12	117 (29%)	77 (49%)	38 (24%)	91 (58%)
Kotecha, 2019 [40]	23	16 (70%)	63±8	NA	6 (26%)	NA	NA
Lee, 2015 [42]	137	38 (28%)	54±11	107 (77%)	74 (53%)	32 (23%)	87 (63%)
Michelsen, 2018 [43]	919	241 (26%)	62±9	919 (100%)	467 (51%)	117 (13%)	580 (63%)
Murthy, 2014 [44]	1218	641 (53%)	62 (53–69)	813 (67%)	894 (73%)	363 (30%)	663 (54%)
Pargaonkar, 2019 [47]	155	34 (22%)	54±13	119 (77%)	68 (44%)	26 (17%)	90 (58%)
Pargaonkar, 2020 [48]	88	32 (36%)	NA	53 (60%%)	NA	NA	NA
Pepine, 2010 [49]	152	74 (49%)	55±10	189 (100%)	57 (30%)	21 (11%)	50 (26%)
Quesada, 2020 [50]	150	67 (45%)	54±12	36 (24%)	75 (50%)	25 (17%)	90 (60%)
Sade, 2009 [53]	65	27 (40%)	55±8	68 (100%)	37 (54%)	NA	35 (52%)
Safdar, 2020 [54]	124	81 (65%)	51±11	91 (73%)	81 (65%)	42 (34%)	53 (43%)
Sakamoto, 2012 [55]	73	12 (16%)	65±8	36 (49%)	33 (45%)	6 (8%)	17 (23%)
Sara, 2016 [56]	926	281 (30%)	52±13	567 (61%)	371 (40%)	59 (6%)	485 (52%)
Schindler, 2005 [58]	72	50 (69%)	58 _ 8	28 (39%)	50 (69%)	3 (4%)	30 (42%)
Sicari, 2009 [61]	394	87 (22%)	61±10	223 (57%)	238 (60%)	69 (18%)	NA
Suda, 2019 [63]	187	75 (40%)	63±12	74 (40%)	100 (54%)	52 (28%)	66 (35%)
Taqueti, 2018 [64]	201	108 (54%)	66 (57–79)	130 (65%)	152 (76%)	129 (64%)	66 (33%)
Uemura, 2016 [65]	61	16 (26%)	59±15	18 (30%)	37 (61%)	15 (25%)	NA
Verna, 2018 [66]	101	45 (45%)	60±11	48 (48%)	58 (57%)	9 (9%)	53 (53%)
Solberg, 2019 [62]	66	11 (17%)	54±9	66 (100%)	15 (23%)	2 (3%)	8 (12%)
Schroder, 2019 [59]	174	49 (28%)	64±10	NA	NA	NA	NA
Sara, 2019 [57]	129	49 (38%)	50±12	61 (47%)	NA	NA	NA
Kumar, 2020 [41]	163	107 (66%)	57±12	79 (48%)	118 (72%)	37 (23%)	122 (75%)
De Vita, 2019 [34]	30	18 (60%)	67±10	19 (63%)	19 (63%)	4 (13%)	16 (53%)
Mygind, 2016 [45]	54	20 (37%)	62±8	54 (100%)	29 (54%)	NA	34 (63%)
Panza, 1997 [46]	66	13 (20%)	49±10	44 (67%)	NA	Na	NA
Schroder, 2018 [60]	97	37 (38%)	62 (31–79)	97 (100%)	NA	NA	NA
Reis, 1999 [52]	48	29 (60%)	54±10	48 (100%)	23 (48%)	6 (13%)	24 (49%)
Kim, 2013 [38]	40	11 (28%)	53±11	NA	NA	NA	NA
Ishimori, 2011 [37]	18	8 (44%)	41±11	18	NA	NA	NA
Rahman, 2019 [51]	85	45 (53%)	57±10	66 (78%)	25 (29%)	11 (13%)	23 (27%)
Konst, 2020 [67]	103	38 (37%)	62±9	NA	NA	NA	NA

Table 2. Number of Positive Patients and Baseline Clinical Characteristics of the Patients Included in the Studies Investigating the Prevalence of Vasospasm.

Study	Patients included	No. positive, n (%)	Age, y	Women, n (%)	Hypertension, n (%)	Diabetes, n (%)	Dyslipidemia, n (%)
Aziz, 2017 [14]	1379	813 (59%)	62±11.9	799 (58%)	970 (70%)	237 (17%)	841 (61%)
Ford, 2018 [33]	151	56 (37%)	61 (53–68)	111 (74%)	NA	29 (19%)	120 (80%)
Hoshino, 2016 [15]	292	90 (30%)	64±11	156 (51.7%)	114 (39%)	33 (11%)	98 (34%)
Kim, 2018 [16]	328	128 (39%)	58±10.4	233 (71%)	128 (39%)	31 (9.4%)	72 (22%)
Mohri, 1998 [17]	117	81 (74%)	63 (54–68)	59 (50%)	56 (48%)	26 (22%)	49 (42%)
Montone, 2018 [18]	80	37 (46%)	63±11	40 (50%)	32 (40%)	8 (10%)	19 (24%)
Montone, 2020 [19]	210	118 (56%)	62±11	82 (39%)	79 (38%)	13 (6%)	54 (26%)
Oh, 2019 [20]	464	156 (34%)	57±11	164 (35%)	60 (13%)	23 (5%)	94 (20%)
Ohba, 2012 [21]	370	264 (71%)	63±11	211 (57%)	197 (53%)	73 (20%)	193 (52%)
Ong, 2014 [23]	847	488 (58%)	62±12	485 (57%)	609 (72%)	142 (17%)	460 (54%)
Ong, 2012 [22]	124	77 (53%)	64±10	100 (%)	102 (71%)	31 (22%)	83 (58%)
Ong, 2014 [24]	137	69 (50%)	63±11	93 (68%)	105 (77%)	27 (20%)	73 (53%)
Pirozzolo, 2020 [25]	96	56 (58%)	65±12	49 (51%)	84 (88%)	15 (16%)	84 (88%)
Quyyumi, 1992 [26]	51	5 (10%)	51±11	31 (61%)	20 (39%)	NA	NA
Suda, 2019 [63]	187	126 (67%)	63±12	74 (40%)	100 (54%)	52 (28%)	66 (35%)
Sun, 2002 [29]	55	14 (26%)	60±10	23 (42%)	26 (47%)	9 (16%)	26 (47%)
Sun, 2005 [28]	131	101 (79%)	59±11	69 (53%)	59 (45%)	30 (13%)	50 (38%)
Tsuchida, 2005 [30]	102	74 (77%)	57±11	15 (15%)	43 (42%)	31 (30%)	NA
Uemura, 2016 [65]	61	15 (28%)	59±15	18 (30%)	37 (61%)	15 (25%)	NA
Verna, 2018 [66]	101	57 (57%)	60±11	48 (48%)	58 (57%)	9 (9%)	53 (52%)
Seitz, 2020 [27]	847	283 (33%)	64±11	529 (63%)	533 (63%)	129 (15%)	411 (49%)
Yamanaga, 2015 [31]	50	29 (58%)	62±13	24 (48%)	28 (56%)	10 (20%)	29 (58%)
Quesada, 2020 [50]	150	83 (55%)	54±12	36 (24%)	75 (50%)	25 (17%)	90 (60%)
Hasdai, 1998 [36]	203	59 (29%)	51 [17–78]	158 (78%)	59 (29%)	8 (4%)	88 (43%)

NA indicates information is not available.

Discussion

The key outcomes of this systematic review can be outlined as follows: (1) Among individuals without obstructive coronary disease, 41% exhibited coronary microvascular dysfunction (CMD), while coronary spasm (whether epicardial or microvascular) was identified in 49% of cases. (2) Women are disproportionately affected by CMD compared to men. (3) Both invasive and non-invasive diagnostic techniques yielded comparable detection rates of CMD. (4) Considerable variability existed among studies in terms of CMD prevalence and vasospastic angina (7, 69).

Clinicians are increasingly recognizing the significance of evaluating microvascular function in patients presenting with no obstructive coronary arteries. Murthy et al. found that even in cases where obstructive coronary atherosclerosis is absent, 53% of patients experiencing chest pain exhibit signs of inducible myocardial ischemia (44, 70). Moreover, CMD has been linked to a higher likelihood of myocardial infarction and mortality. The current reveals that nearly half of individuals undergoing coronary microcirculation assessment without obstructive coronary disease demonstrate CMD. Coronary function testing facilitates the classification of patients based on distinct ischemic end types, which in turn supports the implementation of individualized treatment plans. Establishing a definitive cause for chest pain and tailoring management accordingly can enhance patients' quality of life (33, 71). Additionally, pinpointing CMD or coronary spasm as the underlying issue reduces unnecessary repeat invasive procedures, lowers healthcare expenditures, and refines therapeutic strategies (72).

CMD has historically been perceived as a predominantly female condition (73). The WISE (Women's Ischemia Syndrome Evaluation) study reported that 39% of women with chest pain but no obstructive coronary disease exhibited coronary vasomotor dysfunction and induced myocardial ischemia (49). However, Murthy et al. utilized positron emission tomography and found high CMD prevalence in both genders (51% in men versus 54% in women) (44). The present corroborates that CMD affects both sexes but with a higher frequency in women (44, 49, 74). It is worth noting that many studies did not include men in the same proportion as women, which may have influenced the findings.

The frequency of CMD in patients with angina and no obstructive coronary disease undergoing invasive angiography is contingent upon the diagnostic methods and thresholds applied. The most frequently employed approach for detecting CMD was invasive coronary flow reserve (CFR) assessment, primarily utilizing Doppler or thermodilution techniques (33, 39, 42, 50). Some studies defined CMD using a CFR cut-off of ≤2.5 (13, 36, 50, 51, 52, 55, 56, 66, 75), whereas others set the threshold at ≤2.0 (32, 33, 39, 41, 42). The inconsistency in methodologies and cut-offs likely contributed to the high understudy variability; however, CMD prevalence remained relatively stable across different approaches. A recently published consensus on CMD diagnosis outlined specific criteria to distinguish ischemic end types without obstructive coronary disease (76). According to this consensus, CMD is characterized by myocardial ischemic symptoms, patent coronary arteries (diameter stenosis <50% or fractional flow reserve >0.80), and at least one of the following indicators: an index of microcirculatory resistance >25, CFR ≤2.0, or hyperaemic microvascular resistance >1.9. Vasospastic angina, evaluated using an acetylcholine challenge test, is diagnosed as epicardial spasm when ≥90% diameter stenosis occurs (compared to post-nitrate angiography), accompanied by angina and ischemic electrocardiographic changes. Microvascular spasm, in contrast, is confirmed by the presence of angina and ischemic electrocardiographic alterations without significant epicardial constriction (76).

Despite growing awareness of CMD as a contributor to chest pain, diagnostic methods remain underutilized in clinical practice (77). Two primary barriers hinder widespread adoption. First, specialized diagnostic tools such as positron emission tomography and invasive assessments are not readily available in many healthcare settings. Second, there is a lack of well-established treatment options specifically targeting CMD. Future research should prioritize the development of effective interventions aimed at improving patients' quality of life. Advancements in this area could pave the way for broader adoption of CMD and vaso-function testing in routine medical practice.

Conclusion

Among individuals without obstructive coronary disease, nearly half exhibit either CMD or coronary vasospasm. While CMD is more prevalent in women, a substantial proportion of men are also affected. The wide-ranging methodologies, definitions, and diagnostic thresholds across studies underscore the need for improved standardization. Greater physician awareness of ischemia without obstructive coronary disease is essential for accurate diagnosis and tailored treatment approaches.

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