

Evaluation of Non-invasive Imaging Parameters in Coronary Microvascular Disease: A Systematic Review

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Abstract

Background: Coronary microvascular dysfunction (CMD) is an important underlying cause of angina pectoris. Currently, no diagnostic tool is available to directly visualize the coronary microvasculature. Invasive microvascular reactivity testing is the diagnostic standard for CMD, but several non-invasive imaging techniques are being evaluated. However, evidence on reported non-invasive parameters and cut-off values is limited. Thus, we aimed to provide an overview of reported non-invasive parameters and corresponding cut-off values for CMD.

Methods: Pubmed and EMBASE databases were systematically searched for studies enrolling patients with angina pectoris without obstructed coronary arteries, investigating at least one non-invasive imaging technique to quantify CMD. Methodological quality assessment of included studies was performed using QUADAS-2.

Results: Thirty-six studies were included. Nine cardiac magnetic resonance (CMR) studies reported MPRI ($n = 9$) and nine positron emission tomography (PET) and transthoracic echocardiography (TTE) studies reported CFR. Mean MPRI ranged from 1.47 ± 0.36 to 1.83 ± 0.50 in patients and from 1.50 ± 0.47 to 2.23 ± 0.37 in healthy controls. Reported mean CFR in PET and TTE ranged from 1.39 ± 0.31 to 2.85 ± 1.35 and 1.69 ± 0.40 to 2.40 ± 0.40 for patients, and 2.68 ± 0.83 to 4.32 ± 1.78 and 2.65 ± 0.65 to 3.31 ± 1.10 for controls, respectively.

Conclusions: This systematic review summarized current evidence on reported parameters and cut-off values to diagnose CMD for various non-invasive imaging modalities. Nonetheless, standardization of methodology and reporting of outcome measures is required to provide clinically applicable reference values.

Background

Patients with angina pectoris (AP) often do not show significant obstructive coronary artery disease (CAD) on coronary angiography (CAG) [1, 2]. Consequently, a cardiac cause of AP complaints is frequently deemed unlikely. Yet, a significant fraction of these patients suffer from cardiac ischemia due to coronary microvascular dysfunction (CMD) [2–6], a condition associated with increased risk of adverse cardiovascular events. This emphasizes the importance of accurate diagnosis of CMD [2, 7–11].

The Coronary Vasomotion Disorders International Study Group (COVADIS) determined the following criteria to diagnose CMD: presence of symptoms and objective documentation of myocardial ischemia, absence of obstructive CAD ($< 50\%$ stenosis and/or fractional flow reserve < 0.8) and confirmed reduced coronary flow reserve (CFR) (and/or inducible microvascular spasm). However, assessment of CMD remains challenging, as no tools are available to directly visualize the coronary microvasculature. In fact, the current golden standard to diagnose CMD is invasive measurement of CFR in epicardial arteries without functionally relevant stenosis [12]. The CFR depicts the increase in coronary blood flow in

response to vasoactive agents [2, 4, 9] and provides indirect quantification of coronary microvascular blood flow [5, 13].

The invasive nature and high costs of coronary reactivity testing (CRT) initiated the search for a non-invasive alternative to diagnose CMD, including myocardial perfusion reserve index (MPRI) measured using cardiac magnetic resonance imaging (CMR), and CFR using positron emission tomography (PET) and transthoracic echocardiography (TTE) [13–16]. Yet, the cut-off value for CFR to diagnose CMD differs between these modalities, is not well validated and, even though sex-differences in coronary physiology are known, the need for a sex-specific cut-off value remains under debate [17]. To date, a CFR below 2.0 to 2.5 is deemed diagnostic for CMD [9, 16, 18–20].

The (dis)advantages of these non-invasive imaging techniques in the diagnosis of CMD have been discussed extensively before [21]. However, it is unclear which outcome parameters and corresponding cut-off values should be used to diagnose CMD. As such, this systematic review aims to provide an overview of currently reported reference and cut-off values for diagnosing CMD in a non-invasive manner.

Methods

Search strategy

On October 15, 2018 the PubMed and EMBASE databases were systematically searched for non-invasive imaging studies on CMD. The search was updated on November 7, 2019. Studies were considered for eligibility without date restriction. The search terms and synonyms of ‘coronary microvascular dysfunction’, ‘nonobstructive coronary disease’ and ‘imaging’, including the imaging modalities CMR, PET and TTE were used. A broad search strategy was performed as studies on CMD are limited and nomenclature of CMD is not standardized. Therefore, search terms were searched for in ‘All Fields’. The detailed search strategy is provided in Additional file 1: Search Strategy.

Study selection

To assess eligibility, the results from the literature search were initially screened by title and abstract and subsequently for full text. Article selection and data extraction were performed independently by two reviewers (RGMK and FG). Observational studies and randomized controlled trials providing baseline outcome measurements were considered for inclusion.

Studies were included if they enrolled participants with AP and CAG or coronary computed tomography angiography confirmed absent or nonobstructive CAD (based on the definition described in the study protocol of the included studies), or healthy participants without prior history of cardiovascular disease or AP as a control group and reported the results of a non-invasive imaging method (i.e. flow parameters measured with either CMR, PET or TTE) to diagnose CMD.

Studies written in languages other than English or Dutch, exclusively consisting of participants with comorbidities, i.e. CAD, diabetes mellitus, aortic stenosis or cardiomyopathies, were excluded. Studies

were excluded if outcomes were not reported as flow parameters, if patients were stratified according to the outcome of interest or if patient or control groups contained fewer than 10 participants.

Quality assessment

A methodological quality assessment was performed with the QUADAS-2 (Tool for the Quality Assessment of Diagnostic Accuracy Studies [22]). Studies were assessed for concerns of applicability ('low', 'high' or 'unclear') and for risk of bias ('low', 'high' or 'unclear') on four key domains (patient selection, index test, reference standard and flow and timing). The assessments per domain were combined into an overall risk of bias and concern of applicability.

Data extraction and analysis

The variables of interest were extracted using a standardized data collection form. Post-hoc evaluations within one clinical trial assessing the same imaging modality were considered as one study. Due to heterogeneity of the included studies, a meta-analysis of the results was not possible.

Results

Search results

The search yielded a total of 6,917 results, 2,541 studies in Pubmed and 4,376 studies in Embase. Removal of duplicates resulted in 5,183 unique entries. After title and abstract screening, 442 possibly relevant studies were obtained. The full texts of these studies were screened to select those that met the inclusion criteria as provided in the methods section. One relevant study was obtained through cross-reference checking. Thirty-six studies met the inclusion criteria and were included in the final analysis. The search and inclusion and exclusion of relevant studies are summarized in Fig. 1. The characteristics of the included studies are summarized in Additional file 2: Table S1. Quality assessment of included studies showed a clear description of the reference standard was not part of the study protocol in most of the included studies. The full assessment is provided in the supplemental material (Additional file 3: Table S2)[22].

Demographic information

The number of patients included in each study was generally small, with a median study population of 22 patients (range: 11 to 963, 89% women) and median of 18 controls (range: 10 to 268, 32% women). The mean age in patient groups ranged from 50.0 ± 7.0 to 66.0 ± 10.0 years of age and 35.3 ± 3.9 to 62.6 ± 9.1 years of age in control groups.

Flow parameters

Different flow parameters were reported (Table 1). In CMR studies, the myocardial perfusion reserve index (MPRI) was most often reported. Other parameters reported were myocardial perfusion reserve (MPR) and CFR. MPR is defined as the ratio between the relative upslope of myocardial signal intensity (obtained

with the use of gadolinium as contrast agent) during stress and rest. In contrast to MPR, the MPRI is corrected for left ventricular contrast signal intensity, allowing for a reduction in signal differences within the image and intra-individual level differences in signal intensity due to heart rate and blood pressure [6, 23, 24]. As such, MPRI is often the preferred outcome measure as it seems to be more accurate in quantifying coronary microvascular blood flow. In one study, CMR-derived CFR results were presented [25]. CFR was calculated and measured in the exact same way as the MPR and can therefore be considered as a synonym of MPR.

In PET studies microvascular function was usually quantified with CFR. Other outcome parameters were MPR or myocardial flow reserve (MFR). MPR and MFR were calculated based on the same methods and measurements as CFR and could therefore be used interchangeably. CFR was defined as the ratio between hyperemic and resting myocardial blood flow (MBF) [26, 27] which was expressed in ml/min/g [28]. CFR was often corrected for rate pressure product (RPP), defined as heart rate multiplied by systolic blood pressure and represents cardiac metabolic demand. This correction is recommended as it reduces variability in outcomes due to person-level differences in systolic blood pressure and heart rate [2, 27].

In TTE studies CFR was used. Similar to PET and CMR, a variety of equivalent terms were reported, namely CFR, coronary blood flow (CBF) and coronary flow velocity reserve (CFVR). CFR, CBF and CFVR were all defined as the ratio of peak stress and rest coronary blood flow velocities (CBFV), usually obtained by spectral Doppler measurements.

Table 1
Overview of outcome parameters considered in this systematic review.

Imaging method	Parameters	Definition
Cardiac magnetic resonance imaging (CMR)	Myocardial perfusion reserve index (MPRI)	$MBF_{\text{stress}}/MBF_{\text{rest}} * \text{LV contrast signal intensity.}$
	Myocardial perfusion reserve (MPR)	$MBF_{\text{stress}}/MBF_{\text{rest}}$
	Coronary flow reserve (corrected for rate pressure product) (CFR (corrected for RPP))	$MBF_{\text{stress}}/MBF_{\text{rest}} * (\text{HR} * \text{SBP} / 10.000)$
Positron emission tomography (PET)	Coronary flow reserve (corrected for rate pressure product) (CFR (corrected for RPP))	$MBF_{\text{stress}}/MBF_{\text{rest}} * (\text{HR} * \text{SBP} / 10.000)$
	Myocardial perfusion reserve (MPR)	$MBF_{\text{stress}}/MBF_{\text{rest}}$
	Myocardial flow reserve (MFR)	$MBF_{\text{stress}}/MBF_{\text{rest}}$
Transthoracic echocardiography (TTE)	Coronary flow reserve (CFR)	$MBF_{\text{stress}}/MBF_{\text{rest}}$
	Coronary flow velocity reserve (CFVR)	$MBF_{\text{stress}}/MBF_{\text{rest}}$
	Coronary blood flow (CBF)	$MBF_{\text{stress}}/MBF_{\text{rest}}$
Abbreviations: HR = heart rate, LV = left ventricular, MBF_{rest} = myocardial blood flow in resting conditions, MBF_{stress} = myocardial blood flow during hyperemic circumstances, SBP = systolic blood pressure.		

CMR imaging

CMR was used to diagnose CMD in 14 of the 38 included studies (Additional file 4: Table S3). CMR results are mostly expressed as the MPRI ($n = 10$). The other outcome parameters mentioned were MPR and CFR ($n = 5$). One study assessed MPRI as well as MPR [29]. Patient groups were globally comparable as all studies included patients with AP without CAD on CAG. Absolute mean transmural mean MPRI values in patient groups ranged from 1.47 ± 0.36 to 1.83 ± 0.50 . In healthy controls, mean MPRI ranged from 1.50 ± 0.47 to 2.23 ± 0.37 . The results of CMR studies with MPRI as outcome parameter in patients and controls are summarized in Fig. 2A.

PET imaging

A total of 13 studies used PET to quantify coronary microvascular function (Additional file 5: Table S4). PET studies reporting mean CFR as outcome measure, mean CFR ranged from 1.39 ± 0.31 to 2.85 ± 1.35 in patient groups. In the control group, mean CFR ranged from 2.68 ± 0.83 to 4.32 ± 1.78 . The results of PET studies with CFR as outcome parameter in patients and controls are summarized in Fig. 2B.

TTE imaging

In 11 studies CMD was assessed by TTE (Additional file 6: Table S5). All studies calculated CFR as the ratio of basal and hyperemic diastolic flow velocity measured in the left anterior descending coronary artery (LAD). In the included TTE studies, patient groups were comparable with regard to inclusion of patients with AP and no or nonobstructive CAD on CAG (Additional file 2: Table S1). Two RCTs were included, mentioning CFR at baseline. A mean CFR of 1.69 ± 0.40 to 2.40 ± 0.40 was found in patients with angina and no CAD on CAG, whereas healthy control subjects show a higher mean CFR of 2.65 ± 0.65 to 3.31 ± 1.10 . An overview of the CFR outcomes of TTE studies in patients and controls is presented in Fig. 2C.

Sex differences

Only one of the included studies compared outcomes between men and women. Sestito et al. [30] determined CBF (defined as the ratio of diastolic CBF velocity at peak stress and rest) using TTE in 71 patients diagnosed with CMD (48 women, 67.6%). No significant difference in CBF was found between men and women (CBF 2.09 ± 0.60 and 2.03 ± 0.50 , respectively).

Discussion

We provided an overview of currently used non-invasive imaging techniques and corresponding reference values for CMD in patients with AP and no or nonobstructive CAD as well as healthy subjects. Mean MPRI determined by CMR ranged from 1.47 ± 0.36 [31] to 1.83 ± 0.50 [32] in patients and from 1.50 ± 0.47 [31] to 2.23 ± 0.37 [6] in healthy controls, CFR by PET and TTE ranged from 1.39 ± 0.31 [33] to 2.85 ± 1.35 [34] and 1.69 ± 0.40 [35] to 2.40 ± 0.40 [36] for patients, and 2.68 ± 0.83 [37] to 4.32 ± 1.78 [38] and 2.65 ± 0.65 [39] to 3.31 ± 1.10 [40] for controls, respectively. Due to the heterogeneity between the included studies we were unable to perform a formal meta-analysis.

MPRI was found to correlate well with invasive measurements obtained with CRT, such as index of microcirculatory resistance and CFR [15, 23]. Therefore, MPRI could potentially serve as a non-invasive alternative to CRT. Current literature proposes two different cut-off values, namely 1.40 and 1.84 [6, 15], corresponding with the results found in this review. However, the results of this review suggest a grey area of MPRI values, as some overlap is seen between MPRI in patients and healthy controls. Stress MBF values can aid in differentiating CMD from normal coronary microvascular function. Liu et al. [15] have shown that a decreased stress MBF (i.e. less than 2.30 ml/min/g) is suggestive of CMD in patients with inconclusive MPRI values. Furthermore, some CMR studies now investigate the clinical applicability of quantitative myocardial tissue characterization with rest and stress T1 mapping as an alternative [29, 41]. Ischemic myocardial tissue can be differentiated from healthy tissue based on distinct properties at T1 mapping during rest and stress conditions, without the use of contrast agents. However, the diagnostic value of T1 mapping in diagnosing CMD still needs extensive validation [29].

Currently, PET is the most frequently applied and validated non-invasive imaging technique in quantifying microvascular blood flow. PET is considered the golden standard of non-invasive diagnosis of CMD, although discordance between invasive fractional flow reserve (FFR) and non-invasive CFR is reported in

up to 30% of cases [16, 26, 27, 42]. CMD is generally diagnosed with a CFR less than 2.0 if corrected for RPP or less than 2.5 if uncorrected [28, 38, 43, 44]. However, no evidence-based cut-off values for CFR in PET are available yet. Similarly, no cut-off values for CFR in TTE have yet been determined and generally a cut-off value of less than 2.0 for the diagnosis of CMD is applied [18, 45–49]. TTE assessment of CFR with Doppler echocardiography has been validated against intracoronary Doppler measurements and outcomes correlate well [2, 5, 36, 50].

Causes of heterogeneity

Patient groups

The heterogeneity in outcomes observed in this systematic review is most likely the result of differences in inclusion criteria applied across several studies and differences in the use of imaging techniques. Although most studies investigated patients with typical AP and no or nonobstructive CAD during diagnostic CAG, the setting in which participants were recruited was not reported clearly. Furthermore, the definition of no or nonobstructive CAD was often unclear and, if documented, heterogeneous among the included studies (Additional file 7: Table S6). Therefore, a more homogeneous definition could not be applied in the search method. Hence, we suggest the use and documentation of standardized criteria as reported by COVADIS [12].

Methodological differences

Uncertainty of the used reference standard, as reflected by the risk of bias assessment (Additional file 3: Table S2), may have introduced significant bias. Moreover, it was often unclear whether researchers were blinded to the reference standard when interpreting results from the index test.

Furthermore, measurement of MPRI in CMR might contribute to the inconsistent results observed in this systematic review. MPRI can be measured transmural, but also subendo- or epicardial. Several studies show subendocardial MPRI to be decreased more often than epicardial MPRI in CMD patients [31, 48, 51, 52], which might indicate subendocardial MPRI to be more valuable in diagnosing CMD as compared with epicardial or transmural MPRI. Unfortunately, in this systematic review only transmural MPRI values were included.

Regarding PET, correction for RPP is not standard which results in decreased comparability of outcomes. Moreover, the use of different radioactive tracers (^{15}O -water, ^{13}N -ammonia and Rubidium-82) could result in varying outcomes due to differences in characteristics and processing of images [14, 27, 28]. The use of a specific radiotracer might require a specific cut-off value to diagnose CMD [14]. Similar concerns apply to the use of various vasoactive agents to achieve hyperemia in stress perfusion imaging. Adenosine and dipyridamole are most commonly administered to achieve hyperemia. However, adenosine seems to be superior to dipyridamole with regard to attaining maximal hyperemia [27, 53, 54].

Lastly, this systematic review highlights the discordance in nomenclature and reporting of outcomes. Standardization of outcome parameters reported could increase comparability of studies assessing reference values for the diagnosis of CMD.

Sex differences

Sex differences could contribute to discrepancies between studies. Kobayashi et al. [17] measured coronary vascular diameter with quantitative CAG and intravascular ultrasound in patients with AP and nonobstructive CAD and found a smaller vascular diameter in women. Furthermore, they showed a significantly higher resting CBF in women. The latter is consistent with findings by Opstal et al. [55] and Chareonthaitawee et al. [56] who studied coronary blood flow in healthy subjects with ^{13}N -ammonia PET ($n = 206$) and ^{15}O -water PET ($n = 169$), respectively. These findings suggest sex differences in flow parameters. High resting myocardial flow volumes could decrease CFR (in PET and TTE) or MPRI (in CMR) in women compared to men as flow parameters are determined as the ratio of stress and rest perfusion. Although sex differences in resting MBF and CFR have been observed in invasive CRT [3, 17, 57], only one of the included studies included assessed sex differences regarding CBF and reported no significant sex differences [30]. These findings are consistent with another study comparing non-invasive CFR between men and women using PET [58]. Therefore, further research is needed to establish whether or not sex-specific cut-off values are required for the non-invasive diagnosis of CMD.

Recommendations for future research

The studies included in this review show heterogeneity in study methodology and outcome. This contributes to the discrepancies in outcomes between studies and to the lack of consensus regarding definition and cut-off values for CMD in non-invasive imaging modalities. We emphasize the need for large validation studies and suggest standardization of outcome parameters to reduce heterogeneity and increase comparability of studies. This is needed to provide clinically applicable, possibly sex-specific, reference values for the diagnosis of CMD in the future. Furthermore, during this systematic review, we found several other imaging modalities that are studied for their potential to diagnose CMD, such as myocardial contrast echocardiography (MCE) [47, 59, 60], CT-perfusion [61] and absolute quantification of myocardial perfusion by CMR [62]. However, current evidence is still limited so the clinical significance and applicability in regular care of these modalities in CMD diagnosis remains unclear.

Study limitations

The number of studies investigating non-invasive imaging techniques to diagnose CMD is limited. As such, the results of this systematic review are based on limited data. Hence, only an indication of reference and cut-off values could be provided. Furthermore, a formal meta-analysis could not be performed due to heterogeneity of included studies. In addition, the risk of selection bias in the included studies was high. These limitations emphasize the importance of standardization of imaging protocols and analyses, patient selection and reporting of outcome measurements to obtain reliable and clinically relevant cut-off values for CMD.

Conclusions

This systematic review provided an overview of currently used parameters and cut-off values for CMD in patients with AP and no or nonobstructive CAD as well as healthy subjects. However, no definite cut-off values could be determined as no meta-analysis could be performed due to heterogeneity of studies investigating non-invasive imaging techniques in CMD.

Abbreviations

AP: angina pectoris

CAD: coronary artery disease

CAG: coronary angiography

CFR: coronary flow reserve

CMD: coronary microvascular dysfunction

CMR: cardiac magnetic resonance imaging

COVADIS: Coronary Vasomotor Disorders International Study Group

CRT: coronary reactivity testing

MBF: myocardial blood flow

MPR: myocardial perfusion reserve

MPRI: myocardial perfusion reserve index

PET: positron emission tomography

TTE: transthoracic echocardiography

Declarations

Ethics approval and consent to participate:

Not applicable

Consent for publication:

Not applicable

Availability of data and materials:

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests:

The authors declare that they have no competing interests

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Authors' contributions:

FG and RGMK participated in the design of the study, collected the data, performed the statistical analysis and drafted the manuscript. GBV participated in the design of the study and assisted with manuscript preparation. SHB, NCOM, HMDR and TL assisted with manuscript preparation. ALME participated in the design of the study and drafted the manuscript. All authors read and approved the final manuscript

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