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The prognostic value of coronary endothelial and microvascular dysfunction in subjects with normal or non-obstructive coronary artery disease: A systematic review and meta-analysis☆,☆☆

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ABSTRACT

Aims: Coronary vascular dysfunction is linked with poor cardiovascular prognosis in patients without obstructive coronary artery disease (CAD) but a critical appraisal of the literature is lacking.
Methods and results: We performed a systematic review and meta-analysis to quantify the cardiovascular risk associated with endothelial dependent and non-endothelial dependent coronary vascular dysfunction in patients with normal or non-obstructive CAD (epicardial stenosis <50%). Prospective cohort studies that reported coronary vascular dysfunction at baseline and cardiovascular outcomes at follow-up were included. We identified 52 papers of which 26 were included in the meta-analyses. Study populations included stable angina ($n = 15$), heart failure ($n = 4$), diabetes ($n = 2$), hypertrophic obstructive cardiomyopathy ($n = 2$), chronic kidney disease, aortic stenosis and left atrial enlargement (each $n = 1$): RR estimates were similar in patients with stable angina and other patient groups. For epicardial endothelial dependent dysfunction (six studies, 243 events in 1192 patients) the summarized RR was 2.38 (95% confidence intervals (95% CI) 1.74–3.25), for non-endothelial dependent dysfunction assessed as coronary flow velocity reserve (CFVR) by echocardiography (10 studies, 428 events in 5134 patients) RR was 4.58 (95% CI 3.58–5.87) and for coronary flow reserve (CFR) by PET (10 studies, 538 events in 3687 patients) RR was 2.44 (95% CI 1.80–3.30). However, RR estimates were robust in a series of sensitivity analyses.
Conclusion: The presence of coronary vascular dysfunction in patients with normal or non-obstructive CAD predicts adverse cardiovascular outcome. Multicentre studies and uniform guidelines for assessing coronary vascular dysfunction are encouraged.

1. Introduction

Obstructive coronary artery disease (CAD) is considered the leading cause of myocardial ischemia. Recurrent symptoms of chest pain may, however, occur in the absence of significant epicardial disease confirmed by normal or non-obstructive CAD on coronary angiography (CAG) [1,2]. In recent years more studies have focused on pathological alterations of epicardial and microvascular vessels, suggesting coronary vascular dysfunction as a possible underlying cause of myocardial ischemia [3–6]. The condition is increasingly recognized and was recently coined INOCA – ischemia and no obstructive coronary artery disease [7].

Coronary vascular dysfunction has been linked to cardiovascular risk factors such as age [8], smoking [9–11], hypertension [12], hypercholesterolemia [13], menopause [14] and diabetes [15–18]. The pathogenesis is multifactorial, comprising both vascular and non-vascular dysfunction resulting in impaired vasodilation [19]. Vascular dysfunction may be characterized as microvascular or epicardial and may be through endothelial dependent and non-endothelial dependent mechanisms.

The function of the epicardial vessels is assessed invasively during angiography mainly with stimulation by acethylcholine (ACh) for endothelial-dependent function and adenosine for non-endothelial-dependent function, but other stressors are also used. The healthy epicardial response to ACh is vasodilation but some degree of vasoconstriction in the distal coronary arteries may occur [20]. Endothelial

Abbreviations: ACh, acetylcholine; CAD, coronary artery disease; CAG, coronary angiography; CFVR, coronary flow velocity reserve; CFR, coronary flow reserve; CPT, cold pressor test; MOOSE, meta-analysis of observational studies in epidemiology; NIH, the US National Heart, Lung and Blood Institute; TTDE, transthoracic doppler echocardiography; TEDE, transesophageal doppler echocardiography; PET, positron emission tomography; PRISMA, preferred reporting items for systematic reviews and meta-analyses; PROSPERO, International Prospective Register of Systematic Reviews.

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dysfunction may result in lack of dilation or paradoxical constriction. While endothelial function of the epicardial vessels can be assessed visually, microvascular function can be examined indirectly by assessing baseline and hyperemic blood flow. In the absence of significant epicardial stenoses, flow resistance in the coronary arteries is determined by the microvasculature. The ratio of hyperemic to basal blood flow, the coronary flow reserve (CFR), is thus a measure of the microvascular function. In studies of microvascular function, maximal coronary blood flow is mainly elicited by adenosine or dipyridamole stress, i.e. through non-endothelial dependent mechanisms. The most established non-invasive techniques for CFR are transthoracic Doppler echocardiography (TTDE) and positron emission tomography (PET). Magnetic resonance imaging (MRI) [21,22] and myocardial contrast echocardiography (MCE) have also been applied [23,24]. Cold-pressor test (CPT) may be used to assess endothelial dependent coronary vasodilator function non-invasively by PET or TTDE [25].

In large prospective studies of patients with angina but no evidence of significant epicardial stenosis, the prevalence of coronary vascular dysfunction has been reported to be between 24% and 53% [26–28]. In other conditions such as cardiomyopathy and diabetes the prevalence of microvascular dysfunction has been reported to be high. Furthermore, multiple studies have reported an independent association between presence of coronary vascular dysfunction and adverse outcomes, however, most of these studies are small-scaled with a short-term follow-up. To the best of our knowledge, no systematic evaluation has been done to assess the consistency across these studies.

As stated by Camici et al. [3] multiple mechanisms may lead to coronary vascular dysfunction. The primary task of this systematic review and meta-analysis was to explore and discuss the prognostic value of coronary vascular dysfunction in patients without obstructive CAD and to provide a complete overview of the field across different patient groups. However, it was not our aim to investigate the underlying pathophysiology of coronary vascular dysfunction.

2. Methods

We conducted a systematic review and meta-analysis of prospective cohort studies reporting associations between coronary vascular dysfunction at baseline and cardiovascular events at follow-up. Reporting was done in accordance to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [29] and Meta-analysis of Observational Studies in Epidemiology guidelines (MOOSE) [30] models. This systematic review and meta-analysis was registered at the International Prospective Register of Systematic Reviews (PROSPERO; No.: CRD42016042618) [31].

Further details on method is found in the Online Supplemental Material.

2.1. Literature search

The search design consisted of three categories each containing medical subject headings and keywords separated by OR. The first category defined coronary vascular function, the second described coronary heart disease, and the third identified prospective study design (the exact search strategy is displayed in the Online Supplementary Fig. 1). PubMed and Embase were searched for papers published between January 1990 and September 2017.

Articles were restricted to published literature and English language only. No restrictions were applied in regard to age, gender or race. Animal studies were excluded. Additionally, reference lists of eligible studies and recent systematic reviews were screened to identify relevant studies.

2.2. Selection criteria

Studies were included using the following selection criteria: (i) studies presenting original data from prospective observational studies; (ii) the exposure of interest was coronary vascular dysfunction at baseline examined either invasively during CAG, or non-invasively by PET or TTDE/transesophageal doppler echocardiography (TEDE); (iii) study population samples with suspected CAD/stable angina pectoris, diabetes, chronic kidney disease, heart failure (HF), cardiomyopathies or valvular heart disease; (iv) patients with either normal or non-obstructive CAD (defined as <50% luminal narrowing) on invasive or computed tomography angiography or without evidence of epicardial stenosis assessed by one of the following non-invasive procedures: PET, single-photon emission computed tomography (SPECT), stress TTDE/TEDE or MRI; (v) the outcome of interest was incident fatal and non-fatal coronary heart disease, including myocardial infarction (MI), percutaneous coronary intervention, coronary artery bypass grafting, HF, cardiac death, cerebrovascular events (transient cerebral ischemia, stroke), or all-cause mortality; and, (vi) studies provided enough information to abstract relative risk (RR) or hazard ratio (HR). For studies not reporting results for patients without obstructive CAD separately, results adjusted for ischemia/scar in a multivariable analysis were accepted. When studies assessed CAD invasively and (i) no information on degree of stenosis was available or (ii) findings were described as probable of "moderate/severe" stenosis or (iii) warranted revascularization, we excluded the study.

Studies were excluded if (i) assessment of coronary vascular function was conducted immediately after an acute onset of cardiovascular symptoms, during acute cardiac catheter interventions or elective STENT-procedures; (ii) assessment of coronary vascular function was conducted in a stenosis-free coronary artery in patients with known obstructive CAD; (iii) patients had a heart transplant or known Takotsubo cardiomyopathy, and; (iv) studies of vasospastic angina. We also excluded studies using thermodilution to invasively assess microvascular resistance as this method was regarded as less validated. MRI studies were not included in the analysis because we regarded this approach as currently less validated for assessing microvascular function and only few, small prospective studies have applied this procedure in cohorts with no significant CAD [19,32].

In cases where overlap in study populations were suspected, the senior author of the studies in question was contacted to identify possible overlap. In cases of duplicates, the article with the greatest number of outcomes was included in the meta-analysis.

3. Results

The systematic search identified 14,612 studies (Fig. 1). Of these, 103 studies were assessed in full text.

Five studies [33–37] assessed non-endothelial dependent microvascular function invasively with adenosine in patients with intermediate stenosis (40–70%) and fractional flow reserve >0.80, however, the anatomic evidence of obstructive CAD conflicted with the inclusion criteria and these studies were therefore excluded (Online Supplementary Table 1).

A total of 52 studies met inclusion criteria for the systematic review. Three study groups had published publications on partially overlapping populations, and after contacting the authors, overlaps were identified and 23 studies were excluded. Three more studies were excluded due to insufficient data to calculate RR or too few outcomes (Online Supplementary Tables 2–4). In total, 26 studies were included in the meta-analyses [24,26–28,41,43–63] (Online Supplementary Tables 5–7).

All 52 studies included in the systematic review were prospective studies published between 2002 and 2016. Studies for meta-analyses comprised 10,013 participants, mean age ranging from 44 to 73 years, enrolled in study cohorts from 1989 to 2011. The female proportion ranged from 21% to 100%. The mean follow-up period varied from 0.7 to 9.7 years and the proportion of loss to follow-up varied from 0 to 34%. Eight studies reported on all-cause mortality (444 events) and 18 studies on cardiovascular events (809 events). Most studies assessed stable angina populations but some were dedicated to specific subpopulations: hypertrophic cardiomyopathy [49,56], HF [24,48,55,62], aortic stenosis [54], diabetes [45,52], left atrial enlargement [63] and chronic kidney disease [53]. Cut-off point defining vascular dysfunction varied and is described in the Online Supplementary Tables 2–7. Applying the NIH-quality assessment tool all studies scored a rating of at least 'fair', indicating an acceptable overall quality (Online Supplementary Table 8).

3.1. Classification of studies

Studies were divided into three groups according to pathophysiology assessed and methods of assessment: Studies of epicardial endothelial dependent dysfunction assessed invasively or by PET and studies assessing non-endothelial dependent function as coronary flow velocity reserve (CFVR) or CFR by either TTDE/TEDE or PET (Online Supplementary Fig. 2).

We only identified four studies assessing endothelial dependent microvascular function using different methods [39,41,43,44] and these were not included in the meta-analyses. One study [42] examined non-endothelial dependent microvascular function by CAG