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Flow-mediated dilation and cardiovascular risk prediction: A systematic review with meta-analysis ☆

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ABSTRACT

Background: Flow-mediated dilation (FMD) is an accepted technique to quantify endothelial function and has shown to have prognostic value for future cardiovascular disease (CVD). The predictive strength of FMD in CVD patients compared to populations not diagnosed for CVD warrants further investigation. We systematically reviewed prospective studies that investigated the association between brachial FMD and future cardiovascular events, with particular focus on the role of underlying health status.

Methods: To obtain eligible studies, several literature databases were systematically searched through March 2011. Pooled overall risk estimates were calculated separately for continuous risk estimates for CVD (per 1% higher FMD) and for categorical risk estimates for CVD (having high vs. low FMD), based on random-effects models.

Results: A total of 23 studies including 14,753 subjects were eligible for inclusion in the meta-analysis. For studies reporting continuous risk estimates, the pooled overall CVD risk was 0.92 (95%CI: 0.88; 0.95) per 1% higher FMD. The observed association seemed stronger (P-value<0.01) in diseased populations than in asymptomatic populations (0.87 (95%CI: 0.83; 0.92) and 0.96 (95%CI: 0.92; 1.00) per 1% higher FMD, respectively). For studies reporting categorical risk estimates, the pooled overall CVD risk for high vs. low FMD was similar in both types of populations, on average 0.49 (95%CI: 0.39; 0.62).

Conclusions: Our findings show that brachial FMD is inversely associated with future CVD events, with some indications for a stronger relation in diseased populations. Endothelial dysfunction may be considered relevant for classifying subjects in terms of CVD risk.

1. Introduction

Endothelial cells form the inner lining of all blood vessels and play a central role in vascular homeostasis; they respond to stimuli such as hemodynamic changes or blood-borne signals by releasing vasoactive substances [1]. Disruption of the normal homeostatic endothelial condition is identified as endothelial dysfunction. The pathophysiological role of endothelial dysfunction in the development of atherosclerosis and cardiovascular disease (CVD) is well established [2–4].

Endothelial (dys)function can be quantified by the degree of flow-mediated dilation (FMD) of the brachial artery [5,6]. This technique is widely used and non-invasive. FMD is determined by the change in brachial artery diameter in response to a blood flow stimulus. This stimulus is created by releasing an arm cuff that is inflated to supra-systolic blood pressure level. As a consequence, nitric oxide (NO) is released from the endothelial cells and mediates the relaxation of the smooth muscle cells with subsequent widening of the artery.

The association between brachial FMD and CVD risk has been investigated in several prospective studies. Although not conclusive [7,8], the majority of these studies showed that FMD is inversely associated with future cardiovascular events [9–12]. A meta-analysis summarizing the evidence of 14 prospective studies revealed that per 1% higher FMD, the risk of experiencing a cardiovascular event is 13% lower [13]. Since then, several large prospective studies have been published addressing the same research question, but adding to the evidence especially for asymptomatic populations [14–17] and Asian populations [18–20]. Moreover, recent evidence in asymptomatic populations suggests that, in this specific population, the association between FMD and CVD risk may not be present [15–17]. Thus, the applicability of these data to populations not specifically being diagnosed for any disease remains to be determined. Therefore, we performed a meta-analysis on this association, with particular focus on the impact of underlying health status.

☆ These 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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The purpose of the present study was to systematically review prospective studies that investigated the association between brachial FMD at baseline and future cardiovascular events in populations at different CVD risk. The relationship between FMD and CVD risk was quantitatively assessed, separately for studies that reported continuous relations (risk estimates expressed as the risk of CVD per 1% higher FMD) and for studies that reported categorical relations (risk estimates expressed as the risk of CVD for groups with high FMD compared to those with low FMD), by means of a meta-analysis of studies eligible for this purpose. Sources of variability in results across studies, especially underlying health status, were investigated.

2. Methods

2.1. Search strategy

Potentially relevant prospective studies investigating the association between FMD and CVD risk were searched in the databases Medline, Embase and Chemical Abstracts (through March 2011). Search terms related to the 'exposure variable' included: flow mediated vasodilation (or vasodilatation or dilation or dilatation) or endothelial (or endothelium) dependent vasodilation (or vasodilatation or dilation or dilatation) or endothelial (or endothelium) function (or dysfunction), or FMD or vascular reactivity, and brachial artery. For the 'outcome variable', search terms included the MeSH terms cardiovascular diseases, coronary disease, myocardial ischemia, myocardial infarction, stroke, brain ischemia, and intracranial hemorrhage, and the search terms cardiovascular or vascular or cardiac or myocardial or heart or coronary or cerebrovascular or cerebral or brain, and infarct or attack or event or accident or disease or disorder or isch(a)emia or h(a)emorrhage or death or mortality, or stroke. The systematic search was limited to studies in humans and to the English language. Reference lists from obtained articles were searched for additional potentially relevant studies.

2.2. Selection of trials

Studies were selected following a two-step approach. First, titles and abstracts were screened to identify potentially eligible studies. In a second step, full-texts of the studies were scrutinized to judge eligibility based on the following selection criteria: (a) prospective studies with follow-up time of >1 year; (b) description of risk estimates for the association between endothelial function and future CVD events; (c) measurement of endothelial function as expressed by FMD of the brachial artery; (d) inclusion of human adults; and (e) original data only. When inconclusive, eligibility was discussed among authors until consensus was reached. A few eligible studies did not properly report risk estimates with accompanying variance measures; these studies were therefore excluded from the quantitative analysis [21–26].

2.3. Data extraction

Using a standardized data collection sheet, data were extracted on (a) general characteristics (extraction date and reference information); (b) study characteristics (study objective, type of study population (diseased or asymptomatic population), sample size, country, duration of follow-up, age, body mass index, gender distribution, and medication use); (c) exposure characteristics (baseline FMD, FMD categories (e.g. based on medians or tertiles), and information on FMD methodology (e.g. cuff position and time of occlusion)); (d) outcome characteristics (number of cardiovascular events and type of events (e.g. cardiac death, myocardial infarction (MI) or stroke)) (e) calculated risk estimates for the association between FMD and CVD and covariates adjusted for; and (f) study quality. When data were missing, the original authors were contacted in an attempt to obtain these data.

FMD was defined as the change in brachial artery diameter in response to an increased blood flow after release of an inflated arm cuff. Thus, FMD (%) is expressed as: [(hyperemic diameter − resting diameter)/resting diameter]∗100, where resting diameter is the diameter of the brachial artery before any flow stimulus in the artery is created, and hyperemic diameter is the maximal diameter of the artery reached within minutes of reperfusion following the release of an inflated cuff.

Major CVD outcomes included cardiac death, MI and stroke. The association between FMD and future CVD risk was expressed differently across studies, either as hazard ratio (HR) or as odds ratio (OR). The main difference between these risk estimates is that the HR takes into account the time to event, whilst the OR does not differentiate when the event occurred. In addition, HR and OR were either expressed continuously (i.e. risk of CVD per unit FMD (% or SD)) or categorically (i.e. relative risk of CVD for groups with high vs. low FMD based on the median FMD or based on a defined cut-off point for 'impaired FMD').

For our quantitative analysis, we selected the risk estimates from each study that were adjusted for CVD risk factors (e.g. smoking, diabetes, cholesterol, blood pressure) and other covariates. Two studies solely reported unadjusted risk estimates [8,15] and were used instead. For studies that reported more than one adjusted risk estimate (e.g. risk estimates for more than two FMD categories: intermediate vs. high FMD and low vs. high FMD), the average risk estimate was used in the meta-analysis [7,19,27,28].

Several imputations were made to complete the data set for meta-analysis. In one study [27], the midpoint of the intermediate FMD tertile was taken as the average baseline FMD in that study; in another study, the original authors defined a cut-off point for impaired FMD which was taken as the average FMD at baseline [29]. In a third case [30], it was assumed that the inflation cuff was placed around the forearm, because this type of cuff placement was used in most studies that reported the site of cuff placement (in 19 out of 26 studies).

Quality of studies was assessed using a tool that was developed based on the Downs and Black [31] quality criteria checklist. Through discussion among authors, this list was adapted for use in the current study. Scoring the quality of studies is intrinsically subjective, and therefore, the quality assessment was not used for excluding studies but rather for descriptive purposes and covariate analysis.

2.4. Statistical analysis

We considered HRs as estimates of the relative risk (RR), whereas we converted ORs to RR estimates using the method by Zhang and Yu [32]. This method takes into account the overestimation of the RR by the OR which is especially the case when the outcome of interest is common. For one study, the publication did not provide sufficient information to convert the data [17] and the OR was included as RR.

In order to transform categorical risk estimates into continuous risk estimates, one would need to assume that the relationship between FMD and CVD risk is linear. However, this assumption can be debated [17,28] and, therefore, we discriminated in the current analysis those studies reporting continuous risk estimates and those reporting categorical risk estimates, and conducted separate analyses for each of these outcome measures. Continuous risk estimates were converted if needed so that they were all estimates of the risk per 1% higher FMD. For categorical risk estimates, the inverse was taken of the estimates comparing low vs. high FMD. In this way, the associations between FMD and CVD risk were expressed in the same direction for both continuous and categorical risk estimates.

All logarithmic risk estimates and their 95% confidence intervals (95%CIs) were transformed to the normal scale. Based on the confidence intervals, standard errors (SEs) were calculated. These SEs were used for weighing the studies, giving more weight to studies with less variation. For calculating the pooled overall risk estimate, we used a random-effects model which takes into account both within- and between-study variability [33]. Heterogeneity between studies was tested using the Cochran's Q-statistic and the I^2-statistic [34,35], with an I^2-statistic above 50% as an indicator of significant heterogeneity [36]. To investigate potential sources of heterogeneity, we performed meta-regression with backward selection and subgroup analyses for the predefined variables age, gender, baseline FMD, follow-up duration, population size, annual event rate, FMD methodology (upper arm or forearm occlusion), health status (asymptomatic or diseased), ethnicity (American, European, Asian, Middle-Eastern), and study quality. For the continuous covariates, studies were divided into two subgroups based on the medians. Subgroups with less than three studies were not considered for subgroup analysis. Finally, publication bias was examined based on Egger's regression asymmetry method (intercept P-value<0.1 indicates asymmetry and thus publication bias) [37].

The authors of this manuscript have certified that they comply with the Principles of Ethical Publishing in the International Journal of Cardiology.

3. Results

3.1. Selection process

In total, 1004 studies were obtained with the systematic search; an additional 16 studies were obtained via hand searching. After two selection steps, 29 prospective studies investigating the association between FMD and CVD events in adults were judged eligible for inclusion in the current review, of which 23 studies were suitable for a quantitative meta-analysis (Fig. 1).

3.2. Overview of included studies

In the 23 studies eligible for the meta-analysis, the number of subjects per study ranged from 73 to 3025 subjects, with 14,753 subjects participating in total (Table 1). Subjects were followed for an average duration of 42.9 months (range: 12.1–94.6 months). The mean age was 60.1 years (range: 46.0–78.6 years), and on average two-third of the total study population was men. In eight out of 23 studies, asymptomatic subjects (healthy subjects [15,38], postmenopausal women [27], a multi-ethnic community cohort [16],uncomplicated hypertensives [9] and population-based cohorts of older adults [17,39]) were included whereas in 15 studies, subjects