Inflammation and coronary microvascular dysfunction in middle-aged women, a pilot study

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Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Coronary artery disorders
Study type	Observational non invasive

Summary

ID

NL-OMON43529

Source
ToetsingOnline

Brief title
pilot inflammation MCD

Condition

- Coronary artery disorders

Synonym
microvascular coronary dysfunction

Research involving
Human

Sponsors and support

Primary sponsor: cardiologie
Source(s) of monetary or material Support: aanwezige onderzoeksgeld exp lab afd interne geneeskunde

Intervention

Keyword: endothelial dysfunction, inflammation, microcirculation, women

Outcome measures

Primary outcome

presence and inducible pro-inflammatory cytokines

Secondary outcome

not applicable

Study description

Background summary

Coronary microvascular dysfunction (CMD) consists of abnormalities in the regulation of myocardial blood flow (MBF) and coronary flow reserve (CFR) that cannot be attributed to epicardial coronary arterial disease (CAD). It is considered an early manifestation of a mismatch of myocardial blood flow and myocardial metabolic demand (1). Although CMD is a type of ischemic heart disease (IHD), myocardial ischemia is not apparent in all CMD patients but occurs with longer duration of exposure to this mismatch (2). This disease relatively frequently occurs in middle aged women with multiple cardiovascular risk factors but no obstructive coronary artery disease of the large coronaries. CMD is not a benign disease, but it is associated with increased rates of hospitalization and adverse cardiovascular events, including sudden cardiac death, myocardial infarction, congestive heart failure, and coronary revascularization (3). Although the exact pathophysiologic mechanisms underlying CMD are poorly understood, both endothelial and non-endothelial dependent impaired vasoreactivity plays an important role. Other leading contenders are inappropriate sympathetic tone, microvascular atherosclerosis and inflammation (1, 3, 4).
Both CMD and systemic autoimmune diseases (SAD) occur more often in women than in men and several studies have found that SAD patients exhibit inflammatory mediators in the perivascular layers more frequent than in the general population (2). Chronic inflammation and immune dysregulation play a pathogenetic role in the development of atherosclerosis adding as an additional risk for CVD even in the absence of traditional risk factors (5).
There are numerous studies that indicate that inflammation plays a pivotal role in atherogenesis (5-7) and Increasing data indicate that there are important gender differences in immune mechanisms that play a role in the development of

atherosclerosis (8). However, there is little evidence when it comes to CMD.

It is now widely accepted that the innate immune system plays a central role in the development of atherosclerosis. Recently, it has been reported that monocytes/macrophages can adopt a long-term pro-inflammatory phenotype after microbial stimulation via epigenetic reprogramming; this mechanism is termed *trained immunity* (9). Importantly, endogenous atherogenic substances such as oxidized LDL particles (10) or lipoprotein (a) (unpublished data) can also skew monocytes into this long-term activated phenotype. The trained phenotype is associated with increased production of pro-atherogenic cytokines and chemokines and increased foam cell formation. Therefore, we speculated that trained innate immunity contributes to the development of atherosclerosis. Through this mechanism, monocyte-derived macrophages that are the most abundant immune cells in atherosclerotic plaques, can adopt this long-term proinflammatory phenotype leading to excessive production of cytokines. There are also some reports demonstrating that platelet adhesion and activation not only account for the increased incidence of thrombosis that is associated with acute and chronic inflammatory conditions, but also intensifies, via contact-dependent and-independent mechanisms, the activation of vascular endothelial cells and leucocytes in inflamed microvessels, promoting vascular remodeling (8). Additionally, the members of the matrix metalloproteinase (MMP) family directly modulate platelet activation and thrombus formation under flow and are capable of degrading the underlying collagen matrix, thereby restricting future thrombus formation (4).

Study objective

The goal of this pilot study is to investigate whether circulating monocytes of patients with MCD are characterized by a trained phenotype, so we can ascertain whether trained innate immunity may contribute to microvascular wall inflammation in these patients.

Study design

case-control, pilot study

Study burden and risks

a single venapuncture of 30cc blood

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

12 female patients with microvascular angina and an age-gender-matched controlgroup of 12 women

Exclusion criteria

male participants
obstructive coronary disease

Study design

Design

Study type: Observational non invasive

Intervention model:	Other
Allocation:	Non-randomized controlled trial
Masking:	Open (masking not used)

Primary purpose: Basic science

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	01-07-2016
Enrollment:	0
Type:	Actual

Ethics review

Approved WMO

Date:	14-03-2016
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
CCMO	NL56249.091.15