Myeloid cell reprogramming in aortic valve stenosis

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To test the hypothesis that patients with AoS have a higher prevalence of CHIP driving mutations compared to control subjects. Secondary objectives are to perform extensive phenotyping of circulating monocytes.

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Cardiac valve disorders
Study type	Observational invasive

Summary

ID

NL-OMON52396

Source
ToetsingOnline

Brief title
Monocytes in aortic valve stenosis

Condition

- Cardiac valve disorders

Synonym
Aortic valve stenosis, cardiac valvular disease

Research involving
Human

Sponsors and support

Primary sponsor: Radboud Universitair Medisch Centrum
Source(s) of monetary or material Support: Ministerie van OC&W

Intervention

Keyword: aortic valve stenosis, clonal hematopoeisis, inflammation, monocyte

Outcome measures

Primary outcome

Frequency of CHIP driver mutations in blood cells.

Secondary outcome

Secondary endpoint is cytokine production capacity of isolated innate immunce cells.

Other explorative endpoints include leukocyte composition,cytokine production capacity and ROS production of isolated neutrophils, circulating markers of inflammation, including cytokines and chemokines, circulating metabolome and proteome, deep transcriptional phenotyping of circulating monocytes and neutrophils is a subgroup of patients (from all subjects, these cells will be isolated and stored in liquid nitrogen), detection of epigenetic markers, as a marker for trained immunity, on a selection of samples, histopathological examination of (a selection of) sugically removed valvular tissue.

The researcher will call all participants after 2 and 5 year and check medical files to be able to explore whether the immunological parameters are associated with incident cardiovascular events and disease progression.

Study description

Background summary

Calcific aortic valve stenosis (AoS) is the most common form of valvular heart disease in the Western world, which can cause heart failure, syncope, and angina. Due to the fact that the underlying pathophysiology remains incompletely defined, there are currently no effective medical treatments capable of altering its course, identifying a major unmet need in this growing population of patients. AoS resembles atherosclerosis, which is the main cause of myocardial infarction and stroke, in pathology, and shared risk factors. We have recently reported pro-inflammatory reprogramming of circulating monocytes in patients with atherosclerosis of risk factors of atherosclerosis. In addition, clonal expansion of monocytes with mutations in epigenetic regulators (clonal hematopoiesis of indeterminate potential; CHIP), which enhance cytokine production, is associated with atherosclerosis. Based on these findings, we now propose to test our hypothesis that inflammatory reprogramming of circulating monocytes contributes to the development of AoS. Proof of this hypothesis will have huge clinical implications and paves the road for clinical studies with anti-inflammatory drugs in this patient group.

Study objective

To test the hypothesis that patients with AoS have a higher prevalence of CHIP driving mutations compared to control subjects. Secondary objectives are to perform extensive phenotyping of circulating monocytes.

Study design

This study is a single-center observational prospective case-control study. Between May 2020 and May 2022.

Study burden and risks

There will be no risk, since participation will only include one venous blood sample. Control subjects will also have a cardiac ultrasound, which is non-invasive and does not impose any risk. Participants will not have any direct benefit from participation.

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

- Age > 18 years
- Mild, moderate or Severe degenerative aortic valve stenosis as defined by transthoracic echocardiography according to the 2017 ESC/EACTS guidelines for the management of valvular heart disease.

- for the control group:
- 150 healthy subjects without aortic valve stenosis
- 50 subjects with aortic valve stenosis due to congenital biscuspid valve

Exclusion criteria

For patients and controls:
- Active auto-inflammatory or auto-immune diseases
- Anti-inflammatory drugs
- Vaccination less than one month before inclusion
- Bone marrow transplantation
- Active malignancy, except for local basal cell carcinoma or local squamous cell skin carcinoma, that can be treated curatively by excision.
- History of endocarditis of the aortic valve

- History of radiation therapy aimed at the chest
- Acute ischemic cardiac event less than three months before inclusion
- Systemic inflammation less than one month before inclusion with fever and/or for which antibiotics have been prescribed, with the exception for the use of nitrofurantoin for a urinary tract infection without fever.

Extra exclusion for healthy control subjects:
- History of atherosclerotic cardiovascular events
- Current typical complaints of angina pectoris or intermittent claudication.
- Overt heart failure (NYHA class III/IV)
- Aortic valve stenosis on screenings echocardiography, that will be performed before inclusion. Mild aortic valve sclerosis is allowed.

Extra exclusion for controls with aortic valve stenosis due to a bicuspid valve:
- History of atherosclerotic cardiovascular events
- Current typical complaints of angina pectoris or intermittent claudication.

Study design

Design

Study type:	Observational invasive
Intervention model:	Other
Allocation:	Non-randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Basic science

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	19-11-2020
Enrollment:	400
Type:	Actual

Ethics review

Approved WMO Date:	28-04-2020
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	17-08-2020
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	16-02-2021
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	15-03-2022
Application type:	Amendment
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
ClinicalTrials.gov	NCT04717219
CCMO	NL72973.091.20