Genes and gene-function in bicuspid aortic valves

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

Summary

ID

NL-OMON35653

Source
ToetsingOnline

Brief title
Genes in bicuspid aortic valves

Condition

- Cardiac valve disorders
- Cardiac and vascular disorders congenital

Synonym
bicuspid aortic valve

Research involving
Human

Sponsors and support

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

Intervention

Keyword: bicuspid aortic valve, gene, gene function

Outcome measures

Primary outcome

Identifying gene variations/mutations in patients with a bicuspid aortic valve

and severe aortic stenosis, who will undergo aortic valve replacement therapy.

Occurrence of gene variations/mutations in a cohort of patients with a stenotic

aortic valve.

Secondary outcome

Characterize the nature and effect of any mutations identified.

Study description

Background summary

The prevalence of a bicuspid aortic valve in the general population is 0.5-0.8%. Among family members there is a high heritability. Thus far two studies have found mutations in the NOTCH gene in either related or unrelated patients with a bicuspid aortic valve, important for epithelial mesenchymal transformation (EMT), which is important for valve formation. Several other genes have been suggested important for EMT. To date human research has not focused on the potential importance of mutation in these genes in developing bicuspid aortic valves.
Bicuspid aortic valves progress more rapidly into stenotic pathology than the normal tricuspid aortic valves. Moreover these patients with a bicuspid aortic valve are also more prone for life threatening events such as aortic dissection and sudden cardiac death. Early identification of patients with a bicuspid aortic valve is needed.

Study objective

The primary objective of this study is to identify mutations associated with the development of a bicuspid aortic valve. To this end the study will focus on genes important for aortic valve formation. As an extension of the primary objective, a second objective is to characterize the nature and effect of any

mutations identified, thus generating a more causal link to the development of bicuspid aortic valves.

Study design

This study would be a multicenter observational cross-sectional study.
Patients whom have a planned aortic valve replacement because of severe aortic stenosis are approached for this study. Informed consent is obtained and 20 ml of blood will be drawn for genomic DNA extraction.
On the day of admission all patients undergo a computed tomography of the heart in addition to the standard preoperative diagnostic imaging.
During valve surgery the aortic valves are photographed, excised and these valves are anatomically inspected by the thoracic surgeon. The aortic wall is inspected for dilatation and other aortic pathology. The aortic valve leaflets are immediately taken to the department of pathology. Then the aortic valve leaflets will be inspected and photographed by the pathologist. The aortic valve leaflets will be subsequently bisected. One half of the material will be snap frozen in liquid nitrogen and the remaining half will be placed in formalin for fixation. Both frozen and fixed tissue can be placed in long-term storage at -80 *C and room temperature, respectively, until analysis (in a tissue bank).DNA is sequences as described. Polymerase chain reaction (PCR) will be used to amplify candidate genes of interest, followed by sequencing reactions to screen for mutation within the coding region of such genes.Then the nature and effect of any mutations identified will be characterized by functional analyses.

Study burden and risks

The risks for the patients are increased with the addition of computed tomography of the heart for each patient. However, the risks be equal to the social importance of early identification of these young patients.
Subsequently, 20 ml of blood will be drawn on top of regular vena punction and the aortic valve, when excised, are obtained and stored in a tissue bank.

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

Patients are included in this study with severe aortic stenosis and planned surgical aortic valve replacement when they*re at least 18 years old and not fitting any of the exclusion criteria. Written informed consent.

Exclusion criteria

Patients with concomitant heart disease: previous myocardial infarction, endocarditis, patients with prior aortic valve replacement and aortic insufficiency. Patients younger than 18 years of age are also excluded from participation in this study. Patients who have a syndromic or genetic diagnosis, for example, Marfan*s disease, trisomy 21 and Turner*s syndrome.

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:	Recruitment stopped
Start date (anticipated):	19-06-2007
Enrollment:	434
Type:	Actual

Ethics review

Approved WMO Date:	10-04-2007
Application type:	First submission
Review commission:	METC NedMec
Approved WMO Date:	08-07-2008
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	15-07-2010
Application type:	Amendment
Review commission:	METC NedMec

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	NL15597.041.07