Cardiac disease in Ankylosing Spondylitis

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Primary objective: To investigate left ventricular diastolic function in AS-patients compared with osteoarthritis patients. Secondary objectives: To assess the prevalence of valvular heart diseases and conduction disturbances. To assess left...

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

Summary

ID

NL-OMON41462

Source
ToetsingOnline

Brief title
Cardiac disease in Ankylosing Spondylitis

Condition

- Myocardial disorders
- Arteriosclerosis, stenosis, vascular insufficiency and necrosis

Synonym
Ankylosing Spondylitis

Research involving
Human

Sponsors and support

Primary sponsor: Jan van Breemen Instituut
Source(s) of monetary or material Support: Jan van Breemeninstituut en Vrije Universiteit

Intervention

Keyword: Ankylosing spondylitis, Cardiomyopathy, Electrocardiography, Transthoracic Echography

Outcome measures

Primary outcome

Diastolic dysfunction will be defined as follows: mild diastolic dysfunction

(stage I*impaired relaxation). Characterized by an E/A ratio <1, Em/Am <1,

prolonged DT (>240 ms), and IVRT (>110 ms). Em (<8 cm/s) is reduced. E/Em is

<10. Moderate diastolic dysfunction (stage II* pseudo normalization).

Characterized by an E/A ratio >1, Em/Am <1. Em (<8 cm/s) is reduced and E/Em is

>10. Severe diastolic dysfunction (stage III* restrictive filling). This stage

is characterized by an overt increased E/A ratio (>2), shortened DT (<150 ms),

and IVRT (<60 ms). Em (<8 cm/s) remains at the lowest level. E/Em is >10.

(13,20)

Secondary outcome

Systolic dysfunction will be defined as an ejection fraction of <50%.

Study description

Background summary

Increased cardiovascular mortality and cardiovascular morbidity
The overall mortality rate in AS patients is increased 60-90% compared with the general population(1). This higher mortality rate is predominately caused by increased cardiovascular (CV) risk(2,3). The cause of death in patients with AS is mainly of circulatory origin, ranging in different studies from 17-40% of total deaths(4). This increased mortality of circulatory origin is attributable to both an increase in cardiac diseases such as valvular heart disease, conduction disturbances and cardiomyopathies, and an increase in atherosclerotic disease(2). It should be noted that, although most studies

indicate an increased cardiovascular risk in AS, in some studies this increased risk was not found. A recent large retrospective database study from 2012 with 1686 AS-patients showed no significantly increased rate of myocardial infarction (hazard ratio of 1.28). In addition, the incidence of stroke was also not increased (hazard ratio of 1.0). Remarkably, the prevalence of risk factors for myocardial infarction and stroke, such as diabetes and hypertension, were increased compared with the control group in this study(5).

Cardiac disease

Valvular disease - Aortic valve involvement is often described in AS(6). A few decades ago aortitis was a major complication in AS, but nowadays this is rarely encountered. Nonetheless, the inflammation process in AS patients still causes aortic cusp retraction and thereby aortic regurgitation (prevalence ranging from 0% - 26%), although the exact mechanism of aortic valve involvement is not fully understood(7). A proposed mechanism is that cellular inflammation results in a marked fibroblastic reparative response, adventitial thickening, focal destruction of the medial elastic tissue and intima proliferation. Intimal proliferation of the vasa vasora leads to endarteritis and then root dilatation. This process extends to the aortic annulus and produces basal thickening and downward retraction of the cups. When inflammation spreads, the mitral valve can also be affected(8,9).

Conduction disorders - Inflammation may extend into the ventricular septum, affecting the endocardium and myocardium(10). Damage by inflammation leads to fibrosis of the intraventricular septum causing conduction disturbances in up to 30% of patient(11,12). Also atrioventricular nodal blood supply may be impaired, contributing to these conduction disturbances(13). First-, second-, and third-degree atrioventricular blocks appear to be common conduction aberrations (14).

Cardiomyopathy - Systolic and diastolic dysfunction of the ventricles are both found in AS patients, causing heart insufficiency and increase the risk for stroke caused by arterial tromboembolism.(7,15,16). Left ventricular systolic dysfunction is described less often than diastolic dysfunction (6,17). Diastolic dysfunction is more relevant, as it preludes heart failure and is seen in younger patients(18). Compared with systolic function, diastolic function is difficult to define and therefore difficult to assess. Hence, most studies use markers such as mitral inflow velocities (E and A waves)(19). The E and A waves corresponds with early flow during LV relaxation and subsequent contribution of atrial contraction, respectively. When diastolic function is normal, E wave exceeds A wave. When relaxation is impaired, atrial contraction contributes relatively more to ventricular filling (thus A>E). When LV diastolic pressure increases to the point that atrial contraction contributes little to filling, the E wave again becomes predominant, but with rapid deceleration, first in a pseudo normal pattern and ultimately in a restrictive pattern(20).

Atherosclerosis and AS

The inflammatory process also results in an increased atherosclerotic risk in patients with AS, as it contributes to all stages of atherosclerosis. Endothelial dysfunction, an early key event in atherosclerosis, is more evident in AS patients than in healthy controls(21). Traditional CV risk factors such as dyslipidemia, hypertension and smoking, are increased in AS, and may also contribute to the atherosclerotic risk(3,22-26). Carotid intima media thickness (cIMT) is a well established parameter for quantifying preclinical atherosclerosis. A first meta-analysis of cIMTs revealed an increase in cIMT of 0.07 mm in 272 AS patients versus 195 matched controls, implying a 14% increased cardiovascular risk(25).

Discussion

Some investigators advocate echocardiographic screening of every AS patient, to find cardiac disease in an early stage, and adjusting treatment accordingly in these patients(6). However, most studies only investigated limited number of patients, and are contradictory in the observed prevalences of cardiac disease. Moreover, the observed abnormalities varied. Therefore, the extent of these cardiac diseases, and hence the necessity of routine echocardiographic screening, is still not known. Studies with larger sample sizes are essential to enable firm conclusions about cardiac manifestations in patients with AS.

Preparatory work

A systematic review of our group published in 2004 suggests an increased cardiovascular risk in AS patients(27). Following this, a questionnaire-based study in 593 AS patients was conducted, in which an increased prevalence of myocardial infarction in comparison to the general population was found[peters2010]. In a subsequent investigation we compared 59 AS patients with controls and found that AS patients had a significantly increased cIMT (0.62 ± 0.09mm) in comparison to the control subjects (0.57mm ± 0.09mm). Finally, in a study of 15 AS patients and 12 controls we found that TNF-blocking therapy improved the microvascular dysfunction and lipid profiles in AS patients(28).

Hypothesis and objectives

Our primary goal is to investigate the prevalence of cardiac disease in AS patients, based on the following hypothesis: the prevalence of cardiac disease, such as valvular heart diseases, conduction disturbances and cardiomyopathies in AS-patients is higher compared with patients without AS.

Methods

Echocardiography is an established non-invasive instrument to assess cardiac function. In this study transthoracic echocardiography will be used for assessment of left ventricular function and valvular heart disease. We will us electrocardiography to screen for and investigate conduction disturbances. We will screen AS patients between 50 and 75 years with cardiac echography and electrocardiography. The primary outcome will be diastolic dysfunction.

Secondary outcomes will be to assess the prevalence of valvular heart diseases and conduction disturbances, to assess cIMT thickness as a marker of atherosclerosis and to assess left ventricular systolic function. As cardiac disease is more prominent with older age, we will include subjects between 50 and 75 years and a matched control group will be included.
If cardiac abnormalities are found on TTE or ECG, we ask patients permission to make a cardiac MRI. With a cardiac MRI we attempt to investigated the pathogenesis of cardiac manifestations in AS patients. If a cardiac MRI is made, we will draw one additional blood sample to assess hematocrit.

Study objective

Primary objective:
To investigate left ventricular diastolic function in AS-patients compared with osteoarthritis patients.

Secondary objectives:
To assess the prevalence of valvular heart diseases and conduction disturbances.
To assess left ventricular systolic function.
To assess cIMT thickness

Study design

The study is cross sectional.

Study burden and risks

There are some aspects to this protocol that may cause (some) discomfort to the subjects. First, the subjects have to remain fasted as indicated at the time of blood collection and cIMT measurement. Second, the collection of blood may cause some discomfort. Possible side effects from blood drawing include faintness, inflammation of the vein, pain, bruising, or bleeding at the site of puncture. There is also a slight possibility of infection. Third, during each vascular measurement, namely IMT measurement and thoracic echography the subject has to stay in a fixed position. Fourth, when measuring blood pressure, the inflation of the cuff may cause transient paraesthesia in the hand.
Subjects have to visit the research centre one, two or three times. If possible the visits will be combined.
In case of found abnormalities on ECG or TTE, we ask patients permission to make a cardiac MRI. This cardiac MRI can be discomforting to the subjects. First, patients have lay still in a fixed position for a prolonged period of time in a small space. Second, a contrast fluid is used which has to be administrated intravenously. This could cause faintness, inflammation of the vein, pain, bruising, bleeding or infection at the site of puncture. If a cardiac MRI is made, we will draw one additional blood sample to assess

hematocrit.

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

Ankylosing Spondyilitis according to New York (1984) criteria
Written informed consent
Age 50-75 years

Exclusion criteria

Malignant disease

Study design

Design

Study type:	Observational 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):	17-03-2014
Enrollment:	400
Type:	Actual

Ethics review

Approved WMO Date:	16-05-2013
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	07-10-2014
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	02-07-2015
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	25-11-2015
Application type:	Amendment
Review commission:	METC Amsterdam UMC

Approved WMO Date:	10-04-2018
Application type:	Amendment
Review commission:	METC Amsterdam UMC

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

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

ID: 25008
Source: Nationaal Trial Register
Title:

In other registers

Register	ID
CCMO	NL44202.048.13
OMON	NL-OMON25008