Treating the compromised hearts of patients with Rheumatoid Arthritis * Can we repair the damage?

Published: 14-02-2018
Last updated: 19-03-2025

Primary Objective: To investigate diastolic LV dysfunction before and after 6 months anti-inflammatory treatment with TNF blockers in patients with RA, assessed by exercise-stress echocardiography.Secondary Objective: To investigate whether systolic...

Ethical review	Approved WMO
Status	Pending
Health condition type	Heart failures
Study type	Observational non invasive

Summary

ID

NL-OMON46382

Source
ToetsingOnline

Brief title
Heart failure in RA

Condition

- Heart failures
- Autoimmune disorders

Synonym
diastolic heartfailure, Heart failure with preserved ejection fraction (HFrEF)

Research involving
Human

Sponsors and support

Primary sponsor: Overige Centra
Source(s) of monetary or material Support: Pfizer

Intervention

Keyword: anti-inflammatory therapy, exercise-stress echocardiography, heart failure with preserved ejection fraction, prevention., Rheumatoid arthritis

Outcome measures

Primary outcome

Diastolic dysfunction based on the 2016 ESC guidelines.(Naguah et al, J Am Soc

Echocardiogr. 2016 Apr;29(4):277-314.)

Disease activity: described as DAS28, blood inflammation parameters (CRP, BSE,

IL-6, TNF, leucocytes), HAQ and SF36.

Secondary outcome

Systolic dysfunction: Systolic dysfunction will be defined as an ejection

fraction of <50%.

Study description

Background summary

The most frequent cause of death in patients with chronic inflammatory joint diseases (IJD), including rheumatoid arthritis (RA), is of cardiovascular (CV) origin. The systemic inflammatory activity that underlies IJD is an important risk factor for the development of CV disorders, as inflammation is pivotal in the acceleration of atherosclerosis development, increasing the odds of myocardial infarction, stroke and peripheral vascular disease. In addition, chronic inflammation may lead to microvascular dysfunction, microvascular rarefaction, interstitial fibrosis and stiff cardiomyocytes, decreasing the ability of the cardiac muscle to contract and relax. This could result in preclinical diastolic left ventricular (LV) dysfunction, which can progress to heart failure (HF) with preserved ejection fraction (HFpEF).

Currently, HFpEF represents 50% of HF cases, but its prevalence is increasing as a result of a growing awareness and diagnosis and due to changes in population demographics. While mortality rates in patients with heart failure

with reduced ejection fraction (HFrEF) and HFpEF are comparable, unlike HFrEF no therapy has yet been shown to improve survival and only diuretics can give solely relief of symptoms. Furthermore, studies have repetitively shown a strikingly high prevalence of HFpEF in patients with RA.

Accumulating evidence shows that systemic inflammatory disease activity in general plays a pivotal role in development of cardiac dysfunction. In addition, a recent case control study showed a 70% increase of relative risk of developing heart failure in early onset (<1 year) RA patients compared to the control group. This suggests that there is a relationship between systemic inflammatory activity and cardiac dysfunction which is not solely related to atherosclerosis formation as this is a slowly accelerating process.

We therefore hypothesize that diastolic LV function improves in RA patients responding to anti-inflammatory treatment. Therefore, effective anti-inflammatory treatment can reduce the risk of HFpEF, especially in patients with a high cardiovascular risk profile.
Until now, therapy with biologics such as tumour necrosis factor (TNF) blockers has shown to be the most effective anti-inflammatory treatment in RA. Therefore, we expect that RA patients with high disease activity, in whom TNF blocking therapy is initiated, will show the highest decrease in inflammatory disease activity which can subsequently be related to diastolic LV function.
Our hypothesis is thus that diastolic LV function improves in RA patients responding to anti-inflammatory treatment, as diastolic LV function is also driven by systemic inflammatory processes.

A major challenge in diastolic LV dysfunction remains the debate regarding the proper assessment and diagnostic approach. Currently transthoracic Doppler echocardiography (TTE) is the primary way of non-invasive assessment of diastolic LV function. However, the major drawback of this non-invasive assessment is due to the low sensitivity of the detection of diastolic LV dysfunction. This is explained by the fact that the hemodynamic derangements in HFpEF-patients at rest, even in advanced stages are relatively mild and that TTE is performed only at resting conditions, thus with a chance of missing important diastolic LV dysfunction.

In this light, the Department of Cardiology, VUmc, recently developed exercise-stress echocardiography (ESE), a highly sophisticated diagnostic tool, in which echocardiography images are gained during treadmill exercise until patients become symptomatic. The VUmc is currently one of the few medical centers in Europe offering routine ESE for clinical and research practice.
For the proposed study we will include 50 RA patients that are eligible for anti-inflammatory treatment with TNF blockers. At baseline, before the start of anti-inflammatory treatment, ESE will be performed. After six months of treatment, a second ESE will be performed. Patients will serve as own control and echocardiographic parameters will be compared to baseline.

Study objective

Primary Objective: To investigate diastolic LV dysfunction before and after 6 months anti-inflammatory treatment with TNF blockers in patients with RA, assessed by exercise-stress echocardiography.
Secondary Objective: To investigate whether systolic LV function improves in patients with RA during treatment with anti-inflammatory therapy with TNF blockers resulting in lower disease activity.

Study design

A prospective cohort study in RA patients indicated for anti-TNF therapy who undergo exercise-stress echocardiography before start and after 6 months therapy.

Study burden and risks

We do not expect any severe risks as consequent of the study procedure. There are some aspects to this protocol that may cause (some) discomfort to the subjects. First, during exercise-stress echocardiography the subject has to stay in fixed position in a semi-supine bicycle while cycling against resistance. Second, the exercise-stress echocardiography can cause physical strain as the workload is escalated in a stepwise fashion until the patient reaches a heartrate of 100 bpm and at maximum exertion, while imagining is performed. However, the patient has authority to stop at any moment if the exertion causes too much discomfort. Third, In addition to the blood samples acquired in clinical setting an additional 10ml of blood will be drawn. Possible side effects from blood drawing include faintness, inflammation of the vein, pain, bruising, or bleeding at the site of puncture. here is also a slight possibility of infection. Fourth, when measuring blood pressure, the inflation of the cuff may cause transient paraesthesia in the hand. This study may improve our understanding of the role of inflammation on cardiac dysfunction and the possible reversibility of cardiac dysfunction. Therefore this study has potential to decrease the risk of development of heart failure with preserved ejection fraction in RA patients.

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

Diagnosis of:
o RA, according to the ARC/EULAR 2010 criteria (11)
- Active disease: DAS28*3.2 AND C-reactive protein >10 mg/l OR erythrocyte sedimentation rate (ESR) >15mm/h
- Minimal knee bending/flexion angle of 90 degrees of both knees.
- Age 40-70 years

Exclusion criteria

-medical history of ischemic heart disease of congestive heart failure NYHA class III/IV

Study design

Design

Study type: Observational non invasive

Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Basic science

Recruitment

NL

Recruitment status:	Pending
Start date (anticipated):	01-01-2018
Enrollment:	50
Type:	Anticipated

Ethics review

Approved WMO

Date:	14-02-2018
Application type:	First submission
Review commission:	METC Amsterdam UMC

Approved WMO

Date:	11-12-2018
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: 23785
Source: Nationaal Trial Register
Title:

In other registers

Register	ID
CCMO	NL64203.048.17
OMON	NL-OMON23785