Heart Rate Variability in pre-clinical and clinical arthritis

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With the experimental set-up of this study we would like to address the three following objectives:* Investigate HRV baseline levels in individuals with pre-clinical arthritis, healthy subjects and active RA, to evaluate if pre-clinical arthritis...

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

Summary

ID

NL-OMON36736

Source
ToetsingOnline

Brief title
HRV arthritis

Condition

- Joint disorders

Synonym
RA Reumatoid Arthritis

Research involving
Human

Sponsors and support

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

Intervention

Keyword: Heart Rate Variability, pre clinical arthritis, RA

Outcome measures

Primary outcome

Heart rate variability in subjects with pre-clinical arthritis, patients with active RA and healthy subjects. Heart rate variability is a reflection of the autonomic nervous system and these results will be related to clinical presentation and physical examination of the subjects, furthermore they will be compared with inflammation parameters in the blood.

Secondary outcome

Next to the primary outcome, the 24 hour heart rate variability will be analysed for day and night differences. We will evaluate if the normal day/night HRV found in healthy subjects, is also present in RA patients.

Study description

Background summary

Rheumatoid Arthritis and Pre-Clinical Arthritis
Rheumatoid arthritis (RA) is a chronic systemic inflammatory disease in which specific auto-antibodies can be detected years before RA becomes clinically manifest. These serum auto-antibodies, IgM rheumatoid factor (RF) and anti-citrullinated protein antibodies (ACPA) are first seen at a median of 5 years before clinical symptoms appear. People with these specific rheumatoid auto-antibodies have a chance of 40-70% of developing RA within 5 years. Histological studies in early rheumatoid arthritis patients have shown all features of chronic synovial inflammation to be present in clinically affected joints and extensive inflammation is found in clinically unaffected joints of RA-patients. In addition, a notable percentage of RA patients have signs of joint destruction at the time of initial diagnosis.
Taken together, these data form strong evidence that early RA in fact represents chronic synovitis and that clinical signs and symptoms may be

preceded by a preclinical phase for several years. Patients in this preclinical phase positive for IgM-RF and/or ACPA and having arthralgias are currently being included in clinical observational trials at the Department of Clinical Immunology and Rheumatology in the Academic Medical Center (AMC) Amsterdam

Autonomic dysfunction in Rheumatoid Arthritis
It is known that part of the patients with active RA have autonomic dysfunction, which is a imbalance between the parasympathetic and sympathetic nervous system. Heart rate variability (HRV) is a validated method to assess autonomic nervous system imbalance. RA patients have an increased sympathetic control and decreased parasympathetic control of the heart rate, which results in the finding of a lower heart rate variability. A high variability in heart rate is generally a sign of good adaptability, as to be found in a healthy individual with a well-functioning autonomic nervous system.
HRV can be measured with a Holter 24-hour electrocardiogram (ECG), after which the heart beat (R-R interval) variation is analyzed in two domains, the time-domain and frequency-domain analysis. Analysis in the time domain includes the standard deviation of the mean of R-R intervals (SDNN), which reflects the autonomic nervous system balance and the percentage of R-R intervals differing from each other more than 50 milliseconds (pNN50), which reflects parasympathetic activity. Analysis in the frequency-domain is done by spectral analysis of R-R intervals, resulting in defining a high (HF) and low frequency (LF) component. HF is seen as a marker of parasympathetic activity and LF is a marker of sympathetic activity. The LF/HF ratio reflects the sympathovagal balance.
To assess the adaptability of the autonomic nervous system in the subjects they will be asked to change from supine to standing position during HRV-measurement. The orthostatic stress from standing up will unveil a shift from the mainly parasympathetic supine state to a more sympathetically dominated state in the upright position.

HRV as a biomarker
We suspect that HRV can be used in clinical practice as an indicator for the development of RA. We hypothesize that persons with pre-clinical arthritis will have a lower HRV compared to healthy persons and but still a higher HRV compare to active RA-patients. Follow-up of individuals with pre-clinical arthritis will give insight in the change of HRV over time in relation to the activity and thereby progression of arthritis.

Day/Night HRV
The influence of the autonomic nervous system on HRV changes during the day. Being asleep gives the parasympathetic nervous system the upper hand, resulting in a higher HRV compare to a lower HRV while being awake in healthy subjects. It is known that RA-patients have a mostly sympathetic control of the heart rate, which results in a lower HRV. Our question is if RA patients demonstrate a change in HRV between day and night or that the sympathetic control over the heart does not decrease at night and leaves the HRV unchanged during the whole

24 hour period.

Neuroendocrine hormones
In the last decade increasing evidence has been published about the relationship between neuroendocrine hormones, especially prolactin, and autoimmune diseases such as RA. RA is more common in females and this is possibly due to the role of neuroendocrine hormones. Furthermore, it has been shown that during pregnancy disease activity is relatively low and that after delivery and the start of lactation RA relapses. This phenomenon could possibly be explained by changes in prolactin levels during these episodes.
Recently, our group has studied the prolactin receptor in synovium of RA, psoriatic arthritis (PsA) and osteoarthritis (OA) patients. The expression of the prolactin receptor was higher in RA and PsA patients as compared to OA patients. The prolactin levels in blood of RA patients was decreased in group of responders compared to the non-responders to TNF-treatment. Also higher tertiles of prolactin levels were associated with reumafactor positivity. Therefore, prolactin can be a possible new biomarker in RA, but it*s prognostic value needs to be determined in (pre-)arthritis vs healthy volunteers.

Study objective

With the experimental set-up of this study we would like to address the three following objectives:
* Investigate HRV baseline levels in individuals with pre-clinical arthritis, healthy subjects and active RA, to evaluate if pre-clinical arthritis patients already have an autonomic imbalance, comparable to patients with active RA patients and in contrast to healthy subjects
* Evaluate if HRV can predict progression to active arthritis in the follow-up of individuals with pre-clinical arthritis
* Evaluate if there is a imbalance in day/night autonomic rhythm in patients with active RA

Study design

Visits to outpatient clinic:
* HRV will be measured in individuals with pre-clinical arthritis at three timepoints:
a. Baseline: Subject have been found to have arthralgias and a positive ACPA and/or IgM-RF
b. Timepoint one: At first manifestation of arthritis, characterized by pain and swelling
c. Timepoint two: meets ACR criteria or 5 years after baseline
* HRV in Patients with active RA and healthy subjects will be measured at baseline only

Study burden and risks

The burden for the participants will be minimal. There are no direct benefits for the subjects participating in this study.

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

All subjects: 18-85 years
Individuals with pre-clinical arthritis (n<=60): Arthralgia and elevated ACPA level of > 25 IU/ml, or IgM-RF of > 49 IU/ml.
RA patients with active disease (n<=20): Has been diagnosed according to ACR criteria (Appendix 4: ACR -criteria) and have active arthritis in one or more joints at time of HRV-measurement
Healthy subjects (n<=20): Negative for IgM-RF (level < 49 IU/ml) and ACPA (level of < 25 IU/ml)

Exclusion criteria

All subjects
* Cardiovascular disease; such as ischaemic heart disease, cardiomyopathy, cardiac arrhythmia, cerebrovascular events, hypertension
* Neurological disorders, such as parkinsonism and multiple sclerosis
* Diabetes Mellitus and Hypercholesterolemia
* Medication influencing blood pressure or heart rate
* Pregnancy
* Nicotine use (smoking , nicotinegum or patch)
Individuals with Pre-clinical Arthritis
* Clinically evident arthritis
* Use of Disease Modifying Anti-Rheumatic Drugs (DMARDs)
* Systemic or intra-articular corticosteroid injection less then 28 days before enrolment
Active RA patients
* Use of TNF-blockers or anti-IL6 treatment

Study design

Design

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

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	13-10-2011
Enrollment:	100
Type:	Actual

Ethics review

Approved WMO
Application type: First submission

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

No registrations found.

In other registers

Register	ID
CCMO	NL34802.018.10

Study results

Date completed: 06-02-2015

Actual enrolment: 90