Pain sensitization in patients with symptomatic atrial fibrillation compared with asymptomatic patients

Anna Björkenheim, MD, PhD[1], Adam Jackson, BSc[1] Ole Fröbert, MD, PhD[1], Dennis Boye Larsen BSc PhD[2], Lars Arendt Nielsen, MSci, PhD, DMSci[2]

1. Department of Cardiology, Faculty of Medicine and Health, Örebro University, Sweden.
2. SMI, Faculty of Medicine, Aalborg University, Aalborg, Denmark.

Correspondence:

Anna Björkenheim, MD, PhD

Department of Cardiology

Örebro University Hospital

701 85 Örebro, Sweden

Telephone +46 19 602 54 59

Fax +46 19 602 24 07

Email: anna.bjorkenheim@regionorebrolan.se

Ole Fröbert, MD, PhD

Department of Cardiology

Örebro University Hospital

701 85 Örebro, Sweden

Telephone +46 602 54 13

Fax +46 19 602 54 38

Email: ole.frobert@regionorebrolan.se

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Abstract

Background

Atrial fibrillation (AF) is the most common sustained arrhythmia and the number of patients with AF is expected to increase substantially in the coming decades. One third of patients with AF report no AF-associated symptoms, but up to one fourth report severe symptoms such as chest pain. It is well recognized, but unclear why patients' experience of AF-related symptoms, including chest pain, varies so much. Patients with chronic pain show a high degree of central sensitization, i.e. facilitated pain responses to repeated painful stimulation and impaired conditioned pain modulation, compared with controls. It is possible that patients with symptomatic AF may have developed pronounced pain sensitization even in the absence of chest pain as a symptom. No previous study has investigated pain sensitization in patients with AF.

Objective and methods

The primary objective is to assess differences in pain sensitization in patients with symptomatic AF compared with patients with asymptomatic AF. Secondary objectives are to study the association of age, sex, AF duration, comorbidities and health-related quality of life to pain sensitization. A total of 30 patients with permanent AF (15 symptomatic and 15 asymptomatic) will be recruited. Patients will complete an AF-specific symptom score and a generic health-related quality of life questionnaire, and physicians will assess AF-related symptoms. Quantitative sensory testing recordings will be collected by pressure algometry. Assessment of temporal summation of pressure pain and conditioning pain modulation will be used to investigate the involvement of pain sensitization.

Clinical relevance

This preliminary pilot study will be used to estimate sample size for a larger study in which both patients and control subjects will be recruited, to further investigate whether patients with symptomatic AF have increased pain sensitization compared with patients with asymptomatic AF and controls. The studies may have an impact on individualized management of patients with AF in the future.

Trial registration

The study protocol is registered with ClinicalTrials.gov (NCT…)

Keywords

Atrial fibrillation, Symptoms, Quality of life, Pain, Conditioning pain modulation, Temporal summation

Abbreviations

AF	Atrial fibrillation
AF6	Atrial fibrillation 6 questionnaire
CPM	Conditioned pain modulation
ECG	Electrocardiogram
SF-36	Short form 36 health survey
VAS	Visual analogue scale

Introduction

Background

Atrial fibrillation (AF) is the most common sustained arrhythmia affecting approximately 3% of adults aged 20 years or older in Western countries, and is expected to increase further in the coming decades(1). The presence of AF is independently associated with an increased risk of all-cause mortality and morbidity, largely due to stroke and heart failure, dementia, symptoms, and impaired quality of life(2-7). The management of AF aims to prevent AF-related complications using oral anticoagulation therapy in patients with a high risk of stroke and to reduce symptoms and improve health-related quality of life using a rate (slowing of the ventricular rate) or rhythm control (restoration and maintenance of normal sinus rhythm) strategy(8).

About one third of patients with AF report no AF-associated symptoms, but up to one fourth of patients report severe symptoms such as palpitations, dyspnea, chest discomfort or pain, dizziness and syncope(9-11). In previous studies 9 to 15% of patients with permanent AF reported chest pain as an AF-related symptom(12, 13). In addition, one third of patients with symptomatic AF suffer from psychological distress (anxiety and/or depression), which may also worsen symptoms of AF(11, 14).

It is well recognized, but remains unclear why some patients with AF are asymptomatic whereas others are severely symptomatic. Several studies have evaluated the relationship between patient characteristics and the presence of AF symptoms, and have found that asymptomatic AF is more frequent in men than in women, and in older age(15, 16). Inconsistent results have been reported for associations between asymptomatic AF and comorbidities(17). Patients with all types of AF can be asymptomatic, but asymptomatic AF

is more common in patients with permanent AF(18). The situation is further complicated by the fact that asymptomatic AF episodes are common even in highly symptomatic patients and that AF interventions such as pulmonary vein isolation increase asymptomatic episodes(19). In conclusion, little is known of the pathophysiological mechanisms underlying AF symptomatology but both somatic and psychological factors are likely involved.

The authors have previously shown that central nervous system responses to visceral and somatosensory nociceptive input are altered in patients who have angina despite normal coronary angiograms compared to healthy volunteers(20). Patients with chronic pain conditions such as osteoarthrosis, chronic pancreatitis and irritable bowel syndrome, show a high degree of central sensitization, i.e. facilitated pain responses to repeated painful stimulation and impaired conditioned pain modulation (CPM) compared with controls(21-24). Furthermore, these patients often show a discrepancy between pain intensity and objective measures of disease severity and healthcare personnel often underestimate patients' pain intensity(25, 26). It is also well-known that stress influences pain sensitivity and has been correlated to hyperalgesia in patients with ischemic heart disease(27, 28). It is possible that patients with symptomatic AF have developed pronounced pain sensitization even in the absence of chest pain as a symptom, and in particular facilitated pain responses to repeated painful stimulation, i.e. temporal summation of pressure pain. No previous study has investigated pain sensitization in patients with AF, neither in patients with or without chest pain as a symptom.

Purpose

The primary objective is to assess differences in pain sensitization in patients with symptomatic AF compared with patients with asymptomatic AF.

Hypothesis

We hypothesize that central sensitization is involved in sensing of and discomfort from AF in symptomatic patients, involving neural pathways also involved in perceiving pain. Because of shared pathways, we further hypothesize that patients with AF symptoms have lower pain thresholds than asymptomatic patients with AF.

Clinical relevance

It is well recognized, but unclear why patients' perception of AF varies so much. This preliminary pilot trial will be used to estimate sample size for a larger trial, in which both patients and control subjects will be recruited, to further investigate whether patients with symptomatic AF have increased pain sensitization compared with patients with asymptomatic AF and controls. The studies may have an impact on individualized management of patients with AF in the future.

Material and methods

Study design

Single-center cohort study.

Subject inclusion criteria

Study participants will be recruited from a database of all patients aged 20 years or older with a diagnosis of AF from 1 January 2015 to 31 December 2018 in Örebro County (more than 10 000 patients) extracted from the National Patient Register, that covers all in-patient and outpatient physician visits from both private and public caregivers, and the Medrave 4 patient statistics software that is used in all public general practices in the county. The diagnosis of AF was based on at least one electrocardiogram (ECG) characterized by an absolutely irregular RR interval, no distinct P waves and an atrial cycle length of less than 200 ms. By accepted convention, an episode with these ECG characteristics lasting for at least 30 seconds was diagnostic of AF(8). Permanent AF is defined as persistent AF that is accepted by both the patient and the physician and for which no further attempts to restore or maintain normal sinus rhythm will be undertaken(8).

Further inclusion criteria:

- Male or female subjects ≥ 20 years and ≤ 75 year, primarily 60 to 70 years old.
- Permanent AF
- Previously completed AF-specific symptoms questionnaire Atrial fibrillation 6 questionnaire (AF6)
- Written informed consent

Subject exclusion criteria

- Paroxysmal or persistent AF (AF that terminates spontaneously or with intervention, respectively(8))
- Previous pulmonary vein isolation
- Psychiatric or cognitive condition
- Pregnancy
- Previous/current drug or alcohol abuse
- Previous neurological or concomitant musculoskeletal disorders
- Continuous analgesic medication

Examinations

All potential patients will receive written information about the study and will thereafter be contacted by telephone and offered an outpatient visit to a physician at the Department of cardiology, Örebro University Hospital, Örebro, Sweden. After obtaining written informed consent, patients will be asked to complete the AF6 and the Short form 36 health survey (SF-36) questionnaires before a 12-lead ECG is obtained. Patients will also be asked to rate the symptom chest pain on the Visual analogue scale (VAS) (0 to 10) and to draw the pain area on a body chart. Comorbidities, medications and duration of AF will be documented and a routine clinical examination will be performed, and the modified European Heart Rhythm Association symptoms scale assessed. Quantitative sensory testing recordings will be collected by pressure algometry. The patients will be asked not to take any analgesic medication 24 hours before the examination. No follow-up visits are scheduled. Subjects will be divided into two groups based on their previous AF6 symptom scores; asymptomatic patients with an AF6 sum score of 0, and symptomatic patients with an AF6 sum score of ≥30.

Symptom assessment

The patient-reported AF6 questionnaire includes six items (breathing difficulties at rest and upon exertion, limitations in day-to-day life, feeling of discomfort, tiredness and worry/anxiety due to AF) and a score of 0 (no symptoms) to 10 (severe symptoms) is reported for each item, and all scores are added into a single sum score. Sum scores range from 0 to 60, with higher values reflecting more severe AF-related symptoms. The AF6 includes a recall period of the last 7 days(29, 30).

The physician-assessed modified European Heart Rhythm Association symptoms scale is used for symptom severity assessment in patients with AF, relating specifically to the time when patients feel symptoms of AF. Patients in class I are considered to have no symptoms, in class IIa mild, class IIb moderate, class III severe and in class IV disabling symptoms of AF(8, 31).

Health-related quality of life

The patient-reported SF-36 has a recall period of four weeks and consists of 36 items assessing eight domains ranging from 0 to 100, with higher values indicating better health-related quality of life. The eight domains generate two summary measures: the physical component summary and the mental component summary scores, which will be used to assess health-related quality of life(32).

Clinical examination

A cardiovascular examination including blood pressure measurement will be performed. The blood pressure will be measured after 15 minutes of rest by an automatic sphygmomanometer.

Quantitative sensory testing

Pressure pain threshold

The pressure pain thresholds (PPTs) is defined as the minimal amount of pressure where a sense of pressure first changes to pain. Participants will be instructed to press the 'stop' button of the algometer as soon as the pressure results in the first sensation of pain. Pressure will be increased at a rate of approximately 30 kPa/s. The 1-cm^2 probe of the handheld pressure algometer (Somedic AB, Sweden) will be placed perpendicularly to the skin. PPTs will be assessed over the sternum at the level of intercostal spaces 3–5 and over the tibia bone(27). The PPTs will be measured three times on each site, and the mean of the three measurements will be used for statistical analysis. Low PPTs indicate sensitization.

Temporal summation of pressure pain

A Pin prick (tip area, 0.2mm^2) with a weighted load (Aalborg University, Denmark) will be used to induce temporal summation of pressure pain (TSP) as previously conducted in other pain studies(33-35). A force of 50 g will be applied once over the sternum at the level of intercostal spaces 3–5 and over the tibia bone and the patient will be asked to rate the pain intensity on the VAS (0 to 10). Then 10 consecutive stimuli will be applied (1 s interval between consecutive stimuli) to the same site and the subject will be asked to rate the pain intensity of the last stimulation on the VAS. TSP will be calculated as the difference in the

pain intensity between the first and the last stimulation. High TSP scores indicate facilitated temporal summation.

Conditioning pain modulation

The right hand up to the wrist will be immersed into stirred cold water (2–4 ◦C, measured in the water) for 2 min (the so called cold pressor test). Before the immersion the PPTs will be assessed from the sternum and the tibial bone, at the end of the two min immersion the PPTs will be assessed again and this will be repeated again 10 min after the hand is withdrawn from the water. The conditioning pain modulation index will be assessed as the increase in PPTs during the immersion as compared to the pre-immersion PPTs. The lower the difference is the more sensitization.

Primary endpoint

The primary objective is to assess differences in pain sensitization in patients with symptomatic AF compared with patients with asymptomatic AF.

Secondary endpoint

Secondary objectives are to study the association of age, sex, AF duration and comorbidities and physical and mental component summary scores to pain sensitization.

Ethics approval

The study protocol is approved by the Swedish Ethical Review Authority (2020-01619).

Statistics and data management

Data collected during the study will be coded.

Statistical analysis

Data will be presented as mean and standard deviation. A one-way ANOVA will be used for demographic parameters and to compare the groups. Pearson correlations will be used for linear estimates and Spearman´s correlations for non-linear parameters. All analyses will be adjusted for age. Analyses will be performed using IBM SPSS Statistics 22 (Armonk, NY, USA) or STATA release 14 (College Station, TX, USA).

Sample size calculations

As no previous trial of pain sensitization in patients with AF has been performed, a pilot trial is necessary to calculate sample size for a larger study.

Database and Case report form

A case report form will be filled out and coded for each patient. The investigators are responsible for ensuring the accuracy, completeness, legibility and timeliness of the data recorded in the case report forms.

Documentation and data collection

Criteria for inclusion, informed consent, the decision to include the subject and the subject number will be documented in the subject's hospital record.

Insurance

The subjects in the study are covered by the Swedish patient insurances.

Economy

The trial is an academic study conceived and conducted by healthcare personnel. The study is independent of commercial interests. Study logistics, handling of data and statistical

assessment will be financed by the Department of Cardiology, Örebro University Hospital, Sweden. The investigators will apply for grants from public funds.

Ethical considerations

The study will be conducted in accordance with the Declaration of Helsinki. The cold pressor test activates the sympathetic nervous system and increases blood pressure and heart rate, and there is a slight risk of angina during the test. There are otherwise no known risks or complications associated with the quantitative sensory testing but it may cause some temporary mild to moderate discomfort.

The patient is free to stop the testing at any time, and in case of angina the testing will be stopped and the patient will be closely monitored and administered sublingual nitroglycerin.

Risks, side effects, advantages and disadvantages in participation

Subjects will be treated according to standard clinical practice. There is a slight risk of the test causing angina chest pain. However, we do not expect that subjects will have any disadvantages from participating in the study. The risk of complications during quantitative sensory testing is considered low.

Guidelines for obtaining informed consent

Subjects will enter the study after signing the informed consent form. Candidate participants will receive written information of the study, and oral information by a physician participating in the study. The subjects will be given time to think through participation in the study and to ask questions. Informed consent will be obtained by a Good Clinical Practice qualified physician participating in the study.

Withdrawal

A subject can withdraw from the study at any time. Data collected up to the end of follow-up will be used in the final analysis of the study.

Publication

Results, positive as well as negative or inconclusive, will be published in an international medical journal, primarily in a cardiology journal.

End of trial and archiving

The study will end when the last subject has signed informed consent, completed the questionnaires and has undergone clinical examination and quantitative sensory testing. The steering committee reserves the right to terminate the study prematurely e.g. if the study participant recruitment is too slow, if study participant retention in the study is insufficient or if undue risk related to the quantitative sensory testing arises. Data collected during the study will be archived for at least 10 years after the study has been completed.

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