Reversal of cardiomyopathy by suppression of frequent premature ventricular complexes - a prospective randomized clinical trial

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Primary Objective: The main objective of this study is to demonstrate that PVC suppression therapy on top of conventional heart failure treatment improves cardiac systolic function as assessed by quantitative echocardiography in patients with...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Cardiac arrhythmias
Study type	Interventional

Summary

ID

NL-OMON38290

Source
ToetsingOnline

Brief title
Reversal of PVC-induced cardiomyopathy

Condition

- Cardiac arrhythmias

Synonym
1) Premature ventricular complex induced cardiomyopathy 2) Heart failure due to ectopic heart beats

Research involving
Human

Sponsors and support

Primary sponsor: Medisch Universitair Ziekenhuis Maastricht
Source(s) of monetary or material Support: ZonMw en researchgelden voortkomend uit door de industrie gesponsorde studies verricht op de afdeling cardiologie.

Intervention

Keyword: Cardiomyopathy, Frequent, Premature ventricular complex, Therapy

Outcome measures

Primary outcome

Absolute change in cardiac function using the echocardiographic parameter: Left ventricular ejection fraction (LVEF), assessed by modified Simpsons* rule at baseline versus 6 months follow-up.

Secondary outcome

* Absolute change in cardiac function using other echocardiographic parameters: Left Ventricular End-Diastolic Diameter (LVEDD), Left Ventricular End-Systolic Diameter (LVESD), Left Ventricular End-Diastolic Volume (LVEDV) and Left Ventricular End-Systolic Volume (LVESV) at baseline versus 6 months follow-up.

* Absolute change in functional capacity, using NYHA functional class at baseline versus 6 months follow-up.

* Absolute change in exercise tolerance, using 6 minute walking distance at baseline versus 6 months follow-up.

* Absolute change in patient QoL, using the Minnesota Living with Heart Failure questionnaire score at baseline versus 6 months follow-up.

* Absolute change in NT-proBNP level, using plasma NT-proBNP level at baseline versus 6 months follow-up.

* Absolute change in PVC burden, using PVC frequency at baseline versus 6

months follow-up.

* Number and sort of complications of PVC suppression therapy.

* Cost-effectiveness: costs from a health service perspective during one year

follow-up and effectiveness measured as quality adjusted life years (QALY).

Study description

Background summary

Heart failure accounts for substantial morbidity and mortality in the western world. In addition, the financial burden associated with the disease is considerable. Prognosis is generally poor and quality of life is significantly reduced. The causes of heart failure are diverse. Identification of the underlying pathophysiological mechanism is essential, because a specific patient tailored therapy may help to improve the clinical status of the individual patient. In addition, some patients may have a potentially reversible cardiomyopathy (CMP). The present study will focus on the role of frequent premature ventricular contractions (PVCs) as a cause of left ventricular (LV) dysfunction. This is a potential reversible CMP generally unknown to the cardiological society.

Frequent ventricular ectopy in patients without structural heart disease is generally thought to be a benign finding with no prognostic significance. Suppression of PVCs with anti-arrhythmic drugs or catheter ablation is therefore usually only considered when PVCs are accompanied by disabling symptoms. However, recent data suggest that frequent monomorphic PVCs (symptomatic or asymptomatic) can cause a form of CMP that may be reversible by suppression of the ectopic focus. Furthermore, the high prevalence of frequent PVCs in patients with heart disease suggests that PVC-induced CMP may be a common phenomenon. Suppression of frequent monomorphic PVCs to improve LV systolic function may therefore emerge as a new and effective treatment strategy for patients with heart failure.

Beta-blockers are safe and effective anti-arrhythmic agents and are considered the first line therapy for suppression of PVCs. Most patients with HF are already taking a beta-blocker as part of standard therapy for their underlying disease. According to international guidelines, other AADs can be used if beta-blockers are ineffective, but they have potential adverse (arrhythmic) side-effects, especially in patients with diminished LV function, and may even

be contra-indicated in this patient group. In patients with LV dysfunction and frequent monomorphic PVCs that are refractory to beta-blockers, long-term drug therapy and the potential adverse (arrhythmic) side-effects of AADs can be avoided by using catheter ablation as a first alternative treatment. RFCA is already a frequently applied, widely accepted, safe, effective and potentially curative treatment for symptomatic drugrefractory PVCs. It has also been safely and effectively employed in patients with tachycardia-induced CMP and patients with PVC-induced CMP. A high acute succes rate of 93% and a very low PVC recurrence rate of 3% have been reported. Although recent available data suggest that elemination of the PVC source by RFCA improves LV systolic function in HF patients, it is still applied in a limited fashion for this indication because the evidence supporting this is weak. The patient series published so far were not controlled and retrospective in nature. We intend to conduct a controlled, randomized, prospective study with careful documentation and long-term follow-up to evaluate the effect of PVC suppression therapy (with RFCA as primary treatment) on cardiac systolic function in patients with CMP and beta-blocker refractory frequent monomorphic PVCs. This could establish suppression of frequent monomorphic PVCs as a potential curative treatment strategy for patients with HF.

Study objective

Primary Objective: The main objective of this study is to demonstrate that PVC suppression therapy on top of conventional heart failure treatment improves cardiac systolic function as assessed by quantitative echocardiography in patients with idiopathic or ischemic CMP and frequent monomorphic PVCs.

Secondary Objectives: Secondary objectives are to demonstrate improvement in patient functional capacity (NYHA functional class), exercise tolerance (6 minutes walking test), quality of life (Minnesota Living with Heart Failure Questionnaire) and level of the heart failure marker NT-proBNP. and to assess the cost-effectiveness of additional PVC suppression therapy compared to conventional heart failure treatment.

Study design

The present study is a prospective randomized clinical trial to evaluate the effect of PVC suppression therapy on cardiac systolic function and patient clinical condition in patients with idiopathic or ischemic CMP and frequent monomorphic PVCs.

Intervention

Patients will be randomized into 2 groups. One group will receive PVC suppression therapy on top of conventional heart failure therapy. The other group will receive conventional heart failure therapy alone.

PVC suppression therapy:
PVC suppression therapy will be applied using the following treatment strategy: PVC elimination by RFCA will be used as primary therapy. In case of unsuccessful ablation or if the PVC focus turns out inaccessible by percutaneous approach during electrophysiological study (EPS), drug therapy with Amiodarone, a drug registered for the treatment of ventricular arrhythmias, can be considered as secondary therapy.

EPS and RFCA protocol:
EPS with subsequent RFCA is performed according to current clinical practice. This is a widely accepted, well established procedure which is frequently applied in our hospital. Approximately 250 RFCA procedures are performed in our centre every year (2 per day on average) by experienced electrophysiologists for a variety of indications. In the azM it is a standard treatment for atrial tachycardia, AV nodal re-entrant tachycardia, ventricular tachycardia and premature ventricular complexes. The results of the treatment in our centre are excellent. Our electrophysiologists achieve a high acute and chronic success rate which varies from 80-100% depending on the indication for which it is used.
All electrophysiological procedures will be performed in the fasting state without sedation. Anti-arrhythmic drugs will be discontinued at least 5 days before the procedure. Patients will be locally anesthetized with Lidocaine. 7 F multi-electrode electrophysiology catheters will be inserted into a femoral vein and positioned in the right ventricular apex, the his bundle position and the coronary sinus (CS). A 7,5 - 8 F multi-electrode deflectable tip ablation catheter with a 3,5 mm tip electrode will be used for mapping and ablation. In case of suspected right sided PVC origin, the catheter will be inserted through the femoral vein. In case of suspected left sided PVC origin, a retrograde aortic approach from the femoral artery will be used. Five thousand units of heparin will be administered for right-sided procedures. Systemic heparinization to achieve an activated clotting time of 250*300 seconds will be performed for left-sided procedures. The origin of the PVCs will be identified using an electro-anatomical mapping system. In case of infrequent spontaneous ectopy during the procedure, programmed electrical stimulation will be performed and/or isoprenaline will be administered at rates up to 10microgram/min to induce culprit PVCs. If ectopy is still infrequent despite programmed stimulation and/or isoprenaline, pace mapping will be used to identify the PVC origin. Using activation mapping the site of earliest endocardial activation will be determined and radiofrequency energy will then be delivered to this region. A 7F deflectable quadripolar ablation catheter with a 4 mm tip electrode will be used for mapping and ablation. The radiofrequency energy will be delivered with a preset temperature of 50 to 60 degrees Celsius at the electrode tissue interface and a power limit of 50 W. The applications will be continued for at least 30 s if adequate heating at the electrode-tissue surface is achieved. If the VPBs are abolished the application will be continued for 60 s and followed by another 60 s application. If PVCs are still present after 30 s the energy application will be terminated and

mapping will be continued. In the event of pleomorphic PVCs the predominant PVC morphology will be targeted. Programmed electrical stimulation and/or isoprenaline administration at 2 -10 microgram/min will be used at the end of the procedure to confirm that PVCs are no longer inducible. Ablation is considered acutely successful when repetitive monomorphic ventricular ectopy is abolished during ablation and remains absent for at least 30 minutes after ablation in the baseline state and during programmed stimulation and/or isoprenaline infusion.
In addition, in ischemic CMP patients, the average endocardial scar area will be assessed by electroanatomical mapping using a lower limit of 1,5 mV for normal tissue. The average dense endocardial scar area will be assessed by electroanatomical mapping using a cut-off of 0,5 mV.

Amiodarone protocol:
The treatment is performed according to current clinical practice. Amiodarone is administered orally using 200 mg tablets. A loading dose of 600 mg is given daily (3 tablets per day) for 4 weeks. Thereafter patients will take 200 mg (1 tablet) per day. Tablets should be taken during or immediately after meals.

Study burden and risks

During the period of the study, the participants will pay a maximum of 6 visits to the hospital. During these visits baseline and follow-up measurements are performed and treatment is administered as assigned by randomization. The total study duration for each participant is a maximum of 6 months. The burden and risks of the study procedures are described below.

Potential study subjects (Idiopathic/ischemic CMP; stable optimal heart failure therapy; > 18 years, no exclusion criteria) will be enrolled in the study after giving informed consent. They will receive a diagnostic work-up to assess their eligibility for randomization. This work-up comprises 48 hour Holter monitoring with a 12 lead device and an echocardiogram. These tests are common clinical practice in patients with heart failure. They are non-invasive and do not expose the subjects to any risks. Patients meeting all electrocardiographic and echocardiographic criteria will be randomized to either PVC suppression therapy on top of standard care or standard care alone.

Patients eligible for randomization will undergo further baseline evaluation before treatment which includes NYHA assessement, 2 quality of life (QoL) questionnaires, a cost-effectiveness questionnaire, physical examination, 12 lead ECG, standard 6 minutes walk test (6MWT) and plasma NT-proBNP measurement. There are no risks involved with these commonly applied tests. For NT-proBNP measurements 4ml of blood will be taken by venous puncture in the arm with a very small needle (diameter 0,6 mm). Furthermore, an extra blood sample of 16 ml will be taken at baseline and 6 months follow-up and stored for future research purposes. These are very small clinically irrelevant amounts of blood. Taking this amount of blood is therefore not harmfull for the study subjects.

All the blood is taken using the same needle. Therefore study subjects do not need to be burdened with an extra venous puncture. Ischemic CMP patients will receive an additonal DE-CMR to assess the myocardial scar area and -burden. During CMR a radiographic contrast agent, *Gadovist* (Gadolinium) is administered according to hospital protocol. Side effects of this agent are very rare. Minor side effects (pain during administration, nausea, headache, dizziness) have been reported in 0,1 * 1% of cases. Allergic reactions including anaphylactic shock have been reported in 0,01 * 0,1% of cases. Nefrogenic systemic fibrosis has been reported in patients with a GFR of less than 30 in 0,1 * 0,01 % of cases.

Patients randomized to PVC suppression therapy will be hospitalizd for 24 hours to undergo an electrophysiological study (EPS) and RFCA. These are well established and frequently applied techniques in our hospital. The procedure takes about 2 to 4 hours and is relatively safe, but several complications are possible. Minor complications (account for about 4%) include minor bleeding or infection at the puncture site, thrombo-embolism, temporary catheter induced rhythm disturbances, and temporary changes in blood pressure. More significant complications (account for about 0,1%) include damage to blood vessels or perforation of the heart wall causing cardiac tamponade, extensive bleeding or cardiac arrest. The risk of dying during an EPS is less than 0,1%. Fluoroscopy during EPS exposes patients to relatively low radiation dosages (average effective dosage of 13 mSv +/- 15%). Radiation complications have never been described.

At 3 months follow up Holter monitoring, echocardiography and QoL and cost-effectiveness questionnaires are repeated. Follow up at 6 months includes NYHA assessment, QoL and cost-effectiveness questionnaires, physical examination, 12 lead ECG, standard 6MWT, Holter monitoring, echocardiography and plasma NT-proBNP measurement. Follow up at 12 months only includes QoL and cost-effectiveness questionnaires. Patients treated with RFCA will undergo additional echocardiography 1 day post-ablation and additional Holter monitoring at 2 weeks post-ablation.

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

- CMP (LVEF < 50%) without identifiable cause (idiopathic) or post-infarction, > 6 months.
- Optimal conventional heart failure therapy > 3 months.
- Frequent monomorphic PVCs on Holter monitoring.
* Frequent <= more than 15% of all QRS complexes are PVCs.
* Monomorphic <= more than 75% of PVCs have the same morphology.
- Greater than 18 years of age.
- Willing and capable of giving informed consent.

Exclusion criteria

- Other causes of LV systolic dysfunction:
* Significant valvular disease
* Untreated hypertension (blood pressure > 140 mmHg)
* Primary CMP (HCM, ARVC, LVNC, myocarditis, stress, peripartum)
* Secondary CMP (infiltrative, storage, toxic, neuromuscular/neurological, autoimmune)
- Electrocardiographic PVC characteristics suggestive of a focal origin not accessible by percutaneous approach.
- Sustained supra-ventricular arrhythmia.
- Evidence of significant CAD (>70% stenosis of a coronary artery) on coronary angiogram (CAG) or coronary CT necessitating revascularization (PCI / CABG) in the foreseeable future.
- Signs of current myocardial ischemia on ECG (dynamic STT segments) or during exercise testing (significant ST segment depression/elevation).
- Myocardial infarction within the last 6 calender months prior to enrollment.

- PCI / CABG within the last 6 calender months prior to enrollment.
- Physical status not allowing electrophysiological study (e.g. pregnancy or severe peripheral artery disease)
- Presence of any disease, other than the patients cardiac disease, associated with a reduced likelihood of survival for the duration of the trial.

Study design

Design

Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	30-05-2012
Enrollment:	70
Type:	Actual

Ethics review

Approved WMO Date:	23-12-2011
Application type:	First submission
Review commission:	MEC academisch ziekenhuis Maastricht/Universiteit Maastricht, MEC azM/UM (Maastricht)
Approved WMO Date:	09-03-2012
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)

Approved WMO Date:	24-09-2012
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)

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	NL37355.068.11