The effect of beta-adrenergic receptor blockade on sympathetic activity and coagulation in patients with heart failure (BACH-F study)

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To compare sympathetic and haemostatic activity in rest and after rising in patients with chronic heart failure and healthy subjects, who will be randomly assigned to selective and nonselective beta-blockers. To analyse whether haplotypes of two...

Ethical review	Approved WMO
Status	Pending
Health condition type	Heart failures
Study type	Interventional

Summary

ID

NL-OMON31270

Source
ToetsingOnline

Brief title
BACH-F Study

Condition

- Heart failures

Synonym
Congestive heart failure, systolic heart failure

Research involving
Human

Sponsors and support

Primary sponsor: Academisch Medisch Centrum

Source(s) of monetary or material Support: Nederlandse Hartstichting

Intervention

Keyword: Beta-blockers, Coagulation, Heart failure, Sympathetic activity

Outcome measures

Primary outcome

We will assess two primary endpoints at rest and during exercise: 1. hypercoagulable activity by platelet function and thrombin generation; 2. sympathetic activity by plasma (nor)adrenalin concentration, spectral analysis of blood pressure and heart rate variability. And in patients with heart failure by 123I-MIBG scinitigraphy.

Secondary outcome

1. Changes in coagulation factors;

2. Changes in fibrinolysis;

3. Cardiac output as calculated by Finapres (BMEYE ABM 100 HD);

4. Central blood pressure as measured by Sphygmocor;

5. Patient*s satisfaction with the two different treatments by using a questionnaire.

Study description

Background summary

Chronic heart failure is common and has a poor prognosis. Therapy with beta-adrenergic antagonists (beta-blockers) reduces mortality among patients with heart failure, but guidelines do not differentiate between selective and non-selective beta-blockers. In heart failure patients, sympatho-adrenergic activity is increased at rest and frequently excessive during exercise, which may lead to cardiovascular death, partly due to a hypercoagulable state induced

by this activity. Previous studies have suggested that the release of norepinephrine is partly regulated by prejunctional beta2-adrenergic receptors. This implies that non-selective beta-blockers may have a specific sympathoinhibitory effect that is not present in selective beta1-blockers. Indeed, in the COMET trial, carvedilol, a non-selective beta-blocker, reduced cardiovascular mortality in patients with heart failure compared to the selective beta1-blocker metoprolol. This beneficial effect of carvedilol may be partially explained by a reduced hypercoagulable response upon sympathetic activation. Some (small) studies found that these effects could be completely blocked by propranolol but not by metoprolol or phentolamine, which points to a beta2-adrenergic specific effect.
Another potential influence on survival in chronic heart failure patients receiving beta-blockers may be highly prevalent functional beta2-adrenergic polymorphisms that have been shown to mediate survival in patients with acute coronary syndrome. Variants of the beta2-adrenergic receptor may be of crucial importance of the response to beta-blocker therapy by interfering with both sympathetic activity and hypercoagulable state.
Hypothesis: Sympatho-adrenergic and hypercoagulable activity are enhanced in patients with chronic heart failure, partially mediated by common functional beta2-adrenergic polymorphisms. Non-selective beta-blockers down regulate sympathetic activation via a beta2-adrenergic receptor specific effect. The net effect is a reduced haemostatic response which will reduce cardiovascular mortality.

Study objective

To compare sympathetic and haemostatic activity in rest and after rising in patients with chronic heart failure and healthy subjects, who will be randomly assigned to selective and nonselective beta-blockers. To analyse whether haplotypes of two common functional beta2-adrenergic polymorphisms mediate the sympathetic and haemostatic response before and after beta-blockade.

Study design

Patients with chronic heart failure and healthy controls will be screened for the two beta2-adrenergic polymorphisms. Patients and controls homozygous for the Arg16/Gln27 or the Gly16/Glu27 will be tested for hypercoagulable (defined as platelet response and thrombin generation) and sympathetic activity at rest and after standing, repeated during an open cross-over design with blinded endpoints in which these subjects will be randomly assigned to either carvedilol (a non-selective beta1 and beta2-blocker) or metoprolol (a selective beta1-blocker) for six weeks.

Intervention

In an open randomised crossover with blinded endpoints trial patients and

healthy volunteers will receive carvedilol BID or metoprolol retard once daily. Conform guidelines, heart failure patients are already prescribed beta-blockers on maximal tolerated doses and will be converted to an equipotent dose of the trial medicine. Equipotency will be guided by the heart rate. There will be a minimum of four weeks of maximal beta-blocker treatment in both arms. Depending on the time needed for titration, the total duration of beta-blocker treatment can range from 6 to 8 weeks.
The target dose for healthy volunteers will be equal to the average dose in heart failure patients. Target dose for healthy volunteers will be reached in one week and administered for six weeks. Hereafter subjects crossover to the alternative arm: those having received carvedilol will receive metoprolol and vice versa. There is a wash-out period of 4 weeks in between for healthy volunteers.

Study burden and risks

In total, the study will take 20 weeks for healthy volunteers and 24 weeks for patients with heart failure. During this period study participants will be asked to visit the hospital 9 resp 6 times. Visits will last approximately 10-60 minutes (depending on type of visit). During this period 5 blood samples are taken. There is large experience with carvedilol and metoprolol that have shown the safety of this medication in the treatment of patients with heart failure. Current guidelines recommend the use of beta-blockers in patients with heart failure. The risks associated with this study for patients with heart failure consist of possible side effects to beta-blocker therapy and will be equal to normal treatment. Besides, due to small differences between beta-blockers, temporary worsening of heart failure is possible. Therefore patients will be monitored closely and medication will be tapered or ceased if needed.
For healthy volunteers the risks of the study also consist of possible side effects. These risks are considered low, since healthy volunteers will be closely monitored with predefined stop criteria and the low cardiovascular risk of participating healthy individuals.
In patients with heart failure we will also perform a MIBG-scan at the end of each treatment period. The risk of this diagnostic test is related to the dose of radiation and is within international limits as they are formulated for subjects volunteering in research.
Measuring sympathetic activity is of crucial importance in our study and spectral analysis of blood pressure and heart rate variability is an indirect measure of sympathetic activity. Besides, spectral analysis could be difficult to perform since patients with heart failure may have many extra systoles, which interfere with the calculation used in spectral analysis. Furthermore, noradrenalin and adrenalin serum levels only indirectly reflect sympathetic activity.
Therefore, in patients with heart failure, myocardial sympathetic activity will also be assessed with 123I- meta-iodobenzylguanidine (MIBG) after each treatment period. MIBG is an aralkylguanidine and shows many similarities with

the neurotransmitter norepinephrine. MIBG, in analogy to catecholamines, is primarily removed from the circulation by the pre-synaptic nerve endings and stored in the pre-synaptic storage vesicles. The labelling of MIBG with 123I allows for the scintigraphic assessment of sympathetic activity.
Semi-quantitative parameters of myocardial 123I-MIBG uptake have been shown to have independent prognostic and diagnostic value.19,20 Differences in uptake after each treatment can therefore also be correlated with a prognostic difference, which will make this study more valuable.

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

Patients
1. Between 18 and 80 years of age, competent and willing of giving informed consent;

2. With stable symptoms of chronic heart failure (NYHA II-III);
3. With left ventricular ejection fraction *40%, measured within the previous 6 months; if the ejection fraction is not determined, a left-ventricular end diastolic diameter of greater then 6.0 cm and a fractional shortening of less than 20% as measured by echocardiography;
4. With sinusrhythm; (necessary to perform spectral analysis);
5. On stable medical therapy with ACE-inhibitors for at least three months, unless contraindicated; otherwise angiotensin receptor blockers (ARBs);
6. Already on beta-blocker therapy with maximal tolerated doses;;And healthy subjects between 18 and 80 years of age serve as controls to compare sympathetic and hypercoagulable activity with heart failure patients.

Exclusion criteria

Excluded are patients
1. With a history of adverse reaction on beta-blockers;
2. With a contraindication to *-blocker therapy (Sick-sinussyndrome, second and third AV-block), severe hypotension (systolic blood pressure < 100 mm Hg), cardiogenous shock, clinical relevant sinusbradycardia. Asthma, COPD. Liverfunctiondisorder (defined as elevation of aspartamine transaminase, alanine transaminase or bilirubin levels more than three times upper limit of normal range), renal disease (calculated creatinine clearance <50ml/min; using Cockcorft's formula).Insulin dependent diabetes mellitus.);
3. With an acute coronary syndrome or myocardial revascularisation within the preceding 3 months;
4. Who are using anticoagulant therapy. Aspirin is allowed;
5. With severe aortic or mitral valve disease or aortic regurgitation;
6. With right ventricle failure;
7. Requirement for intravenous inotropic therapy, current treatment with calcium channel blockers (of the diltiazem or verapamil class), amiodaron (>200mg per day) or class-I antiarrhythmic drugs, or administration of any investigational drug in the preceding 30 days.
8. Uncontrolled hypertension (blood pressure systolic >170 mmHg or diastolic >105mmHg),
9. Symptomatic and sustained ventricular arrhythmias within the preceding two months not adequately treated with antiarrhythmic drugs or without implantation of an automatic defibrillator;
10. With implanted pacemaker (necessary for spectral analysis); ICD is allowed
11. Pregnancy and women with childbearing potential on inadequate contraception
12. Known drug or alcohol misuse
13. Poor compliance with treatment
14. Any other serious systemic disease that might complicate management and reduce life expectancy.
15. With a known allergy for Iodine;Excluded are healthy controls
1. Taking any medication that will affect our outcome measurements for at least 2 weeks before entering the study
2. With a history of adverse reaction on beta-blockers
3. With a contraindication to beta-blocker therapy as described for patients with heart failure
4. With pregnancy and women with childbearing potential on inadequate contraception

5. Known drug or alcohol misuse
6. Known with poor compliance with treatment

Study design

Design

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

Recruitment

NL

Recruitment status:	Pending
Start date (anticipated):	01-09-2007
Enrollment:	80
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Brand name:	carvedilol
Generic name:	carvedilol
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	metoprolol
Generic name:	metoprolol
Registration:	Yes - NL intended use

Ethics review

Approved WMO

Date:	03-09-2007
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	18-10-2007
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	13-08-2008
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

No registrations found.

In other registers

Register	ID
EudraCT	EUCTR2007-001994-27-NL
Other	Het Nederlands Trial Register (Volgt nog)
CCMO	NL18547.018.07