The effect of Beta-Adrenergic receptor blockade on sympathetic activity and Coagulation in patients with Heart failure (BACH-F study).

No registrations found.

Ethical review	Positive opinion
Status	Recruitment stopped
Health condition type	-
Study type	Interventional

Summary

ID

NL-OMON21698

Source
NTR

Brief title
BACH-F study

Health condition

1. Heart failure;

2. Hemostasis;

3. Sympathetic activity.

Sponsors and support

Primary sponsor: P.W. Kamphuisen, internist, Vasculair Geneeskundige.
Source(s) of monetary or material Support: Netherlands Heart Foundation (NHS, Nederlandse Hartstichting).

Intervention

Outcome measures

Primary outcome

Sympathetic activity as measured by spectral analysis of blood pressure and heart rate vaiability and by MIBG-scintigraphy. Hemostasis (platelet activity and thrombin generation and other coagulaiton factors). Both measured at the end of each treatment period. In healthy volunteers also as a baseline measurement.

Secondary outcome

Central blood pressure / augmentation index.

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 receptor 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.

Objectives: 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, repeated during a open crossover design in which these subjects will be randomly assigned to either carvedilol (a non-selective beta1 and beta2-blocker) or metoprolol retard (a selective beta1-blocker) for six weeks.

Study population: Patients who are between 18 and 80 years of age with (previous) symptoms of chronic heart failure and with left ventricular ejection fraction ¡Ü40% and stable medical therapy for >3 months are eligible. Healthy volunteers who are between 18 and 80 years of age not taking any medication for at least 2 weeks before entering the study serve as controls. Both groups should be homozygous for Arg16Gln27 or Gly16/Glu27.

Intervention: Conform guidelines, heart failure patients are already treated with beta-blockers on maximal tolerated doses and will be converted to an equipotent dose of the trial medication. 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.

Main study parameters/endpoints:

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, by spectral analysis of blood pressure and heart rate variability and in patients with heart failure by 123I-MIBG scintigraphy.

Study objective

Sympatho-adrenergic and hypercoagulable activity are enhanced in patients with chronic heart failure, partially mediated by common functional beta2-adrenergic receptor 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.

Intervention

Carvedilol versus Metoprolol retard in crossover design.

Contacts

Public
Academic Medical Center - University of Amsterdam
Department of Vascular Medicine (Room F4-139)
PO BOX 22660

O.R. Peuter de
Amsterdam 1100 DD
The Netherlands
+31 (0) 20-5667516
Scientific
Academic Medical Center - University of Amsterdam
Department of Vascular Medicine (Room F4-139)
PO BOX 22660

O.R. Peuter de
Amsterdam 1100 DD
The Netherlands
+31 (0) 20-5667516

Eligibility criteria

Inclusion criteria

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 ¡Ü40%, 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; Digitalis or other vasodilatators can be used at the discretion of the treating physicians;
Healthy subjects between 18 and 80 years of age serve as controls to compare sympathetic and hypercoagulable activity with heart failure patients.

Exclusion criteria

1. With a history of adverse reaction on beta-blockers;

2. With a contraindication to â-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 Cockcroft¡¯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. Known with an 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:	Single blinded (masking used)
Control:	Active

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	01-09-2007
Enrollment:	80
Type:	Actual

Ethics review

Positive opinion

Date:	26-09-2007
Application type:	First submission

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
NTR-new	NL1034
NTR-old	NTR1067
Other	: 2007-001994-007
ISRCTN	ISRCTN wordt niet meer aangevraagd

Study results