Primary hyperaldosteronism and endothelial ischemia-reperfusion injury

Published: 17-10-2013
Last updated: 22-04-2024

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Ethical review	Approved WMO
Status	Recruiting
Health condition type	Coronary artery disorders
Study type	Observational non invasive

Summary

ID

NL-OMON38730

Source
ToetsingOnline

Brief title
Primary hyperaldosteronism and ischemia-reperfusion injury

Condition

- Coronary artery disorders
- Vascular hypertensive disorders

Synonym
primary aldosteronism, primary hyperaldosteronism

Research involving
Human

Sponsors and support

Primary sponsor: Universitair Medisch Centrum Sint Radboud
Source(s) of monetary or material Support: Ministerie van OC&W,Netherlands Foundation for Cardiovascular Excellence (NFCVE)

Intervention

Keyword: CD73, Flow mediated dilation, Ischemia-reperfusion injury, Primary hyperaldosteronism

Outcome measures

Primary outcome

To study whether forearm IR impairs brachial artery FMD to a greater extent in

patients with hypertension due to PHA than in patients with primary

hypertension.

Secondary outcome

To study whether CD73 activity on mononuclear cells is lower in patients with

PHA, compared to patients with primary hypertension

To study whether the circulating adenosine concentration in lower in patients

with PHA

Study description

Background summary

Primary hyperaldosteronism is a common cause of hypertension, with an estimated prevalence of 10% in the hypertensive population. Importantly, patients with PHA experience more cardiovascular events, including atrial fibrillation, stroke, and myocardial infarction, compared to patients with primary hypertension, independent of the blood pressure level. Also, in patients without PHA, a high aldosterone level or high aldosterone-to-renin ratio (ARR) is associated with an increased risk of cardiovascular events. In the setting of acute myocardial ischemia and reperfusion (an acute myocardial infarction), aldosterone levels are associated with cardiovascular death and heart failure, even when aldosterone levels are within the normal range. Furthermore, in patients with heart failure, aldosterone levels are increased and treatment with MR antagonists improves outcome. Two large trials showed a reduced morbidity and mortality in patients with heart failure during treatment with the MR antagonists spironolactone and eplerenone.

Preclinical studies have provided data that aldosterone has direct adverse cardiovascular effects and increases infarct size in animal models of myocardial infarction, although this latter result has not been reported in other studies. In addition, the administration of MR antagonists consistently reduces myocardial infarct size in these animal models.
Based on these abovementioned preclinical and clinical findings, we hypothesize that patients with PHA are more susceptible to ischemia-reperfusion (IR)-injury.

To study IR in humans in vivo, a safe and well-validated method is to examine brachial artery flow mediated dilation (FMD) before and after forearm ischemia and reperfusion. FMD is reduced after forearm IR, which is a measure of endothelial IR-injury. We have recently used this approach to demonstrate that prevention of IR-injury by ischemic preconditioning is impaired in elderly patients. It has been shown previously in patients with hypertension that brachial artery FMD is lower in patients with a high aldosterone-to-renin-ratio, but the effect of IR on FMD has never been studied in these patients.

The mechanism of the potentially deleterious effect of aldosterone on IR-injury is still unknown. Recently, Schmidt et al. showed that the infarct size-limiting effect of MR-antagonists was abolished by concomitant administration of an adenosine receptor antagonist. In addition, the cardioprotective effect was abolished in mice with a genetic deficiency of the enzyme ecto-5*-nucleotidase (CD73; catalyses extracellular formation of adenosine) and in adenosine A2B receptor knock-out mice. These observations suggest that the formation of extracellular adenosine by CD73 is critical for the cardioprotective role of MR antagonists.

Adenosine is an endogenous purine nucleoside, which is formed by intra-, and extracellular degradation of adenosine monophosphate by CD73. Degradation of adenosine occurs in the intracellular compartment. As a consequence, facilitated diffusion of adenosine over the cellular membrane by the equilibrative nucleoside transporter (ENT) is normally directed inwards. Stimulation of membrane-bound adenosine receptors induces various effects, including vasodilation, inhibition of inflammation, and protection against IR-injury. Indeed, endogenous adenosine acts as a key mediator of the infarct size-limiting effect of several pharmacological and non-pharmacological strategies.

Based on the abovementioned preclinical data, we hypothesize that susceptibility to IR is increased in patients with PHA due to reduced CD73 activity by aldosterone. To gain better insight into this hypothesis, we will investigate endothelial IR-injury in patients with PHA and control patients with essential hypertension. In addition, the expression and activity of CD73 will be measured on isolated mononuclear cells.

Study objective

The results of these studies will provide a possible explanation for the increased risk of cardiovascular events in patients with PHA. Our study is the first to explore the hypothesis that patients suffering from PHA are more vulnerable to IR injury, and that a reduced adenosine formation contributes to this more vulnerable state. The finding that a reduced extracellular adenosine concentration contributes to the accelerated rate of cardiovascular morbidity and mortality in patients with PHA, would provide us novel pharmacological targets for these patients.

Study design

In this clinical trial, we will test the following hypotheses:

1. The reduction in FMD by forearm IR will be greater in patients with PHA, compared to matched control patients with primary hypertension.
2. CD73 activity is lower in patients with PHA
3. The circulating adenosine concentration is lower in patients with PHA.

Twenty patients (age 18-75 years) with PHA and without interfering antihypertensive treatment will be asked to participate. Twenty matched controls with primary hypertension will be sought. After signing for informed consent, history taking, a physical examination, and electrocardiography will be performed.

As explained in detail the research protocol, most patients will at the time of inclusion use calciumchannel blockers and/or alpha-adrenergic-receptor antagonists and/or hydralazine as antihypertensive drugs, since only these drugs are allowed during the diagnostic workup for primary hyperaldosteronism because they do not (significantly) affect the renin/aldosteron plasma concentration. To ensure a similar use of antihypertensive drugs in both groups, we will change the drugs into diltiazem with or without hydralazine (dependent on the blood pressure level and the number of antihypertensive drugs) one week before the experiment. This will be done in consultation with the treating physician. Patients with primary hyperaldosteronism often have a low serum potassium. Therefore, many patients will use potassium suppletion at the time of the diagnostic work up for PHA. If the plasma potassium concentration was <3.5 mmol/l upon inclusion, the potassium suppletion will be increased to ensure a plasma potassium level of >3.5 mmol/l at the moment of the experiment. Finally, when patients use statins for cholesterol lowering, these drugs will be stopped one week before the experiment.

At least one week after changing the medication (whenever necessary), the volunteers will participate in the following experiment. Because all antihypertensive drugs can potentially affect the tolerance against

ischemia-reperfusion, the patients will not take the antihypertensive drugs at the morning of the experiment.

Ultrasonographic measurement of brachial artery Flow Mediated Dilation (FMD)
Brachial artery FMD will be measured before and after 20 minutes of forearm ischemia and 20 minutes of reperfusion. This protocol of IR, will result in an immediate decrease in brachial artery FMD, which is believed to reflect IR-induced endothelial dysfunction. In previous studies with this experimental design, 20 minutes of ischemia and 15 minutes of reperfusion was used. However, in our recent study with this method, we observed that the FMD had not yet completely returned to baseline values after 15 minutes of reperfusion. Therefore, we have chosen to use 20 minutes of reperfusion in the current study.
All measurements will be performed in a temperature-controlled room (22.5 °C) and using recent guidelines of FMD. The patients will rest in a supine position with both arms extended and immobilized, supported at an angle of ~80° abduction from the torso. Heart rate and mean arterial pressure will be determined. For the assessment of FMD, a rapid inflation/deflation pneumatic cuff will be placed distal to the olecranon process to provide an ischemic stimulus distal from the brachial artery to provoke vasodilation and subsequent shear stress. The brachial artery will be imaged in the distal third of the upper arm. We will simultaneously obtain a continuous Doppler velocity assessment, and data will be collected using the lowest possible insonation angle (always <60°), which does not vary during each study.
After a resting period of at least 15 minutes, 1 minute of baseline recording of the arterial diameter and velocity will be performed. This is followed by inflation of a pneumatic cuff around the forearm for 5 minutes. The arterial diameter and velocity recordings will be restarted at least 30 seconds before cuff deflation and continued for at least three minutes after deflation. We will record peak arterial diameter and flow, and the time to reach this peak after cuff deflation.
Subsequently, a rapid inflation/deflation cuff will be positioned around the upper arm, so that the brachial artery will be within the ischemic zone. The cuff will be inflated for 20 minutes to 220 mmHg, which will be followed by 20 minutes of reperfusion. Afterwards, the same FMD measurement is performed as described above.
CD73 activity on mononuclear cells
Before start of the FMD experiment, blood will be drawn to isolate mononuclear cells. We will determine the activity of CD73 exposed on the surface of intact mononuclear cells, by quantifying the conversion of 1,N6-ethenoadenosine 5*-monophosphate to 1,N6-ethenoadenosine in the presence and absence of the CD73-specific inhibitor α,β-methyleneadenosine 5*-diphosphate.

Circulating adenosine concentration
It is tempting to measure the circulation adenosine concentration because of its very short half life of <1 second. We have recently published a method to determine the plasma adenosine concentration using a purpose-built syringe.

Using this syringe, the blood mixes immediately at the end of the needle with a solution containing pharmacological blockers of the proteins involved in adenosine formation, transport, and degradation. Before the start of the experiment, 3 ml of blood will be drawn with this syringe system to measure the plasma adenosine concentration.

Additional blood drawing
Before start of the experiment 3 mL of blood will be drawn to determine caffeine concentrations. Subjects with a circulating caffeine concentration > 1.0 mg/l will be excluded from analyses, since caffeine is a potent adenosine receptor antagonist. Also 16 ml of blood will be drawn for the determination of the plasma glucose, creatinine, sodium, potassium, and cholesterol concentration (to evaluate in- and exclusion criteria; these factors could modify the effect of IR on the endothelium) and the renin and aldosterone concentration

Study burden and risks

Brachial artery FMD will be measured in all patients before and after 20 minutes of forearm ischemia and 20 minutes of reperfusion. This can cause mild discomfort, but is otherwise without any side-effects.
Blood drawing (during screening and before the experiment) can cause a hematoma.

To participate in the study the patients will have to come to the research centre during half a day and this will come along with extra costs (of travelling).

Contacts

Public
Universitair Medisch Centrum Sint Radboud

Geert Grooteplein 21
Nijmegen 6525 EZ
NL
Scientific
Universitair Medisch Centrum Sint Radboud

Geert Grooteplein 21
Nijmegen 6525 EZ
NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

For patients with primary hyperaldosteronism:
-Age 18-75 years
-Confirmed primary hyperaldosteronism (aldosterone >0.28 nmol/L after salt loading)
-Serum potassium >= 3.5 mmol/L (with or without potassium supplementation)
-Written informed consent;For control patients with primary (essential) hypertension:
- Age 18-75 years
- Primary hypertension
- Baseline aldosterone <0.30 nmol/l and ARR<0.09.
- Serum potassium >= 3.5 mmol/L
- Written informed consent

Exclusion criteria

-Smoking
-History of atherosclerotic disease (myocardial infarction (MI), stroke, or peripheral vascular disease)
-Not possible to change the antihypertensive medication into only diltiazem with or without hydralazine, or to temporarily stop statins according to the treating physician
-Severe renal dysfunction (MDRD < 30 ml/min)
-Second/third degree AV-block on electrocardiography
-Cardiac failure
-Diabetes mellitus
-Use of acetylsalicylic acid, NSAID*s, theophylline, and dipyridamole

Study design

Design

Study type:	Observational non invasive
Intervention model:	Other
Allocation:	Non-randomized controlled trial
Masking:	Open (masking not used)

Primary purpose: Basic science

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	06-11-2013
Enrollment:	40
Type:	Actual

Ethics review

Approved WMO Date:	17-10-2013
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	21-12-2015
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	28-04-2016
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	09-11-2016
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)

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	NL45381.091.13