Role of adrenaline in the inflammatory response in people with diabetes mellitus type 1, and healthy individuals

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Objective: The aim of the present study is to study the effect of increased adrenaline levels on the inflammatory response (e.g. leukocyte phenotype, cytokines, inflammatory proteins) by administering exogenous adrenaline. Secondary aims consist of...

Ethical review	Approved WMO
Status	Completed
Health condition type	Cardiac disorders, signs and symptoms NEC
Study type	Interventional

Summary

ID

NL-OMON53203

Source
ToetsingOnline

Brief title
Adrenaline induced inflammation

Condition

- Cardiac disorders, signs and symptoms NEC
- Diabetic complications
- Arteriosclerosis, stenosis, vascular insufficiency and necrosis

Synonym
Adrenaline induced inflammation, inflammation of the whole body caused by the stress hormone adrenaline

Research involving
Human

Sponsors and support

Primary sponsor: Radboud Universitair Medisch Centrum
Source(s) of monetary or material Support: Ministerie van OC&W

Intervention

Keyword: Adrenalin, Diabetes type 1, Hypoglycaemia, Inflammation

Outcome measures

Primary outcome

The amount of monocytes following 60 minutes of adrenaline infusion compared to baseline to asses the adrenaline effect on the inflammatory response. .

Secondary outcome

* Leukocyte count at the time points 30 minutes, 60 minutes, +1 day, +3 days and 1 week after start infusion.

* Leukocyte phenotype using flow cytometry (e.g. Granulocytes, NK-cells)

* Ex vivo production of pro- and anti-inflammatory cytokines and chemokines after ex vivo stimulation of isolated monocytes, including TNF-α, IL-6, IL-10 and IL-1β.

* Distribution of pro- and anti-inflammatory monocyte subsets using FACS (Fluorescence-activated Cell Sorting)

* Pro-inflammatory proteins using Olink Proteomics AB inflammation panel with 92 circulating inflammatory proteins (29) (e.g. EN-rage, FIT3L)

* Inflammatory plasma protein using ELISA, (e.g high sensitive-crp)

* Atherogenic parameters using ELISA method including but not limited to, VCAM-1, ICAM-1, E-Selectin, P-selectin, PAI-1, Plasma Endothelin

* Plasma levels of hormones (Cortisol, insulin, glucagon, growth-hormone,

adrenaline, noradrenaline)

* Glucose variability measured by the blinded continuous glucose monitor

including but not limited to, measuring time within range, amount of

hypoglycaemic events, amount of hyperglycaemic events.

Other study parameters

- HbA1c

- Creatinine

- Vitals (blood pressure and heart rate)

- BMI

- Age

- Sex

- Duration of diabetes (years)

- Hypoglycaemia awareness using the Clarke questionnaire

owth-hormone)

Study description

Background summary

Patients with type 1 diabetes mellitus requiring insulin are at daily risk of hypoglycaemia, as a consequence of insulin therapy. Severe hypoglycaemia is associated with a two-fold increased risk for cardiovascular complications. The reasons for which are unclear. Several lines of evidence have showed that hypoglycaemia causes a sustained pro-inflammatory response, which could promote a pro-atherogenic state.
It has been established that the pro-inflammatory and adrenaline responses to hypoglycaemia are strongly correlated. Whether adrenaline is the driving factor in the hypoglycaemic inflammatory response and whether the reaction in people with diabetes differs is unknown. Our hypothesis is that adrenaline is the

driving factor behind the hypoglyceamia induced inflammatory response.

With this project we will elaborate on the role of adrenaline, by including people with type 1 diabetes and facilitating a week long follow-up. This will enable us to examine whether inflammatory response seen during hypoglycaemia can be replicated by adrenaline infusion. In addition we will be adding to understanding of the adrenaline induced inflammatory response by including a wide array of leukocyte phenotype analyses and proinflammatory proteins.

Study objective

Objective: The aim of the present study is to study the effect of increased adrenaline levels on the inflammatory response (e.g. leukocyte phenotype, cytokines, inflammatory proteins) by administering exogenous adrenaline. Secondary aims consist of the effect of adrenaline on atherogenic parameters.

Primary Objective:
- The aim of the present study is to study the effect of increased adrenaline levels on the inflammatory response (e.g. leukocyte phenotype, cytokines, inflammatory proteins) by administering exogenous adrenaline in participants with type 1 diabetes and healthy participants.
Secondary Objective(s):
- To study the change in inflammatory and anti-inflammatory proteins (e.g hs-crp, Olink-proteomics AB inflammation panel with but not limited to FGF-21, SLAMF-1)
- To study the ex vivo production of cytokines by isolated monocytes after exposure to adrenaline
- To study the duration of the inflammatory response to adrenaline
- To study the leukocyte phenotype changes seen in exposure to adrenaline seen in hypoglycaemia
- To study the effects of glucose variability on the inflammatory response during adrenaline infusion
- To study the effect of adrenaline on atherogenic plasma biomarkers

Study design

Intervention study

Intervention

Participants will receive a continuous adrenaline infusion at a continuous rate of 0.04 µg/kg/min for 60 minutes. The infusion will start after a 30 minute equilibration period follow insertion of the venous cannula and drawing blood for baseline.

Study burden and risks

The subjects will not benefit directly from participation to the study.

The main study burden is the infusion of adrenaline, which might induce symptoms (palpitations, sweating, increased blood pressure, and feelings of anxiety). However, a previous study in which adrenaline was infused at a higher rate showed that these symptoms are usually mild, if at all present, and will resolve after cessation of the adrenaline infusion.The use of venous catheters may lead to hematomas or phlebitis, yet these are self-limiting and have in our hands never led to permanent damage. Finally, the time spent with frequent hospital visits (5 times) is a burden on the time spent by the participants.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)

Inclusion criteria

Ability to provide written informed consent Body-Mass Index: 19-30 kg/m2 Age

>=16 years, <= 75 years Blood pressure: <140/90 mmHg Non-smoking Electrocardiogram not showing any serious arrythmia*s (PVC*s and PAC*s accepted)

Exclusion criteria

Any event of cardiovascular disease in the past 5 years (e.g. myocardial infarction, stroke, heart failure, symptomatic peripheral arterial disease) Pregnancy or breastfeeding or unwillingness to undertake birth control measures Epilepsy, Current treatment with Alpha or beta blockers (doxazosin, propranolol) History of panic disorders History of Arrhythmias Use of immune-modifying drugs or antibiotics Use of tricyclic antidepressants or MAO inhibitors Use of statins (e.g. stop statins >2 weeks before performing blood sampling. Any infection with systemic symptoms in past 2 weeks Vaccination in the past 2 weeks Proliferative retinopathy Nephropathy with an estimated glomerular filtration rate (by MDRD) *60ml/min/1.73m2 Overt impaired hypoglycaemic awareness assed by the Clarke Questionnaire 4 or highe

Study design

Design

Study type:	Interventional
Intervention model:	Other
Allocation:	Non-randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Basic science

Recruitment

NL

Recruitment status:	Completed
Start date (anticipated):	23-11-2023
Enrollment:	30
Type:	Actual

Ethics review

Approved WMO Date:	07-09-2023
Application type:	First submission
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	NL84355.091.23