A comparison of two modalities to visualise the microcirculation: Contrast Enhanced Ultrasonography and capillary videomicroscopy

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We will investigate how video microscopy compares to CEUS in its assessment of insulin-mediated vasoreactivity.

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Glucose metabolism disorders (incl diabetes mellitus)
Study type	Observational invasive

Summary

ID

NL-OMON33075

Source
ToetsingOnline

Brief title
CCC

Condition

- Glucose metabolism disorders (incl diabetes mellitus)
- Vascular hypertensive disorders

Synonym
disturbed vasodilation, Microvascular dysfunction

Research involving
Human

Sponsors and support

Primary sponsor: Vrije Universiteit Medisch Centrum

Source(s) of monetary or material Support: Ministerie van OC&W

Intervention

Keyword: capillary videomicroscopy, CEUS, Insulin, Microcirculation

Outcome measures

Primary outcome

1. percentage change in muscle microvascular blood volume as measured by CEUS.

2. percentage change in number of capillaries as measured by nailfold

capillaroscopy.

Secondary outcome

1. muscle microvascular flow velocity (percentage change)

2. muscle microvascular blood flow (percentage change)

3. time to peak flow

4. muscle microvascular flow distribution

5. whole body glucose uptake

6. total forearm blood flow (percentage change)

7. blood pressure

Study description

Background summary

The global epidemic of obesity is bringing in its wake a catastrophic increase in the prevalence of metabolic diseases. As a result, obesity-related diseases, such as diabetes, hypertension, dyslipidaemia have surpassed tobacco use as a cause of death. Obesity is a major cause of insulin resistance, which has been implicated in the rising prevalence of the metabolic syndrome, a cluster of risk factors which confers an increased risk for type 2 diabetes and cardiovascular disease (CVD)3. The mechanisms underlying this clustering are incompletely understood. Obesity-associated microvascular dysfunction explains

part of this clustering and predisposes obese subjects to CVD. Microvascular dysfunction, by affecting both flow resistance and perfusion, is important not only in the development of obesity-related target-organ damage in the heart and kidney, but also in the development of cardiovascular risk factors such as hypertension and insulin resistance.

As explained in previous protocols, insulin *besides its function in glucose-uptake of the cell- has both a vasodilator and vasoconstrictor response, of which the vasodilator response is blunted in obesity. The blunted vasodilator response to insulin in obesity is one of the hallmark signs of microvascular dysfunction, and is in part responsible for insulin resistance, because of a decreased delivery of insulin and glucose to the target cells. The different effects on microvascular tone are mediated by two independent pathways, which are initiated by the binding of insulin to the insulin receptor.

Over the past years, the department of internal medicine has performed several research protocols studying the insulin-mediated vasoreactivity of the microcirculation, using mainly 2 techniques; LaserDoppler flowmetry and capillary video microscopy.
Capillary microscopy is performed as described previously in several publications from our group. Briefly, using an epi-illuminated microscope linked to a CCD camera, erythrocyte filled capillaries are visualized and recorded with a videorecorder. Two separate fields of view just below the nailfold of the 3rd digit of the non-dominant hand are investigated. Images are stored on tape before and after digital arterial occlusion (4 minutes) as well as before and after digital venous occlusion. The images are later analyzed, counting the number of capillaries in an area of 1 mm2. Reported intra- and interobserver variability is 4.5% and 10.1%, day-to-day variations amount to 15.9%±8.4.

LaserDoppler flowmetry utilises a laser beam which penetrates the skin. A fraction of the light is backscattered by moving blood cells and undergoes a frequency shift according to the Doppler principle, generating a received signal proportional to local tissue perfusion.

These techniques have several advantages such as non-invasiveness, repeatability and reproducibility. The major drawback of these methods however is the fact that they only enable measurement of the microcirculation in skin. Although earlier (invasive) studies showed a correlation between skin and skeletal muscle responses to (insulin-augmented) peak reactive hyperaemia, the main interest is to measure microvascular function directly in skeletal muscle, as skeletal muscle is the main site of insulin-mediated glucose uptake and peripheral vascular resistance.

Recently a new non-invasive technique has been developed to measure skeletal muscle perfusion with ultrasound. The contrast enhanced ultrasound method (CEUS), uses echogenic microbubbles as contrast. Because of their size, these

hexafluoride-filled lipid spheres are able to reach and traverse the smallest capillaries. Because microbubbles are compressible by ultrasonic waves, and their diameter is smaller than the wavelength of diagnostic ultrasound signals, microbubbles undergo oscillation when the ultrasound beam is directed at them. The oscillation creates acoustic signals which exceed the signal of conventional ultrasound. When using high acoustic powers, microbubbles can be destroyed, when this occurs, an even stronger signal is created .
The department of internal medicine has recently added an ultrasound device capable of CEUS to its research-arsenal.
CEUS is widely used in clinical practice to study cardiac function, however over last years it has found an application in studies involving skeletal muscle perfusion.

A study comparing the different techniques could be regarded as a mandatory step linking the past results, obtained with the videomicroscope in skin, with future research with CEUS in muscle as well as future protocols using videomicroscopy.

Study objective

We will investigate how video microscopy compares to CEUS in its assessment of insulin-mediated vasoreactivity.

Study design

A randomised within-subject comparison of 2 techniques
The study consists of one screening-visit and one study-day.

Study burden and risks

Screening day
1. history - none
2. physical examination - none
3. bioelectrical impedance analysis - none

Test day

4. blood samples - venapunction can cause discomfort and can result in a temporary local haematoma (subjects will not use anticoagulant medication).
5. venous catheter - intravenous catheterization can cause similar discomfort as venapunction during insertion of the needle. Risk of haematomas is bigger due to slower closure of the entry wound. Prolonged intravascular dwelling of catheters increases risk of local thrombosis, which can present as self-limiting thrombophlebitis or superficial vein thrombosis (1 in 100 clamps). The latter risk is also partly attributable to the hyperinsulinaemic state during the hyperinsulinaemic euglycaemic clamp.

6. hyperinsulinaemic euglycaemic clamping infusion with insulin - the insulin solution consist of saline 0.9%, insulin (Actrapid*, Novo nordisk) and albumin (Cealb*, Sanquin). Allergic reactions have been described for the latter two. Rare: (self-limiting) flushing, urticaria and nausea. Very rare (< 1 in 10.000): anaphylactic shock. The obvious direct effect is hypoglycaemia. Glucose infusion - prolonged infusion of glucose can cause some discomfort at the site of cannulation. This can in most cases be alleviated through addition of bicarbonate to the iv solution. High(er) infusion rates can induce hyperglycaemia.
Personal experience of the principle investigator (MdB): 0 AE*s in ~ 50 procedures.
7. Contrast Enhanced Ultrasound (CEUS) infusion of microbubbles (Sonovue*; Bracco diagnostics) The most common side effects with Sonovue* (in 1 to 10% of studies) are headache, facial flushing, nausea, dizziness, (moderate) hypotension, injection site pain and injection site reactions (bruising, burning, and paraesthesia). In a post marketing study, serious adverse events occurred in 0,009% of patients (2/23188). The serious adverse events consisted of dyspnoea, bronchospasm, slight hypotension and bradycardia in a patient who recovered in 30 minutes. The other serious adverse event consisted of clouding of consciousness, back pain, severe hypotension and a cutaneous rash, which also lasted for 30 minutes. No fatalities occurred 23. The cardiology department at the VUmc has several years of experience using CEUS (and Sonovue* bubbles in particular). Close collaboration (for CEUS application) exists between the departments of internal medicine and cardiology (Dr Otto Kamp and Drs Jeroen Slikkeveer).
8. Capillary video microscopy - none
9. blood pressure - none
10. blood samples (from venous catheter) - local in-catheter (3-way connectors) thrombus formation occurs quickly. Patency is checked regularly and forming thrombi are removed as soon as possible (the 3 way connector set-up makes this possible without the risk of injecting thrombi intravascular). The proposed sampling volumes will not influence hemodynamics.
11. 24-hr blood pressure * discomfort of the cuff when inflating.

As the above mentioned side effects are well known, care will be taken throughout the protocol to prevent them from occurring (for example, adequate application of pressure at the cannulation sites after removal of catheters or frequent sampling of plasma glucose levels after initiation of insulin infusion (and adequate co-infusion of glucose) to prevent hypoglycaemia). The subsequent and thus step-wise administration of the different substances (Sonovue*, insulin) in the protocol enables us to discriminate between them and respond appropriately in case of the occurrence of less known side effects.

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

1. Caucasian*
2. age 18-55 years
3. 20 < BMI > 35
* because capillaries are not visible in the nailfold in a pigmented skin

Exclusion criteria

1. cardiovascular disease (stroke, coronary artery disease, peripheral vascular disease, heart failure)
2. pulmonary disease
3. diabetes mellitus (FPG > 7.8 mmol/l)

4. liver dysfunction (ASAT, ALAT and/or alkaline phosphatase >3 times the upper limit of normal)
5. renal failure
6. smoking
7. alcohol use > 4 U/day
8. use of medication (antihypertensive drugs, lipid lowering drugs, corticosteroids, NSAIDs, ciclosporin A, rifampicin)
9. pregnancy
10. insufficient knowledge of the Dutch language.
11. known previous allergic reaction to ultrasound contrast-agent (e.g. Sonovue)

Study design

Design

Study type: Observational invasive

Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Basic science

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	26-08-2009
Enrollment:	20
Type:	Actual

Ethics review

Approved WMO

Date:	11-08-2009
Application type:	First submission
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
CCMO	NL27575.029.09