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Research Protocol: Ultra low iodine loaded spectral CT angiography (CTA) of the aorta and lower limb: A randomized controlled trial.

1. Background

1.1 Aortic and peripheral arterial disease

Aortic and peripheral arterial disease are important causes of morbidity and mortality. The prevalence of aortic and peripheral arterial disease (PAD) increases progressively with age, beginning after age 40. Total disease prevalence of PAD is in the range of 3% to 10%, increasing to 15% to 20% in persons over 70 years [2,3]. CT angiography (CTA) of the aorta and the lower limb is one of the most important tools for diagnostic, evaluation of the severity of the disease, decision making, treatment planning and follow-up; but usually requires the use of iodine contrast medium.

1.2 Renal impairment

Due to the high prevalence of renal impairment (eGFR < 90 ml/min/1.73m) in the elderly hospitalized population (more than 90% among inpatients aged over 60 years) contrast-medium-induced nephropathy is a major concern in this population. [1] This is found to be correlated with the ratio between dose in gram iodine and eGFR [4-8]. Current practice at our hospital is to calculate the maximum amount of iodine contrast medium considered as safe using OmniVis calculator. There is however uncertainty whether this calculator is sufficiently validated for the patient population with stage 3-5 of chronic kidney disease.

1.3 Contrast medium and diagnostic quality

An iodine load of less than 20 g is considered insufficient for a standard diagnostic CT imaging of the abdominal aorta and arteries in the lower limb. The risk of contrast-medium-induced nephropathy has limited options for diagnostic imaging in patients with severely reduced kidney function. Some of these patients have been offered CO2 angiography which is inferior in diagnostic quality. Others have not received imaging, thereby limiting the therapeutic options.

1.4 Spectral CT

The recently introduced spectral CT technique utilizes x-rays covering a spectrum of energy-levels as opposed to conventional CT in which x-rays are set to one specific energy level. Spectral Detector CT (SDCT) utilises a single X-ray tube but has two layers of detectors to simultaneously collect low and high energy data in all patients.
This technology offers many possibilities, such as “boosting” the x-ray contrast effect of iodine. This improves the vascular enhancement of the contrast medium using low-energy, virtual monoenergetic imaging (VNI).
Akershus University Hospital has recently acquired the first spectral CT scanner in Norway, the Philips iQon.

1.5 This study

We plan to perform a randomized controlled trial for CT examinations of the abdominal aorta and lower extremities. In this RCT, a new ultra-low iodine contrast medium examination procedure tailored for spectral CT on the Philips iQon is compared to the standard examinations.

2 Objectives:

The objectives of this study are:
Evaluation of ultra-low iodine load CTA protocols of the aorta and lower extremities.

To investigate whether dual-layer in combination with virtual monoenergetic imaging (VNI) allows for reduction of contrast medium (CM) in CTA of the aorta and lower limbs with sustained objective and subjective examination quality parameters.

3 Materials and Methods:

3.1 Design

Randomized Controlled Trial.
Patients consenting to participation will be randomized to either examination by standard protocol or examination with ultra-low contrast medium protocol on the iQon scanner. Randomization will be conducted by opening consecutive numbered envelopes which assigns the patient either to "study" or "control".

3.2 Population, Sample size and Recruitment (Inclusion & exclusion)

In-patients and outpatients at AHUS.
Sample size: alfa (level of significance): 0.05, beta (power) 80%. Assuming a mean difference of 0.5 points (on the subjective 5-point scale) with a standard deviation between 1 and 1.5 results in a sample size of 100 in each group.

With SD = 0.8 sample size is 50 in each group.
With SD = 1 sample size is 63 in each group.
Med SD 1.5 sample size is 141 in each group.

Estimated inclusion time: 2 years.

3.2.1 Inclusion Criteria

- Inpatients and outpatients with kidney function (eGFR) allowing for safe administration of standard contrast dose (as calculated with the OmniVis calculator).
- Patients with clinical suspicion of disease of the aorta and/or arteries in the lower limb.
- Referral to CTA diagnosis, treatment planning or follow-up.

3.2.2 Exclusion Criteria

- Iodine contrast medium allergy
- Age < 18 years
- Lack of informed consent
- Critical ischemia of the lower extremities

3.3 Location

Akershus University Hospital, Department of diagnostic imaging.

3.4 CT Scanner and protocol

Scanner:
All patients: Philips Iqon Detector-based spectral CT (SDCT; Philips Healthcare, Clevland, OH, USA)
Imaging protocols:
Randomized either to standard CTA or a dilution DL (dual layer) CTA examination.
In the dilution examinations the amount of injected iodinated contrast medium will be reduced by means of a dilution technique. The dilution technique is efficient and safe since it allows the use of the standard injection protocol (flow rate, volume, iodine concentration, saline chaser) from conventional CT. We set a limit for the contrast injection speed to less than 7,0 ml/s. In order not to exceed this contrast flow rate limit, the maximum volume is limited to 130 ml. Minimum contrast volume is limited to 60 ml. The contrast injection is followed by a flush of 50ml saline at the same flow rate. Injection rate will be determined using formula:

$$\text{Injection Speed (ml/s)} = \frac{\text{Contrast medium volume (ml)}}{\text{Injection time}}$$

21s (CTA of lower limb)

The examination (study and controls) may be supplemented with a feet to hip scan after the main scan if there is suspicion of suboptimal examination quality.

All dual layer dilution examinations are checked by radiologist before the patient leaves the lab.

IQon Spectral CT	CTA of lower limb K+
Patient related parameters	
Contrast concentration, mg I/ml	350
Volume iodine contrast medium, ml	Control group: 1.Bolus:1,4ml/kg max 130ml. 2.Bolus: 50ml NaCl Study group: 1.Bolus:70%NaCl and 30%iodine 2.Bolus: 50ml NaCl Injection time:21s
Technical related parameters	
Flow rate, ml/s	Adjust to achieve desired injection
Trigging threshold, HU	120
Post threshold delay, s	15
NaCl	50ml

Scan parameters	CTA lower extremities
kV	120
Scan	Helical
Scan type	CTA Carotid
Slice Thickness	0,9mm

Increment	0,45mm
Collimation	Auto
Average mAs	228
Min/max mAs	70/200
DRI	27
Dose right	3D
Pitch	1,171
Rotation time	0,5
Resolution	Standard
iDose	4?
IMR	Routine level 1
MonoE40	Spectral 3
MonoE45?	Spectral 3
CTDIw	20,6mGy

3.5 Patient data and Measurements:

3.5.1 Patient data / Variables:

Demographics: Age, gender, weight, height, BMI.
Medical parameters: Creatinine, eGFR.
Comorbidities: Diabetes, cardiovascular disease
Contrast medium: Iodine contrast medium concentration/volume, iodine injection flow rate.

3.5.2 Objective examination quality analysis:

From each imaging examination from the iQon a total of three datasets of vni at 40, 50 keV levels, and conventional, will be reconstructed with spectral 3 level. Conventional images from the control group are compared to vni at 40 and 50 keV in the study group.
For study and control examinations arterial attenuation, image noise, Signal to Noise Ratio (SNR) and Contrast to Noise Ratio (CNR) is recorded.
Arterial attenuation is measured by an experienced radiology technician (where appropriate) in the:

- Abdominal aorta (at the midpoint between the renal arteries and the aortic bifurcation)
- Iliaca communis (at the midpoint between the aortic bifurcation and iliac bifurcation)
- Femoralis superficialis (ca 10 cm inferior to the branching of the deep femoral artery)
- Poplitea (p3 – inferior part of a. Poplitea).

The measurements are performed by placing a region of interest (ROI) within the artery at predefined levels.
Image noise is measured by placing a ROI in air and measuring the standard deviation of the attenuation.
Signal to Noise Ratio (SNR) is measured by dividing the mean arterial attenuation (at defined levels) by mean image noise.
Contrast to Noise Ratio (CNR) is measured by dividing the difference between arterial and muscular attenuation by the image noise: (arterial attenuation - muscular attenuation) / Image noise

Vascular pathology is classified according to the TASC II grading system by an interventional radiologist.

Pas id: nummer – (0=standard, 1=studie, a = keV40, b=keV50)

3.5.3 Subjective /semiquantiative assessment of examination quality:

Subjective examination quality will be rated on a 4-point scale separately by 2 interventional radiologists who are blinded to each other's rating. Discrepancies will be resolved by a third rater.
The subjective rating is performed at the same anatomical levels as the objective measurements. Additionally subjective examination quality is rated in the calf as the best of the three arteries: a. tibialis post., a. tibialis ant. eller a. fibularis.

The rating is performed separately on the left and right side and on conventional, MonoE 40 keV and MonoE 50 keV.

Images that cannot be assessed due to metal artifacts such as hip replacements are labelled "missing" - 9.

Rating	Definition
1	Excellent: The demarcation of the vessel lumen is excellent, more than sufficient for confident diagnosis or exclusion of stenosis or occlusion.
2	Good: The demarcation of the vessel lumen is sufficient for confident diagnosis or exclusion of stenosis or occlusion.
3	Adequate: The demarcation of the vessel lumen is adequate for diagnosis or exclusion of stenosis or occlusion but with limited confidence.
4	Non-diagnostic: There is insufficient demarcation of the vessel lumen for diagnosis or exclusion of stenosis or occlusion.
8	Thrombosis or occlusion at this anatomic level. Enhancement cannot be assessed
9	Missing

3.6 End points:

3.6.1 Primary endpoint:

Mean attenuation in the aorta, common and external iliac artery, femoral artery.

3.6.2 Secondary endpoints:

Rate of diagnostic quality angiography (defined as arterial enhancement > 200 HU)
Subjective examination quality

3.7 Statistical Analysis

Descriptive statistics of subjective and objective examination quality data.
Comparison of subjective and objective examination quality between study and control group.
Inter-observer agreement analysis of the measurements and ratings provided by the observers.

4 Ethics and Approvals

4.1 Ethics

Both study- and control examinations performed in this study are clinically appropriate. Study examinations are performed with a reduced amount of iodine. There might be a very small increase in the risk of inconclusive examinations which will necessitate a repeat examination.

However, the amount of iodine administered (even with a repeat examination) will be less than with the standard protocol.
It is expected that the study examinations have equal (or even better) diagnostic quality compared to standard examination. Hence the risk to the patient is negligible.

4.2 Data Protection Officer (Personvernombud)

The study will comply with requirements of the Data Protection Officer, and Approval will be obtained prior to inclusion. Patient data will be de-identified.

4.3 Regional committees for Medical and Health Research Ethics (REK)

The study will comply with requirements of the Regional committees for Medical and Health Research Ethics, and approval will be obtained prior to inclusion.

4.4 Consent

All study participants will give informed, written consent to participate and to the use of their de-identified data.

5 Funding

The study is funded by Akershus University Hospital, Department of diagnostic imaging.

6 Research Group

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