CT-Angiography versus Angiogram as Ancillary tests in the Determination of Death by neurologic criteria

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Swedish title

"Fastställande av total hjärninfarkt med skiktröntgenangiografi"

English title

"CT-Angiography versus Angiogram as Ancillary Tests in the Determination of Death by Neurologic Citeria”

1 Scientific Question

Can multiphase computed tomography (CT) angiography replace four-vessel angiography as a supplementary radiological examination for the determination of total brain infarction within the Swedish legal framework? An evaluation of a robust CT-Angiography protocol and a direct comparison between these radiological modalities.

2 Background

Total brain infarction, which is equivalent to human death, is confirmed after a two-step clinical neurological exam. This exam assesses cranial nerve functions and the individual's ability to breathe independently. In some instances, it is necessary to verify this diagnosis with a radiological method to confirm that total brain infarction has occurred. Such situations include when brain function is affected metabolically or pharmacologically, when body temperature is too low, when the cause of total brain infarction is unclear, or when injuries to the brainstem or posterior cranial fossa make clinical diagnosis difficult. Additional cases include situations where the clinical exam is incomplete, such as in cases of high spinal injury, facial injury, severe chronic obstructive pulmonary disease, chronic hypoxia, or pacemaker dependency.

In summary, a significant proportion of clinical neurological examinations need to be supplemented with a radiological examination to determine total brain infarction and establish conditions for so-called DBD donation – donation after brain death (donation after injury that has given rise to brain death). The gold standard for such radiology in Sweden is aortocranial angiography, or four-vessel angiography, a catheter-guided injection of contrast medium to demonstrate the absence of blood flow to the brain's vessels.

Four-vessel angiography can mainly be performed at regional and university hospitals by a radiologist with neuro- or vascular intervention competence and is a resource-intensive procedure. The lack of equipment and necessary competence at smaller hospitals poses challenges for performing the examination locally. Today, four-vessel angiography has essentially no indication other than determining total brain infarction, which is why the method is not part of every radiologist's competence or every hospital's routine examination.

If a patient with probable arrested circulation to the brain needs to be transported to another hospital for such an examination, difficult emotional decisions sometimes arise for next of kin and ethical decisions for healthcare providers. It also places great logistical demands on healthcare and risks constituting an obstacle to a donation process.

A consensus document from The World Brain Death Project emphasizes that additional radiological diagnostic modalities beyond four-vessel angiography may be applicable for determining total brain infarction, including radionuclide methods (Single Photon, Emission Computed Tomography, e.g., SPECT or perfusion scintigraphy) or transcranial Doppler. However, the consensus advises against CT angiography or MR angiography (MRA)/diffusion-weighted MRI (dMRI) for the time being, pending further studies demonstrating favorable sensitivity and specificity. They emphasize the need for standardized criteria adaptable to different healthcare systems. Further the consensus concludes that four-vessel angiography constitutes the reference method against which other modalities are compared in research contexts (1).

Central aspects for comparisons between methods are the methods' sensitivity and specificity. Internationally, different guidelines and regulations are applied. In Germany, for example, four-vessel angiography is not advocated due to its invasive nature (2); in the USA, CTA and MRA are advised against due to insufficient validation of the methods (3). In Polish guidelines, a combination of CT-Angiography and CT-perfusion (CTP) is recommended (4,5), whereas in French guidelines, only CT-Angiography is the recommended diagnostic modality (6,7). In Sweden, there is a binding regulation that establishes how the diagnosis of total brain infarction is to be made when the clinical examination needs to be supplemented; four-vessel angiography or radionuclide methods constitute possible alternatives (8).

A significant proportion of these patients are potential organ donors, for whom medical principles and national legislation place particularly high demands on diagnostic reliability. Furthermore, there is a need to make diagnostic methods available outside regional and university hospitals where specialized neuroradiological competence may be lacking. Against this background, SBU (Swedish Agency for Health Technology Assessment and Assessment of Social Services) investigated in 2018 the scientific basis for assessing the reliability of two alternative diagnostic methods to four-vessel angiography: CT-Angiography and dMRI. The summary conclusion of the report was that CT-Angiography was still a method under development, that there were insufficient studies with a desirable and direct comparison between four-vessel angiography and CT-Angiography, and that there were too few studies with dMRI to make an assessment (9).

The difficulties presented were that many studies included in the report used clinically established brain infarction as a reference standard for comparison with CT-Angiography, meaning that the specificity of CT-Angiography could not be assessed. Furthermore, in several patients the clinical neurological examination was inconclusive, and objections were raised that there were no consensus or clear protocols for how the examination should be applied. On behalf of the Swedish National Donation Centre, SBU produced documentation on diagnostic reliability for nuclear medicine methods for determining total brain infarction. It was stated that the diagnostic reliability of gamma camera examination with Technetium was the same as that of four-vessel angiography in adults and children over two years and constituted an acceptable substitute (10). However, we note that nuclear medicine techniques cannot compete with CT-Angiography in terms of availability, should such a practice be enabled.

The question of whether a CT protocol could replace four-vessel angiography is thus not new but has not been studied in a way that would allow the question to be clearly adressed. The main advantages of applying CT-Angiography for this purpose, in addition to increased

availability, are that the method has a very high degree of sensitivity to intravascular contrast and that robust, operator-independent protocols can be developed and distributed.

Frampas and colleagues showed in 2009 that CT-Angiography set against clinically diagnosed brain death achieves a sensitivity of approximately 86% when applying a four-point protocol including measurement points at four cortical segments of the middle cerebral artery as well as central cerebral veins, with a specificity of 100% i.e., absence of false positive outcomes (11). Taylor and colleagues conducted a meta-analysis in 2014 of available studies on the sensitivity of CT-Angiography in confirming clinically established cessation of circulation to the brain. The ten included studies yielded a sensitivity estimate of 0.85 for a four-point evaluation as above, concluding that the method could not be recommended as a mandatory element in confirming brain death (12).

In a study by Garret and colleagues which, among other things, directly compared CT-Angiography against four-vessel angiography, a sensitivity of 75% and a specificity of 100% was reached; they stated that the low sensitivity could likely be attributed to an intradural "stasis filling", i.e., pendulum filling without sustaining circulation, and that the high specificity is far more important, i.e., the absence of false positive outcomes (that ceased circulation is determined in a patient where circulation has not ceased) (13). Suarez-Kelly and colleagues conducted a direct comparison between CT-Angiography and a nuclear medicine perfusion test, i.e., a method accepted in Sweden as a substitute for four-vessel angiography. They found that if a quantitative analysis of opacification at CT-Angiography (<80 Hounsfield units) was performed in the vessel segments M1, A1, and BA, sensitivity could be increased to 97%, with a specificity of 100% (14).

Although The World Brain Death Project states that CT-Angiography cannot replace four-vessel angiography at present (1), there is strong international support for a transition. Thomas and colleagues presented a consensus document in the UK in 2023, arguing that the examination shows 100% specificity with respect to clinically established cessation of circulation to the brain and that the 85% sensitivity is acceptable, as the method represents a safe standard that prioritizes specificity over sensitivity (15). In summary, the four-point protocol shows 100% specificity for clinically established cessation of circulation to the brain and compared with nationally accepted methods, can thus achieve 97% (14).

3 Project Description

3.1 Overall purpose and conditions of the project

We intend to establish and evaluate a new, robust protocol for CT-Angiography to determine total brain infarction. The protocol will methodologically mirror four-vessel angiography, with radiological review of cessation of intradural blood flow incompatible with life. The protocol, which differs significantly from recent recommendations regarding how such a protocol could be designed (15), is intended to be readily available in all modern CT scanners.

The protocol's performance is compared with four-vessel angiography as a confirmatory test for determining cessation of circulation after clinical diagnostics, first in a local, smaller study at Karolinska University Hospital and, in the next step, in a national multicenter study, with the goal of achieving "non-inferiority". Computed tomography angiography is performed according to a clinically standardized protocol, with contrast dose and administration fully in

accordance with CE marking requirements. The study intends to elucidate key aspects of establishing novel ROIs in computed tomography and is to be equated with an interrater assessment study.

In parallel, we also intend to study the patient-near ultrasound modality, Transcranial Doppler (TCD), regarding its predictive and diagnostic performance for this purpose.

The timeline for the pilot study depends on the number of patients cared for in the intensive care units at Karolinska University Hospital, Solna, with suspected total brain infarction requiring confirmation by four-vessel angiography.

3.2 Study Center

The local study is conducted at the Department of Perioperative Medicine and Intensive Care, in collaboration with the Department of Neuroradiology, Karolinska University Hospital, Solna.

The national multicenter study is coordinated by the study group at Karolinska University Hospital, Solna. We intend to include university hospitals that conduct neurointensive care and possess high neuroradiological competence, such as Gothenburg, Lund, Linkoping, Umea, Uppsala, and Orebro. A supplementary ethical application will be submitted upon completion of the pilot study, before recruiting additional national study centers.

3.3 Study Period and Project Plan

A recent trend towards a larger proportion of donation processes going to DCD (Donation after Circulatory Death) carries the risk of reducing the number of potential research subjects for assessment. We need to consult with next of kin in a challenging situation, which can further affect the recruitment of research subjects. Over the past few years, approximately 15 four-vessel angiographies have been performed annually in our hospital. We believe that a sufficient study basis for statistical comparison of diagnostic performance in a local pilot study can be achieved with approximately 50 patients, during a timeframe of three years. Upon a favorable outcome of this pilot study, we intend to move the project into a second phase, in which the corresponding question is studied within the framework of a national multicenter study with far more patients, providing a stronger statistical foundation.

Local study: Patient inclusion is planned from December 2025, or as soon as the ethical application allows. Patient inclusion is planned to continue through December 2028, given an annual decline in the number of examinations. The goal is to recruit approximately 15 patients each year, totaling approximately 50 examinations. An interim analysis is planned after approximately eight examined research subjects, to inform decision-making regarding the reduction and selection of the number and/or phases (image sequences) to be included in the final protocol.

National multicenter study: Study start is planned preliminarily for May 2029 and will continue until May 2032 with an ambition to recruit a total of 200 additional patients.

Compilation and presentation:

- After the interim analysis, the data will be compiled, and the manuscript will be ready for peer review, estimated for 2026–2027.
- After the local study's completion, the data are compiled and the manuscript is ready for peer review, estimated for 2029.
- After the national multicenter study, data are compiled, and the manuscript is ready for peer review, estimated for 2033.

3.4 Study Registration

Both the local pilot study and the national multicenter study will be registered on ClinicalTrials.gov or equivalent registry.

3.5 Power Analysis

Calculating the statistical power of the study is associated with significant uncertainty. The first local study is hypothesis-generating and motivates a subsequent national multicenter study for validation. An approximate calculation gives an estimated sample size of approximately 250 examinations.

Project's Specific Question

- Can computed tomography angiography replace four-vessel angiography as a supplementary radiological examination to determine total brain infarction within the Swedish legal framework?
- How is a new CT-Angiography-based protocol interpreted in comparison with four-vessel angiography, where there is a need for radiological confirmation of ceased circulation to the brain?

3.6 Method

Patient Recruitment

Recruitment of research subjects occurs in connection with the decision or execution of clinical diagnostics with direct criteria. After two consecutive clinical neurological examinations with at least two hours in between, where the clinically responsible physician has not been able to demonstrate remaining cranial nerve functions or spontaneous breathing, a suspicion is formed according to clinical practice that complete brain infarction is present, and a decision on four-vessel angiography is made.

- Patient undergoes transcranial Doppler (TCD) to assess the flow profile or its absence. The examination takes approximately 10 minutes. Images/data/results are blinded for the responsible neuroradiologist.
- Research subjects are randomized to undergo computed tomography before or after four-vessel angiography and are examined in the order specified by randomization.
- Images/data/results of computed tomography examination are blinded for the responsible neuroradiologist to avoid bias. The computed tomography examination is performed on one occasion; the time required is approximately 5 to 10 minutes, including transfer from bed to stretcher to bed.
- Research subject undergoes two consecutive four-vessel angiographic examinations performed by a neuroradiologist, with at least 30 minutes between them.

- A trained interventional neuroradiology (INR) operator confirms or denies ceased circulation to the brain's vessels based on four-vessel angiography.
- In the event of a cessation of cerebral circulation, death is documented with date and time, in accordance with clinical practice.
- Research subject returns to the intensive care unit.

Collected Research Data:

eCRF:

- Patient data, demographic variables, injury mechanism and date, execution date and time for clinical neurological examination (see eCRF below). Cardiopulmonary physiological data.
- Kidney function parameters include fluid balance, creatinine, urea, estimated glomerular filtration rate, and electrolytes.

Computed Tomography Angiography:

- According to a prespecified examination protocol.
- Four consecutive computed tomography examinations from cervical vertebra 2 to the skull's vertex, of which the first examination is without contrast for reference and the following three examinations constitutes a multiphase examination of the same contrast bolus.
- Subsequent examinations according to calculations for time regarding contrast propagation in relation to time point 0 which is defined as when a sufficient amount of contrast reaches a specific measurement point in the aortic arch.
- Image sequences are clearly marked with respect to time relative to T=0.
- Standardized contrast medium volume is administered (according to clinical practice) with a minimum of 5 ml/second via power injector.
- Image sequences are acquired with the lowest possible slice thickness and at the lowest possible tube current. Tube currents above 100 kV are not allowed to increase the iodine sensitivity.
- Images are saved locally in the Karolinska Picture Archiving and Communication System (PACS).

Conventional Four-Vessel Angiography:

- Two consecutive four-vessel angiographies are performed with at least 30 minutes in between.
- Images are saved locally in the Karolinska Picture Archiving and Communication System (PACS).
- Date and time for established outcome (positive or negative examination).

Processing of Computed Tomography Angiography:

- The validity of the X-ray examination is tested by reviewing the entire series and confirming that it meets the requirements for contrast filling of extracranial vessels.
- Two board certified neuroradiologists will conduct an initial training session determining allowed contrast filling over the phases.

- Following a washout period of a minimum of two weeks, the neuroradiologists will independently re-review all images and determine a binary outcome of cessation of blood flow compatible with brain death in the same manner as the four vessel angiography is evaluated.
- After an additional wash out period of a minimum of four weeks the images will be independently re-reviewed.
- Following the two reading sessions inter- and intrarater agreements will be determined and comparison to gold standard test will be performed.

Timestamps:

- Time for established neurological examination.
- Time for computed tomography angiography.
- Time for four-vessel angiography (start = skin puncture, end = contrast catheter is extracted).
- Time for established outcome regarding four-vessel angiography (positive, negative).

Statistical Analyses:

- The computed tomography angiography examination's sensitivity and specificity are determined in relation to four-vessel angiography.

3.7 Patient Selection Criteria

Inclusion Criteria:

- Adult individuals, 18 years or older.
- Ongoing intensive care after critical brain injury.
- Need for four-vessel angiography, according to the Swedish National Board of Health and Welfare's guidelines, to confirm ceased cerebral circulation (16).

Exclusion Criteria:

- Examination too risky with regard to circulatory or respiratory instability or equivalent, as assessed by clinically responsible physician.
- Ongoing treatment with extracorporeal membrane oxygenation (ECMO).

> As exclusion criterion, we specify treatment with extracorporeal membrane oxygenation (ECMO), since such treatment makes contrast bolus propagation in the pulmonary and systemic circulation difficult to predict, including cerebral vessels.

3.8 Case Report Form – CRF

eCRF is established with pseudonymized data on a platform approved by the Region and Karolinska Institutet, REDCap, an encrypted database with authentication and two-step verification. The patient key is stored in a local safe on the study premises, where access is pass-card protected in two steps.

- Baseline variables including age, sex, comorbidities, and ordinary medications.

- Baseline variables including cardiopulmonary data including biomarkers such as troponin and NT-proBNP, ECG & echocardiography for assessment of left and right ventricular function.
- Kidney function parameters include fluid balance, creatinine, urea, estimated glomerular filtration rate, and electrolytes.
- Injury mechanism, time of injury.
- Clinical basis for suspicion of total brain infarction, incl. biomarkers such as NSE, S100, SEP, EEG, and MRI.
- Ongoing drug infusions, including vasopressors and inotropes. Relevant drug administrations, such as Desmopressin.
- Current hemodynamic parameters during radiological examinations, including blood pressure.

3.9 Follow-up and Reporting

Written reporting, in the form of a manuscript submission to a peer-reviewed scientific journal, is planned first after an interim analysis of three examined research subjects and thereafter as soon as possible after completed data collection and analysis within the framework of the local study in 2028. Finally, after completing data collection and data analysis within the framework of the national multicenter study in 2032.

3.10 Planned Analyses

Descriptive statistics. Intra- and interrater reliability. Sensitivity, specificity, positive and negative predictive values.

4 Ethical Considerations

The ethical considerations are several and complex when conducting a study of this nature. The study concerns critically ill people where cessation of circulation to the brain has been clinically determined and where consent from the research subject cannot be obtained due to severe brain injury. At the same time, next of kin are often in crisis and may face challenges in establishing consultation. We find that the study itself has great potential to address a long-standing, complex question of great medical and societal importance, which motivates its implementation. At the intensive care units at Karolinska University Hospital, we have extensive experience conducting clinical studies in critical illness and an adaptive, empathetic approach to both patients and next of kin. The research project has been approved by The Swedish Ethical Review Authority, diary number 2025-06415-01.

5. Clinical Relevance, Patient and Societal Benefit

The study's overall goal is to establish a protocol for CT-Angiography as a simple, robust, and accessible radiological modality for confirming total brain infarction when such confirmation is needed, with diagnostic performance comparable to four-vessel angiography. If such were to gain medical and medico-legal support, great gains stand to be made. The study has the potential to establish a basis for future care processes to determine total brain infarction outside regional and university hospitals. This creates conditions for more equal care. The project also has the potential to increase the likelihood of DBD donations and more

transplants. In addition to significant health gains for those who can receive transplants, substantial economic gains can be achieved. A health economic study from the Department of Clinical Sciences, Lund 2015 (referenced in SOU 2015:84) showed that an increase of 100-150 donors annually in Sweden can lead to savings of 70-80 million kronor annually, only regarding the number of donated kidneys, additionally possibility for savings of 70% per transplanted patient (of expected costs without kidney transplantation) (17).

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