Health Council of the Netherlands

Brain Death Protocol

Gezondheidsraad
Health Council of the Netherlands

To the Minister of Health, Welfare and Sport
P.O. Box 20350
2500 EJ Den Haag

Subject : Presentation of advisory report *Brain Death Protocol*
Your reference : IBE/E 2251274
Our reference : -132/GtV/ts709-U
Enclosure(s) : 1
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Dear Minister,

On 25 January 2002, the former Minister of Health, Welfare and Culture asked the Health Council of the Netherlands to advise once more on the diagnosis of brain death for organ donation. I hereby present to you the *Brain Death Protocol* Advisory report, which at my request was compiled by the Brain Death Protocol Committee established on 6 October 2003. The Standing Committee on Medicine and the Standing Committee on Health Ethics and Health Law have evaluated the Advisory report. I support the conclusions and recommendations of the Committee.

The Advisory report concerns a modification to the Brain Death Protocol stated in article 15 of the Organ Donation Law (WOD): the method to be used for indicating brain death according to current medical insight. The Health Council of the Netherlands has already advised on brain death criteria seven times in the past. The proposed Advisory report is a revision of the document published in 1996. The Committee used the rights and interests of the potential donor as a starting point in drafting its Advisory report.

According to the report, an update of the protocol is desirable particularly because, in future, it allows for brain death also to be diagnosed in patients with brain injury who received medication to suppress brain function in order to limit further brain damage. The current protocol does not allow for this. Based, among other things, on an analysis of the current scientific state of affairs, the Committee has concluded that this situation has now changed due to the availability of new, safe and reliable methods for examining brain perfusion. This also allows for the procedure for brain death diagnosis in young children to be modified in the protocol.

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I can inform you that – due to the significance of the subject matter – the Committee had various meetings with external experts whilst forming its Advisory report on individual matters, such as the effect of medicines on brain death diagnosis and the safety and validity of the new research methods. In my opinion, the protocolled method described in the Advisory report guarantees a thorough brain death diagnosis as a result.

As new scientific insight will also be gained in the field of brain death diagnosis over the next few years, I expect that the guidelines provided in this Advisory report may need to be revised in four to five years.

Yours sincerely,
(signed)
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President of the Health Council of the Netherlands

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to:

the Minister of Health, Welfare and Sport

No. 2006/04E, The Hague, April 11, 2006

The Health Council of the Netherlands, established in 1902, is an independent scientific advisory body. Its remit is "to advise the government and Parliament on the current level of knowledge with respect to public health issues and health (services) research..." (Section 22, Health Act).

The Health Council receives most requests for advice from the Ministers of Health, Welfare & Sport, Infrastructure & the Environment, Social Affairs & Employment, Economic Affairs, Agriculture & Innovation, and Education, Culture & Science. The Council can publish advisory reports on its own initiative. It usually does this in order to ask attention for developments or trends that are thought to be relevant to government policy.

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Contents

Executive summary

This advisory report, compiled by the Brain Death Protocol Committee of the Health Council of the Netherlands, concerns an adjustment of the Brain Death Protocol referred to in Article 15 of the Dutch Organ Donation Act (Dutch acronym: WOD). According to prevailing medical insight this is the approach to be used for diagnosing brain death. Since the Health Council of the Netherlands issued its advisory report on brain death criteria in 1996, new scientific data have become available and new insights have arisen concerning brain death determination for the purposes of organ donation. The Committee is therefore of the opinion that various parts of the Brain Death Protocol, which is used nationally with respect to the Dutch Organ Donation Act, need to be adjusted.

Firstly, this concerns the diagnosis of brain death under special circumstances, such as treatment with neurosupressants (medical neurodepression, including barbiturate coma and such) or if certain tests (such as EEG or apnea test) cannot be properly carried out. The former situation in particular was found to cause problems in practice. According to the current protocol, it is not possible to accurately establish brain death under these conditions. However, this is now possible with new, safe and reliable methods for investigating brain circulation, such as Transcranial Doppler ultrasonography (TCD) and CT angiography (CTA). Demonstrating permanent cerebral circulatory failure is then equivalent to brain death. The older methods referred to in the current protocol for cerebral angiography (conventional angiography and digital subtraction angiography) should be replaced by the combination of

TCD and CTA. In the Committee's opinion, the two investigations combined provide maximal validity and guarantee careful brain death diagnosis. Furthermore, in the case of brain death determination in young children, these techniques offer a second, less time-consuming technique than the repetition of investigations.

The Committee recommends modifying the protocol in the above manner. A proposal to this end is presented in this advisory report (Annex C). Finally, the Committee advises a new assessment in four to five years time to see how far scientific advancements necessitate a revision of the guidelines given in this advisory report.

Chapter 1

Introduction

1.1 History

The Health Council of the Netherlands has advised on brain death criteria seven times since 1973. The most recent Advisory report, titled *Brain Death Criteria*, dates from 1996. In that Advisory report, the Committee not only documented the scientific state of affairs, but also informed itself of the insights and experiences of the professional groups involved. The Committee examined the conditions required for determining brain death and the order for these conditions, the possible risks of certain examinations for the patient, the logistical consequences and finally, the doctors to whom the execution of the various examinations should be allocated.

The Minister for Health, Welfare and Sport and the Minister for Justice accepted the Health Council of the Netherlands' Advisory report in 1997 and the Brain Death Protocol was established by law. The protocol came into force on March 1,1998.

In the submission letter accompanying the Advisory report in 1996, the President of the Health Council of the Netherlands indicated that revision of the procedures described in the Advisory report would probably be necessary after a period of approximately five years. A report by the Healthcare Inspectorate about

the functioning of the Organ Donation law (WOD)* reached the same conclusion.[1]

1.2 Request for Advisory report

In a letter dated 25 January 2002 (Annex A), the President of the Health Council of the Netherlands received a request from the then Minister for Health, Welfare and Sport to provide a new Advisory report on the diagnosis of brain death and to update the protocol if necessary. The request for an Advisory report relates mainly to the possible role of transcranial Doppler Examination (TCD) in patients undergoing (or who have undergone) treatment with medicines that suppress brain function.

1.3 Method

The President of the Health Council of the Netherlands established the Committee on Brain Death Protocol (see Annex B) on 6 October 2003 and assigned this Committee the task of assessing the extent to which scientific advances have necessitated amendment of the brain death protocol.

The Committee held seven plenary meetings. Three meetings, on different topics, involved a meeting with one or more external experts (see Annex B). During the consultations, the Committee focused on the following points of interest:

- the current diagnostic options for determining brain death in patients who have received treatment with medicines that suppress brain function (therapeutic medicinal neurodepression);
- the desirability of implementing these methods, the availability in hospitals, the technical and professional requirements;
- other developments, or new insights (such as those relating to determination of brain death in children) that demand modification of the protocol or parts of the protocol.

On 2 November 2005, the Committee discussed the draft version of its final Advisory report and then submitted the Advisory report for testing by the Standing Committee on Medicine and the Standing Committee on Health Ethics

* This law assigned the Health Council of the Netherlands two tasks, namely to present the scientific methods and criteria for determining brain death according to the most recent state of affairs and also to draft the national *Brain Death Protocol*.

& Health Law. After further changes, partly based on recommendations from both Standing Committees, the Committee then finalised its Advisory report.

1.4 Design of the Advisory report

In the Advisory report, the Committee first examines the current practice of brain death diagnosis. The Committee then discusses new insights and diagnostic opportunities. Finally, the Committee provides an amendment to the current protocol.

Chapter 2

Current execution brain death diagnosis

2.1 The concept of 'brain death'

The international literature provides various notions on the concept of 'brain death'. This has already been discussed in the Advisory report on *Brain Death Criteria* of 1996 by the relevant Committee of the Health Council of the Netherlands.[2] As indicated in that Advisory report, these notions can be grouped as follows:

- death of the brain
- brain stem death, and
- cerebral cortex death.

The first vision is also described in the literature as the whole brain death concept. It presumes the complete and definitive loss of the functions of the brain and the brain stem, including the extended spinal cord. To date, this concept defines the practice in most Western countries.[3,4]

2.2 Determination of brain death

In the Dutch brain death protocol, the legislator has also decided in favor of the above-mentioned whole brain death concept. This means that the most stringent

definition of the concept of 'brain death' is used*. In our country – as in the majority of the European countries – brain death has until now been determined based on three diagnostic phases:[5-9]

a Pre-existing conditions: determining the cause of death and the cause of the brain injury, as well as the untreatable nature thereof; excluding reversible causes of unconsciousness or unresponsiveness (such as hypothermia, intoxication, hypotension, blockade of the neuromuscular junction, severe biochemical or metabolic disorders).
b Clinical neurological examination; lack of consciousness, lack of brain stem reflexes, ventilator dependency (in other countries: spontaneous respiration).
c Additional examinations**, in the following order: a) conducting one electroencephalogram (EEG); b) in case of iso-electric EEG: apnea test; c) cerebral angiography (aortic arch angiography, preferably in the form of digital subtraction angiography, DSA): if EEG or apnea test cannot be performed.

In addition, both the clinical neurological examination and the additional examination (except the apnea test) must be repeated for children younger than 4 years of age.

Evaluation of organ donation and WOD

Six years ago, the Healthcare Inspectorate (IGZ) examined the efficacy of organ donation in Dutch hospitals and the functioning of the Organ Donation Law (WOD), which was introduced in 1997.[1] The IGZ investigators concluded that the brain death protocol drafted by the Health Council of the Netherlands and linked to the WOD is broadly applied and is generally viewed as a significant improvement both logistically and according to content.

* For additional information on the less strict definitions of 'brain death', such as cerebral cortex death and brain stem death, the Committee refers to the Health Council advisory report on Brain death criteria of 1996.[2]

** In other European countries the additional examinations (mandatory or otherwise) usually include: an EEG (except for the United Kingdom), an apnea test (unlike the Dutch protocol this test is usually considered to be part of the clinical neurological examination), angiography. In some countries transcranial Doppler ultrasonography (Germany, Austria, Slovak Republic), and/or an evoked potential response test (Belgium, Germany, former Yugoslavian Republic, Luxembourg, Portugal), and/or scintigraphy (Germany, Greece, Luxembourg, Switzerland), are additionally performed.

2.3 Neurodepressive medicines influence diagnosis

The request for an Advisory report (Annex A) shows that an update to the protocol is considered desirable mainly in view of the diagnosis of brain death in patients with brain damage being treated with medicines that suppress brain function. Medicines are used to sedate patients, to counteract increased intracranial pressure (cerebral edema) or to prevent epilepsy (status epilepticus).[10-21] The medicines – sedatives, hypnotics, anaesthetics, anti-epileptics – primarily used in patients with severe brain damage (see box on next page) are barbiturates (thiopental, pentobarbital), propofol (a sedative-hypnotic) and benzodiazepines (for example, midazolam). Barbiturates and propofol are used more often in adults and benzodiazepines are used more often in children. These medicines suppress all brain functions such as consciousness, the reflexes, the electrical activity of the brain and the breathing.

Over the last few years, the so-called iatrogenic barbiturate coma has received particular attention, also in other countries. In order to counteract cerebral edema and an increase in intracranial pressure, a patient will be administered a high dosage of barbiturates among other medicines. These are usually trauma patients that have been admitted to an intensive care unit. The literature contains varying opinions on the therapeutic value of the barbiturate coma.*

If the patient's condition – despite the use of abovementioned medicines – is such that brain death is suspected, then this brain death cannot be determined in the usual manner. After all, the prerequisite condition 'exclusion of intoxication' – according to the current protocol – can no longer be met.**

The suppressive medicines can influence the clinical neurological examination and parts of the additional examinations (EEG, apnea test, not the angiography). If these tests produce a response, then the patient is not brain dead, but conversely, the absence of a response does not guarantee that brain death has occurred.

The literature recommends ('reasonable approach') to wait for at least four times the half time of the relevant medicine (provided that another administered

* According to a recent Cochrane review (2002), there is no evidence that the use of barbiturates for severe brain trauma improves the outcome.[21]

** Because this is a medicinal form of treatment, the iatrogenic barbiturate coma is listed as a special form of intoxication in the current brain death protocol.

Frequently used medicine in therapeutic, medicinal neurodepression

Barbiturates

Thiopental is the most commonly used. It is a highly lipophilic substance that perfuses the brain rapidly. The medicine has a half time of 10 to 12 hours. Pentobarbital (a metabolite of thiopental) is also used. It has a half time of 30 to 50 hours.

It cannot be excluded that the half time of these medicines is much longer in a sick person. Waiting until there is no longer an effective blood concentration* can take too long (days).

Most hospitals can determine the blood concentration. However, the problem is: what level is acceptable? Is there a minimum level for the blood concentration, below which one can assume to be safe for the purposes of brain death diagnosis? In practice, a zero value has not been defined. However, some hospitals in our country apply a practical threshold value of 5 mg/L as 'safe', namely a concentration at which a healthy individual would be awake or responsive.

Propofol

This is a short-acting medicine. The half time is 3 to 4 hours, probably increasing to more than 5 hours in a critically ill patient. The properties, such as pharmacokinetics and relationship between concentration and effect are relatively well known. However, the question remains whether this can be extrapolated to patients with brain damage. There is also a logistical problem: determination of the blood concentration can only be performed at a few sites in the Netherlands.

Benzodiazepines

These medicines display a large variation in effects and blood concentrations. An antidote is available: flumazenil, which binds competitively to the receptor. It is not certain whether this antidote is also sufficiently effective at high benzodiazepine dosages in patients with severe brain damage.

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* The maximum effectiveness, demonstrated by a flat EEG, appears to occur at barbiturate levels above 50 mg/L.[23,24]

medicine does not interfere with its elimination) after termination of such medication before performing brain death diagnosis.[22]

For pharmaceuticals that suppress brain function – such as barbiturates, benzodiazepines and propofol – the Committee cannot define a low blood concentration (threshold value) with certainty, below which no significant effect exists on the components of the brain death diagnosis. For various medicines, waiting – after termination of the medication – until there is no effective blood concentration can take a long time (days). This is also true because we cannot exclude that the half time of these medicines may be much longer in patients with severe brain damage than in a healthy individual.

Intoxication versus targeted treatment

The Committee deems it important to distinguish between the usual concept of accidental 'intoxication' and the situation in which intended medicines are used. The latter situation involves targeted medical actions with a therapeutic goal. In future, the Committee would prefer to refer to the use of barbiturates (barbiturate coma) or similar medication as 'therapeutic medicinal neurodepression'.

2.4 A different approach: examination of brain perfusion

Treatment with neurodepressant medicines – or: therapeutic medicinal neurodepression – will lead to a situation where the usual method of brain death diagnosis, consisting of an examination of the functioning of the nervous system, does not provide enough certainty.[22,25] A different approach is required in that case. This could be in the form of an examination of brain perfusion.[25-31] This involves demonstrating persistent cerebral circulatory arrest: a situation in which the primary working conditions of the brain have changed to such an extent that this organ can no longer function. Persistent cerebral circulatory arrest can then be compared to brain death. This is the case when brain perfusion is absent for a sufficient length of time – thirty minutes is a generous and safe measure – and there is no hypothermia, in other words a body temperature lower than 32°C. The latter is important, because the absence of brain circulation with (deep) hypothermia does not necessarily mean that brain function has been lost irreversibly.*

* This could be the case for severely hypothermic (trauma) patients or with certain types of surgeries. Some operations – for example on the heart or aorta – in which brain perfusion is stopped for half an hour or more during the procedure, are performed under deep hypothermia: the patient is cooled until an iso-electric EEG is obtained at a body temperature of 14 tot 16°C.

Chapter 3

Additional diagnostics: new techniques

In this Chapter, the Committee will discuss new(er) techniques for additional diagnostic examinations and their possible role in an amended brain death protocol. Included are: radiological imaging techniques, ultrasound examination and scintigraphy.

In addition to implementation aspects and the availability in hospitals, the Committee will also focus on the validity of various examination methods. The discriminating powerof a test method is particularly important. This is determined by the extent to which a test can correctly indicate the presence or absence of the abnormality (in this case: brain death): called sensitivity and specificity respectively. Ideally, both should be a hundred percent. If the specificity of a test is lower, there is a chance that the test incorrectly indicates the presence of the abnormality (false positive result). If the sensitivity is less than a hundred percent, the test can incorrectly indicate the absence of the abnormality (false negative result). When demonstrating brain death, it is important that the specificity of a test is as high as possible: preferably a hundred percent. This is less important for the sensitivity: from the point of view of due caution diligence towards the (possibly) deceased individual, as part of possible organ removal, it is safer that there is a certain chance that the individual is declared ‘not brain dead’ – when this is in fact the case – rather than vice versa. Therefore, specificity prevails over sensitivity for brain death diagnosis. However, a moderate sensitivity can result in life support measures being continued in some cases when this is no longer necessary.[2]

3.1 Radiological imaging techniques

3.1.1 Cerebral angiography

The current brain death protocol states that cerebral angiography should preferably be performed in the form of digital subtraction angiography (DSA). This technique determines whether or not brain perfusion is present. The broader use of 'cross-sectional' techniques, CT and MRI, has resulted in a marked decrease in the use of DSA over the last ten years.

The benefits of DSA for brain death diagnosis are that the interpretation of the examination is unambiguous and that the value of DSA in determining brain death is supported in the literature.[2,32-34]

The disadvantages are that the examination is invasive (contrast administration via intra-arterial catheterisation) and is associated with a slight morbidity (such as the risk of thrombo-embolic complications) and mortality. The administration of an iodine-containing contrast agent is also required. These agents can cause kidney damage (nephrotoxicity). Another disadvantage is that the (ventilated) patient has to be transported from the terminal phase of a nursing ward to an examination room. This is difficult for the patient and his/her family and also a logistical problem. DSA requires a lengthy examination. It can easily take 45 minutes to an hour. A final disadvantage is that the DSA expertise with selective carotid injections is currently only available in a limited number of hospitals in our country.

3.1.2 MRI, MR-angiography (MRA)

MRI can be used to observe various phenomena associated with the death process of the brain: decrease in intracranial flow (with MR-angiography: MRA techniques), edematous swelling and entrapment of the brain (with conventional MRI techniques) and also the cytotoxic edema that occurs with ischaemia of the brain parenchyma (with diffusion-weighted MRI techniques).

MRI applied as MR-angiography (MRA) provides both anatomical and functional information. The Health Council of the Netherlands' Advisory report from 1996 was relatively optimistic about the future use of MRA for brain death diagnosis. However, the current literature provides little support for this.

The benefits of MRA are that MRI equipment is available in virtually all hospitals and that they provide both anatomical and functional information when

used diagnostically. The technique has no detrimental biological effects: no nephrotoxic contrast agents are required and no ionising radiation is used.

A disadvantage is that MRA is not one hundred percent specific. For example, slow intracranial flow can easily be missed with MRA techniques. The value of MRA in determining brain death is also not well supported in the literature. Another disadvantage is that few hospitals in our country have MRI(MRA) compatible ventilators available. As a result, MRA cannot be used in many cases, because brain death diagnosis is performed on ventilated patients. Another disadvantage of MRA is that the (ventilated) patient has to be transported from a nursing ward to an examination room. As with DSA, the examination can take 45 minutes to an hour. Finally, reliable use of MRA requires specific experience.

3.1.3 *Computer tomography*

Computer tomography (CT) can play a role in determining brain death, in the form of CT-angiography (CTA). CTA has become a valuable angiographic technique thanks to the development of single-detector row and, more recently, multi-detector row systems (spiral CT technique). CTA can be used for the purpose of brain death diagnosis by determining whether or not intracranial flow is still present.[35,36]

The advantage of CTA for brain death diagnosis is that the technique is widely used in the Netherlands. The technique provides optimum image quality thanks to three dimensional imaging based on digital image reconstruction. The necessary equipment* is available in nearly all hospitals. The interpretation of the examination is unambiguous and the procedure does not take a long time. It takes only a few minutes. However, again there is the disadvantage that the (ventilated) patient has to be transported from a nursing ward to an examination room. The method is invasive, but less so than DSA. For CTA, the (iodine-containing) contrast agent is administered through a vein (intravenous injection) and not an artery. This results in a smaller risk of kidney damage than with DSA. In contrast to DSA, there is also no risk of thrombo-embolic complications with CTA.

There is a lot of (international) experience with CTA as a method for examining brain circulation. For example, extensive studies have been performed on the detection of aneurysmata in the circle of Willis. In this field,

* Currently, nearly all centres in our country have a multi-slice CT scanner (multi-detector row system), but some hospitals still have a single-slice scanner (single-detector row system). It is expected that all centres will have a multi-slice scanner within one to two years.

CTA was also compared to DSA, MRA and TCD in recent systematic reviews.[37,38] Although DSA is still considered the standard method for the detection of cerebral aneurysmata – according to one of these reviews (a meta-analysis of 21 studies with a total of 1251 patients) – many authors state that CTA is equally effective, or even better, for this application when compared to DSA and is also associated with fewer risks and less discomfort for the patient.37 Detection and examination of aneurysmata is complicated due to the complex flow that is present. This involves the detection of subtle abnormalities in the blood flow pattern in very small vessels.

This problem does not apply to the use of CTA for brain death diagnosis. One only needs to demonstrate whether or not there is brain perfusion in the large brain vessels. This makes this method particularly suitable as an imaging technique for the determination of brain death. However, until now, there has only been limited support for the value of CTA for this purpose in the literature.[39] The only methodologically sound study performed to date was published in 1998.[35] In this study, a (two phase) spiral CTA technique was prospectively studied in 11 healthy individuals and 14 patients whose diagnosis of 'brain death' had already been confirmed with an EEG (7 patients), conventional cerebral angiography (5 patients), or with both methods (2 patients). Using the CTA technique, the investigators were able to detect the absence of brain perfusion in the basilar artery, the posterior cerebral arteries, the pericallosal arteries, the terminal cerebral cortex arteries and also in the venous circulation of the brain. In some patients, weak contrast colouring was found in the M1 segment of the middle cerebral artery and the A1 segment of the anterior cerebral artery. According to the authors' calculations, the specificity of the method was 100 percent.

This study and the previously mentioned extensive experience with CTA in the (more complicated) diagnosis of cerebral aneurysms – in combination with the technical properties of the method – justify the use of CTA according to the Committee as an additional examination for demonstrating brain death based on the absence of brain circulation.

3.1.4 Evaluation of the radiological imaging techniques

Comparison of the above-mentioned imaging techniques according to relevant aspects gives the following picture:

1	Availability of technique	: CTA	>	MRA	>	DSA
2	Logistical ease	: CTA	>	MRA	>	DSA
3	Patient comfort	: CTA	>	MRA	>	DSA
4	Absence of nephrotoxicity	: MRA	>	CTA	>	DSA
5	Unambiguous interpretation	: CTA	=	DSA	>	MRA
6	Evidence based	: DSA	>	CTA	>	MRA

Based on a comparison of the various radiological methods, the Committee is of the opinion that CT, in the form of CT angiography (CTA), is currently the most suitable imaging (supplemental) technique to verify the absence of brain perfusion and thereby confirm brain death. This test method for demonstrating cerebral circulatory arrest is safe, easy to use in the practical hospital situation, reliable and not invasive in nature.

The Committee is of the opinion that CTA (preferably in combination with TCD, see 3.2, 4.1 and 4.2) should replace the angiography methods (conventional method and DSA) mentioned in the current protocol. Experience in these techniques is decreasing. CTA not only has practical benefits – unambiguous interpretation, short examination time, available expertise – but is also safer for the patient.

3.2 Doppler ultrasound examination

The transcranial Doppler examination (TCD) can be used at the hospital bedside to demonstrate the disappearance or complete absence of brain perfusion in a non-invasive manner. The method is based on the fact that – in the process that ultimately leads to brain death – brain edema causes increased pressure inside the skull (a ‘sealed box’), which increases the resistance of the brain vessels and ultimately results in cerebral circulatory arrest. The latter is expressed by characteristic Doppler signals that indicate a so-called high resistance profile. Two patterns of signals are possible: a) reverberating pattern; b) systolic spikes. The skull must not be malleable. Therefore, the method often cannot be used in the case of a flexible skull or open fontanelles (infants), skull fractures, but also after skull trepanation or the use of ventricular drains. These situations decrease the sensitivity, but do not affect the specificity of the test method.

3.2.1 *The validity of TCD*

With the cooperation of several members of the Committee, a (as yet unpublished) systematic literature review has been performed to determine the validity of TCD as a confirmatory test for brain death. The six reviewers searched PubMed for relevant (English) clinical and neurophysiological articles over the period 1980 – 2004 using the search terms 'transcranial', 'transforaminal', 'transorbital', 'transtemporal', 'Doppler' or 'ultrasonography' in combination with the terms 'brain death' or 'cerebral circulatory arrest' (CCA). In addition, the literature lists of the articles found were screened for any missed studies. Letters, editorials, case studies, commentaries and overview reports were not included in the systematic review.

The following criteria applied for inclusion in the systematic review: 1) listing of a flow pattern characteristic for CCA: reverberating flow or systolic spikes in both the front and rear brain circulation; 2) listing of a specified reference test (clinical diagnosis, with or without EEG, angiography or radionuclide scan); 3) brain death defined as a coma with complete loss of brain stem reflexes and the presence of apnea; 4) prospective study; 5) availability of clinical patient data. Studies in which only the extracranial vessels were examined or which included only neonates or children younger than one year were excluded. The quality of each article was determined by two researchers independently. Using a checklist for diagnostic tests from the Dutch Cochrane Centre*, the reviewers distinguished between publications of high and low quality. For the evaluation of the validity of TCD, the reviewers examined the discriminating power of the test method in the selected publications: the sensitivity and the specificity. They used the following standards for this. If the reference test indicated brain death and the TCD examination showed a flow pattern characteristic for CCA, this was classified as a true positive result. If the reference test did not indicate brain death and the TCD examination did not show a flow pattern characteristic for CCA, this was classified as a true negative result. A TCD result was considered a false negative when no intracranial Doppler signal could be registered, whilst the patient was brain dead according to the reference test. This TCD result was defined as true negative if the patient was not brain dead according to the reference test. Finally, a result was designated as

* See: http://www.cochrane.nl/index.html. Cochrane Library 2005.

false positive if the reference test did not indicate brain death, but the TCD examination did show a flow pattern characteristic for CCA.*

The literature study initially yielded 223 articles. The validity of TCD examination for brain death was studied in 43 publications. In the end, only ten publications met the inclusion criteria.27,29,30,40-46 Two of these were studies of a high quality: the results of the clinical study were blinded to the investigators.[30,46] The eight remaining articles were studies of a lower quality.[27,29,40-45] Here the results of the clinical examination, EEG or angiography were kept unblinded to the investigators. A meta-analysis of the data from the two high quality publications yielded a sensitivity of 95 percent (with a confidence interval of 95 percent, CI: 92-97 percent) and a specificity of 99 percent (95 percent CI: 97-100 percent). Addition of the data from the lower quality publications resulted in a decrease in sensitivity to 89 percent (95 percent CI: 86-91 percent) and the specificity remained at 99 percent, but with a more limited confidence interval (95 percent CI: 99-100 percent). The limited meta-analysis (two publications) contained the data on 270 patients and the extended analysis (ten publications) contained data on 684 patients.

The reviewers found twelve articles in the literature in which false positive TCD findings are reported.

They determined that the description for a false positive result corresponded to the above-mentioned definition in two articles. In one study, this concerned a patient who exhibited weak breathing movements, whilst TCD had already demonstrated cerebral circulatory arrest (CCA) in the middle cerebral artery and the basilar artery.[30] This patient developed complete brain death within a few hours. The other publication describes how TCD was used to demonstrate CCA in the circle of Willis and the basilar artery in a clinically brain dead patient (the circulatory arrest in the brain was confirmed by angiography) and the EEG only became iso-electric several hours later.[45] However, the observed TCD pattern measured according to current standards was not specific for CCA.

In ten publications the description of a false positive result deviated from the above-mentioned definition.[27,42,43,47-53] TCD evaluation of the rear brain circulation was omitted in nine studies.[42,43,47-53] In three studies, performed on patients with a (subarachnoid) cerebral haemorrhage, the CCA demonstrated with TCD was not constant (not in a steady state).[47,48,53] Finally, there was one

* If TCD reveals a flow pattern characteristic for CCA, but the TCD examination was incomplete – in other words: only the front brain circulation (middle cerebral artery) or only the rear brain circulation (basilar artery) was examined with TCD – then the result was not marked as false positive. Furthermore, a flow pattern characteristic for CCA must be present for thirty minutes or more (steady state).

publication that reported a patient with persistent spontaneous respiration for several minutes, after CCA had been demonstrated with TCD. This study does not contain any information about which brain vessels were examined and under which conditions the TCD examination was performed.[27]

3.2.2 *Current practice for performing ultrasound examination*

A distinction is made between examination of the intracranial vessels (middle cerebral artery, basilar artery) and the extracranial vessels (common carotid artery, external carotid artery, internal carotid artery, vertebral arteries).

Examination of the intracranial vessels

This can be performed using Doppler examination without imaging (transcranial Doppler examination, TCD). The TCD equipment is available in many hospitals. The examination could not be performed on approximately ten percent of the patients (failure rate) because a temporal ‘skull window’ (insonation window) is not present due to altered structure of the skull bones. One benefit is the direct nature of the examination: the intracranial circulation is examined directly. The sensitivity increases if imaging is also performed (TC duplex examination). TC duplex equipment is only available in a limited number of centres in our country. TCD is often combined with extracranial Doppler examination (as is the case in Austria and Germany), but this does not provide any additional information for brain death diagnosis. The quality of the examination is largely dependent on the experience and skills of the technicians and doctors.

Examination of the extracranial vessels

This can also be performed using a Doppler examination without imaging. The failure rate is negligible. The sensitivity increases if imaging is also performed (TC duplex examination). The specificity does not change in that case. One disadvantage is the indirect nature of the method: the intracranial circulation is not examined directly. However, it should be obvious that there can be no blood flow in the intracranial vessels in the case of circulatory arrest in the extracranial vessels. In Austria and Germany the examination is only performed in combination with transcranial Doppler examination (TCD) of the intracranial vessels. This requires experience and skills of the technicians and doctors.

3.2.3 *Evaluation of the Doppler ultrasound examination*

The intracranial examination (transcranial method) in the form of TCD (without imaging) is sufficient for brain death diagnosis. TCD is a safe, easy-to-use, validated, non-invasive, 'bedside' testing method to demonstrate cerebral circulatory arrest. The required equipment is available in many hospitals. It is not necessary to perform imaging studies too, using TC duplex equipment: the sensitivity may increase slightly, but the specificity remains unchanged. TC duplex equipment is only available in a limited number of centres. If a hospital has access to this equipment and the required expertise and would prefer to use this method, then this method is also suitable according to the Committee. If performed correctly, the specificity for both methods can be close to 100 percent.

3.3 Scintigraphy

In this type of examination, a radioactively labelled pharmaceutical (radiopharmaceutical) is administered into the blood via an intravenous injection, after which the behaviour of the radiopharmaceutical in and around the skull can be visualised using a gamma camera*.[22,39,54-72] The commonly used radioactive marker for this purpose is ^{99m} technetium (^{99m}TC), which has a half time of approximately 6 hours. The most commonly used pharmaceutical for brain death scintigraphy is HMPAO (hexamethyl-propylene-amine-oxime). Use of other substances such as DTPA (di-ethylene-triamine-penta-acetic acid) or ECD (ethyl-cysteinate-dimer) is decreasing. Both the perfusion and the metabolism in the brain tissue can be examined using ^{99m}Tc-HMPAO. However, with ^{99m}Tc-DPTA or ^{99m}Tc-ECD, only brain perfusion can be studied. Therefore, ^{99m}Tc-HMPAO is a more specific tracer.

3.3.1 *Validity of scintigraphy*

A literature search in PubMed spanning the past 35 years (with the search terms 'brain death' and 'scintigraphy') yielded two methodologically usable and informative articles. One study was a retrospective study of 56 patients for whom the clinical diagnosis of brain death was not possible.[66] The other was a

* This is usually a gamma camera with two heads. In a more advanced type of camera, the gamma heads rotate around the patient, making tomography possible (single photon emission computer tomography: SPECT). The international literature about brain death scintigraphy refers to the use of mobile gamma cameras. In practice, these are not available in Dutch hospitals.

prospective study of 38 brain dead and 12 deep-comatose patients.[61] A specificity and a positive predictive value (PPV) of 100 percent were found in both studies. However, the validity of these results is limited. For example, a retrospective study has a lower evidence value than a prospective study. Although the second study was prospective, the outcome of the study is problematic because an independent gold standard was missing in the study. Finally, both studies included only a small number of patients.

3.3.2 *Scintigraphy in practice*

The literature also contains recently published guidelines. According to the guidelines of the American College of Radiology[55] and the Society of Nuclear Medicine[59], brain death scintigraphy is only applicable as an additional diagnostic test and the method cannot be used as an independent test for determining brain death.

From a radiopharmaceutical perspective, brain death scintigraphy requires a large amount of technical preparation and organisation. The interpretation demands specific skills and experience. Although the nuclear medicine departments in the Netherlands are technically capable of performing the examination, the required experience and infrastructure are usually missing – even in the academic hospitals.

3.3.3 *Evaluation of scintigraphy*

According to the Committee, scintigraphy is a safe, technically feasible, non-invasive testing method. However, for brain death diagnosis, there is limited validation and the method is complex, with a lack of experience in the Netherlands.

Chapter 4

Amendment of brain death protocol

The previous Chapter demonstrated that new, safe and reliable methods for examining brain circulation have become available: transcranial Doppler examination (TCD) and CT-angiography (CTA). The use of these techniques offers more scope for confirming brain death for the purpose of organ donation in certain situations. Therefore, the Committee is amending the current brain death protocol on two points. The first point concerns the replacement in the protocol of the older methods for cerebral angiography by the new test methods TCD and CTA, to be applied in special circumstances such as therapeutic medicinal neurodepression. The second point concerns the performance of brain death diagnosis in children.

4.1 Determining brain death in special circumstances

The Committee previously discussed (see 2.4) under which conditions the absence of brain perfusion can be equated with brain death. The Committee is of the opinion that TCD has been crystallised into a suitable, additional (bedside) test for demonstrating cerebral circulatory arrest in special circumstances such as therapeutic, medicinal neurodepression (barbiturate coma and the like) or if certain tests (such as EEG or apnea test) cannot be performed properly. In order to obtain definitive certainty about persistent cerebral circulatory arrest (and thereby brain death), cerebral angiography in the form of CTA should be performed following TCD in these specific circumstances. The older methods for

cerebral angiography (conventional method and DSA) listed in the current protocol should be replaced: TCD and CTA not only have practical benefits, but are also safer for the patient.

In the working method envisaged by the Committee, TCD should always be used as a preliminary examination (screening) prior to CTA. The two examinations together provide maximum validity and guarantee a thorough brain death diagnosis. If TCD indicates the presence of brain perfusion, then it is not (yet) necessary to perform CTA – for which the patient would have to be moved from the ward to the examination room. If necessary, the test can be repeated at a later stage to determine whether any indications for cerebral circulatory arrest have since arisen. If the test indicates the absence of brain perfusion, then CTA can definitively confirm this state and thereby confirm the diagnosis of 'brain death'.

4.2 Brain death diagnosis in children

The Committee is of the opinion that, due to the availability of the new tests, two diagnostic routes are possible: one in which, as is the case at the moment, clinical-neurological and additional examinations are repeated after a certain observation period, and another in which more extensive additional examination in the form of TCD and CTA is selected instead of repeat testing. A thorough diagnosis of brain death is guaranteed as a result of this expansion of tests.

The first diagnostic route ensures thoroughness by adhering to an age-dependent observation period. In the Committee's opinion, these periods can be shorter than indicated in the current protocol (for children younger than four years). The literature shows that extra caution is only advisable for children younger than one year – and in particular children younger than two months – and that a relatively long observation period is desirable.[56,73] There are two main reasons for this. As indicated in the Health Council of the Netherlands' Advisory report from 1996, it is generally assumed that the brains of young children are able to tolerate hypoxia for a longer period than the adult brain. In addition, the presence of open fontanelles, the relatively immature nervous system and the less differentiated clinical reactions hamper the diagnosis of brain death in young children.[2] In the guidelines published in 1987 by the American Task Force for the Determination of Brain Death in Children, there is no significant difference between children and adults after the first year of life.[74,75] Since these guidelines were drafted, there have been no publications that justify a separate procedure for children after the first year of life.

Finally, the Committee is of the opinion that the now widely used Paediatric Glasgow Coma Scale (PGCS), which applies to children up to the age of six years, should be used instead of the Children's Coma Scale (CCS).

Annex C contains the revised brain death protocol.

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Annexes

Annex **A**

Request for advice

Letter dated January 25, 2002 (reference IBE/E 2251274) from the Minister of Health, Welfare and Sport to the President of the Health Council of the Netherlands.

I received the Advisory report on Brain Death Criteria from the then President of the Health Council of the Netherlands on 28 November 1996.

In his submission letter, the President of the Health Council of the Netherlands states that he expects that a revision of the guidelines given in the Advisory report will be necessary after four to five years due to advancing scientific understanding. I have received various signals that indicate that the time for revision has now come. For example, the Healthcare Inspectorate pleaded for an update of the Brain Death Protocol in its report about a study of the workings of the Organ Donation law, published a year ago. An update is deemed desirable particularly due to the possible role of the transcranial Doppler examination in patients being treated with hypnotics/sedatives.

I would appreciate if the Advisory report and the updated protocol could be published in the course of 2002.

The Minister of Health, Welfare and Sport,

(signed) Dr. E. Borst-Eilers

Annex **B**

The Committee and consulted experts

- Prof. A.C. van Huffelen, *chairman*
  clinical neurophysiologist; University Medical Centre Utrecht
- Dr R.G.A. Ackerstaff
  clinical neurophysiologist; St. Antonius Hospital, Nieuwegein
- Dr D.J. Bakker
  surgeon (n.p.); Academic Medical Centre, Amsterdam
- Prof. L.H.D.J. Booij
  anaesthesiologist; University Medical Centre St. Radboud, Nijmegen
- Prof. M.A. van Buchem
  neuroradiologist; Leiden University Medical Centre, Leiden
- Prof. B.M.G. van Engelen
  neurologist; University Medical Centre St. Radboud, Nijmegen
- Prof. L.M.E. Smit
  paediatric neurologist; Free University Medical Centre, Amsterdam
- Prof. A.J. van Vught
  paediatrician-intensivist; University Medical Centre Utrecht
- Ms R.M. den Hartog-van Ter Tholen, *advisor*
  Ministry for Health, Welfare and Sport, The Hague
- Dr G.H.M. ten Velden, physician, *secretary*
  Health Council of the Netherlands, The Hague

Secretarial support: Ms. T.M.E. Smith-Mets.

Consulted experts

The Committee interviewed the following external experts on specific topics:

- during its third meeting discussing the effect of medication on brain death diagnosis:
  - Prof. A.F.A.M. Schobben, pharmacologist, University of Utrecht
- during its fourth meeting discussing the application options of scintigraphy for determining brain death:
  - Dr. J. Pruim, nuclear medicine specialist, Academic Hospital Groningen
- during its sixth meeting discussing the application options of TCD and CTA:
  - Dr. A. van der Lugt, neuroradiologist, Erasmus MC, Rotterdam
  - Dr. B.K. Velthuis, neuroradiologist, University Medical Centre Utrecht
  - Prof. W.H. Mess, clinical neurophysiologist, Academic Hospital Maastricht.

The Health Council and interests

Members of Health Council Committees are appointed in a personal capacity because of their special expertise in the matters to be addressed. Nonetheless, it is precisely because of this expertise that they may also have interests. This in itself does not necessarily present an obstacle for membership of a Health Council Committee. Transparency regarding possible conflicts of interest is nonetheless important, both for the chairperson and members of a Committee and for the President of the Health Council. On being invited to join a Committee, members are asked to submit a form detailing the functions they hold and any other material and immaterial interests which could be relevant for the Committee's work. It is the responsibility of the President of the Health Council to assess whether the interests indicated constitute grounds for non-appointment. An advisorship will then sometimes make it possible to exploit the expertise of the specialist involved. During the inaugural meeting the declarations issued are discussed, so that all members of the Committee are aware of each other's possible interests.

Annex C

Brain Death Protocol*

C.1 Introduction

C.1.1 Definition of brain death

Brain death is the complete and irreversible loss of the functions of the brain, including the brain stem and the extended spinal cord (medulla oblongata).

C.1.2 Procedural conditions

When the intention exists to remove an organ from a ventilated potential donor, brain death should be demonstrated by a qualified physician according to the methods and criteria described below.

Demonstrating brain death is based on a combination of various types of examinations. The examinations required – depending on the circumstances – and the doctors exclusively charged with performing these examinations are listed below. These doctors may not be involved in the removal or implantation of the organ.

* Updated according to the outcome and conclusions of previous Chapters.

Responsibility, recording

The doctor performing the clinical-neurological examination is responsible for determining brain death. He/she ensures that the procedures described in this protocol are followed and that the relevant information from the examinations performed is recorded in the relevant declaration (see below: Paragraph C.4).

C.1.3 Prerequisite conditions

The diagnosis of 'brain death' can only be made in the event of a fatal brain injury for which the cause is known and that cannot be treated. This diagnosis is only possible once it has become plausible that there are no other causes of unconsciousness and unresponsiveness, with the exception of the causes listed in this protocol.

C.2 Diagnosis of brain death

The definitive determination of brain death is based on three pillars, namely:
- the prerequisite conditions
- the clinical neurological examination
- the additional examination(s).

The three diagnostic phases listed below, which must be completed in this order, relate to this.

C.2.1 Phase 1: (hetero-)anamnesis and general examination

This first diagnostic phase must determine whether the prerequisite conditions have been met.

This entails firstly taking note of the history – also via third parties (hetero-anamnesis) – and obtaining a number of elementary diagnostic details to exclude other causes of unconsciousness and unresponsiveness. If the examining doctor (usually the treating doctor) has any doubts, or if there are any uncertainties about the anamnestic or diagnostic findings, the general examination – or parts thereof – can be repeated after some time and/or another qualified doctor (again not involved in the transplant) can be consulted.

The general examination should be used to obtain certainty about the fatal nature of the brain injury, the cause of the injury, as well as the lack of treatment

options. This evaluation should always be performed by a (paediatric) neurologist or a neurosurgeon. Finally, he/she should use the available anamnestic and general diagnostic information (physical examination, biochemical examination) to ascertain that there are no causes of unconsciousness or unresponsiveness involved that could make the diagnosis of brain death unreliable. This relates particularly to the following causes:

- hypothermia (core body temperature equal to, or lower than 32°C)
- intoxication, to be distinguished from therapeutic, medicinal neurodepression (such as a barbiturate coma)
- hypotension (systolic blood pressure equal to, or lower than 80 mmHg or 10.7 kPa)
- blockade of the neuromuscular junction
- severe biochemical or metabolic disorder, insofar as this does not form part of the failure of the brain stem or extended spinal cord.

An explanation is provided below.

Hypothermia

Cooling (hypothermia) is usually the result of accidents at low temperatures (winter, drowning, cold store room), but can also form part of failure of the extended spinal cord. A definitive answer can be provided by measurement of the core body temperature and the response to treatment. The (core) body temperature must be increased to above 32°C for the diagnosis of brain death.

Intoxication

Taking note of the history – also via third parties (hetero-anamnesis) – and of the circumstances in which the individual was found, can provide information about the existence (or not) of a relevant intoxication, for example due to alcohol, drugs or certain medicines. On the one hand, these intoxications can hamper the diagnosis of brain death and on the other hand they can make the organs unsuitable for transplantation. This can also hamper the diagnosis of ‘brain death’ in trauma patients, either because the affected individual took certain medicines or other substances himself, or because medicines were administered. If there are indications for intoxication – to be distinguished from therapeutic, medicinal neurodepression: see below – the relevant toxins/substances should be traced in the blood or urine. If the intoxication cannot be ascertained in this manner and the detrimental clinical effects on the function of the brain or other

organs cannot be stopped, the determination of brain death for organ donation is not possible.

Special situation: therapeutic, medicinal neurodepression

This concerns a targeted treatment with medicines – such as sedatives, hypnotics, anaesthetics or anti-epileptics – in order to prevent further brain damage. Barbiturates (barbiturate coma) are primarily used, particularly in trauma patients, to combat cerebral edema and increased intracranial pressure. These substances can influence the usual tests of brain function (suppression of brain activity can give a false positive test result, not a false negative result). Brain death can be ascertained in these cases by expanding the additional examination to include transcranial Doppler examination (TCD) and CT angiography (CTA).

Hypotension

If measurement reveals that the systolic blood pressure is too low, this is called hypotension. In adults this is defined as a pressure lower than 80 mmHg or 10.7 kPa. For children, there are no figure-based definitions for hypotension available in the literature, partly due to the fact that this is strongly age-dependent. A systolic pressure more than two standard deviations lower than the average value (corresponding to the P-2.5 value or the 2.5% lower limit value) for the relevant child age, definitely means hypotension (see table 1).

The response to treatment can be used to determine whether the hypotension forms part of the relevant condition (hypovolaemic shock) or the failure of the extended spinal cord. If the blood pressure does not respond adequately to hypertensive treatment, this indicates loss of the relevant brain function (extended spinal cord). Modified treatment, namely prevention of a large decrease in blood pressure is then required. If the blood pressure is too low, the additional brain death diagnostics (such as the apnea test, TCD or CTA) described in this protocol cannot be performed reliably.

Blockade of the neuromuscular junction

This situation also makes brain death diagnosis basically unreliable. This often involves a blockade due to administration of specific medicines for anaesthesia or artificial ventilation. If the blockade can be removed, due to the availability of new medicines, without this affecting other organ systems, then brain death diagnosis can be performed reliably.

Severe biochemical or metabolic disruption

This entails the exclusion of disorders that do not form part of the failure of the brain stem or extended spinal cord, such as coma caused by metabolic or endocrine disorders (uraemic coma, hypoglycaemic coma, hepatic coma and the like).

C.2.2 Phase 2: clinical neurological examination

In this phase, a clinical neurological examination can be used to evaluate a number of functions that are typical for the brain, the brain stem or the extended spinal cord. If one of the following tests reveals that the function that was examined is entirely or partially intact, then brain death has not occurred.

The clinical neurological examination should always be performed by a (paediatric) neurologist or neurosurgeon not involved in the proposed transplant. If there is any doubt about the findings, the examination can be repeated after some time and/or another (paediatric) neurologist or neurosurgeon – again not involved in the proposed transplant – can be consulted.

The clinical neurological examination should demonstrate:

1 absence of consciousness, evidenced by the absence of reactions to (painful) stimuli, as defined in the Glasgow Coma Scale (GCS) for adults and in the Paediatric Glasgow Coma Scale (PGCS) for children under the age of 6 years.
2 absence of brain stem reflexes, namely:
   - no reactions of the pupils to light
   - no corneal reflexes
   - no reactions to vestibular stimuli (negative oculocephalic and oculovestibular reactions)
   - no cough reflex
   - indication(s) for the absence of spontaneous respiration.

C.2.3 Phase 3: additional examination

The definitive diagnosis of ‘brain death’ is obtained with the aid of the so-called additional examination, which consists of demonstrating:

- the absence of electrical brain activity, demonstrated by an iso-electric electro-encephalogram (EEG) and

- the absence of spontaneous respiration, demonstrated by the apnea test.

Diagnosis in children younger than one year: two pathways

There are two pathways that one can follow to establish the definitive diagnosis of 'brain death':

- repeat testing
- more extensive additional examination: permitted as an alternative to the first route, but required in the case of therapeutic medicinal neurodepression.

Pathway 1: repeat examination

The usual protocol is followed for this method: determination of the prerequisite conditions, clinical neurological examination, EEG and apnea test. The definitive diagnosis of 'brain death' is obtained after repeating the clinical neurological examination and the EEG. Repetition of tests, after a certain observation time, is necessary to gain certainty about the interpretation of the clinical symptoms and for confirming the irreversibility of the complete loss of function. The interpretation of clinical symptoms can be hampered in some cases. For example, the brain stem reflexes may not be completely developed yet in very premature infants. Furthermore, the caloric vestibular stimulation is very difficult to evaluate in young infants. In addition, spinal disinhibition reflexes in infants and young children can make evaluation of the motor response for the coma score hard to interpret.

The required observation period varies with age. No signs of recovering brain function may occur during this period. The required observation period for children is:

- in the neonatal period (first week of life): 48 hours
- thereafter until the age of two months: 24 hours
- for the ages two to twelve months: 12 hours.

Since guidelines were drafted in 1987 by the American Task Force for the Determination of Brain Death in Children, there have been no new publications that justify a separate procedure – such as long observation times – in children after the first year of life.

Pathway 2: more extensive additional examinations

In this method – to be used on children without cor-vitium (congenital malformation of the heart) – instead of repeat testing, the diagnosis is extended with TCD and CTA. This method is permitted as an alternative to route 1 (repeat of examination in children can involve a long waiting time before the diagnosis of 'brain death' is confirmed), but is a requirement in children treated with barbiturates (barbiturate coma) or other forms of therapeutic medicinal neurodepression (see below).

If characteristic TCD patterns (reverberating pattern or systolic spikes) are observed, this points to the absence of cerebral circulation. The diagnosis of 'brain death' becomes definitive if CTA confirms the conclusions of TCD.

Comments

TCD can be used if the skull is sufficiently rigid: a false negative (but not a false positive) TCD result is possible with a flexible skull or open skull fontanelles (infants).

The method should not be used on children with an uncorrected cor vitium, for example severe aortic valve insufficiency. In that case the blood can flow back and forth extracranially and intracranially, creating a TCD pattern that looks like a signal characteristic of cerebral circulatory arrest (reverberating pattern): a false positive TCD result.

Special circumstances

This involves situations in which the clinical neurological or additional examination may have been influenced by medicines that were administered or situations in which an additional test method cannot be performed properly.

Therapeutic, medicinal neurodepression

In persons who were treated with barbiturates (barbiturate coma) or other forms of medicinal neurodepression, the suppressive medicines can influence the results of the clinical neurological examination, the EEG and the apnea test. If these tests give a response, then brain death has not occurred. Any further diagnostic examinations aimed at confirming brain death are pointless. Conversely, the absence of a response does not definitely mean that brain death

has occurred. In that case, expansion of the examination with TCD and CTA is required.

If characteristic TCD patterns (reverberating pattern or systolic spikes) are observed, this points to the absence of cerebral circulation. The diagnosis of 'brain death' becomes definitive if CTA confirms the conclusions of TCD.

EEG or apnea test cannot be performed

If an EEG cannot be performed (damaged skull or the like), or if the apnea test cannot be performed properly (occurrence of severe cardiac arrhythmias; significant decrease in blood pressure as a result of the test; spontaneous respiration impossible due to high cervical cord lesion, or a bilateral lesion of the phrenic nerve) or is considered too risky for the patient involved, these tests can be substituted by TCD, followed by CTA performed at the required minimum systolic blood pressure.

For children younger than one year, the clinical neurological examination should be repeated in these conditions, followed by TCD and – if this test points to cerebral circulatory arrest – CTA should be performed for the definitive answer.

C.3 Performance criteria for testing methods

C.3.1 Clinical neurological examination

The clinical neurological examination should be performed by a (paediatric) neurologist or neurosurgeon not involved in the proposed transplant. If there is any doubt about the findings, the examination can be repeated after some time and/or another (paediatric) neurologist or neurosurgeon – again not involved in the proposed transplant – can be consulted.

Coma scales

The scales that should be used are the Glasgow Coma Scale (GCS) for adults and children aged 6 years and older and the Paediatric Glasgow Coma Scale (PGCS) for children younger than 6 years. The GCS score, or for young children the PGCS score: E (eyes open) = 1, M (motor response) = 1, V (verbal response) = 1, or 't' (tube, or tracheostomy) is given if the eyes do not open and no motor or verbal response occurs in response to any stimuli that run via the brain or the

brain stem (see coma scales: table 2 and 3). Standard painful stimuli that are administered are to the nail bed, the sternum, the skin fold of the chest or – except in children younger than 6 years – the upper orbital rim. Reflexes that run via the spinal cord may be present.

Brain stem reflexes

- The pupil response must be examined using a bright light. One must confirm that there are no pharmacological explanations for the absence of a pupil reflex (for example: atropine in the eye; high dose of intravenous dopamine).
- The stimulus for the oculocephalic reflex is given by rapid rotation of the head over 45 degrees. Eye movements may not occur during the test.
- The stimulus for the oculovestibular reflex is given by injecting at least 20 ml (millilitres) of ice-cold water into the external auditory canal with the head flexed at an angle of 30 degrees. Eye movements may not occur within two minutes. The other ear is tested after one minute of rest. If the eardrum has been damaged, ice water can be injected into a finger stall in the auditory canal. Ten (10) ml of ice water is sufficient for children (up to the age of 12 years).
- The cough reflex is deemed absent if no reactions occur in response to suctioning or movement of the tracheal tube.

Ventilator dependency

The use of artificial ventilation does not necessarily mean that spontaneous respiration is entirely absent. Therefore, it is essential to confirm ventilator dependency. One should confirm whether the cause of loss of spontaneous respiration is still present or whether spontaneous respiration is now absent if ventilation was started due to insufficient respiration. This exploratory examination should be distinguished from the apnea test (see C.3.3), which ultimately provides certainty about the absence of spontaneous respiration.

Comments

The coma scales do not take grimacing into consideration. However, this can be the only motor response to pain, for example in the case of a high spinal cord injury. If grimacing occurs in response to a painful stimulus, this always excludes brain death.

Reflexes that run via the spinal cord may be present in the case of brain death. This can include myotatic reflexes or a triple response of the legs, but can also include unusual motor responses, such as shoulder movement (unilateral downward and inward rotation) and arm movement (stretching and pronation) with ipsilateral stimulation or apparently spontaneous movements. The latter includes diaphragmatic myoclonus and the so-called Lazarus sign. This involves abduction of the shoulders, bending of the lower arms and placement of the hands in front of the sternum or even the chin. Flexing of the trunk can also occur. The abovementioned movements are caused by disinhibition of spinal motor neurons.

Disrupted temperature regulation, disrupted blood pressure regulation or the existence of diabetes insipidus is not required for the diagnosis of 'brain death' as defined in this protocol.

C.3.2 Electro-encefalogram (EEG)

An EEG should be performed by, or under the supervision of, a (paediatric) neurologist qualified in 'clinical neurophysiology'.

Technical criteria

a To be used: all surface electrodes of the 10-20 system. These should have a transition resistance < 5 kOhm. Needle electrodes may only be used if it has been determined in advance that they will not negatively affect the frequency bandwidth of the registration system.
b Required sensitivity: 20 microvolt/cm.
c Required bandwidth: 0.27 - 30 Hz (-3 dB).
d Lead combinations: A combination with a large inter-electrode distance must be used. If possible, all electrodes of the 10-20 system should be present continuously in the lead combination used. This implies registration with an EEG machine with at least 16 channels.
e The (effective) registration time should be at least 30 minutes.
f Responses to stimuli should be checked:
   - noise stimuli: apply at the level of both ears
   - light flash stimuli: apply both high (e.g. 18 Hz) and low (1 – 3 Hz) frequencies.

   It is recommended that the electrocardiogram (ECG), respiration and artefacts of movement are also registered. A retinogram, if present, does not contradict the diagnosis of an iso-electric EEG.

g Short-acting muscle relaxants may be used during the registration in order to suppress any electrically observable muscle activity (‘motor unit’ activity).
h Hum and noise levels should be less than 5 microvolt. Any artefacts still present should be marked as such during the registration.
i The EEG is termed ‘iso-electric’ if no electrical activity of cerebral origin is present.
j Evaluation of the EEG via data transmission (telephone, cable, Internet) is not permitted due to the risk of signal disturbance.

C.3.3 Apnea test

This examination should be performed by an anaesthesiologist, a physician-intensivist, or a pulmonologist, or by an internist or neurologist with expertise in the field of breathing abnormalities.

The following conditions apply before performing the test:

a indications of ventilator dependency (see C.3.1)
b exclusion of causes for the absence of spontaneous respiration not located in the brain; in addition to the causes listed in the prerequisite conditions (C.2.1), the following should be excluded: a high cervical cord lesion and a double-sided lesion of the phrenic nerve
c a previously recorded iso-electric EEG (follow other method if electro-encephalography cannot be performed, see C.2.3)

Technical criteria

a Preparation: after 10 minutes of artificial respiration with 100 percent oxygen, the artificial respiration is changed to achieve a p_aCO_2 of 40 mmHg (5.3 kPa) – starting value – measured via blood gas analysis, or a p_aCO_2 of at least 45 mmHg (6 kPa) in people with chronic pulmonary conditions.
b During the test one must ensure:
- continuous registration of the peripheral oxygen saturation using a pulse oxymeter, ensuring a level of 90 percent or higher at all times
- continuous registration of the CO_2 level in the breathable air, via a capnograph connected to the endotracheal tube.
- an electrocardiogram should be produced for registration of the heart rate and any cardiac arrhythmias
- the blood pressure should be measured at intervals of no more than 3 minutes – if continuous monitoring via an intra-arterial ‘line’ is not taking

place; the systolic blood pressure must always be at least 80 mmHg (10.7 kPa).

c The apnea test starts – at the required p_aCO_2 starting value – by switching off the ventilator, which must be followed immediately by oxygen administration at 6 litres per minute via a catheter, inserted (in adults: 20 centimetres) into the endotracheal tube. Patients who were undergoing ventilation with PEEP (positive end expiratory pressure) due to decreased gas exchange in the lungs, should receive 100 percent oxygen not via a catheter, but via CPAP (continuous positive airway pressure) – with the apparatus set to pressure triggering at the most sensitive setting: usually -2 cm H_2O.

d The apnea test can be terminated when no respiration movements have occurred after achieving a p_aCO_2 of 50 mmHg (6.65 kPa) or higher (or 60 mmHg – or 8 kPa – in patients with chronic pulmonary conditions), as measured via a second blood gas analysis.
The starting value measured at the beginning can be used – assuming an average increase in p_aCO_2 of 2 mmHg (0.27 kPa) per minute – to estimate the time that will probably be needed to achieve the required minimum end value (usually 5 to 10 minutes).
Respiration movements are sometimes difficult to distinguish from muscle spasms of the chest. A *true* respiration movement has occurred if the capnograph shows a temporary increase in the CO_2 level in the breathing air.

e The apnea test must be stopped and the ventilation resumed immediately if complications occur; the p_aCO_2 should also be determined (blood gas analysis). The test cannot be performed/completed in that case. This applies among others to:
- a decrease in systolic blood pressure below 80 mmHg (10.7 kPa), or – for children – a decrease of more than two standard deviations below the average value for the relevant child age (see table 1)
- a decrease in the oxygen saturation measured via the pulse oxymeter below 90 percent (a decrease to 85 percent is acceptable in patients with chronic pulmonary conditions).
- the occurrence of severe cardiac arrhythmias.

f The interruption of the apnea test means that brain death cannot be determined (as yet) with this form of additional examination. There is only a slim chance that the test can be performed later, on repeat. There are two options then, namely:
- to decide that brain death cannot be diagnosed

- to attempt a definitive diagnosis of brain death via TCD and confirmed by CTA.

C.3.4 Transcranial Doppler examination (TCD)

A TCD should be performed by, or under the supervision of, a clinical neurophysiologist or (paediatric) neurologist with specific expertise. Specially trained technicians may perform the test, but the doctor must be present for the final evaluation of the examination.

Examination of the intracranial vessels (TCD) is sufficient. Examination of the extracranial vessels is not necessary. The test has a positive response if it points to the absence of cerebral perfusion.

Technical criteria

a The presence of a temporal and suboccipital insonation window should first be determined.
b The test then consists of two series of Doppler measurements performed in succession.
c Equipment to be used: pulsed wave apparatus with an insonation frequency < 2 MHz.
d The intracranial vessels that require examination are:
   - the middle cerebral artery on both sides (via the temporal window) and
   - the basilar artery (via the suboccipital window, with the patient positioned on his/her side).
e Each Doppler measurement is performed for at least 10 heartbeats per blood vessel.
f The second series of measurements must be started no sooner than twenty minutes after the start of the first series. The entire examination should take approximately half an hour.
g A so-called high resistance profile should be recorded in both series of measurements. This is evidenced by the presence of a reverberating pattern or by systolic spikes and indicates the absence of cerebral circulation.

Comments

The test is not suitable if a temporal or suboccipital window – accessible for ultrasound – is not available due to altered structure of the skull bone (in 10 to 15 percent of patients), the absence of a ‘rigid’ skull (flexible skull, open skull

fontanelles, skull fractures, skull trepanation) or in the presence of a ventricle drain. The tests can give a false negative result in these cases: cerebral circulatory arrest will not be registered. TCD is also unsuitable for certain uncorrected cor vitia, for example severe aortic valve insufficiency. A flow pattern that looks like a reverberating pattern can then give a false positive result: the test response is incorrectly interpreted as ‘cerebral circulatory arrest’.

C.3.5 CT angiography (CTA)

This examination should be performed by a (neuro)radiologist with expertise in the field of CTA vascular diagnostics in the head and neck region.

Technical criteria

a The method to be used is cerebral CT angiography (CTA), which can be performed using a multi-detector row CT scanner.
b The required minimum systolic blood pressure is 80 mmHg (10.7 kPa), or – for children – not lower than two standard deviations below the average value for the relevant child age (see table 1).
c A non-ionic agent (containing > 300 mg iodine per ml) should be used as a contrast agent.
d 100 ml of contrast agent is administered intravenously via mechanical injection (for example into a vein in the arm or into a central venous ‘line’) at a flow rate of > 3 ml per second.
e Two CTA scans are produced. The start of the first CTA scan is 25 seconds after the start of the injection of contrast agent. The second CTA scan is started 60 seconds after the start of the injection.
f Scan parameters: detector collimation ≤ 1 mm, pitch of £ ≤.5 kV and mAs are based on – and correspond to – the settings for the local CTA protocols for the head and neck region.
g Scan range: non-angulated scan from C3 to the vertex. Scan direction: caudo-cranial.
h Reconstruction with a slice width of ≤ 1.25, with 50 % overlap and an FOV that shows the entire skull.
i Cerebral circulatory arrest – and thereby brain death – can only be confirmed if there is proof that the contrast agent was actually injected into the blood. This is the case if there is contrast filling of the extracranial vessels (side

branches of the external carotid artery, such as the superficial temporal artery).

j The examination should preferably be evaluated at a workstation, with the option of reconstructing slab-MIPs in various directions. There may be intracranial contrast filling visible in the internal carotid artery through to the M1 segment of the middle cerebral artery and the A1 segment of the anterior cerebral artery and to the basilar tip and the P1 segment of the posterior cerebral artery.

k Cerebral circulatory arrest – and thereby brain death – is deemed to have occurred if both CTAs show no colouration of the pericallosal artery, cortical arteries and the deep venous structures (internal cerebral vein, vein of Galen and the straight sinus).

C.4 Reporting

The way in which brain death is determined should be documented in a declaration (see Table 4: 'form for recording brain death'), recording details about the various diagnostic phases (prerequisite conditions, clinical neurological examination and additional examination) and the official time of death, namely the moment at which the definitive diagnosis of 'brain death' was established. This declaration should be signed by the (paediatric) neurologist or neurosurgeon who performed the clinical neurological examination.

Table 1 The 2.5% lower limit values (P-2.5 values, corresponding to two standard deviations below the average value) for systolic blood pressure in boys and girls according to age, for various heights (height percentiles).

Boys

Systolic blood pressure		Age															
Normalized height	*Height percentiles*	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
-1,28	0,10	60,8	64,3	66,9	68,9	70,4	71,7	73,0	74,3	75,8	77,5	79,5	81,7	84,1	86,7	89,3	91,8
-0,84	0,20	62,1	65,6	68,2	70,2	71,7	73,0	74,3	75,6	77,1	78,8	80,7	83,0	85,4	87,9	90,6	93,1
-0,52	0,30	63,0	66,5	69,1	71,1	72,6	74,0	75,2	76,5	78,0	79,7	81,7	83,9	86,3	88,9	91,5	94,1
-0,25	0,40	63,8	67,3	69,9	71,9	73,4	74,7	76,0	77,3	78,8	80,5	82,4	84,7	87,1	89,7	92,3	94,8
-0,00	0,50	64,5	68,0	70,6	72,6	74,1	75,4	76,7	78,0	79,5	81,2	83,2	85,4	87,8	90,4	93,0	95,5
0,25	0,60	65,1	68,7	71,3	73,2	74,8	76,1	77,4	78,7	80,2	81,9	83,8	86,0	88,5	91,0	93,7	96,2
0,52	0,70	65,8	69,4	72,0	73,9	75,5	76,8	78,1	79,4	80,9	82,6	84,5	86,7	89,2	91,7	94,4	96,9
0,84	0,80	66,6	70,1	72,7	74,7	76,3	77,6	78,8	80,2	81,6	83,3	85,3	87,5	89,9	92,5	95,1	97,7
1,28	0,90	67,6	71,1	73,7	75,7	77,2	78,5	79,8	81,1	82,6	84,3	86,3	88,5	90,9	93,5	96,1	98,6

Girls

Systolic blood pressure		Age															
Normalized height	*Height percentiles*	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
-1,28	0,10	63,8	65,4	66,9	68,4	70,0	71,6	73,3	75,1	77,0	78,9	80,9	82,8	84,6	86,2	87,4	88,3
-0,84	0,20	64,6	66,2	67,8	69,3	70,8	72,4	74,2	76,0	77,8	79,8	81,7	83,6	85,4	87,0	88,3	89,2
-0,52	0,30	65,3	66,9	68,4	69,9	71,4	73,1	74,8	76,6	78,5	80,4	82,3	84,2	86,0	87,6	88,9	89,8
-0,25	0,40	65,8	67,4	68,9	70,4	72,0	73,6	75,3	77,1	79,0	80,9	82,9	84,8	86,6	88,2	89,5	90,4
0,00	0,50	66,3	67,9	69,4	70,9	72,5	74,1	75,8	77,6	79,5	81,5	83,4	85,3	87,1	88,7	90,0	90,9
0,25	0,60	66,8	68,4	70,0	71,5	73,0	74,6	76,4	78,2	80,0	82,0	83,9	85,8	87,6	89,2	90,5	91,4
0,52	0,70	67,4	69,0	70,5	72,0	73,6	75,2	76,9	78,7	80,6	82,5	84,5	86,4	88,2	89,7	91,0	91,9
0,84	0,80	68,0	69,6	71,2	72,7	74,2	75,9	77,6	79,4	81,2	83,2	85,1	87,0	88,8	90,4	91,7	92,6
1,28	0,90	68,9	70,5	72,0	73,6	75,1	76,7	78,5	80,3	82,1	84,1	86,0	87,9	89,7	91,3	92,6	93,5

Source: these values were derived from blood pressure data from The Fourth Report on the Diagnosis, Evaluation, and Treatment of High Blood Pressure in Children and Adolescents. National High Blood Pressure Education Program Working Group on High Blood Pressure in Children and Adolescents. Pediatrics 2004; 114:555-76 (data processed by C.W. Bollen, paediatrician-intensivist, University Medical Centre Utrecht).

Table 2 The Glasgow Coma Scale (GCS) for adults + children from 6 years of age.

Active opening of the eyes: E-score (E = Eye)	no	1
	in response to painful stimuli	2
	in response to verbal commands	3
	spontaneous	4
Motor responses of the arms to stimuli: M-score (M = Motor)	no response	1
	flexing	2
	abnormal bending	3
	withdrawal	4
	localisation	5
	performs commands	6
Verbal response: V-score (V = Verbal)	tube / tracheostomy	t
	no response	1
	unintelligible (only sounds)	2
	inadequate (only words)	3
	altered (confused sentences)	4
	oriented, alert	5

Explanation

Criteria and points of attention for GCS:

- observation: 1) observe spontaneous reaction, if no response: 2) observe reaction to loud commands; if no response: 3) observe reaction to painful stimuli
- registration: record the E, M and V scores independently and in order. Record the best responses + details. Not performed = np; tube / tracheostomy = t.
- reporting: report each decrease in response (double check if in doubt)
- eyelids that cannot close are not the same as opening of eyes
- painful stimuli: on nail bed, sternum, skin fold on chest or supra-orbital
- localisation: bring hand over midline abdomen/chest or above the chin.

Table 3 The Paediatric Glasgow Coma Scale (PGCS) for children < 6 years of age.

Active opening of the eyes: E-score (E = Eye)	no	1
	in response to painful stimuli	2
	in response to verbal commands	3
	spontaneous	4
Motor responses of the arms to stimuli: M-score (M = Motor)	no response (0 – 6 months: flexion)	1
	stretches in response to pain (6 months – 2 years: localisation)	2
	flexion in response to pain	3
	localises pain	4
	performs commands (2 to 6 years)	5
Verbal response: V-score (V = Verbal)	tube (ventilation)	t
	no response	1
	cries / screams	2
	vocal sounds	3
	words	4
	oriented	5

Explanation.

Normal total score PGCS:
- 5 years and older: E4, M5, V5
- 2 – 5 years: E4, M5, V4
- 1 – 2 years: E4, M4, V4
- 6 months – 1 year: E4, M4, V3
- 0 – 6 months: E4, M3, V2

Criteria and points of attention for PGCS:
- observation + registration + reporting: same as GCS
- eyelids that cannot close are not the same as opening of eyes
- painful stimuli: on nail bed (no pen / pencil) or skin fold in the chest, do not administer supra-orbital painful stimuli
- M3: no distinction between abnormal bending and withdrawal
- localisation: every movement in the direction of a painful stimulus
- oriented: child mentions own name or knows where he/she is.

Table 4 Form for determining brain death.

General patient details		
Surname, initials:		
Date of birth:		
Gender:		
Address:		
Diagnosis		
Primary brain injury:	.....	
Time of accident / start of illness:	date	time
Time of examination:	date	time
Exclusion criteria[a]		
Do any of the following apply:		
Hypothermia:	☐ yes	☐ no
Hypotension:	☐ yes	☐ no
Intoxication, medication:	☐ yes	☐ no
Blockade of neuromuscular junction:	☐ yes	☐ no
Metabolic / endocrine disorder:	☐ yes	☐ no
Clinical neurological examination		
Time:	date	time
Consciousness:		
(P)GCS score:	E = / M =	/ V =
Brain stem function:		
Pupil response to light:	☐ yes	☐ no
Corneal reflex:	☐ yes	☐ no
Oculocephalic reflex:	☐ yes	☐ no
Caloric nystagmus:	☐ yes	☐ no
Cough reflex:	☐ yes	☐ no
Spontaneous respiration:	☐ yes	☐ no
Time interval between tests in children < 1 year:*	..... hours	
Examination performed by:	Name	signature
[(paediatric) neurologist/neurosurgeon]		
EEG performed:	☐ yes	☐ no
Time:	Date	time
Iso-electric (also with response to stimuli):	☐ yes	☐ no
Time interval between tests in children < 1 year:*	..... hours	
Evaluated by:	name	signature
[(paediatric) neurologist / clinical neurophysiologist]		

Table 4 Continued.

Apnea test performed:*	☐ yes	☐ no
Time:	date	time
Oxygen saturation (pulse oxymeter) at start of test:	%	
Oxygen saturation (pulse oxymeter) at end of test:	%	
$paCO_2$ starting value:	... mmHg, or ...kPa	
$paCO_2$ end value:	... mmHg, or ...kPa	
Reason for stopping test prematurely (if applicable):	.....	
Apnea demonstrated:	☐ yes	☐ no
Apnea confirmed by: (anaesthesiologist / intensivist / pulmonologist or internist/neurologist with expertise in this field)	name	signature
Transcranial Doppler examination (TCD) performed:*	☐ yes	☐ no
Time:	date	time
Cerebral circulatory arrest demonstrated:	☐ yes	☐ no
Evaluated by: [clinical neurophysiologist / neurologist with experience in the field of Doppler vascular diagnostics]	name	signature
Cerebral CT angiography (CTA) performed:*	☐ yes	☐ no
Time:	date	time
Cerebral circulatory arrest demonstrated:	☐ yes	☐ no
Evaluated by: [(neuro) radiologist with experience in the field of vascular diagnostics]	name	signature

Declaration

Signed by:	name	.....
(paediatric) neurologist, neurosurgeon at:	place.	.....
declares that the abovementioned patient		
has been confirmed brain dead on:	date/time	.....
	signature	.....

[a] Explanation: see next page.

Hypothermia
-a core body temperature < 32°C

Hypotension
-systolic blood pressure < 80 mmHg (10.7 kPa), or – for children – not lower than two standard deviations below the average value for the relevant child age.

Medication
-medicines that could partly explain the decrease in consciousness

Metabolic/endocrine disorder
-that could partly explain the decrease in consciousness.

Diagnosis in children, two possible routes:
a) repeat the examination (clinical neurological, EEG, apnea test) after required observation period:
   - in the neonatal period (first week of life): 48 hours;
   - thereafter until the age of two months: 24 hours;
   - for the ages two to twelve months: 12 hours.

b) after first examination (clinical neurological, EEG, apnea test): TCD and then CTA.

Apnea test
-ventilate for 10 minutes with 100% O_2
-Blood gas analysis: p_aCO_2 must be at least 40 mmHg (5.3 kPa), or 45 mmHg (6 kPa) in patients with a chronic pulmonary condition
-Stop ventilating, continue to administer 100% O_2 at 6 litres/min via tube/canula
-Terminate apnea test if a p_aCO_2 of 50 mmHg (6.65 kPa) is reached – measured by a second blood gas analysis – or 60 mmHg (8 kPa) in patients with a chronic pulmonary condition
-During the examination, the systolic blood pressure must be at least 80 mmHg (10.7 kPa), or – for children – not lower than two standard deviations below the average value for the relevant child age.

Transcranial Doppler examination (TCD)
-During the examination, the systolic blood pressure must be at least 80 mmHg (10.7 kPa), or – for children – not lower than two standard deviations below the average value for the relevant child age.

Cerebral CT angiography (CTA)
-During the examination, the systolic blood pressure must be at least 80 mmHg (10.7 kPa), or – for children – not lower than two standard deviations below the average value for the relevant child age.