

Transcranial Doppler as an Confirmatory Test in Brain Death

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1. Introduction

Brain death in a normothermic, nondrugged comatose patient with a known irreversible massive brain lesion and no contributing metabolic or hormonal derangements, is declared when brainstem reflexes, motor responses and respiratory drive are absent.

Loss of brain function in a mechanically ventilated patient has been observed since the early days of intensive care units, but criteria for brain death in the United States were not forthcoming until 1968 after publication of a report of the Harvard Medical School ad hoc committee using the neurologic criteria (JAMA 1968.). The report defined totally destroyed unsalvageable brain for the first time, and one of the criteria was the isoelectric, flat electroencephalography (EEG) despite the heartbeat. However, its value became much less important when the clinical picture became defined and the technical difficulties became recognized. Due to a number of confounders that mimic or partly mimic brain death, like hypothermia, intoxication or acute metabolic or endocrine derangements, different ancillary tests to confirm cessation of brain functions by means of electrophysiology or showing the cessation of flow, developed. EEG would show no electrical activity of the cerebral cortex. However, in one consecutive series of patients fulfilling the clinical diagnosis of brain death, 20% of patients had residual EEG activity, and also, considerable artifacts in the intensive care unit can limit interpretation. Somatosensory evoked potentials and auditory brainstem responses should show no brainstem electrical activity, and were tested in small series of patients with brain death, and most patients were found to have no responses. Isotope angiography by rapid intravenous injection of serum albumin labeled with technetium 99m and following by bedside imaging with a portable gamma camera would show absent intracranial radioisotope activity. However, its sensitivity and specificity have not been defined in adults. The same procedure can be performed with technetium-99m hexamethylpropyleneamineoxime (^{99m}Tc -HMPAO), and the sensitivity has been reported to be as low as 94% with a specificity of 100%, but the reproducibility has been tested in only a few patients. Due to high costs and technique is not widely available, expertise is limited. Four vessel angiogram showing absent intracerebral filling at the level of the carotid bifurcation or circle of Willis seemed to be an ideal method showing cessation of the intracranial flow thus confirming cerebral circulatory arrest. Repeated contrast injections

may increase the risk of nephrotoxicity and decrease the acceptance rate in organ recipients. Multislice computerized angiography is a more sensible method for assessment of cerebral circulatory arrest, but its disadvantage is that it may show tinny filling of contrast in one of the arteries of the Willis circle, disabling the confirmation of circulatory arrest. In such instances repeated application of contrast injections and imaging is performed until complete cessation of flow. Up to now there is no unified agreement of criteria for assessment of the cerebral circulatory arrest with this method, and nephrotoxicity due to repeated contrast injections is a disadvantage. Transcranial Doppler sonography is an easy bedside method, reporting characteristic signals indicating circulatory arrest. Its disadvantage is that the velocities can be affected by marked changes in $p\text{CO}_2$, hematocrit, cardiac output, it requires considerable practice and skill, and suboptimal temporal bone window may be a problem.

Due to perceived need for standardized clinical examination criteria for the diagnosis of brain death in adults, large differences in practice in performing the apnea test, and controversies over appropriate utilization of confirmatory tests in the year 1995., brain death was selected as a topic for practice parameters (Wijdicks EFM. *Neurology* 1995.). The committee defined practice parameters that should serve as guidelines in management patients with brain death (Report of the Quality Standards Subcommittee of the American Academy of Neurology. *Neurology* 1995.). Despite such definition, criteria varies between countries, and guidelines have recently been updated (Wijdicks EFM, et al. *Neurology* 2010.).

A survey on brain death criteria (Wijdicks EFM. *Neurology* 2002.) throughout the world revealed uniform agreement on the neurologic examination with exception of the apnea test. Major differences between countries were present between presence of legal standards on organ transplantation, presence of practice guidelines for brain death for adults, number of physicians required to declare brain death, observational period or presence of required expertise of examining physicians. Only 28 of 70 (40%) national practice guidelines require confirmatory testing. Therefore, a necessity of a universal consensus for brain death determination exists, and agreement must be found and set due to medical, legal, and ethical reasons.

2. Recommendations for diagnosing brain death

By recently published guidelines (Wijdicks EFM et al. *Neurology* 2010.), the criteria for the determination of brain death given in the 1995. by American Academy of Neurology practice parameters have not been invalidated by recently published reports of neurologic recovery in patients who fulfill these criteria, so that the guidelines remains the same.

The determination of brain death can be considered to consist of four steps:

1. The clinical evaluation establishing irreversible and proximate cause of coma by history, examination and neuroimaging. Clinical conditions that may confound the clinical assessment must be ruled out like severe electrolyte, acid-base or endocrine disturbances, administration of neuromuscular blocking agents or central nerve system (CNS) depressant drugs by history or laboratory tests. Normal core temperature and normal systolic blood pressure should be achieved. The clinical examination must show

absence of brain and brainstem functions, and irreversibility by adequate observational period.

2. The clinical evaluation (neurological assessment) must show coma, absence of brainstem reflexes and apnea.
3. Ancillary tests accepted in practice are electroencephalography (EEG), cerebral angiography, nuclear scan, transcranial Doppler (TCD), computerised tomography angiography (CTA) and magnetic resonance imaging/angiography (MRI/MRA), with the expertise in interpretation of each of the tests. In some countries tests are mandatory, in other countries may serve to shorten the observational period. They cannot replace a neurologic examination. Rather than ordering ancillary tests, physicians may decide not to proceed with the declaration of brain death if clinical findings are unreliable.
4. The time of brain death is documented in the medical records. Time of death is the time the arterial $p\text{CO}_2$ reaches the target value. In patients in whom ancillary test has been performed, the time of death is the time the test has been officially interpreted. Federal and state law requires the physician to contact an organ procurement organization following determination of brain death.

3. Transcranial Doppler sonography

Soon after Doppler sonography has been introduced for cerebrovascular evaluation, typical findings for cerebral circulatory arrest were described as oscillating flow or systolic spikes (Yoneda S, et al. Stroke 1974.). The reliability of the method increased with the introduction of TCD, and standardization of the insonating protocol (Ducrocq X, et al. J Neurol Sci 1998.).

Extensive death of brain tissue causes extreme increase of intracranial pressure (ICP). When the ICP equals the diastolic arterial pressure, the brain is perfused only in systole and with further increase of ICP over the systolic arterial pressure, cerebral perfusion will cease. Due to elasticity of the arterial wall and the compliance of the vasculature distal to the recording site, such cerebral circulatory arrest is associated with Doppler evidence of oscillatory movement of blood in the large arteries at the base of the brain. However the net forward flow volume is zero. With time the oscillations decrease in amplitude of spectral spikes until no pulsations are detectable. This development correlates with a more proximal demonstration of the angiographic flow arrest (Hassler W, et al. J Neurosurg 1989.). At the time of angiographic flow arrest at the internal carotid artery, the TCD shows an oscillating flow pattern in the middle cerebral artery, because the contrast medium progresses slowly toward the brain. From the clinical experience from cardiac arrest, such cerebral ischemia of about 10-15 minutes in vivo at normal body temperature, leads to irreversible total loss of brain function.

TCD is actually evaluating the blood flow velocities from basal cerebral arteries, depending of the systemic blood pressure (BP) and ICP. Figure 1. represents time course of spectral changes and flow velocities in middle cerebral artery (MCA) from normal condition up to development of cerebral circulatory arrest in relation of ICP with BP. With increase of ICP, a higher pulsatility in basal cerebral arteries can be registered, and with further increase of the ICP over diastolic BP, only forward flow persists in systole.

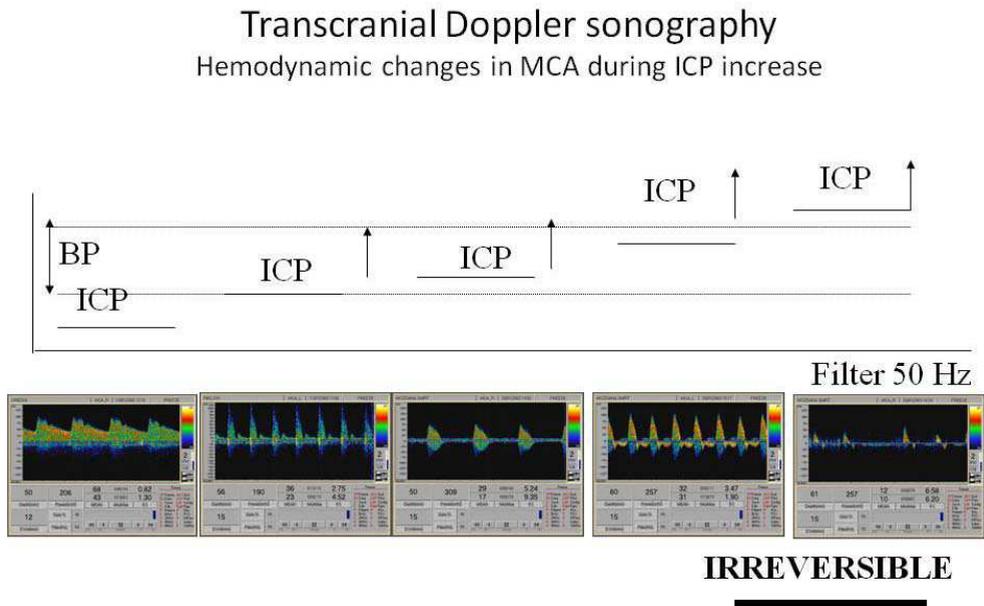


Fig. 1. Hemodynamic changes in middle cerebral artery (MCA) during increase of intracranial pressure (ICP)

With further increase of ICP that equals the systolic BP, reverberating flow with forward and reverse flow are nearly equal and cerebral perfusion ceases. Net flow is zero when the equality of both flow components are present and if the area under the envelope of the positive and negative deflection is the same. This finding correlates with the angiographic appearance of cerebral circulatory arrest (Hassler W, et al. J Neurosurg 1989).

With further increase of ICP over the systolic BP, only systolic spikes can be registered, and their amplitudes decreases with time. Such systolic spikes have characteristic pattern for cerebral circulatory arrest, but may resemble high resistance pattern with reduction of diastolic flow, the phase before development of reverberating flow. Due to the usage of high pass filters for elimination of artefacts from wall movement, reverberating flow can be missed. Therefore the filters must be set at its lowest level, at 50 Hz.

With further reduction of blood movement, the further decrease of amplitude can be registered until the complete cessation of signals. Failure to detect flow signals alone as the first finding, may also be a result from ultrasonic transmission problems. In such cases, the extracranial findings showing typical hemodynamic spectra in common carotid arteries (CCA), internal carotid arteries (ICA) and vertebral arteries (VA), represent important criterion (Fig 2., Fig 3., Fig 4.), but cannot replace the intracranial finding. At the same time flow in the external carotid arteries remain patent, with normal hemodynamic spectras. Flow in the ICA can be influenced by flow through the ophthalmic artery, although the volume of the ophthalmic artery flow plays a minor portion of the ICA flow.

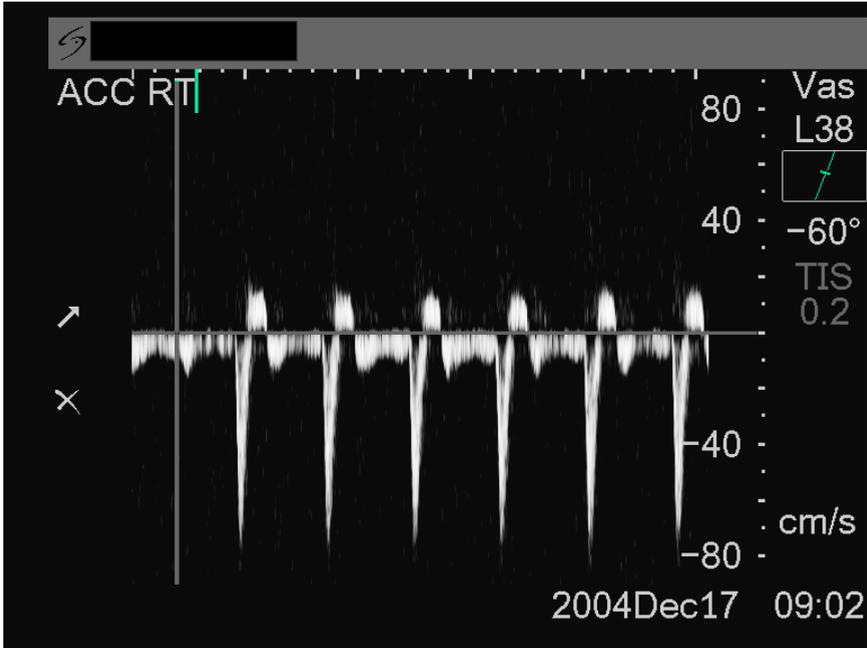


Fig. 2. Reveberating flow in common carotid artery (CCA)

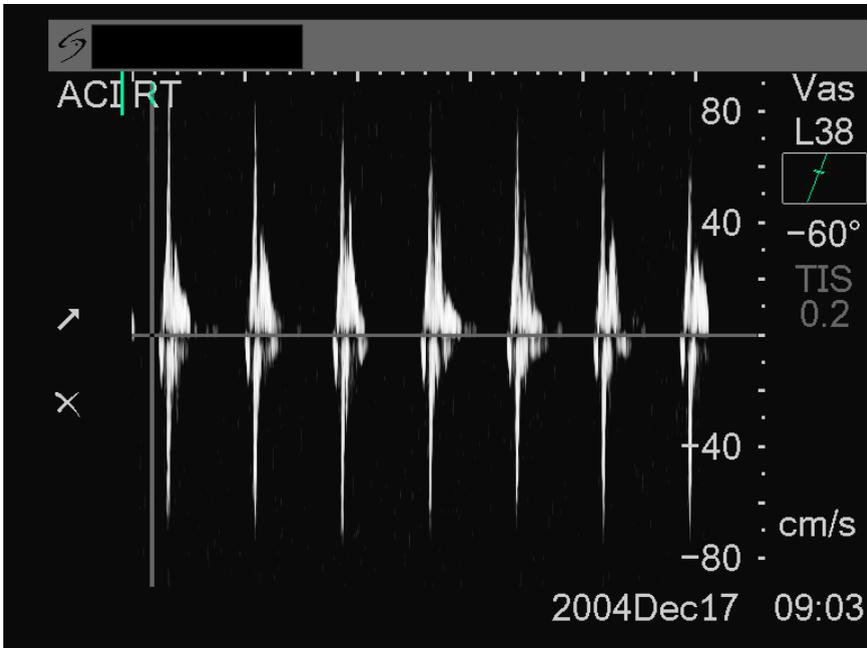


Fig. 3. Systolic spikes in internal carotid artery (ACI)

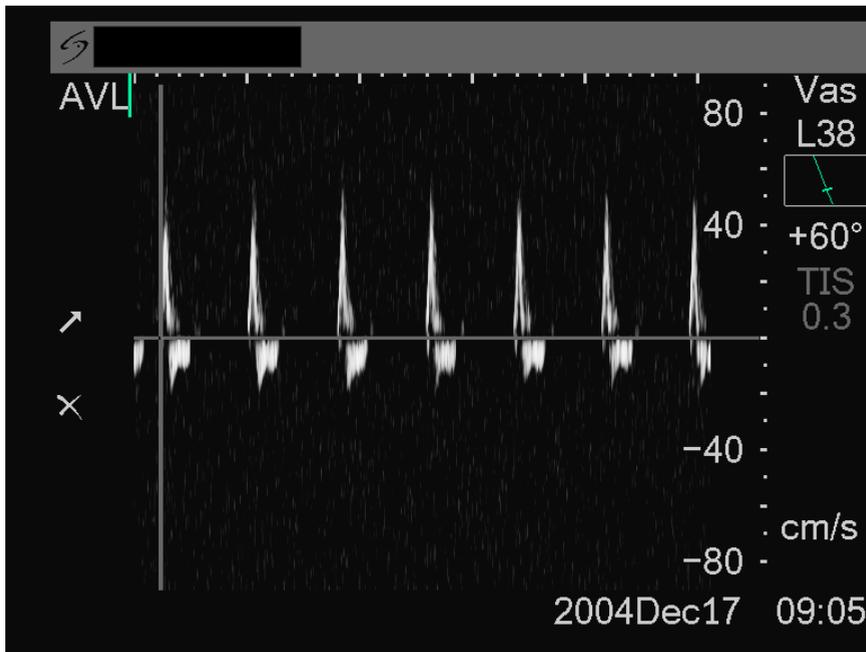


Fig. 4. Reveberating flow in left vertebral artery (AVL)

4. Guidelines for the use of Doppler sonography in brain death

The Neurosonology Research Group (NSRG) of the World Federation of Neurology (WFN) created a Task Force Group in order to evaluate the role of Doppler sonography as a confirmatory test for determining brain death, and created criteria which are defined and guidelines for the use of Doppler-sonography in this setting (Ducrocq X, et al. *J Neurol Sci* 1998.), and these guidelines were adopted and endorsed by numerous national societies (Demarin V, et al. *Acta clin Croat* 2005, Lovrencic-Huzjan A, et al. *Acta clin Croat* 2006., Alexandrov AV, et al. *J Neuroimaging* 2010., Segura T, et al. *Rev Neurosci* 2009., Calleja S, et al. *Neurologia* 2007., Marinoni M, et al. *Neurol Sci* 2011.).

According to aforementioned findings, Task Force Group of the NSRG WFN, (Ducrocq X, et al. *J Neurol Sci* 1998.) set guidelines for the use of Doppler sonography as a confirmatory test for cerebral circulatory arrest as follows:

4.1 Prerequisites

Doppler sonography can be used to confirm cerebral circulatory arrest thus confirming brain death only if the following diagnostic prerequisites are fulfilled:

1. The cause of coma has been established and is sufficient to account for a permanent loss of brain function.
2. Other conditions such as intoxication, hypothermia, severe arterial hypotension, metabolic disorders and others have been excluded.

- Clinical evaluation by two experienced examiners shows no evidence of cerebral and brainstem function.

4.2 Criteria

Cerebral circulatory arrest can be confirmed if the following extra- and intracranial Doppler sonographic findings have been recorded and documented both intra- and extracranially and bilaterally on two examinations at an interval of at least 30 min.

- Systolic spikes (Fig. 5.) or oscillating flow (Fig. 6.) in any cerebral artery which can be recorded by bilateral transcranial insonation of the ICA and MCA, respectively any branch, or other artery which can be recorded (anterior and posterior circulation). Oscillating flow is defined by signals with forward and reverse flow components in one cardiac cycle exhibiting almost the same area under the envelope of the wave form (to and fro movement). Systolic spikes are sharp unidirectional velocity signals in early systole of less than 200 ms duration, less than 50 cm/s peak systolic velocity, and without a flow signal during the remaining cardiac cycle. Transitory patterns between oscillating flow and systolic spikes may be seen. In order to enable visualisation of the low signals, wall filter must be set at its lowest level (50 Hz).
- The diagnosis established by the intracranial examination must be confirmed by the extracranial bilateral recording of the CCA, ICA and VA.

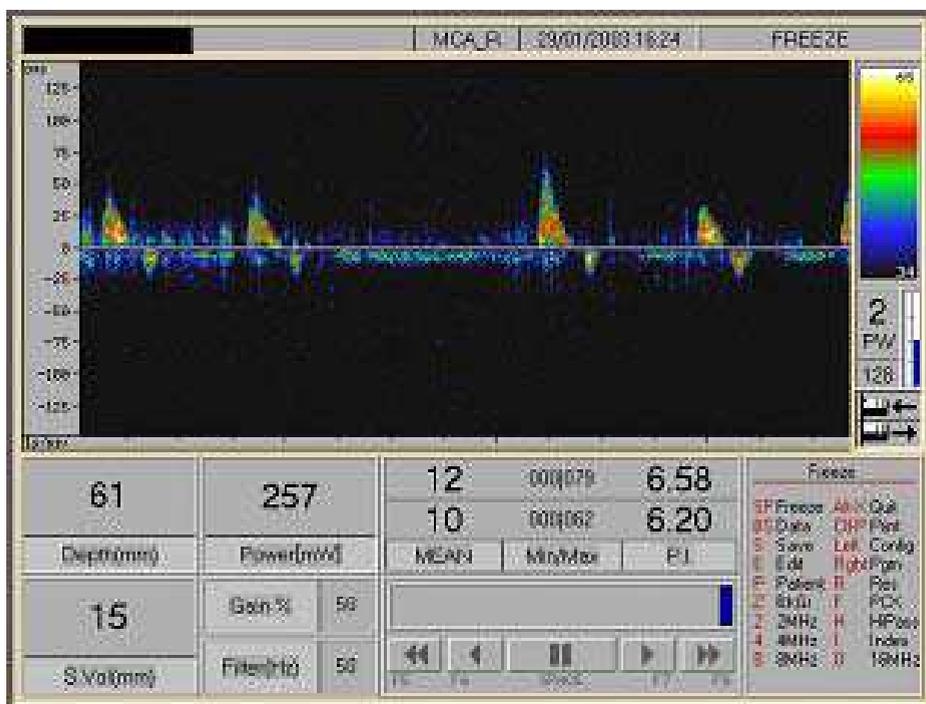


Fig. 5. Systolic spikes in middle cerebral artery (MCA)

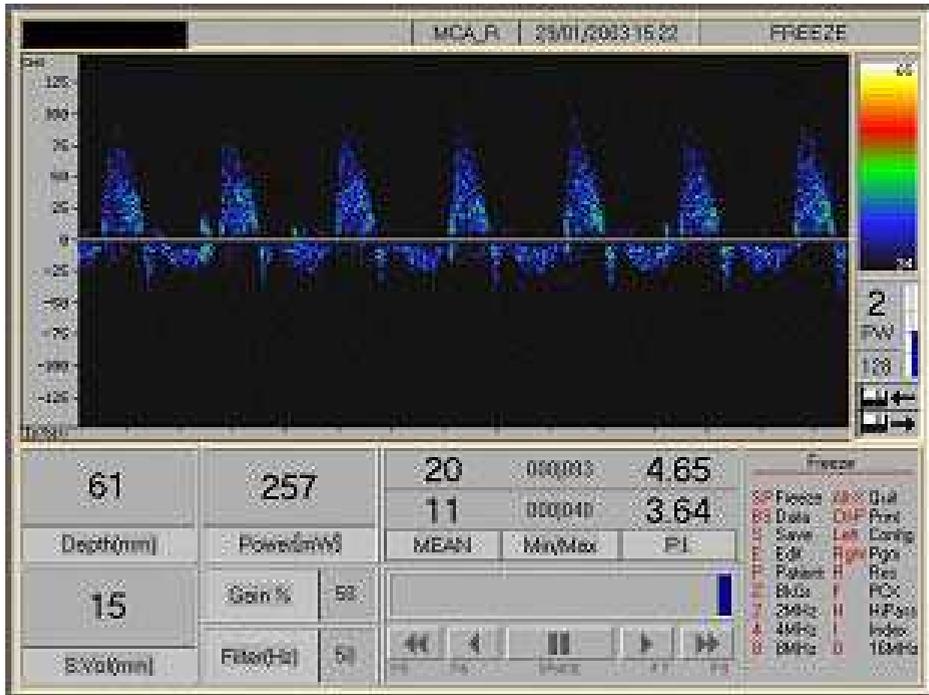


Fig. 6. Oscillating flow in middle cerebral artery (MCA)

3. The lack of signal during transcranial insonation of the basal cerebral arteries is not a reliable finding because this can be due to transmission problems. But the disappearance of intracranial flow signals in conjunction with typical extracranial signals can be accepted as proof of circulatory arrest.
4. Ventricular drains or large openings of the skull like in decompressive craniectomy possibly interfering with the development of the ICP is not present.

If the clinical prerequisites are fulfilled and cerebral circulatory arrest has been documented by Doppler sonography according to the above mentioned criteria, the diagnosis of brain death may be confirmed without further observation time, (Ducrocq X, et al. J Neurol Sci 1998.).

5. False positive and false negative TCD findings

There are no reports of previously published literature of a child or adult patient «surviving» who demonstrated bilateral signals or oscillating flow or systolic spikes in the MCA and ICA for at least half an hour. Only false positive reports with «some flow» in MCA or basilar artery were the result of the skull defects (Zurynski Y, et al. Neurol Res 1991.). Since the TCD registers the blood flow velocities (BFV) in relation to ICP, the skull defects are contraindications for examination (Fig. 1.). Due to the relation of BFV to BP, hypotension should be corrected before starting the examination (Fig. 1.), and during the examination.

5.1 Sonographic condition in which false positive findings can be detected

Acutely raised intracranial pressure due to bleeding or rebleeding from an aneurysm has been observed with transient flow patterns similar to those in cerebral circulatory arrest (Eng CC, et al. *Anesthesiology* 1993., Grote E & Hassler W. *Neurosurgery* 1988.). A similar high resistance pattern can occur shortly after cardiac arrest during the «no reflow phase». Both conditions are transient and the flow abnormalities will reverse at least partially within less than 30 minutes. During this initial phase, patients are clinically not brain dead. A proportion of these patients may later deteriorate to brain death.

Since brain death is a clinical condition, the clinical findings must first be fulfilled. In patients with both ICA distal occlusion, only systolic spikes in both ICAs would be detected. These patients would be mistaken if examination of the posterior circulation is not part of the protocol. Aortic insufficiency, especially in aortic dissection, may also pose problems for interpretation of the flow pattern of the CCA and ICA (Fig.7.,8.,9.,10.,11.,12.,13.), and also in basilar artery (Fig.14.). The reverse component, if present, is smaller than the forward component of the flow signals. If the flow signals transtemporally cannot be registered, the transmission problems can be suspected. Up to 20% of individuals have strong ossification of the temporal bones making the insonation impossible.

An experienced investigator is required. During the development of cerebral circulatory arrest, marked changes of hemodynamic spectras develop. Therefore, an unexperienced examiner may mistake ECA for ICA, due to patent flow in extracranial circulation, with normal spectrum, and therefore a lower pulsatility than in intracranial circulation (which is contrary to normal situation).

TCD provides indirect information on cerebral blood flow regardless of brainstem status. It is important to fulfill the prerequisites because after excluding the skull opening or low BP, all together three false positive cases were described in the literature. Recently one case reported comatose patient with TCD brain death pattern detected without absence of brainstem reflexes (Wijdicks EFM. 2010.). In the meta-analysis (Monteiro LM, et al. *Intensive Care Med* 2006.) including ten studies of the usage of TCD in brain death, two false-positive results were reported, but in both patients brain-stem function did show brain death shortly thereafter. In the first (Hadani M, et al. *Intensive Care Med* 1999.) weak respiratory movements in response to an apnea test persisted for some hours after the first TCD signals of cerebral circulatory arrest were detected. The second (Velthoven van V, et al. *Acta Neurochir (Wien)* 1988.) a clinically brain-dead patient, with cerebral circulatory arrest by TCD in the basilar artery and the circle of Willis, confirmed by angiography, became iso-electric only several hours later. Ten other false-positive results in literature from that meta-analysis were not in agreement with predefined criteria of a false-positive result, examination of the posterior circulation was not performed, or the changes were transient. Ducrocq et al. described one case with continued spontaneous respiration for some minutes after TCD examination showing typical spectras, but without data available as to which vessels were examined and under which condition TCD examination took place (Ducrocq X, et al. *J Neurol Sci* 1998.). Since TCD was never meant to be a replacement for clinical investigational, and if the prerequisites are met, it doesn't decrease the reliability of TCD and can be used with high confidelity in assessment of cerebral circulatory arrest.

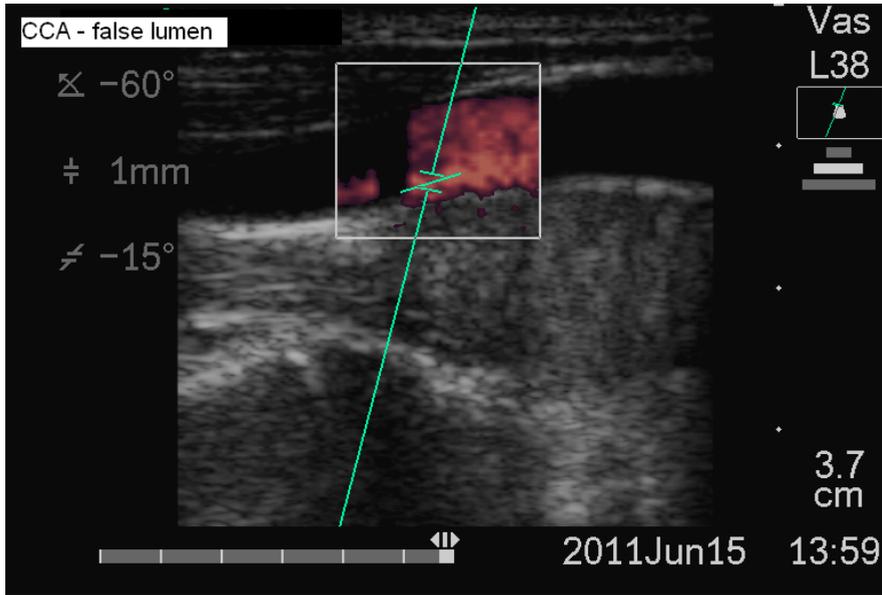


Fig. 7. Dissection of common carotid artery (CCA), measurement of hemodynamic in false lumen (B mod)

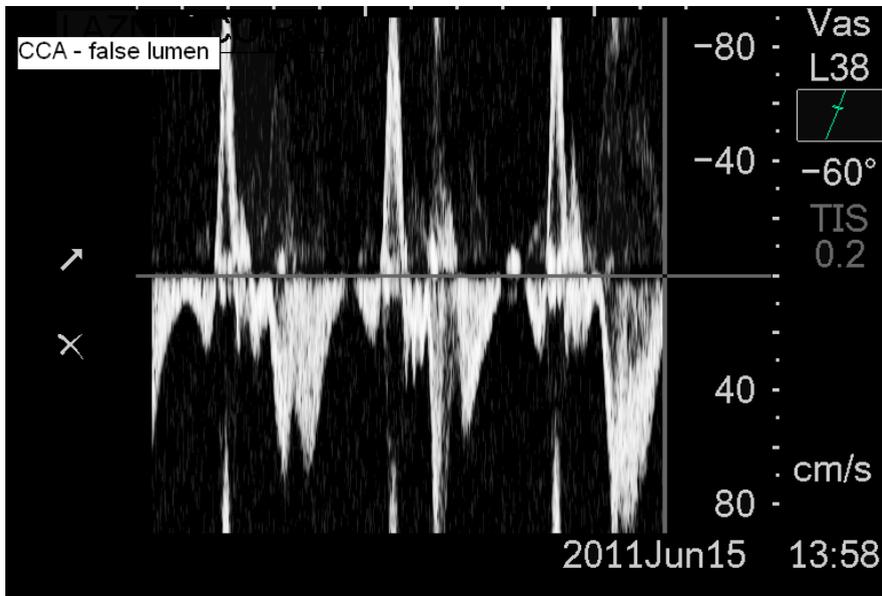


Fig. 8. Reverberating flow in false lumen of common carotid artery (CCA) dissection as a result of aortic insufficiency in aortic dissection

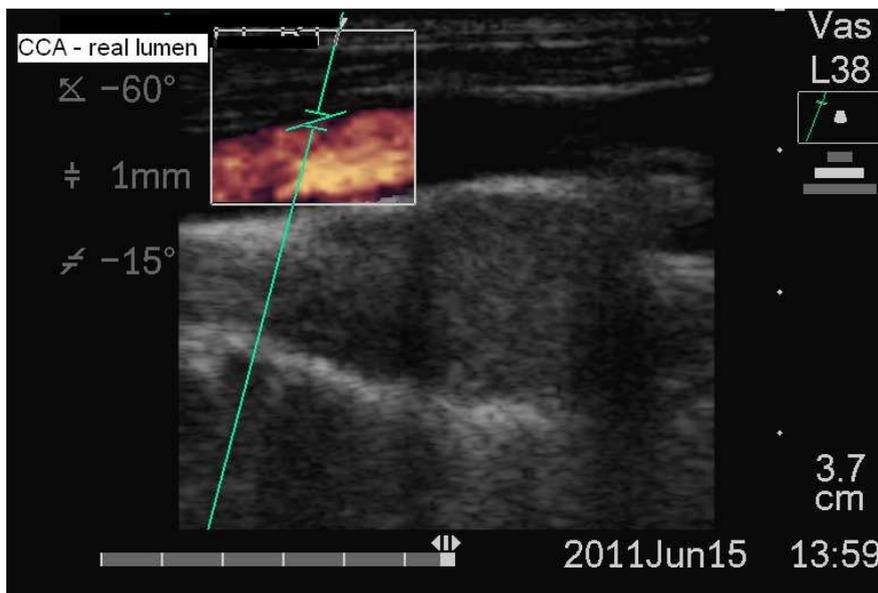


Fig. 9. Dissection of common carotid artery (CCA), measurement of hemodynamic in real lumen (B mod)

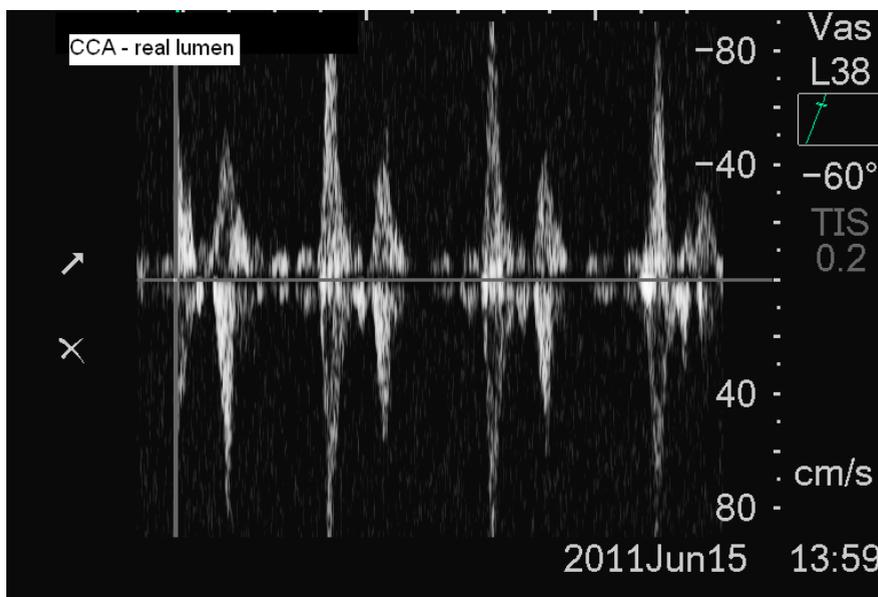


Fig. 10. Reverberating flow in real lumen of common carotid artery (CCA) dissection as a result of aortic insufficiency in aortic dissection

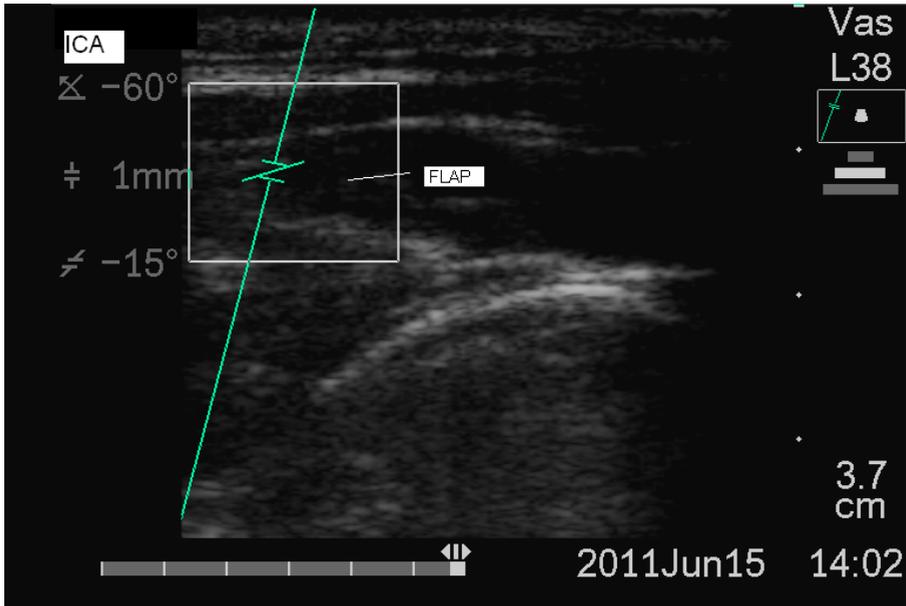


Fig. 11. Dissection of internal carotid artery (ICA) with intimal flap in B mod

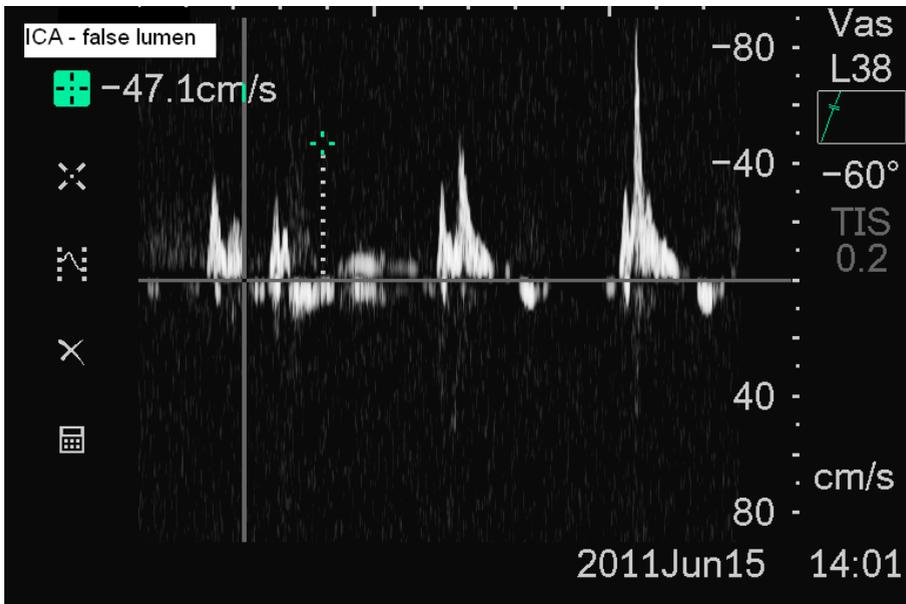


Fig. 12. Systolic spikes in false lumen of internal carotid artery (ICA) as a result of aortic dissection

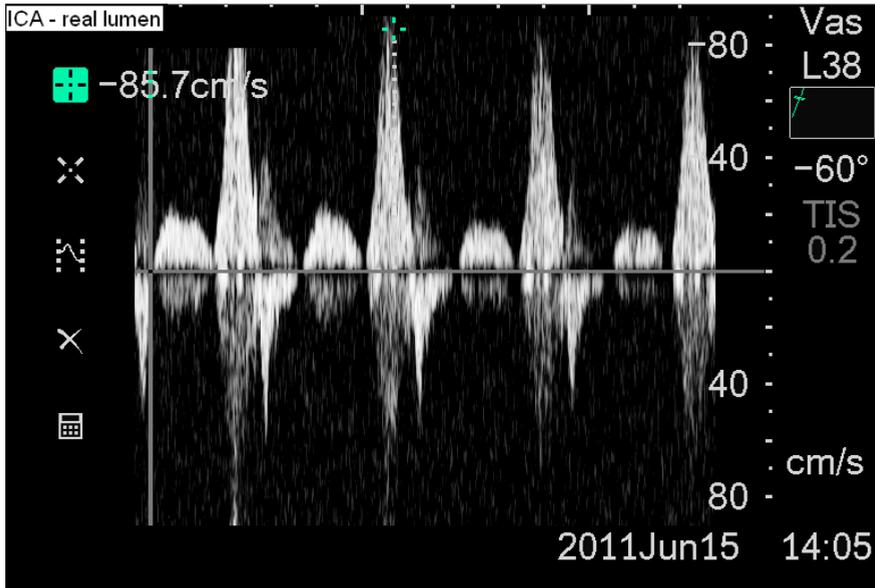


Fig. 13. Reverberating flow in real lumen of internal carotid artery (ICA) as a result of aortic dissection

5.2 Sonographic condition in which false negative findings can be detected

Few years ago, a report of false negative results due to the presence of diastolic flow in intracranial ICA obtained through orbital window in clinically brain dead patients was published (de Freitas GR, et al. *J Neurol Sci* 2003.). Although not specifically stated in the article, presumably all patients who had ICA flow consistent with cerebral circulatory arrest also had other intracranial arteries demonstrating a similar flow pattern. The authors propose that the ICA should not be routinely studied for confirmation of brain death, except in patients whose transtemporal windows are inadequate, leading to the inability to insonate the MCA. In editorial of the article (Jacobs BS, et al. *J Neurol Sci* 2003.), reasons for reviewing current criteria for TCD diagnosis of brain death were presented. Beside the de Freitas's (de Freitas GR, et al. *J Neurol Sci* 2003.) reasons for exclusion of the intracranial ICA insonation, is the suggestion for exclusion examination of the extracranial arteries, which was reviewed and refuted by a recent study (Jacobs BS, et al. *J Neurol Sci* 20034.). The suggestion (Jacobs BS, et al. *J Neurol Sci* 2003.) was to be less conservative in the brain death confirmation. Since, no new statement of the NSRG WFN were published, the confirmation of cerebral circulatory arrest using Doppler sonography should be done according to aforementioned criteria (Ducrocq X, et al. *J Neurol Sci* 1998.). Since the introduction of TCD in brain death confirmation is preferable, a numerous clinicians adopted its usage. That resulted in a number of publications. Some (Poullaras J, et al. *Transplant Proc* 2006.), reported lower sensitivity than previously reported, but the specificity was 100%. Already mentioned, a meta-analysis of studies assessing the validity of TCD in confirming brain death, was done (Monteiro LM, et al. *Intensive Care Med* 2006). A systematic review of articles published in English on the diagnosis brain death by TCD, between 1980 and 2004,

was performed. TCD oscillating or reverberating flow and systolic spikes, were considered to be compatible with cerebral circulatory arrest. The quality of each study was assessed using standardized methodological criteria. The literature was searched for any article reporting a false-positive result. Two high-quality and eight low-quality studies were included. The high sensitivity 95% (95% CI 92-97%) and high specificity 99% (95% CI 97-100%) for brain death detection using TCD was obtained.

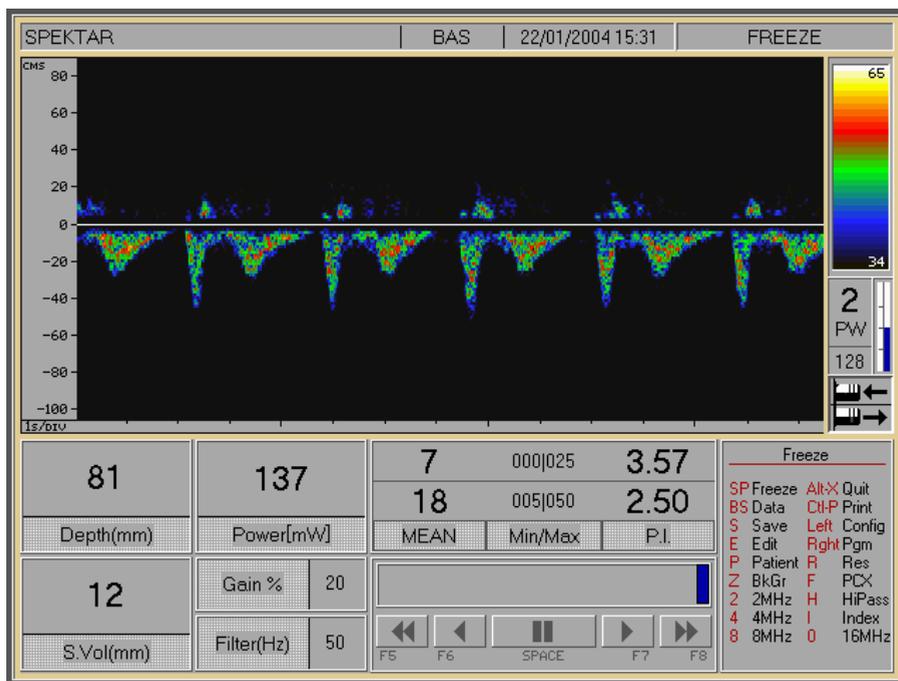


Fig. 14. Reverberating flow in basilar artery due to aortic dissection

6. Advantages and disadvantages of Doppler sonographic evaluation

The greatest advantage of Doppler sonography is the possibility of bedside evaluation, which enables close monitoring and intervention in unstable patient. It must be pointed out, that prerequisites should be fulfilled. No contrast agents are applied, preserving the residual organ function. The recent publication (Lovrencic-Huzjan A, et al. *Ultraschall Med/ Europ J Ultrasound* 2011.) showed the shortest time to confirm the clinical diagnosis of brain death, and in most patients (61%) cerebral circulatory arrest was confirmed within 2 hours from clinical diagnosis. This is important since the delay of brain death determination has a negative impact on organ donation (Lustbader D, et al. *Neurology* 2011.), and in study

consent for organ donation decreased from 57% to 45% as the brain death declaration interval increased. Conversely, refusal of organ donation increased from 23% to 36% as the brain death interval increased. Also 12% sustained a cardiac arrest between the two examinations or after the second examination.

The disadvantages of TCD is that in up to 20% of individuals the insonation is not possible due to bone hyperostosis. In patients with skull defects or drainage false results can be detected due to inappropriate ICP recording, and therefore the TCD is not a method of choice for brain death confirmation. The blood flow velocities can be affected by marked changes in PCO₂, hematocrit and cardiac output. It cannot be performed in hypotensive patients. Transcranial Doppler ultrasonography requires considerable practice and skill.

7. Conclusion

In comatose patients with absent motor and brainstem reflexes, and evidence of brain damage compatible with the diagnosis, brain death is suspected. After an observational period repeated examination should be performed according to the protocol. Apnea testing should be done, and TCD can be used as an ancillary test for diagnosing cerebral circulatory arrest. It is a preferable test due to noninvasiveness, bedside evaluation. Besides it is easy to perform, thus the diagnosis can be confirmed within short time period, mostly in two hours after the clinical diagnosis.

8. Acknowledgment

I thank all the colleagues and staff in Central intensive care unit in Department of Anaesthesiology and Neurology intensive care in University Department of Neurology University Hospital Center "Sestre milosrdnice" in Zagreb, Croatia, where the recording of patients and brain death persons were performed.

I thank DWL for financial support of this chapter.

I thank Marijana Bosnar Puretic, MD, PhD for technical support in preparation of the manuscript.

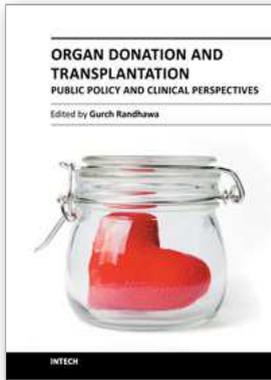
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Organ Donation and Transplantation - Public Policy and Clinical Perspectives

Edited by Dr. Gurch Randhawa

ISBN 978-953-51-0039-3

Hard cover, 284 pages

Publisher InTech

Published online 08, February, 2012

Published in print edition February, 2012

Transplantation has succeeded in prolonging the lives of those fortunate enough to have received the gift of a body organ. Alongside this life-saving development, there lies another sadder side to the story - there are not enough organs to meet the ever increasing demand. This not only places an increasing emotional and physical burden among the waiting patients and families but heaps a great financial burden upon health services. This book provides an analysis and overview of public policy developments and clinical developments that will hopefully ensure an increased availability of organs and greater graft survival. Medical, policy, and academic experts from around the world have contributed chapters to the book.

How to reference

In order to correctly reference this scholarly work, feel free to copy and paste the following:

Arijana Lovrencic-Huzjan (2012). Transcranial Doppler as an Confirmatory Test in Brain Death, Organ Donation and Transplantation - Public Policy and Clinical Perspectives, Dr. Gurch Randhawa (Ed.), ISBN: 978-953-51-0039-3, InTech, Available from: <http://www.intechopen.com/books/organ-donation-and-transplantation-public-policy-and-clinical-perspectives/transcranial-doppler-as-an-confirmatory-test-in-brain-death>

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