

Louisa M. Monteiro
Casper W. Bollen
Alexander C. van Huffelen
Rob G. A. Ackerstaff
Nicolaas J. G. Jansen
Adrianus J. van Vught

Transcranial Doppler ultrasonography to confirm brain death: a meta-analysis

Received: 5 January 2006
Accepted: 26 July 2006
Published online: 21 September 2006
© Springer-Verlag 2006

L. M. Monteiro · C. W. Bollen ·
N. J. G. Jansen · A. J. van Vught (✉)
University Medical Center Utrecht,
Department of Pediatric Intensive Care,
KG 01.319.0, 85090, 3508 Utrecht,
The Netherlands
e-mail: a.vanvught@umcutrecht.nl
Tel.: +31-30-2504002
Fax: +31-30-2505347

A. C. van Huffelen
University Medical Center Utrecht,
Department of Clinical Neurophysiology,
F.02.230, 85090, 3508 Utrecht,
The Netherlands

R. G. A. Ackerstaff
St. Antonius Hospital Nieuwegein,
Department of Clinical Neurophysiology,
Koekoekslaan 1, 3435 Nieuwegein,
The Netherlands

Abstract Objective: Barbiturate therapy or hypothermia precludes proper diagnosis of brain death either clinically or by EEG. Specific intracranial flow patterns indicating cerebral circulatory arrest (CCA) can be visualized by transcranial Doppler ultrasonography (TCD). The aim of this study was to assess the validity of TCD in confirming brain death. **Design:** Meta-analysis of studies assessing the validity of TCD in confirming brain death. **Methods:** A systematic review of articles in English on the diagnosis brain death by TCD, published between 1980 and 2004, was performed. An oscillating or reverberating flow and systolic spikes were considered to be compatible with CCA. The quality of each study was assessed using standardized methodological criteria. The literature was searched for any article reporting a false-positive result. **Results:** Two high-quality and eight low-quality

studies were included. Meta-analysis of the two high-quality studies showed a sensitivity of 95% (95% CI 92–97%) and a specificity of 99% (95% CI 97–100%) to detect brain death. Meta-analysis of all ten studies showed a sensitivity of 89% and a specificity of 99%. In the literature we found two false-positive results; however, in both patients brain-stem function did show brain death shortly thereafter. **Conclusions:** CCA by TCD in the anterior and posterior circulation predicted fatal brain damage in all patients; therefore, TCD can be used to determine the appropriate moment for angiography. Further research is needed to demonstrate that CCA by TCD on repeated examination can also predict brain death in all patients.

Keywords Brain death · Cerebral circulatory arrest · Ultrasonography · Transcranial Doppler

Introduction

Since transplant surgery became a common procedure, early diagnosis of brain death has become an important issue. The duration of the diagnostic process should be as short as possible to avoid cardiac arrest and to preserve function of donor organs [1, 2]. In general, brain death is primarily diagnosed by absence of any clinical sign of brain stem activity [3, 4, 5, 6] and can additionally be confirmed by absence of electric activity on the electroencephalogram (EEG) [7, 8]. Barbiturate therapy or hypothermia precludes proper diagnosis of

brain death either clinically or by EEG [9]. In these situations demonstrating cerebral circulatory arrest (CCA) by angiography or radionuclear cerebral flow studies can be used to support the diagnosis of brain death, as CCA will lead to brain death; however, angiography is an invasive technique and both additional tests require transport of a critically ill patient. Theoretically, contrast can cause vascular obstruction harmful to any residual brain function or precipitate renal failure [10].

Intracranial flow patterns demonstrating CCA can also be visualized by transcranial Doppler ultrasonography (TCD). The TCD is a non-invasive and inexpensive tech-

nique which can be performed at the bedside. A number of investigators have used TCD to document CCA in brain-dead patients [11, 12, 13, 14]. Persistent CCA leads to the state of brain death as blood supply to the brain is mandatory to establish cerebral function. The TCD can demonstrate CCA by specific intracranial Doppler flow patterns caused by increased intracranial pressure due to brain death. Diastolic perfusion pressure drops first when intracranial pressure increases, and it finally diminishes to zero. If intracranial pressure is elevated to values above diastolic blood pressure, an oscillatory movement of blood with reversal of diastolic flow appears. With increasing intracranial pressure a pattern of systolic spikes appears. Both an “oscillating flow,” also described as “reverberating flow,” and “systolic spikes” are flow patterns without any net forward flow, i. e., no cerebral blood supply, and are considered to be compatible with CCA [15].

We did a systematic review of relevant literature to assess the validity of TCD in confirming brain death [16]. Medical and legal communities can only accept TCD as a confirmatory test when false-positive results, i. e., diagnosing CCA by TCD in a non-brain-dead patient, do not occur; therefore, we paid special attention to any article reporting possible false-positive results.

Methods

Literature search

A search for English-language articles on the diagnosis of brain death by TCD published between 1980 and January 2004 was performed using Pub Med. The search terms used were “transcranial,” “transforaminal,” “transorbital,” “transtemporal,” and “Doppler” or “ultrasonography” combined with “brain death” or “cerebral circulatory arrest.” Reference lists of retrieved articles were scanned for additional studies. Literature was also searched for any false-positive result of TCD examination of intracranial vessels using the same search terms.

Study selection

Letters, editorials, case reports, commentaries and reviews were excluded. To be included a study had to meet the following criteria: (a) specification of a persistent intracranial flow pattern specific for CCA: oscillating flow or systolic spikes (Fig. 1); (b) presence of a specified reference test (clinical diagnosis alone or combined with EEG, angiography or radionuclear cerebral flow studies); (c) brain death defined as a non-reactive coma with complete loss of the brain-stem reflexes and apnea; (d) prospective study; and (e) extractable data of patients classified as brain dead or non-brain dead. Studies only involving examination of ex-

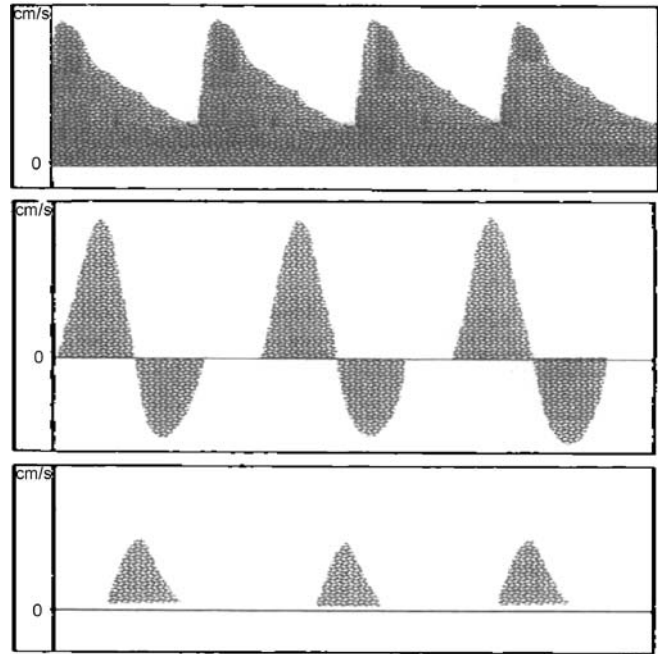


Fig. 1 Transcranial Doppler flow patterns. Transcranial Doppler flow patterns demonstrate normal flow with systolic and diastolic forward flow (*top*), oscillating flow with systolic forward flow and reversed diastolic flow (*middle*), and brief systolic forward flow (*bottom*)

tracranial vessels or neonates and infants (< 1 year) were excluded.

The quality (validity) of each article was assessed independently by two authors (L.M. and C.B.). High-quality studies, low-quality studies, and non-valid studies were distinguished according to a checklist for diagnostic tests published by the Dutch Cochrane Center. Disagreements were resolved by discussion. Four primary criteria were used: (a) presence of an independent blind comparison with a reference (gold) standard; (b) the population studied included an appropriate spectrum of patients to whom the test would be applied in clinical practice; (c) inclusion of consecutive patients who fulfilled the inclusion criteria; and (d) sufficient description of TCD to allow reproduction of the method. High-quality studies had to fulfill all four criteria. Low-quality studies had to fulfill criterion (a) [but not necessarily a *blind* comparison with a reference (gold) standard] and criterion (d). All other studies were qualified as non-valid studies.

Data extraction

A result was considered false positive when the reference test was performed according to standardized criteria and did not confirm brain death while TCD did show a flow pattern indicating CCA. If TCD showed a flow pattern con-

sistent with brain death in a non-brain-dead patient, but the TCD examination was incomplete, i. e., only the anterior circulation (middle cerebral arteries) or the posterior circulation (basilar artery) was visualized, the result was not defined as false positive. Moreover, a TCD pattern specific for CCA had to be persistent (steady state) during TCD examination. Clinically brain-dead patients with CCA by TCD in the middle cerebral arteries and basilar artery with skull defects who died of cerebral damage, but in whom angiography still showed some flow, were defined as true positives.

Statistical analysis

Data from high-quality studies and low-quality studies were combined in two-by-two tables that specified brain-dead and non-brain-dead patients according to the reference test and positive (CCA) or negative (no CCA) TCD results. Heterogeneity was assessed by visual examination of overlap of 95% confidence intervals of estimates of sensitivity and specificity. If no significant heterogeneity was assumed, weighted averages of sensitivity and specificity were calculated from results of high-quality studies. Sensitivity analysis to test the robustness of these estimates was performed by adding low-quality studies to the meta-analysis.

Results

Initially, the literature search yielded 223 citations. Forty-three eligible diagnostic studies that evaluated the validity of TCD in brain death were identified. Finally, 10 studies (684 patients) were included (Fig. 2). Two studies were classified as high-quality studies [17, 18].

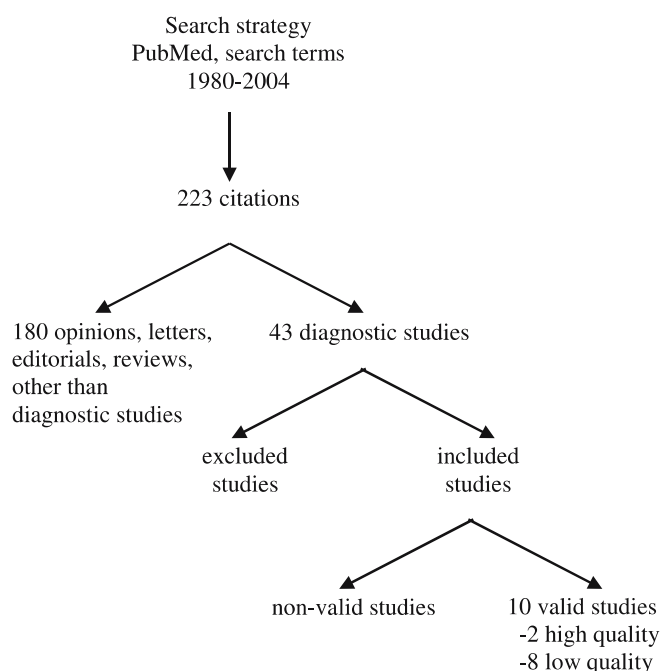


Fig. 2 Meta-analysis profile

Eight studies were classified as low-quality studies [14, 19, 20, 21, 22, 23, 24, 25]. In these studies, investigators performing TCD were not blinded to clinical, electroencephalographic, or radiographic results (Table 1).

Zuryski et al. [18] studied 140 consecutive comatose patients. According to the reference test 111 patients were brain dead. In 100 brain-dead patients reliable intracranial signals were obtained. In 6 patients results of intracranial TCD examination were not in agreement with the reference test. In 3 cases TCD showed CCA, but

Table 1 Included studies. *TP* true positive, *FN* false negative, *TN* true negative, *FP* false positive, *CA* cerebral angiography, *EEG* electroencephalogram, *RCS* radionuclide scan, *MCA* middle

Reference	Number	TP	FN	TN	FP	Quality	Reference test	Vessel
[18]	133	97	7	29	0	High	Clinical criteria (64) and CA (47)	MCA, BA, ICA < 50% when no MCA/BA
[17]	137	80	3	53	1	High	Clinical criteria	ICA, MCA, VA, BA
[19]	54	21	5	28	0	Low	Clinical criteria and EEG	Anterior circulation, BA
[21]	37	18	4	15	0	Low	Clinical criteria and EEG	MCA
[22]	75	22	4	49	0	Low	Clinical criteria and EEG	MCA
[23]	135	123	12	0	0	Low	Clinical criteria and EEG (88) and/or CA (64)	ICA, MCA, BA (24/130)
[20]	15	8	7	0	0	Low	Clinical criteria and CA	MCA
[24]	29	26	3	0	0	Low	Clinical criteria and CA (9) and EEG (8)	Willis, BA
[14]	12	11	1	0	0	Low	Clinical criteria and RCS	MCA
[25]	57	45	12	0	0	Low	Clinical criteria	BA, VA, MCA
Total	684							

cerebral artery, *BA* basilar artery, *VA* vertebral artery, *ICA* internal carotid artery

angiography failed to confirm this. All of these patients had skull defects and none survived. In 3 cases TCD did not show CCA while the reference test showed brain death. Hadani et al. studied 137 consecutive comatose patients [17]. The CCA was demonstrated by TCD in 80 of 83 brain-dead patients. In two of 83 brain-dead patients no intracranial signals were obtained. In 1 brain-dead patient a flow pattern not consistent with CCA was obtained. Petty et al. [19] examined 54 comatose patients. In 5 patients no adequate signal was obtained. Three of these 5 patients met the clinical criteria for brain death. Twenty-three of the remaining 49 patients with TCD examinations were brain dead. The CCA was found in 21 of those 23 brain-dead patients. Feri et al. [21] performed TCD examination in 37 patients with intracranial hypertension. In 18 of 22 brain-dead patients TCD showed CCA. In 4 patients it was impossible to obtain an adequate TCD signal. Dominguez-Roldan et al. [22] recorded TCD waveforms in 26 brain-dead patients and in 49 non-brain-dead patient. In 22 of the 26 brain-dead patients TCD showed CCA. Ducrocq et al. [23] did a TCD study in 135 brain-dead patients. In 12 patients no detectable signal was found or TCD did not show bilateral CCA. The TCD showed CCA in 123 patients. Paolin et al. [20] studied 15 patients with clinical diagnosis of brain death. The TCD showed CCA in 8 patients. Angiography confirmed CCA in all 8 cases. Van Velthoven et al. [24] performed TCD examination in 29 patients. In 26 brain-dead patients a flow pattern specific to CCA was found. In 9 clinically brain-dead patients an angiography was performed which confirmed CCA. In 8 clinically brain-dead patients an EEG was performed. Newell et al. [14] performed a TCD study in 12 clinically brain-dead patients. In 1 patient they were unable to obtain an adequate signal. In 11 patients TCD confirmed CCA. Lample et al. [25] examined 57 clinically brain-dead patients. In 45 patients TCD showed CCA. In 4 patients no flow was visualized. In all other patients CCA was not confirmed.

Twelve studies reported false-positive results of TCD examination of intracranial vessels (Table 3). Two results were consistent with our predefined criteria of a false-positive result [17, 24]. In one study a patient with CCA by TCD in the middle cerebral arteries and basilar artery showed preserved weak respiration after TCD examination [17]; however, CCA resulted in brain death within several hours. Velthoven et al. [24] reported a clinically brain-dead patient, with CCA by TCD in the basilar artery and the circle of Willis, which was confirmed by angiography, in whom EEG examination became iso-electric only several hours later [24]. Ten other false-positive results in literature were not in agreement with our predefined criteria of a false-positive result [12, 14, 20, 23, 26, 27, 28, 29, 30, 31]. Examination of the posterior circulation was not performed in the studies by Kirkham et al. [12], Newell et al. [14], Paolin et al. [20], Qian et al. [26], Shioyai et al. [27],

Table 2 Meta-analysis of high quality studies and sensitivity analysis of all included studies. *CI* confidence interval

Primary analysis: only high-quality studies			
	95% CI		
Sensitivity (%)	95	92	97
Specificity (%)	99	97	100
Sensitivity analysis: all studies. Velthoven et al. [24]: cerebral angiography and clinical criteria as reference test			
	95% CI		
Sensitivity (%)	89	86	91
Specificity (%)	99	99	100
Sensitivity analysis: all studies. Velthoven et al. [24]: EEG and clinical criteria as reference test			
	95% CI		
Sensitivity (%)	89	86	91
Specificity (%)	99	98	100

Powers et al. [28], Steinmetz et al. [29], Grote et al. [30], and Eng et al. [31]. In patients with subarachnoid hemorrhage CCA was transient (no steady state) [29, 30, 31]. In those cases a temporary elevation of intracranial pressure produced reversible CCA for some minutes. Ducrocq et al. described one case with continued spontaneous respiration for some minutes after TCD examination showed CCA. No data are available as to which vessels were examined and under which conditions TCD examination took place [23].

Meta-analysis of the two high-quality studies showed a sensitivity of 95% (95% CI 92–97%) and a specificity of 99% (95% CI 97–100%) to detect brain death (Table 2). After adding the results of the low-quality studies, sensitivity changed to 89% (95% CI 86–91%) and specificity changed to 99% (95% CI 99–100%) using cerebral angiography as a reference test in the study performed by Velthoven et al. (Table 3) [24]. When EEG was used as a reference test in the study by Velthoven et al. [24], sensitivity remained the same and specificity changed to 99% (CI 98–100%). When patients of the ten studies with no intracranial signal were excluded from our meta-analysis, specificity did not change and sensitivity of TCD of the two high-quality studies increased to 98 and 94% of all ten studies. On visual examination there was considerable overlap between confidence intervals of the different studies of both sensitivity and specificity, so homogeneity between studies was assumed.

Discussion

This meta-analysis showed that TCD is a reliable test that can extend clinical criteria in the assessment of the diagnosis brain death. Sensitivity and specificity for a positive pattern of oscillating flow and systolic spikes, indicating CCA, were high in selected patient populations. Few false-positive cases were reported in the literature. Only two

Table 3 False-positive results mentioned in literature. *MCA* middle cerebral artery, *PCA* posterior cerebral artery, *BA* basilar artery, *ICA* internal carotid artery, *CCA* common carotid artery, *BD* brain death, *RDF* retrograde diastolic flow, *FF* forward flow, *NF* no-flow diastole, *DRF* diastolic reverse flow, no diastolic forward flow, *DFI* direction of flow index, *1-R/F*, *R* velocity of diastolic reverse flow, *F* velocity of systolic forward flow, *DFI* no net *FF*, *DFI* only *FF*, *DFI* <1 of some retrograde diastolic flow, *Net* velocity systolic antegrade velocity-retrograde velocity, *SAH* subarachnoidal hemorrhage, *FP* false positive

Reference	True FP	Flow	Vessel	Number	Description of cases	Comment
[17]	Yes	Oscillating flow	ICA, MCA, VA, BA	1	CCA on TCD with preserved weak respiration in response to an apnea test for some hours	
[24]	Yes	Reverberating flow	Willis, BA, carotid siphon	1	CCA on TCD with a non-iso-electric EEG	TCD flow pattern demonstrated in the article not specific of CCA according to our criteria
[26]	No	RDF	MCA	5	RDF in 2 surviving patients (DFI > 0.8) and 3 non-BD patients; 2 patients with DFI > 0.8 and 1 patient with DFI < 0.8. All 3 non-BD patients asystolic before meeting clinical criteria of BD	No posterior circulation
[20]	No	Systolic spikes, oscillating flow	MCA	3	CCA on TCD, EEG not iso-electric, but CCA on angiography	No posterior circulation
[27]	No	DRF, NF	MCA, ICA, CCA		NF and DRF in MCA in a patient with an acute epidural/intracerebral hematoma; FF in the PCA was preserved (survived)	No standardized EEG
[28]	No	Net velocity	MCA	3	2 patients clinically non-BD: net velocity +4 and +6 cm/s (died); 1 patient clinically non-BD: net velocity +26 cm/s (survived). All 3 patients showed systolic antegrade velocity	No posterior circulation
[14]	No	Reverberating flow	MCA	1	CCA on TCD and no flow on radionuclide scan with preserved respiration for 1 h (died)	No posterior circulation
[12]	No	DRF	MCA	4	3 patients recovery of FF in diastole and 1 patient recovery of brain-stem function with MCA velocity 10–25 cm/s with DRF (DFI > 0.8)	No posterior circulation
[23]	No			1	CCA on TCD with preserved respiration for some minutes	
[29]	No	Oscillating flow	MCA	3	Transient CCA on TCD during SAH	No steady state
[30]	No	Oscillating flow, diastolic no flow	MCA	3	Transient CCA on TCD during SAH	No posterior circulation
[31]	No	Oscillating flow	MCA	1	Transient CCA on TCD during SAH	No steady state
						No posterior circulation

instances were defined as false positive according to our predefined criteria. Both these patients became brain dead shortly after the false-positive TCD examination.

To our knowledge, our study is the first systematic review on the subject of TCD diagnosis of CCA. The meta-analysis included a large population of 684 patients. Only the high-quality studies were used to calculate the sensitivity and specificity. Thereupon, a sensitivity analysis, by adding the low-quality studies to the meta-analysis, showed the robustness of our results. Possible false-positive findings were carefully analyzed using objective criteria.

The quality of many published studies was questionable according to standardized criteria for a diagnostic test; only two articles were classified as high-quality articles. The high sensitivity and specificity that were found cannot be attributed to selective inclusion of only brain-dead patients as 26% of patients in this meta-analysis were not diagnosed as brain dead. Sensitivity in some studies was as low as 70%; however, these studies were of very low and unacceptable quality. To us, this mainly proves that TCD examination is only reliable in experienced hands. This meta-analysis included studies with an age distribution from infants to adults. Data of specified age groups were not extractable; therefore, it is difficult to extrapolate conclusions drawn from this meta-analysis to a specific age group, in particular to children.

In the analyzed studies clinical criteria alone or combined with an EEG, cerebral angiography and, in one study, radionuclide cerebral scan, were used as reference tests; however, the validity of these reference tests can be compromised. In a clinically brain-dead patient EEG can still show minor activity due to technical artifacts. Furthermore, it is hypothesized that cerebral angiography can still show some flow in a brain-dead patient because of an active injection of contrast that increases intra-arterial pressure [32] in case of diffuse anoxic injury [33] or skull defect [23, 34, 35, 36] without major intracranial hypertension.

Most authors excluded patients in their study in whom it was impossible to obtain an intracranial signal. Failure to detect an intracranial signal can indicate CCA but can also result from failure to localize the vessel by TCD. In our meta-analysis these patients were included because in those patients TCD could not confirm brain death and in that sense constituted negative results. Excluding these patients from the meta-analysis would lead to spuriously high sensitivity values. Two instances of CCA were defined as false positives according to our predefined criteria; however, the TCD pattern of the patient demonstrated in the article by Van Velthoven et al. [24] was not specific for CCA according to our clinical

assessment. Moreover, angiography also showed that CCA and EEG became iso-electric only several hours later. In the other study a patient with CCA by TCD showed preserved weak respiration for some hours after TCD examination but ultimately was brain death some hours later as well. In our opinion, this demonstrates that CCA is not the same as brain death. The CCA must be present for a certain period to give rise to brain death.

The CCA by TCD predicted fatal brain damage in all patients; therefore, TCD can be used as a diagnostic test for fatal brain damage. As a prognostic test it could be performed to determine the appropriate moment for angiography. Thereby unnecessary transportation to a radiology department could be avoided and the observation period to confirm the diagnosis of brain death could be reduced; however, a CCA should be demonstrated in both the anterior and posterior circulation. Furthermore, TCD examinations should always be performed and analyzed by experienced clinicians.

With respect to the two reported false-positive findings, we hypothesize that TCD can predict brain death in all patients when CCA is visualized by TCD on repeated examination within a certain time frame. This way TCD could possibly replace other confirmatory tests such as angiography; therefore, further research to determine the window between two TCD examinations to confirm brain death is needed. We do not expect that with TCD a 100% sensitivity can be achieved. This technique will not be usable in all patients. Ten to 20% of patients lack a patent acoustic bone window. Whether the specificity is 97 or 100% has important implications. The level of uncertainty that can be accepted is an important subject of debate. A single study powered to yield a confidence interval of, at most, 99–100% for an estimated specificity of 100% would require about 700 patients.

In the literature there is no evidence that barbiturate therapy can induce a TCD flow pattern specific for CCA. Studies showed that barbiturate therapy only leads to a moderate decrease of middle cerebral artery blood velocities [37, 38]. Segura et al. described a patient with high-dose barbiturate therapy who was electroencephalographically and clinically brain dead with a normal TCD flow pattern [39].

In conclusion, CCA by TCD in the basilar and both middle cerebral arteries correctly predicted fatal brain damage in all patients; therefore, TCD could be used to determine the appropriate moment for angiography. To accept a test for defining brain death, specificity should be 100%. We do believe that further research is needed to demonstrate that repeated TCD examination is able to produce this level of specificity.

References

- Darby JM, Stein K, Grenvik A, Stuart SA (1989) Approach to management of the heartbeating "brain dead" organ donor. *J Am Med Assoc* 261:2222–2228
- Lopez-Navidad A, Domingo P, Caballero F (1997) Organ shortage: viability of potential organ donors and possible loss depend on health care workers who are responsible for the organ procurement program. *Transplant Proc* 29:3614–3616
- Wijdicks EF (1995) Determining brain death in adults. *Neurology* 45:1003–1011
- Guidelines for the determination of death (1981) Report of the medical consultants on the diagnosis of death to the President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research. *J Am Med Assoc* 246:2184–2186
- Guidelines for the determination of brain death in children (1987) Task Force for the determination of brain death in children. *Neurology* 37:1077–1078
- Practice parameters for determining brain death in adults (summary statement) (1995) The Quality Standards Subcommittee of the American Academy of Neurology. *Neurology* 45:1012–1014
- Silverman D, Saunders MG, Schwab RS, Masland RL (1969) Cerebral death and the electroencephalogram. Report of the ad hoc committee of the American Electroencephalographic Society on EEG Criteria for determination of cerebral death. *J Am Med Assoc* 209:1505–1510
- Guideline three: minimum technical standards for EEG recording in suspected cerebral death (1994) American Electroencephalographic Society. *J Clin Neurophysiol* 11:10–13
- Powner DJ (1976) Drug-associated iso-electric EEGs. A hazard in brain-death certification. *J Am Med Assoc* 236:1123
- Mason RA, Arbeit LA, Giron F (1985) Renal dysfunction after arteriography. *J Am Med Assoc* 253:1001–1004
- Lewis RR, Padayachee TS, Beasley MG, Keen H, Gosling RG (1983) Investigation of brain death with Doppler-shift ultrasound. *J R Soc Med* 76:308–310
- Kirkham FJ, Levin SD, Padayachee TS, Kyme MC, Neville BG, Gosling RG (1987) Transcranial pulsed Doppler ultrasound findings in brain stem death. *J Neurol Neurosurg Psychiatry* 50:1504–1513
- Ropper AH, Kehne SM, Wechsler L (1987) Transcranial Doppler in brain death. *Neurology* 37:1733–1735
- Newell DW, Grady MS, Sirota P, Winn HR (1989) Evaluation of brain death using transcranial Doppler. *Neurosurgery* 24:509–513
- Yoneda S, Nishimoto A, Nukada T, Kuriyama Y, Katsurada K (1974) To-and-fro movement and external escape of carotid arterial blood in brain death cases. A Doppler ultrasonic study. *Stroke* 5:707–713
- Monteiro LM, Bollen CW, Van Huffelen AC, Ackerstaff RG, Jansen NJG, Van Vught AJ (2005) Can transcranial Doppler ultrasonography confirm the diagnosis of brain death? *Intensive Care Med* 31:S1–S174
- Hadani M, Bruk B, Ram Z, Knoller N, Spiegelmann R, Segal E (1999) Application of transcranial Doppler ultrasonography for the diagnosis of brain death. *Intensive Care Med* 25:822–828
- Zurynski Y, Dorsch N, Pearson I, Choong R (1991) Transcranial Doppler ultrasound in brain death: experience in 140 patients. *Neurol Res* 13:248–252
- Petty GW, Mohr JP, Pedley TA, Tatemichi TK, Lennihan L, Duterte DI, Sacco RL (1990) The role of transcranial Doppler in confirming brain death: sensitivity, specificity, and suggestions for performance and interpretation. *Neurology* 40:300–303
- Paolin A, Manuali A, Paola F di, Boccaletto F, Caputo P, Zanata R, Bardin GP, Simini G (1995) Reliability in diagnosis of brain death. *Intensive Care Med* 21:657–662
- Feri M, Ralli L, Felici M, Vanni D, Capria V (1994) Transcranial Doppler and brain death diagnosis. *Crit Care Med* 22:1120–1126
- Dominguez-Roldan JM, Murillo-Cabezas F, Munoz-Sanchez A, Santamaria-Mifsut JL, Villen-Nieto J (1995) Changes in the Doppler waveform of intracranial arteries in patients with brain-death status. *Transplant Proc* 27:2391–2392
- Ducrocq X, Braun M, Debouverie M, Junges C, Hummer M, Vespignani H (1998) Brain death and transcranial Doppler: experience in 130 cases of brain dead patients. *J Neurol Sci* 160:41–46
- Velthoven van V, Calliauw L (1988) Diagnosis of brain death. Transcranial Doppler sonography as an additional method. *Acta Neurochir (Wien)* 95:57–60
- Lamplé Y, Gilad R, Eschel Y, Boaz M, Rapoport A, Sadeh M (2002) Diagnosing brain death using the transcranial Doppler with a transorbital approach. *Arch Neurol* 59:58–60
- Qian SY, Fan XM, Yin HH (1998) Transcranial Doppler assessment of brain death in children. *Singapore Med J* 39:247–250
- Shiogai T, Sato E, Tokitsu M, Hara M, Takeuchi K (1990) Transcranial Doppler monitoring in severe brain damage: relationships between intracranial haemodynamics, brain dysfunction and outcome. *Neurol Res* 12:205–213
- Powers AD, Graeber MC, Smith RR (1989) Transcranial Doppler ultrasonography in the determination of brain death. *Neurosurgery* 24:884–889
- Steinmetz H, Hassler W (1988) Reversible intracranial circulatory arrest in acute subarachnoid haemorrhage. *J Neurol Neurosurg Psychiatry* 51:1355–1356
- Grote E, Hassler W (1988) The critical first minutes after subarachnoid hemorrhage. *Neurosurgery* 22:654–661
- Eng CC, Lam AM, Byrd S, Newell DW (1993) The diagnosis and management of a perianesthetic cerebral aneurysmal rupture aided with transcranial Doppler ultrasonography. *Anesthesiology* 78:191–194
- Vatne K, Nakstad P, Lundar T (1985) Digital subtraction angiography (DSA) in the evaluation of brain death. A comparison of conventional cerebral angiography with intravenous and intraarterial DSA. *Neuroradiology* 27:155–157
- Marrache F, Megarbane B, Pirnay S, Rhaoui A, Thuong M (2004) Difficulties in assessing brain death in a case of benzodiazepine poisoning with persistent cerebral blood flow. *Hum Exp Toxicol* 23:503–505
- Heiskanen O (1964) Cerebral circulatory arrest caused by acute increase of intracranial pressure. A clinical and roentgenological study of 25 cases. *Acta Neurol Scand* 40(Suppl 7):1–57
- Spittler JF, Langenstein H (1991) Diagnosis of brain death: limitations of angiography after osteoclastic trepanation. *Dtsch Med Wochenschr* 116:1828–1831
- Alvarez LA, Lipton RB, Hirschfeld A, Salamon O, Lantos G (1988) Brain death determination by angiography in the setting of a skull defect. *Arch Neurol* 45:225–227

37. de Bray JM, Granry JC, Monrigal JP, Leftheriotis G, Saumet JL (1993) Effects of thiopental on middle cerebral artery blood velocities: a transcranial Doppler study in children. *Childs Nerv Syst* 9:220–223
38. Rath SA, Richter HP (1993) Transcranial Doppler sonography as a reliable diagnostic tool in craniocerebral trauma. *Unfallchirurg* 96:569–575
39. Segura T, Jimenez P, Jerez P, Garcia F, Corcoles V (2002) Prolonged clinical pattern of brain death in patients under barbiturate sedation: usefulness of transcranial Doppler. *Neurologia* 17:219–222