Evaluation of Cerebral Circulatory Arrest

Armando Mario Cacciatori Castro

Development

TCD has become a valuable multimodal neuromonitoring (MNM) tool applicable in ICUs that treat neurocritically ill patients. It allows monitoring of a wide range of neurological pathologies, with the advantages of being a method that can be practiced next to the patient's bed, in a serial manner at low cost. Aaslid et al. published in 1982 the first results regarding the study of cerebral arteries, using a low frequency pulsed Doppler and demonstrating specific patterns thereof as distinctive of CCA [1]. TCD has constituted a significant step forward in the diagnosis of CCA. The normal sonographic appearance of extracerebral intracranial arteries that form the circle of Willis (CoW) is of continuous flow, with average rates that vary in accordance with each other (Fig. 1). The alterations observed on TCD of a patient with brain injury, on its way to CCA, are due to an increase in intracranial pressure (ICP) [2]. In 1998, TCD diagnostic criteria for BD were published by a task force of the World Federation of Neurology (WFN) [3]. CCA develops in four steps according to the WFN:

A. M. C. Castro (✉)
National Institute of Donations and Transplants, Clinic Hospital, Montevideo, Uruguay

W. C. Ziai, C. L. Cornwell (eds.), *Neurovascular Sonography*,
https://doi.org/10.1007/978-3-030-96893-9_8

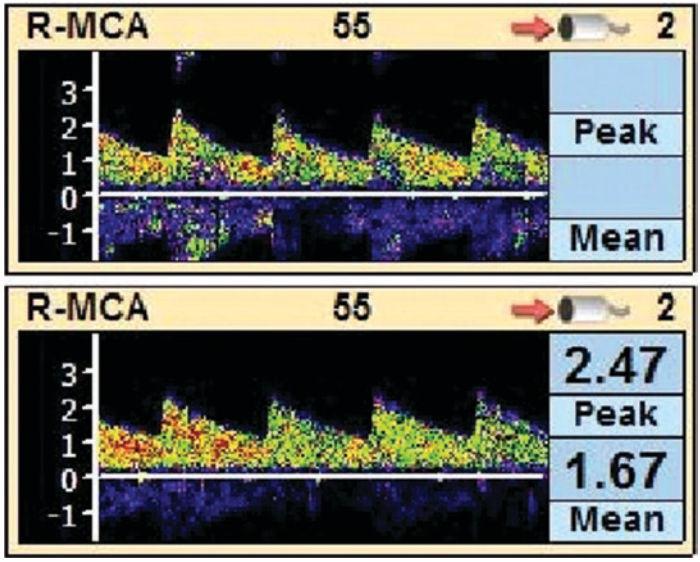

Fig. 1 Normal TCD study of right middle cerebral artery (R- MCA), near the bifurcation of the internal carotid artery (ICA). Male, 24 years old

1. Increasing pulsatility index with decreasing diastole until the cerebral blood flow velocity at the end of diastole equals zero. This occurs when the ICP reaches the diastolic blood pressure (DBP). Extensive TCD monitoring studies in patients with traumatic brain injury (TBI) have provided information regarding the relationship between ICP and TCD. The diastolic flow rate is influenced by the cerebral vascular resistance, mostly determined by the ICP and the vessel diameter. TCD images show that the diastolic flow rate becomes zero when the ICP equals DBP [4]. Since forward flow persists in systole, this stage does not correspond to CCA. This is a warning signal, at which point the TCD diastolic waveforms are comparable with the DBP (instead of the systolic or mean pressure) [5].
2. Biphasic or oscillating flow (Fig. 2). When the ICP is equal to or higher than the systolic blood pressure (SBP), cessation of cerebral perfusion occurs and "positive and reverse" flow

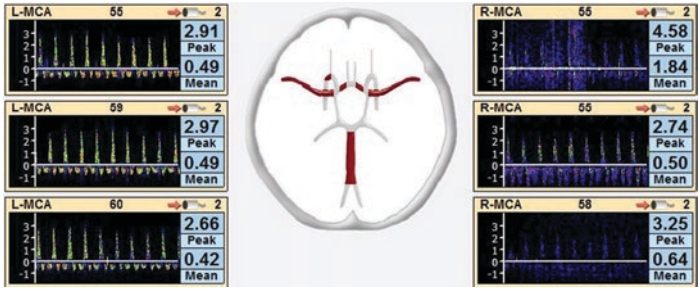

Fig. 2 TCD study that shows reverse/oscillating /reverberant diastolic flow pattern registered in both MCAs. Male, 26 years old. TBI due to firearm injury

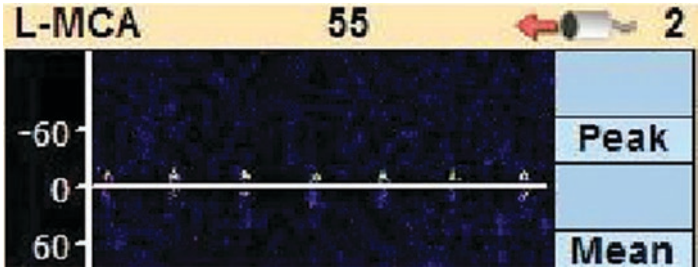

Fig. 3 TCD study that shows systolic spikes pattern in L- MCA. Male, 31 years old. Subarachnoid hemorrhage, DC and evolution into CCA

waveforms are almost alike, with a zero net flow. This correlates with circulatory arrest on the cerebral arteriogram.

3. Systolic spikes (Fig. 3). This pattern is highly distinctive of CCA. With further reduction in blood flow, only a small peak of systolic velocity can be seen. At this stage, we can assume that the slowness of the reverse flow component could be hidden by the filters. Every TCD machine uses high pass filters in order to remove signals that come from vessel wall motion. For CCA diagnosis this filter should be set at its lowest levels (for example, 50 Hz).
4. There is no flow signal. If ICP continues to increase, obstruction of flow occurs more proximally in the CoW and no flow

signal is detected distally. The failure of signal detection may be due to problems in the transmission of sound (bad sonic window); in these cases, it is paramount to examine the extracranial carotid and the vertebral arteries, since they represent important diagnostic criteria [3]. It is a major concern whether the absence of signal corresponds to CCA or to the absence of a sonic window. In order to accept this finding as a criterion for CCA, the TCD should be conducted under the same clinical conditions and by the same expert examiner who previously found flow in the patient [6]. Recall that the TCD probe may penetrate through the skull barrier, in areas where the bone is thinner; these areas of greatest transparency are called windows, and three of them are used: temporal, orbital and suboccipital or transforaminal. Cervical Color Doppler (CCD) sonography may be considered a valid and accurate diagnostic tool for detecting CCA, with a general sensitivity of 78% in comparison to other ancillary tests. Pedicelli et al. have demonstrated in their study that in a subgroup of patients with appropriate bone windows on TCD, the CCD sensitivity was around 80%, showing the same flow patterns as TCD and implying that in most cases CCD may document the same CCA pattern detected by TCD [7].

In certain jurisdictions (ex. the Spanish legislation, Royal Decree 1723/2012) [8], the documentation of these criteria which signify the existence of CCA allows a BD diagnosis to be confirmed without prolonging the observation period. In order to complete the diagnosis, it would be advisable to carry out some instrumental test [8]. However, on account of the description in the literature, of some isolated cases in which cerebral blood flow (CBF) was only temporarily interrupted (generally patients with subarachnoid hemorrhage (SAH) in which the TCD study coincided with a sudden increase in ICP due to rebleeding), some societies (ex. the Spanish Society of Neurosonology) recommend to confirm the CCA through a second study of flow velocities after at least 30 minutes [9]. It is interesting to highlight that a systolic-diastolic separation pattern can show up before biphasic or oscillating flow. This pattern is characterized by the presence of

an anterograde flow systolic wave in the sonogram (also called "systolic peak" by some authors) associated with another flow wave, also anterograde, of short duration during the mesodiastolic (middle of diastole) period. In protodiastole (period in the cardiac cycle between the end of systole and closure of the aortic valve marking the start of diastole) and telediastole (towards the end of ventricular diastole) the flow equals zero [10]. According to Domínguez Roldán et al., it is the pattern with the lowest frequency, given that it has a short time of existence [10]. We believe it is important to note that, when such a pattern is observed, the TCD should be repeated within the following 12 hours. We also emphasize that, when the systolic-diastolic separation pattern is seen, the clinical neurological examination should simultaneously be performed [11]. In a previous study of 9 cases with this TCD pattern, we reported in one case, a 22-year-old male with severe TBI, persistence of cough reflex and spontaneous breathing (Fig. 4) [11]. Based on these concepts, the following questions emerge:

1. Is CCA associated with BD?
2. Does interruption of brain circulation cause neuronal death?

The neuron is a remarkably hypoxia-ischemia-sensitive cell. The global brain ischemic threshold with the production of irreversible lesions is around 5 minutes [12]. Therefore, every such

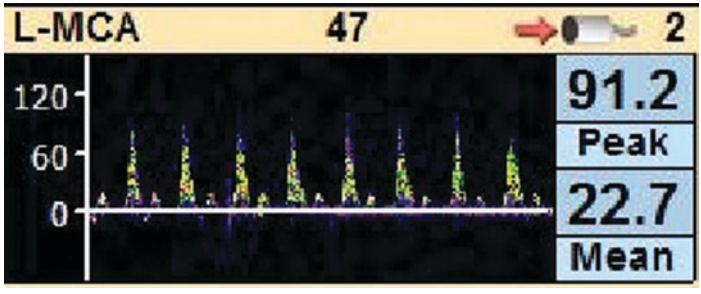

Fig. 4 Systolic-diastolic separation image registered in the left middle cerebral artery (L-MCA). Male, 22 years old. Severe TBI due to traffic accident

situation that modifies the normal brain circulation may provoke changes in neuron function and structure. The neuron is nourished via telediastole (the interval in which neurotransmitters are released), which means that if in that phase a deficit in the circulation occurs and, hence, in the supply of oxygen and glucose, the neuron will suffer injuries of variable severity. The neuron has practically no capacity for anaerobic metabolism. Flow drops below 10 ml/min/100 g cause irreversible neuronal injury [13]. In structural SBI of different types (traumatic, vascular, tumoral, anoxic-ischemic, infectious) it may be an increase of the brain volume (cerebral edema) which provokes intracranial hypertension (ICH), which has a negative impact on cerebral blood flow (CBF), causing decreases to critical levels. The CBF measurement with TCD shows a good correlation with other direct measurements thereof, such as the xenon method [14]. Moreover, the waveform morphology in the diastolic phase may earlier or later indicate signs of ICH, with subsequent mitigation of diastolic cerebral flow [14]. The interplay of pressures inside the cranial cavity affects the equation: cerebral perfusion pressure (CPP) = mean blood pressure (MBP) – ICP, and, in accordance with its values, will be translated into changes in the morphology of the velocity waveform. The attenuation of the waveform's diastolic phase, a sign of ICH with a subsequent decrease in cerebral perfusion, is associated with a decrease in the blood supply to the neuron. When ICP surpasses DBP initially, and then SBP, CBF decreases to zero and there is no forward flow in the arterial circulation. At this time, the TCD will show patterns suggesting CCA. This phenomenon, which is a result of cerebral herniation, does not allow neuronal telediastolic nutrition, leading to its functional and structural damage, culminating, after a short period, in neuronal death. This is the reason why CCA can be correlated to neuronal death and, hence, to BD, although it is worth emphasizing that these are not synchronous phenomena, but can be separated by a short period. There are, however, cases of complete and irrecoverable absence of brain function, even in the presence of continued CBF [15]. An example is reperfusion in patients after cardiac arrest. Under these circumstances, the patient's brain is irreversibly damaged due to global ischemia. Nevertheless, CBF

is reestablished and persists for a while, so the discovery of flow does not rule out BD [16]. If cardiorespiratory function in this patient is artificially maintained, however, dead brain cells cause edema and intracranial hypertension, which finally leads to a decrease in the CPP and the absence of flow. If the ultrasound study is repeated, it will eventually show the CCA pattern [15]. The TCD as ancillary test for BD is highly sensitive and specific, with rates of 89% and 98%, respectively [17]. In order to establish a CCA diagnosis that accompanies BD, the anterior and posterior territories of the Circle of Willis must be insonated, while the CCA findings must be sustained for a period of 30 minutes. This process entails the insonation of the middle cerebral arteries (MCA), on a bilateral basis, through the temporal window and following the blood vessel track as much as possible, as well as the basilar artery (BA), through the suboccipital or transforaminal window. There are reports of infratentorial injuries associated with CCA in which the anterior cerebral circulation may be preserved by means of the internal carotid artery circulation [18]. In one of my latter investigations, two cases of patients with brain stem (BS) infarcts had TCD studies that observed continuous flow in both MCAs and an arrest pattern in the BA. In both cases, the neurological examination confirmed BD. For this reason, the TCD may not be a reliable ancillary method for CCA in infratentorial processes, since it cannot confirm CCA in all the CoW vessels [19]. The clinical neurological examination remains the primary method of BD determination in most situations. The use of TCD as an ancillary test for making a diagnosis of BD has long sparked the interest of researchers. One of the questions posed by the American Academy of Neurology (AAN) Quality Standards Subcommittee is whether there are ancillary tests that accurately identify those patients with BD, giving the greatest importance to the clinical examination. Within the recommendations published in this document, there is insufficient evidence to determine whether the complementary tests accurately confirm the cessation of function of the whole brain (Level U) [20]. In the AAN evidence-based guideline, TCD is useful only if a reliable signal is found, and accepted abnormalities can only include either reverberating flow or small systolic peaks in early systole. Com-

plete absence of flow is not reliable due to possibility of inadequate transtemporal windows for insonation. The other requirement is bilateral insonation and both anterior and posterior circulation insonation [20].

In some practical guides for the determination of BD, TCD is included in the ancillary tests used in adults. Its application would be in those situations that do not allow a complete neurological examination, including the apnea test. This requires expertise of the specialist to interpret the results, and that physicians be aware of the possibility of false positive results [20]. An important fact is that in patients with an aborted apnea test, the time of death is when the ancillary test has been officially interpreted [20]. In a TCD study observing CCA, many patterns that express the same findings may concur, as we have demonstrated in our series of investigative articles [10]. In the first series, CCA patterns most frequently found were: reverse, oscillating, reverberant diastolic flow in 66 studies (75%); systolic spikes in 48 (54.5%), and absence of flow in only 2 cases (2.3%) [11]. In the second, CCA patterns most frequently found were: reverse-oscillating diastolic flow (77%), followed by systolic spikes (55%) (Figs. 3 and 4). This finding reflects a chronological progress in the patterns of CCA, linked to an increase of ICP. The same study noted the frequency distribution of the insonated arteries, corresponding to the insonation of the MCAs and BA in 30% of studies [21]. Also important to consider when using TCD to asses CCA is the chance of false negative and false positive results. False negatives correspond to individuals with clinical BD and continuous CBF. These can appear in situations in which the cranial cavity is not closed: decompressive craniectomy (DC), ventriculostomy, open fractures, open fontanelles (in the case of children). Decompressive craniectomy (DC) is an increasingly popular therapeutic alternative for managing ICH and cerebral edema in SBI. The procedure results in a loss of cranial impenetrability with the aim of alleviating ICP. When DC is performed, CBF is maintained [22]. TCD

performed after DC (compared to pre-operatively) shows a substantial increase in CBFVs, not only on the side of the procedure, but also in the contralateral hemisphere [23]. It may be necessary to repeat the study [22].

A false positive corresponds to individuals with a CCA pattern and negative apnea test or other findings for the BD diagnosis. The occurrence of CCA and BD may not be synchronous and the false positive can appear during a short period of minimum brainstem activity after CCA (persistence of a BS reflex) [22]. In the same way as for making a clinical diagnosis of BD, a series of clinical conditions or previous requirements must be met, for the performance of TCD in diagnosing CCA. The patient's hemodynamic and blood gas status must be stable during the course of the study, with a MAP ≥70 mmHg (SBP and DBP not <90/50 mmHg) and a $PaCO_2$ between 35 and 45 mmHg [9]. Furthermore, it is recommended that before performing a TCD for evaluation of CCA, the neurological examination be performed. Finally, there are several limitations of TCD as pertains to confirming BD:

- TCD has lower sensitivity in comparison with the clinical examination.
- Sensitivity of TCD is associated with the mechanism of neurological injury.
- The impossibility of preventing false-positive results [17].

With reference to the neurological injury mechanism, there are situations in which, due to supratentorial unilateral injuries, a large vessel can show a CCA pattern, without this occurring in the contralateral vessel [24]. This was reported in a 20-year-old male patient, who suffered a structural SBI due to a penetrating cranial wound, involving injury to the M1 segment of the MCA. This resulted in deformation of the vascular architecture of the CoW, preventing a complete sonographic examination in order to diagnose CCA. BD was confirmed by clinical examination (Fig. 5).

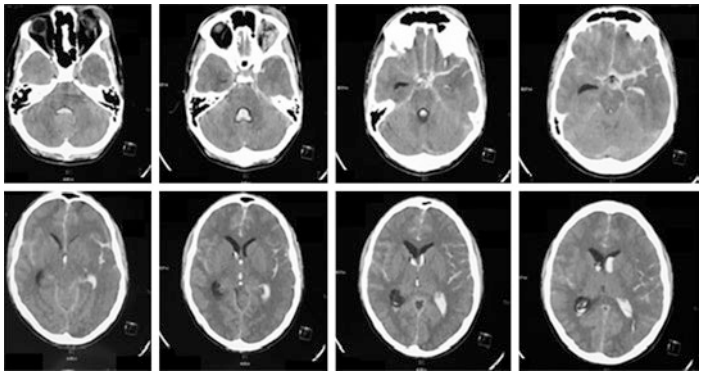

Fig. 5 Tomographic study that reveals penetrating head injury with wound in M1 segment of the L- MCA. Male, 20 years old. BD diagnosed by clinical examination

Conclusions

Cerebral circulatory arrest (CCA) derives from cerebral tamponade or herniation, as the final stage of SBI and which in quasi-real time accompanies BD. There exist specific patterns thereof that can be identified by TCD which can be performed serially and economically at the bedside. It has a sensitivity of 89% and a specificity of 98% [15], taking into account situations that may cause both false negatives and positives.

Personal Perspectives

In many jurisdictions, TCD for evaluation of CCA is an accepted ancillary test to accompany the diagnosis of BD, notably in situations in which the clinical preconditions for a complete neurological examination for BD are not met. The addition of TCD to the BD diagnostic process is considered a major milestone in the procurement of organs, since it may enable the recruitment of individuals with BD who may be otherwise lost to the organ donation option.

References

1. Hadani M, Bruk B, Ram Z, Knoller N, Spiegelmann R, Segal E. Application of transcraneal Doppler ultrasonography for the diagnosis of brain death. Intensive Care Med. 1999;25:822–8.
2. Perez Calatayud AA, Carrillo Esper R, Díaz Carrillo A, Zepeda Mendoza AD. Doppler transcraneal y cese de la circulación cerebral en Muerte encefálica. J Mex Assoc Crit Med Intensive Care. 2016;XXX(1):59–60.
3. Ducrocq X, Hassler W, Moritake K, Newell DW, von Reutern GM, Shiogay T, et al. Consensus opinion on diagnosis of cerebral circulatory arrest using Doppler-sonography. Task Force Group on cerebral death of the Neurosonology Research Group of the World Federation of Neurology. J Neurol Sci. 1998;159:145–50.
4. Hassler WI, Steinmetz H, Gawlowski J. Transcranial Doppler ultrasonography in raised intracranial pressure and in intracranial circulatory arrest. J Neurosurg. 1988;68:745–51.
5. Sidi A, Mahla M. Noninvasive monitoring of cerebral perfusion by transcranial Doppler during fulminant hepatic failure and liver transplantation. Anesth Analg. 1995;80:194–200.
6. Escudero D, Otero J, Quindós B, Viña L. Doppler transcraneal en el diagnóstico de la muerte encefálica. ¿Es útil o retrasa el diagnóstico? Intensive Med. 2015;39(4):244–50. https://doi.org/10.1016/j.medin.2014.11.005.
7. Pedicelli A, Bartocci M, Lozupone E, D'Argento F, Alexandre A, Garignano G, et al. The role of cervical color Doppler ultrasound in the diagnosis of brain death. Neuroradiology. 2019;61:137–45. https://doi.org/10.1007/s00234-018-2111-4.
8. Royal Decree 1723/2012, 28th of December, by which the activities of obtaining, clinical use and territorial coordination of human organs destined for transplantation are regulated and quality and safety requirements are established. Health, Social Services and Equality Ministry. "BOE" number 313, 29th of December of 2012. Reference: BOE-A-2012-15715.
9. Calleja S, Tembl JL, Segura T. Recomendaciones sobre el uso del Doppler transcraneal para determinar la existencia de paro circulatorio cerebral como apoyo diagnóstico de la muerte encefálica. Neurology. 2007;22(7):441–7.
10. Dominguez Roldán JM, Barrera Chacón JM, Rivera Fernández MV, García Alfaro C. Sonografía Doppler transcraneal: su utilidad en el diagnóstico de las parada circulatoria cerebral que acompaña a la muerte encefálica. Intensive Med. 2000;24:151–60.
11. Cacciatori A, Godino M, Mizraji R. Systodiastolic separation expresses circulatory cerebral arrest? Transplant Proc. 2018;50:412–5.
12. Roig C. Chap. 19: Muerte Encefálica causada por anoxia encefálica. In: López-Navidad A, Kulisovsky J, Caballero F, editors. El donante de órganos y tejidos. Evaluación y manejo. Barcelona: Springer –Verlag Ibérica; 1997. p. 202–9.

13. Jimenez OC, Guerrero Peral AL. Chap. 3: Fisiología de la circulación cerebral. In: Castillo Sánchez J, Alvarez Sabín J, Martí-Vilalta JL, Martínez Vila E, et al., editors. Manual de enfermedades vasculares cerebrales. Barcelona: J. R. Prous, S.A; 1995. p. 20–5.
14. Raghavan M, Marik P. Therapy of intracranial hypertension in patients with fulminant hepatic failure. Neurocrit Care. 2006;04:179–89.
15. Consensus Group on Transcranial Doppler in the Diagnosis of Brain Death. Latin American Consensus on the use of transcranial Doppler in the diagnosis of brain death. Braz J Intensive Ther. 2014;26(3):240–52.
16. Flowers WM Jr, Patel BR. Persistence of cerebral blood flow after brain death. South Med J. 2000;93(4):364–70.
17. Chang JJ, Tsivgoulis G, Katsanos AH, Malkoff MD, Alexandrov AV. Diagnostic accuracy of transcraneal Doppler for brain death confirmation: systematic review and meta-analysis. AJNR Am J Neuroradiol. 2016;37:408–14. www.ajnr.org.
18. Escudero D. Diagnóstico de muerte encefálica. Intensive Med. 2009;33(4):185–95.
19. Cacciatori A, Godino M, Mizraji R, Domínguez Roldán JM. Diagnosis of brain death in infratentorial neurological pathology how to approach it in the Intensive Care Unit? Case reports. Transplant Proc. 2020;52:1042–8.
20. Wijdicks Eelco FM, Varelas PN, Gronseth GS, Greer DM. Evidence – based guideline update: determining brain death in adults. Report of the Quality Standards Subcommittee of the American Academy of Neurology. Neurology. 2010;74:1911–8.
21. Cacciatori A, Godino M, Mizraji R. Utility of transcranial Doppler in the coordination of transplants. 10 years of experience. Transplant Proc. 2018;50:408–11.
22. Correa H, Puppo C, Biestro A, Mizraji R, Cancela M, Grille P, et al. Actualización de Consenso de Muerte Encefálica en adultos. 5th edn. National Institute of Donations and Transplants of Cells, Tissues and Organs of the Republic of Uruguay. Ministry of Public Health – School of Medicine, University of the Republic; 2016. p. 1–18.
23. Bon-Seng-Shu E, Jacobsen Teixeira M, Hirsch R, Ferreira de Andrade A, Marino R Jr. Transcranial Doppler sonography in two patients who underwent decompressive craniectomy for traumatic brain swelling: report of two cases. Neuropsychiatric Arch. 2004;62:715–21.
24. Paolin A, Manuali A, Di Paola F, et al. Reliability in diagnosis of brain death. Intensive Care Med. 1995;21:657–62. CrossRef Medline.