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Commentary and concepts

All human death is brain death: The legacy of the Harvard criteria

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Abstract

Fifty years ago, the ad hoc committee of the Harvard medical school provided the influential first guidance on confirming death using neurological criteria (DNC). Now 70% of countries have a legal or professional framework enabling DNC. While there is virtually universal acceptance of a three staged approach to the clinical diagnosis of brain death, international variation in practice continues. The need to develop international consensus and standards is essential in the future if public and professional confidence in the diagnosis is to be maintained and increased. The legacy of the Harvard ad hoc committee has been a continuing development of our concepts of human death. There is a growing acceptance that ultimately all human death is brain based whether diagnosed using neurological criteria or using circulatory criteria after cardiac arrest.

Keywords: Brain death, Brainstem death, Intensive care, Ethics

Background

In the past death was readily confirmed and recognised clinically as the simultaneous onset of continuous apnoea, pulselessness, unconsciousness and unresponsiveness. This represents the loss of cardiovascular, respiratory and brain functions. It was also understood that the loss of any one of these three vital functions was inevitably followed by loss of the other two. The ease of feeling for a pulse and the introduction of the stethoscope into clinical practice meant that identifying the irreversible loss of the circulation became the most common way to diagnose death, and remains so today. It also led to the common belief that a beating heart is essential to life. However, the advent of advanced cardiopulmonary resuscitation (CPR), extracorporeal circulatory support and mechanical ventilation changed all this. It became clear that it was not a beating heart *per se* that sustained life, but the presence of a circulation delivering oxygenated blood across capillary beds (i.e. perfusion) to the organs and tissues. After cardiac arrest the spontaneous circulation could often be restored and respiration could be supported, often, but not always, preventing the irreversible loss of brain function.

When the primary vital function lost is brain function, rather than cardiac arrest, it became apparent that in some circumstances, despite cardiovascular and respiratory functions being restored or supported, brain function would not resume and was irreversibly lost. This scenario was first described by Mollaret and Goulon in 1959 as "le coma depassé" (a state beyond coma),[1] characterised by unresponsive apnoeic coma, poikilothernia, loss of all brain stem reflexes and loss of the electroencephalogram (EEG), a state from which no patient ever regained consciousness or started to breathe again. Pathological examination of these patients showed that this state of irreversible coma and apnoea was associated with autolysis of the brainstem.[2]

Developing the concept and criteria for brain death

The futility of continuing to artificially support circulatory and respiratory functions while the third vital function, brain function, was irreversibly lost became increasingly recognised in ICUs around the world. The Harvard ad hoc committee on brain death, led by an anaesthetist–ethicist, took the lead by addressing this ethical issue

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and publishing its landmark paper on the Harvard criteria for brain death in 1968, calling for death to be confirmed using neurological criteria as well as the established cardiovascular criteria.[3] At the same time other organizations including the World Health Organization, the English and Sottish Health Ministries, and the World Medical Association also held meetings attempting to agree on the concept of brain death, but these were primarily concerned with donation, procurement and transplantation of organs. The ad hoc Harvard committee was different and unique in concentrating on the concept of brain death and the specific criteria to confirm it, rather than organ transplantation. The report was influential and led to neurological criteria for the determination of death being legally adopted in all states in the United States of America. Following further committee reports the criteria eventually settled there with the American Academy of Neurology guidelines for determination of brain death, last updated in 2019.[4] Various adaptations of the Harvard criteria were soon introduced in many countries around the world.

Brain death today in the context of cardiopulmonary arrest

Today, fifty years on from the publication of the ad hoc committee's report the concept of brain death is generally well accepted. Brain death is diagnosed following catastrophic brain injuries such as trauma, intracranial haemorrhage or hypoxic brain injury while the circulation is present, and ventilation is provided mechanically. Approximately 70% of all countries in the world currently have a legal provision or professional guidance supporting the diagnosis of death using neurological criteria, predominantly those countries with transplantation programs.[5] This adoption of criteria to diagnose death using neurological criteria has also been accompanied by an increasing acceptance of the concept that all human death is ultimately death of the brain.[6,7] This principle allows other concepts to be developed: while the determination of death using neurological criteria retrospectively confirms irreversible loss of brain functions, the onset of cardiorespiratory arrest is merely a prospective predictor that irreversible loss of brain functions is inevitable unless the circulation and cerebral perfusion are restored. Brain functions and activities are lost quickly after loss of the circulation: consciousness is lost within 21 s; the EEG is isoelectric within 30 s, and visual evoked potentials are lost within 35 s of loss of the circulation.[8] Since these functions and activities cannot resume without restoration of the circulation and perfusion, brain death can be diagnosed confidently once the possibility of spontaneous return of the circulation (autoresuscitation) has passed,[9] as long as no interventions that can restore cerebral perfusion are undertaken beyond this point. In other words, loss of the circulation inevitably leads to cessation of brain functions, initially permanently (autoresuscitations not possible) and then irreversibly (cerebral perfusion cannot be restored by any intervention). Death in this context can therefore be defined as the permanent cessation of brain functions, determined by the permanent cessation of brain circulation and perfusion,[10] effectively bringing the confirmation of brain death in line with the world wide everyday clinical practice of confirming death using circulatory criteria.

These concepts have clear applications in cardiopulmonary resuscitation. While restarting the heart is rightly the primary focus of this intervention, it is restoration of the circulation with subsequent intact brain function that is the ultimate aim. Increasingly, in the short-term, technologies such as extracorporeal-assisted CPR are being used to provide a circulation to the brain and other organs while attempts to restart the heart continue. Clearly the only long-term chance of survival is currently restarting the heart and restoration of spontaneous circulation (ROSC). However, the success of CPR should not be judged solely on restarting the heart and ROSC, but on ROSC with preservation of brain function. Current and future research to identify interventions that increase survival with minimal cognitive or physical sequalae after cardiac arrest must be the way forward.

Current challenges in brain death

The recent unhelpful and unnecessary debate about differences between the "whole brain" and "brainstem" formulations of brain death is largely resolved since it has become increasingly clear that, while the two formulations may be semantically different, they are clinically synonymous. Now the debate has moved away from these unhelpful anatomically based definitions for brain death and more towards avoiding any controversy in the clinical diagnosis of brain death in patients with an "isolated" brainstem lesion or disruption of the posterior cerebral circulation.[11] The clinical determination of brain death now adopts a standardised three-stepped approach around the world. This firstly identifies an established cause for the condition, secondly excludes confounders and reversible causes, and thirdly confirms that all brainstem reflexes, including the capacity to breathe are absent.[12] Hypoxic brain injury following increasingly successful CPR and ROSC after cardiac arrest is recognised as one of the more common aetiologies of brain death.

Challenges will continue to arise and will require addressing in the future. The need to develop standardised guidance to diagnose brain death in unusual situations such as in neonates whose brain can tolerate lower rates of perfusion that older infants and adults,[13] or in patients receiving extracorporeal membrane oxygenation after unsuccessful CPR[14] continues, as does the need for continued engagement of the public, community and religious leaders to increase the acceptability of brain death, particularly important given the intense interest generated by recent cases.[15] Perhaps the main challenge is to address the significant regional and international variation in brain death policies that has the potential to undermine the confidence of the public and the profession to accept the diagnosis of brain death.[5,16] Calls for international consensus on this issue[17] and attempts to achieve this by standardising practice and reducing variability[18] have already been made previously. How to achieve international consensus on such a topic that incorporates legal, ritualistic, cultural, spiritual, religious and professional issues, as well as scientific ones, remains unclear. Much of the variability relates to the observation time required before testing, particularly after hypoxic brain injury, conduct of the apnoea test, the number of times the tests are undertaken, excluding the continuing effects of sedatives, the expertise of the physician undertaking the tests and the requirement for ancillary tests.[5] While the primary importance of the clinical bedside examination remains undisputed,[19] the requirement for ancillary tests continues to be debated.[20] In some jurisdictions the use of ancillary tests is optional, in others they are only required when it is not possible to complete the clinical examination, and in others they are mandatory.[16] Ancillary tests confirming the presence or absence of cerebral blood flow are being increasingly used. However, it is recognised that in 15% of patients meeting the clinical criteria for brain death, CT angiography will show some persistent intracranial blood flow,[21] but CT perfusion studies show that cerebral perfusion is lost.[22]

The place of these technologies remains to be fully assessed but they suggest that while there can be no cerebral perfusion without flow, there can be flow without cerebral perfusion.

Efforts to develop consistency in the determination of brain death continue to be made with an initiative involving the co-operation and participation of the world's main medical societies that represent those clinicians who undertake brain death determination. In the meantime, it should be possible for individual countries that do not currently have professional or legal guidance for the determination of death using neurological criteria, to work within their own legal, cultural, ethical and professional boundaries and develop national guidelines by achieving consensus among all the relevant stakeholders in that country.

Conclusion

Fifty years after publication of the Harvard criteria clinical assessment continues to be the basis for the diagnosis of brain death, and the primary role of ancillary testing remains to serve as a surrogate means of assessment when components of clinical brain death evaluation cannot be ascertained.[4] The influence and long-lasting legacy of the publication of the Harvard criteria is undeniable. It has paved the way for, and shaped the introduction of, brain death practices and legislation worldwide. Furthermore, it has challenged concepts of what constitutes human death, a debate that continues to this day; it decreased the burden of ongoing futile treatment; and saved many lives by establishing an ethical basis for the practice of donation after brain death that observes the dead donor rule.

Conflicts of interest

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Contribution

The manuscript was conceived and written by the author.

Ethics approval

Consent for publication and availability of data and materials not applicable.

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