Case report/narrative review.

Resuscitation Medicine and death definition

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ABSTRACT

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Death is the reason for the existence of resuscitation. The Western definition of death has evolved continuously over the last three centuries. Today, the world recognizes two types of biological death: cardiac or "real" death (I,e. definitive cease of cardiac , respiratory and cerebral function) and encephalic death. The latter (brain death) has been accepted worldwide medically and legally as the biological state of death of the organism. However, the conception and the determination of brain death continue to raise scientific, legal, philosophical, and religious controversies. As the medicine progress, the advance of the resuscitation medicine (in intensive care units or not) profoundly modified the durations of agony and the survival times, and perhaps also the essential meaning of death. Thus, is it time for a new definition of death? Should it continue to evolve? Is determination of the moment of death (and thus determination of the end of resuscitation efforts or palliative care) sufficient? This chapter will try to synthesise the available literature about the subject.

Keywords: Death, Brain death, Resuscitation

DEATH DEFINITIONS - HISTORY

According to Cambridge dictionary resuscitation is "the act of bringing someone or something back to life or waking them" or in medical terms the process of reviving someone from

unconsciousness or apparent death[1]. Thus, the begging point of resuscitation is the definition of life and death. However, the latter seems to continue to evolve along with medical progress (Table 1)[2,3].

Table 1. Evolution of death definitions till the emergence of the concept of the brain death[3].

PERIOD/YEAR	DEFINITION
17th–18th c.	Notification of death "by evidence", on the initiative of the pastor (excepted for forensic cases where this initiative is left to a doctor or a surgeon who will make the first physical examination). Signs of death are the sensation of the last breath, the end of agony, immobility, the absence of reaction to stimuli, apnea (tested by the absence of condensation on a mirror placed close to the mouth), pallor, lower body temperature. Practitioners, in case of doubtful death (drowning, plague, childbirth) can also use 2 other techniques: feather on a nostril, glass filled with water on the stomach.
1745	Appearance of the concept of "apparent death" opposing the "real and constant death" in France. Bruhier isolates the "signs of death". Only sure sign of death: abdominal green patch.
1755	Antoine Louis, France: the unmistakable signs of death are cadaverous rigidity and the flaccidity of the eye.
End of 18th c.	Thiéry's "intermediate death"concept (transitional but irreversible state where, after the last sigh, death takes possession of the whole body.)
19th c.	Scientific craze for finding "indubitable signs of death". Most of the time, it is recommended to wait until the signs of putrefaction occur (abdominal green spot), leaving the body to be stored in mortuary deposits. Others propose the identification of: Hippocratic facies, absence of pulse, rigidity, drop in temperature, lack of response to stimulation (loud cry in the ear, bottle of ammonia placed on a nostril, sting, burn, pinching on the soles of the feet, at the end of the fingers or the nipples, etc.).
1848	Bouchut sign introduction: absence of perception of the cardiac pulsations to the auscultation of the heart by the stethoscope of Laennec.
2nd half of 19th c.	Use of tools to objectify the signs of death (thermometer, reagents confirming the acidity of the body, lancet showing the absence of bleeding at the cut of the superficial veins/arteries, lighter to create non-bleeding blisters, etc.).
1948	One French circular retains as the criterion of death the cessation of any cardiac activity.
1959	Mollaret and Goulon create the notion of "out-of-date coma" /" coma dépassé "(state where the relationship life is abolished, and the vegetative life condemned if it is not supplemented)
1968	Harvard Committee proposes the concept of "brain-dead state" (absence of cerebral vasculature objectified by 2 flat and 30-minute EEGs at least 4 hours apart in the absence of sedation and sedation, hypothermia, or absence of intra-cranial enhancement in arteriography).

Thus, we have passed from the "absence of life signs" and, later, cardiac death to brain death; whose criteria have also continuously evolved[4]. Today, we are moving more towards whole-brain death concept. Steps in death determination include both clinical examination of brain stem activity (oculocephalic, oculovestibular and corneal reflexes; facial muscle activity to

pain; pharyngeal and tracheal reflexes, apnoea test) and use of ancillary tests more or less accurate, such as Four vessel cerebral angiography, electroencephalogram (EEG) or somatosensory evoked potentials (SSEP), transcranial doppler (TCD), magnetic resonance (MRI) or computer tomography (CT) cerebral imaging[5].

Despite the huge progress in medical knowledge, technology, and research; the definition of death is far from definite. The latter creates controversies in medical practice that affect social, legal, financial, cultural, and religious aspects of everyday life globally. These inconsistencies in concept, criteria, practice, and documentation of brain death/death by neurologic criteria (BD/DNC) both internationally and within countries. International efforts like the World Brain Death Project try to provide global recommendation both for adults and children[6]; yet some key concerns only get addressed tangentially.

THE CONTROVERSIES AND THE GAPS

Death is the end-result state of a process (dying) that varies both in intensity and duration; resuscitation aims at preventing the occurring of that state. It intervenes within dying process and whenever successful, it either stops further progression or even reverses the process to restore normal organ/system functions. Since death is a time-dependent term, difficulties can arise either in its formal declaration (the point of time of its occurring), in its operational definition (which include the biomedical criteria that describe the death state) and/or its determination (i.e. the processes and tests followed to diagnose it according to its operational definition)[7].

Autoresuscitation describes the return of spontaneous circulation after termination of resuscitation (TOR) following cardiac arrest. The phenomenon is underestimated and not fully explained. In a recent literature review covering publication between 1982-2018, there were identified 65 patients with ROSC after TOR, with 28% of them making to full recovery[8]. The phenomenon has been reported both in adult and paediatric patients[9]. The longest time of occurrence of autoresuscitation was in a patient with COVID-19 20 minutes after TOR[10]. On another report, a patient was declared dead after cardiac death, redeclared alive during organ donation procedure (which was stopped) and redeclared dead after 20 minutes[11]. Despite the recommendation that all authors of such reports suggest, it is more than obvious that more research is needed to clarify the frequency and predisposing factors associated with that phenomenon. And more caution in daily practice, till the results of that research are transformed into guidelines.

Restoration of brain circulation and cellular function hours post-mortem in recent years has provoked an intense debate about the definitions of life and death. In a remarkable study, scientists have managed to restore circulation and cellular activities and functions in brain

pigs that had been decapitated 4 hours before, via BrainEx®, a formulated unique solution and circulated it through the isolated brains using a network of pumps and filters[12]. Even though no electroencephalographic activity was recorded, restoration of brain circulation and cellular function in brain tissue that had not received any oxygen, glucose (or other nutrients) for a period of 6 hours, opened a whole new perspective. The claim of the leading researcher that "This is not a living brain, but it is a cellularly active brain" and the latter noted facts about the study conduction (all phenomena were observed at different degrees of hypothermia; the physiological and biochemical milieu of the experimental preparation is radically different than the clinical setting of hypoxic-ischemic brain injury; and the study was confounded by uncontrolled traumatic brain injury and lifelong stress in all the animals) are only adding questions for the future[13] . The possibility of evaluating this method in advanced models of engineering biomaterials in creating increasingly biomimetic neural microenvironments, is only a small example of those questions[14].

BrainEx® is not the only medical technology that creates an ethical debate. On the contrary, every new technological introduction increases the complexity of possible ethical dilemmas regarding their use. A more interesting fact: the more advanced technology is applied in the clinical setting; the more treatment limitation guidelines are created[15].

Extracorporeal life support (ECLS) systems, especially ECRP (extracorporeal cardiorespiratory resuscitation) has been deployed as advanced resuscitation techniques for refractory cardiac arrest. Yet, there is no uniform agreement on when a cardiac arrest is refractory and thus ECRP should be applied, or death has occurred[16]. But, even after the ECLS application, the problem remains. ECRP is a bridge towards definite therapy and the time for discontinuation of its application if ROSC has not been achieved remain unresolved[17].

Difficulties are also related to the criteria used for death determination. Clinical criteria and conditions available may not be applicable to neonatal patients (term 36 weeks, age 30 days). Further research is required in the neonatal population. Furthermore, clinical examination is unreliable to assess the presence of latent and covert conscious awareness in this neurological condition, when cognition may be dissociated from behavioral motor responses, a condition like that found in patients with severe brain injuries. In addition, motor reflexes cannot be used to establish the presence or absence of higher integrative functions of the telencephalon, diencephalon, and limbic system. Apnea test, which aims to detect irreversible injury to the respiratory centers in the medulla, is inconsistent with clinical findings showing that patients who have been clinically diagnosed as brain dead continued to have both spontaneous movements and motor responses to stimuli.

Additionally, clinical determination of brain death ignores the most important factor for reversibility, which is the time from the initial brain injury to the potential recovery of conscious awareness. Given that neuroplasticity allows the restoration/regeneration of neural connectivity in severely injured human brain, the preservation of neuronal substrates in brain dead patients could play a role in the subsequent reemergence of consciousness. These facts support the fact that contrary to the claims of the validity of the criteria for determining brain death, modern neuroscientific findings show that some of its basic hypotheses are proven to be wrong[18].

Electroencephalography (EEG) is a widely accepted ancillary test, yet practicians should be aware of its limitations and possible artifacts, Moreover, research about electrical brainstem function after cardiac arrest remain limited. Rarely, patient may have transient electrocerebral activity following the last recorded QRS (less than 5 min) and estimated cessation of cerebral blood flow. Slowing EEG activity has been also recorded in cases of ictal asystole-where it is suggested that this slowing may act therapeutically[19]. Still, we are far for finding the electrocerebral signature of cardiac death[20]. Biomarkers and methods used for determination of time since death (such as tympanic temperature or tau-protein) could also be used in the interval from cessation of circulation to death claim[21]. Findings from studies of time-dependent changes in gene expression in post-mortem brain samples could also be useful[22].

Consciousness loss moment and its evaluation is also critical for death determination; yet it is not fully researched. There have been reports both for maintenance during witnessed asystole before the onset of CPR [23] and reports for CRP induced consciousness[24].

Finally, one should note the controversies based on the philosophical, medical, legal, religious and in general culturally different behaviors and values that exist around the world.

CONCLUSION-PERSPECTIVES

Medicine is aiming at restoring health and prolonging life. Resuscitation resuscitation aims at preventing imminent death. Despite the unprecedented progress in medical knowledge and technological advance; we are still in search for the fundamental definition of death. Maybe, it is time to think for a “human” death definition and not for a “scientific”, “medical”, “social”, “cultural” or “organ-based” definition. This is a difficult medicine-related but, certainly, not only medical task.

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