



The Lazarus phenomenon – coming back from the underworld: current knowledge and novel perspectives

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ABSTRACT

Death is a process, rather than a time specific event. Lazarus phenomenon/syndrome is a rare occurrence of restoration of spontaneous circulation after a patient has been declared dead. It is also known as autoresuscitation. We sought to review the relevant literature to investigate the features, frequency, pathophysiology and clinical implications of the syndrome. It seems that autoresuscitation usually takes place in the first few minutes after termination of resuscitation efforts. Approximately 82% of reported cases occur within 10 min of CPR discontinuation. There are a few outliers of Lazarus phenomenon appearing as late as 20 to 50 minutes. The prognosis of the syndrome is dismal, as the majority die before hospital discharge. However, studies report full recovery in 14-28% of patients. The exact cause of Lazarus phenomenon is not fully understood. Several theories have been proposed (e.g. hyperventilation/air trapping, delayed drug action, myocardial stunning), but it is likely that the mechanism is multifactorial. The resumption of cardiac activity after withdrawal of life-sustaining measures has been studied. All the cases occurred within 4 minutes and 20 seconds after a period of pulselessness. We would like to emphasize that autoresuscitation is possible in any cardiac arrest victim, regardless of whether CPR was applied. Current evidence suggests that a “no touch” period of no less than 5 minutes is sufficient for controlled donation after circulatory death (DCD). However, in the case of uncontrolled DCD (organ donation after unsuccessful CPR), a longer “no touch” period may be needed to exclude Lazarus phenomenon.

KEY WORDS: Cardiac arrest, death, resuscitation, return of spontaneous circulation, Lazarus phenomenon.

INTRODUCTION

Cardiac arrest (CA) is a leading cause of death worldwide. The term CPR relates to the specific technical skills of cardiopulmonary resuscitation, which is the mainstay of CA treatment. The initial rhythm of arrest is one of the most important prognostic factors for short- and long-term survival. There is substantial international variation in survival rates and neurological outcomes [1, 2]. The International Liaison Committee on Resuscitation reports that survival to hospital discharge or 30-day survival ranges from 3.4% to 15.6%. Some areas report even lower values (e.g. China 2.8%) [3].

Although CPR is typically initiated with explicit instructions in the absence of breathing and pulse, the timing of termination of resuscitation (TOR) is much less clear [4]. TOR is largely an ethical decision and disagreements regarding TOR are frequent during resuscitation. Therefore, it should be a team decision. The European Resuscitation Council proposed guidance to aid TOR decision, highlighting the importance of a holistic approach considering patient values and preferences and the combined picture of dismal prognostic factors including duration of CPR, the absence of reversible causes and the absence of response to advanced life support (ALS) [5]. After cessation of CPR there is generally a requirement for 2-5 minutes of sustained absence of signs of life before a person is declared dead. Although circulatory death determination practices may vary slightly between countries and hospitals, declaration of death is universally a permanent, one-time and non-reversible act [6].

Lazarus phenomenon/syndrome is a rare occurrence of restoration of spontaneous circulation (ROSC) after a patient has been declared dead (Figure 1). It is also known as autoresuscitation. In the New Testament (second part of Christian Bible), Jesus raised from the dead Lazarus of Bethany four days after his death, hence the name of the syndrome. In the past there was more uncertainty regarding the diagnosis/confirmation of death. Special coffins were even constructed which enabled communication of the deceased with those alive, out of fear that one may “wake up” after being buried. In the era of modern medicine, the knowledge on cardiac arrest and its causes has evolved and death confirmation is more straightforward and accurate [7]. Although the diagnosis is still clinical i.e. loss of consciousness, plus absence of breathing, plus absence of central pulse (e.g. carotid pulse), we commonly utilize ancillary diagnostic tests such as the electrocardiogram (ECG), echocardiography and the arterial waveform (if an arterial line is in place). Therefore, the possibility of an erroneous declaration of death is nullified.

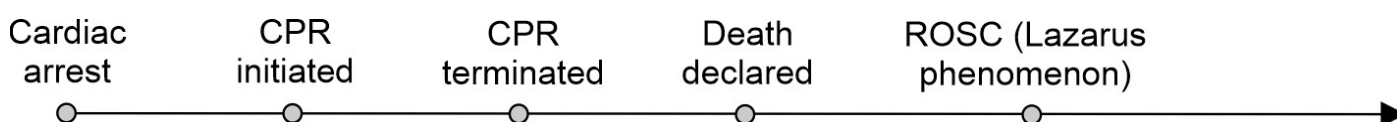


Figure 1. Timeline of Lazarus phenomenon.

Lazarus phenomenon does not refer to cases of death misdiagnosis, but it is defined as a clinical entity of resumption of life functions in patients with failed CPR who were thought to be or were declared dead. We sought to review the relevant literature to investigate the features, frequency, pathophysiology and clinical implications of the syndrome.

LITERATURE REVIEW

HISTORICAL ASPECTS – WHAT DO WE KNOW?

The first case of autoresuscitation after CPR discontinuation was described in 1982 by Linko et al. [8]. We searched the literature from 1982 and onwards using the keywords: “Lazarus phenomenon”, “Lazarus syndrome”, “autoresuscitation”, “auto-resuscitation” and combinations of them. PubMed and Scopus databases were screened and reviewed independently by two different authors (GK and FF). The search strategy was designed to capture case reports, observational studies and review articles in the English language. Selected articles were chosen based on their importance and relevance to the topic, and their key findings were critically assessed to provide a comprehensive review of current knowledge.

Bray [9] in 1993 first named “this delayed return of native circulation” as the “Lazarus Phenomenon”. It is believed that autoresuscitation or auto-ROSC is a phenomenon of the heart, which restarts after termination of CPR. Thus, CPR has been attempted but at some point, has been deemed unsuccessful and abandoned [10, 11]. The actual incidence and outcomes of this phenomenon have yet to be determined. It is estimated to occur in 0-3% of patients following TOR [12]. However, this is confronted by certain surveys showing that 37-50% of intensivists and emergency physicians have encountered it in clinical practice. The condition might be grossly under-reported by healthcare professionals due to fear of litigation and guilt of malpractice [11].

Most of the data comes from case reports. It seems that autoresuscitation usually takes place in the first few minutes after TOR. In a recent review, the median time from termination of CPR to autoROSC was 5 min and 78% of the patients eventually died before hospital discharge [13]. Approximately 82% of reported cases occur within 10 min of CPR discontinuation. There are a few outliers of Lazarus phenomenon appearing as late as 20 to 50 min, but it is possible that in such cases lack of continuous monitoring led to a delayed diagnosis of ROSC. The prognosis of the syndrome is dismal, as the majority die before hospital discharge. However, studies report full recovery in 14-28% of patients [11, 13]. Pediatric cases of Lazarus phenomenon are significantly less common, with only 10 documented occurrences. The youngest reported child was 9 months old [7].

PATHOPHYSIOLOGY OF THE SYNDROME

The spontaneous recurrence of signs of life in an individual who is thought to be dead or declared dead is a bizarre and stressful event even for experienced healthcare professionals. A rational scientific explanation is a matter of interest to this narrative review.

The exact cause of Lazarus phenomenon is not fully understood. Nevertheless, several theories have been proposed, but it is likely that the mechanism is multifactorial. We present the key pathophysiological characteristics:

- Air trapping/dynamic hyperinflation. Hyperventilation during CPR can increase intrathoracic pressure. Patients with chronic obstructive respiratory disorders (e.g. COPD, asthma) are more susceptible to this condition. Elevated pressures impede venous return to the heart. When CPR stops, pressure release ensues and there is a subsequent improvement in blood flow towards the heart.
- Delayed drug action. According to ALS guidelines, epinephrine (adrenaline) is administered as soon as possible in non-shockable rhythms (asystole, pulseless electrical activity), while epinephrine and amiodarone are indicated for shock-refractory ventricular fibrillation/pulseless ventricular tachycardia (VF/pVT) [14]. The half-life of epinephrine is about 2-3 min, whereas amiodarone has a long half-life [15]. Increased venous return after CPR termination might facilitate a delayed drug effect on the heart that can trigger ROSC.
- Myocardial stunning. Myocardial dysfunction is common after ROSC and represents the primary cause of death in the immediate post-resuscitation period. The term stunning describes a transient severe contractile dysfunction due to ischemic injury, defibrillation and drug effects [16]. ALS guidelines call for resuming chest compressions for 2 min after each defibrillation attempt before the next rhythm check. This manual support of the heart is necessary even if VF/pVT has been terminated after the shock. A “stunned” myocardium can sometimes recover shortly after cessation of CPR.
- Reversible causes/special circumstances. It is widely accepted that treatment of the reversible causes of CA (the 4Hs and 4Ts) is important for achieving ROSC. Metabolic/electrolyte disorders (e.g. hyperkalemia, hypoglycemia, acidosis) and toxins (e.g. drug overdose, illicit drug abuse, poisoning) have deleterious effects on the heart. Correction of these disturbances or the delayed effect of their treatment can lead to ROSC after TOR. Moreover, hypothermia should prompt for a prolonged course of CPR accompanied by rewarming – “no one is dead until he/she is warm and dead” [17]. In such cases, autoresuscitation might follow early CPR termination.

The etiology of autoresuscitation remains a knowledge gap, since the proposed pathophysiological mechanisms are difficult to prove for every case scenario. However, it is reasonable to avoid hyperventilation during CPR, to be vigilant and treat adequately possible reversible causes of arrest and to closely monitor the patient for a period of time after the cessation of resuscitation efforts.

THE BRAIN FUNCTION DURING CARDIAC ARREST

The definition of Lazarus phenomenon focuses on the spontaneous restart of the heart. What happens to the brain? It is known that loss of consciousness occurs within 30 seconds after abrupt circulatory arrest when no intervention is undertaken, but cortical evoked potentials may persist for several minutes after loss of circulation [18]. CPR induced consciousness is a newly reported condition. The patient might become conscious during CPR in the absence of ROSC. The 2025 ERC/ILCOR guidelines recommend using small doses of sedative or analgesic drugs to prevent pain and distress to patients who are conscious during CPR [14]. Furthermore, around one-third of cardiac arrest survivors report the occurrence of near-death experiences (NDEs). These are vivid and structured experiences often involving out-of-body sensations, observation of lights and colors, life review while some patients recall specific details of their resuscitation verified by healthcare professionals. NDEs cannot be merely attributed to hypoxia induced hallucinations. They rather represent a conscious state during CA and often lead to positive life attitude changes, such as reduced fear of death and increased spirituality [19]. Lazarus phenomenon must not be confused with Lazarus sign, which is a misnomer to a spinal cord reflex observed in brain-dead patients [20].

ORGAN DONATION AFTER CIRCULATORY DEATH (DCD) AND THE LAZARUS PHENOMENON

Typically, Lazarus phenomenon occurs after unsuccessful CPR. During the last decades DCD programs have been developed in many countries. Controlled DCD (Maastricht classification III) starts with the decision to withdraw life support (e.g. ventilator, vasopressors) from patients with terminal illness or severe brain injury due to futility. After removal of life-sustaining treatment the patient goes into CA. CPR is withheld and after a “no-touch” waiting period, death is declared and then the surgery for organ harvesting begins [21]. The rationale of the “no-touch” period is to exclude the possibility of autoresuscitation. There is a global variation in DCD protocols regarding the duration of “no-touch” period, ranging from 2 to 20 min [22]. The resumption of cardiac activity after withdrawal of life-sustaining measures has been studied. In a prospective observational study of 631 patients, autoresuscitation was observed in 5 of them (1%). All the cases occurred within 4 minutes and 20 seconds after a period of pulselessness [23]. In a recent systematic review, the incidence of autoresuscitation during controlled DCD was 1.8% and all resumptions occurred within 5 minutes of circulatory arrest. Since no ALS interventions were provided all patients died [24]. The occurrence of Lazarus phenomenon in this category of patients is odd and cannot be explained by the mechanisms proposed for autoresuscitation after unsuccessful CPR (e.g. hyperventilation/air trapping, delayed drug action, myocardial stunning etc.).

CONCLUSIONS

Death is a process, rather than a time specific event. Nevertheless, society and medical practice demand clear cut criteria for death determination and a specified time of death. Lazarus phenomenon may challenge confirmation/diagnosis of death.

We would like to emphasize that Lazarus phenomenon or autoresuscitation is possible in any cardiac arrest victim, regardless of whether CPR was applied. This is a call for a broader definition of the phenomenon. DCD adheres to the dead donor rule: “vital organs should only be taken from dead patients and correlatively, living patients must not be killed by organ retrieval” [25]. Current evidence suggests that a “no touch” period of no less than 5 minutes is sufficient for controlled DCD. However, in the case of uncontrolled DCD (organ donation after unsuccessful CPR), a longer “no touch” period may be needed to exclude Lazarus phenomenon.

Autoresuscitation after cardiac arrest is considered a rare event which is not fully understood. There are indications that it might be under-reported. Clinicians must be aware of the syndrome, and it is advisable to maintain an observation time of at least 5 minutes after cessation of CPR before declaring death. They must be also encouraged to report Lazarus phenomenon without fear of legal implications. National cardiac arrest registries must include relevant data to shape a better understanding of the epidemiology and pathophysiology of this condition.

SUPPLEMENTARY INFORMATION

Funding: No fund was received related to this study.

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Conflicts of Interest: The authors declare no conflicts of interest.

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