Abstract: Cerebral hypoxia during cardiac arrest is the leading cause of mortality and morbidity in survival victims. To reduce cerebral damage, studies focus on finding effective treatments during the resuscitation period. Our report focuses on a 36-year-old police officer who had had two cardiac arrests (one at home and one at the hospital). After acute treatment, his cardiac and brain functions recovered impressively. Neuropsychological results were normal except for mild anomia. He also reported some retrograde memory loss. Surprisingly, he also reported an improvement in a very specific capacity, his episodic memory. We here review the possible causes and mechanisms that may have affected his memory abilities.

Key words: Out-of-hospital cardiac arrest; cardiopulmonary resuscitation; brain function; episodic memory.

Introduction

Up to 40,000 cardiac arrests occur each year in Canada. Close to 30% of all cardiac arrests occur in hospitals. Approximately 85% of out-of-hospital arrests (OHCA) happen at the patients’ residence (1). Hypoxic–ischemic/reperfusion brain damage is the leading cause of morbidity and mortality after a patient is resuscitated (2-4). Despite all efforts and progress in cardiopulmonary resuscitation, along with technological advances, survival rates after OHCA have remained almost the same for the 30 past years in North America (5, 6). However, in European studies, it has been shown that survival rate has improved (4, 7). Overall, hospital discharge and long-term survival rates after out-of-hospital cardiac arrest are respectively 10% and 5% (1, 5, 8). After successful resuscitation and survivor discharge, the 6-month survival rate is between 50 and 75% (7, 9-11), and chances for full cerebral recovery after OHCA remain very low (2). Memory problems are the most common cognitive impairments of survivors (12, 13).

We here illustrate a case of out-of-hospital cardiac arrest, where the patient survived and was discharged from hospital, and also returned to his previous full-time job. During follow-up, he mentioned that a specific aspect of his memory, namely the ability of remembering numbers, was better than before the cardiac arrest episode.

Case presentation

With the informed consent of the patient, a 36-year-old police officer, we present this case of out-of-hospital cardiac arrest. He collapsed at home shortly after getting out of bed. He was found unconscious by his wife who immediately called the emergency services and then started cardiac compressions. First, a police officer arrived and continued the cardiopulmonary resuscitation. Paramedics arrived 10 minutes after the emergency call. The patient’s initial cardiac rhythm was recorded as ventricular fibrillation and after four direct-current shocks, sinus rhythm was restored. The return of spontaneous circulation (ROSC) was reported 21 minutes after the initial emergency call was made.

Forty minutes after the initial event, the patient arrived at the emergency room of the local hospital. He remained unconscious with sinusoidal rhythm.
Few minutes after arrival, he had another episode of ventricular fibrillation. Resuscitation and tracheal intubation were performed, and he was treated with five 200 J direct-current shocks and adrenaline 1 mg, amiodarone 150 mg as adjuvants, magnesium 2 gr, lidocaine 100 mg, sodium bicarbonate, calcium chloride 1 gr (10 ml), fentanyl 100 mcg, and ranitidine 100 mg. The patent was given heparin 5000 UI bolus IV, acetylsalicylic acid (ASA) 320 mg, and clopidogrel 600 mg. The ROSC for the second arrest was 15 minutes. One hour and 15 minutes after the initial cardiac arrest, the patient was stable and was transferred to a referral cardiac hospital.

On arrival at referral hospital, the patient was admitted to the Cardiac Coronary Care Unit (CCU). He was sedated and hemodynamically stable. The electrocardiograph (ECG) showed a sinus rhythm and elevated ST-segment in V2-V4. Chest X-rays showed a normal cardiac silhouette and signs of pulmonary venous congestion along with pulmonary hemorrhage. The brain computed tomography (CT) scan was unremarkable. Elevated creatinine and elevated ST-segment in V2-V4. Chest X-rays was completed. Only mild anomia on the Boston Naming Test was observed. Digit span was found to be average, and anterograde memory measurements ranged from average to superior. Full scale intelligence quotient (I.Q.) was found to be average.

During the clinical interview, the patient also described isolated but permanent retrograde memory loss. When he first returned to work, he realized that he had forgotten about a colleague with who he worked for a month prior to the cardiac arrest. He explained that during a party where he saw people who he worked with from 1998 to 2000, he had only a vague memory of individuals he knew well in that period, but he clearly remembered other people he barely knew from that same period. He also noticed he forgot the names of many criminals he crossed paths with in the sector where he had worked from 1998 to 2000, and he described having a much better memory for the faces and names of criminals from another sector where he worked from 2000 to 2008. Lastly, he felt as if it was the first time when he entered the municipal court building where he had been many times before the cardiac arrest.

He also reported difficulties recalling the names of people that he recently met, although their faces seemed familiar. However, when he went back on car patrol, he and his colleagues noticed that his memory for some types of information had improved after the cardiac arrest. He was consequently surprised that he could remember the numbers for hours (and sometimes days) after encoding license numbers, plate numbers, birthdates and phone numbers. He and his colleagues insisted on the fact that remembering this type of information was actually a weakness for him before.
DISCUSSION

Outcome after the cardiac arrest

The leading causes of death after resuscitation are central nervous system injury and myocardial failure (3, 4, 14). The nervous system is the most vulnerable organ during cardiac arrest as its tolerance to hypoxia is very limited due to lack of ability of anaerobic energy production. In less than 10 seconds after circulatory arrest, the patient loses consciousness, intracellular acidosis develops, mitochondrial oxidative phosphorylation stops, and lactate accumulates (15). After a few minutes of circulatory arrest, the neurons lose their storage of energy. During the anaerobic period, hazardous substances like lactic acid, free radicals and carbon dioxide accumulate in the cells. These substances change the integrity of the cell microstructure (due to osmolality changes, ion canals reformation, synthesis of new proteins, etc.) that remain after reperfusion, and cause post reperfusion injury (16). On the other hand, during circulatory arrest, blood stasis triggers platelets adhesion, red blood-cell aggregation (Rouleaux formation), and neutrophil activation. Finally, intra-capillary coagulation and micro-thrombi are present. After reperfusion, these micro-vessels damages impair recovery and ischemia continues. Simultaneously, free oxygen radicals cause damage to endothelial membrane cells.

Without considering the cause of cardiac arrest, the main goal of resuscitation is reperfusion maintaining a minimum flow in brain, and minimizing no-flow time which is the most important factor determining patient outcome (13). This strategy explains why studies have shown that the survival rate in OHCA is different from in-hospital-witnessed cardiac arrest (10, 17, 18). The outcome after OHCA is time sensitive and related to prompt use of cardiopulmonary resuscitation (CPR), defibrillation, advanced care, and access to emergency medical care; this is called “the chain of survival” (9, 19). Several studies have shown that rapid use of mechanical chest compression after an OHCA with ventricular fibrillation is the most important factor determining the outcome (20, 21).

In the specific case of our patient, the outcome was very favorable in every domain: physical, psychological and cognitive. On the cognitive level, almost all neuropsychological results were normal with only mild anoma on testing. The patient also reported significant retrograde amnesia but only for certain types of information during defined time periods. Surprisingly, he also reported a very specific improvement in his episodic memory for numbers. There are no standardized tests to evaluate this specific capacity, and all neuropsychological tests were administered two years after the cardiac arrests, so we do not have premorbid data. However, the patient reported this cognitive improvement spontaneously, clearly, and consistently. He estimates that over a two-year period, his improved memory for numbers was apparent in approximately 30 separate events. It should also be emphasized that his partner and his colleagues also observed this specific cognitive improvement.

Memory theories

Encoding, storage and recall are the three main steps of episodic memory processing (22, 23). Sensitive neurons are activated by sensory input (sight, sound, feeling, etc.) and transmit (electrical, neurotransmitter, etc.) sensory information. After receiving the information in the brain, the storage of information begins. Memory is usually divided into short-term memory (STM) and long-term memory (LTM). Short-term memory is typically induced by a single train of high-frequency (tetanic) stimulation of an afferent pathway which causes modification of preexisting proteins and lasts only one to three hours. However, LTM is induced by several repetitions of such stimulations and persists for years or even a lifetime, which finally induces synthesis of new proteins (23, 24). Recent studies demonstrated that epigenetic mechanisms have played an important role in mature neurons involved in LTM. Epigenetic means almost permanent changes to chromatin molecules which are non-heritable. The two important and well known processes that are involved in encoding epigenetic information are covalent modification of histone proteins and DNA methylation (25).

Protective mechanisms during ischemia/reperfusion injury

In general, all cells activate protection mechanisms during hypoxic/ischemic stress. They include different changes that delay cell death especially after a chronic episode of hypoxia. Although the precise mechanisms of hypoxic/ischemic tolerance have not been elucidated, in general, the early phase of tissue hypoxia tolerance (less than 30 minutes following sub-lethal stress) is thought to be due to the flow-metabolism-mediated event, whereas delayed tolerance (after 30 minutes) involves new
genes induction and protein synthesis (26). Due to limited energy reserves, the different regions of the brain (cortex, cerebellum, basal ganglion, white and gray matters) have different tolerance to ischemia, and the mechanisms responsible for brain damage following global cerebral ischemia and cardiac arrest are complex (27).

During hypoxic conditions, many substances are produced or released in the brain tissue. These substances could change the cellular micro-anatomical structure and/or could modify the bio-molecular function of the cells. Hypoxia-inducible factor-1α (HIF-1α), first discovered in human hepatoma, is one of those factors. The HIF-1α increases expression of glycolytic enzymes and erythropoietin (EPO) in the central nervous system. It has been shown that EPO has a protective effect during the reperfusion phase. In addition, EPO also activates anti-apoptotic genes such as inhibitor of apoptosis (IAP) proteins (28). Although in severe hypoxia HIF-1α is responsible for cell apoptosis, in mild hypoxia it is shown to increase the brain development. Moreover, hypoxia appears to activate mitogen-activated protein kinase (MAPK) that stabilizes HIF-1α (29). The oxidative stress produced by hypoxia can activate signalling pathways and transcription factors like Protein Kinase C (PKC), Adenylate Cyclase (ADCY), Mitogen-Activated Protein Kinase (MAPKs), and Ubiquitin-Like Binding Protein (UHRF1) that increase the synthesis of memory proteins. Oxidative stress could also be involved in gene overexpression of the neurons and in enhancing the development of memory at different levels in areas of the brain such as the hippocampus, neocortex, and cerebellum, which are the most vulnerable locations during cerebral anoxia (24, 29, 30).

The brain-derived neuropathic factor (BDNF) family, which is increased during ischemia/reperfusion injury, is one of the best characterized neurotropic factors among the nerve growth factors. Ischemia/reperfusion injury suppresses the glutamate-triggered accumulation of peroxide and cellular Ca²⁺ homeostasis during hypoxia. During hypoxic and traumatic brain injury, motoneurons and substantia-nigra dopaminergic cells are rescued by BDNF (31, 32). It also plays a role in cognition as well as in neural survival and plasticity. Specifically, BDNF appears to facilitate both early and late long-term potentiation processes critical to the formation and maintenance of memory (25, 33). In addition, it has been shown that carbon monoxide (CO) plays an important role in protection from free radicals, reperfusion injury, and revascularization (34). Carbon monoxide can change MAPK activation. In laboratory conditions, CO can change the apoptotic signalling pathways in endothelial cells (34-36). Moreover, CO can protect neurons from oxidative stress-induced apoptosis by inhibiting Kv2.1 channels, which mediate cellular K+ efflux as an early step in the apoptotic cascade (37).

**Conclusion**

The patient is young, has a healthy life style, and good cerebral functions. Based on the information found in the patient’s chart, cardiopulmonary resuscitation was started immediately and was efficient. His cardiac function was restored intermittently between the two consecutive cardiac arrests, so he had two short periods of hypoxia and restoration. His final treatment was done with minimum delay. His episodic memory changes could be explained by the hypoxic neuron tissues releasing HIF-1α, MAPK, UHRF1 and BDNF which had modified the gene expression, altered ion canal structures, and induced new protein synthesis. In addition, in this patient, the pulmonary hemorrhage that contributed to the formation of bilirubin and CO might play an important role in the protection of neurons from free radicals, the reperfusion injury, and revascularization.

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**References**