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Periarrest intestinal bacterial translocation and resuscitation outcome

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ABSTRACT

During the periarrest period, intestinal ischemia may result in barrier dysfunction and bacterial translocation, which has clear mechanistic links to inflammation and cascade stimulation, especially in patients who are treated with therapeutic hypothermia. Despite optimal management, periarrest bacterial translocation may worsen the outcome of cardiac arrest victims.

1. Introduction

Cardiac arrest remains a daunting medical emergency as more than 1 million cases occur worldwide each year. Advantages in cardiopulmonary resuscitation (CPR) science have substantially increased survival rates from out-of-hospital cardiac arrest (OHCA) in the United States from 5.7% in 2005 to 9.8% in 2012 with lower rates of neurological disability over time among survivors [1]. On the other hand, the overall rate of survival to discharge after inhospital cardiac arrest is 17% [2].

One of the main goals both during CPR and postresuscitation period is hemodynamic optimization to preserve adequate coronary and cerebral perfusion. However, intestinal ischemia, a neglected consequence of circulatory collapse, and subsequent reperfusion may be extremely detrimental by enhancing bacterial translocation [3]. This phenomenon is likely more common in patients presenting with asystole or pulseless electrical activity (PEA) rather than ventricular fibrillation or pulseless ventricular tachycardia due to the prolongation of whole-body ischemia in nonshockable cardiac arrest. Asystole has been reported as the most common presenting rhythm in OHCA victims with bacteremia followed by PEA and ventricular fibrillation [4], whereas, in a retrospective analysis, shockable rhythms were uncommon among patients with preexisting pneumonia compared with initial arrest rhythms in patients without pneumonia [5]. Although the initial rhythm in OHCA is rarely recorded and may have evolved to asystole at the time of the recording, we have also reported PEA as the initial cardiac arrest rhythm in severe sepsis and septic shock [6].

Research so far has shown that more than one third of OHCA victims are bacteremic upon presentation [4]; however, it is difficult to know if sepsis is the reason for cardiac arrest or bacteremia is a downstream effect of intestinal hypoperfusion.

2. Intestinal ischemia

More than 1000 bacterial species live in the digestive tract and benefit the human organism by fulfilling various functions, including digestion of unused energy substrates, stimulating cell growth and differentiation, repressing the growth of harmful microorganisms, and training the immune system to respond to pathogens. The latter is the passage of live bacteria, inert particles, and/or other antigenic macromolecules (endotoxin, peptidoglycan) from the intestinal tract, through the intestinal mucosa, to physiologically sterile tissues [7,8]. In some patients, however, enteric bacteria can cross the intestinal barrier and infect the mesenteric lymph nodes due to mucosal structural abnormalities, thus entering the blood circulation [9]. Of note, spontaneous bacterial peritonitis is associated with complications, such as circulatory failure, cardiac dysfunction, coagulopathy, and relative adrenal insufficiency, ultimately leading to multiorgan failure [10]. Although we do not know much on the role of intestine during the periarrest period, research so far has shown that hemorrhagic shock can damage the gut barrier, leading to barrier dysfunction [11], while patients with markedly increased intestinal permeability have increased possibilities to develop multiple organ dysfunction [12].

3. Periarrest bacterial translocation

A major pathophysiological manifestation of the periarrest period is ischemia and reperfusion (I/R), which may have devastating effects on

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organs, especially after return of spontaneous circulation (ROSC) [13,14]. Before the onset of cardiac arrest, hypotension-induced disturbances in microvascular blood flow and alternations of arteriolar vasoconstriction and vasodilation may lead to intestinal I/R injury [15]. During the cardiac arrest interval, the loss of effective blood flow and the subsequent intestinal ischemia result in cellular hypoxia, intracellular acidosis, and increased epithelial permeability [16]. Considering that the ischemia period is longer than the average cardiac arrest and CPR time, some plausible mechanisms may be the exogenous release of endotoxins or circulating bacteria with endotoxins, both of which result in inflammatory cascades, and the endogenous release of catecholamines, which centralizes the minimum cardiac output that is produced during effective CPR [13,16,17].

After the onset of CPR, the compression-related cardiac output is between 25% and 40% of prearrest values with the gut receiving less than 5% of this value. Therefore, the major disturbance during CPR continues to be ischemia (rather than reperfusion) and its associated injury. Of note, cardiac arrest and resuscitation cause metabolic changes in the intestine, which reflect ischemic metabolism and are equally or (in the case of lactate) even more pronounced than those monitored in brain, indicating that the intestine is less protected than the brain during cardiac arrest and CPR [18].

Postresuscitation syndrome is composed of 4 different phenomena that emerge after prolonged cardiac arrest and/or resuscitation intervals, the postresuscitation myocardial dysfunction, brain injury, the systemic inflammatory response, and the precipitating pathology. Postresuscitation myocardial dysfunction manifests by severe but temporary ventricular systolic and diastolic dysfunction. Postcardiac arrest brain injury is the cause of death in 68% of patients after OHCA and in 23% after inhospital cardiac arrest [13]. Its clinical manifestations include coma, seizures, myoclonus, varying degrees of neurocognitive dysfunction, and brain death. Although the pathophysiological cascade of postcardiac arrest syndrome is activated by the onset of cardiac arrest, many of the brain injury triggering mechanisms and their clinical manifestations are executed from hours to days after ROSC [14]. In addition, the postresuscitation disease may be related to an early systemic inflammatory response, leading to an exacerbation of the inflammatory balance. It is similar to that seen in severe sepsis as it characterizes by high levels of circulating cytokines, the presence of plasma endotoxin, and increased leukocyte production, which further depress myocardial function, aggravating postresuscitation hemodynamics and tissue perfusion and promoting intestinal translocation and bacteremia.

After ROSC, rapid isotonic saline infusion predictably results in hyperchloremic acidosis [19], whereas hyperchloremia has been associated with reduced gastric mucosal perfusion [20]. The reperfused intestine is characterized by increased formation of reactive oxygen species, activation of polymorphonuclear leucocytes, alterations between arteriole vasospasm and vasodilation, increased vascular permeability, and microvascular thrombosis, which increase intestinal permeability and mucosal rupture [21,22]. The resulting bacterial translocation activates several inflammatory cascades, which, in turn, enhance the intestinal permeability and aggravate mucosal rupture, creating a devastating vicious cycle. Interestingly, the decreased expression of claudin 3 and tight junction protein (ZO-1) and the increased expression of claudin 2 increase intestinal permeability, enhance bacterial translocation, and may result in mesenteric node colonization within 48 hours [22,23]. This may explain in part the early onset of fever in postcardiac arrest patients, which is common after CPR and is associated with a poor neurologic outcome [24,25]. In addition, Toll-like receptors participate in detection and identification of bacteria and are the main contributors to pathogen-induced inflammation and injury-induced inflammation; various endogenous ligands are cleaved in the inflamed tissue and activate Toll-like receptor 4, initiating an inflammatory response and activating intestinal, myocardial, and cerebral I/R injuries [21-23]. Moreover, the resulting intestinal phagocytosis increases local inflammation, whereas nodal colonization enhances systemic inflammation, increasing the chances of systemic inflammatory response/sepsis, which ultimately impact cardiovascular response and the heart [13,26,27].

4. Effects of bacteremia

As bacterial translocation has clear mechanistic links to inflammation and cascade stimulation, it is plausible that bacterial circulation may have an immediate impact during the periarrest period. Bacteremia can cause cardiac arrest (Fig. 1), while it can decrease the effectiveness of resuscitation efforts and lead to multiple organ failure, thus increasing the severity of postcardiac arrest syndrome (Fig. 2). Until now, 2 studies seem to confirm this speculation. In the first, Carr et al reported that, in patients with preexisting pneumonia, cardiac arrest may occur in the absence of preceding shock or respiratory failure [5]. In the second study, Coba et al reported that of the 173 OHCA victims, 65 (38%) were found to be bacteremic, whereas mortality in the emergency department was significantly higher in bacteremic OHCA (75.4%) compared to nonbacteremic OHCA [4]. Nevertheless, whether bacteremia is the immediate byproduct of cardiac arrest or the major contributing factor of unrecognized severe sepsis leading to sudden cardiac arrest remains unanswered. We know, however, that bacterial translocation from the gastrointestinal tract can result to accumulation of bacteria in the lung or other tissues, stimulating local and systemic inflammation and resulting in tissue damage [28].

Bacteremia may increase the inflammation-induced oxidants, which stimulate leukocyte recruitment and activation, followed by increased microvascular permeability and a loss of endothelial integrity, leukocyte plugging, vasomotor dysfunction, and capillary narrowing, all of which lead to microvascular thrombosis, tissue ischemia, and (at least) local I/R injury [29]. Of note, the inflammatory response induced by lung I/R is rapid in onset and is strongly influenced by intestinal microbiota [30]. The increase in inflammatory cytokines worsens cardiac function through direct and indirect mechanisms, leading to impaired adrenergic and cholinergic stimulation. This reduces ventricular compliance, thus decreasing cardiac output and coronary perfusion, which predisposes to myocardial ischemia and cardiac arrest [13,26,31]. Interestingly, patients with pneumonia have been reported to be in increased risk for new-onset arrhythmias during and posthospitalization, especially those with greater severity of illness [32].

5. The role of therapeutic hypothermia

Interestingly, therapeutic hypothermia is associated with an increased risk of early onset pneumonia after OHCA and increase rates of bacteremia by intestinal flora [33,34]. The most intriguing is that therapeutic hypothermia may be a key aggravating factor for intestinal injury and bacterial translocation [33-35]. Although cardiac arrest patients have an impaired immune response, which is not influenced by induced hypothermia [36], studies demonstrate increased rate of bacteremia after cardiac arrest [37]. A possible mechanism may be the diminished microvascular blood flow and intestinal barrier injury due to the combined effect of hypothermia and vasopressor use on intestinal microvessels [38]. In addition, there is evidence that the bactericidal activities of antibiotics are dramatically reduced as temperature drops [39,40], suggesting that bacteremia-induced shock and/or cardiac arrest could be positively impacted by therapeutic hypothermia.

Interestingly, there is evidence that autonomic reflex circuits perceive immune and inflammatory signals within the viscera [41], whereas bacterial-induced neuronal activation can occur through direct interactions between the bacterial products and neuronal membrane proteins, bypassing the innate immune system. This engages neural receptors, which regulate the activity of infiltrating immune cells, limiting inflammation and damage in normothermic patients [42,43]. Consequently, a critical emerging issue is whether therapeutic hypothermia, which significantly improves neurologic outcome and is one of the

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