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Review

Cardiac arrest among patients with infections: causes, clinical practice and research implications

D. Leoni [1], J. Rello [2, *]

[1)] Tor Vergata University Hospital, Infectious Disease Department, Rome, Italy
[2)] CIBERES, Universitat Autonoma de Barcelona, Vall d'Hebron Institut of Research, Barcelona, Spain

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ABSTRACT

The incidence of sepsis is increasing, and the condition is now the leading cause of death in general intensive care units. Our review failed to identify studies of the causes of cardiac arrest among infected patients, even though non-cardiac causes represent 15% of out-of-hospital cardiac arrests and though one-third of events have positive blood cultures. Sudden cardiac arrest is the result of local damage to the heart and of the impact of systemic and pulmonary conditions on cardiac performance, and its danger is underestimated. Necropsy findings in sudden death often identify myocarditis as an unexpected cause. The role of hypoxaemia, severe pulmonary thromboembolism with subsequent pulseless cardiac activity, alterations of electrolytes and hydrogen concentrations, distort fluid distribution with reduced pre-load, direct myocyte damage and adverse cardiac effects related to antibiotic use need to be defined. Many cardiac arrests might be preventable. Because cardiopulmonary resuscitation is challenging and usually unsuccessful in patients with sepsis, research is needed to help predict which patients are at risk. Only half of pneumonia patients with cardiac arrest in the ward receive prior ECG monitoring. Telemedicine and non-invasive monitoring in the ward, avoidance of antibiotics associated with prolonged QT syndrome, and adequate haemodynamic resuscitation might be important in preventing in-hospital arrests among patients with infections. **D. Leoni, Clin Microbiol Infect 2017;23:730**

Introduction

Cardiac arrest is defined as the cessation of cardiac mechanical activity confirmed by the absence of signs of circulation [1]. Most cardiac arrests are of cardiac origin (65%), but in 15% of patients the cause is pulmonary. Cardiopulmonary resuscitation in patients with severe sepsis and septic shock is challenging and usually unsuccessful, with a high risk of developing cerebral anoxic damage [2].

The aim of this article is to describe the causes of cardiac arrest among patients with infections, and to discuss some new areas of interest in clinical practice and research.

Materials and methods

We performed a systematic search of the PubMed database from inception until 23 October 2016 without any time or language restrictions, using the search terms 'sepsis' OR 'infection', AND 'cardiac arrest'. We excluded experimental studies and studies focusing on infection or sepsis after cardiac arrest. No predefined review protocol was registered. The search strategy yielded no eligible records presented as clinical or interventional studies, after assessment of titles and abstracts. Several case reports were identified, most involving single patients (see the summary in Table 1). Among 720 identified sources, 113 were selected for inclusion as references on the basis of quality and relevance to understanding the problem and its consequences, recent trends, and current efforts underway to address severe infections and cardiac arrest.

Key conceptual issues

Epidemiology

The incidence of in-hospital cardiac arrest is one to five events/1000 patient admissions, with a reported survival-to-discharge rate of 20% (0%–42%) [3]. In-hospital heart arrest in hospitalized patients tends to be due to pulmonary embolism, cardiac dysfunction and progressive hypoxaemia. In comparison, in out-of-hospital events, pneumonia and positive blood cultures are more common. The

* Corresponding author. J. Rello, Clinical Research/Innovation in Pneumonia & Sepsis (CRIPS), Pg Vall d'Hebron 119, AMI- 14a Planta, 08035 Barcelona, Spain.
E-mail address: jrello@crips.es (J. Rello).

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Table 1
Causes of cardiac arrest among case reports of patients with sepsis

- Pneumonia
- Myocarditis
- Pulmonary embolism
- QT prolongation syndrome
- Severe grade tetanus
- Lemierre syndrome
- Endocarditis
- Pericarditis
- Aortic rupture caused by mycotic aneurysm
- Meningitis
- Mediastinitis associated with deep neck infection
- Occult splenic rupture with cardiovascular collapse
- Anaesthesia induction
- Secondary abdominal compartmental syndrome

overall incidence of fatal arrhythmias is unknown, but many case reports associated with azoles, quinolones and macrolides suggest that these entities are under-reported and that interactions with conditions that increase the risk have important clinical implications.

Cardiopulmonary resuscitation, cardiovascular drug support and electrical stimulation treatments are the main instruments for dealing with cardiac arrest. Since the 1990s, a number of studies have evaluated the efficacy of extracorporeal membrane oxygenation, with controversial results [2,4]. Many syndromes and conditions affecting different vital functions can lead to cardiac arrest, and guidelines recognize the need to target efforts in specific settings [5]. However, little information is available on the relation between cardiac arrest and sepsis.

Sepsis is one of the most frequent causes of death in critically ill patients [6]. Its incidence is rising with a reported rate in the USA of 436 severe cases/100 000 persons in 2012 and an overall mortality of 17.5% [7]. Increasing attention is being paid to the role of heart dysfunction in sepsis outcome, but the objective of this paper is not to describe this in detail [8,9]. Among the major causes of pulseless electrical cardiac activity, the European Resuscitation Council guidelines report hypoxaemia, hypovolaemia, hypokalaemia or hyperkalaemia, hypocalcaemia and acidosis, all conditions that can occur during sepsis [10,11]. Septic systemic inflammatory syndrome can directly induce myocardial depression: decreased contractility, impaired ventricular response to fluid therapy and ventricular dilatation are frequent findings and septic myocardiopathy has also been reported [12,13]. Furthermore, sepsis-induced coagulopathy and endothelial damage can promote acute myocardial infarction (AMI) and pulmonary thromboembolism [14]. Fatal heart events can be driven by respiratory failure (often in severe pneumonia) [15]; in addition, hydroelectrolytic imbalance and acidosis due to cellular hypoxia, catabolism, renal failure and third-space fluid shift may critically reduce heart performance and lead to fatal arrhythmias [5,16] precipitated by antimicrobial agents that prolong the QT interval. Secondary or primary septic involvement of the abdomen, with intra-abdominal hypertension (IAH), induces pre-load decrease and threatening respiratory and cardiovascular alterations [17], which may trigger a cardiovascular collapse mimicking a 'cardiac tamponade'.

Finally, sepsis management may produce risky concomitant conditions that hasten cardiac arrest, such as central catheter-induced arrhythmias and pro-arrhythmogenic antimicrobial side effects (especially QT prolongation with polymorphic ventricular tachycardia or *torsades de pointes*) [18,19].

Physiopathology of cardiovascular impairment in sepsis

Sepsis-associated cardiac dysfunction has two different phases. Initially, the inflammatory disorder, with a high oxygen demand from the periphery, induces a hyperdynamic circulation phase with high frequency, high cardiac index and normal or high output; patients present warm, red extremities despite the frequent occurrence of low systolic pressure (warm shock) [20]. As sepsis progresses, the scenario switches to a 'cold shock' with a reduced cardiac output, which contributes to peripheral hypoperfusion, tissue hypoxaemia, acidosis and organ failure [21,22]. Cardiac arrest can be triggered in both phases. The reduced heart function can be attributed to primary sepsis-induced cardiomyocyte alterations and to injuries due to the systemic inflammatory involvement.

Both tumour necrosis factor-α and interleukin-1β are primary players in the hierarchy of pro-inflammatory cascades, whereas nitric oxide and oxygen-free radicals are secondary effectors in the setting of cardiodepression [23]. Sepsis leads to the expression of inducible nitric oxide synthetase in the myocardium, followed by high levels of nitric oxide production. The action of these players attenuates the adrenergic response of cardiomyocytes, impairs autonomic neural control, alters intracellular calcium trafficking and changes the calcium sensitivity of contractile proteins, so affecting cardiac muscular performance [24].

Heart arrest can be caused either by a volume problem or by a contractility problem. Crucial issues are how sepsis affects cardiac volumes and cardiac contractility (hypoxia, direct damage to myocytes, changes in membrane permeability), and how it causes hypoxia and direct damage to myocytes. Detailed insights into these issues are provided elsewhere [23–25]. Finally, persistent changes in pre-load, after-load, contractility or severe inflow or outflow obstruction can induce pulseless electrical activity [26].

Pulmonary thromboembolism

Sepsis is associated with a high risk of pulmonary embolism as a result of systemic coagulopathy and disseminated endothelial damage. Pulmonary embolism can rapidly cause cardiac arrest, which occurs within 1–2 h in up to 90% of cases [27]. The commonest cause of thromboembolic or mechanical circulatory obstruction is a massive pulmonary embolus with sequential pulseless electrical cardiac activity [15].

Endotoxins like bacterial lipopolysaccharide and inflammatory response mediators (tumour necrosis factor-α) rapidly activate thrombin generation, tissue factor release and endogenous anticoagulant down-regulation; additionally, induced endothelial apoptosis releases intracellular pro-thrombotic molecules and enhances platelet adhesion [28,29]. As a consequence, the incidence of venous thromboembolism during sepsis was estimated to be 37.2% [14]. The systemic pro-thrombotic effect of sepsis can be recognized in sepsis-induced disseminated intravascular coagulation, with possible venous thrombosis leading to massive embolism and cardio-respiratory arrest [30]. Indeed, participation of specific anatomic areas can produce local venous thrombosis; thrombotic fragment detachments may produce metastatic lung infection and partial or massive embolic occlusion of lung circulation.

Septic pulmonary embolism is a complication associated with an in-hospital mortality of 30%, the most frequent causative pathogens being *Klebsiella pneumoniae* (50%) *and Staphylococcus* aureus (35%). The most common sources are liver abscess (50%) and pneumonia (25%). Acute kidney injury, disseminated intravascular coagulation and lung abscesses are common in non-survivors [31,32].

Septic involvement of the lower extremities, like necrotizing fasciitis or severe skin infections, can lead to septic pulmonary embolism and many other local foci such as arthritis, throat abscess, endocarditis, osteomyelitis and urinary tract infections can predispose to pulmonary embolism [33–35]. Conditions associated with septic emboli such as Lemierre syndrome should be identified promptly to avoid a possible cardiovascular collapse with subsequent heart arrest.