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**Ischemic cardiogenic shock: should we consider basal inflammation - and how? An editorial on the manuscript entitled: "C-Reactive Protein Levels and Outcomes in Infarct-Related Cardiogenic Shock: Data from the ECLS-SHOCK Trial"**

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**Inflammatory processes** play a pivotal role in the pathophysiology of cardiovascular diseases, especially artery disease<sup>1</sup>, regarding both acute conditions such as acute coronary syndromes (ACS)<sup>2</sup> and chronic states typified as stable coronary artery disease (CAD)<sup>3</sup>. These insights have given rise to promising therapeutic approaches<sup>4</sup>. Additionally, inflammation significantly influences the progression of heart failure (HF), instigating processes such as fibrosis, apoptosis, and tissue or cellular dysfunctions. This pivotal role of inflammation underscores its relevance in ACS complicated by cardiogenic shock (CS).

**CS** is a complex heterogeneous clinical syndrome characterized by hypotension and hypoperfusion primarily attributed to reduced cardiac output resulting mainly from myocardial dysfunction<sup>5</sup>. Despite advancements in medical care, CS remains associated with a high mortality rate, approaching 50-60% at the end of one year<sup>6 7</sup>. Acute inflammation in the initial stages of CS has been widely acknowledged as a predictor of poorer prognosis, worsening both short- and long-term mortality<sup>8</sup>. While ACS is a major cause of CS, CS can arise from various etiologies in clinical practice. Differentiating alternative diagnoses such as septic shock is not always easy, as CS and septic shock share intricate pathophysiological pathways and can both ultimately lead to multiorgan failure (MOF). The precise mechanisms by which inflammation contributes to CS in patients predominantly afflicted with CS, as opposed to septic shock, remain unclear. That's why comparing real-life patients with heterogeneous CC and very specific causes, such as ACS-related CC, makes sense.

Our group has recently reported in a **large national Frenshock registry**, that baseline inflammation, as indicated by C-reactive protein (CRP) levels upon admission, offers valuable prognostic insights for patients admitted with CS<sup>9</sup>. Patients presenting with highest levels of CRP, particularly in the fourth quartile (Q4) with CRP exceeding 68 mg/L, exhibited a 2.2 folds increase in 1-month mortality, (95% CI:1.23-3.97,  $p < 0.01$ ) and a 2.14 folds increase in 1-year mortality (95% CI:1.43-3.22,  $< 0.01$ ) compared to patients with lower levels of CRP on admission. Conversely, patients with CRP levels below than median (approximately 30mg/L) display significantly favorable outcomes. These findings remained robust even after a sensitivity analysis excluding patients with septic trigger, suggesting that inflammatory processes may contribute to the complex pathophysiological pathways underpinning CS.

This aligns with the conventional concept of CS as a vicious circle wherein hemodynamic deterioration triggers MOF, which in turn, may exacerbate inflammation.

**In case of ACS**, inflammation could possibly act as a marker and even a contributor to myocardial dysfunction. Levels of CRP are important prognostic markers, providing additional information when integrated with other ones such as troponins, renal function or natriuretic peptides<sup>10</sup>. One important aspect is the timing of systemic inflammation following reperfusion, which should be similar but with more intense systemic answer followed by MOF in case of CC. Classically, in case of ACS, the peak of CRP is observed around day 3 (**Figure panel A**). In the COLCOT trial<sup>2</sup>, the pleiotropic anti-inflammatory agent colchicine given to post-AMI patients regardless of their initial inflammatory status, offered a cardioprotective effects, that was not found in the recent CLEAR-SYNERGY trial<sup>11</sup>.

More especially, regarding **Infarct-Related Cardiogenic Shock**, CRP has been well-established as a crucial prognostic biomarker, independent of other ones. CRP has been suggested to be associated with pathophysiological phenomena such as obviously systemic and regional inflammation, but also with more specific myocardial involvement such as

micro-vascular occlusion in a myocardial infarction<sup>12</sup>, which is known to be associated with an increased risk of heart failure and mortality. Consistently, baseline inflammation in patients experiencing AMI complicated by CS, was established as a strong prognostic factor, in an important study conducted in two centers over an extended time frame<sup>8</sup>.

**In the present work, the authors studied the prognostic impact of CRP levels on admission in patients with AMI-CS**, as well as the effect of ECLS stratified by the CRP levels on admission in 371 patients enrolled in the ECLS-SHOCK trial.<sup>13</sup> They present an elegant sub study of the ECLS-SHOCK trial. Because of the randomized design, the level of evidence, although subanalysis, was higher than previous data. Briefly, the median CRP level on baseline was 18.0 mg/L in 371 patients with AMI-CS. The level of CRP is noticeably lower than in the Frenshock registry, which was expected due to the very acute onset. Secondly, tertiles are not comparable with quartiles. However, the authors depict a continuous association, since the association of CRP levels with the risk of 30-day all-cause mortality is still observed when included per 10 mg/dl increase (OR=1.05; 95% CI 1.01-1.08; p=0.012). This is important because 1/ the higher the inflammation, the poorer the diagnosis; 2/ high inflammation would need strong drugs to be controlled.

The highest tertile (i.e., CRP >61.0 mg/L) was associated with an increased risk of 30-day all-cause mortality compared to patients with lower CRP levels (lowest tertile: ≤5.0 mg/L) (adjusted Odds Ratio (OR): 3.54; 95% confidence interval (CI) 1.88-6.68; p=0.001). The use of ECLS did not reduce 30-day all-cause mortality, irrespective of CRP levels on admission. The additional inclusion of CRP to the IABP-SHOCK II score was able to improve significantly the prediction of 30-day all-cause mortality. In other words, the authors demonstrate that a simple biomarker, widely available on admission, can improve the prognostic discrimination in these very severe patients when integrated into a validated CS risk score.

Due to missing data and a relatively small population, these findings should be considered only hypothesis-generating. This is especially important as some biases are unavoidable, particularly imbrication with sepsis. However, patients are considered at the very beginning of the acute onset, unlike in the Frenshock registry, and sepsis did not differ across the three tertiles. Additionally, some drugs, such as early statin administration or colchicine (indicated for ACS), could interfere. Some clinical conditions could also be biased, but the randomized trial mitigates these risks (e.g., tabagism, illicit drugs, COPD, preexisting inflammatory diseases, or concurrent diseases). Interestingly, the placement of assist devices was not associated with higher CRP levels, likely due to the early stage of assessment.

The presence of inflammation upon admission for CS emerges **as a strong independent prognostic indicator for clinical outcomes including mortality**. As mechanical support failed to prove efficiency, there is a compelling need to 1/identify individuals in whom excessive and detrimental inflammatory processes are at play, 2/ evaluate whether antiinflammatory approaches could be promising or not. Given the involvement of inflammation in pathophysiology, whether controlling harmful mechanisms (like ischemia-reperfusion injury, microvascular occlusion, endothelial dysfunction, but also bacterial translocations, iatrogenic infections or thromboses) might be efficient deserve investigations (**Figure, Panel D**). However, it remains challenging to determine whether exclusively targeting inflammatory processes would be effective or safe, given that inflammation serves

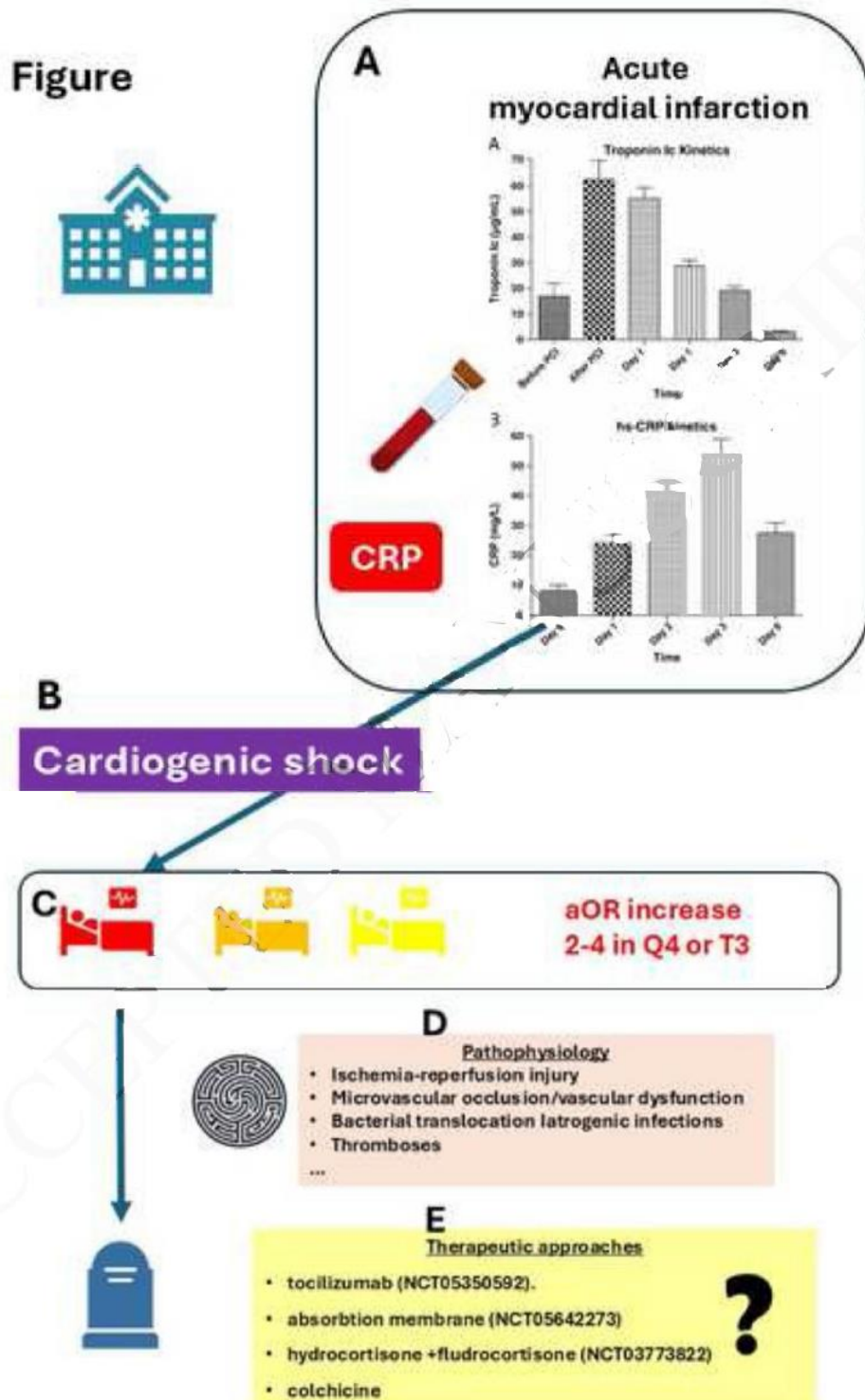
important physiological functions. In line with this, several clinical trials are presently underway, using various strategies such as: tocilizumab, an anti-interleukin-6 therapy, in 100 patients admitted with AMI complicated by CS (NCT05350592), or even a specific membrane capable of absorbing cytokine and lipopolysaccharide in 60 patients requiring veno-arterial extracorporeal membrane oxygenation (NCT05642273). Recently, a large trial conducted in France enrolled 380 CS (NCT03773822), allocated randomly to the treatment group (hydrocortisone and fludrocortisone) or control group.

However, this therapeutic approach has some limitations. Whereas COLCOT and LoDoCo2 I were positive, our group failed to evidence the reduction of infarct size in ACS14. Above ACS, CS is likely a very challenging clinical setting to treat due to its various and highly regulated ways. An integrative approach, including inflammatory aspects, is essential, and current trials may help in better tailoring effective tools.

***In conclusion,** considering inflammatory processes as potential contributors might improve early risk assessment in patients admitted for ACS-related CC. This approach paves the way for more tailored management and potential innovations targeting inflammatory pathways.*

**Figure.** CRP as a tool for a better stratification of the risk of patients admitted for acute myocardial infarction, especially when complicated by cardiogenic shock. **Panel A.** Biomarkers kinetics following acute myocardial infarction. The peak of CRP is around day 3, that is strongly relayed in comparison with troponins. **Panel B.** Development of cardiogenic shock. **Panel C.** Potential pathophysiological phenomena involved. **Panel D.** Potential therapeutic approaches.

## Figure



**Figure.** CRP as a tool for a better stratification of the risk of patients admitted for acute myocardial infarction, especially when complicated by cardiogenic shock. **Panel A.** Biomarkers kinetics following acute myocardial infarction. The peak of CRP is around day 3, that is strongly relayed in comparison with troponins. **Panel B.** Development of cardiogenic shock. **Panel C.** Potential pathophysiological phenomena involved. **Panel D.** Potential therapeutic approaches.



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