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EDITORIAL

Cardiogenic shock: from standardization to precision—a new era in critical care cardiology?

Sabri Soussi[1,2] and Alain Combes[3,4*]

Cardiogenic shock (CS) remains one of the most devastating conditions encountered in intensive care and emergency cardiovascular medicine. Despite decades of technological and therapeutic advances, mortality rates remain unacceptably high, and the clinical trajectory is often unpredictable. In their recent comprehensive review published in *Intensive Care Medicine*, Møller and colleagues deliver a timely synthesis of the current landscape of CS, offering both a sobering reality check and a roadmap for the future [1].

The review effectively highlights the evolving paradigms in our understanding and management of CS. Once viewed as a uniform hemodynamic failure predominantly caused by acute myocardial infarction (AMI), CS is now recognized as a heterogeneous syndrome with varied etiologies, trajectories, pathways and therapeutic responses [2]. Møller et al. argue convincingly for a move away from the 'one-size-fits-all' approach and toward a nuanced, subphenotype-driven approach that combines clinical judgment, advanced hemodynamic monitoring, molecular insights, and machine learning tools.

Redefining time-sensitive care

One of the central tenets reiterated in this review is the importance of early and precise diagnosis and management. CS, like stroke and STEMI, is a true medical emergency, and outcomes are closely tied to the speed and appropriateness of the initial response. The authors champion the 'golden hour' concept for CS, emphasizing that the first 60 min after medical contact are critical for initiating effective therapy. This time-sensitive approach demands not just early recognition, but also the rapid deployment of diagnostic modalities particularly bedside echocardiography and lactate assessments as well as streamlined activation of multidisciplinary "shock teams".

The review also highlights the limitations of relying solely on conventional clinical signs or pressure-based measurements, advocating for a multimodal diagnostic and therapeutic strategy. Complementary information from point-of-care tools such as left-ventricular (LV) outflow tract velocity time index (LVOT-VTI) assessments, lactate measurement and biomarkers reflecting key underlying pathways (e.g., interleukin-6 [IL-6], bio-adrenomedullin [Bio-ADM], dipeptidyl peptidase 3 [DPP3]) although not yet standard in clinical care, may provide valuable insights into a patient's hemodynamic and metabolic status, enhance risk stratification, and help guide targeted therapies [3].

From staging to phenotyping

The implementation of the Society for Cardiovascular Angiography and Interventions (SCAI) staging system marked a turning point in the standardization of CS classification based on clinical severity. It is worth emphasizing the distinction between severity grading (SCAI stages A–E) and true phenotyping independent from clinical severity, which may integrate etiology (AMI, myocarditis, decompensated heart failure), presence of cardiac arrest, rhythm status and metabolic/molecular profile.

*Correspondence: alain.combes@aphp.fr
[3] Institute of Cardiometabolism and Nutrition and Service de Médecine Intensive-Réanimation, Sorbonne Université, INSERM, UMRS_1166-ICAN, Assistance Publique-Hôpitaux de Paris (AP-HP), Sorbonne Université Hôpital Pitié-Salpêtrière, Paris, France
Full author information is available at the end of the article

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Phenotyping may allow prognostic enrichment (i.e., identifying high-risk patients) and/or predictive enrichment (i.e., identifying more responsive patients to a specific treatment) [4]. Prognostic and predictive enrichment may not be aligned, and the phenotyping strategy may lead to one or the other.

Phenotyping granularity is essential not only for prognostication but for guiding therapeutic choices, particularly when considering mechanical circulatory support (MCS). Future clinical trials and bedside decisions must move beyond SCAI stages to incorporate clinically and biologically meaningful subphenotypes using artificial intelligence (AI) and unsupervised learning approaches [5, 6]. Identifying biomarker-driven subphenotypes is promising, but it does not necessarily reveal distinct pathways causally linked to treatment effects that could enable personalized interventions in CS patients.

Mechanical circulatory support: promise and pitfalls

One of the most contentious areas in CS management is the use of temporary MCS devices. While the physiologic rationale for unloading the failing heart is compelling [7, 8], clinical evidence remains inconsistent and device-related complications are frequent. The DanGer-Shock trial, referenced prominently in the review, finally offered some long-awaited support for the use of microaxial flow pumps (e.g., Impella CP) in AMI-related CS, demonstrating a mortality benefit [9]. Yet this benefit came at the cost of increased bleeding and renal complications, underscoring the narrow therapeutic window within which these interventions must operate. It should also be noted that the 60% mortality among DanGer Shock control patients was remarkably high while other analyses based on large randomized controlled trials (RCTs) and registries have shown a mortality of approximately 50% in patients with similar or worse baseline clinical condition [10].

Conversely, the ECLS-SHOCK trial results (where VA-ECMO showed no survival advantage) are a sobering reminder that more support is not always better [11]. However, several factors may explain its neutral outcome. Notably, 78% of patients had cardiac arrest prior to randomization (significantly higher than previous trials such as CULPRIT-SHOCK [12] (53%) or IABP-SHOCK II (45%) [13]) with a prolonged low-flow duration (median 20 min). Hypotension was the sole hemodynamic inclusion criterion, raising the possibility of vasoplegic profiles with preserved cardiac output. Supporting this, only 35% received dobutamine, and < 3% met echocardiographic thresholds for LV unloading, suggesting that VA-ECMO may have been inappropriate in many cases. Furthermore, 26% of control group patients received MCS (13% VA-ECMO, 13% other devices), meaning the study effectively compared early VA-ECMO to rescue MCS strategies. These elements highlight the need to refine patient selection (patients with a low risk of anoxic brain injury as in DANGer-Shock) and hemodynamic profiling in future trials assessing MCS in CS [14].

The unseen battlefield: inflammation and organ dysfunction

One of the most valuable aspects of the review is its focus on systemic inflammation and multi-organ dysfunction in CS. As the authors detail, shock is not merely a cardiac phenomenon; it is a systemic syndrome marked by immune dysregulation, endothelial injury, and microcirculatory collapse. The inflammatory cascade represents both a prognostic factor and a potential early target of therapy (i.e., inflammation/endothelial modulation) before the onset/aggravation of organ dysfunction.

Active circulating markers such as IL-6, Bio-ADM, and DPP3 may not only help better understand underlying mechanistic signatures, but also represent potential biotargets for novel interventions (i.e., antibody treatment [15]). As an example, DPP3 measurement could help identify patients who may better respond to anti-DPP3 biotherapy. The specific inhibition of DPP3 enzyme activity may allow the restoration of the renin–angiotensin–aldosterone system (RAAS) homeostasis, the reduction of vasopressor doses and the improvement of renal perfusion.

Yet, as with MCS, biologic plausibility has not always translated into clinical benefit, and rigorous trial design remains essential (i.e., selection of a population of CS with a specific biological profile to test a targeted treatment).

The road ahead: precision medicine in critical care cardiology

Møller et al. close their review by advocating for a future grounded in precision medicine, where clinical subphenotypes, omics technologies, and real-time data converge to inform tailored interventions. This vision is compelling, but it requires not only technological infrastructure and bioinformatics but also a cultural shift in how clinicians approach critical care heterogeneous syndromes like CS.

Equally important is the role of international collaboration and data sharing. The rarity and heterogeneity of CS cases make single-center trials insufficient. Clinical research networks such as the Critical Care Cardiology Trials Network registry [16] and the Cardiogenic Shock Working Group (CSWG) [17], large-scale registries and global translational consortia (The Shock and acute

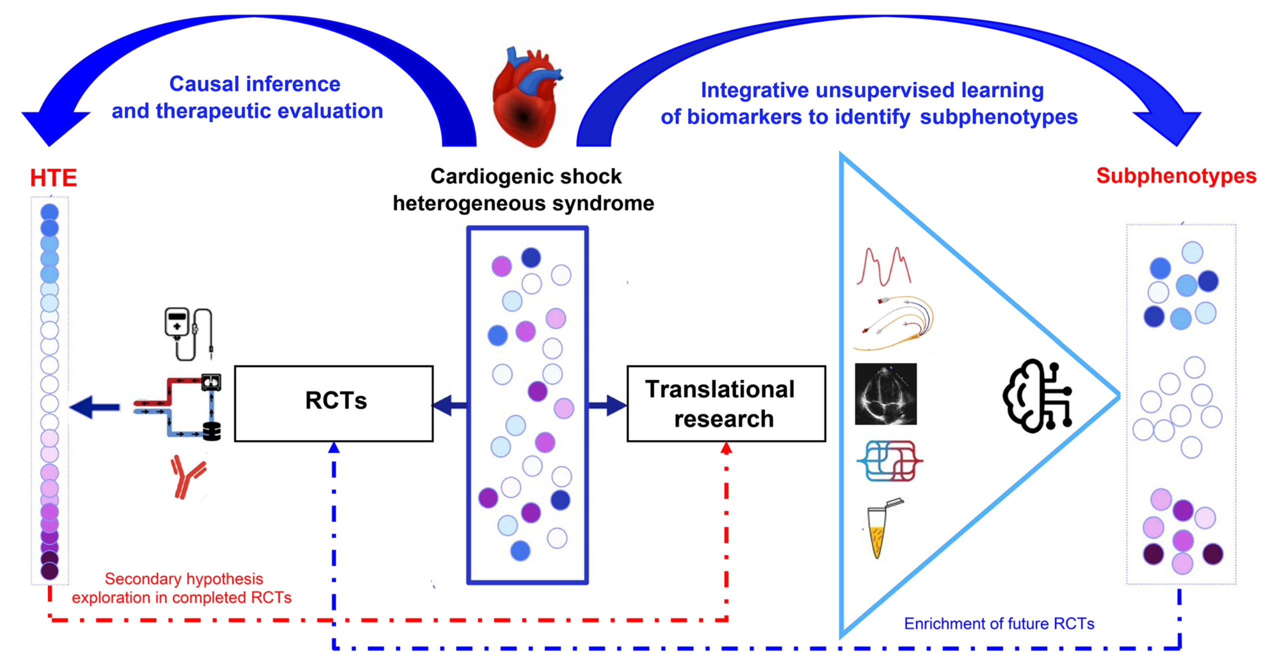

Fig. 1 Considering Heterogeneity of treatment effect in cardiogenic shock research. Recognizing heterogeneity is essential to advance precision medicine in cardiogenic shock. Treatment-based (e.g., vasopressors, mechanical circulatory support [MCS], antibodies) and biomarker-driven approaches (e.g., high-frequency physiological waveforms, cardiac/microcirculatory imaging, omics) provide complementary insights, with findings from one informing the other. Iterative integration of these methods may enable progressive enrichment of pathophysiologically similar patient subgroups (i.e., subphenotypes), enhancing therapeutic precision and ultimately improving patient outcomes. *RCT* randomized controlled trials, *HTE* heterogeneity of treatment effect

Conditions OutcOmes Platform [ShockCO-OP], https://www.3ctmeeting.com/shockco-op) [15] will be instrumental in refining risk scores, validating clinical/molecular subphenotypes, and designing informed mechanistic clinical trials (Fig. 1).

This review by Møller and colleagues calls for a new way of thinking about CS. Precision/individualized management based on clinical/biological subphenotypes is promising and could replace the standardized cardiac-centered syndromic paradigm. As we stand at the intersection of technology and sophisticated biology, this approach may face challenges in low and middle-income countries that may lack the required infrastructure. The phenotyping approach has also to be associated with patient-centered outcomes (e.g., win ratio and net treatment benefit based on generalized pairwise comparisons) to optimize its efficiency in future RCTs [18].

Author details
[1] Department of Anesthesia and Pain Management, University Health Network (UHN), University of Toronto, Toronto Western Hospital, Toronto, Canada. [2] Inserm UMR-S 942, Cardiovascular Markers in Stress Conditions (MASCOT), University of Paris, Paris, France. [3] Institute of Cardiometabolism and Nutrition and Service de Médecine Intensive-Réanimation, Sorbonne Université, INSERM, UMRS_1166-ICAN, Assistance Publique-Hôpitaux de Paris (AP-HP), Sorbonne Université Hôpital Pitié-Salpêtrière, Paris, France. [4] Service de Médecine Intensive-Réanimation, Institut de Cardiologie, Assistance Publique-Hôpitaux de Paris (AP-HP), Sorbonne Université, Hôpital Pitié-Salpêtrière, Paris, France.

Declarations

Conflicts of interest
SS reports being advisory editor for Anesthesia, Critical Care & Pain Medicine (French Society of Anaesthesia and Critical Care) and for Intensive Care Medicine Experimental (ICMx, ESICM). AC reports honoraria for lectures from Getinge and Baxter outside of the submitted work.

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