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► **To cite this version:**

Clément Delmas, Laurent Bonello, François Roubille. For the best management, please ask for assistance!. European Journal of Heart Failure, 2023, 25 (4), pp.573-575. <10.1002/ejhf.2826>. <hal-04034678>

HAL Id: hal-04034678

<https://hal.science/hal-04034678v1>

Submitted on 14 Feb 2024

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For the best management, please ask for assistance!

Clément Delmas ^{1 2}, Laurent Bonello ^{3 4 5}, François Roubille ⁶

¹ Intensive Cardiac Care Unit, Rangueil University Hospital, Toulouse, France.

² REICATRA, Institut Saint Jacques, CHU de Toulouse, Toulouse, France.

³ Aix-Marseille Université, Marseille, France.

⁴ Intensive Care Unit, Department of Cardiology, Assistance Publique-Hôpitaux de Marseille, Hôpital Nord, Marseille, France.

⁵ Mediterranean Association for Research and Studies in Cardiology (MARS Cardio), Marseille, France.

⁶ PhyMedExp, Université de Montpellier, INSERM, CNRS, Cardiology Department, INI-CRT, CHU de Montpellier, Montpellier, France.

***Corresponding author.**

Intensive Cardiac Care Unit, Rangueil University Hospital, 1 Avenue Jean Poulhes, 31059 Toulouse Cedex, France. Tel: +33561322426 / +33 673147951,

Email:

delmas.clement@chu-toulouse.fr, clement23185@hotmail.fr.

Cardiogenic shock (CS) is defined as a profound impairment of cardiac function, leading to severe and life-threatening systemic organ malperfusion. Long considered to be largely secondary to acute myocardial infarction (AMI), it is now recognized as being of non-ischaemic (NI) origin in more than one out of two cases.¹ Over the past years, despite extensive research efforts, the CS-associated mortality risk has remained unacceptably high and even probably under-evaluated.²

A recent multidisciplinary international impetus has enlightened numerous observational and then interventional studies in CS, however the vast majority of these studies have focused on AMI-CS and neglected shocks occurring in other contexts. Future and ongoing studies also focus on AMI-CS (Table 1) with only few allowing the inclusion of NI-CS (as exclusive or possible aetiologies). Indeed, according to a recent analysis of 1305 unselected CS referred in a tertiary centre, only 31.8% met the enrolment criteria for any of the largest current and past CS trials (IABP-SHOCK II, ECLS-SHOCK, EURO-SHOCK or DanGer-SHOCK) with between studies differences (eligibility from 11.9% to 26.9%). The NI cause of the CS explained 50% to 70% reason for ineligibility questioning the representativity and potential translation in clinical practice regarding NI-CS.³

Importantly, ischaemic and NI-CS differ substantially in terms of both pathophysiology including neurohormonal activation and clinical features from haemodynamic initial presentation until baseline characteristics such as age, gender, comorbidities or history. Especially in case of preexisting acutely decompensated chronic heart failure (ADCHF), NI-CS usually have a substrate of chronic compensatory mechanisms including ventricular dilatation, increase in circulating catecholamines and upregulation of the renin-angiotensin-aldosterone axis.⁴ They present then with less profound haemodynamic instability (stage B and C Society for Cardiovascular Angiography and Interventions [SCAI]), higher systemic overload, lower left ventricular ejection fraction and cardiac index, and more renal and liver dysfunction. By contrast, AMI-CS are characterized by an acute loss of myocardial tissue and ventricular stunning with early and sometimes profound systemic inflammatory response syndrome (SIRS) due to the lack of compensatory mechanism with systemic vascular resistance rapidly crumbled which participate in the complexity of its management.⁵ However, these data should be tempered because they differentiate well AMI-CS from ADCHF-CS but probably not from acute de novo NI-CS (fulminant myocarditis or toxics for example).

To improve patients' diagnosis, management and outcomes, studies dedicated to NI-CS are urgently needed. Trials on CS are difficult to conduct due to consent in timely acute severe condition but also due to heterogeneity of patients and practice.² To date only the ECMO-CS randomized trial reported the place of extracorporeal membrane oxygenation (ECMO) in miscellaneous CS but results were non-significant probably limited by its underpowered size (117 patients) and the large cross-over in the no early ECMO group (39% received an ECMO).⁶ Moreover, the EURO-SHOCK trial designed to include ischaemic and NI-CS patients randomized between ECMO and medical management was recently prematurely stopped for slow inclusion rate (only 22 inclusions on 428 planned).⁷

Table 1 Ongoing and future studies dedicated to acute mechanical circulatory support in patients admitted for cardiogenic shock

NCT	Type of CS	Status	Acronym	n	Protocol	Primary endpoint
Acute MCS in CS patients						
NCT04369573	NI-CS	Recruiting	Altshock-2	200	Early IABP (<6 h of CS onset)	60-day survival and/or successful bridge to heart replacement therapies (HTx or LVAD)
NCT03813134	All	Stopped prematurely	EUROSHOCK	428	VA-ECMO	30-day all-cause mortality
NCT04184635	AMI-CS	Recruiting	ANCHOR	400	VA-ECMO	30-day death or rescue ECMO
NCT01633502	AMI-CS	Recruiting	DanGer-SHOCK	360	Impella CP	6-month all-cause mortality
NCT03637205	AMI-CS	Recruiting	ECLS-SHOCK	420	VA-ECMO	30-day all-cause mortality
NCT05366452	AMI-CS	Recruiting	ULYSS	204	Impella CP	30-day survival free from ECMO, LVAD and HTx
NCT05106491	All	Not yet recruiting	PulseSE	21	Pulsatile synchronized VA-ECMO	Cardiocirculatory stabilization and end-organ perfusion (lactate) up to 14 days
LV unloading under VA-ECMO supported CS patients						
NCT03431467	All	Recruiting	REVERSE	96	Impella CP + VA-ECMO vs. VA-ECMO alone	30-day survival free from MCS, HTx or inotropic support
NCT04775472	All	Not yet recruiting	EARLY-UNLOAD	116	Early atriostomy in VA-ECMO CS	30-day all-cause mortality
NCT05577195	All	Recruiting	UNLOAD ECMO	198	Impella + VA-ECMO	Time to death from any-cause within 30 days

We report all future or ongoing or completed studies without report to date which are interventional, prospective, multicentre and open-label dealing about acute MCS in cardiogenic shock in ClinicalTrials.gov on 11 February 2023.
AMI, acute myocardial infarction; CS, cardiogenic shock; HTx, heart transplantation; IABP, intra-aortic balloon pump; LV, left ventricular; LVAD, left ventricular assist device; MCS, mechanical circulatory support; NI, non-ischaemic; VA-ECMO, veno-arterial extracorporeal membrane oxygenation.

In this issue of the Journal, Schrage et al.⁸ used a large, retrospective, international, multicentre database to evaluate mechanical circulatory support (MCS) use in NI-CS. This is the first large-scale analysis of the relationship between MCS use and mortality in these severe patients. First, beyond the largest series on NI-CS published to date (n=890), they showed that MCS was used in 43% of the cases despite absence of evidence for this indication. Second, based on a propensity-score matching analysis to consider baseline differences between MCS and non-MCS patients, they showed a significant 30-day mortality reduction in favour of the MCS use in all tested subgroups (hazard ratio 0.76, 95% confidence interval 0.59–0.97) at the price of higher early complications (e.g. severe bleeding [16.5% vs. 6.4%] and access site-related ischaemia [6.7% vs. 0%]).

Nevertheless, several limitations should be highlighted and discussed. First, the definition of NI-CS as a CS due to severe de novo or ADCHF with no need for urgent revascularization, exclude AMI-CS but without precision on the CS cause or trigger, and no comparison between severe de novo and ADCHF-CS was reported preventing further analysis of this heterogeneous population. Indeed, to differentiate patients and management according to the probability of heart recovery seems legit and important from high probability (myocarditis, de novo dilated cardiomyopathy) versus low probability (previous advanced heart failure). Beyond myocardial recovery, the project is important to consider the possibility of heart replacement therapies such as heart transplantation or ventricular assist device (VAD). Second, they reported only early outcomes at 30 days and did not differentiate the type of support used (ECMO vs percutaneous VAD [pVAD]), although we need to consider also the risk of heart failure with the paradox of ‘saving the patient but no the heart’. Long-term data in this severe population are mandatory even more with the change of several heart allocation

systems (US, France) which prioritizes access for patients under acute MCS. Notably, the prioritization of patients under ECMO is questionable based on a large analysis on US heart transplantation showing a 2.4 increase of 1- and 5-year mortalities for patients under ECMO at transplantation compared with patients without support or with other support (pVAD or left VAD).⁹ Third, as acknowledged by the authors many biases, including the retrospective design, prevent from strong conclusions. The size of the effect is suggested important (until 50% less events) but the confidence interval is wide, near to statistical significance. So, we cannot but support prospective larger trials on this topic, as proposed by the authors, in spite of the difficulties mentioned above.

Cardiogenic shock is a complex disease and haemodynamics is just one problem cascade which ultimately leads to death. Indeed, the simplistic view of CS as a unique problem of output is definitely false. Associated SIRS notably may not be reversed by device alone. So, the possible benefit of the device in terms of output may be counterbalanced by their associated adverse effects (haemolysis, bleedings, vascular complications). Patient selection and timing of implantation seem crucial when dealing with CS patients' outcomes since it can be estimated that up to 40–50% will die in absence of specific management and MCS may be helpful for them. But more 50% to 60% will survive without MCS and may be exposed to potential undeserved side effects from bleedings or acute limb ischaemia to death.¹⁰ More, through the overall survival, myocardial recovery and survival without heart replacement therapy remains crucial.

This benefit/risk ratio depends on multiple factors from the type of device used, the timing of implantation, associated management, to centre experience and expertise.

The support needed and the type of device may probably be different between AMI-CS and NI-CS. For the latter, output need is probably less important thanks to chronic tissue adaptation to low perfusion but also to the lower associated SIRS. So, less efficient and less invasive MCS may be used for NI-CS support and intra-aortic balloon pump (IABP) with less associated adverse events (<3% vs. up to 40–50% for pVAD and ECMO) could be a good candidate. In a recent small randomized controlled trial (n=32) IABP was associated with a significant improvement in cardiac power output, decongestion and organ perfusion (mixed venous oxygen saturation) without serious adverse events, compared to inotropes (enoximone or dobutamine) in ADCHF patients.¹¹

Although in AMI-CS the earlier implantation seems the better with pVAD or extracorporeal life support in observational studies, Schrage et al. showed only a significant improvement in 30-day mortality for NI-CS stage D when the SCAI classification was considered. They confirmed that too late is probably futile¹² but also that the benefit/risk ratio is not in favour of too early implantation (stage C or earlier) in NI-CS. First step associating aetiological management, inotropes and vasopressors should stay mandatory in this specific population.

Based on (i) pre-clinical studies showing an increase in left ventricular pressure and alteration in coronary perfusion on ECMO, and (ii) the association of left overload with higher mortality or need for heart replacement therapies in patients with left ventricular predominant failure,¹³ the concept of left ventricular unloading has emerged. Recently, the association between early (until 2 h after ECMO) left ventricular active unloading by pVAD was reported to be associated with a lower 30-day mortality in an adjusted and propensity-matched population of NI-CS. These results question the best type of device to choose and its timing, since this strategy was associated with a higher complication rate.¹⁴

Perspectives

Future trials dedicated to NI-CS are needed to address unmet goals of NI-CS management and improve its outcomes. To this purpose, the ongoing Altshock-2 study compares early IABP versus medical management in NI-CS.¹⁵ Beyond the device itself, specific dedicated algorithms to optimize medical management and pathways are urgently needed through network organization with multidisciplinary CS centres. The ideal study should be multicentre, international, with four groups and ban cross-over. It should compare medical management alone versus its association with IABP, or pVAD or ECMO (with and without systematic left ventricular unloading) with composite primary endpoint of survival free from heart replacement therapy and a specific medico-economic analysis, but its feasibility seems very unlikely.

In a large international registry, Schrage et al. showed for the first time a significant association between MCS use and lower early mortality in NI-CS. Despite attractive results, this study is only hypothesis-generating and future dedicated studies are necessary to address unanswered questions in a prospective way.

Conflict of interest:

none declared.

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