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The hemodynamic envelope in cardiogenic shock: A novel paradigm on the safe use of heart failure therapies during temporary mechanical circulatory support

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ABSTRACT

Cardiogenic shock (CS) is a life-threatening condition characterized by severe systemic hypoperfusion that may progress into multi-organ failure. Immediate optimization of organ perfusion is therefore considered a critical priority. However, first-line therapy with inotropes and vasopressors carries significant risks, adding stress to an already severely failing heart, and may eventually contribute to further clinical deterioration. Subsequent temporary mechanical circulatory support (tMCS) has been traditionally viewed upon as a means to restore systemic circulation. Recent approaches have, however, suggested that the hemodynamic buffer provided by tMCS may create a therapeutic window for the initiation of evidence-based heart failure therapies. Nevertheless, interfering in a jeopardized hemodynamic and failing homeostasis is extremely challenging and the devices carry a significant risk of serious adverse events. In this review, we discuss the potential use of heart failure therapies in patients with CS who are supported with tMCS. We highlight the feasibility and potential efficacy of this combined therapeutic approach from the perspective of a novel, aviation-inspired safety framework referred to as the '*hemodynamic envelope*'. This concept may inspire future study designs and support clinicians in initiating established heart failure therapies during tMCS.

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Introduction

Cardiogenic shock (CS) is an acute manifestation of severe heart failure (HF) that leads to critical tissue hypoperfusion and is associated with mortality rates exceeding 50 and 80 percent in SCAI (Society of Cardiovascular Angiography and Intervention Shock Stages) stages D and E, respectively [1]. CS treatment strategies traditionally rely on optimizing organ perfusion through augmentation of cardiac output and blood pressure, classically by using inotropic and vasoactive medication in addition to tailored fluid management [2,3]. In severe cases, these interventions may fail to improve organ perfusion and may even cause additional damage to the heart. Inotropes and vasopressors can thus paradoxically inflict additional injury—as a 'second hit'—that may ultimately prevent cardiac recovery. Of note, both real-world evidence and clinical trial data have consistently failed to demonstrate a survival benefit for the use of inotropes and vasopressors in CS and severe heart failure [4–6].

Temporary mechanical circulatory support (tMCS) systems, e.g., veno-arterial extracorporeal membrane oxygenation (V-A ECMO), micro-axial flow pumps or combined approaches (ECMELLA), can swiftly restore organ perfusion, irrespective of a failing native cardiac output. In this way, tMCS could allow clinicians to reduce or even completely cease vaso-inotropic stressors, and instead, to initiate cardioprotective heart failure (pharmaco)therapies [7,8]. This concept of using tMCS to phase out inotropes and vasopressors and even introduce otherwise contraindicated heart failure medication in acute and severe CS represents a new paradigm which may help to improve patient outcomes where recent conventional tMCS efforts failed to show their treatment benefits [9,10].

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This review provides a comprehensive overview of different therapeutic approaches that could promote myocardial recovery in patients with severe CS under the umbrella of tMCS. From a safety perspective, a novel framework is introduced, referred to as the "*hemodynamic envelope*" adding innovative perspectives to future tMCS care and research.

Treating heart failure in the context of mechanical circulatory support

CS typically represents the worst side of the HF with reduced ejection fraction (HFrEF) spectrum, where a severely reduced myocardial contractility causes low arterial blood pressures, elevated intracardiac filling pressures [11], and ultimately insufficient tissue perfusion. Although initially ignited by the underlying myocardial disease, the common pathophysiological pathway of CS is driven by a plethora of disease-related factors aggravating each other into a vicious circle. This "perfect storm" is formed by metabolic derangements due to anaerobic metabolism and oxidative stress, an increased systemic oxygen demand (e.g., secondary to a systemic inflammatory response syndrome and increased work of breathing), ongoing myocardial ischemia, and excessive sympathetic stress. This devastating condition requires prompt management through optimization of fluid status and the administration of inotropes and vasopressors. However, these therapies also paradoxically further aggravate the situation. The intensive (and prolonged) use of inotropes causes not only beta-receptor desensitization [12], but also impaired calcium handling and cell loss (necrosis and apoptosis), in concert contributing to poor patient outcomes [13]. Several historical randomized clinical trials (RCTs) have shown that inotropic stimulation via the beta-receptor and its downstream pathways in HFrEF led to increased risks for arrhythmias and (cardiac) death (Supplementary Table 1).

The vicious circle of CS can be broken through application of tMCS devices, which can directly provide sufficient blood flow to all organs and tissues. A recently published RCT found a survival benefit in patients with acute ST-segment elevated myocardial infarction induced CS receiving early support with a microaxial flow pump (Impella CP) versus those receiving conservative care with inotropic, vasoactive medication and in selected patients tMCS escalation [14,15]. Potent tMCS devices, such as the Impella 5.5, V-A ECMO or combined ECMELLA support (V-A ECMO with impella), have the potential to completely substitute cardiac function in safeguarding systemic organ perfusion through (supra-)physiological extracorporeal device-mediated flows. Theoretically, this could allow clinicians to completely phase out vaso-inotropic stressors from the myocardium and vasculature, while facilitating the application of heart failure therapies directed towards myocardial salvage, protection and reconditioning. Thus, by lowering heart rate and myocardial contractility, and alleviating overload conditions, cardiac expenditure can be reduced, thereby preserving myocardial integrity and limiting reverse remodeling. These pathophysiological processes are already well established therapeutic targets in other patient categories of HFrEF and occur in extremis in CS [16].

Following this concept, the subsequent section addresses potential heart failure treatments in CS patients under tMCS. Each therapy is associated with specific risks in the setting of CS which are summarized in Table 1. This text, table and graph are partitioned into therapies for both ventricles separately because the anatomical and functional sites of action typically differ for the left (LV) and right ventricle (RV).

Therapies potentially promoting left ventricular recovery during tMCS for CS

The majority of patients with HFrEF suffer from isolated or predominant LV failure as its underlying cause [17]. As such, substantial knowledge accrued over the years on how to optimally treat this specific pathology.

Table 1
Heart failure therapies and their hypothetical benefits and risks in the setting of tMCS for CS.

			Potential benefits					Specific risks						
		Ventricle	MvO2	Myocardial perfusion	Anti-arrhythmic	Cardiac unloading	Reversed remodeling	CO ↓	Bradycardia	Hypoperfusion	Congestion	Renal dysfunction	Cardiac thrombosis	Bleeding
Medication	Beta blocker	LV	↓↓↓↓	↑	↑↑↑	↑	↑↑	↑↑↑↑*	↑↑	↑↑	↑↑↑*	↑	↑↑↑	=
	ACE inhibitors	LV	↓*	=	=/↑	↑	↑↑	=	=	↑	=	↑↑	=	=
	ATII antagonists	LV	↓*	=	=/↑	↑	↑↑	=	=	↑	=	↑↑	=	=
	ARNI	LV	↓*	=	=/↑	↑↑	↑↑↑			↑	=	↑↑	=	=
	MRA	LV	↓*	=	=/↑	↑	↑	=	=	=/↑	=	=	=	=
	Ivabradine	LV	↓	=	=/↓**	=	=	↑↑	↑	↑	↑	=	↑	=
	Nitric oxide	RV	↓*	↑	=	↑↑	=	=	=	=	=	=	=	=
	SGLT2 inhibitor	LV	↓*	=	=/↑	↑	↑	=	=	=	=/↑	↑	=	=
Interventions	Catheter thrombectomy	RV	↓*	↑	↑	↑↑	=	=	↑	↑*	=	=/↓	↑	↑↑↑
	PEEP levels ↑	RV & LV	↓#	↑	=	↑	=	=	=	=	=	=	↑	=
	MAP ↓	LV	↓*	=/↓	=/↑	↑	=	=	=	↑	=	↑	=	=
	Volume condensation	RV & LV	↓	↑	=/↑&	↑	=	↑	=	↑	=	↑	↑$	=
Mechanical devices	IABP	LV	↓	↑	↑*	↑	↓	=	=	=	=	=	=	↑
	Impella	LV	↓↓	↑↑	↑↑*	↑↑	↓	=	=	=	=	=	↑	↑↑
	LA/LV venting	LV	=/↓	=	=/↑*	↑↑	↓	↑↑	=	↑	=	↑	↑↑	=

Legend: ↑ : mild, ↑↑ : moderate, ↑↑↑ : strong, ↑↑↑↑ : very strong, = : no effect

* Through a lowering in afterload. # Through a reduction in preload. & Depending on the fluid status of a patient. ^Through a systemic inflammatory response. $ In case severe hypovolemia occurs. % This risk is lower in case of transaortic axial blood pump (Impella) support. ** slight arrhythmic effect.

CO: Cardiac output. MvO2: myocardial oxygen consumption. ACE: Angiotensin converting enzyme. ARNI: Angiotensin receptor-neprilysin inhibitor, ATII: Angiotensin 2. MRA: Mineralocorticoid receptor antagonist. SGLT2-inhibitor: Sodium-Glucose Co-Transporter 2 inhibitor, PEEP: Positive end-expiratory pressure. MAP: Mean arterial pressure. IABP: Intra-aortic balloon pump. LA: Left atrium. LV: Left ventricle.

An important and well-established strategy in the management of HFrEF involves lowering of LV mechanical loading conditions, notably preload and afterload. In the context of CS, the latter could be accomplished by decreasing or, ideally, ceasing vasopressor administration while assuring a minimally acceptable blood pressure under individually optimized tMCS. When mean arterial blood pressure exceeds 70–80 mmHg, vasodilator therapy should be initiated and would preferentially encompass angiotensin-converting enzyme (ACE) inhibition [18], angiotensin (AT)-II antagonists plus/minus neprilysin inhibition [19] or hydralazine [20] given additional beneficial effects on cardiac remodeling in the setting of HFrEF. An equally important goal would be to lower LV preload as much as possible and condensate volume status as soon as the clinical situation permits [8]. The use of a pulmonary artery catheter could guide these processes by measuring pulmonary artery occlusion pressures and mixed venous oxygen saturation [21]. Therapies of choice include diuretics or renal replacement therapy (RRT) [22]. Of special note, mineralocorticoid receptor antagonists (MRA) and sodium glucose cotransporter 2 (SGLT-2) inhibitors could also be of added value as they act through different potentially beneficial mechanisms and have shown to improve mortality in general HFrEF populations. Especially SGLT2i could be of benefit given its hemodynamic profile and apparent benefit on outcome even within weeks after initiation [23].

In the context of V-A ECMO support, the (retrograde) extracorporeal blood flow from the V-A ECMO pressurizes the aorta which may increase LV afterload [24] and cause signs of LV dilatation and congestion in 20–40 percent of patients, particularly early after support initiation [25]. When tailoring of medication and ventilatory settings would insufficiently mitigate the potential negative sequelae, adjunct mechanical unloading through an intra-aortic balloon pump (IABP), a transaortic microaxial flow pump (Impella), or left atrial/ventricular venting may effectively help to lower LV afterload [26]. Two recently published randomized clinical trials showed that routine early left atrial venting was not superior over an initially conservative approach with regard to 30 day survival [27,28]. However, a large cross-over (50 and nearly 80 %) prevents from drawing solid conclusions. Whether routine unloading through IABP (*Randomized Embedded Multifactorial Adaptive Platform in ECMO*) [29] or Impella (*ECMO-UNLOAD, NCT05577195*) as adjunct intervention to V-A ECMO truly improves patient outcomes is currently under investigation in ongoing RCTs. At this moment, expert opinion recommends restricting the use of adjunct mechanical unloading devices to situations where insufficient trans pulmonary blood flow is accompanied by symptomatic increases in intracardiac pressures [30].

In case of ST-elevated myocardial infarction induced CS, coronary revascularization was shown to improve six months survival and currently is the only Class 1 recommendation supported by RCT data [31]. From a metabolic perspective, the myocardium seems best served by omitting beta-adrenergic drugs (e.g. dobutamine, adrenaline) [32]. Prolonged inotrope exposure causes calcium overload, β-receptor desensitization, and cell death, hindering recovery. Clinically, it increases the risk of arrhythmias, sudden death, and overall mortality [4,33,34]. Oppositely, beta-blockers have been shown to restore beta-adrenergic signaling [35] and significantly improve survival and quality of life, making it a cornerstone treatment in HFrEF patients [2]. Of special interest, a predefined subgroup analyses of the COPERNICUS RCT showed that the beneficial effects of carvedilol on all-cause mortality were most profound in a subgroup of HFrEF patients at highest risk (hazard ratio (HR): 0.20 (95 % CI: 0.06–0.89) vs (0.75 (0.41–1.35)) [36]. Highest risk was defined by ejection fraction <15 %, recurrent cardiac decompensation, hospitalization, need for inotropic agents or signs of decompensation at randomization. Despite having been pre-treated with beta-blockers, cardiomyocytes are still susceptible to inotropic drugs [37]. This concept especially holds for phosphodiesterase inhibitors while the effects of beta-adrenergic substances depend on the type of beta-blocker administered [38]. Moreover, the use of ultra short acting beta-blockers in cardioplegia solutions during cardiac surgery has been associated with a reduction in the incidence of myocardial ischemia, arrhythmias, and an increased susceptibility to inotropic drugs [39].

The use of beta-blockers in CS remains, up till now, a largely unexplored territory and current data are insufficient to support routine use in HF patients supported by tMCS. Case series have suggested safety and potential benefits by promoting weaning success from V-A ECMO [40,41] and Impella [42] support in carefully selected CS patients. To structurally investigate the feasibility and safety of beta-blocker usage in V-A ECMO supported CS patients, we initiated a phase 2 RCT (“*REMAP ECMO beta-receptor modulation trial domain”, NCT06522594*). This trial compares a strategy in which dobutamine is phased out and esmolol is initiated and uptitrated (“Beta receptor inhibition arm”), to a routine clinical care approach where a dobutamine drip is typically continued throughout V-A ECMO support. Importantly, this strategy is implemented under an umbrella of V-A ECMO and milrinone, and subject to careful monitoring of organ perfusion and trans pulmonary blood flow. Of importance, great caution should be exerted as an increased heart rate may be the only compensatory reaction left to sustain cardiac output in patients with severely depressed LV function [43].

Therapies potentially promoting right ventricular recovery during tMCS for CS

The RV is a comparatively thin-walled structure which operates at low pressures and generates sufficient cardiac output in the context of low afterload [44]. These characteristics render the RV more sensitive to acute pressure- and volume- overload cumulating into RV failure [45]. This concept is supported by the hemodynamic functionality of a total cavo-pulmonary conduit (Fontan circulation) in the virtual absence of contractile RV tissue [46]. Hence, from a mechanistic perspective, RV function will particularly be affected by therapies alleviating unfavorable hemodynamic loading conditions rather than those merely stimulating and potentially exhausting intrinsic myocardial properties. RV failure during tMCS can be identified and monitored by a combination of hemodynamic criteria (e.g. high central venous pressure relative to the pulmonary capillary wedge pressure (PCWP), low cardiac index (CI), low pulmonary artery pulsatility index (PAPi $<$ 1.0 – 1.5)), and echocardiographic criteria (RV dilation, reduced tricuspid annular plane systolic excursion (TAPSE), S', fractional area change or RV strain, and interventricular septal shift) [47]. It must be noted that evidence guiding the assessment of RV function in the setting of MCS remains limited, and much of the current practice is extrapolated from data obtained in patients not receiving MCS.

RV afterload can be reduced by intervening in pathways negatively influencing pulmonary (vascular) resistance. Strategies to reduce pulmonary vascular resistance include maintaining partial oxygen-, and carbon dioxide- pressures, and pH within physiological ranges. Inhaled nitric oxide (NO) ventilation can aid in selected cases [48]. In addition, vasopressin seems associated with less pulmonary vasoconstriction than noradrenaline [49]. Patients with predominant RV failure should also be aggressively screened and treated for pulmonary atelectasis, as RV function can significantly benefit from prone position [50] and optimization of PEEP levels [51]. Higher PEEP levels may also be preferable in the context of pulmonary edema where the prevention of pulmonary hypoxemia may avert an increase in pulmonary vasoconstriction [52]. Fluid overload is one of the major risks for an already failing RV

and can importantly contribute to refractory RV failure. Early decongestion is therefore of substantial importance to mitigate this risk and can be realized with diuretics or RRT, though this should be carefully balanced against maintaining adequate systemic perfusion. RV preload can also be significantly influenced by respiratory patient efforts during spontaneous ventilation which typically add to dynamic fluctuations in preload [45,53,54]. In contrast to the LV, the RV is actively unloaded by V-A ECMO as the parallel extracorporeal circuit bypasses the pulmonary circulation [55]. The V-A ECMO induced increase in renal perfusion pressure, along with the reduction in acute kidney injury (AKI) events requiring RRT, might also be attributable to effective decongestion [56].

Few studies have addressed the role of heart failure strategies in patients with isolated RV failure. Therapeutic options directly affecting RV myocardial function seem however very limited because of the RV's limited inotropic reserve. This especially holds for beta-blockers. Although their use was shown to improve RV function in patients with HFrEF [57], this did not translate into improved survival rates [58]. In the specific setting of pulmonary hypertension, beta-blockers and ACE inhibitors have even been associated with harm [59]. In addition, maintenance or restoration of sinus rhythm and heart rate control seems important to preserve the contribution of an 'atrial kick', particularly in the setting of RV failure [60]. When RV failure persists despite medical therapy, escalation to mechanical RV support, such as percutaneous short-term RV assist devices (e.g. Impella RP, or ProtekDuo), can be considered to allow more time for RV recovery [61]. However, durable MCS options for isolated RV failure are currently limited, and in cases where RV recovery does not occur, heart transplantation is often the only solid exit strategy [62].

A "hemodynamic envelope" for the management of CS

Although potent tMCS devices, like V-A ECMO, Impella 5.5, and ECMELLA, can fully support a patient's severely failing circulation, important hemodynamic risks still remain. Contemporary risk monitoring relies on the monitoring and interpretation of numerous clinical variables with respect to universal reference values which are typically based on healthy populations. This one-size-fits-all approach overlooks key differences in disease aetiology and severity, does not account for interactions among variables, and is increasingly harder to interpret given the rapidly expanding technology and patient complexity.

In aviation, a similar challenge was faced with regards to flight safety which was solved by the development of the so called "*flight envelope*" forming the basis for the creation of automated envelope protection algorithms and autopilot systems [63]. The classical flight envelope concept typifies an airplanes' specific safety window as a function of air speed, altitude and several dynamic factors including load factors and wind gusts (Fig. 1). A flight envelope indicates safe boundaries within which an aircraft can be operated. The boundaries are tested in a flight test program for each aircraft specifically and are published in the flight manual available to the pilots. The published boundaries include safety margins relative to the limits verified in flight tests. The flight envelope is not a static set of boundaries. The boundaries can change during a flight, depending on the airplanes' configuration. For instance, extending the flaps at the rear end of the wing during take-off and landing allows the aircraft to fly safely at lower speeds. This safe zone is indicated by the green area in the figure. When an airplane would exceed its defined envelope thresholds, it is said to "*fly out of the envelope*" and the risks for structural hazards vastly increase. In modern aircraft, onboard computers employ envelope protection algorithms to ensure the plane remains within the safe limits of the flight envelope, warning pilots in time when limits are being reached so they can take appropriate action(s) before the boundaries of the flight envelope are exceeded.

Though the complexity of critically ill patients exceeds that of aviation "physiology" by far, we are profoundly inspired by this aviation approach and translated this concept to CS and developed a framework we called "the hemodynamic envelope". We hypothesized that a full hemodynamic envelope during tMCS support would be composed of the following nine axes:

1) Systemic oxygen consumption (VO_2)
2) Systemic blood flow (totaling native cardiac output and tMCS blood flow)
3) Native cardiac output / transpulmonary blood flow
4) Organ perfusion

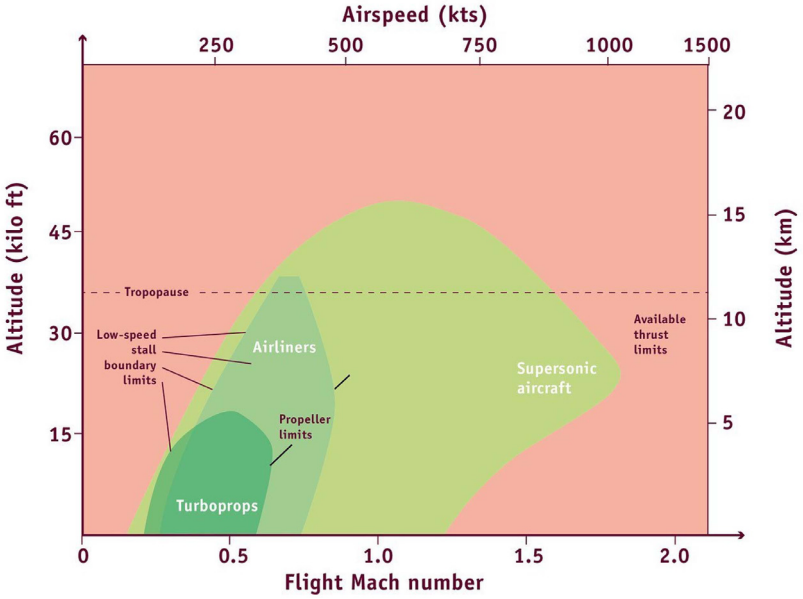


Fig. 1. A graphical illustration of the flight envelope. A graphical illustration of the flight envelope as a function of altitude and airspeed where the green area denotes a safe zone and the red area represents a zone of risk. The envelopes are defined by critical stall thresholds on the left side, with the upper boundary marked by the ceiling altitude and the right side limited by the maximum thrust and the aircraft's structural integrity. The different green areas denote flight envelopes for different type of planes.

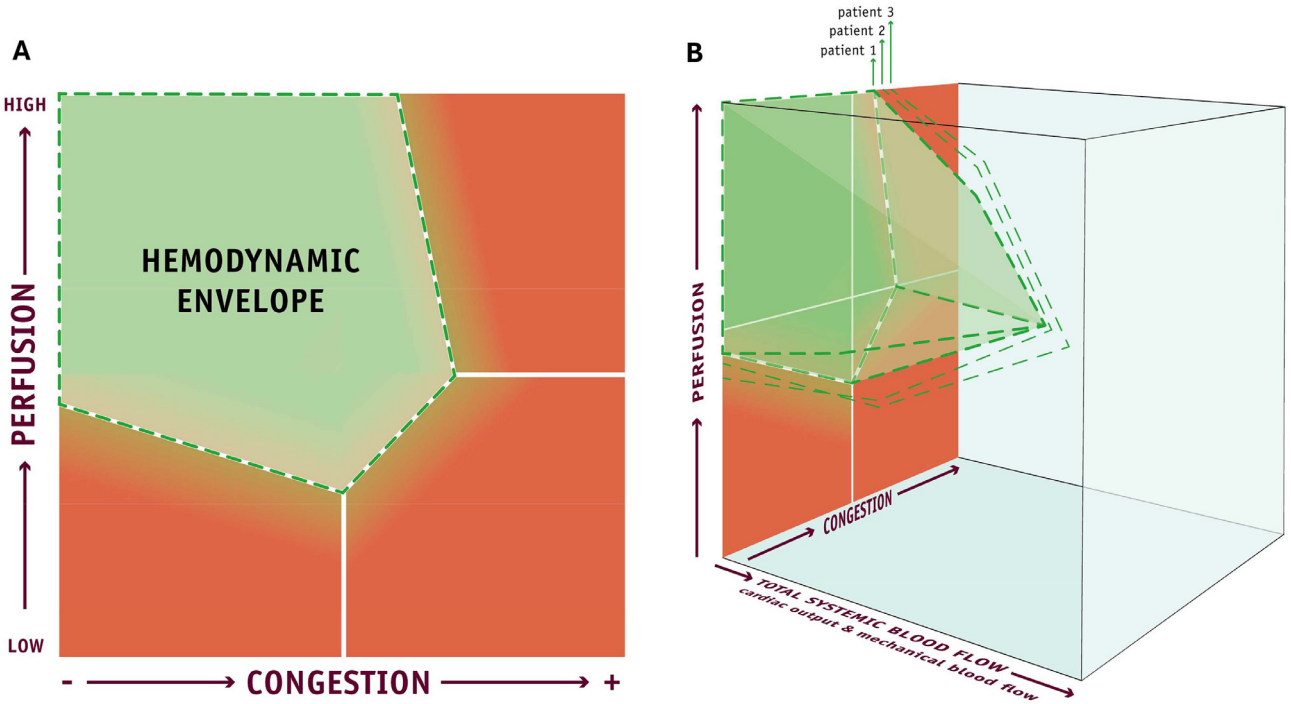


Fig. 2. A graphical illustration of the hemodynamic envelope. Simplified graphical illustrations of the hemodynamic envelope framework in a two dimensional- (A) and a three dimensional- version (B). In these graphs, the green zones denote an area of hemodynamic safety. Around this green zone lies an initial orange zone of relative risk, beyond which the red zone reflects higher danger. The safety boundaries of the hemodynamic envelope are likely patient- and context-specific, as illustrated by the different dashed lines in panel (B).

5) Mean arterial blood pressure
6) Left ventricular end-diastolic pressure
7) Right ventricular end-diastolic pressure
8) Arterial oxygen saturation
9) Hemoglobin concentrations

An overview of golden standard measurements for these axes values are summarized in Supplementary Table 2. In a situation without V-A ECMO, native cardiac output would equal total systemic blood flow reducing the model to eight axes. A simple version of the hemodynamic envelope framework can be illustrated in a two- and three-dimensional (Fig. 2A, and B respectively) using a modification of the Nohria Stevenson classification illustration [64]. In these figures, the green area denotes the hypothetical area of hemodynamic safety. Its boundaries are likely both patient- and time- specific, as for example organ sensitivity to hypoperfusion and congestion differs between individuals and changes across disease states. However, these limits are at this moment speculative as no data yet exist on this approach.

We envision that the hemodynamic envelope could be operationalized in two ways; 1) by employing deterministic cardiovascular physiological models that represent the cardiovascular system through all relevant interactions among hemodynamic variables [16,65,66]. In doing so, these models could continuously estimate hemodynamic-envelope variables that are not directly measured, along with their critical thresholds, based on their relationship with known inputs such as VO_2. 2) By training artificial intelligence (AI) models, such as long short-term memory recurrent neural networks (LSTM) [67], on cohorts of CS patients with highly granular data. LSTM neural networks have the advantage of capturing and selectively managing multiple streams of long-range temporal dependencies while effectively handling irregular patterns and nonlinear physiological dynamics encountered in CS. Their gating mechanisms allow them to retain or discard information as needed, making them well suited for complex, variable time-series data where important signals may be distributed unevenly over time.

The hemodynamic envelope framework can be brought to the bedside using real-time automated data streams from modern ICU monitoring systems. These typically include arterial pressure waveforms, pulmonary artery catheter data (e.g., cardiac output, SvO_2), ventilator parameters, and surrogates of oxygen consumption (e.g., $etCO_2$, $ScvO_2$). Its core function is to determine a patient's position within their individualized envelope relative to axis-specific thresholds. This position—and how it changes over time—can then inform treatment decisions of pharmacologic or mechanical hemodynamic support (e.g., adding an LV-unloading device), and the initiation of heart-failure therapies [68].

Using the hemodynamic envelope framework to apply heart failure therapies in cardiogenic shock

In CS, the balance between oxygen supply and demand is typically defined by a fine line. The application of potent tMCS devices (e.g. V-A ECMO, Impella 5.5 and ECMELLA) can bring a patient to within the safe (green) "*hemodynamic envelope*" area (Fig. 3A). This newly created space and buffer can then be used to apply heart failure therapies which have classically been considered contraindicated because of their risks for hemodynamic deterioration. As such, tMCS is used as an "umbrella" to introduce heart failure therapies.

Proven heart failure therapies (e.g. beta-blockers, ACE/AT2/neprilysin inhibitors) which by nature may temporarily compromise hemodynamics as part of their action, carry a higher risk than other interventions and, as such, demand more hemodynamic buffer. This concept can be illustrated in relation to the hemodynamic envelope (Fig. 3B and C for both left and right ventricle, respectively). The circles illustrate the areas where

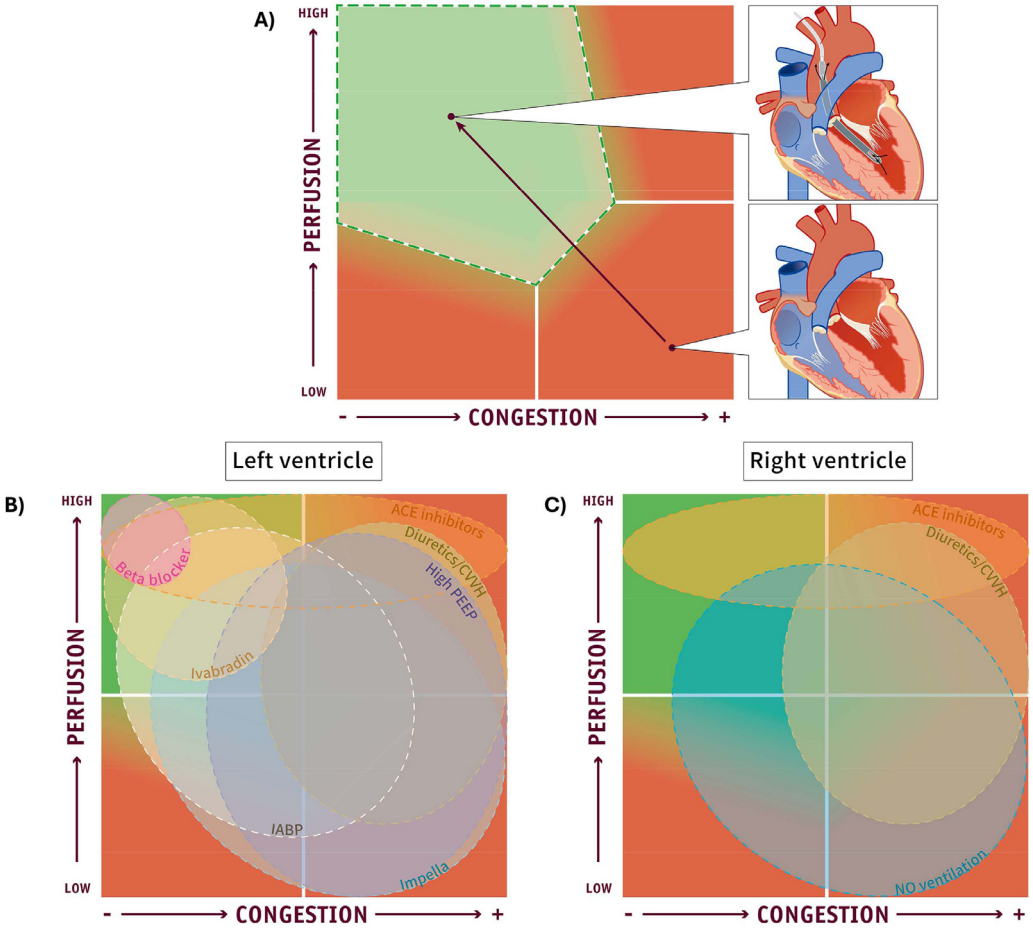


Fig. 3. The potential effect of tMCS devices and heart failure therapies on a patients' position within the hemodynamic envelope framework. The hemodynamic envelope framework can be used to illustrate the stabilizing effects of tMCS and other hemodynamic supports for patients who are outside the hemodynamic envelope (green) area (A). Using this concept, indication areas for heart-failure therapies can be mapped onto the hemodynamic envelope for the left ventricle (B) and right ventricle (C). In both panels, circles indicate the areas where potential indication and hemodynamic space exists to initiate specific heart failure therapies to promote LV and RV recovery. Other evidence-based therapies, such as SGLT2 inhibitors or angiotensin receptor–neprilysin inhibitors (ARNIs), could similarly be incorporated into this conceptual framework, but were omitted to avoid overcrowding the figure.
IABP = intra-aortic balloon pump, ACE = angiotensin-converting enzyme, CVVH = continuous veno-venous hemofiltration, PEEP = positive end-expiratory pressure, NO = nitric-oxide

potential indications and hemodynamic space exist for specific heart failure therapies. In a congested patient for example - whose profile is on the lower corner of the graph - administration of diuretics or RRT should be considered. When this patient would happen to be on V-A ECMO support and would also have low trans pulmonary blood flow and high intracardiac pressures, LV unloading through adjunct Impella support should be considered. The combination where trans pulmonary blood flow is relatively high in the context of LV failure without any compromise of organ perfusion could theoretically provide the space to initiate beta-blocker therapy.

The position of a patient within the *hemodynamic envelope* and the available hemodynamic space can guide decisions surrounding the initiation and tailoring of heart failure therapy in CS patients (Fig. 4). In the scenario, where a patient would be outside their hemodynamic envelope (scenario A), focus should go out to bringing the hemodynamic status within safety margins first, for example through the use of adjunctive tMCS. Such a scenario could involve a patient with clear radiographic evidence of congestion, ongoing arrhythmogenic events, or persistent underfilling as indicated by pulmonary artery catheter readings. In the alternative scenario, when a patient would reside within their hemodynamic envelope, this would provide the buffer to initiate heart failure therapies (scenario B).

This whole process should be considered dynamic as a patient's position within the hemodynamic envelope can significantly and suddenly change as a result of disease related factors and intercurrent. From this perspective, it seems rational to use pharmacological agents with short half-lives for treatment approaches with the highest risk. For example, esmolol and landiolol are ultra selective beta-blockers with very short half-lives as their degradation depends on plasma esterase activity instead of organ functioning [69]. Within an individual patient and over time, dosages could then be tailored and maximized according to the hemodynamic buffer within the corresponding envelope.

This novel approach of using tMCS and the hemodynamic envelope to initiate heart failure therapies in patients with severe CS warrants further investigation. Future studies should focus on the feasibility and efficacy of heart failure interventions in the acute CS setting, as current evidence is still very limited (Supplementary table 3). In parallel, studies on the hemodynamic envelope framework should be performed to identify patient-specific and context-specific thresholds being associated with increased risk for clinical deterioration. The process of tMCS weaning should be considered in separate as this challenges the critical thresholds of the hemodynamic envelope and may require temporary support with inotropic medication and vasopressors with or without the maintenance of heart failure medication. For a discussion of

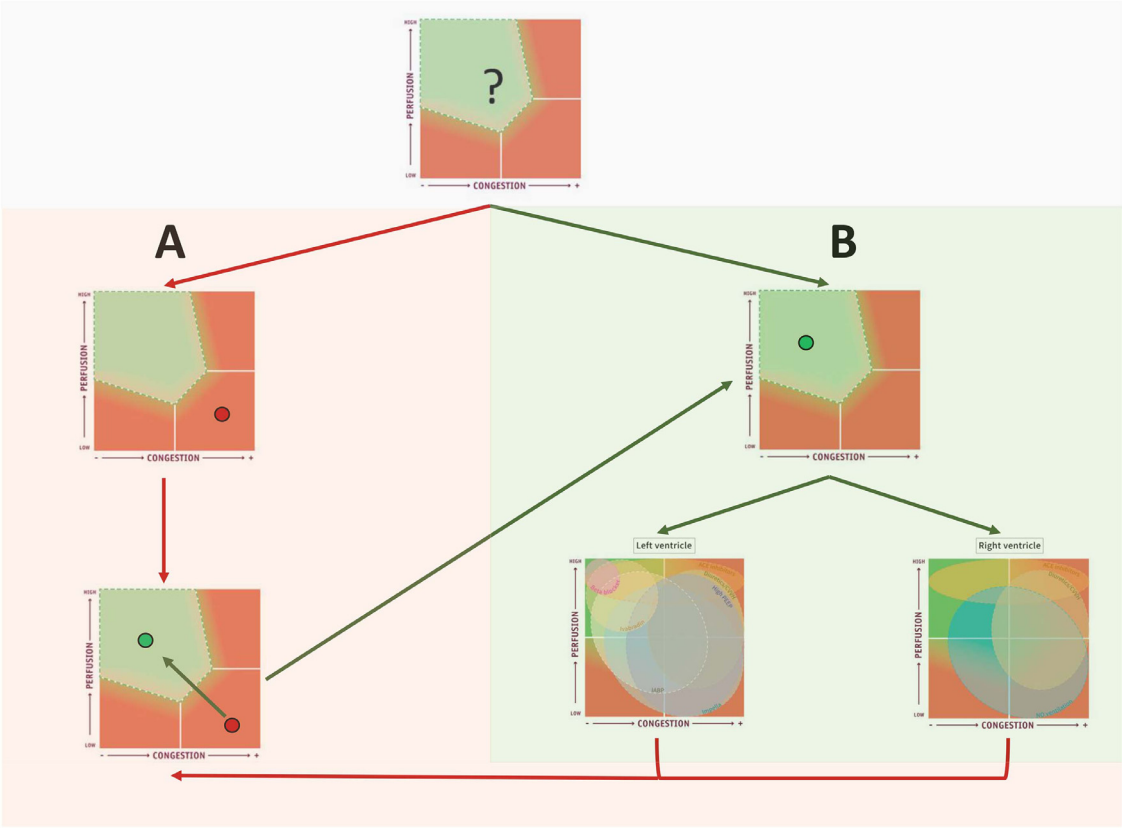


Fig. 4. An algorithm to tailor heart failure therapies based on a patient's position within the hemodynamic envelope. Scenario A illustrates the situation where a patient would reside outside their safe hemodynamic envelope thresholds and focus should go out to bringing the patient within their envelope, for example by initiation of temporary mechanical support devices. In scenario B, patients are within the hemodynamic envelope allowing for the introduction of heart failure therapies. The possibilities of heart failure therapies depend on the type of cardiogenic shock (RV vs LV) and degree of hemodynamic buffer available. During this process, a patient's position should be continuously monitored against updated envelope thresholds, with actions taken as needed.

factors maximizing V-A ECMO weaning success in the weaning phase itself, we refer the reader to dedicated literature [8,70].

Conclusions

In patients with CS, tMCS systems have traditionally been viewed upon and used as a tool to increase systemic organ perfusion. We outline an innovative approach in which potent tMCS is used as an umbrella in CS to enable the initiation of potentially beneficial heart failure therapies that are traditionally considered hazardous in this setting. This combined tMCS-protected pharmacological strategy may importantly enhance cardiac recovery and outcomes of patients with the most severe and acute manifestations of heart failure. To catalyze the use of this treatment approach focused on myocardial recovery in CS, we introduce a novel, aviation inspired, safety framework denoted as the "*hemodynamic envelope*". This framework has the potential to help clinicians identify specific heart failure therapy (contra)indications, monitor patient safety, and provide guidance for future studies.

Declaration of competing interest

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CRediT authorship contribution statement

C.L. Meuwese: Writing – review & editing, Writing – original draft, Conceptualization. **M.P.J. van Steenwijk:** Writing – review & editing, Writing – original draft. **J.E. Møller:** Writing – review & editing. **J.A. Melkert:** Writing – review & editing. **D.W. Donker:** Writing – review & editing, Resources. **R.A. de Boer:** Writing – review & editing.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.tcm.2025.12.006.

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