Cardiogenic Shock: From Defining Hemodynamic Phenotypes to Targeted Therapy

Cardiogenic shock (CS) is variably defined as a state of end-organ hypoperfusion due to the heart’s inability to deliver sufficient oxygen to tissues to meet metabolic demands in the presence of adequate intravascular volume .

Cardiogenic shock (CS) remains a major unsolved problem with mortality rates of 40–50%

- The clinical definition of AMI-CS often used in clinical trials is a combination of low systolic blood pressure (SBP) of < 90 mmHg and evidence of low CO (CI < 2.2 L/min/m2) in patients with elevated filling pressures (pulmonary-capillary wedge pressure [PCWP] > 15 mmHg)

- Certain patients have clear evidence of reduced CI and elevated PCWP but with an SBP greater than 90 mmHg. In addition to including absolute blood-pressure parameters in the definition of CS, the degree of hypotension relative to the patients preexisting blood pressure should be considered in the diagnosis of CS.

- In the SHOCK trial registry, 5.2% of patients were in CS but had an SBP > 90 mmHg, and 7.1% had no evidence of organ hypoperfusion with an SBP < 90 mmHg.

- Both SvO_2 and $ScvO_2$ are markers of oxygen delivery/consumption imbalance and thus indirectly of inadequate .
- Arterio-venous difference in CO_2 from sampling of mixed/central venous and arterial blood may be also used to detect patients with inadequate CO (i.e., delta $CO_2 \geq 6$ mmHg).
- Laboratory evaluation of CS is mostly based on markers of tissue hypoperfusion and end-organ damage. Lactate represents the reference standard in laboratory assessment of tissue hypoperfusion and hypoxia

Table 1 Society for Cardiovascular Angiography and Interventions (SCAI) cardiogenic shock stages

Shock stage	Description	LACTATE	Hemodynamics
A	No shock yet, but patient is at risk (e.g., large AMI or heart failure) with no signs of hypoperfusion	< 2 mmol/L	SBP ≥ 100 mmHg or at baseline
B	Early or "pre-shock" with hemodynamic instability, but *without* end-organ hypoperfusion	< 2 mmol/L	SBP < 90 mmHg MAP < 60 mmHg > 30 mmHg drop from baseline Heart rate ≥ 100 bpm
C	Hypotension with clear hypoperfusion (e.g., cold extremities, confusion, and low urine output) requiring intervention (inotropes and/or mechanical support)	> 2 mmol/L	SBP < 90 mmHg MAP < 60 mmHg > 30 mmHg drop from baseline Heart rate ≥ 100 bpm
D	Shock that is worsening or refractory—initial measures have failed to stabilize the patient, and escalation (multiple vasopressors or mechanical circulatory support) is needed.	> 2 mmol/L	Any of stage C and requiring escalating doses or increasing numbers of vasopressors or addition of a mechanical circulatory support device to maintain perfusion
E	Impending cardiovascular collapse, with refractory shock (often featuring cardiac arrest, pulseless electrical activity, or requiring cardiopulmonary resuscitation) despite maximal support	> 8 mmol/L	Profound hypotension despite maximal hemodynamic support

- he initiating event in CS is a significant alteration of cardiac function, with the resultant reduction in CO and elevation in filling pressures perpetuating myocardial ischemia, further exacerbated by reduction in aortic root pressure ultimately leading to impaired myocardial per fusion (increased left-ventricular pressure and decreased diastolic pressure).

- Compensatory vasoconstriction leads to coronary/systemic vascular bed dysfunction, potentially worsening myocardial and other organ ischemia . CS can additionally precipitate a systemic inflammatory response, resulting in pathological peripheral vasodilation and altered microcirculation via release and activation of reactive oxygen species, pro-inflammatory cytokines, and activation of damage-associated molecular patterns.
- Therefore, beyond the traditional cardio centric approach, CS is increasingly recognized as a systemic disease resulting in multi-organ dysfunction .

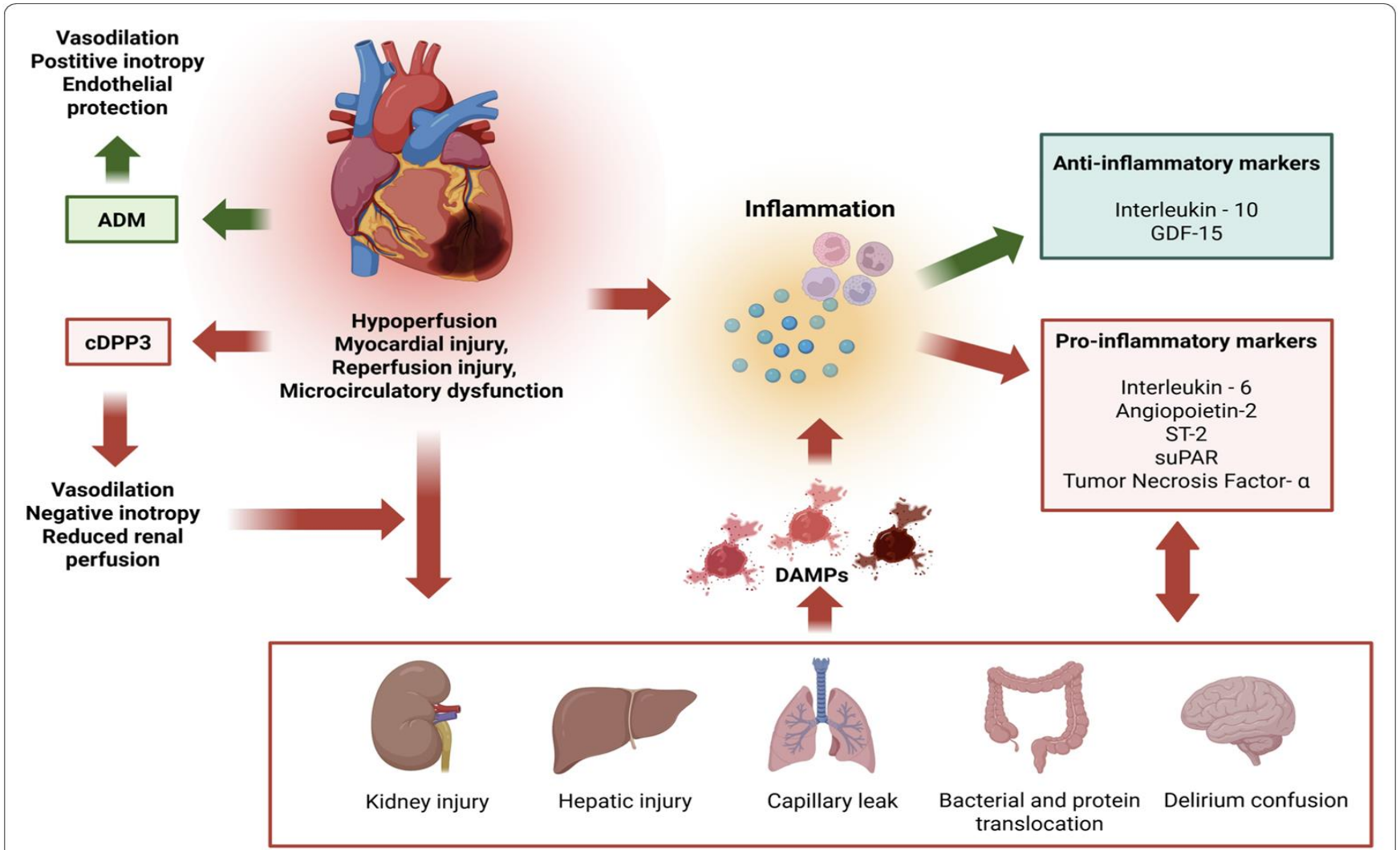


Fig. 3 Cardiogenic shock effects on organ function and systemic response. CS may trigger immune system and may initiate a downward spiral leading to microcirculatory collapse and multi-organ failure. It has detrimental effects on end-organs, including the kidneys (kidney failure), the liver (hypoxic hepatitis, impaired coagulation factor synthesis), the gut (bacterial and protein translocation), the lungs (capillary leak, pulmonary edema), the brain (mental confusion), and the heart itself (myocardial depression). Selected specific cytokines and biomarkers involved in main pathophysiologic pathways are shown. *ADM* Adrenomedullin, *cDPP*3 circulating dipeptidyl peptidase, *DAMP* damage associated molecular patterns, *GDF*-15 growth differentiation factor 15, *ST*-2 soluble suppressor of tumorigenicity 2, *suPAR* soluble urokinase-type plasminogen activator receptor

- These pathophysiological events are part of the downward spiral in CS. In the light of the fact that these events happen in a rapid sequence and stepwise worsen the prognosis , it is of paramount importance to therapeutically support the patient at the top of the CS spiral, rather than at the bottom to interrupt the chain of events.



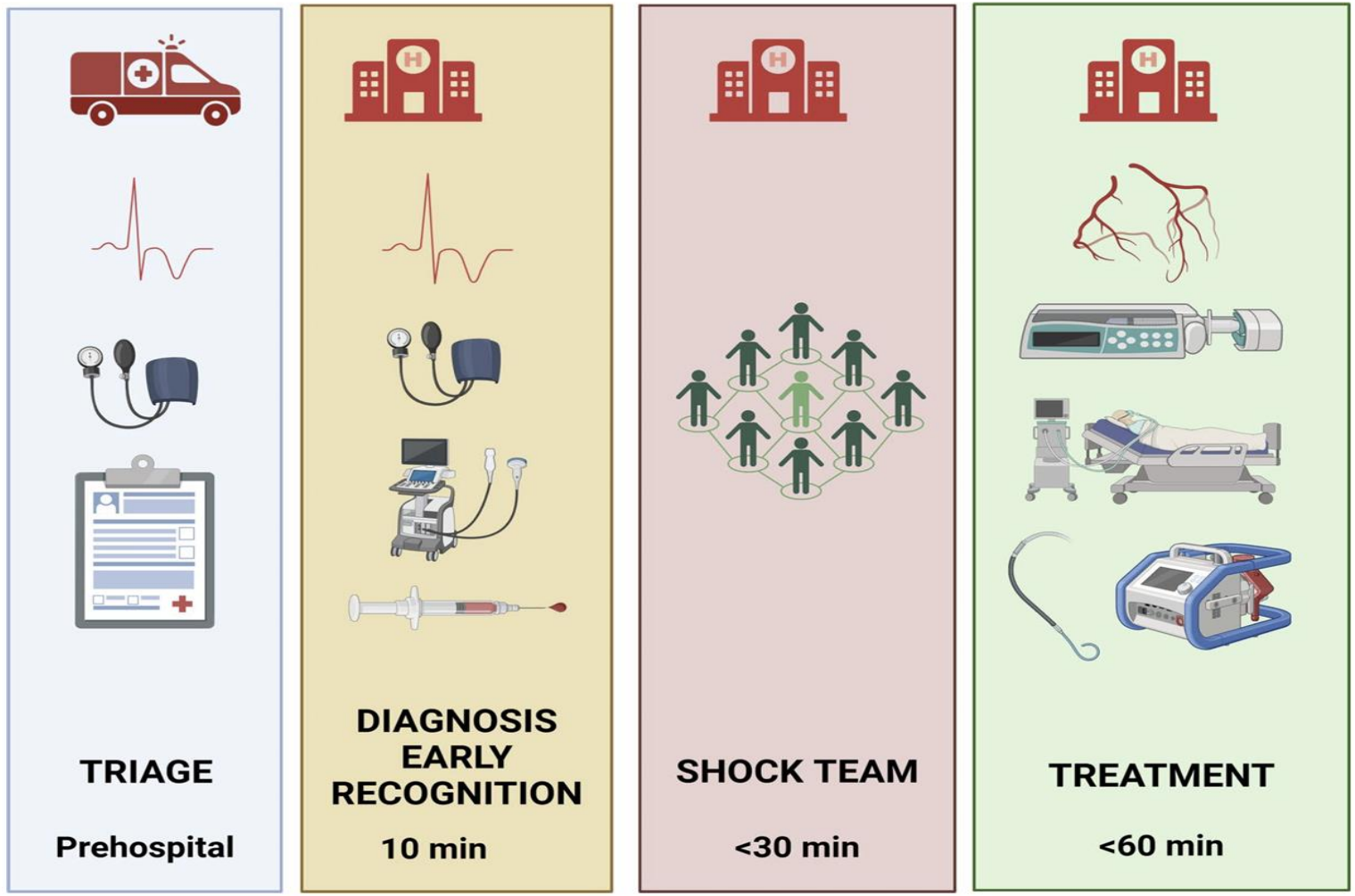


Fig. 1 The golden hour of cardiogenic shock diagnosis and treatment. Early recognition and initiation of therapy is a cornerstone in improving care of patients with CS. Already in the prehospital setting AMICS should be identified with rapid transfer to a catheterization laboratory. If admitted to an emergency department, the evaluation of patients with signs of shock should be prioritized and done within 10 min after arrival. Once CS is suspected, the shock team should convene and evaluate the patient within less than 30 min after admission. The aim is to initiate therapy within 60 min after first medical contact

Pharmacologic management of CS

- In AMI-CS, for example, AMI is the causal trigger . Drugs may help reducing the infarct area, and afterwards keeping the vessel open.
- Acute inflammatory myocarditis might need immunosuppressive therapy

- Basically, stroke volume as key parameter in CS depends on preload, afterload, contractility, and heart rate. All these single factors can pharmacologically be influenced both in one direction or another. There is growing evidence from observational data that complete hemodynamic phenotyping might be associated with improved outcome in CS

Pharmacologic management of CS

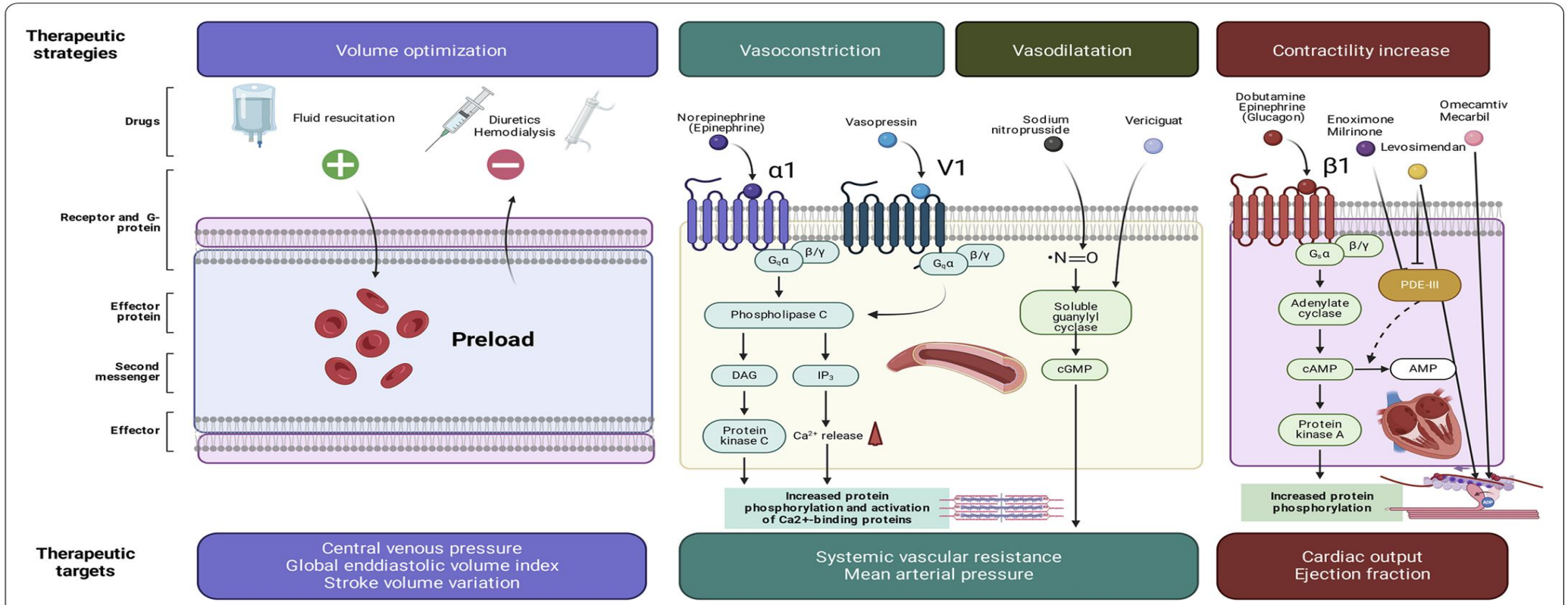


Fig. 2 Therapeutic strategies, pharmacologic mechanisms, and potential treatment targets in cardiogenic shock. *AMP* Adenosine Monophosphate, *Beta 1* β1 Adrenergic Receptor, *cAMP* Cyclic Adenosine Monophosphate, *cGMP* Cyclic Guanosine Monophosphate, *DAG* Diacylglycerol; Gs α- Stimulatory G protein α subunit, *Gs β/γ* Stimulatory G protein β/γ subunit, *Gq α* Gq alpha subunit, *Gq β/γ* Gq beta/gamma subunit, *IP3* Inositol Trisphosphate, *PDE-III* Phosphodiesterase-III, *V1* Vasopressin receptor subtype 1 (V1 receptor), *α1-Receptor* α-1 Adrenergic Receptor

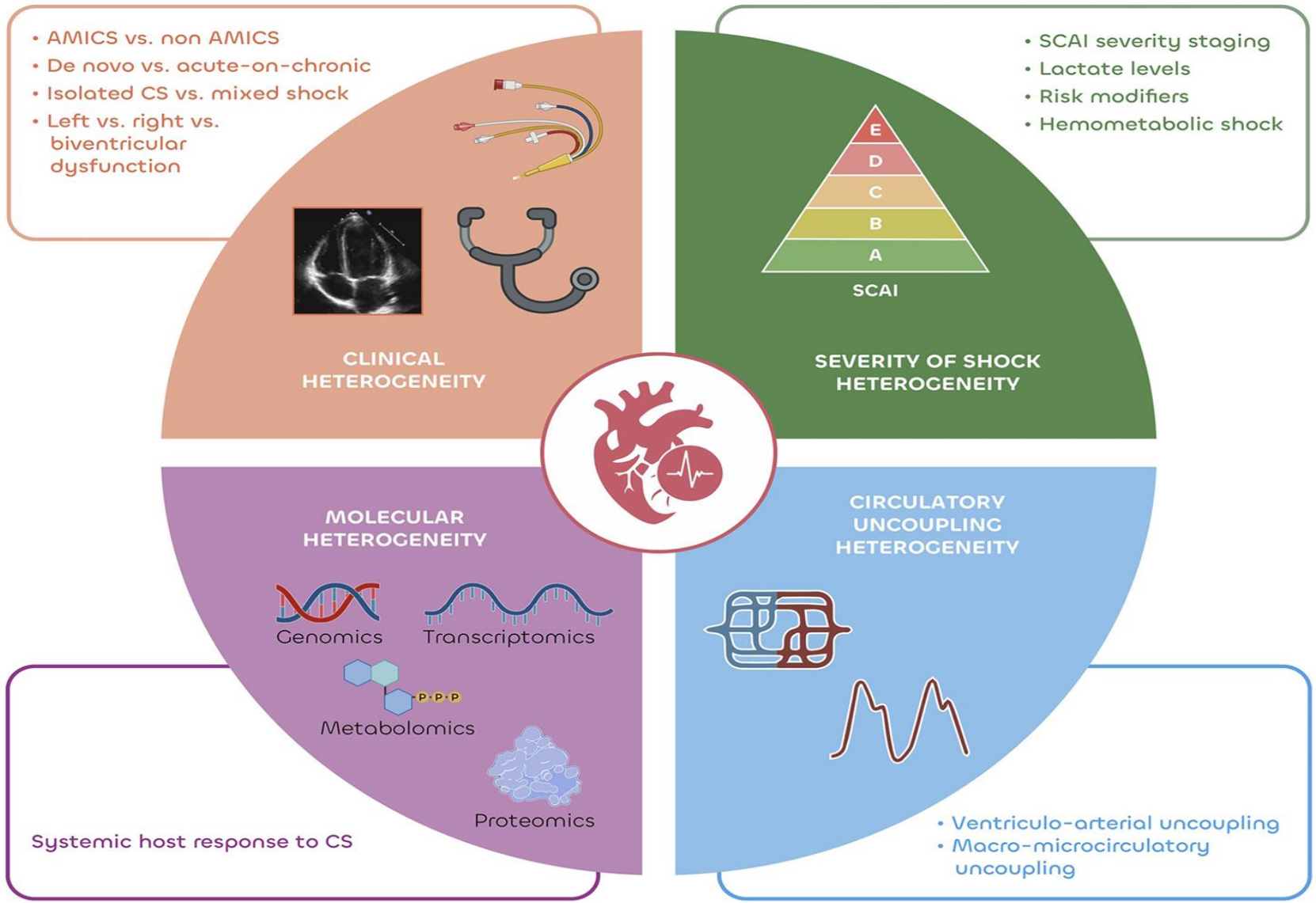
- The most commonly used vasopressor is norepinephrine (noradrenaline) , which is both recommended from the ESC and AHA , although a rather low level of evidence .
- However, its use should be limited to the shortest duration and low est dose, because escalating vasopressor requirement is linked to higher mortality in AMI-CS.

- There is no compelling evidence supporting the efficacy of any specific inotropic therapy in reducing mortality for hemodynamically unstable patients with CS, as neither the ESC nor the AHA guidelines make definitive recommendations, emphasizing the absence of robust evidence favoring one inotrope over another.

- Even though the 2016 ESC guidelines for heart failure recommended dobutamine as a “first line” inotrope, the current guidelines do not make specific recommendations . Observational studies and a recent RCT indicate favorable outcomes with dobutamine use in comparison to dopamine or epinephrine.

- In consequence, the DOREMI trial gives no reason to change current practice to use dobutamine as first choice inotropic agent. Currently, LevoHeartShock (NCT04020263) investigates the effect of early use of levosimendan versus placebo on top of a conventional inotropic strategy in CS, while DOREMI-2 (NCT05267886) evaluates the impact of inodilators (milrinone/dobu tamine) versus placebo with results being awaited . In the future, more tailored pharmacological manage ment approaches should be evaluated in clinical trials

(B)


• AMICS vs. non AMICS
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• Isolated CS vs. mixed shock
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CLINICAL HETEROGENEITY
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• Lactate levels
• Risk modifiers
• Hemometabolic shock
E
D
C
B
A
SCAI
SEVERITY OF SHOCK HETEROGENEITY
MOLECULAR HETEROGENEITY
Genomics
Transcriptomics
Metabolomics
Proteomics
Systemic host response to CS
CIRCULATORY UNCOUPLING HETEROGENEITY
• Ventriculo-arterial uncoupling
• Macro-microcirculatory uncoupling

- The manipulation of V–A uncoupling (i.e., heart rate control, titration of vasopressors) could serve as a potential physiology-based strategy to personalize CS management in complex clinical sce narios but still needs clinical validation

EJAIC

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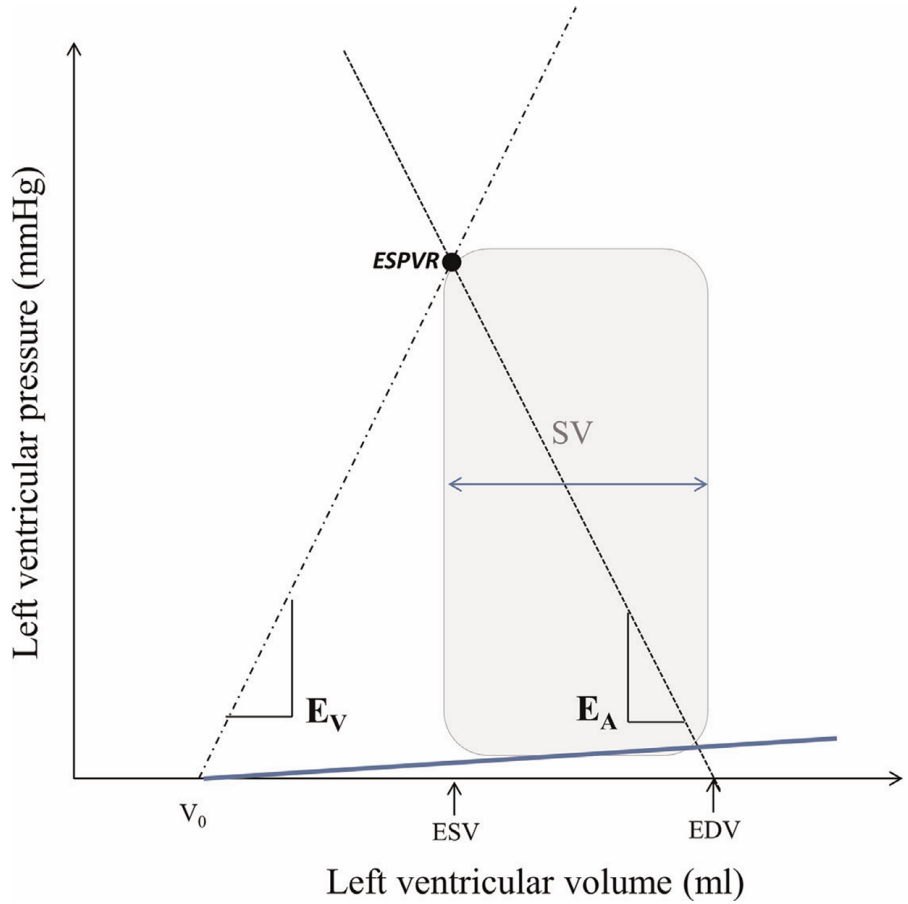
OPEN

REVIEW ARTICLE

Ventriculo-arterial coupling: from physiological concept to clinical application in peri-operative care and ICUs

Pierre-Grégoire Guinot, Stefan Andrei and Dan Longrois



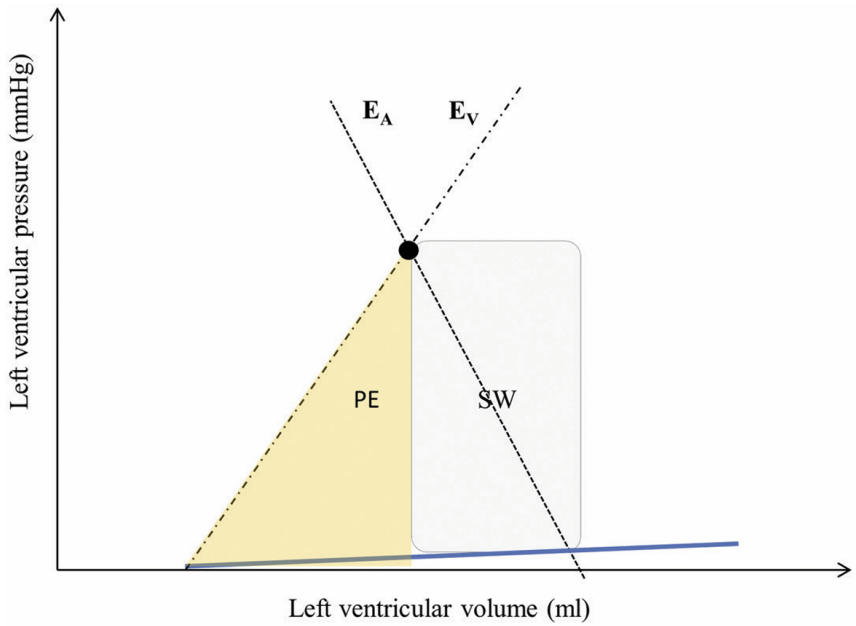
E_V is the slope of the line connecting V_0 to the ESPVR

Load independant ventricular function
E_V = 2.3 +/- 1 mmHg ml^{-1}

E_A is the slope of the line connecting the LV end-diastolic volume to the ESPVR

Vascular function : pulsatile and continuous component of arterial load
E_A = 2.2 +/- 0.8 mmHg ml^{-1}

- Ventriculo-arterial coupling :
E_A/E_V : 1 +/- 0.36

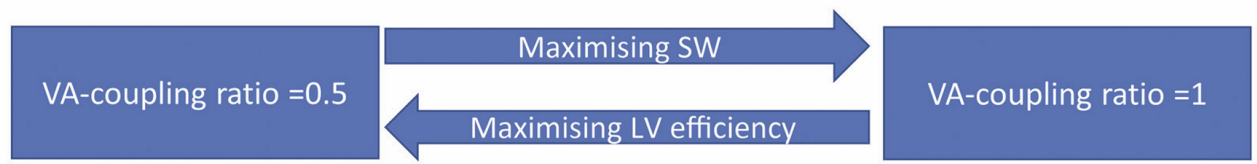


Stroke work (SW): ventricular energy delivered to the vascular system to maintain pressure

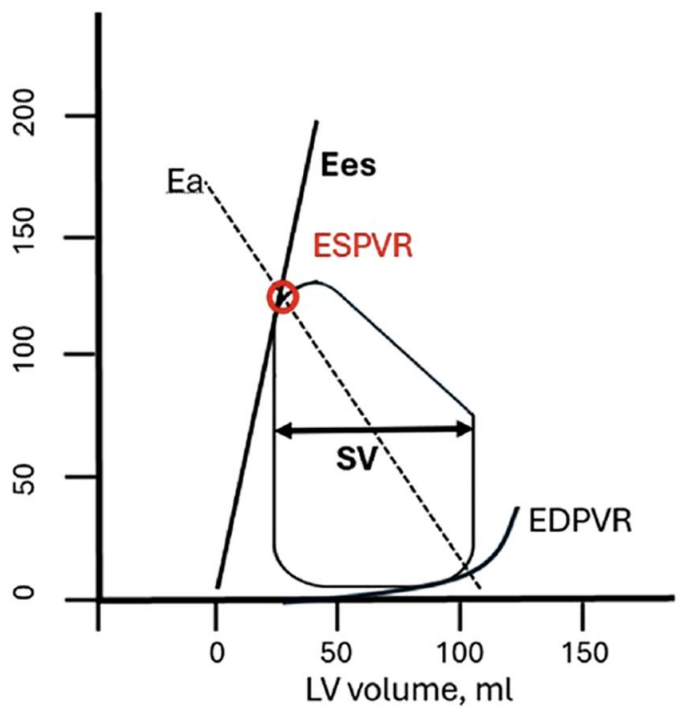
Potential energy (PE) : ventricular energy dissipated during isovolumetric contraction

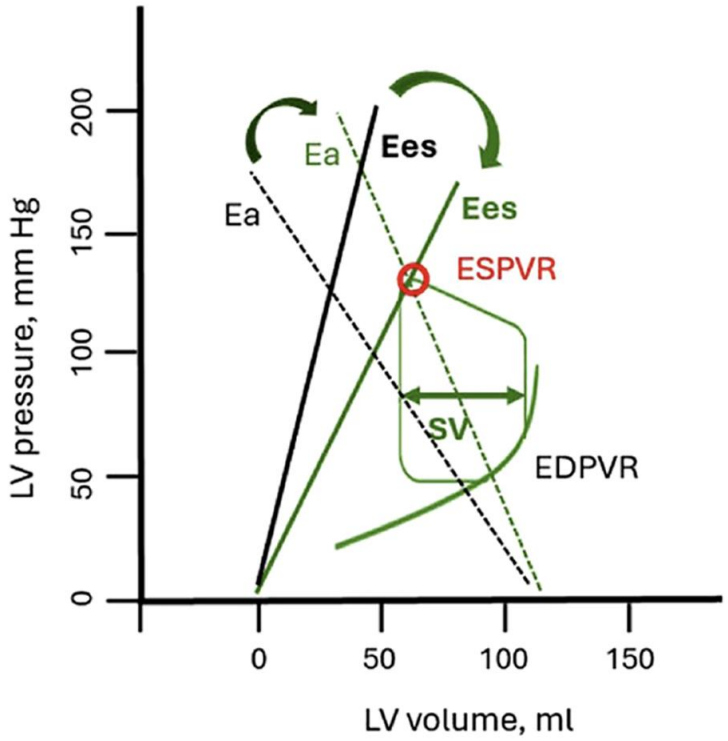
Pressure volume area (PVA): SW + PE
Correlated to myocardial O_2 consumption

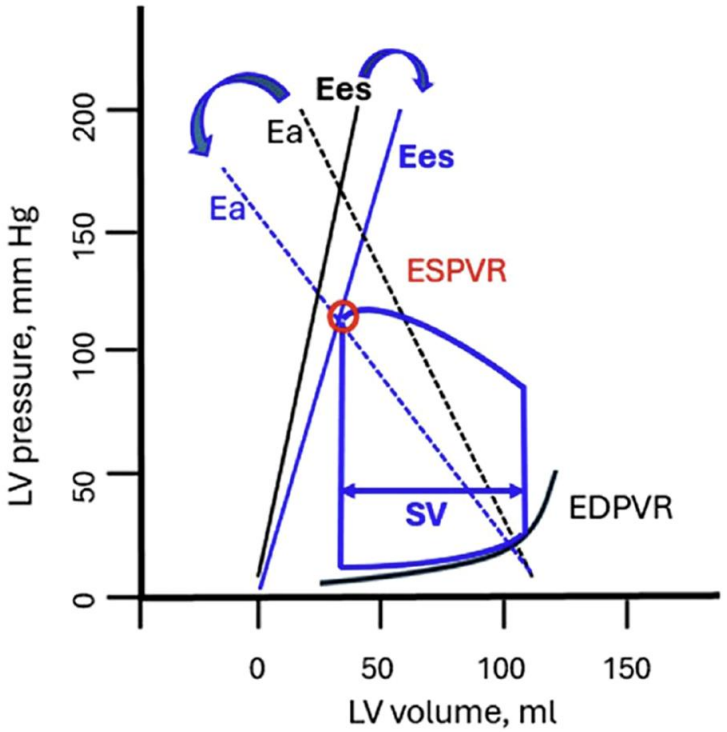
Left ventricular efficiency = SW/PVA



LV loop in a healthy patient,initial phase of CS due to severe LV systolic failure ,a mixed shock profile (systolic LV dysfunction and vasoplegia)







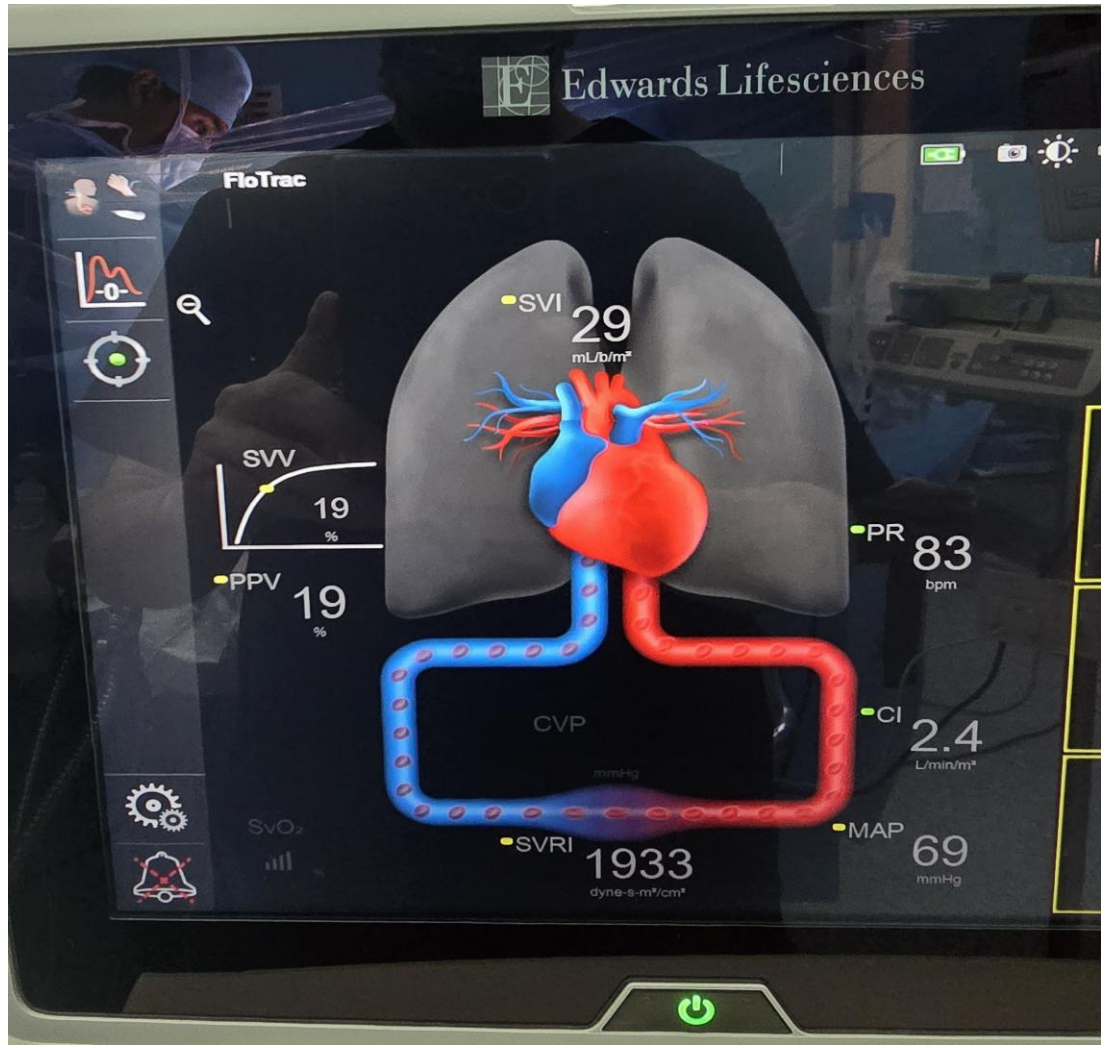

Edwards Lifesciences
FloTrac
SVI
29
mL/b/m²
SVV
19
%
PPV
19
%
PR
83
bpm
CVP
mmHg
CI
2.4
L/min/m²
SvO₂
SVRI
1933
dyne-s-m²/cm⁵
MAP
69
mmHg

TABLE 1 **Ventriculo-arterial coupling and its determinants in common cardio-circulatory failure.**

Cardiocirculatory failure	Phenotype	E_V	E_A	E_A/E_v ratio
Vasoplegia		~	↓↓	↓↓
Sepsis	Hyperkinetic	~	↓↓	↓↓
	Normokinetic	~/↓	~/↓	~/↑
	Hypokinetic	↓↓	~/↑	↑
Left heart failure	Systolic heart failure	↓↓	~/↑	↑
	'Diastolic' heart failure (heart failure with preserved ejection fraction)	↑	↑	~/↑
	Cardiogenic shock	↓↓↓	~/↓↓	↑↑
Right heart failure	Pulmonary embolism	~/↑	↑	↑
	Pulmonary hypertension	~/↑	↑	↑
	Ischemic	↓↓	↑	↑
Tachycardia		~/↑	↑↑	~/↑
Severe arterial hypertension		~/↓	↑↑	↑
Hypovolemia		~	↑↑	↑
Trauma	Haemorrhage	~/↓	↑↑	↑
	Systemic inflammatory response syndrome	~	↓↓	↓
Anaphylaxis		~	↓↓	↓

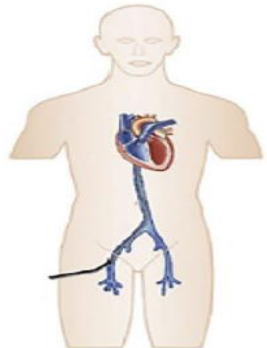
Compiled from ref.[6–51]

Treatment	Effects E_A	E_V
Inotrope/inodilator	↓	↑↑
Phenylephrine	↑↑	~↓
Norepinephrine	↑↑	↑
Epinephrine	↑↑	↑
Vasodilator	↓	~
Volume expansion	↓	~
Beta-blocker	↓	~↓
Loop diuretics and decongestion	↓	~
VA-ECMO (retrograde arterial flow)	↑	~↓
Axial pump flow (LV unloading)	↓	~↑

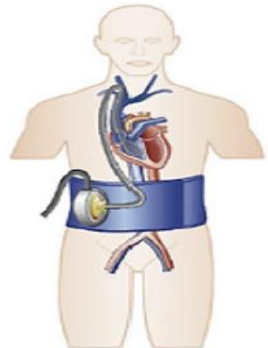
Mechanical circulatory support devices

- Temporary mechanical circulatory support is a potential option for enhancing end-organ perfusion in patients with de novo or refractory.
- It provides short-term hemodynamic intervention lasting from hours to weeks, is usually managed in a hub-and spoke system available in tertiary centers, and is serving as a bridge-to-decision, bridge-to-recovery, bridge-to LVAD (left-ventricular assist device), or bridge-to-trans plantation.

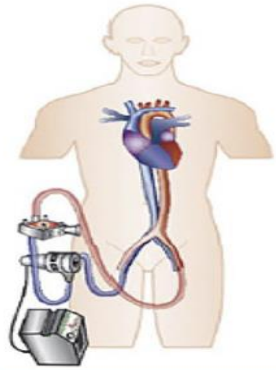
RIGHT HEART SUPPORT



A. Impella RP (flex)

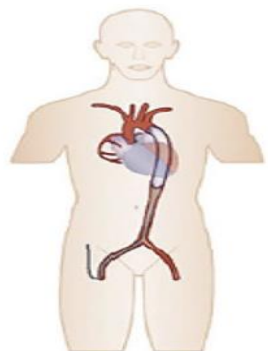


B. TandemHeart
RA-PA

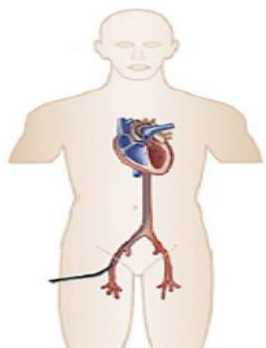


C. VA-ECMO

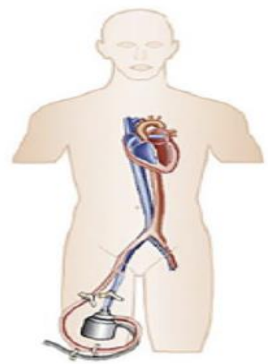
LEFT HEART SUPPORT



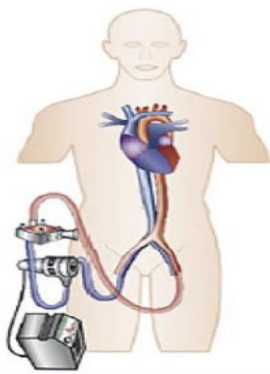
A. IABP



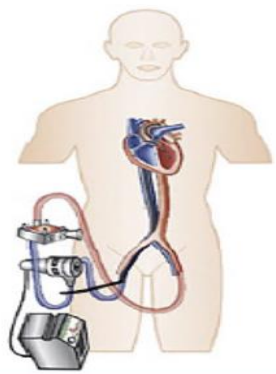
B. Impella CP
Impella 5.5



C. TandemHeart



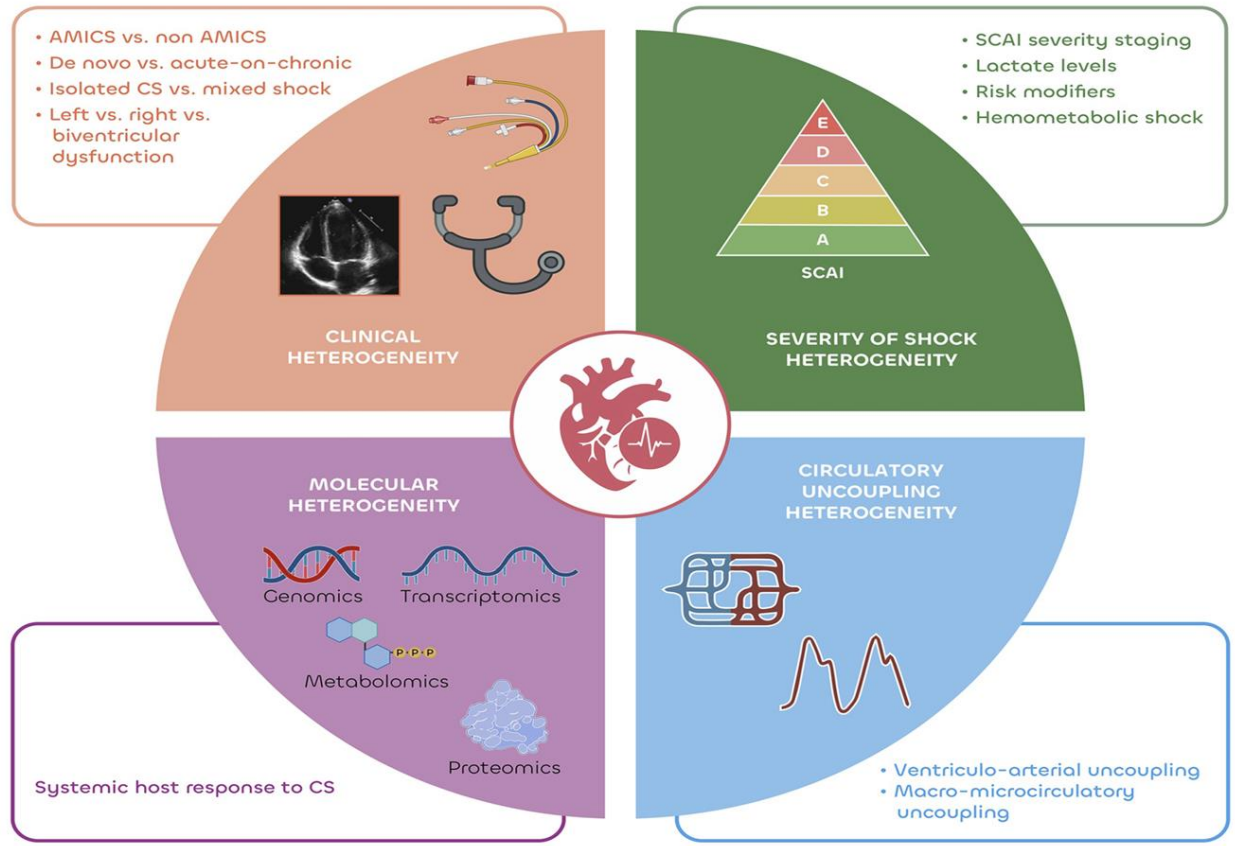
D. VA-ECMO



E. ECMELLA

	Size of the cannulae	Key contraindication / limitation	Ability to oxygenate blood	Recommanded max. use - practical use may be much longer
Impella RP	22F	Mechanical tricuspid valve	No	14 days
TandemHeart RA-PA	16-31F	Mechanical tricuspid valve	Yes	14 days
VA-ECMO	15-25F	No suitable access site	Yes	14 days
IABP	7-8F	Severe aortic regurgitation	No	30 days
Impella CP / 5.5	CP: 14F 5.5: 21F	Mechanical aortic valve	No	10 days
TandemHeart	15-21 F	Moderate to Severe aortic regurgitation	Yes	14 days
VA-ECMO	15-25F	No suitable access site	Yes	14 days
ECMELLA	15-25F	Mechanical aortic valve	Yes	14 days

(B)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• Ventriculo-arterial uncoupling
• Macro-microcirculatory uncoupling

- The clinical and severity approaches fail to fully address the underlying mechanistic signatures, impact of CS biological heterogeneity, and the host response .
- Recent research based on host–response biomarkers highlighted important molecular heterogeneity (i.e., inflammation, myocardial fibrosis, and endothelial dysfunction) within the spectrum of CS

- Advances in artificial intelligence (AI) and machine learning are providing interesting avenues for the future; unsupervised machine learning (i.e., agnostic to outcome) identifies different classes in CS patients (“non-congested”, “cardiorenal”, and “cardiometabolic”) based on readily available laboratory data associated with early mortality independently from the SCAI classification .

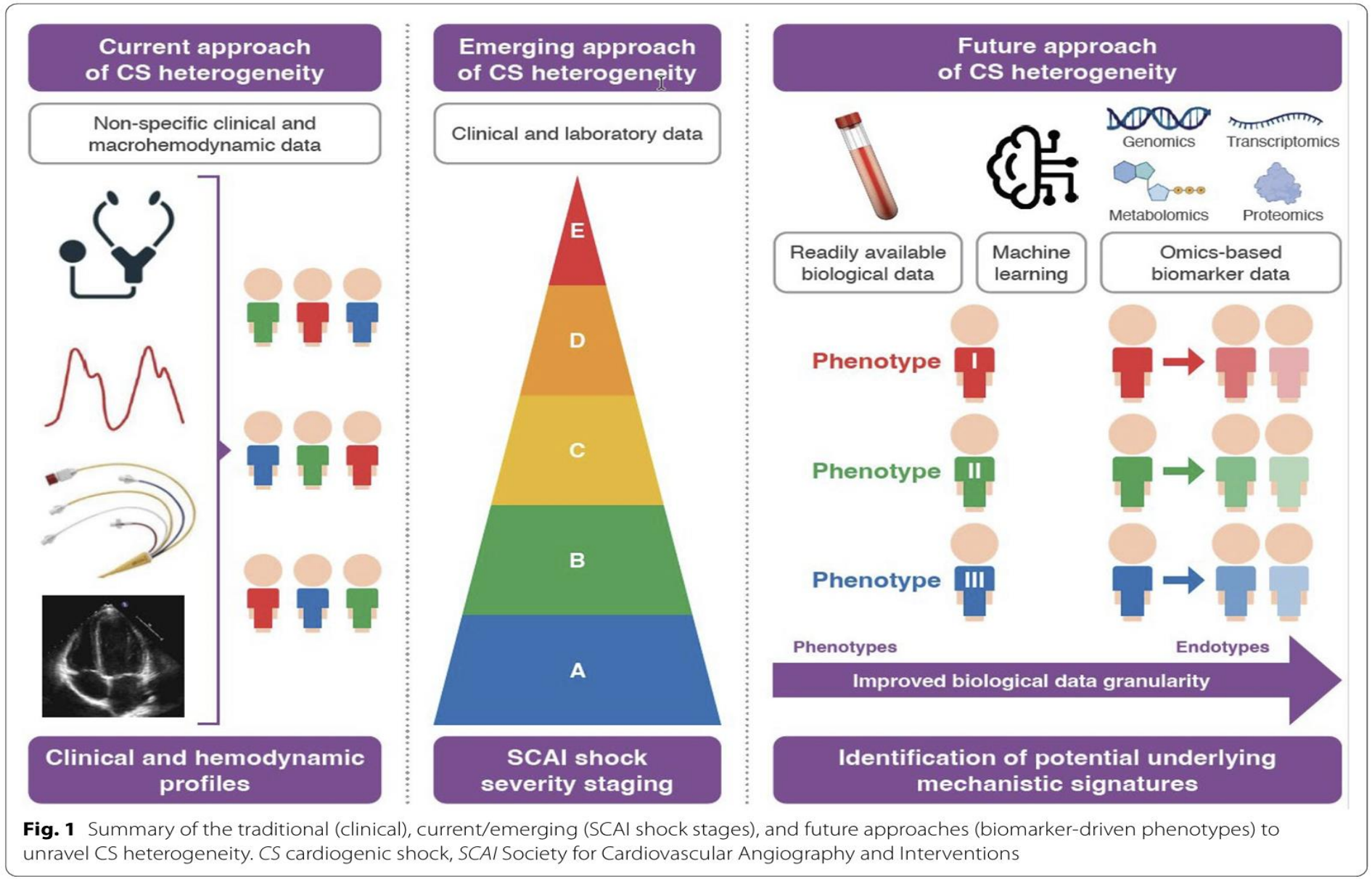

Fig. 1 Summary of the traditional (clinical), current/emerging (SCAI shock stages), and future approaches (biomarker-driven phenotypes) to unravel CS heterogeneity. *CS* cardiogenic shock, *SCAI* Society for Cardiovascular Angiography and Interventions

How we use critical care ultrasonography in the management of cardiogenic shock: a strategic game of chess in intensive care

Filippo Sanfilippo[1*], Siddharth Dugar[2,3] and Michelle S. Chew[4,5]

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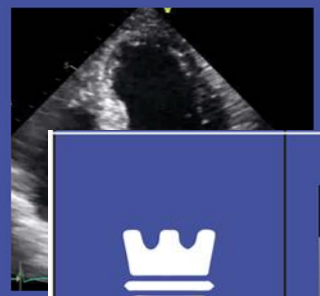
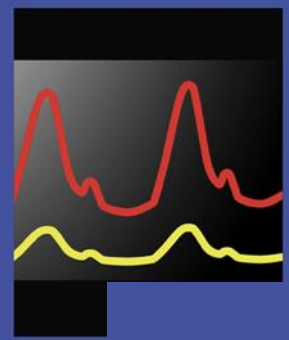
CHESS PIECE	MONITORING TOOLS	USEFULNESS IN CARDIOGENIC SHOCK LIMITATIONS IN CARDIOGENIC SHOCK
		CCE is first-line imaging modality for diagnosis of CS; Preferred modality to assess for complications (i.e. valve dysfunction); Unique for monitoring response to therapy; Essential for escalation to MCS, Cath-lab or cardiac
		
		*Pulse contour analysis:* Allows continuous blood pressure monitoring; can track CO changes in response to interventions; may be used to test FR
		PAC: Gold standard for measuring CO; allows direct measurement of PAP and LVFP; differentiates pre- and post-capillary pulmonary hypertension
		Both: not diagnostic of CS etiology of shock; Not feasible as first-line approach; Variations in use among centers
		
		Telemedicine and AI might allow provision of distant support in remote centers with image transfer and case discussion; Identification of phenotypes and early prognostication
		Not yet established role; Sensible data sharing; Need of adequate data quality.

