Sepsis-related cardiomyopathy : pathophysiologic insight and hemodynamic consequences

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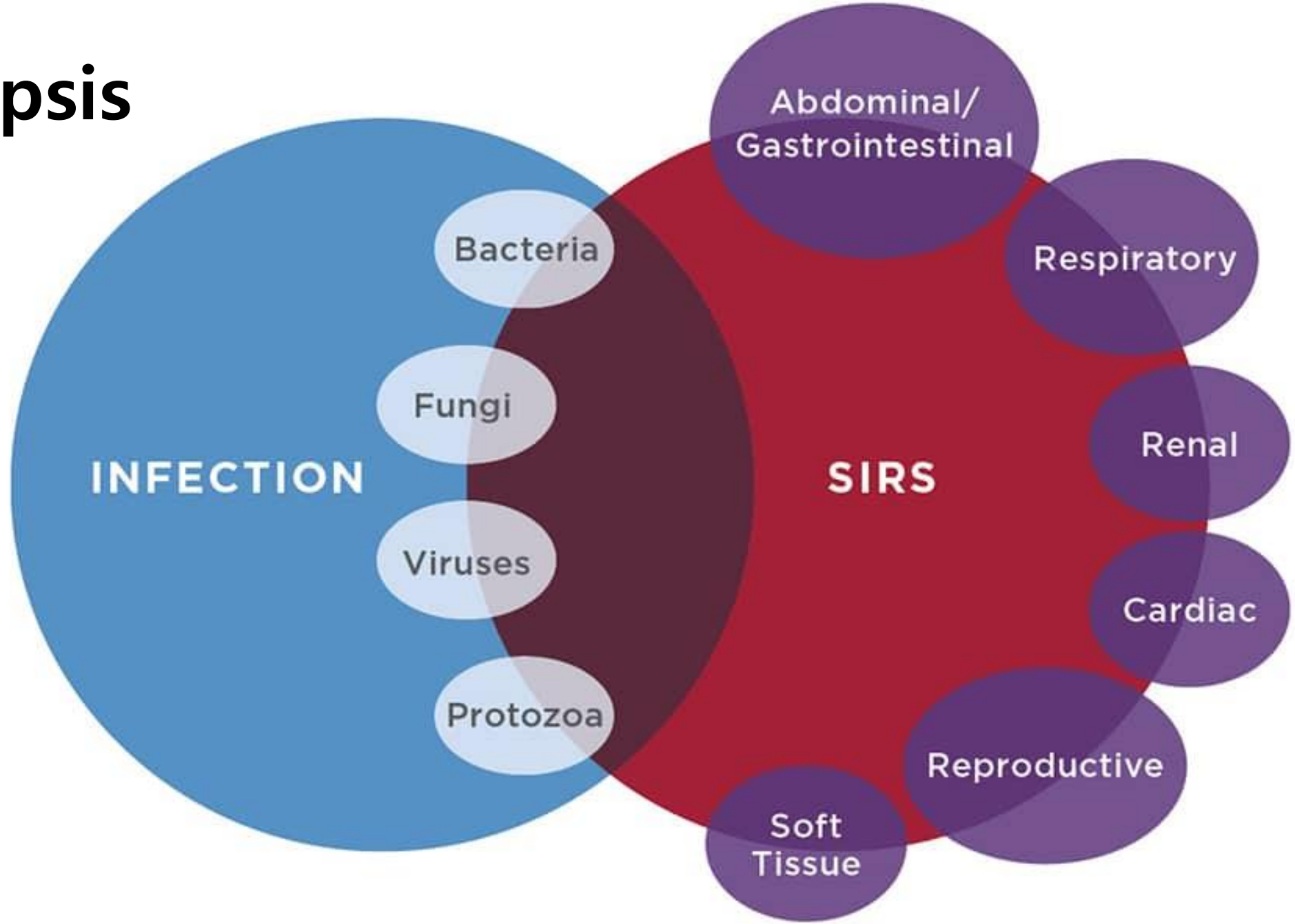
Sepsis


Abdominal/
Gastrointestinal
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Bacteria
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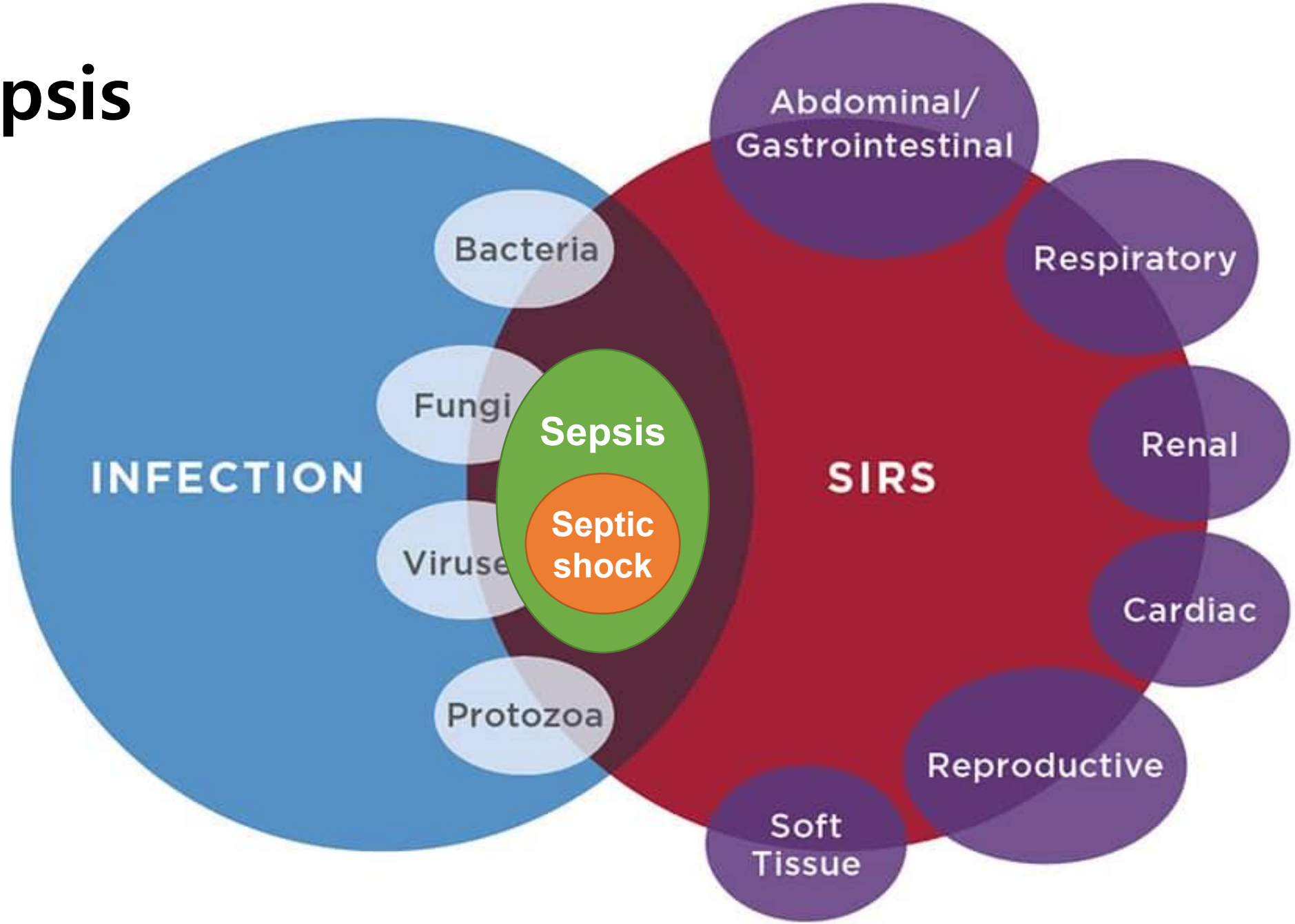
Viruses
Protozoa
INFECTION
SIRS

Sepsis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INFECTION
Sepsis
Septic
shock

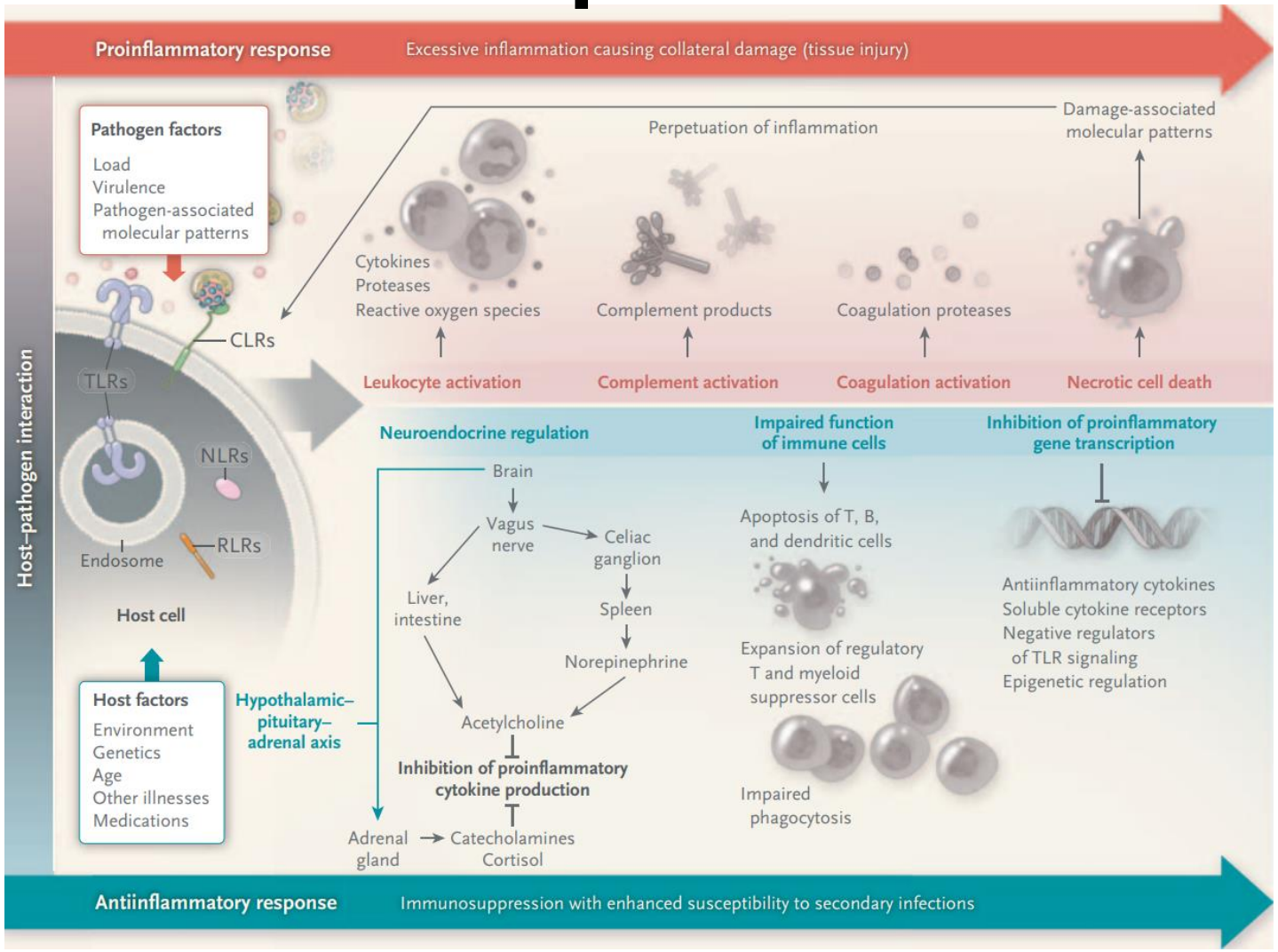
The definition of Sepsis & Septic shock

- **Sepsis is** life threatening organ dysfunction caused by a dysregulated host response to infection

- *defined as* the presence of an infection combined with an acute change in SOFA score of 2 points or more (with the baseline assumed to be 0 in patients without any known pre-existing organ dysfunction).

- **Septic shock is** a subset of sepsis in which underlying circulatory, cellular, and metabolic abnormalities are profound enough to substantially increase the risk of mortality
- *described as* a clinically defined subset of sepsis cases, wherein, despite adequate fluid resuscitation, patients have hypotension requiring vasopressors to maintain a mean arterial blood pressure above 65 mm Hg and have an elevated serum lactate concentration of more than 2 mmol/L

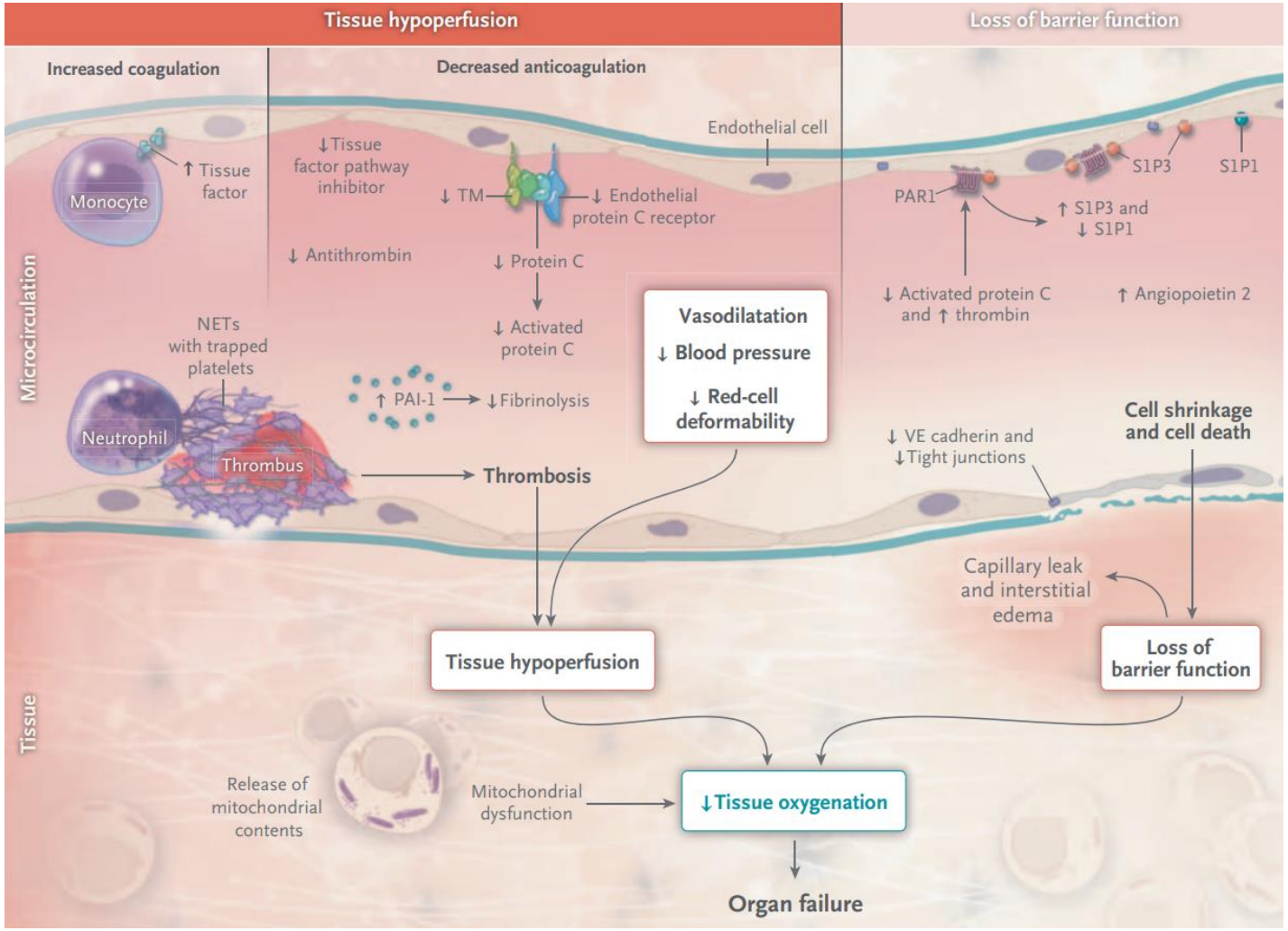
Dysregulated host response of sepsis : Anti, and pro-inflammatory response



- Pro and anti-inflammatory response occur simultaneously which is initiated by PAMP-PRR interaction (TLRs NLRs)
- Tissue damage triggers DMAP which interact with PRR sustains inflammation.
- Host and pathogen factors determine the trajectory and severity of the immune response

N Engl J Med 2013;369:840-51

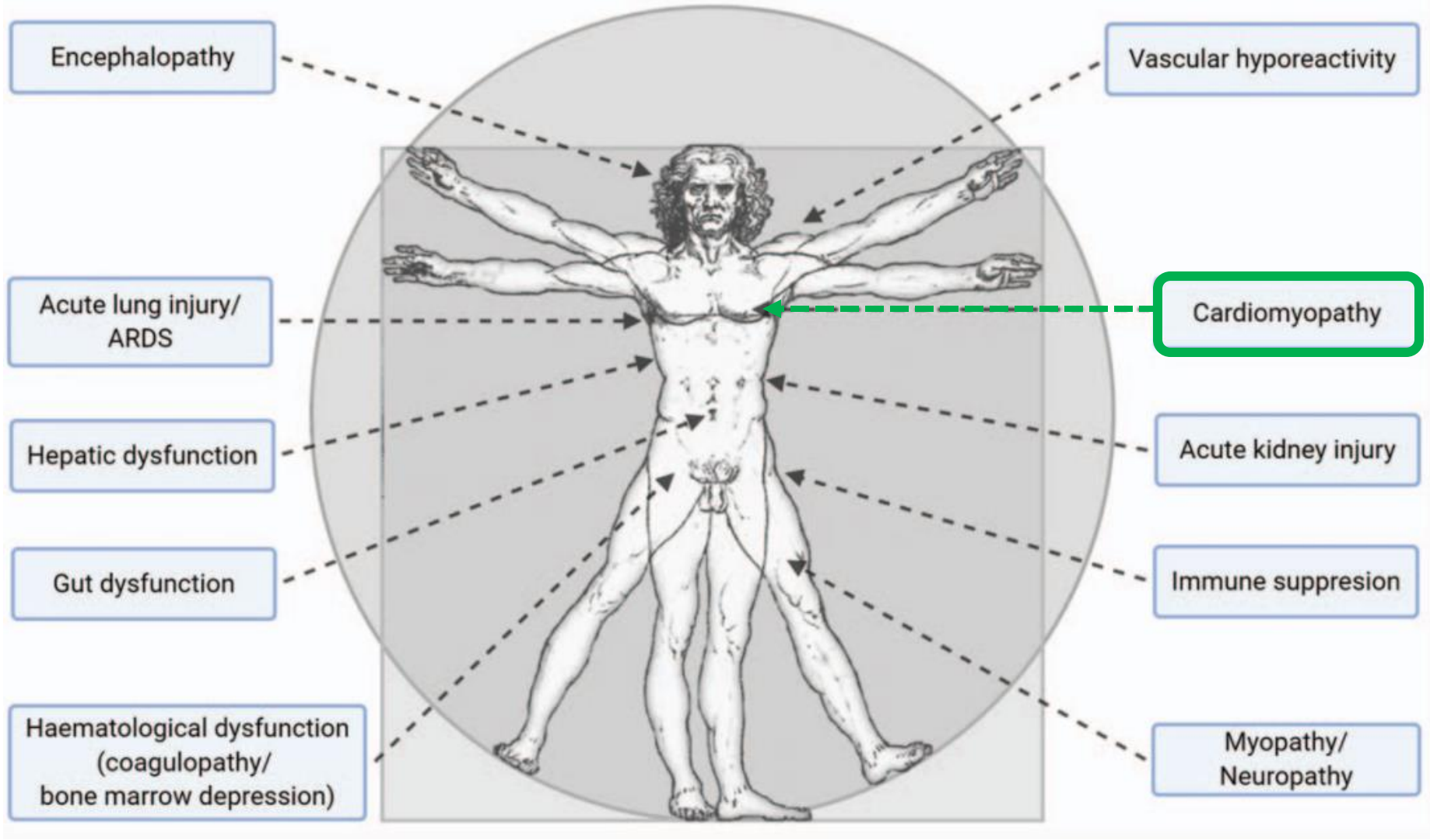
Dysregulated host response of sepsis : Endothelial dysfunction



- Microvascular thrombosis caused by activation of coagulation and impaired anticoagulant mechanism causes tissue hypoxia
- Vasodilation, hypotension and reduced RBC deformability further facilitate tissue oxygenation

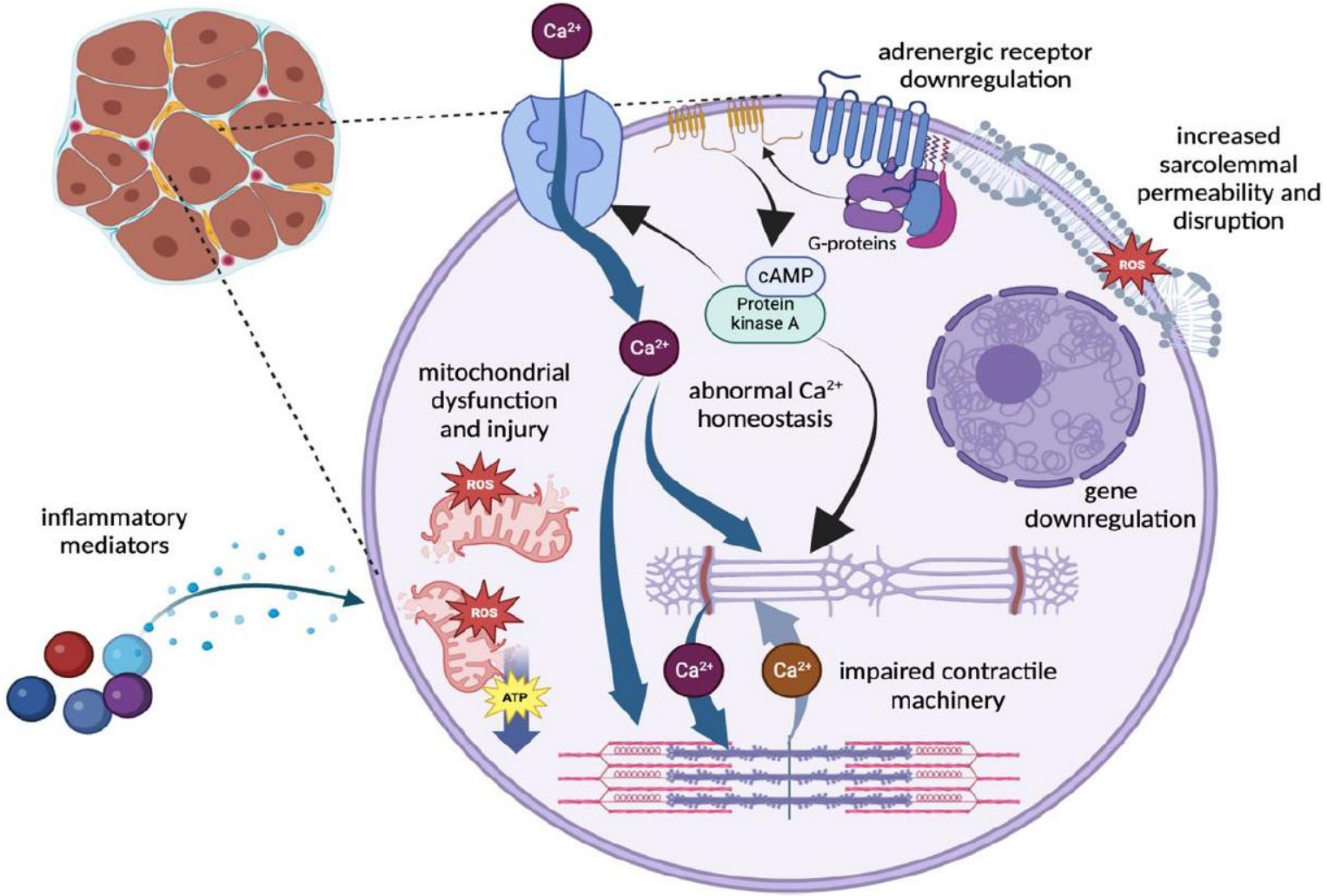
N Engl J Med 2013;369:840-51

Sepsis and organ failure



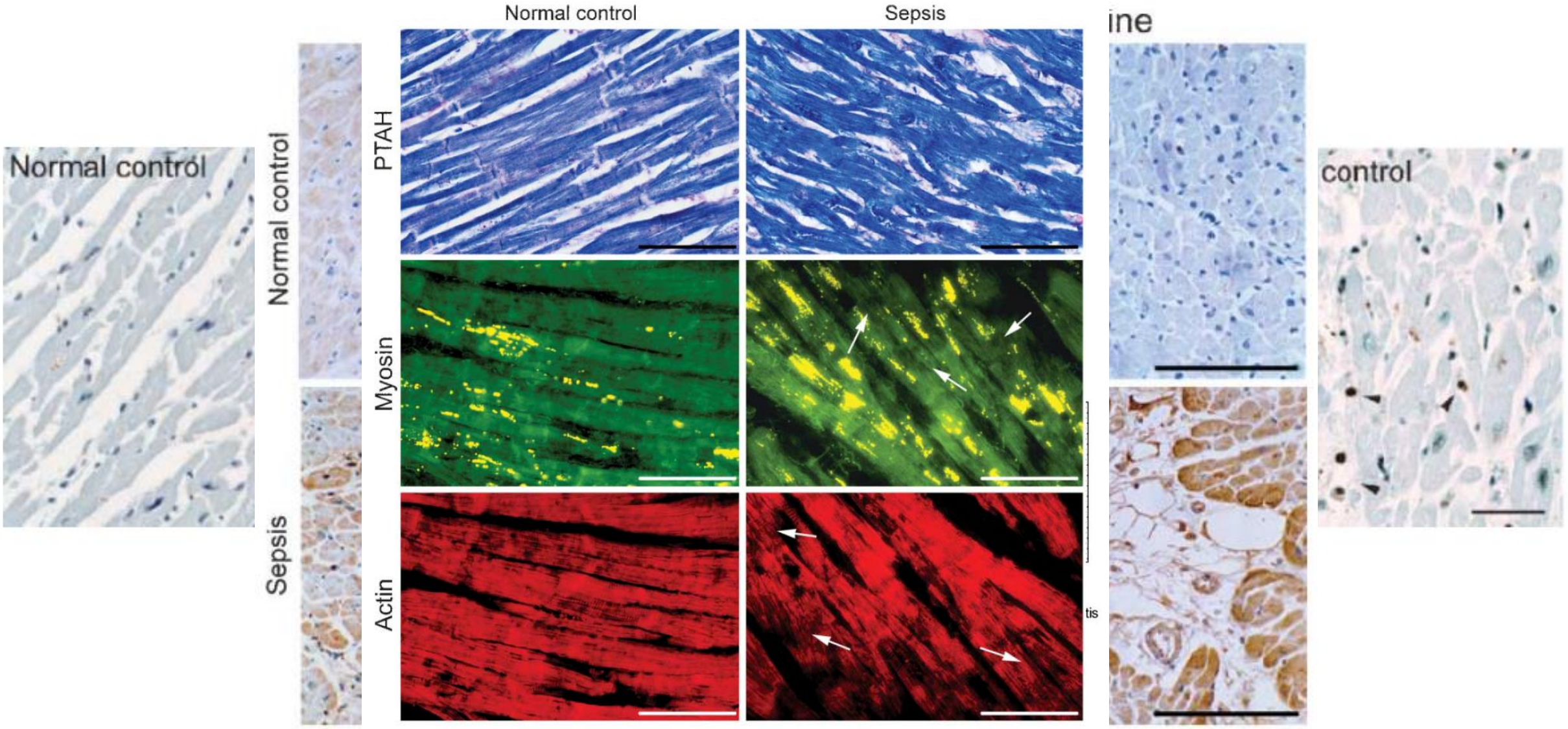
Curr Opin Anesthesiol 2021; 34:77–84

Direct Myocardial Depression in Sepsis



European Heart Journal 2025; 00: 1–15

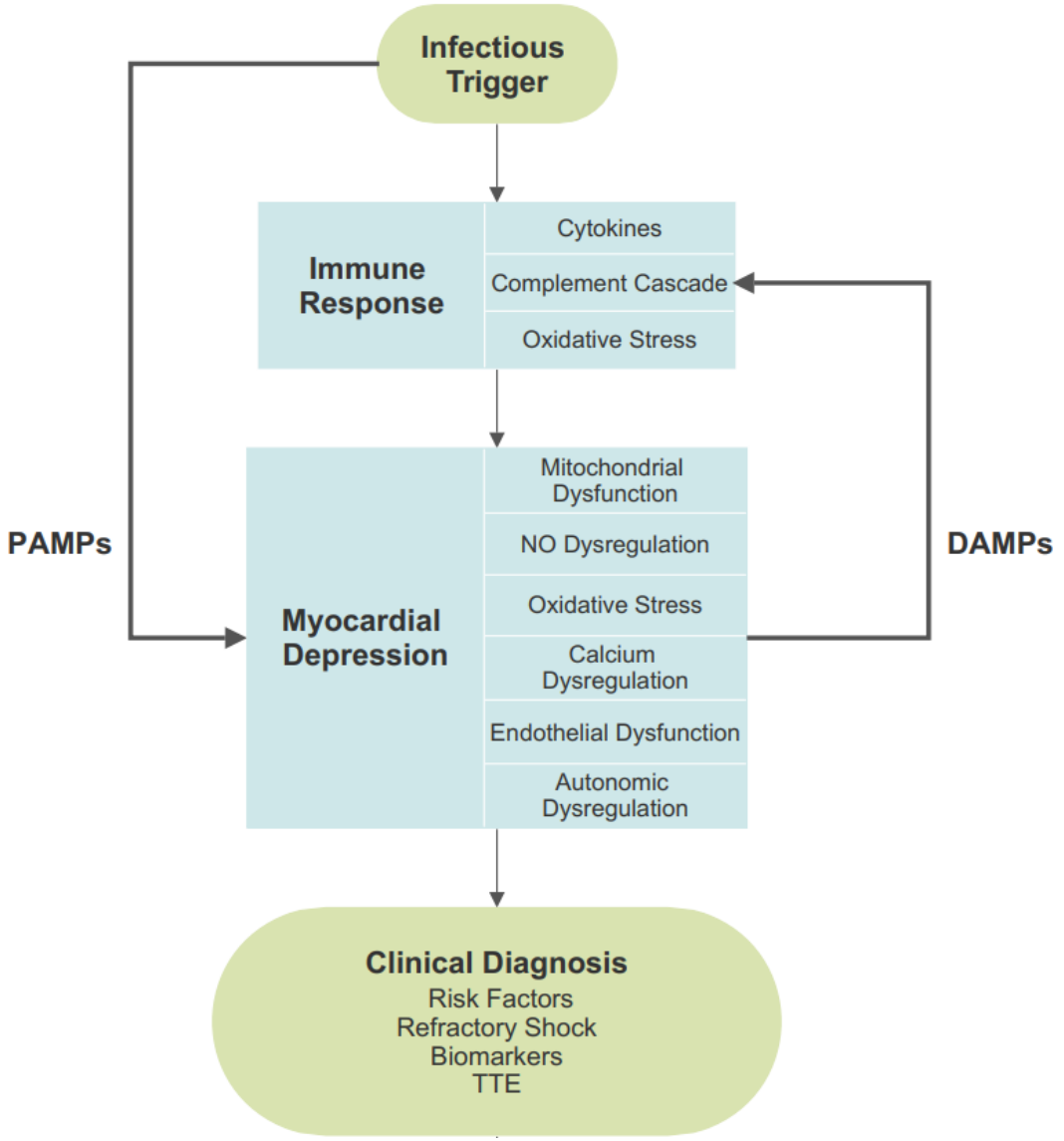
Direct Myocardial Depression in Sepsis



Myocardial dysfunction in Sepsis

- Myocytolysis
- Interstitial fibrosis
- Contraction band necrosis
- Interstitial edema

>> Myocardial depression



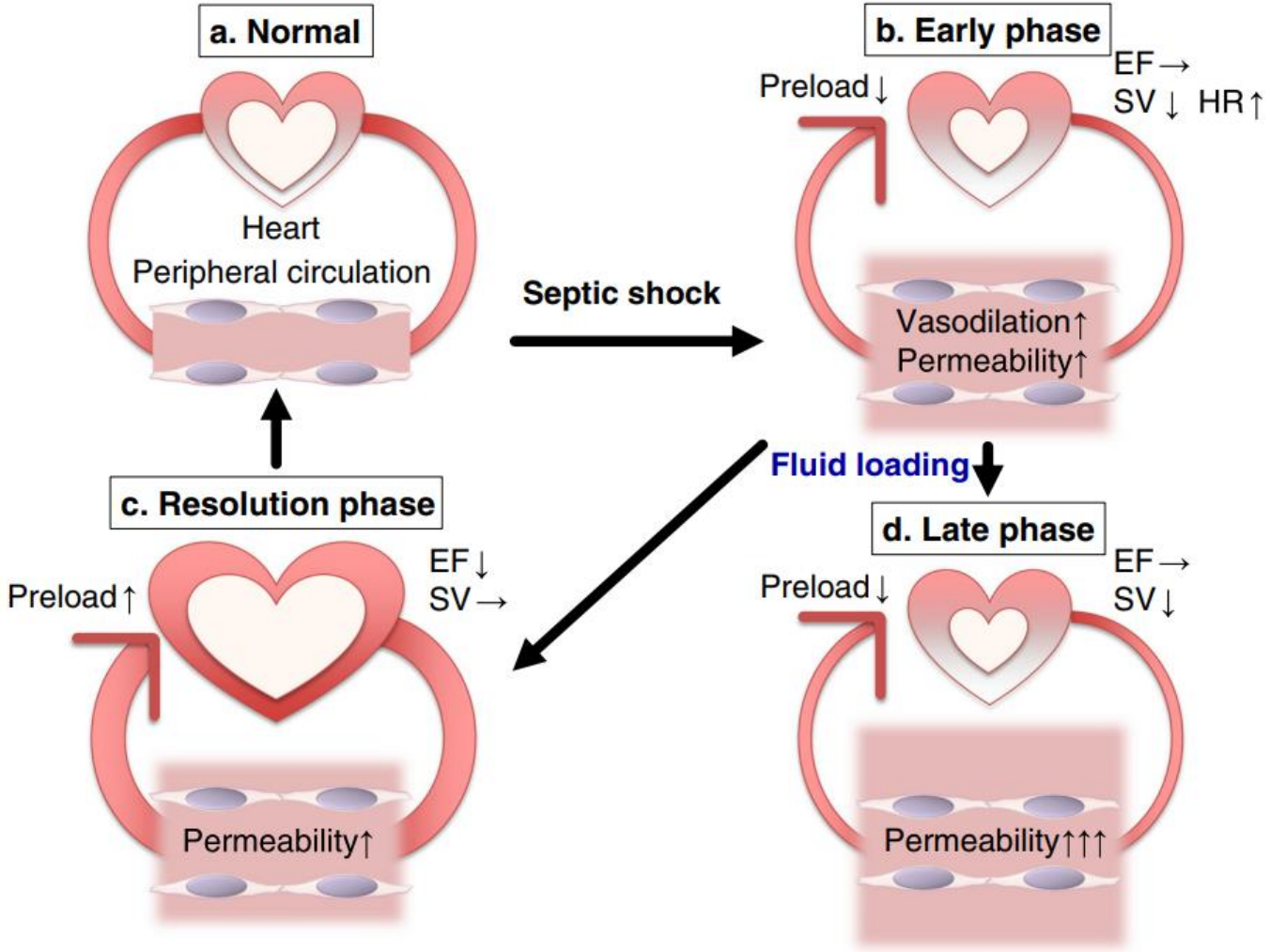
Hemodynamic change in septic shock

Table 1 Characteristics of different stages of resuscitation: 'Fit for purpose fluid therapy'. GDT, goal directed therapy; DKA, diabetic keto acidosis; NPO, nil per os; ATN, acute tubular necrosis; SSC, surviving sepsis campaign

	Rescue	Optimization	Stabilization	De-escalation
Principles	Lifesaving	Organ rescue	Organ support	Organ recovery
Goals	Correct shock	Optimize and maintain tissue perfusion	Aim for zero or negative fluid balance	Mobilize fluid accumulated
Time (usual)	Minutes	Hours	Days	Days to weeks
Phenotype	Severe shock	Unstable	Stable	Recovering
Fluid therapy	Rapid boluses	Titrate fluid infusion conservative use of fluid challenges	Minimal maintenance infusion only if oral intake inadequate	Oral intake if possible Avoid unnecessary i.v. fluids
Typical clinical scenario	- Septic shock - Major trauma	- Intraoperative GDT - Burns - DKA	- NPO postoperative patient - 'Drip and suck' management of pancreatitis	- Patient on full enteral feed in recovery phase of critical illness - Recovering ATN
Amount	Guidelines, for example, SSC, pre-hospital resuscitation, trauma, burns, etc.			

LV filling pressure & cardiac function
by pre & afterload change???

Hemodynamic change of septic shock and secondary myocardial dysfunction



Journal of Intensive Care (2016) 4:22

Challenges in diagnosing septic cardiomyopathy and hemodynamic phenotypes of sepsis

Dynamic patient condition

- Premorbid cardiac condition
- Inotropic use
- Autonomic dysregulation of HR in sepsis
- Fluid challenge
- Metabolic abnormality
  lactic acidosis, decreased mixed venous oxygen saturation
- Differentiation from Tacotsubo syndrome or myocarditis

Wide spectrum of the disease

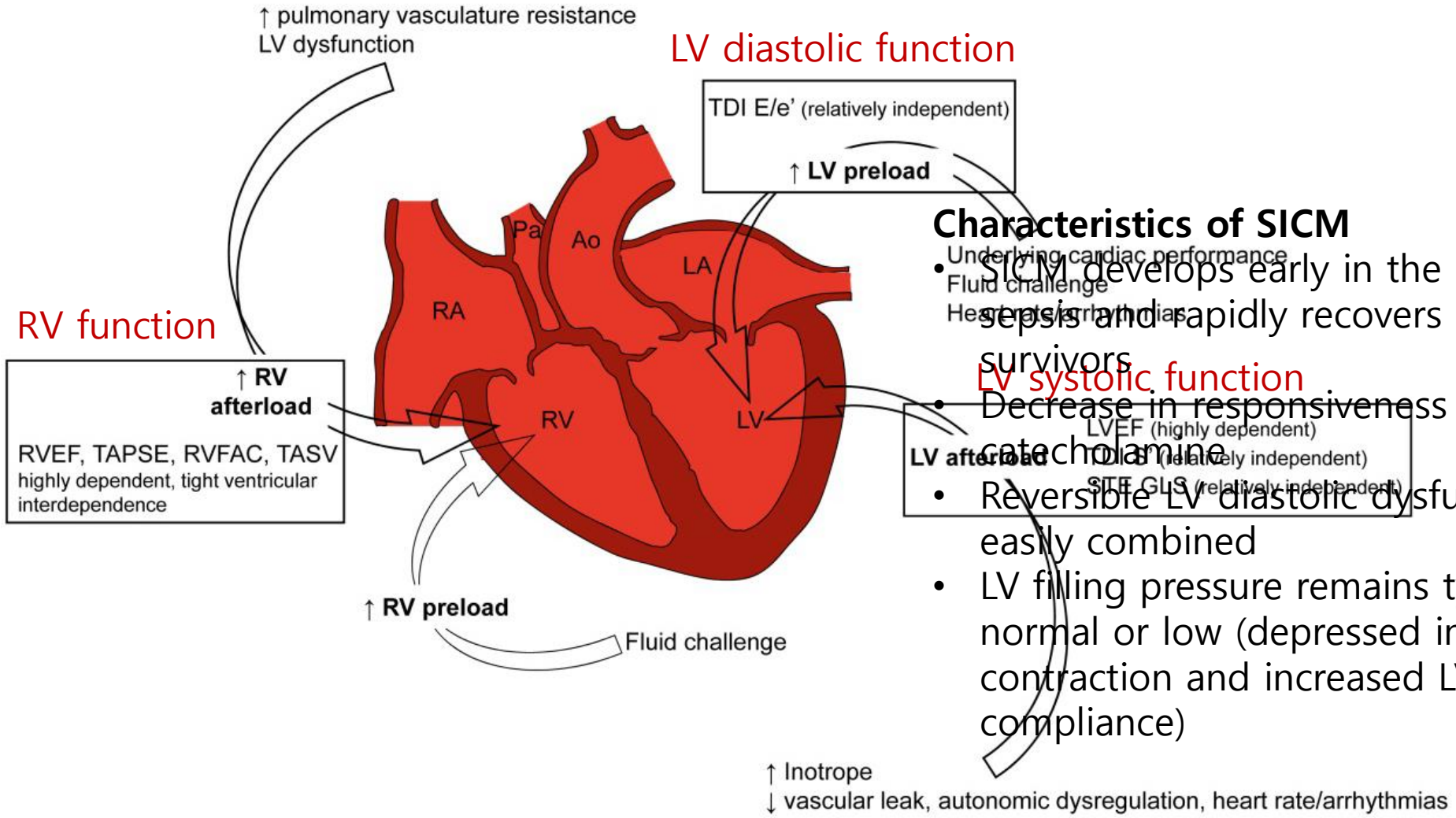
- No evidence of cardiac dysfunction
- LV systolic dysfunction
- Hyperkinetic LV
- RV failure
- Persistent hypovolemia

Definition of Septic Cardiomyopathy

- No consensus definition

- Reversible myocardial depression
- New-onset bi-ventricular systolic and/or diastolic dysfunction unrelated to coronary disease, and with no alternative aetiology
- Condition of isolated diastolic or RV dysfunction is under debate

Diagnosis of septic cardiomyopathy



Characteristics of SICM

- SICM develops early in the course of sepsis and rapidly recovers in survivors
- Decrease in responsiveness to catecholamine
- Reversible LV diastolic dysfunction is easily combined
- LV filling pressure remains typically normal or low (depressed intrinsic LV contraction and increased LV compliance)

Cells 2022;11:2833

Diagnosis of septic cardiomyopathy

Table 1 Main parameters routinely used to characterize the cardiovascular phenotype of septic cardiomyopathy using echocardiography

Parameters	Thresholds	Value	Limitations	Comments
Left ventricular systolic function				
LV ejection fraction	<50% or ≤ 40% according to definitions[67,68,77]	High feasibility Allows rapid assessment (eye-balling) Reproducibility	Highly influenced by loading conditions[14]	Fails to reflect myocardial contractility Reflects LV/aortic coupling
LV fractional area change	<45%	Can be used as a surrogate of LVEF[67,68]	LV apex is not assessed	Reflects perfusion territories of main coronary arteries
Mitral annular plane systolic excursion	<1.2 cm[67]	Feasible despite suboptimal two-dimensional imaging quality	Angle-dependency Only assesses longitudinal shortening Not valid if RWMA	Few validation studies
Tissue Doppler imaging Maximal systolic velocity at the mitral annulus (s′)	Septal mitral annulus <8.1 cm/s Lateral mitral annulus <10.2 cm/s Averaged value <9.2 cm/s[67]		Angle-dependency Only assesses longitudinal shortening Not valid if RWMA	Few validation studies
Global longitudinal strain (speckle tracking)	<−20%[a67]	Angle-independent More sensitive than LVEF[67] Allows segmental assessment	Not universally available Highly dependent on two-dimensional	Global and regional index with higher sensitivity than conventional parameters of systolic function

European Heart Journal 2025; 00: 1–15

Parameters	Thresholds	Value	Limitations	Comments
			imaging quality Vendor-dependent	
Left ventricular diastolic function				
Mitral E/A	<0.8 (low) > 2 (high)[79]	Global index grossly reflecting left ventricular filling pressure Highly reproducible	Influenced by various factors unrelated to left ventricular diastolic function	Takes into account variables influencing cardiac load (e.g, volemia)
Mitral septal e′	<7 cm/s[79]	Feasible despite suboptimal two-dimensional imaging quality Reproducible	Angle-dependency Influenced by preload variations Not valid if RWMA	Cardiology diagnostic criteria not adapted to ICU patients[80,81]
Mitral lateral e′	<10 cm/s[79]	Feasible despite suboptimal two-dimensional imaging quality Reproducible	Angle-dependency Not val	gy diagnostic criteria not adapted to ICU s[80,81] ss sensitive to preload variations[79–81]
Averaged E/e′	>14[79]		alues (8–13) do not permit precise evaluation of LV filling pressure	Cardiology diagnostic criteria not adapted to ICU patients[80,81]
Right ventricular function				
Tricuspid annular plane systolic excursion	<17	Feasible despite suboptimal two-dimensional imaging quality	Only assesses longitudinal shortening	Preserved despite (severe) RV pressure overload
Tricuspid systolic lateral annular velocity s′	<9.5 cm/s[67]	Feasible despite suboptimal two-dimensional imaging quality	Angle-dependency Only assesses longitudinal shortening	Few validation studies
RV fractional area change	<35%[67]	More representative of circumferential shortening	Requires clear depiction of free wall (anisotropy)	Large range of normal values
RV dilatation	Right/left ventricular end-diastolic area >0.6[67]	High feasibility Allows rapid assessment (eye-balling) Largely validated	Early (sensitive) marker of RV impairment (afterload, contractility defect)	Indicator of RV/pulmonary artery uncoupling

No evidence of cardiac biomarkers or ECG findings for the diagnosis of septic cardiomyopathy

Echocardiographic parameters and outcome

Table 2 Summary of selected articles on septic cardiomyopathy

	Echo parameter	Study	Study design/ setting	*N*	Measured outcome	Results
Left ventricle						
Systolic	EF	Sevilla Berrios et al. (2014) [33]	Meta-analysis	585	To evaluate the significance of reduced LVEF in patients with severe sepsis and septic shock. Primary outcome was association between depressed LVEF and 30-day mortality	Depressed LVEF had a sensitivity of 52% (95% CI 29–73%) and specificity of 63% (95% CI 53–71%) for mortality and was therefore not a sensitive nor specific predictor of mortality
		Huang et al. (2013) [32]	Meta-analysis	762	To evaluate the association of both reduced LVEF and increased LV dimensions with mortality in patients with severe sepsis and septic shock	No significant difference in LVEF and LV dimensions in survivors vs non-survivors
		Jardin et al. (1999) [24]	Single-center prospective cohort study	90	To evaluate changes in LV function, including LVEF and LV volumes, during volume resuscitation in patients with septic shock	LVEF was depressed in all patients. LV parameters were additionally unaffected by fluid loading
		Parker et al. (1984) [1]	Single-center prospective cohort study	20	To evaluate cardiac function in septic shock	10/20 patients (50%) had depressed LVEF (< 0.40). Mean LVEF was lower among survivors (LVEF 0.32 ± 0.04) when compared to non-survivors. Mean ESV and EDV were increased in survivors

Critical Care 2018;22:112

Echocardiographic parameters and outcome

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Echo parameter	Study	Study design/ setting	*N*	Measured outcome	Results
GLS	Boissier et al. (2017) [17]	Single-center prospective cohort study/ICU	132	To evaluate the role of GLS, LVEF, and TDI in patients with septic shock. Primary outcome was the role of loading conditions on evaluation of cardiac contractility	GLS was impaired in a majority of the patients (> 70%); however, feasibility was limited (< 50%)
	Chang et al. (2015) [39]	Multi-center prospective cohort study/ICU	111	To evaluate LV function, as well as the prognostic value of GLS, in septic patients. Primary outcome was both ICU and hospital mortality	GLS is an independent prognostic indicator of ICU mortality. Patients with GLS ≥ − 13% had higher ICU mortality rates (HR 4.34; $p < 0.001$)
	De Geer et al. (2015) [43]	Single-center prospective cohort study/ICU	50	To evaluate GLS in patients with septic shock. Primary outcomes were mortality at 30 and 90 days	GLPS did not correlate between survivors and non-survivors and therefore could not be used to predict mortality
	Innocenti et al. (2016) [41]	Single-center prospective cohort study/ED observation unit	147	To evaluate LVEF and GLS in septic patients. Primary outcome was all-cause mortality at 7 days	LVEF is not an independent indicator of prognosis
	Kalam et al. (2014) [37]	Meta-analysis	5721	To assess if GLS is a more accurate predictor of cardiovascular outcome compared to LVEF. Primary outcome was all-cause mortality. Secondary outcome was	GLS is a better predictor of adverse outcomes (HR 0.50; $p < 0.002$) and mortality (HR 1.62; $p = 0.009$) than LVEF (HR 0.81; $p = 0.572$)

Critical Care 2018;22:112

Echocardiographic parameters and outcome

Table 2 Summary of selected articles on septic cardiomyopathy

	Echo parameter	Study	Study design/ setting	*N*	Measured outcome	Results
Right ventricle						
Systolic	TAPSE	Gajanana et al. (2015) [64]	Single-center prospective cohort study/ICU	120	To evaluate the prognostic value of TAPSE in patients with critical illness	A reduced TAPSE measurement (< 2.4 cm) was correlated with increased in-hospital mortality ($\chi(2) = 4.6$, $P = 0.03$) and a longer length of hospital stay
	TAPSE TDI RV FAC	Vallabhajosyula et al. (2017) [67]	Single-center retrospective cohort study/ICU	388	To evaluate the prognostic significance RV dysfunction in patients with severe sepsis and septic shock. Primary outcome was 1-year survival	Isolated RV dysfunction is an independent predictor of 1-year survival (HR 1.6; $p = 0.002$). Combined RV/LV dysfunction was not an independent predictor of 1-year survival (HR 0.9; $p = 0.52$)

Critical Care 2018;22:112

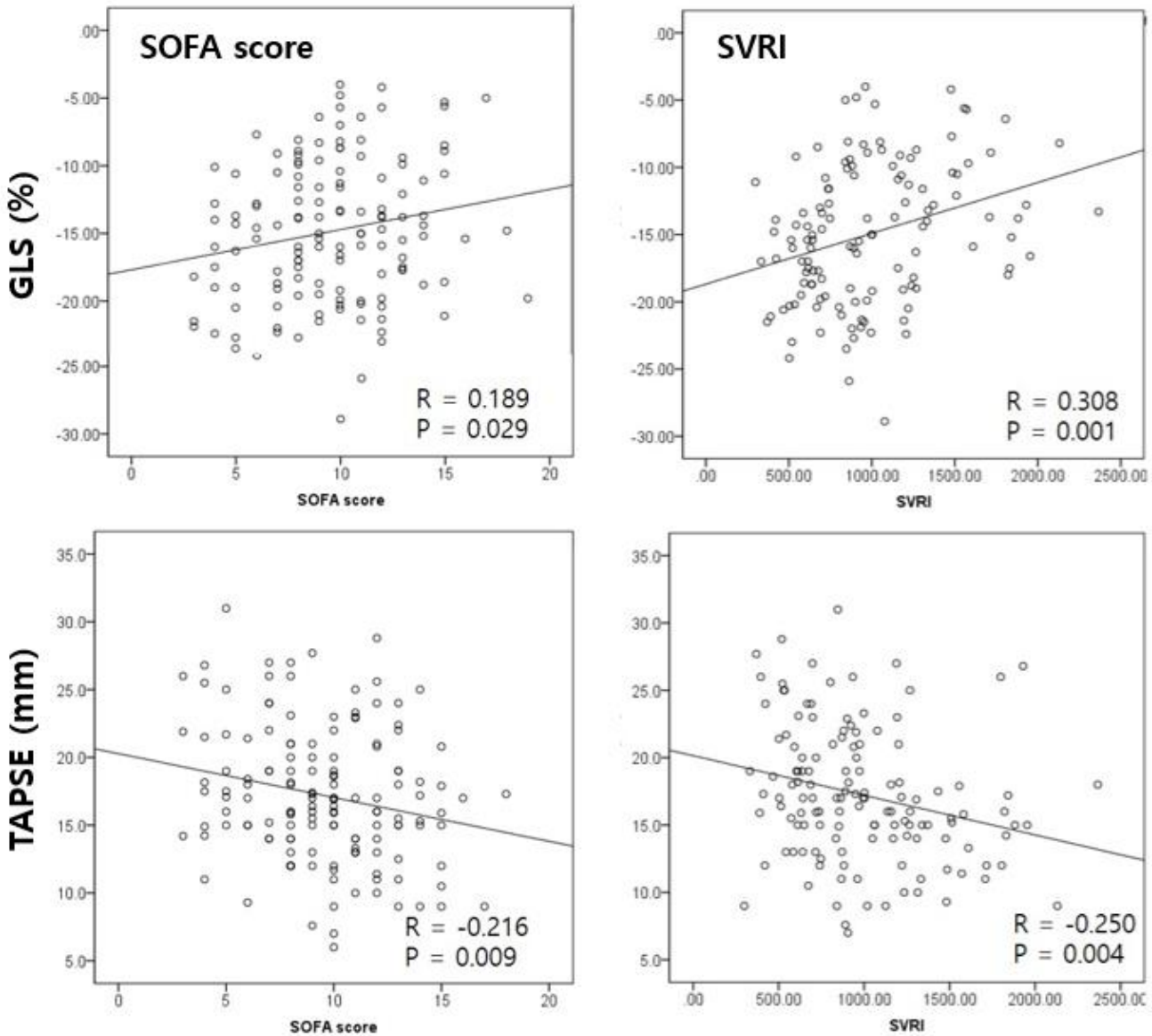
Ejection fraction
Global longitudinal strain ?
E/e'
TAPSE ?

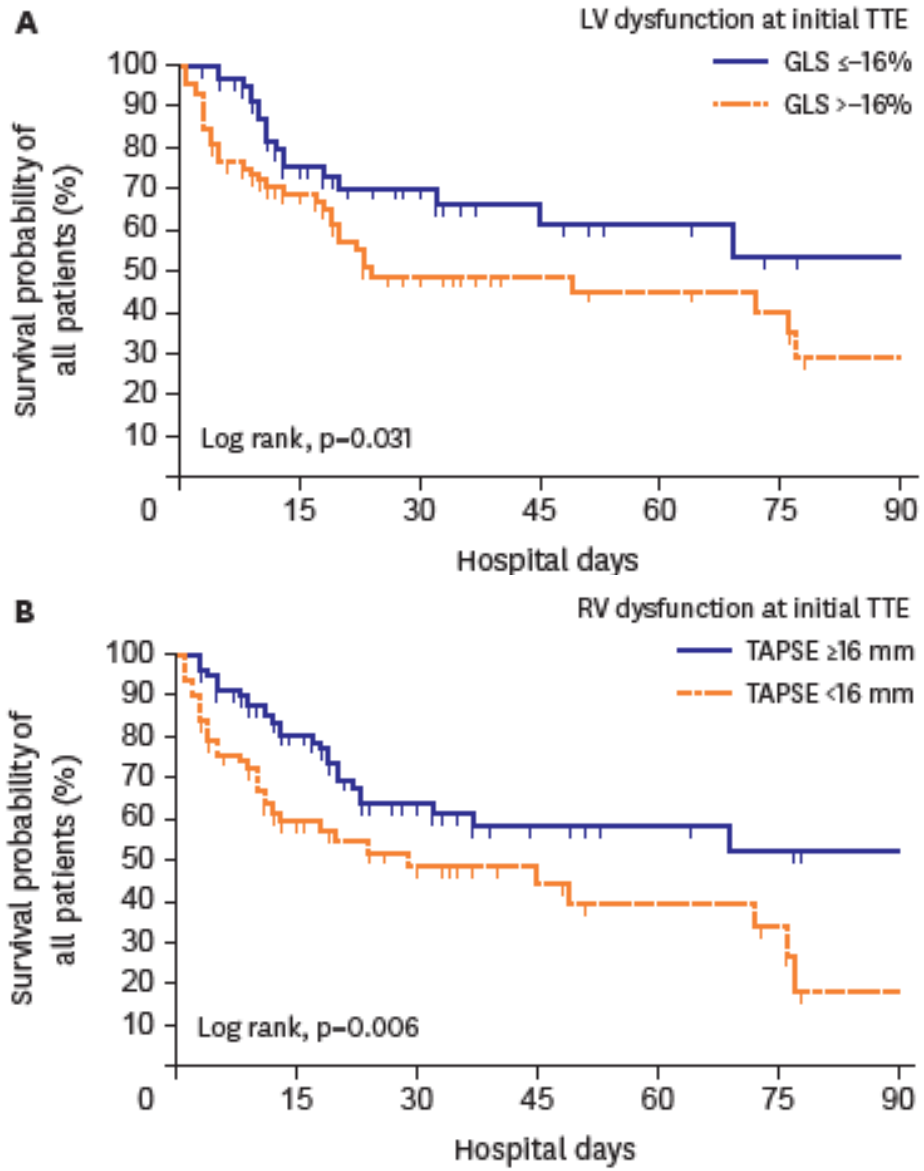
Prognostication of septic cardiomyopathy

Table 1. Baseline characteristics of the patients by 7-day mortality and their evaluation of cardiac function and hemodynamic condition

	All patients (n=162)	Seven-day survivor (n=138)	Seven-day non-survivor (n=24)	p value
Age (years)	70.7±13.4	70.3±13.5	72.5±13.1	0.461
Male	83 (51.55)	73 (53.3)	10 (41.7)	0.378
Body surface area (m^2)	1.61±0.17	1.61±0.16	1.64±0.25	0.344
Charlson comorbidity index	4.50±2.00	4.41±2.08	5.17±1.71	0.038
APACHE II				<0.001
Mean±SD	30.60±9.20	29.38±8.70	39.32±7.70	
Median (IQR)	31 (23–38)	29 (22–36)	41 (33–44)	
SOFA score	9.51±3.24	9.07±2.99	12.04±3.56	<0.001
Vasoactive-inotropic score				0.001
Mean±SD	29.90±62.40	20.09±31.86	88.41±132.99	
LV EDV (mL)	59.00±20.67	59.63±17.81	60.87±28.61	0.842
LV ESV (mL)	27.11±13.96	26.78±13.04	31.09±18.00	0.280
LVEF				0.054
Mean±SD	55.20±14.13	56.43±12.42	48.23±18.44	
Median (IQR)	58.40 (45.00–65.15)	58.8 (47.59–65.65)	50.50 (34.25–63.87)	
E/e'	13.23±13.84	12.05±5.35	12.27±4.97	0.869
GLS				<0.001
Mean±SD	−14.90±5.21	−15.54±5.03	−10.57±4.32	
Median (IQR)	15.00 (10.60–19.00)	15.90 (12.10–19.50)	9.30 (7.70–13.70)	
TRVmax (m/sec)	2.73±0.47	2.72±0.47	2.78±0.44	0.596
TAPSE (mm)				0.003
Mean±SD	16.90±5.54	17.67±4.87	14.18±4.43	
Median (IQR)	17.00 (14.00–20.80)	17.00 (14.22–21.00)	15.00 (9.65–17.40)	
LVEF <50%	50 (31.17)	40 (29.0)	10 (41.7)	0.224
GLS >−16%	74 (54.4)	57 (48.7)	17 (89.5)	0.001
TAPSE <16 mm	63 (42.9)	48 (38.4)	15 (68.2)	0.011
Cardiac output (L/min)	4.92±3.65	4.75±1.66	4.11±1.70	0.091
Cardiac output index (L/min/m^2)	3.06±2.10	2.97±0.98	2.53±1.09	0.207
Systemic vascular resistance (dynes sec/cm^5)	1,556.23±650.98	1,537.12±646.94	1,714.79±597.49	0.088
Systemic vascular resistance index (dynes sec/cm^5m^2)	2,493.62±1,076.98	2,434.611±1,072.59	2,826.21±1,064.88	0.116
7-day mortality	24 (14.9)	0 (0)	24 (100.0)	

Korean Circ J. 2023;53:813-825





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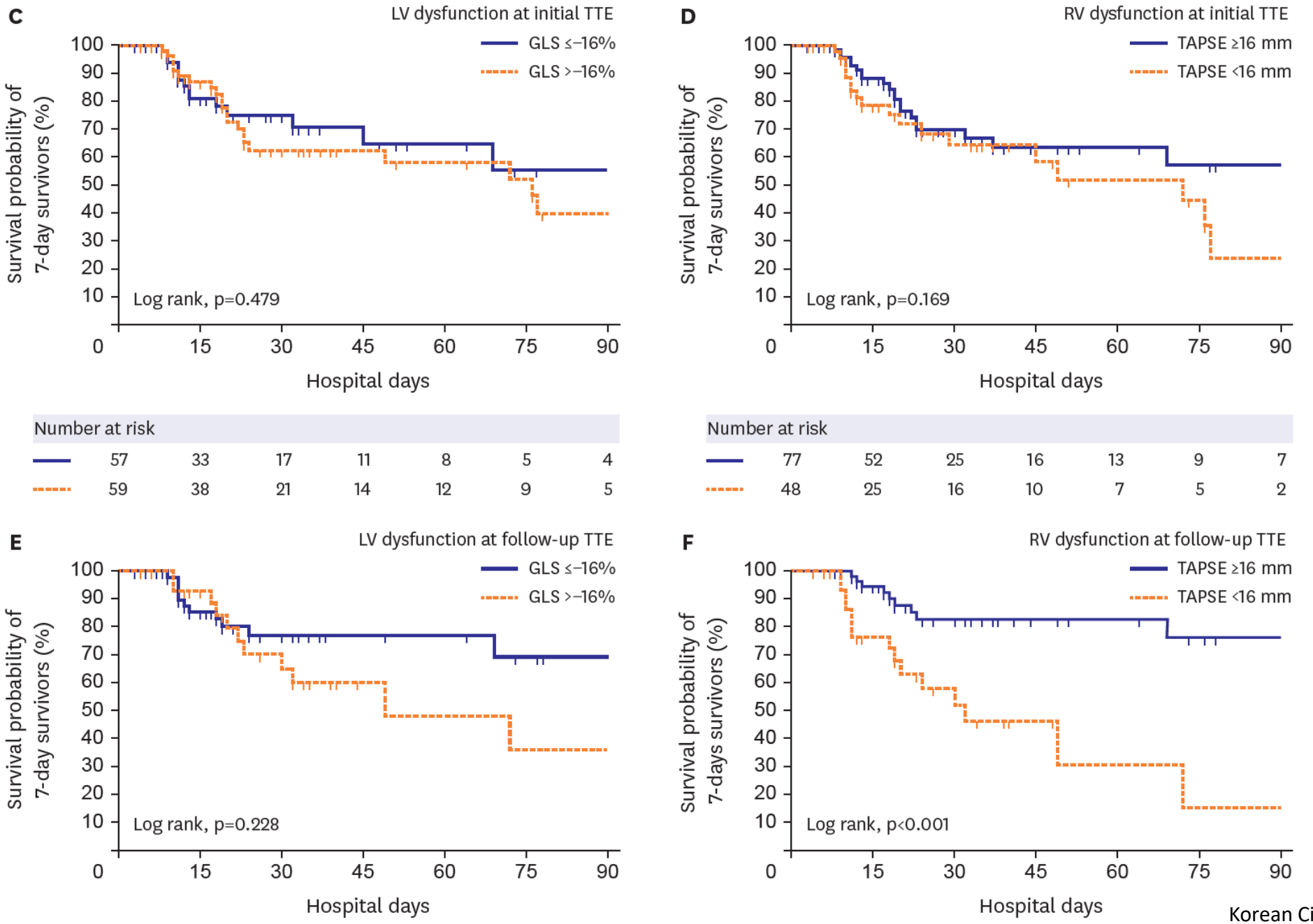

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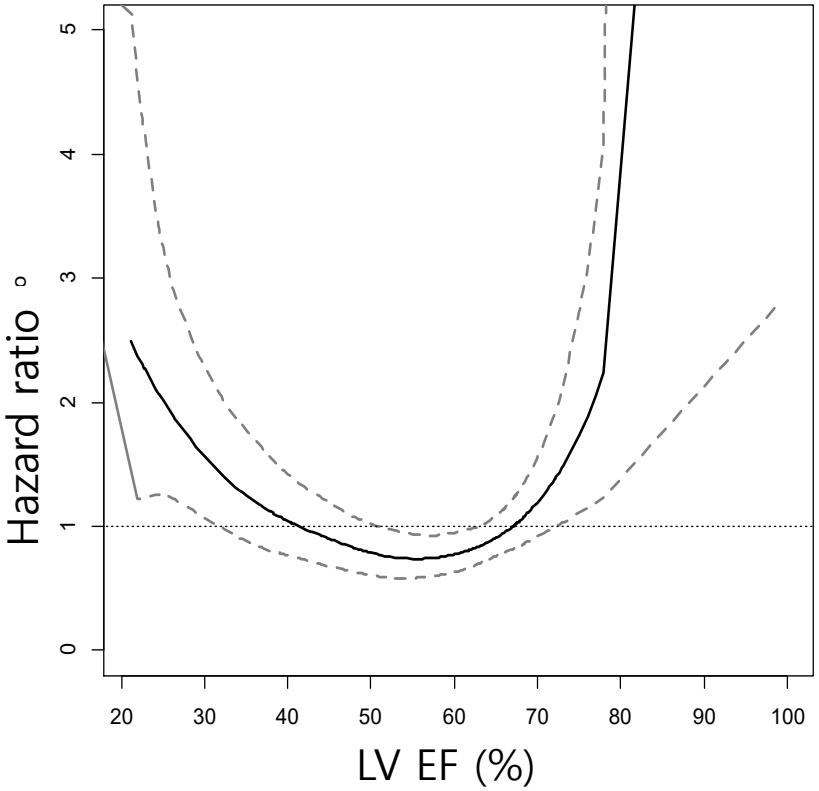
Left ventricular ejection fraction and overall survival

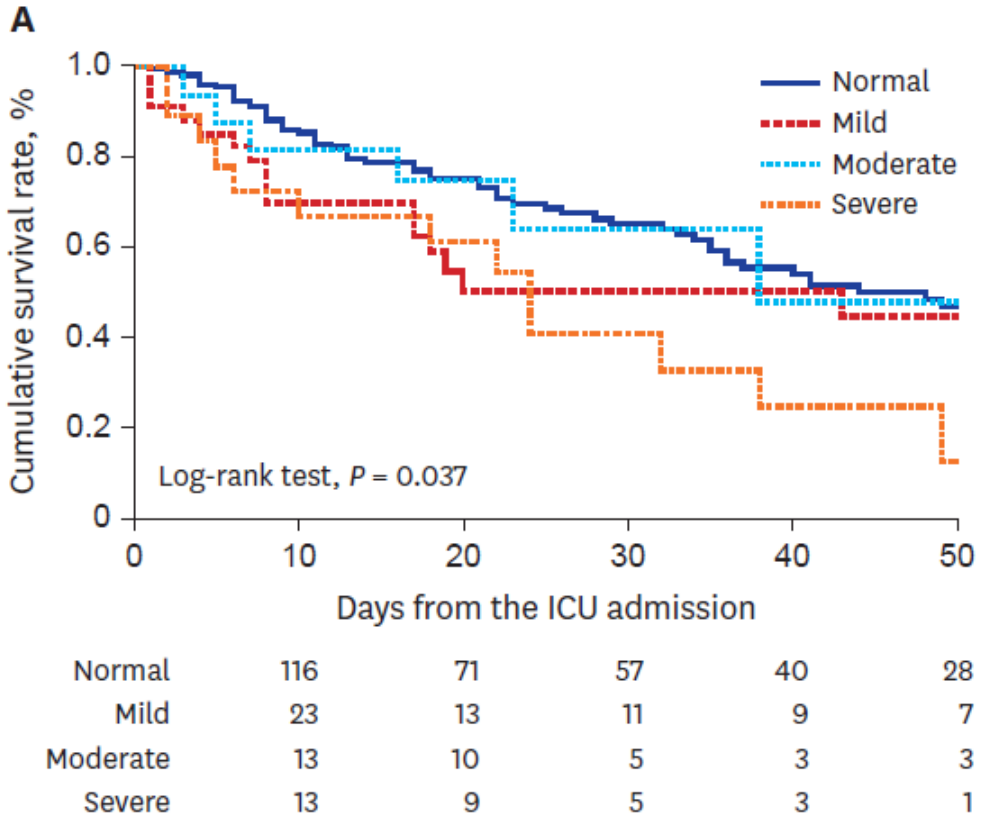
LV systolic function	Hazard ratio (95% CI)	p-value*
Hyperdyanamic	1.74 (1.05–2.90)	0.032
Normal	1.00 (ref)	-
Mild	1.28 (0.71 - 2.30)	0.410
Moderate	1.78 (0.84 – 3.79)	0.135
Severe	2.66 (1.41 – 5.02)	0.002

* Adjusted for age, sex, underlying disease, and APACHE II score

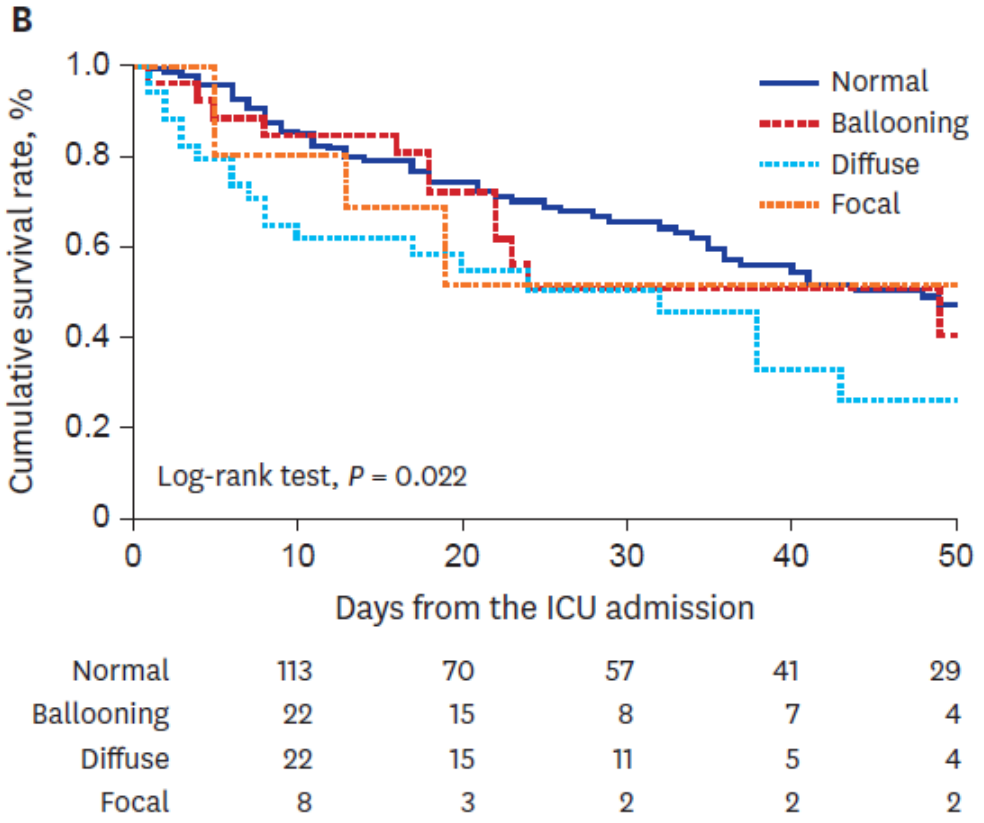


J Korean Med Sci. 2020;35(4):e24

Kaplan-Meier curve for mortality in patients with septic shock. The overall survival in patients with septic shock was compared by the LV systolic function (**A**) and by the pattern of LV wall motion impairment (**B**)



Normal	116	71	57	40	28
Mild	23	13	11	9	7
Moderate	13	10	5	3	3
Severe	13	9	5	3	1



Normal	113	70	57	41	29
Ballooning	22	15	8	7	4
Diffuse	22	15	11	5	4
Focal	8	3	2	2	2

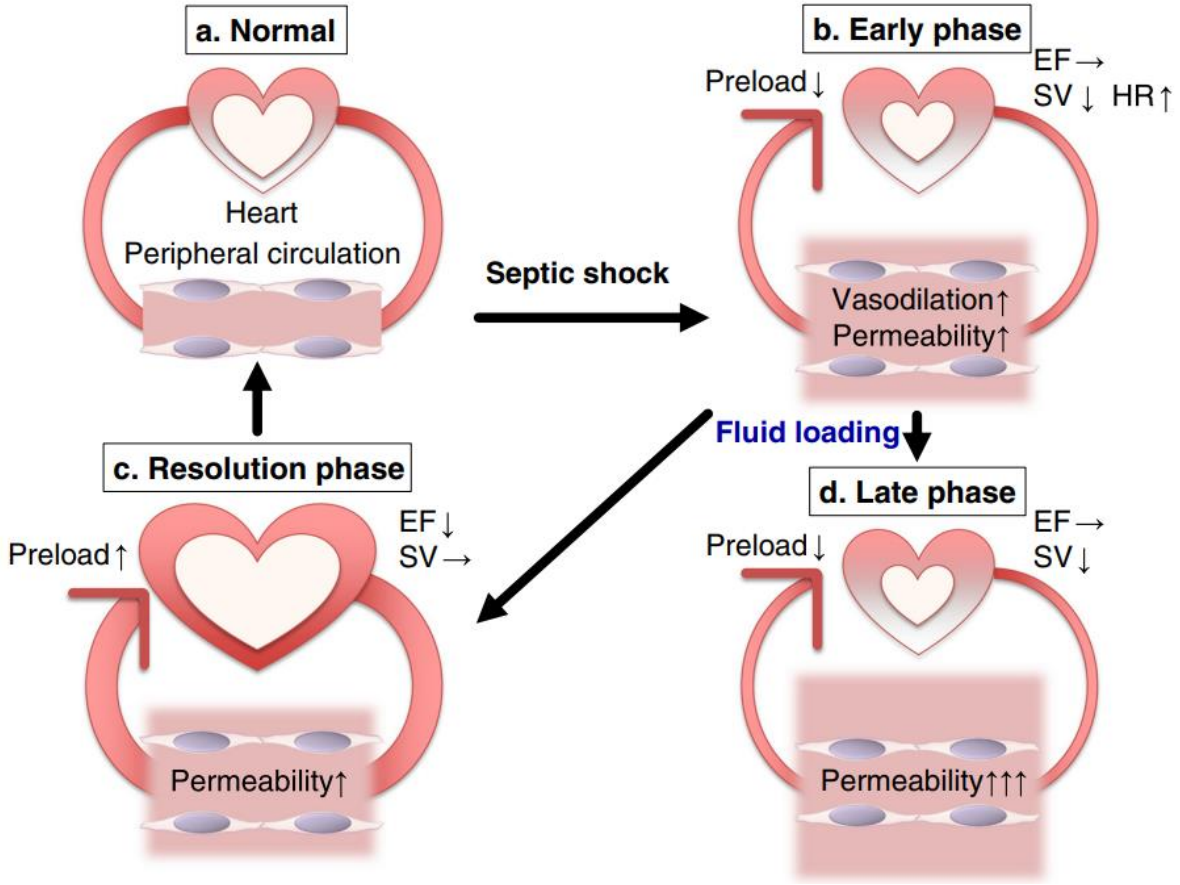
J Korean Med Sci. 2020;35(4):e24

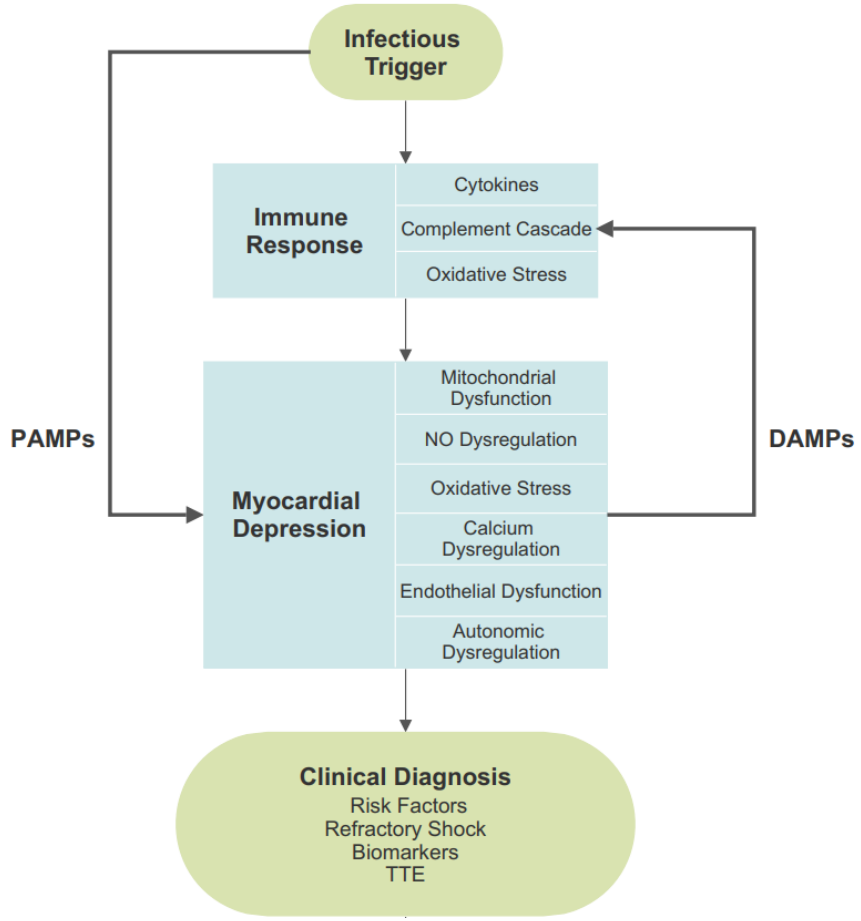
Table 2 Management of sepsis-induced cardiomyopathy

Therapy	Mechanism of action	Pro	Con
Vasopressors	Vasoconstriction by alpha or beta adrenergic, vasopressin, or dopamine receptor stimulation	Physician familiarity. Well studied in septic shock. Alpha-adrenergic, dopamine, and vasopressin activity will help with decreased afterload. Beta and dopamine activity will increase contractility	Increasing afterload too much may "unmask" cardiac dysfunction (especially with isolated vasoconstrictive drugs phenylephrine and vasopressin). The beta-adrenergic and dopamine activity could increase myocardial demand leading to worsening cardiomyopathy and/or arrhythmias
Fluids	Increasing preload with increase stroke volume based on Frank–Starling relationships	Increasing stroke volume will increase cardiac output	Cardiomyopathy will shift the Frank–Starling curve and overaggressive fluid management can lead to worsening organ failure
Dobutamine	Beta-adrenergic selective agent	Physician familiarity. Most studied with proven improvement in cardiac parameters (i.e., CO)	Increased myocardial demand and vasodilation may worsen hemodynamics. Risk of arrhythmias. May not improve outcomes
Milrinone	Phosphodiesterase inhibitor increases cAMP	Increased contractility without adrenergic activity. No trials for SICM	Vasodilation. Limited by renal dysfunction. Risk of arrhythmias
Levosimendan	Calcium sensitizer and potassium channel activator	Helps with calcium signaling to increase contractility in an adrenergic-dependent manner so less oxygen demand	Vasodilation. Mixed information about mortality with the largest trial suggesting increased mortality
Beta blockers	Beta-adrenergic blockade	May help decrease the pathogenesis of SICM by decrease myocardial demand	Negative inotropic effect. Patients with cardiac dysfunction were excluded from the largest trials
Ivabradine	Selective inhibitor of the I_f channel	Lower myocardial demand without negative inotropic effect found in beta blockers	Possible worsened mortality, but data sparse and not specific to SICM
Methylene blue	Nitric oxide metabolism	Treats vasoplegia. Improves catecholamine responsiveness. May improve vasopressor requirement	No change in outcomes. Risk of serotonin syndrome. Can cause worsening oxygenation by pulmonary vasoconstriction. Hemolytic anemia in G6PD deficiency. Interference with pulse oximetry. Contraindicated with renal dysfunction
Mechanical support	Provide bypass or mechanical assistance of cardiac output	Provides aggressive supportive care until reversibility occurs	Invasive with relatively high risk of complications. Must choose right device

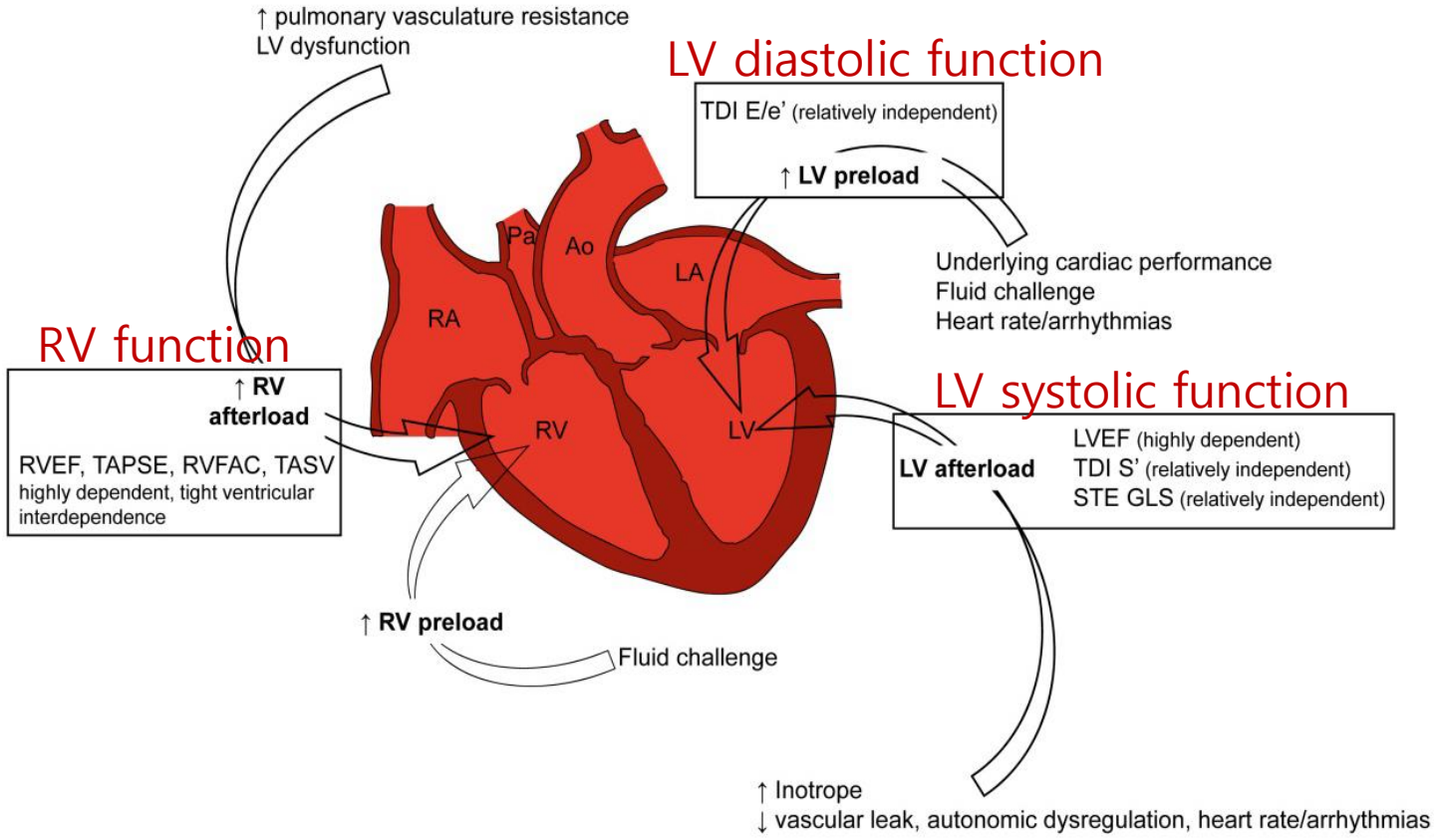
In Summary

Suspicion of cardiac damage:
Insensitivity to catecholamine use in sepsis





In Summary



No evidence of cardiac biomarkers or ECG findings for the diagnosis of septic cardiomyopathy

Thank you for your attention!