31 GIORNATE CARDIOLOGICHE TORINESI

TURIN
October
24th-26th
2019

CARDIOGENIC SHOCK: EARLY SUPPORT IS INDICATED

Nuccia Morici

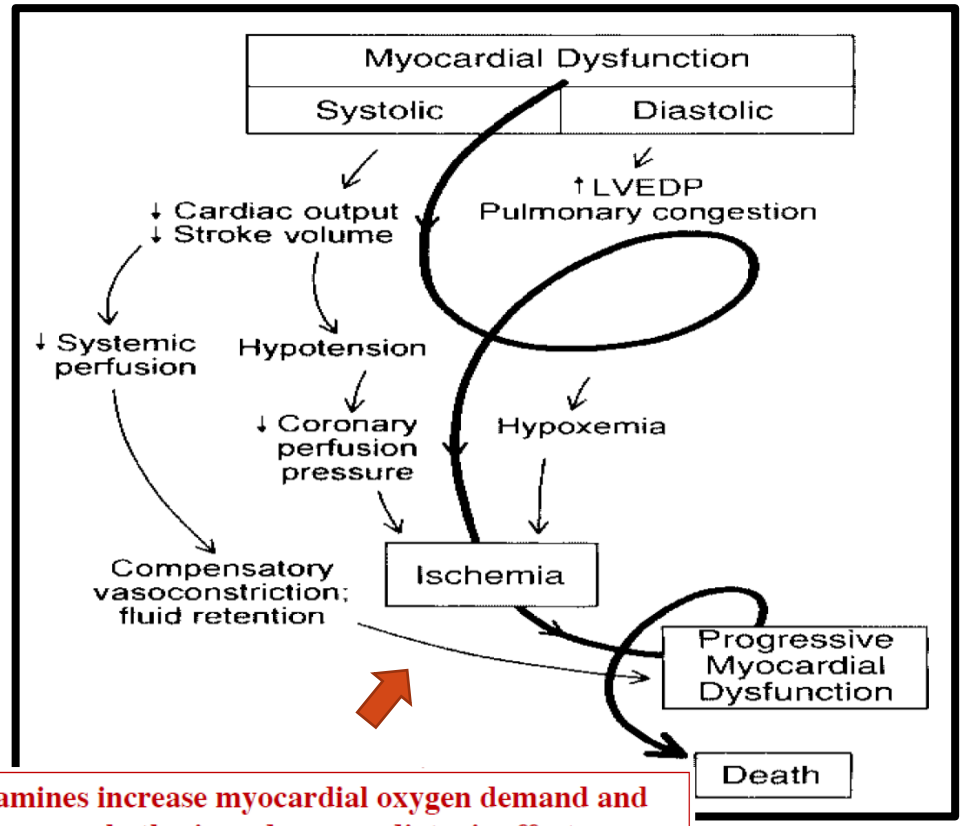
Unità di Cure Intensive Cardiologiche

ASST Grande Ospedale Metropolitano Niguarda, Milano

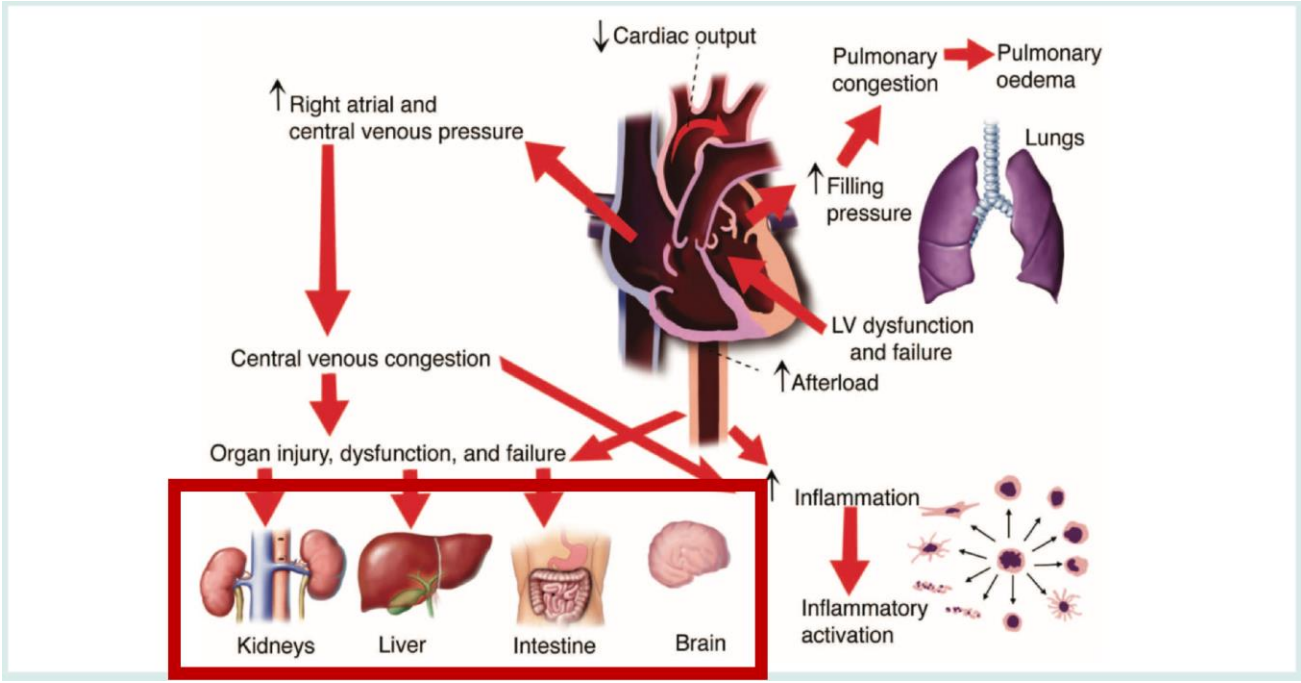
CARDIOGENIC SHOCK DEFINITION

Systemic illness in reaction to general organ hypoperfusion, involving inflammation and nitric oxide production

Curr Opin Crit Care. 2019 Aug;25(4):403-409

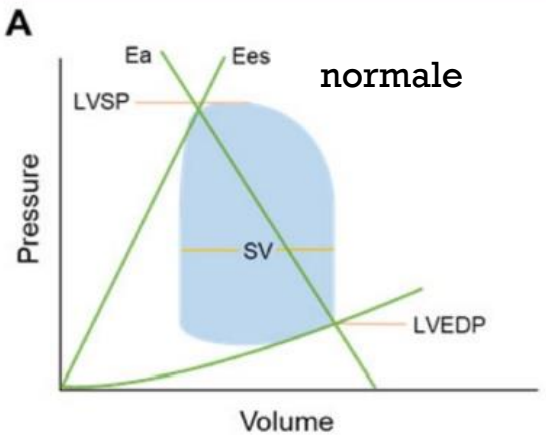


catecholamines increase myocardial oxygen demand and have proarrhythmic and myocardiotoxic effects

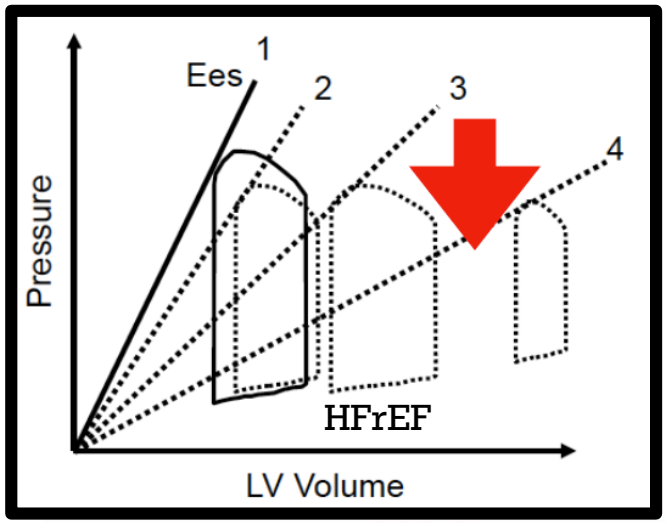


Hollenberg, Annals of Internal Medicine *1999*

PRESSURE VOLUME LOOP



normale



J Clinic Med 2019, 8, 1209

Cardiogenic shock in ADHF

Variables predicting 30-day mortality on multivariate analysis			
Variables	Odds ratio	95% Confidence limits	p Value*
Age	1.07	1.03–1.10	0.001*
Body mass index	0.93	0.86–1.00	0.054
Mechanical ventilation	1.32	0.43–3.99	0.628
Current smoker	1.12	0.39–3.18	0.826
Prior cerebrovascular accident	2.74	0.94–8.00	0.066
Baseline heart rate	0.99	0.98–1.00	0.313
Baseline creatinine	1.34	0.98–1.82	0.068
Inotropes prior to IABP	1.39	0.88–2.20	0.16
Inotropes post-IABP	2.03	1.44–2.84	0.000*
Time to IABP	1.05	1.01–1.09	0.009*
Cardiopulmonary resuscitation	2.44	1.04–5.72	0.041*

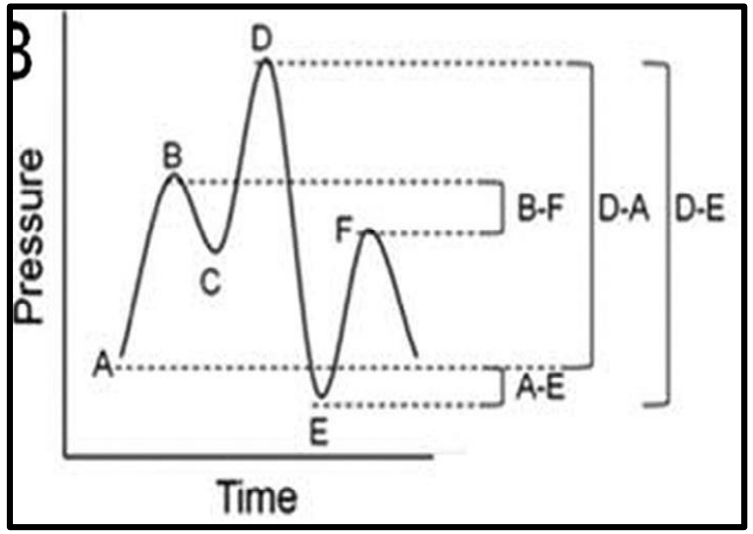
Am J Cardiol 2019;123:750–756

Cardiogenic shock in ADHF: summary of evidence

"hemodynamic stabilization" before LVAD/Heart Transplantation

Study	Outcome
Norkiene I, 2007 (11 patients)	Improved hemodynamics, mortality 27%
Imamura T, 2015 (22 patients IABP) INTERMARCS 2	Improved hemodynamics, kidney and hepatic function, ICU stay, 1 year survival 96%
Bezerra CG, 2016 (223 patients)	Improved lactates, ScVO2, vasopressors use, mortality 31%
Annamalai SK, 2017 (10 patients)	Improved hemodynamics, echo parameters, RV parameters
Viola G, 2019 EHJ (30 patients)	Improved hemodynamics, kidney and hepatic function, ICU stay, mortality 17%

One explanation for the continued use of IABPs is that a subset of patients may benefit from counterpulsation therapy; however, the characteristics that define this "responder" population have not been identified.



Cardiogenic shock in ADHF: summary of evidence

"hemodynamic stabilization" before LVAD/Heart Transplantation

Tabella I - Parametri emodinamici pre 12h - 24h - 48h post IABP.

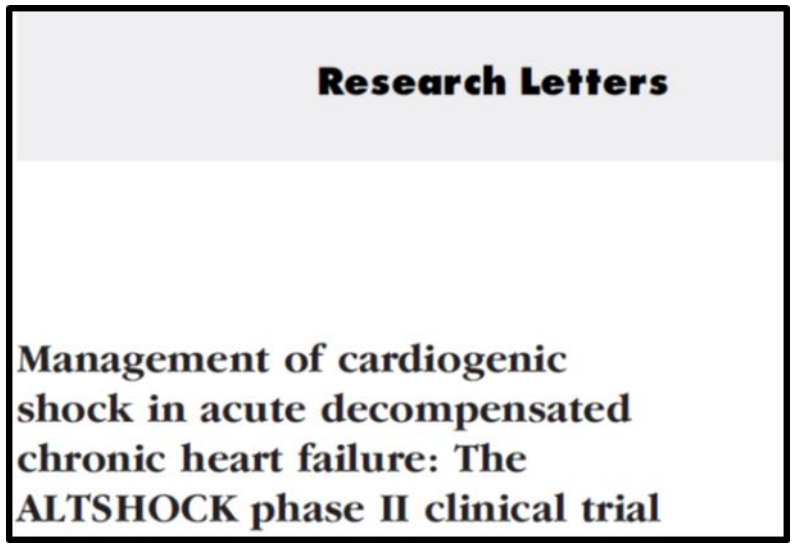
Parametri emodinamici	*Pre IABP media±DP*	*12h IABP media±DP*	*24h IABP media±DP*	*48h IABP media±DP*	*Post IABP media±DP*	*p value*
Pressione arteriosa media (mmHg)	62.3±8.1	71.6±9.7	72.9±10.1	73.5±11.8	82.7±7.5	<0.001
Frequenza cardiaca (bpm)	107.2±19.5	93±14.4	88.2±12.1	91.1±14.9	90.7±8.2	<0.001
Pressione venosa centrale (mmHg)	10.6±4.6	6.9±4.9	5.4±3.9	5.3±4	3.5±3.5	<0.001
Diuresi oraria (cc/h)	27.7±17.9	148.6±65.1	170.7±65.9	141.3±56.2	182.6±41.6	<0.001
Temperatura (°C)	36.7±0.6	36.8±0.8	36.8±0.7	36.7±0.6	36.7±0.7	0.687

Tabella II - Dati di laboratorio pre 12h - 24h - 48h post IABP.

Parametri laboratoristici	*Pre IABP*	*12h IABP*	*24h IABP*	*48h IABP*	*Post IABP*	*p trend*
Emoglobina (g/dl)	11.8±2.3		11.9±2.2	11.8±2.3	12.0±2.1	0.136
Leucociti (/mm³)	10.7±3.3		11.4±3.5	11.9±6.1	11.6±3.3	0.631
Piastrine (/mm³)	232.4±68.6		219.3±69.2	197.7±72.3	218.3±95.9	0.013
Creatinina (mg/dl)	1.1±0.3		1.0±0.3	0.9±0.2	0.9±0.3	0.210
Urea (mg/dl)	56±33.7		48±21.1	43.6±19.2	47.2±13.1	0.297
Bilirubina (mg/dl)	1.9±2.0		1.9±2.1	1.6±2.1	1.1±0.7	0.413
AST (U/L)	43 (24-150)		131 (26-245)	33 (24-110)	60 (25-78)	0.482
INR	1.8±0.6		1.8±0.6	1.7±0.6	1.3±0.3	0.438
PCR (mg/dl)	6.6 (2.1-9.5)		7.1 (3.1-15.8)	4.9 (4-15)	5.7 (2.6-9)	0.088
SvO_2 (%)	44.1±7.9	64.5±10.8	66.5±8.3	63.9±7.5	63.4±4.6	<0.001
Lattati (mmol/L)	4.0±2.2	2.3±2.0	1.4±0.6	1.5±1.2	1.1±0.4	<0.001
pH	7.4±0.1	7.4±0.1	7.4±0.1	7.4±0.1	7.4±0.1	0.826
BNP (pg/ml)	7.097 (6.368-10.133)		5.357 (1.033-10.345)	3.532 (652-9.209)	2.335 (2.187-6.156)	0.187

Cardiogenic shock: old and new circulatory assist devices: the role of counter-pulsation. **Viola G**, Eur Heart J Suppl. 2019 Mar

ALT-SHOCK 1


Research Letters

Management of cardiogenic shock in acute decompensated chronic heart failure: The ALTSHOCK phase II clinical trial

1st step: goal reached if at least 6/9 of the following

If not: intensification of treatment with IABP and/or MV

- Heart rate <130 and >60
- Mean arterial pressure >65 mm Hg
- SVO_2 >60%
- PaO_2 >60
- Trend in reduction of serum lactates
- Respiratory rate <30/min
- Diuresis >0.5 mL/kg/h
- Epinephrine dose <0.07 µg/kg/min
- Reduction of at least 20% compared to admission CVP

2nd step: goal reached if at least 5/8 of the following

If not: intensification of treatment with ECMO

- Heart rate <130 and >60
- Mean arterial pressure >65 mm Hg
- SVO_2 >60%
- PaO_2 >60
- Lactates decrease ≥25% with respect to V3
- Wedge pressure <18 or E/E' <14
- Diuresis >0.5 mL/kg/h

Epinephrine dose <0.12 µg/kg/min without upgrade of other inotropes/vasopressors

24 patients: 16 patients were transitioned to IABP and 1 to IABP and venoarterial extracorporeal membrane oxygenation ***21 patients (87.5%) survived at 60 days (primary outcome);*** among them, 13 (61.9%) underwent LVAD implantation, 2 (9.5%) underwent HTx, and 6 (28.6%) improved on medical treatment

Morici N et al. Am Heart J. 2018

Primary intra-aortic balloon support versus inotropes for decompensated heart failure and low output: a randomized trial

		IABP (n=16)	Inotropes (n=16)	*p*-value
Primary endpoint				
ΔSvO_2 (3h-0h), %		+17 [+9; +24]	+5 [+2; +9]	<0.001
Secondary endpoints				
CPO at T48h, W		0.73 [0.62-0.96]	0.59 [0.48-0.80]	0.17
ΔCPO (48h-0h), W		+0.27 [+0.17; +0.45]	+0.09 [–0.04; +0.21]	0.004
NT-proBNP level at T48h, ng/L		4,907 [3,254-7,628]	8,772 [5,957-16,712]	0.01
ΔNT-proBNP (48h-0h), % change		–59.3 [–78.5; –46.7]	–16.0 [–40.4; +3.3]	<0.001
Cumulative fluid balance at T48h, mL		–3,066 [–3,876; –2,205]	–1,198 [–2,251; –70]	0.006
ΔDyspnoea severity score at T48h*		–4 [–6; –3]	–2 [–3; 0]	0.02
Crossover or other escalation of therapy		3 (19%)	7 (44%)	0.25
Crossover		2 (13%)	3 (19%)	
Other escalation of therapy¶		1 (6%)	6 (38%)	
Length of stay in the hospital‡		29 [23-57]	15 [10-18]	0.02
MACE§	30 days	5 (31%)	10 (63%)	0.16
	90 days	6 (38%)	11 (69%)	0.16

*Because eight patients were sedated and intubated, dyspnoea severity score was available for 10 IABP/14 INO patients. ¶Start norepinephrine or extracorporeal membrane oxygenation. ‡In patients who survived until discharge. §Combined endpoint of crossover or other escalation of therapy, death, heart failure rehospitalisation, TIA/stroke. CPO: cardiac power output; MACE: major adverse cardiac events; SvO_2: mixed-venous oxygen saturation

den Uil CA, Eurointervention 2019

ALT-SHOCK 2

Patients with acute decompensated heart failure (ADHF) complicated by cardiogenic shock

Swan-Ganz Catheter or echodynamic

R

early IABP at admission

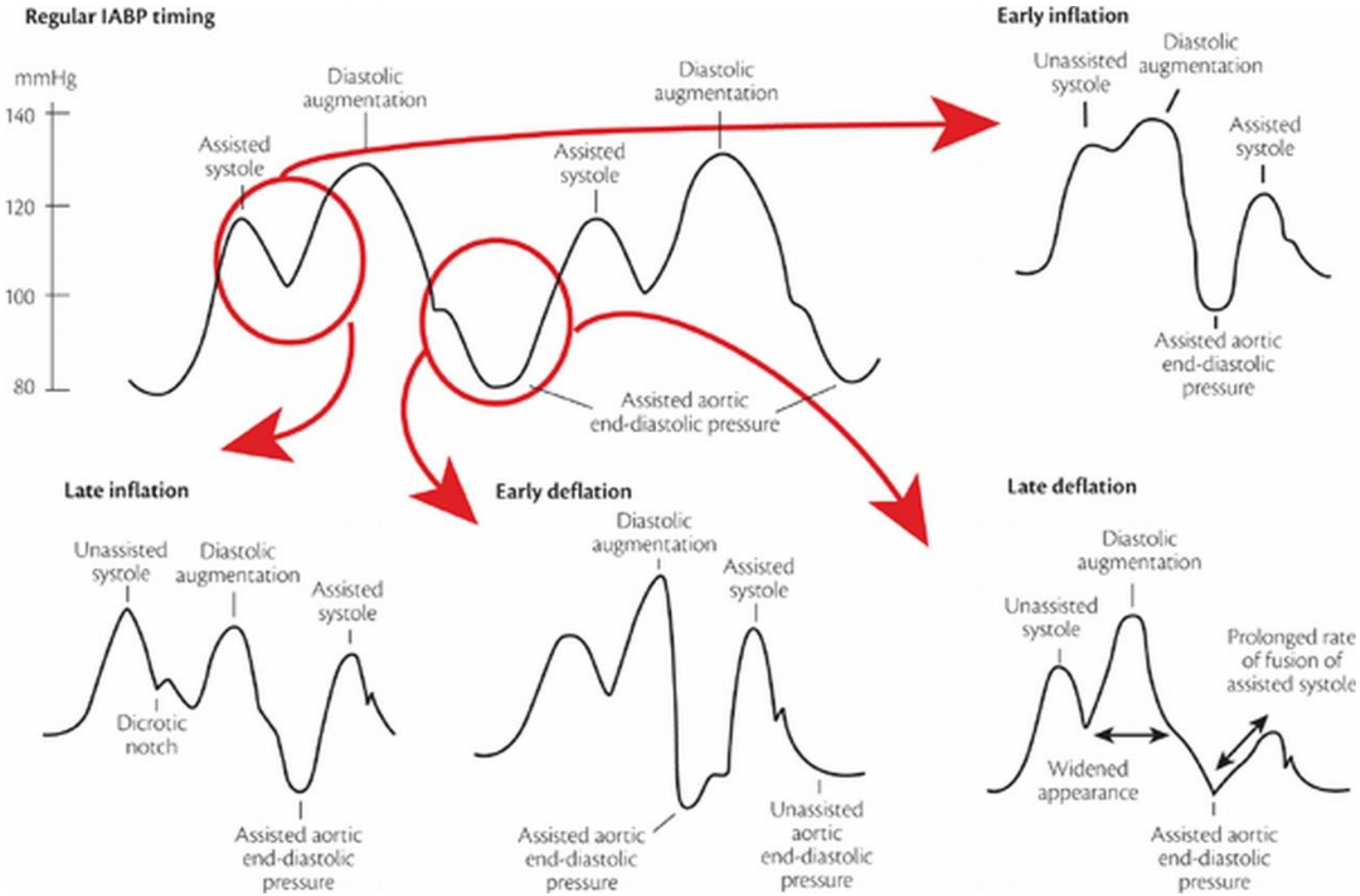
«Standard» clinical practice

Tailored Therapy

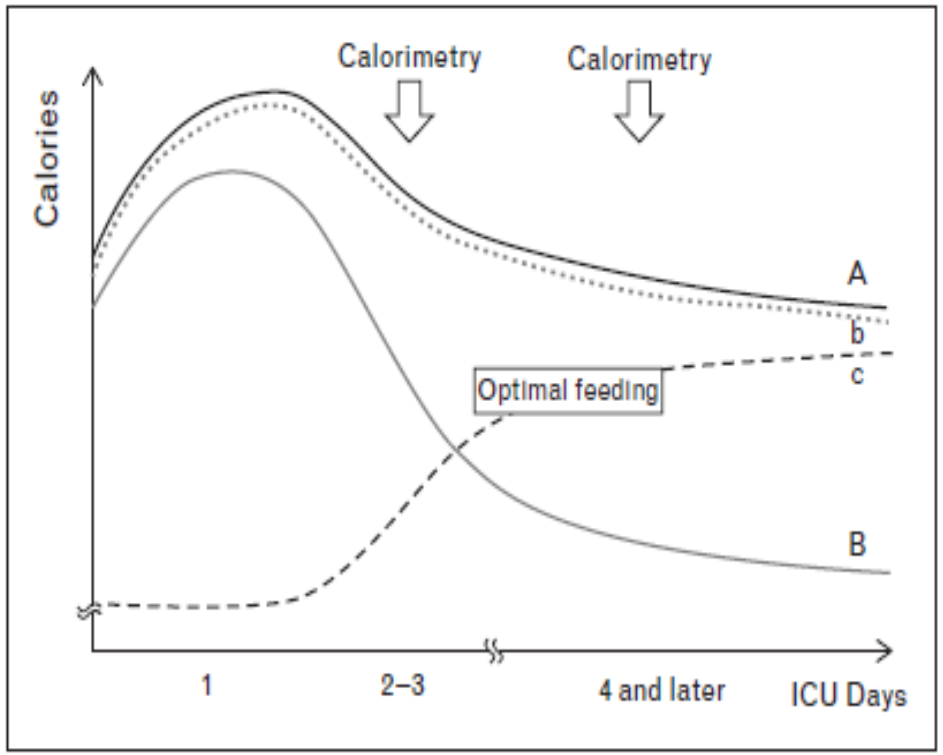
Metabolomic Analysis

Primary Endpoint: *60 day survival or succesful bridge to HRT*

CARDIOGENIC SHOCK: EARLY SUPPORT IS INDICATED..BUT CHECK IT!



CARDIOGENIC SHOCK: EARLY SUPPORT IS INDICATED



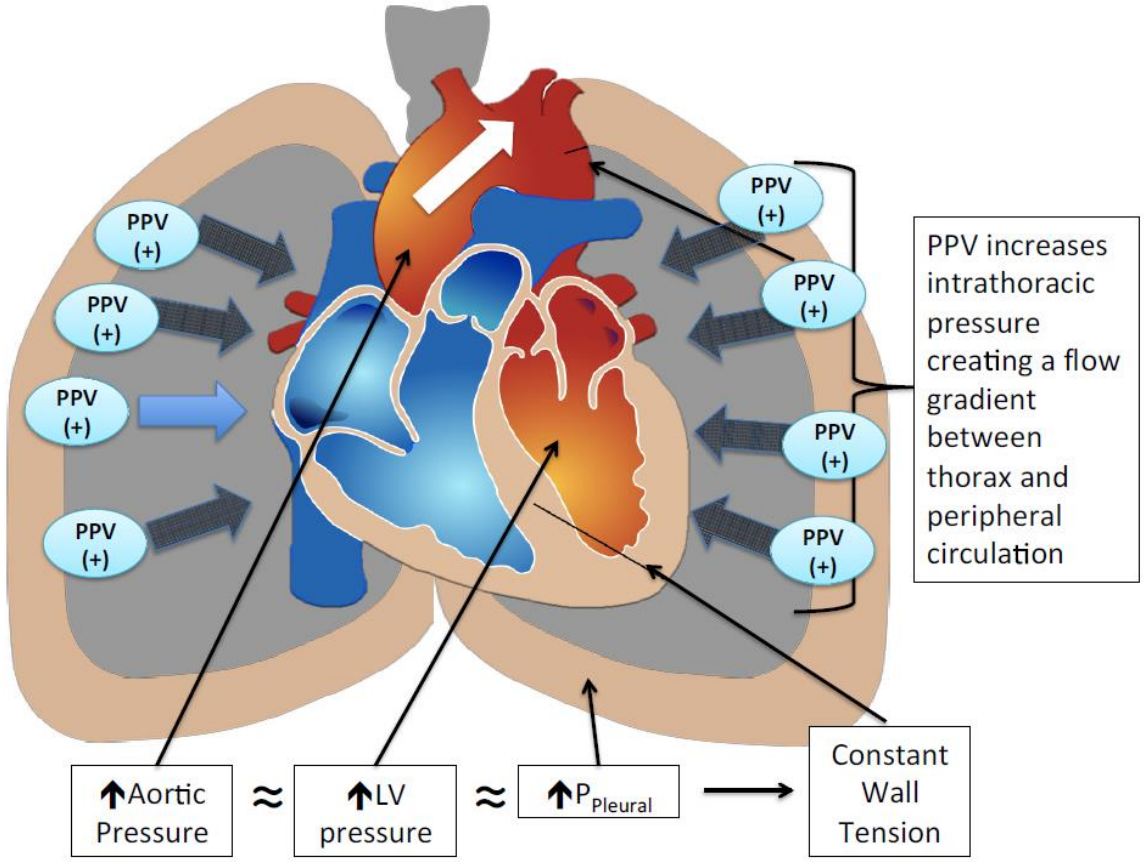
Every critically ill patient staying for more than 48 h in the ICU stay should be considered at risk of malnutrition

Table 4 Recommendations for the management of nutritional support in ICU patients with CS

	Enteral nutrition	Parenteral nutrition	Combination enteral/parenteral
Indications	All patients unable to meet their energy needs by oral intake in the 72 h following ICU admission (C)	All patients with the indications for EN but complicated by GI intolerance or intestinal ischaemia (C)	All patients whose protein-energy needs are not met after 48 h of EN
Recommendations	Early EN should be initiated in the first 24 h in patients fully resuscitated and/or stable (C)	Strict glycaemic control should be obtained to avoid the deleterious effects of hyperglycaemia and overfeeding (C)	The same recommendations as for EN and PN alone are applicable
	EN should be begun at a low flow rate (20 ml/h) during the first 48 h to evaluate GI tolerance (E) EN should be stopped in hypotensive patients (mean arterial blood pressure <60 mmHg) or if the doses catecholamine agents[a] need to be escalated (E) Strict monitoring for early signs of intestinal ischaemia (abdominal distension, high residual gastric volumes, hypoactive bowel sounds, metabolic acidosis) is mandatory (E)		Consider de-escalation of PN together with an increase in EN energy delivery (E)
Choice of solution	Polymeric (E) Fibre-free (E) No pharmaconutrients (E)	'All-in-one' solution (E) No pharmaconutrients (E)	See beside

ESPEN guidelines 2018

CARDIOGENIC SHOCK: EARLY SUPPORT IS INDICATED



As pleural pressure (Ppleural) increases, left ventricular (LV) pressure and aortic pressure also increase, maintaining wall tension constant. PPV also generates a pressure and flow gradient between thorax and peripheral organs (**intra-aortic balloon pump-like effect**).

JACC VOL. 72, NO. 13, 2018

TAKE HOME MESSAGE

CS is a complex time-dependent disorder

THANKS!

BUT WAIT……

There is more……

BACKUP SLIDES

ALT-SHOCK 2 INCLUSION CRITERIA

Age ≥ 18 and < 75, men and women

SBP < 90mmHg or MAP < 60 mmHg, after an appropriate fluid challenge if there is no sign of overt fluid overload; OR 2) need of vasoactive agents to maintain SBP > 90 mmHg or MAP > 60 mmHg.

Reduced ejection fraction (left ventricle systolic function ≤35%).

Moreover, eligible patients have to fit at least ONE of the following criteria/items of overt hypoperfusion: mixed venous oxygen saturation < 60%; arterial lactates > 2 mmol/L; oliguria < 0.5 ml/Kg/h for at least 6 hours.

Eligible patients shouldn't have contraindications to HRT.

ALT-SHOCK 2 EXCLUSION CRITERIA

CS symptoms beyond 6 hours;

septic shock with evident septic focus;

CS following acute myocardial infarction, acute myocarditis, pulmonary thromboembolism;

Reiterating major arrhythmias: ventricular tachycardia (VT) or ventricular fibrillation (VF) or atrial fibrillation (AF) with ventricular rate > 160 bpm;

severe aortic valve disease;

obstructive hypertrophic cardiomyopathy or constrictive pericarditis or severe congenital cardiomyopathy;

severe peripheral vascular disease that contraindicates mechanical support insertion;

CS secondary to cardiac and non-cardiac surgery;

estimated glomerular filtration rate severely impaired before enrolment (eGFR<30 ml/min/1.73 m2) or severe chronic obstructive pulmonary disease or liver cirrhosis;

comorbidities with ominous prognosis (life expectancy < 1 year);

any other significant disease or disorder which, in the opinion of the Investigator, may either put the participants at risk because of participation in the trial, or may influence the result of the trial, or the participant's ability to participate in the trial;

participants involved in other clinical trial;

pregnant, lactating or women planning pregnancy during the course of the trial.

ALTSHOCK 2 ENDPOINTS

Follow up duration	**60 days**
Planned Trial Period	*36 months*
Primary Objectives	***To compare the effect of early IABP versus standard of care according to local practice in terms of 60-day survival or successful bridge to HRT.***
Secondary	• *To compare 60-day overall survival among the two groups (early IABP vs standard)* • *To compare 60-day need for renal replacement therapy among the two groups (early IABP vs standard)* • *To compare maximum inotropic score among the two groups (early IABP vs standard)* • *To compare maximum duration of inotropic/vasopressor therapy among the two groups (early IABP vs standard)* • *To compare maximum sequential organ failure assessment (SOFA) score among the two groups (early IABP vs standard)* • *To identify new biomarkers for prognosis prediction of acute heart failure in cardiogenic shock, by means of a multiscale analysis of blood samples and hemodynamic data*
Safety endpoint	• *Moderate and severe bleeding events according to BARC definition* • *Vascular complications related to IABP (bleedings and limb ischemia)* • *Systemic embolism (non-cerebral)*

ALTSHOCK 2 TRIAL DESIGN

Group sequential, prospective controlled randomized, multi-center trial.

Patients with ADHF and overt CS will be randomized 1:1 to early IABP (***within 6 hours since CS symptoms onset***) versus standard of care as vasoactive agent. Any agent (inotropes and vasopressors) will be allowed. However, the following guide is provided to increase uniformity:

vasopressors allowed will be either epinephrine or norepinephrine;

as inotropic agent milrinone or dobutamine or levosimendan could be used;

dopamine will be allowed in association with milrinone or dobutamine or levosimendan;

the maximum inotropic score allowed will be 20.

The inotropic score (IS) gives an estimate of the severity of circulatory compromise related to concomitant requirements of inotropic and/or vasopressor agents. IS summarizes the total dosing equivalents of inotropes and vasopressors and will be calculated according the modified formula suggested by Champion et al: IS (mcg/kg/min) = [dopamine, dobutamine + 100 x (norepinephrine+epinephrine) +15 x IPDE-3 +10 for levosimendan].[38]

Patients will be evaluated every 2 hours during the first 12 hours and every 24 hours thereafter

ALTSHOCK 2 SAMPLE SIZE

The proportion for the primary endpoint – i.e. survival at 60 days or 60-day successful bridge to HRT - is estimated to be 0.75 in the IABP group and 0.55 in the standard group. With a type I error α set to 0.05 and a power 1- β set to 0.8, a total of 200 subjects will be enrolled in the trial, 100 of whom will be randomized to IABP and 100 to standard. The trial will be designed considering a group sequential design with one interim analysis. This means that a preliminary test to potentially stop the trial for efficacy is performed after 100 out of 200 planned subjects (50 randomized to IABP and 50 to standard reference) have completed the trial. If the trial is not stopped early, a final test is performed once 100 percent of the planned subjects will be enrolled.