Management of septic cardiomyopathy

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The problem in focus

- Incidence of sepsis is increasing
- Severe sepsis and septic shock are leading cause of death in ICU
- Septic patients developing myocardial dysfunction have significantly higher mortality (70%) than those without cardiovascular impairment (20%)

Blanco j et al. Crit Care 2008;12:R158

Topics

- Clinical manifestation of sepsis induced cardiac dysfunction
- Pathophysiological mechanisms
- Novel therapeutic strategies?
- From bench to bedside

Clinical manifestation of sepsis induced cardiac dysfunction

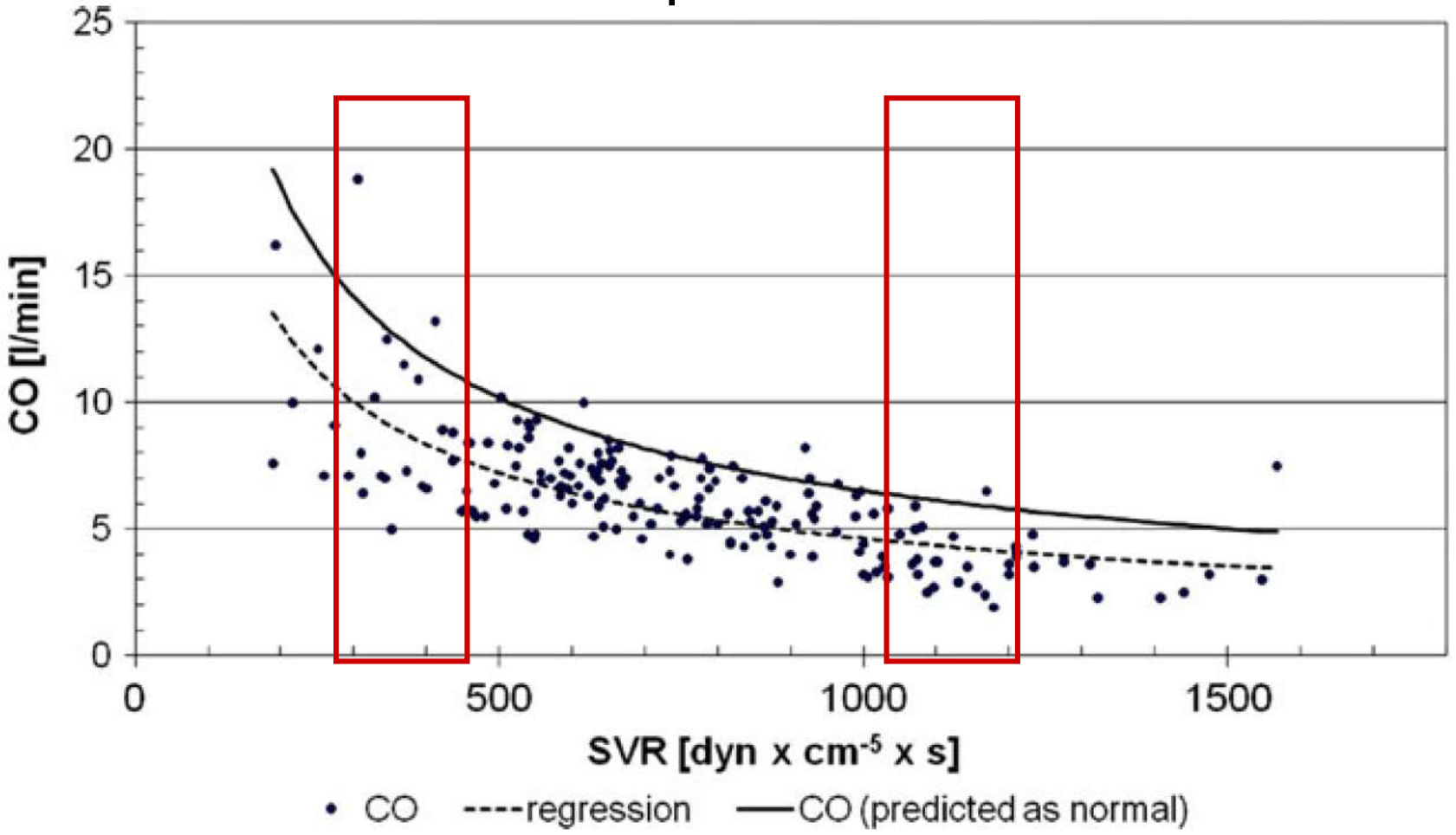
- A not adequately enhanced cardiac output
  - Decreased contractility
  - Impaired response to fluid therapy
  - Ventricular dilation
- Autonomic dysfunction
- Reduced heart rate variability
- Impaired baro- and chemoreflex sensitivity

Warm or cold shock?

- Early sepsis: decreased iv volume leads to low cardiac output
- Volume resuscitated patients develop high cardiac output due to low systemic vascular resistence

- Cold shock = inadequate volume resuscitation?

The extent of septic cardiomyopathy can be more correctly quantified by taking the afterload into consideration, thus measuring the afterload-related cardiac performance.



Werdan K et al. Clin Res Cardiol (2011) 100:661–668

Mechanisms of myocardial dysfunction in sepsis

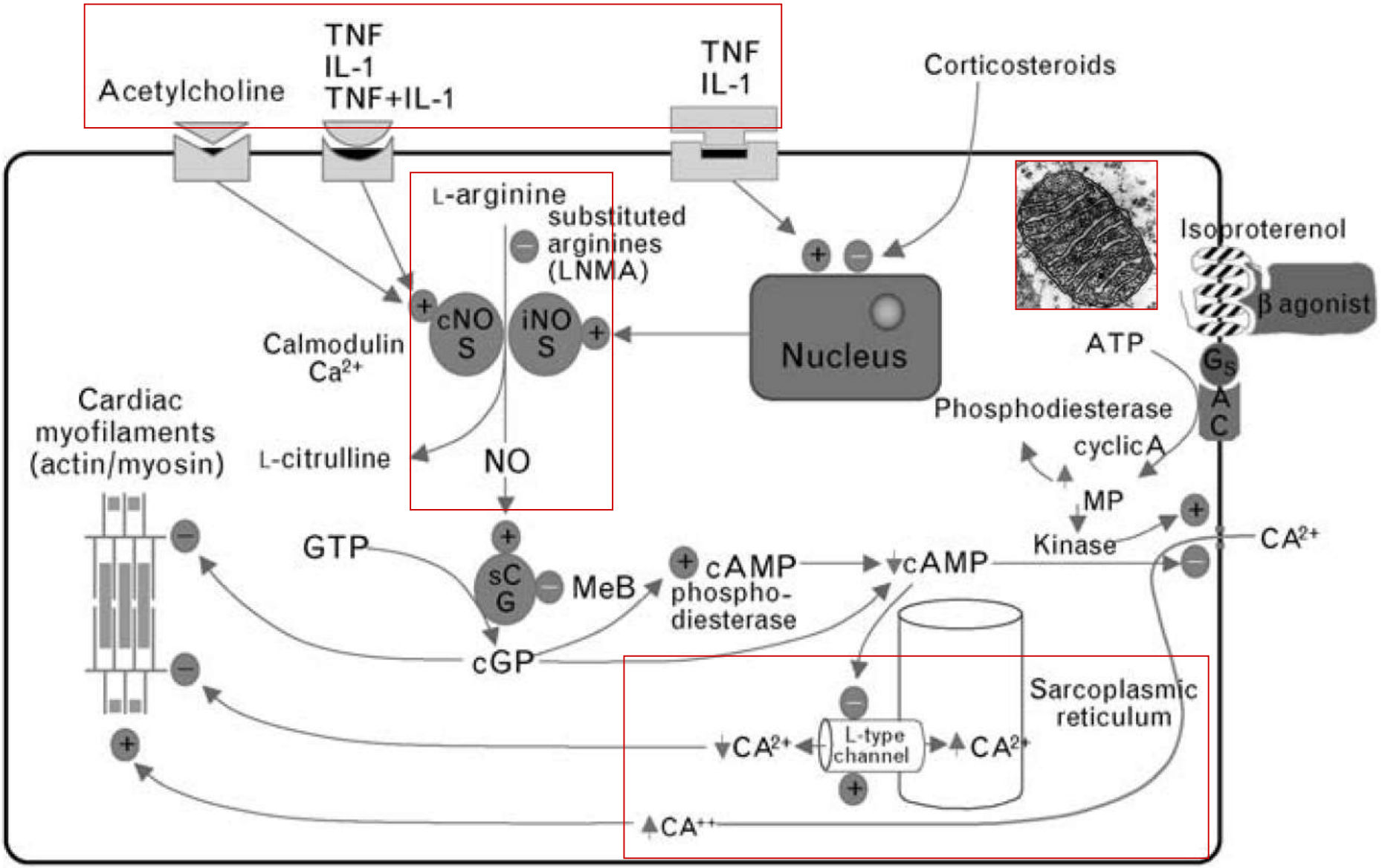
- Hypothesis of global myocardial ischemia

- High coronary flow, decreased myocardial O_2 consumption
- No evidence of significant myocardial necrosis

- Functional rather than anatomical abnormalities?

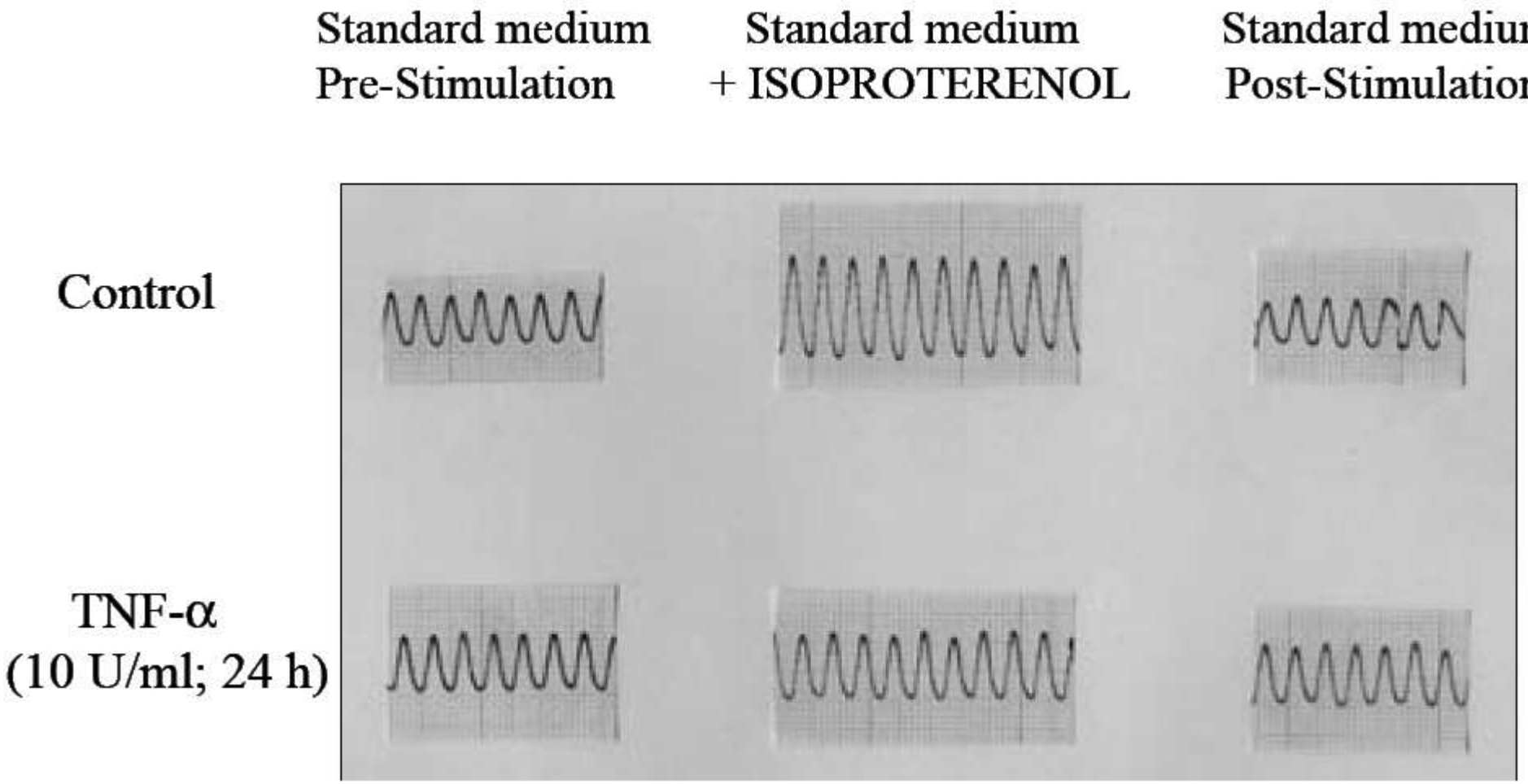
Cunnion RE et al Circulation 1986;73:637-644

Mechanisms of myocardial dysfunction in sepsis



Zanotti-Cavazzoni SL et al. Curr Opin Crit Care 2009;15:392-397

Preincubation of beating neonatal rat cardiomyocytes in culture with TNF-α blocks βadrenoceptor-mediated increases in pulsation amplitude



Muller-Werdan U et al.Exp Clin Cardiol 2006;11(3):226-236.

Blocking myocardial suppressant factors (TNF-α, IL-1β), the same as attempts to inhibit NO production could not prove any benefit.

Treatment	CI	SVR	LVSWI
Endotoxin antibody (HA-1A)	∅	∅	∅/↓
TNF-α antibody/soluble receptors	∅	∅/↑	∅/↑
Hemofiltration	∅	↑	∅
Plasma separation	∅	∅	∅
Hydrocortisone	∅	↑	∅
NO synthase inhibitors	∅	↑	∅/↓/↑
Methylene blue	∅/↓	↑	↑
Pentoxifylline	∅	∅	∅
Hemoperfusion/endotoxin absorption	↓	↑	∅

Muller-Werdan U et al.Exp Clin Cardiol 2006;11(3):226-236.

Role of levosimendan in septic heart failure

- Theoretical advantages compared with dobutamine:
  - does not increase oxygen demand
  - correction of calcium desensitisation
  - reduction in apoptosis
  - reduction in inflammatory response
- May exacerbate hypotension (PVR↓)
- RCTs required

RCTs with levosimendan use in septic shock

Study, year (ref)	Population	N	Levosimendan dose (length of infusion)	Comparator dose (length of infusion)	Definition of septic shock and/or inclusion criteria	Clinical outcome(s) with levosimendan	Follow up
Alhashemi 2009[55]	Severe sepsis/ septic shock	42	0.05-0.2 μg/kg/min (24 hours)	Dobutamine 5-20 μg/kg/min (24 hours)	Trial drugs increased until $ScvO_2$ ≥70%. Rescue therapy with noradrenaline	ICU mortality was less (48% *vs* 62%). CI was less in the levosimendan group and both required similar noradrenaline rescue therapy	ICU length of stay
Morelli 2006[54]	ARDS and septic shock	35	0.2 μg/kg/min	Placebo	Septic shock (ACCP/SCCM) and ARDS	The combination of inotropic and pulmonary vasodilating effects of levosimendan may be beneficial with RV failure in patients with ARDS and sepsis	24 hours
Morelli 2005[45]	Refractory septic shock	28	0.2 μg/kg/min	Dobutamine 5 μg/kg/min	LVEF >45%, PCWP ≥12mmHg Not fluid responsive	Improved haemodynamics and regional perfusion under conditions where dobutamine is no longer efficacious	30 days

Mathieu S et al. JICS 2011;12:15-24

Statins?

- Apoptosis contributes to septic cardomyopathy
  - increased release of caspases,
  - mitochondrial cytochrome c
- Statins influencing the process of apoptosis through their pleiotropic effects might turn out to be a potential therapy.

Buerke U et al. Shock 2008;29:497-503

Kopterides P et al. Clin Microbiol Infect 2009;15:325-334

THE LANCET Infectious Diseases

For sepsis, the drugs don't work

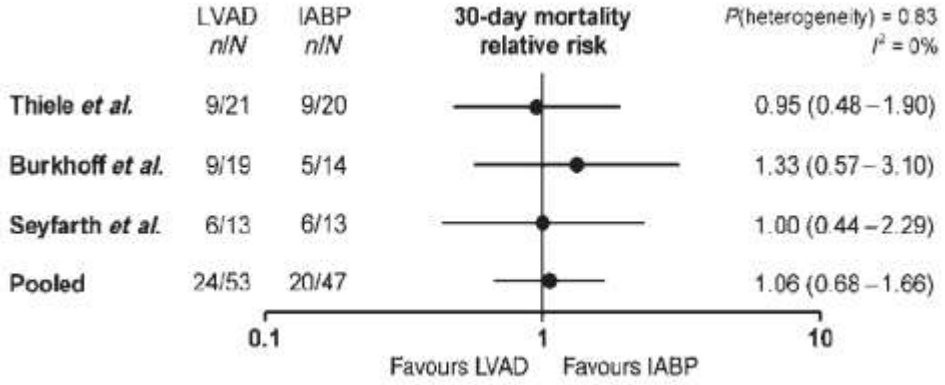
www.thelancet.com/infection Vol 12 February 2012

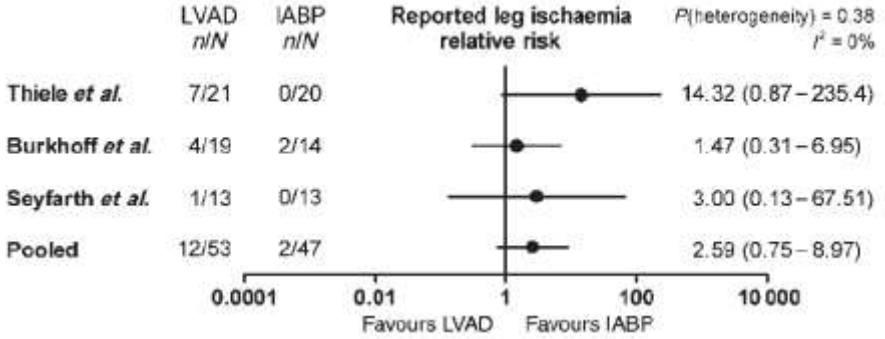
- HA-1A; Centoxin; monoclonal antibody; withdrawn 1993
- Drotrecogin alfa; Xigris; activated protein C; withdrawn 2011
- AZD9773; CytoFab; TNF-antibody; withdrawn 2012 (F IIb)
- ASEPSIS Trial; atorvastatin 40 mg; sepsis progression↓? 2012

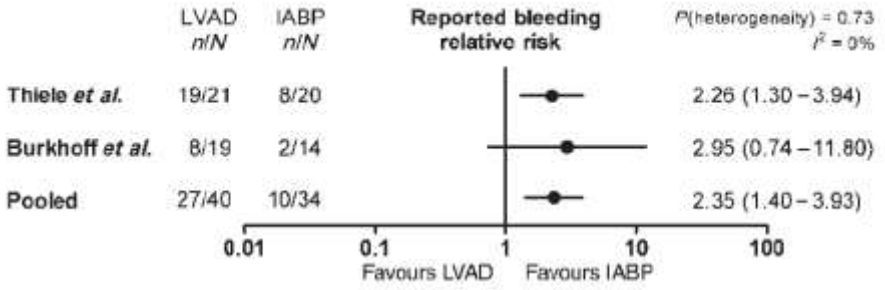
- EUPHRATES Trial; polimyxinB HP endotoxine elim. 2013
- OASIS Trial; talactoferrin alfa; immunmodulant protein 2014

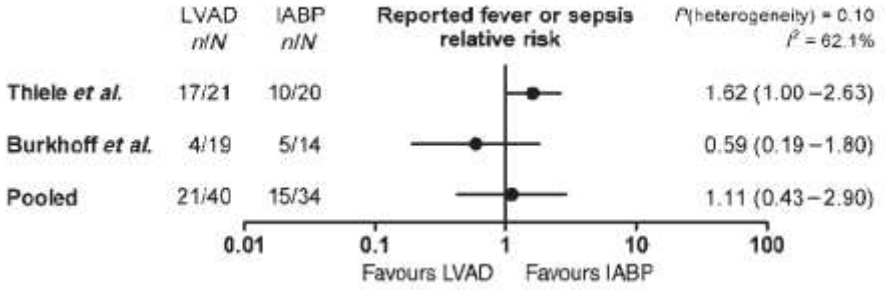
Role of mechanical circulatory support (?)

- Use of ECMO is limited to refractory **pediatric** septic shock and/or respiratory failure (2C)
- IABP?
- LVAD?









Brierley J et al. Crit Care Med 2009;37:666-688

Cheng JM et al. Eur Heart J 2009;30:2102-2108

Changing conceptions: Volume therapy

1. Quantitative resuscitation 6-12 hours (CO)
2. Qualitative resuscitation (glycocalix)
3. De-resuscitation (oedema)

Hypervolemia could be as harmful as hypovolemia

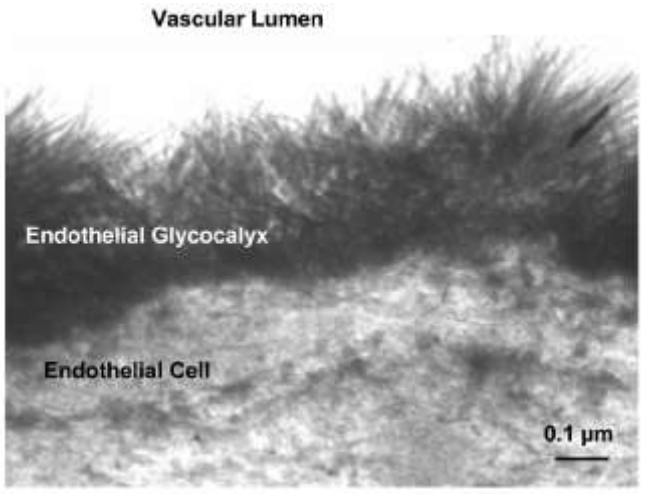


Photo by Welsch U.

Rehm M et al. Anaesthesiology 2004;100:1211-23

Changing conceptions: Vasoactive therapy

- Norepinephrine is first choice (1B)
- **Epinephrine** when additional agent is needed (2B)
- **Dobutamin** in case of myocardial dysfunction (high filling pressure, low CO, hypoperfusion) (1C)
- Vasopressin (0.03 U/min) can be added to NE, but never initial treatment (**UG**)
- Dopamine in highly selected patients (2C)
  - arrhythmia

Dellinger RP et al. Crit Care Med 2013, 41:2:580-637

Sepsis induced cardiac dysfuntion

- Leads to significantly higher mortality
- Understanding of the complex mechanism leads to potential novel therapeutic targets
- Novel drugs and mechanical circulatory support still have not brought break through
- What works: early and proper volume therapy, goal-directed vazopressor and inotropic support, infection source control.
  - What changed is not what to do, but **how** to do it properly?