International CytoSorb Users' Meeting

Brussels, March 20th, 2017

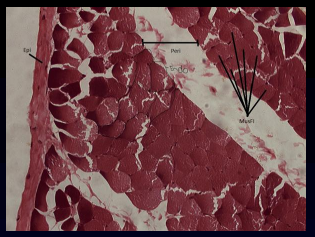
New therapeutic options in Rhabdomyolysis

Blanca Martinez

Department of Anesthesiology. Cardiac Anesthesia Unit
ASUITS Cattinara University Hospital
Trieste, Italy

blancamartinezlopez@asuits.sanita.fvg.it

Rhabdomyolysis: definition



Destruction of striated muscle

that produces a non specific clinical syndrome due to the extravasation of toxic intracellular contents from the myocytes into the circulatory system

- ✓ Asymptomatic
- ✓ elevation CK level
  - > 1000 UI/L
  - >10000 UI/L, statins

→

- Extreme elevation of CK
- Electrolytic imbalances
- Acute renal failure
- DIC

Huerta-Aladin AL. Critical Care 2005, 9:158-169
Visweswaran P. Crit Care Clin 1999, 1582):415-428

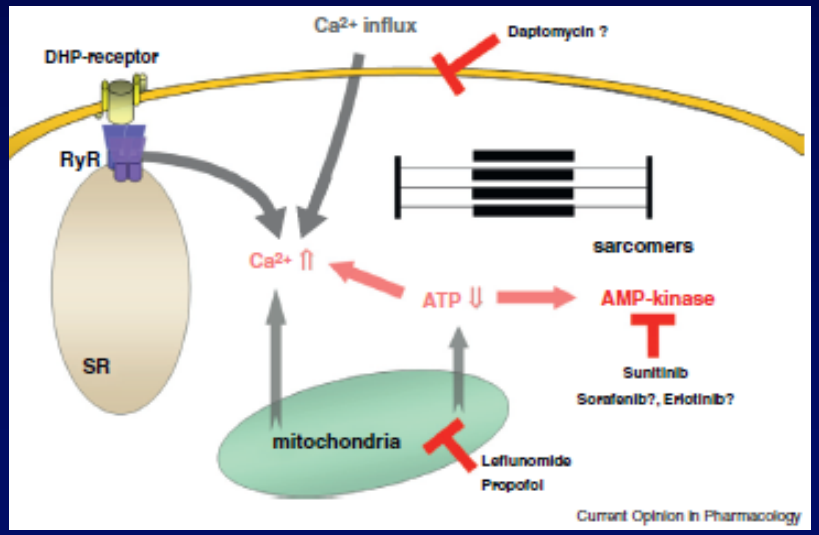
- Global incidence unknown
- Global mortality 2-46%

- Population risks groups:

- Crush syndrome (direct trauma, injury or compression)
- Chronic users of statins
- Postoperative patients
- Morbid obese patients

Etiology

- **Traumatic**
  - Crush syndrome
- **Non traumatic**
  - Drugs
  - Infection
  - Surgery (immobilization)
  - Extreme temperatures
  - Inherited or acquired myopathies
  - Toxins
  - Extreme physical exercise



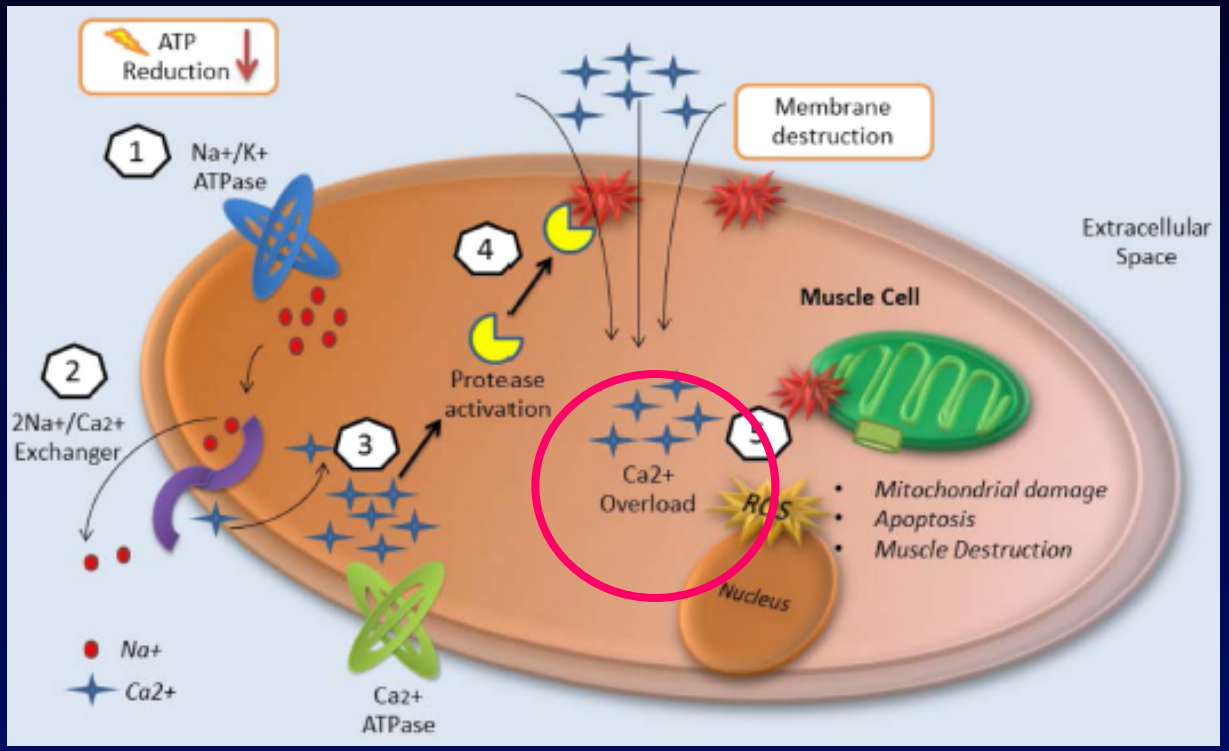
Chavez et al. Critical Care (2016) 20:135
DOI 10.1186/s13054-016-1314-5

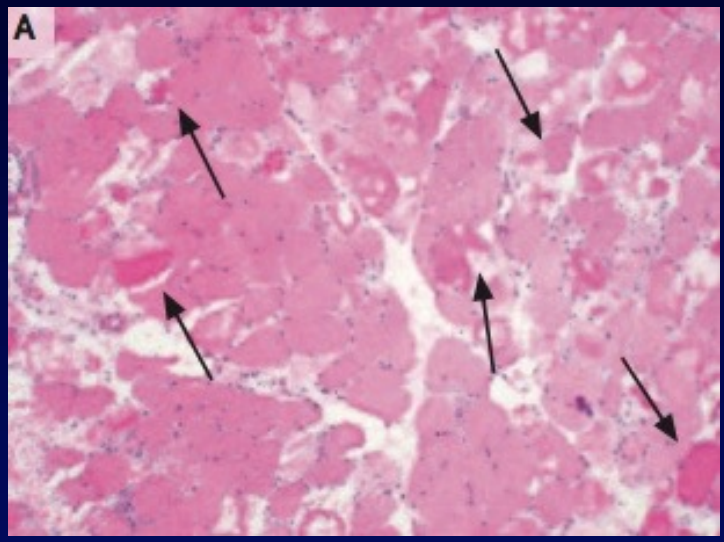
Critical Care

REVIEW Open Access

Beyond muscle destruction: a systematic review of rhabdomyolysis for clinical practice

Luis O. Chavez[1], Monica Leon[2], Sharon Einav[3,4] and Joseph Varon[5*]





The muscle cell is affected either by

direct cell or membrane destruction or by energy depletion

Clinical symptoms

- ✓ Acute Kidney injury is the most common systemic complication of rhabdomyolysis
- ✓ 20-50% of patients with some degree of rhabdomyolysis develop AKI and this is associated with poor outcome
- ✓ Rhabdomyolysis contributes to 5-25% of all cases of AKI

Huerta-Aladin AL. Critical Care 2005, 9:158-169

- ✓ Mortality of ARF secondary to rhabdomyolisis 59%

vs

22% in case of normal renal function

De Meiejer AR. Intensive Care Med 2003;29(7):1121-1125

Woodrow G. Ren Fail 1995;17(4): 467-474)

The NEW ENGLAND JOURNAL of MEDICINE

REVIEW ARTICLE

CURRENT CONCEPTS

Rhabdomyolysis and Acute Kidney Injury

Xavier Bosch, M.D., Ph.D., Esteban Poch, M.D., Ph.D.,
and Josep M. Grau, M.D., Ph.D.

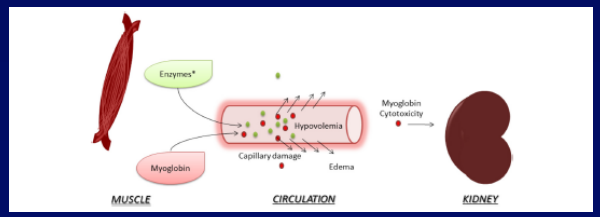
Mechanisms

Rhabdomyolysis-associated AKI

Hypovolemia

Myoglobine

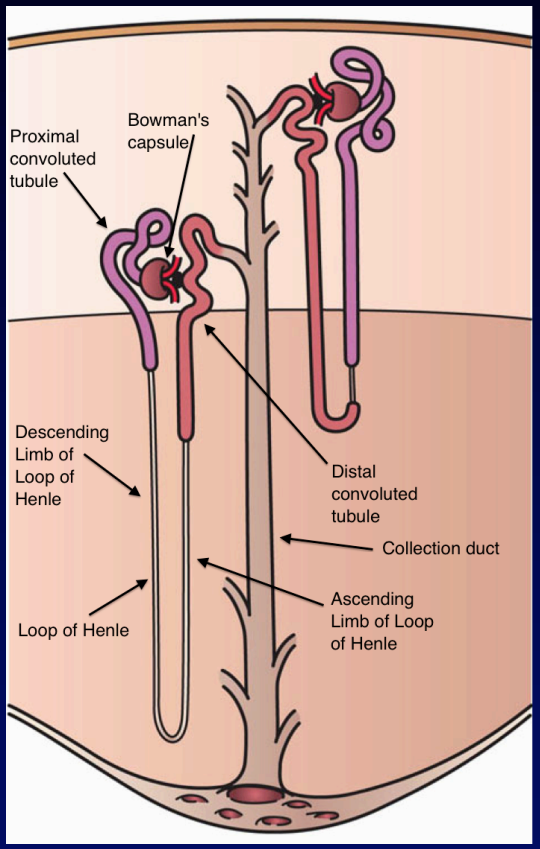
Metabolic acidosis



Mechanisms of renal toxicity by myoglobin

- **Renal vasoconstriction**

  (reduce renal blood flow due to hypovolemia and secondary activation of the renin-angiotensin-aldosterone system)



- **Tubular obstruction**

(by intratubular casts following reaction of myoglobin with Tamm-Horsfall tubular protein)

- **Direct renal oxidative cytotoxicity of epitelial cells of the proximal tubules**

Review

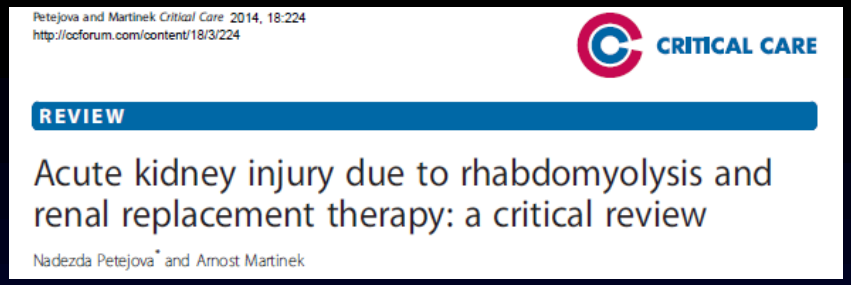
Non-traumatic rhabdomyolysis: Background, laboratory features, and acute clinical management

Gianfranco Cervellin [a,*], Ivan Comelli [a], Mario Benatti [a], Fabian Sanchis-Gomar [b,c], Antonella Bassi [d], Giuseppe Lippi [e]

CK biochemical "gold standard" for diagnosis

Myoglobin biochemical "gold standard" for prognostication

Clin Biochem 2017



CK concentration are the most sensitive indicator of myocyte injury in patients with RML

Treatment of RML should start when CK > 5000 U/L

But myoglobin concentration has the best accuracy to predict the risk of AKI

Predict ARF risk in rhabdomyolysis

n=1800 patients

Best cutoff values for prediction of AKI were CK>773 U/L and serum myoglobin >368 µg/mL

(El-Abdellati. Ann Inten Care 2013;3:8)

	Model corrected for known risk factors*			
		95% confidence interval		
	OR	Lower	Upper	*p* value**
CK > 773, sMb ≤ 368	1.06	0.45	2.27	0.8818
CK ≤ 773, sMb > 368	4.29	2.71	6.8	<0.0001
CK > 773, sMb > 368	5.11	3.03	8.63	<0.0001

Original Investigation

A Risk Prediction Score for Kidney Failure or Mortality in Rhabdomyolysis

Gearoid M. McMahon, MB, BCh; Xiaoxi Zeng, MD; Sushrut S. Waikar, MD, MPH

Table 3. Risk Score

Variable	β	Score
Age (continuous)	0.022	...[a]
Age, y		
>50 to ≤70	...[b]	1.5
>70 to ≤80	...[b]	2.5
>80	...[b]	3
Female sex	0.404	1
Initial creatinine, mg/dL		
1.4 to 2.2	0.589	1.5
>2.2	1.083	3
Initial calcium <7.5 mg/dL	0.933	2
Initial CPK >40 000 U/L	0.805	2
Origin not seizures, syncope, exercise, statins, or myositis	1.301	3
Initial phosphate, mg/dL		
4.0 to 5.4	0.565	1.5
>5.4	1.221	3
Initial bicarbonate <19 mEq/L	0.811	2

- The C-statistic for the model was 0.82
- RRT or in-hospital mortality

- A low risk score predicted a favorable outcome:
  - Score<5: pts with a 3% risk of primary outcome
  - Score>10: risk of 59%

- Cutoff 5: NPV 97%, PPV 30%
- Each 1-point increase in the risk score was associated with an adjusted odds ratio of 1.49 for the primary outcome

JAMA Intern Med. 2013;173(19):1821-1828.

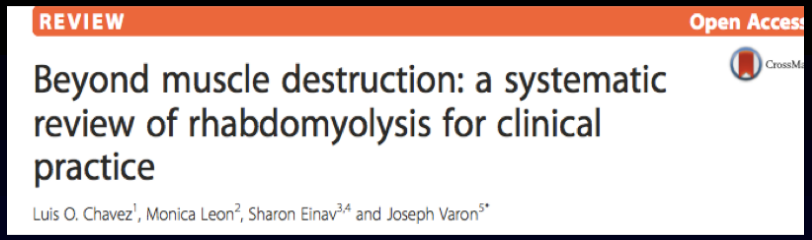
Treatment and prevention

- Basic principle:
  - Treatment of the underlying source of muscle injury (stop harmful drug, control of temperature, treatment of infection, etc)
  - prevent myoglobinuric-induced ARF

- Aggressive resuscitation with crystalloid solution to maintain urinary output (no fluid has been demonstrated to be superior)

- Bicarbonate to promote alkalinization of the urine to reduce precipitation of myoglobin and mannitol (controversial, lack of enough evidence)
- Diuretics after restoration of intravascular volume
- Early RRT (treat hyperkalemia and metabolic acidosis, remove the offending nephrotoxic agent)

De Meiejer AR. Intensive Care Med 2003;29(7): 1121-1125; Woodrow G. Ren Fail 1995;17(4): 467-474)


REVIEW Open Access

Beyond muscle destruction: a systematic review of rhabdomyolysis for clinical practice

Luis O. Chavez[1], Monica Leon[2], Sharon Einav[3,4] and Joseph Varon[5*]

- No guidelines for management
- No RCTs available

Chavez *et al. Critical Care* (2016) 20:135

Commentary

Extracorporeal therapies in acute rhabdomyolysis and myoglobin clearance

Claudio Ronco

CRITICAL CARE

Rhabdomyolysis-induced AKI

Aims of renal replacement therapy RRT:

- Replace the failing kidney
- **Prevent** further damage by circulating myoglobin that cause

- Renal tubular obstruction
- Intra-renal hemodynamics alteration
- Tubular cell dysfunction

} Perpetuating the pathological insult and delaying renal function recovery

Critical Care 2005, 9:141-142

All attempts to produce a significant removal of myoglobin by traditional extracorporeal therapies:

- Controversial results
- Modestly useful
- Disappointing

Continuous renal replacement therapy (CRRT) for rhabdomyolysis (Review)

Zeng X, Zhang L, Wu T, Fu P 2014

THE COCHRANE COLLABORATION®

Implications for practice

Data from three small RCTs indicated that although mortality and adverse events did not differ significantly among patients treated with CRRT and conventional therapy, CRRT may be more effective in removing myoglobin and modifying parameters related to muscle lysis and kidney function. Poor methodological quality and absence of some clinically important measurements from the included studies were significant limitations. We were unable to conclude whether or not CRRT is a safe and effective option to treat people with rhabdomyolysis.

Why are extracorporeal techniques poorly effective in removing myoglobin?

- Nature of myoglobin molecule
- The distribution of myoglobin
- The mechanism of solute transport
- Structure of the membrane in the extracorporeal technique

Ronco C. Critical Care 2004;9

Can we do anything else?

Review

Molecular Mechanisms and Novel Therapeutic Approaches to Rhabdo-myolysis-Induced Acute Kidney Injury

Molecular mechanisms

- ✓ Oxidative stress
- ✓ Inflammation
- ✓ Apoptosis
- ✓ Vasoconstriction

Novel therapeutical approaches

- Iron chelators
- Antioxidants (acetominophen, N-acetylcisteina, Vit E, Vit C)
- Anti-inflammatory treatments (pentoxifillina)
- Vasoconstriction inhibitor (agents capable of increasing NO, L-arginina)

Only animal studies, lack of RCT, NAC study concluded

Kidney Blood Press Res 2015;40:520-532

Research

Open Access

Myoglobin clearance by super high-flux hemofiltration in a case of severe rhabdomyolysis: a case report

Toshio Naka[1], Daryl Jones[2], Ian Baldwin[3], Nigel Fealy[4], Samantha Bates[5], Hermann Goehl[6], Stanislao Morgera[7], Hans H Neumayer[8] and Rinaldo Bellomo[9]

Continuous technique + hyperpermeable membrane

Method Initially continuous veno-venous hemofiltration was performed at 2 l/hour ultrafiltration (UF) with a standard polysulphone 1.4 m^2 membrane (cutoff point, 20 kDa), followed by continuous veno-venous hemofiltration with a SHF membrane (cutoff point, 100 kDa) at 2 l/hour UF, then at 3 l/hour UF and then at 4 l/hour UF, in an attempt to clear myoglobin.

Sieving coefficient and clearance of myoglobin using conventional and super high-flux (SHF) continuous veno-venous hemofiltration in a patient with severe rhabdomyolysis secondary to serotonin syndrome

Filter type	Ultrafiltration rate (l/hour)	Myoglobin concentration (μg/l)			Sieving coefficient (%)	Myoglobin removal (g/day)	Myoglobin clearance (ml/min)
		Pre-filter	Post-filter	Ultrafiltrate			
Conventional (polysulphone)	2	>100,000	>100,000	23003	<0.23	1.1	<8
SHF	2	>100,000	>100,000	>100,000	Unable to calculate	>4.8	Unable to calculate
SHF	3	100,000	68,776	60,912	0.722	4.4	30.5
SHF	4	91,058	64,587	53,527	0.698	5.1	39.2

Limit : albumin leakage

Critical Care 2005, **9**:R90-R95

CytoSorb®

- Biocompatible porous polystyrene polymer beads able to remove substances from whole blood based on pore capture and surface adsorption.
- Each cartridge 10 grams
- Surface > 40.000 m2,
- max pressure 500 mmHg, max blood flow 400ml/min
- Substances that are larger than the pores and very small substances, such as electrolytes are not captured.
- Appropriate sized molecules in the 5–55 kDa range
- CytoSorb® was specifically designed to target this molecular weight range, given that the majority of cytokines and inflammatory mediators fall within this size spectrum.
- The technology is not an affinity-based sorbent and does not use antibodies, ligands, cells or drugs

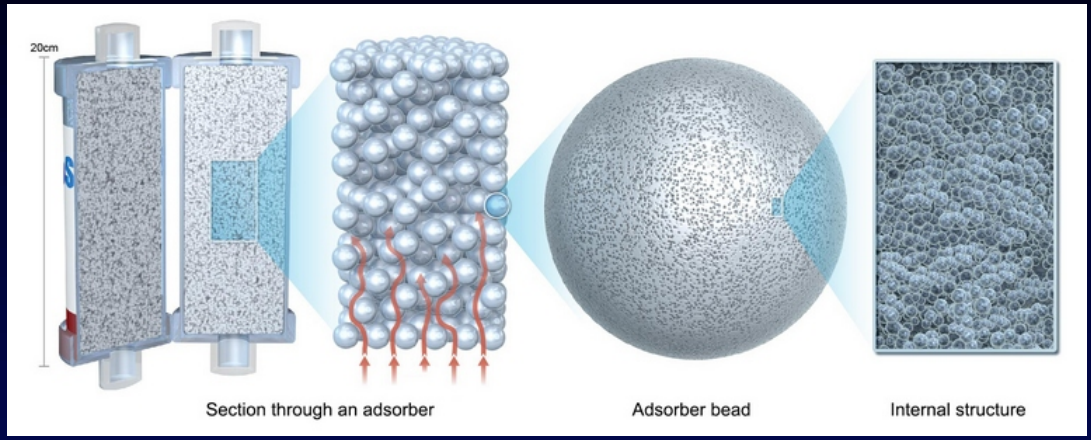
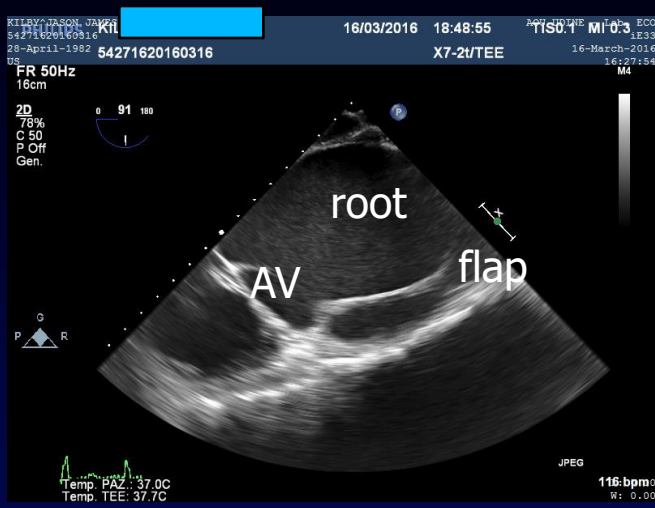


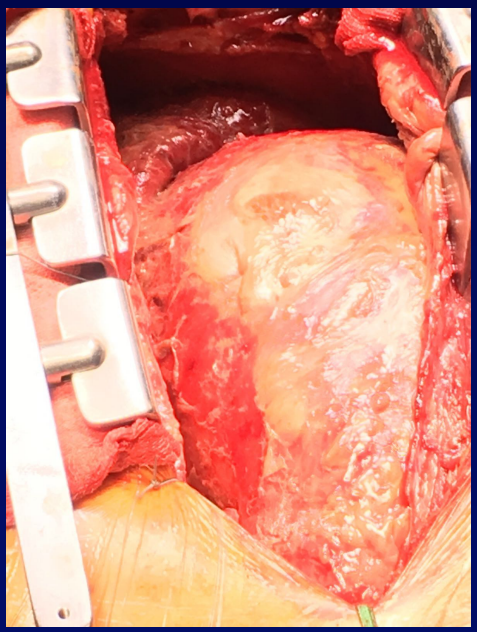
Table 1 Technical data of the CytoSorb® adsorber according to the manufacturer information

Extracorporeal blood volume:	120 mL
Blood flow rates min-max	100–400 mL/min
Max. treatment duration	24 hours
Anticoagulation	Possible with heparin or citrate
Sterilisation	Gamma sterilisation
Further details	Latex- and polyhexahydrotriazines-free product
Storage conditions	1 to 40 °C; upright storage

Case report

- K.J.J 34 y-o male, body builder
- Emergent ascending aorta and aortic arch replacement, sovra-aortic vessels reimplantation, Tirone-David in 45’ DCHA at 24° C with Kazui and splanchnic perfusion due to **Standford type A aortic dissection, massive AR and cardiac tamponade.** CPB time 612 min, X clamp 340 minutes.
- Severe biventricular failure during CPB weaning: peripheral V-A ECMO



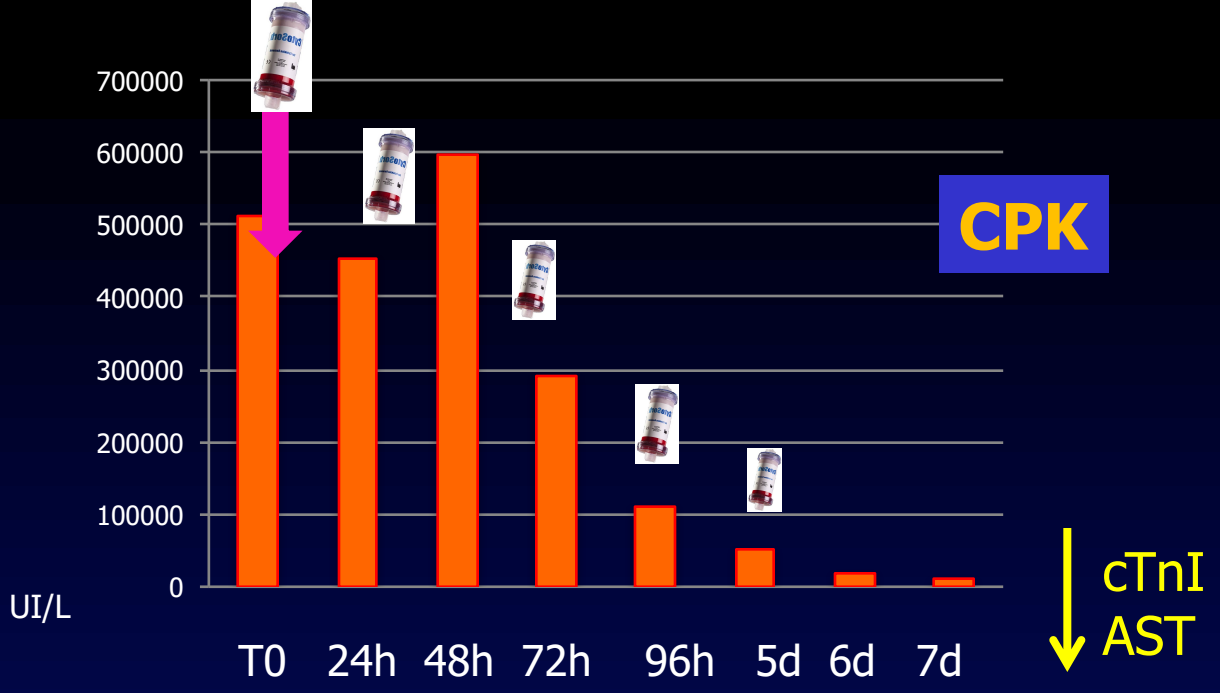


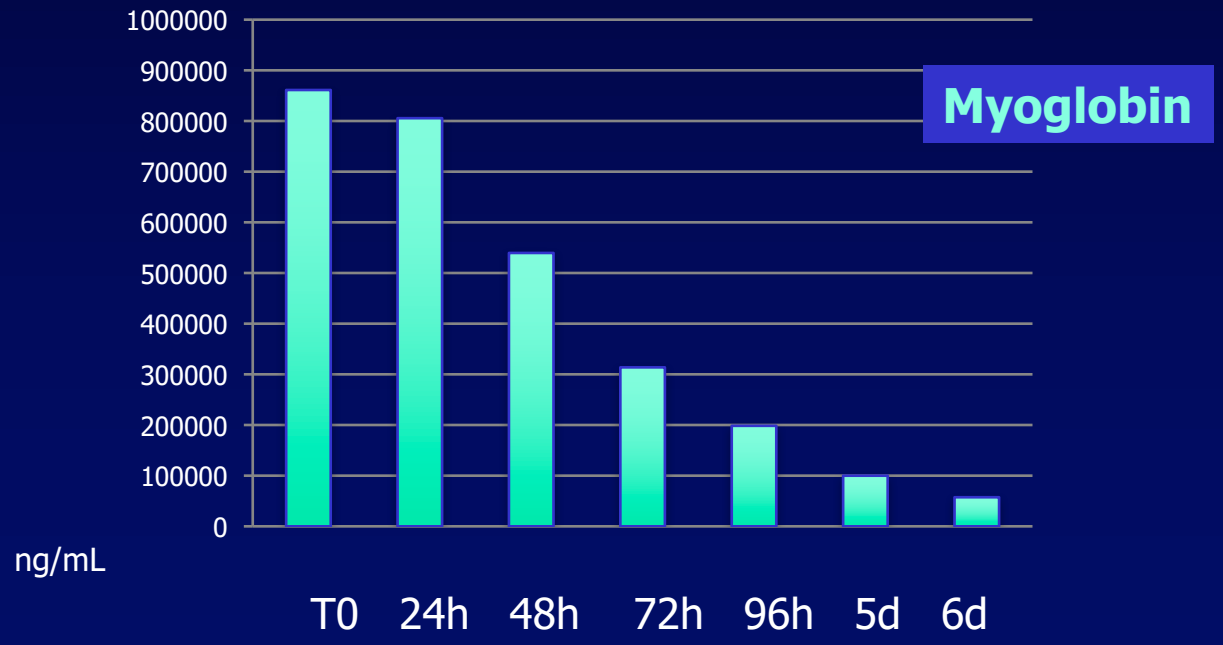
- Log EuroSCORE 8 %, APACHE II score 24, SOFA score 10

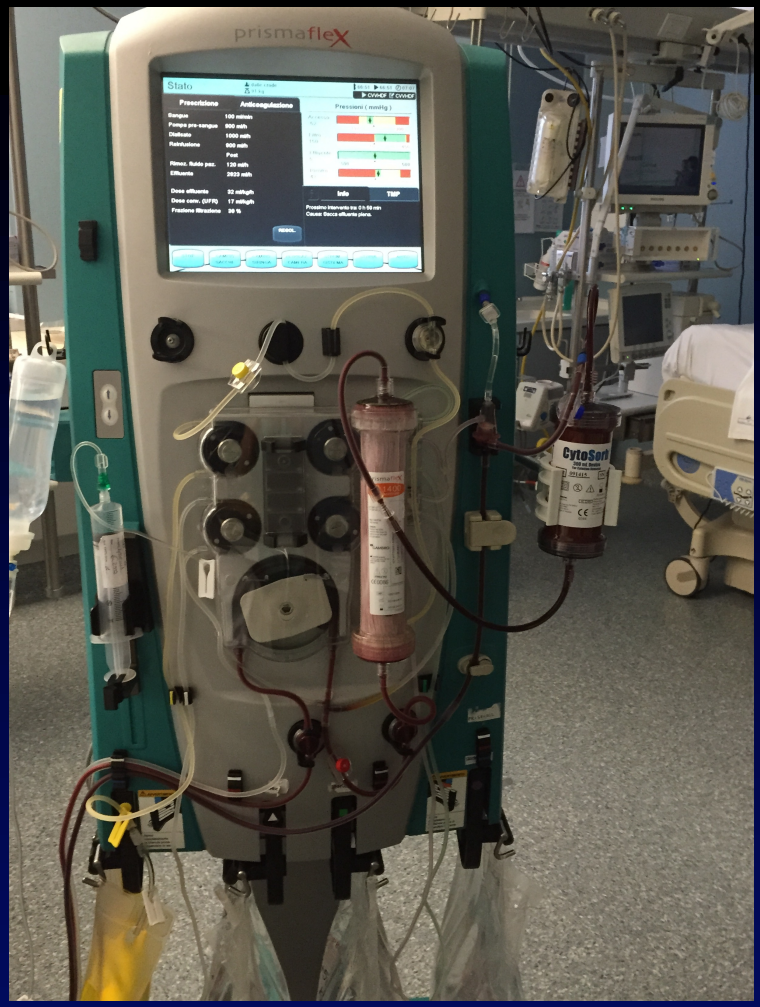
- On ICU admission : Lactate 20, HR 110/min, MAP 62 mmHg, ECMO blood flow 6 L/min, norepinephrine 0.6 mcg/kg/min, epinephrine 0.085, levosimendan 0.05

- Myoglobin 24178 ng/mL, CPK 17843 UI/L, cTnI 929, bilirrubin tot 2.87, AST 1210
- Anuria: CVVHDF started in POD 1
- Hydrocortison started in POD 1

- MOF, liver dysfunction and rhabdomyolysis (swelling and stiffness of legs) in POD 4
- Hyperkalemia (7,3 mM/L) and peak of myoglobin 860000 ng/ml and CPK 511000 UI/L

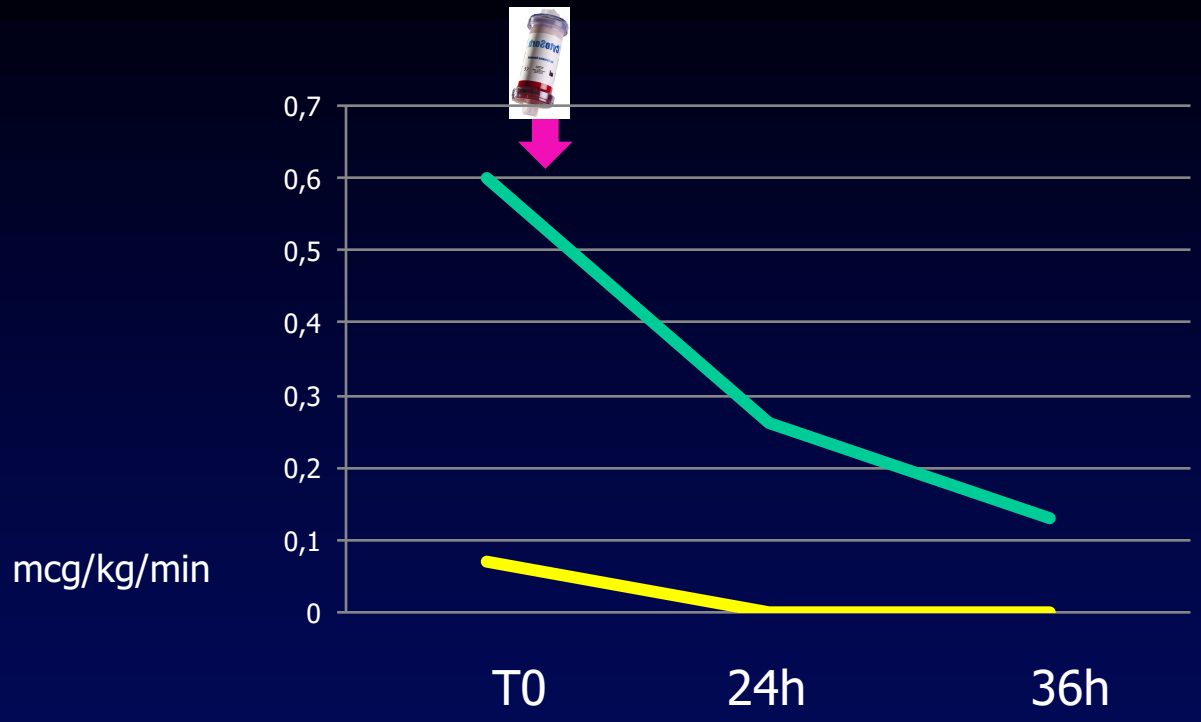






- ✓ SIRS
- ✓ Ischemic reperfusion syndrome
- ✓ MOF
- ✓ Rhabdomyolysis

Case report: vasopressors



Norepinephrine

Epineprhine

- ✓ Weaning from VA ECMO in POD 14
- ✓ LVEF 25%
- ✓ Pneumonia: Ps. Aeruginosa MDR
- ✓ CIPN
- ✓ Urine output > 2.5 ml/kg/h in 36 POD
- ✓ ClCr 10 ml/min (HD)

Rhabdomyolysis in CPB

Incidence 19% after CABG with CPB!!

Sudarsanan et al. BMC Research Notes 2014, 7:152
http://www.biomedcentral.com/1756-0500/7/152

BMC Research Notes

CASE REPORT Open Access

Acute kidney injury associated with rhabdomyolysis after coronary artery bypass graft: a case report and review of the literatures

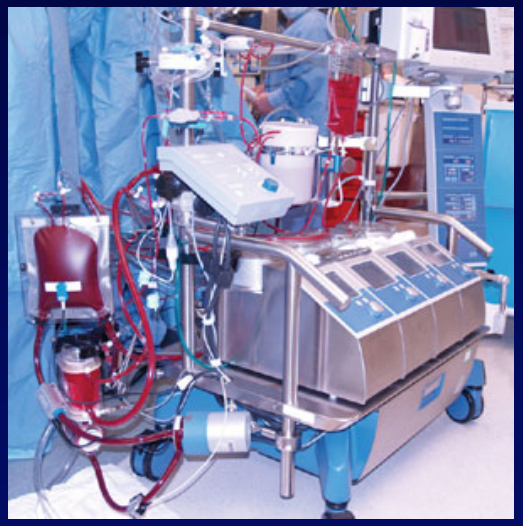
Suraj Sudarsanan[1], Amr S Omar[1,2*], Rasheed A Pattath[1] and Abdulwahid Al Mulla[1]

Acute kidney injury after coronary artery bypass grafting: Does rhabdomyolysis play a role?

Umberto Benedetto, MD,[a] Emiliano Angeloni, MD,[a] Remo Luciani, MD,[b] Simone Refice, MD,[a] Manuel Stefanelli, MD,[a] Cosimo Comito, MD,[a] Antonino Roscitano, MD,[a] and Riccardo Sinatra, MD[a]

Co-factors:

- Preoperative medication
- Direct femoral artery cannulation
- Arteriopathy
- Prolonged extracorporeal circulation and surgical time
- Low cardiac output syndrome
- Continuous intravenous infusion of ephinephrine
- IABP



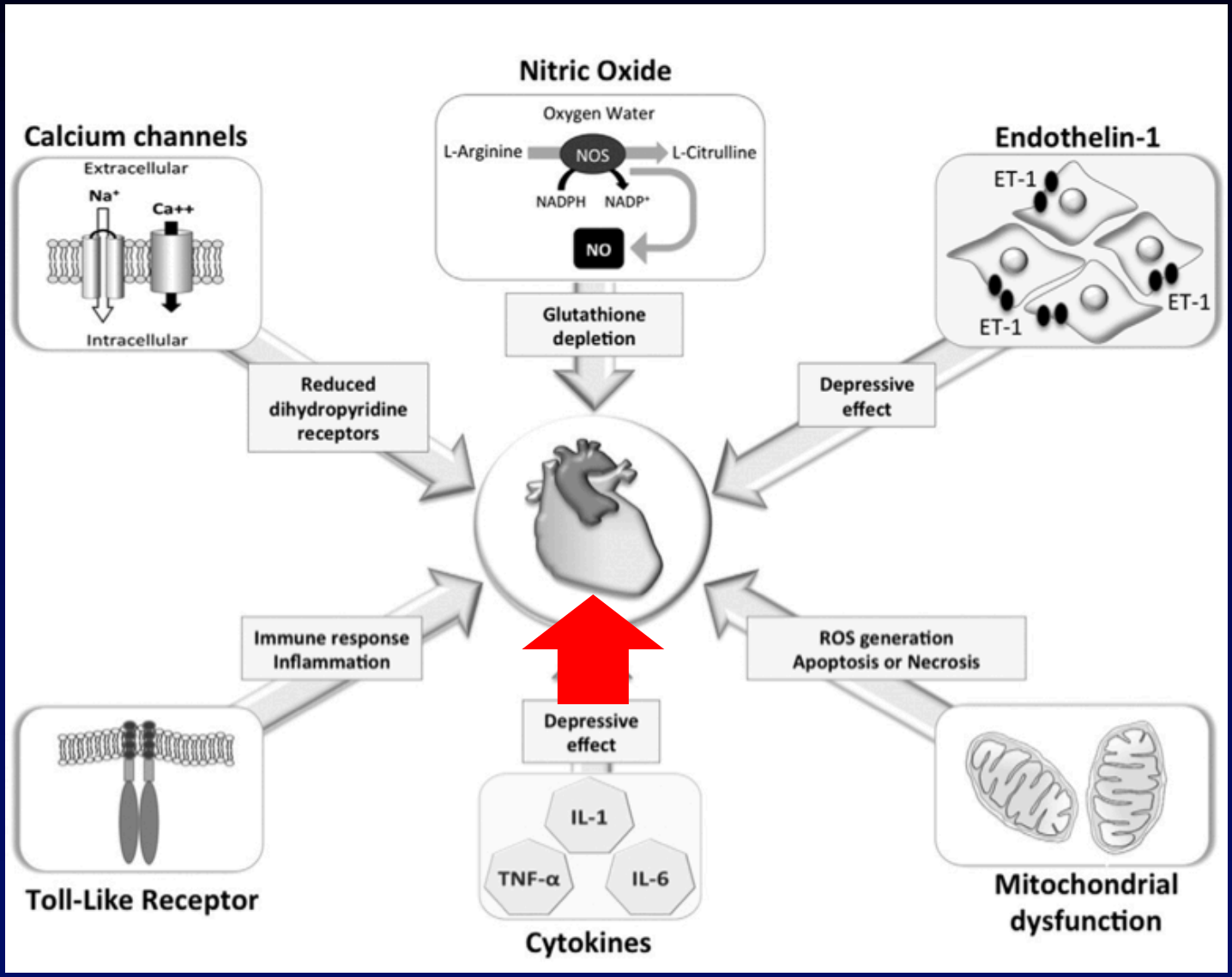
As in order surgical settings serum myoglobin concentrations predicts the incidence of AKI and RRT requirement in CABG with CPB

Benedetto U. J Thorac Cardiovasc Surg 2010, 140(2):464-470
Hajjar L. Crit Care 2008;12(2): 470
Maccario M. J Cardiovasc Surg 1996;37(2):153

Myocardial depression in sepsis: From pathogenesis to clinical manifestations and treatment ☆

Elio Antonucci, MD [a], Enrico Fiaccadori, MD [a], Katia Donadello, MD [b], Fabio Silvio Taccone, MD
Federico Franchi, MD [c], Sabino Scolletta, MD [c,*]

Journal of Critical Care 29 (2014) 500–511



CPB causes SIRS that induces sympathetic over-stimulation or *catecholaminergic storm:*

Impaired diastolic function
Tachycardia
Tachyarrhytmias
Myocardial ischemia
Stunning, apoptosis, necrosis

Cytokines induce down-regulation of beta ARs

IL 6 is associated with postop myocardial ischemia, development of low CO

ECMO
+
cytokines absorber
in non-cardiac
surgery

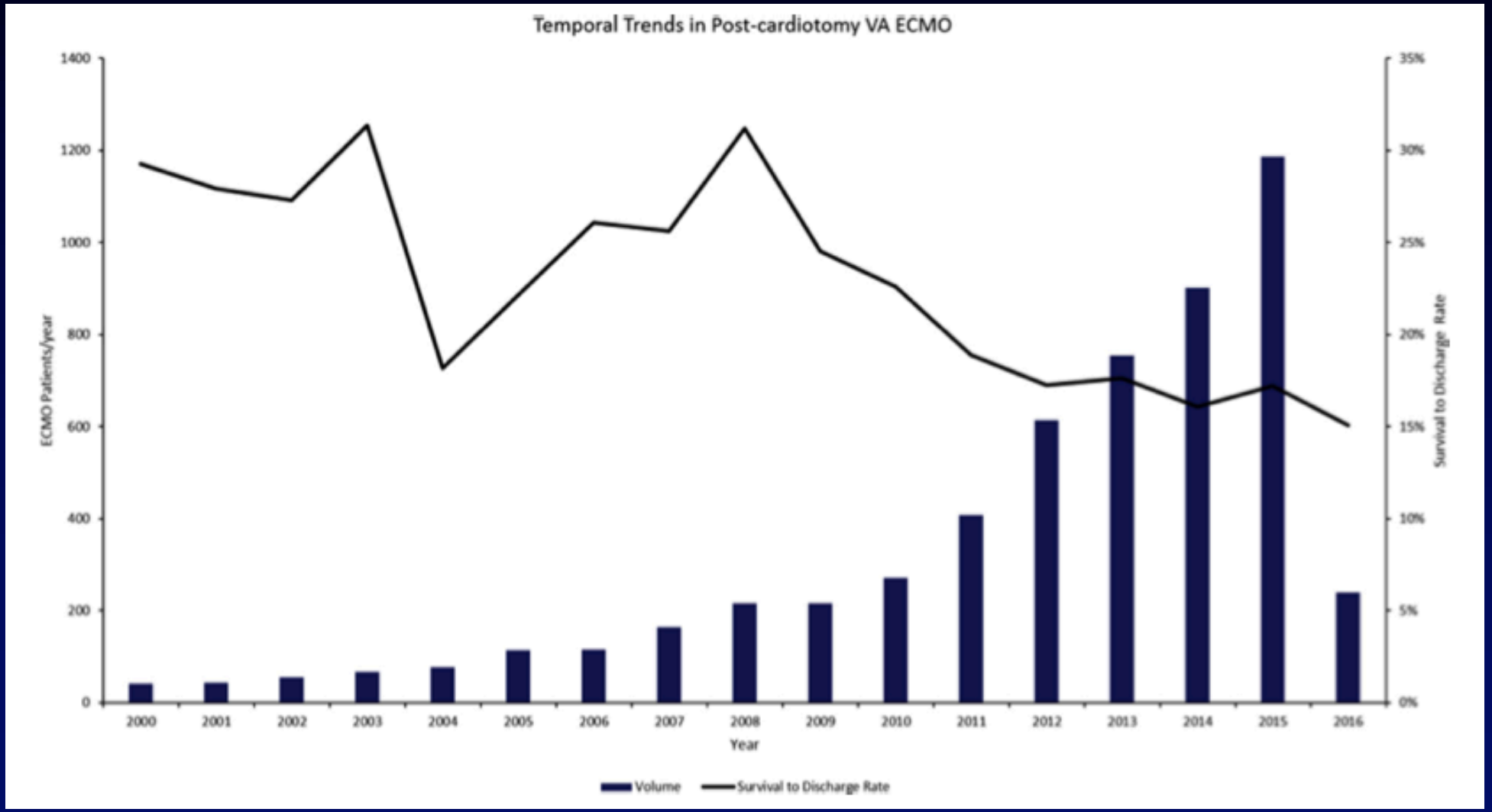
Post CPB
inflammatory
syndrome

Postcardiotomy VA-ECMO + Cytosorb:
rescue therapy

Extracorporeal membrane oxygenation for the treatment of postcardiotomy shock

Glenn J. R. Whitman, MD

(J Thorac Cardiovasc Surg 2016;■:1-7)



Case report 2

A 64-year-old male

2nd "Re-do" surgery: AVR and aortic root reconstruction due to detachment of aortic prosthesis in previous Bentall procedure

Suspicion of endocarditis

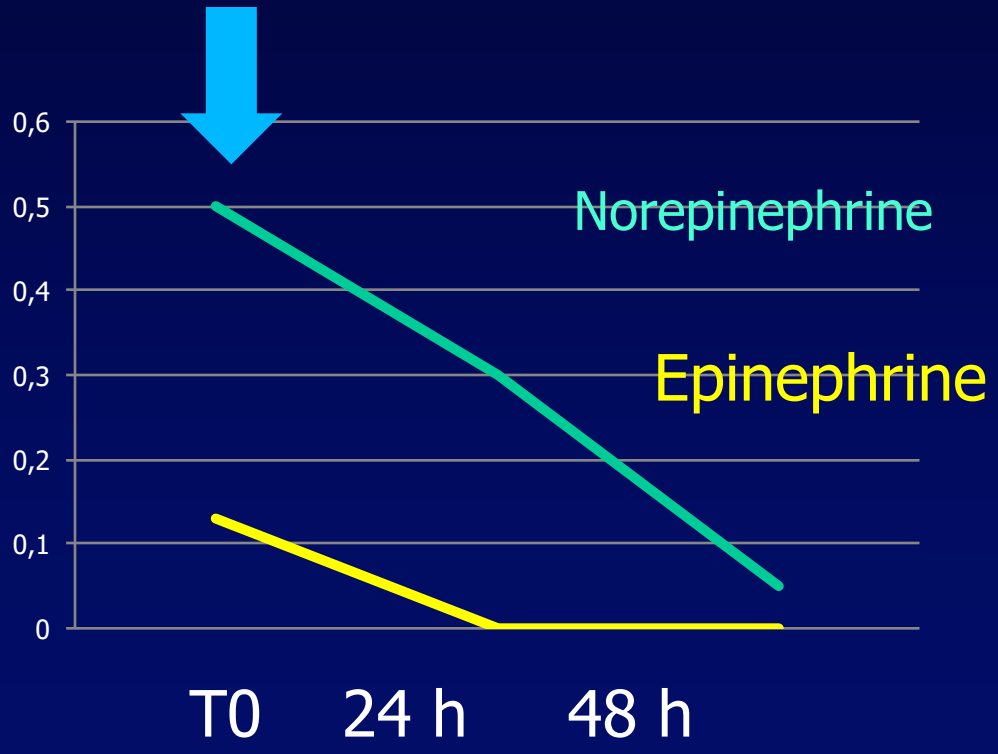
Preop LVEF 50%, normal CrCl

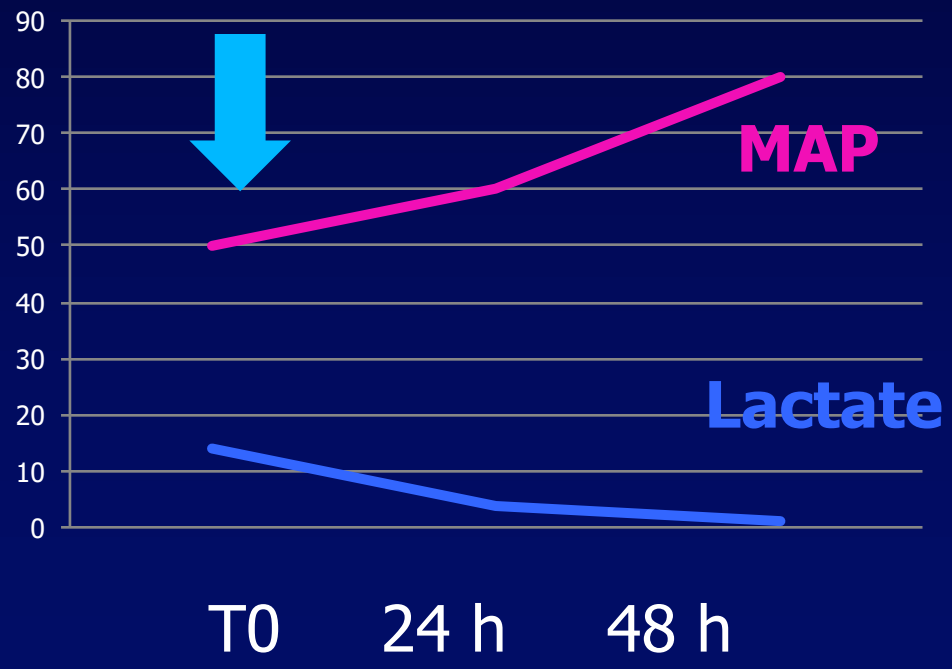
POD 1 2 3 4 5 6

Vasoplegia
Cardiac tamponade
Reintervention

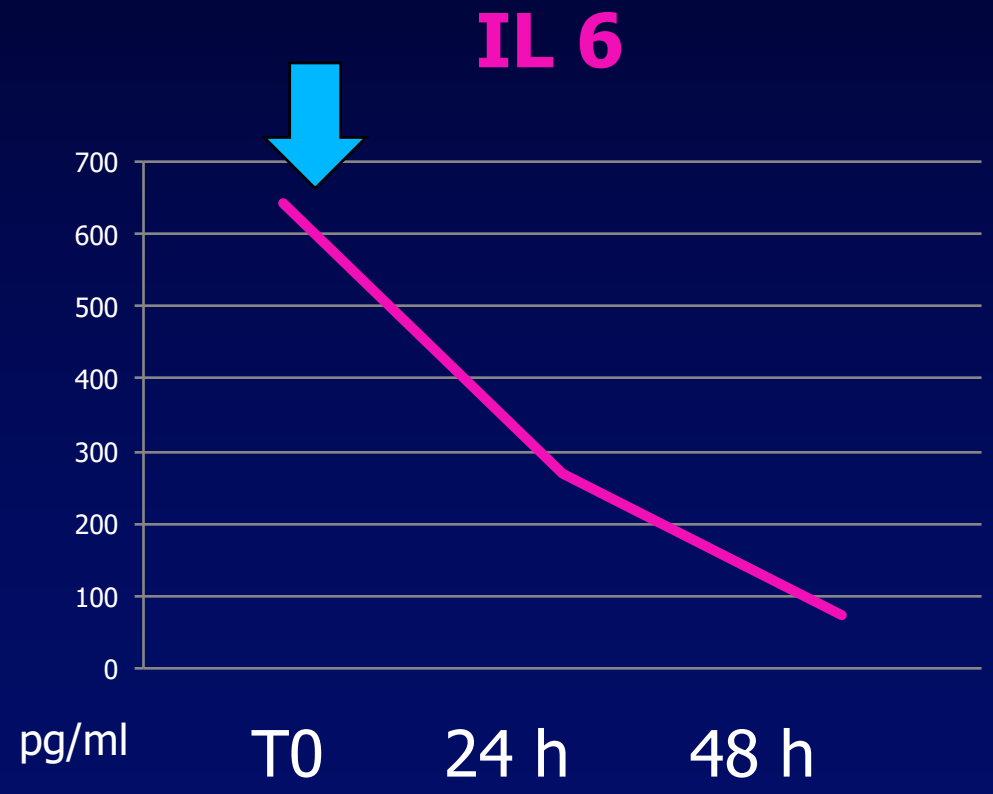
Vasoplegia
MOF
CRRT

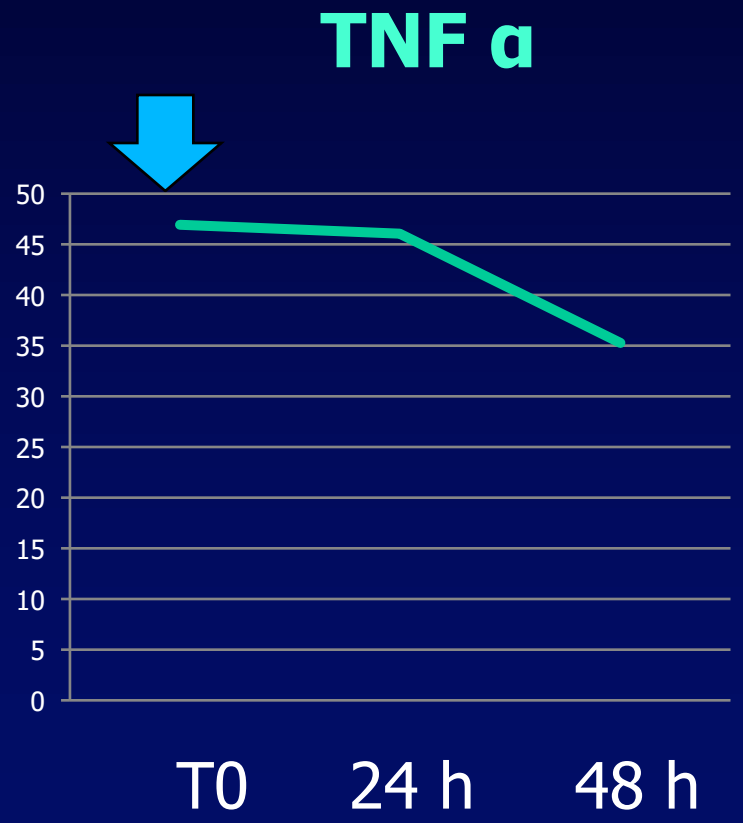
Cytosorb +
VA ECMO





Interleukins plasma levels





Cytosorb: prevention of AKI in traumatic rhabdomyolysis

- Rabdomiolisi post-traumatica CK>5000 U/L emoperfusione isolata con Cytosorb per 24h (flusso sangue medio: 200 ml/min, infusione eparina media: 500 unità/ora)

- 247 pazienti post-traumatici
- 78 % (n=178) ha sviluppato rabdomiolisi (CK>1000 U/L)

- 171 pazienti terapia classica
- 7 hanno ricevuto sorbente Cytosorb

- Nei pazienti trattati con Cytosorb, in 24h di emoperfusione si è osservata una riduzione di

  CK (riduzione media: 52,2%,)

  Mioglobina (riduzione media: 58,3%).

- Nessuno di questi pazienti ha sviluppato IRA ne ha avuto necessità di supporto renale durante il ricovero
- Pazienti trattati solamente con terapia classica IRA 15.7%

Mioblobina ng/ml nei Pazienti trattati con filtro Cytosorb
T0 prima del trattamento - T1 dopo il trattamento

CASO	T0	T1	RIDUZIONE %
1	1390	640	53.9%
2	2072	978	52.8%
3	6818	1753	74.2%
4	61263	29300	52.1%
5	1292	624	51.3%
6	2003	820	59%
7	1960	680	65.3%
RIDUZIONE MEDIA			58.3%

Courtesy of Dr A Iacono.

U.O.S.D. Trauma Center e UOC Anestesia e Rianimazione I
P.O. Villa Sofia.
A.O. Ospedali Riuniti Villa Sofia-Cervello, Palermo, Italia
Palermo

Conclusion

- Rhabdomyolysis remains a major clinical challenge
- Non-specific symptoms, multiple etiologies, and systemic complications obscure the diagnosis and complicate the treatment of this condition
- RCTs lack regarding the type of fluid and the adjuvant pharmacological therapies (mannitol and bicarbonate) for AKI prevention
- CRRT improves myoglobin clearance but does not change mortality

Conclusion

- CytoSorb associated to CVVH might represent a novel approach to the treatment of acute rhabdomyolysis not only because efficient renal replacement is provided but also because a potential protective effect can be envisaged in the rapid and efficient removal of circulating myoglobin

- Easy to perform, safe and well tolerated (in ECMO and in CRRT)

Conclusion

- RCTs would be of interest in comparing innovative and traditional approaches

Grazie!

blancamartinezlopez@asuits.sanita.fvg.it

Myoglobin and RRT

- Conventional hemodialysis does not eliminate myoglobin
- Convection technique should be used (because of the molecular mass)
- Standard cellulosic membranes are practically impermeable to the molecule
- High-flux membranes should be used
- Limits: low sieving coefficient (even high-volume hemofiltration or pulse high-volume hemofiltration may be inneficient)
- Plasmapheresis: higher sieving coefficients, but clearance of myoglobin is minimal because of the limitations imposed by low volume exchanges

ECMO, CRRT and Cytosorb: technical aspects