Poisoned and Poisonous

Inter-hospital Meeting

Dr. Winston Fung
Prof. CC Szeto

Case History

- 65/F with background of:

- DM since age of 32
- recurrent thrombocytopenia, treated as ITP
- Obesity, hyperlipidaemia

- On Metformin 1000mg TDS, Mixtard 34 units om/10 units pm, Danazol 200mg BD, Prednisolone 5mg daily, Simvastatin 40mg nocte

Presenting complaint

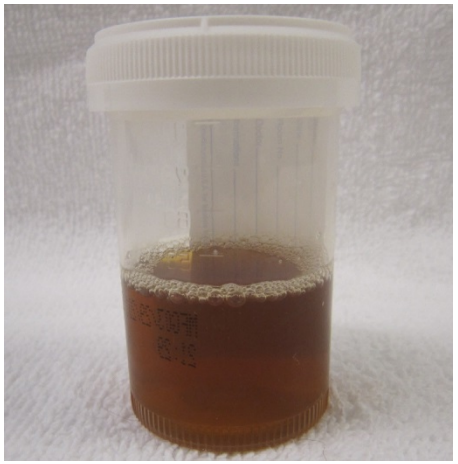
- Presented with progressive pain over the shoulders/ thigh bilaterally over 1 week

- Generalised weakness/ malaise.
- No numbness
- No neck/ back pain
- No rash/ ulcer/ arthralgia

Presenting complaint

- Noted to have reduced amount of urine output
- Described as darkish urine
- No dysuria.

- Nil recent diarrhea / vomiting
- Nil recent illness
- Nil fever/ chills/ rigors.



Examination

- Afebrile
- BP 120/60 P 110
- SaO2 100%
- H’stix 10.2

- Hydration dry side
- HS 1+2+0
- Chest clear
- Abdomen SNT

- Discomfort over the thighs, nil erythema/ swelling
- Pain on movement. Otherwise, good range of movement.
- No joint deformity/ bruising

Initial investigation

- Cbc: Hb 14.7/ Wcc 19.3/ Plts 78 (static)
- RFT: Na 135/ K 7.0/ Ur 23.6/ Creat 465 (baseline normal)
- LFT: Bili 14/ ALP 89/ ALT 538
- Ca 2.05/ PO4 2.9
- pH 7.15/ pCO2 3.8/ PO2 10.4/ HCO3 16

- Urine dipstix: WCC –ve/ RBC +ve/ Alb +ve/ nitrite –ve

- CXR: clear

Questions

1. What are the differential diagnosis for the AKI?

2. What investigations would you arrange?

Progress

- Given dextrose insulin infusion / IV rehydration / $NaHCO_3$ overnight
- Acute haemodialysis provided in views of persistent hyperkalaemia/acidosis and anuria
- Urgent USG: age-related change or mild renal parenchymal disease. No hydronephrosis.

Further investigation

- Urine microscopy: no RBC noted.

- Creatinine Kinase 131020
- LDH 3883

- ANA/DsDNA/ENA/ANCA unremarkable
- C3 0.93/C4 0.4
- Ig/SPE unremarkable
- TSH 0.54
- HBsAg/ anti HCV/ HIV negative

Further history

- No hx of TCM/herbal med/OTC
- No history of injury, fall, prolonged lie or immobilisation
- Nil signs of autoimmune disease

- On further questioning, patient has history of poor medication compliance.

- However, she decided to take her medication diligently recently…

Diagnosis

- AKI due to simvastatin-induced rhabdomyolysis, precipitated by interaction with danazol

Poisoned and Poisonous

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Causes of rhabdomyolysis

- traumatic
  - crush syndrome
  - exertion, e.g. strenuous exercise, seizure
  - muscle hypoxia, e.g. limb compression, arterial ligation

- non-traumatic
  - drug / toxin, e.g. statin, alcohol, cocaine
  - metabolic / electrolyte disorders
  - body temperature change, e.g. heat stroke, neuroleptic malignant
  - genetic, e.g. glycogen storage, lipid metabolism, mitochondrial
  - infection, e.g. influenza, coxsackievirus, bacterial myositis

Zager RA. Kidney International, Vol. 49 (1996), pp. 314-326.
Vanholder R, et al. J Am Soc Nephrol 11: 1553–1561, 2000.

Statin-induced myopathy

- usually defined as muscle pain or weakness
  ± elevated creatine kinase level

- risk from original RCT seems lower than post-market survey

- treatment of 10,000 patients for 5 years with an effective regimen (e.g. atorvastatin 40 mg daily) would cause about 5 cases of myopathy

- 20% cases may progress, esp. if the statin therapy is not stopped, to the more severe condition of rhabdomyolysis

Rory Collins. Lancet 2016; 388: 2532–61.

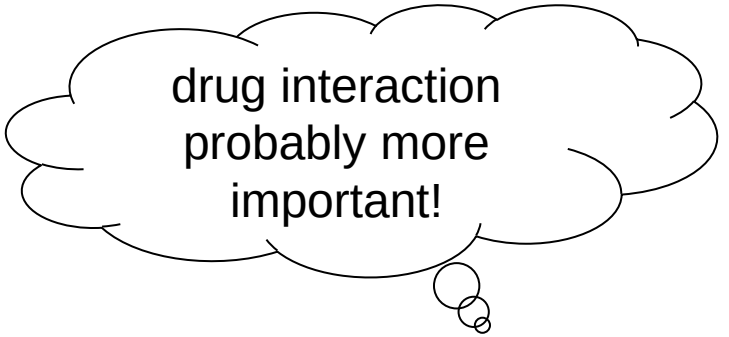
Mechanism of statin-induced muscle injury

- reduce cholesterol in sacrolemma
- reduce mitochondrial ubiquinone (coenzyme Q)
- reduce mitochondrial oxidative phosphorylation

<u>precipitant</u>

- gemfibrosil (inhibit glucuronidation)
- cyclosporin / erythromycin (CYP3A4 inhibition)
- warfarin, itraconazole

Dosage related ?



	Statin comparison higher vs lower	Medical condition of participants	Alanine transaminase three times upper limit of normal higher vs lower	Creatine kinase ten times upper limit of normal, or myopathy higher vs lower	Rhabdomyolysis higher vs lower
PROVE–IT (4162)[7,37]	A 80 mg vs P 40 mg	Acute coronary syndromes	69 (3·3%) vs 23 (1·1%)	2 (0·1%) vs 3 (0·15%)	0 (0%) vs 0 (0%)
Phase Z of the A to Z trial* (4497)[36]	S 80 mg vs S 20 mg	Acute coronary syndromes	19 (0·9%) vs 8 (0·4%)	9 (0·4%) vs 1 (0·04%)	3 (0·1%) vs 0 (0%)
TNT* (10 001)[5,38]	A 80 mg vs A10 mg	Stable CHD	60 (1·2%) vs 9 (0·2%)	(0·0%) vs (0·0%)	2 (0·04%) vs 3 (0·06%)
IDEAL (8888)[6]	A 80 mg vs S 20–40 mg	Stable CHD	43 (0·97%) vs 5 (0·11%)	6 (0·14%) vs 11 (0·25%)	2 (0·05%) vs 3 (0·07%)
SPARCL* (4731)[39]	A 80 mg vs placebo	Post stroke or TIA (no CHD%)	51 (2·2%) vs 11 (0·5%)	7 (0·3%) vs 7 (0·3%)	2 (0·1%) vs 3 (0·1%)

Jane Armitage. Lancet 2007; 370: 1781–90.

Are all statins equal ?

- no direct head-to-head comparison

- lipophilic statins (e.g. lovastatin, simvastatin, atorvastatin) are generally believed to be more likely to cause myotoxicity because they cross muscle cell membrane more readily than hydrophilic statins (e.g. pravastatin, rosuvastatin)

- rationale to change from one statin to another after an episode of severe rhabdomyolysis ?
- cf.
  - re-start at lower dose
  - review indication
  - choose another agent (e.g. ezetimibe)

Common drug interactions

- cyclosporin
- fibrates
- azol anti-fungals
- macrolide antibiotics
- anti-arrhthymics (verapamil, amiodarone)
- protease inhibitors

Jane Armitage. Lancet 2007; 370: 1781–90.

Interaction with danazol

- danazol is a synthetic steroid derived from ethisterone
- liver metabolism
- mechanism of interaction with statin uncertain

- FDA Professional Drug Information:
  “The risk of myopathy and rhabdomyolysis is increased by concomitant administration of Danazol with statins such as simvastatin, atorvastatin and lovastatin.”

- many published case reports, e.g.
  - Stankovic I, et al. Clin Ther. 2010 May;32(5):909-14.
  - Andreou ER, et al. Can J Clin Pharmacol. 2003 Winter;10(4):172-4.

Statin-induced myopathy: a single entity?

Necrotizing autoimmune myositis

- a sub-type of inflammatory muscle disease

cause

- post-viral infection
- a/w malignancy
- a/w connective tissue diseases (esp. scleroderma)
- statin-related

autoantibodies

- anti-signal recognition particle (SRP)
- anti-hydroxyl-methyl-glutaryl-coenzyme A reductase (HMGCR)

Marinos C. Dalakas. N Engl J Med 2015;372:1734-47.

What is the relevance?

- myopathy typically continue to worsen after statin withdrawal

  cf. myopathy improves within 4 to 6 weeks after discontinuation of statin in toxic myopathy

- treatment similar to dermatomyositis / polymyositis

  i.e. steroid, immunosuppressive agents, or IVIG

Marinos C. Dalakas. N Engl J Med 2015;372:1734-47.

What are the toxins from the muscle?

- creatine (phosphate) kinase
- myoglobin
- phosphate
- uric acid ?

Pathogenesis of kidney injury

- hypovolemia / hypotension
- renal vasoconstriction
- direct toxicity to renal tubular cells
- intra-luminal cast obstruction

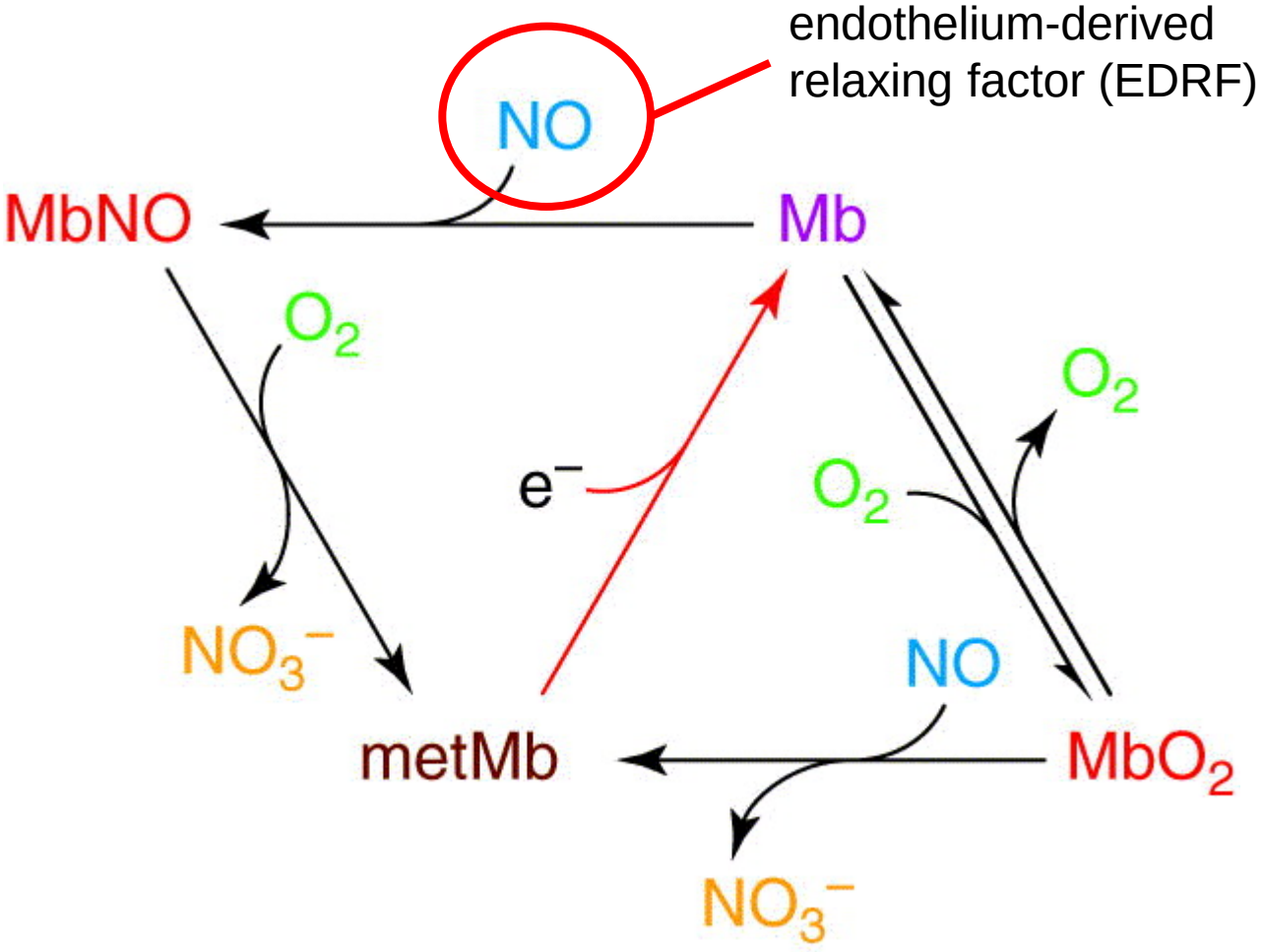
Zager RA. Kidney International, Vol. 49 (1996), pp. 314-326.
Vanholder R, et al. J Am Soc Nephrol 11: 1553–1561, 2000.

Why hypotensive ?

- redistribution of the extracellular fluid into the injured muscle, resulting in gross swelling of the limbs and hypovolemia
- excessive production of vasodilatory mediators in the crushed muscle
- negative inotropic effect of
  - severe hyperkalemia
  - lactic acidosis

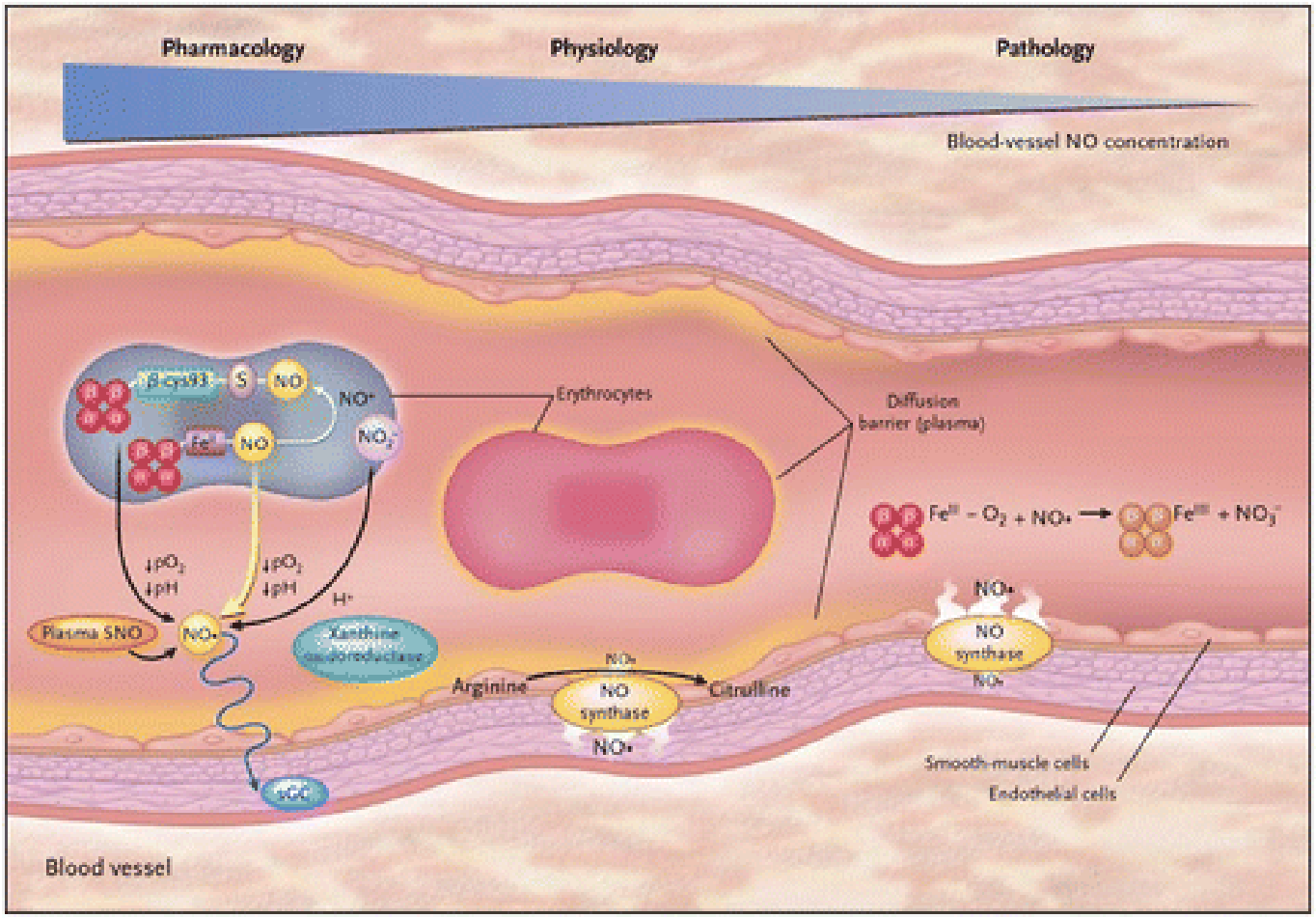
Ori S. Better, et al. Nat. Rev. Nephrol. 7, 416–422 (2011).

Why renal vasoconstriction?



Maurizio Brunor. Trend Biochem Sci 2001; 26: 209-210.

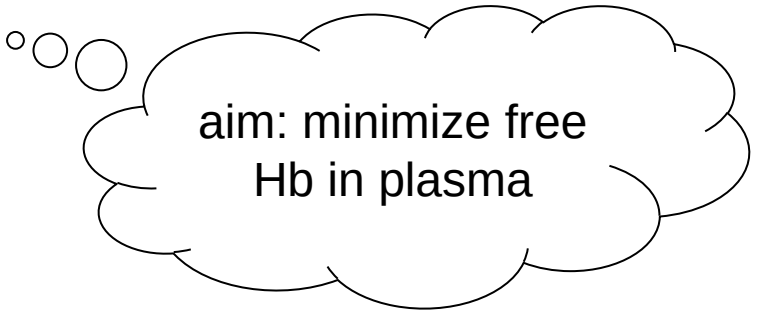
Same for hemoglobin…



Alan N. Schechter, et al. N Engl J Med 2003; 348: 1483-1485.

Hemoglobin after hemolysis

- bind with haptoglobin, then degrade by liver
- oxidized to methemoglobin,
  then dissociate into globin and ferrihaem
  - bind to hemopexin, then degrade by liver
  - bind to albumin to form methemalbumin

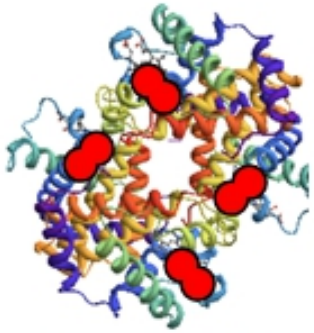


- direct excretion in urine: hemoglobinuria / hemosiderinuria

Dacie and Lewis Practical Haematology Expert Consult Online.

But myoglobin more nephrotoxic?

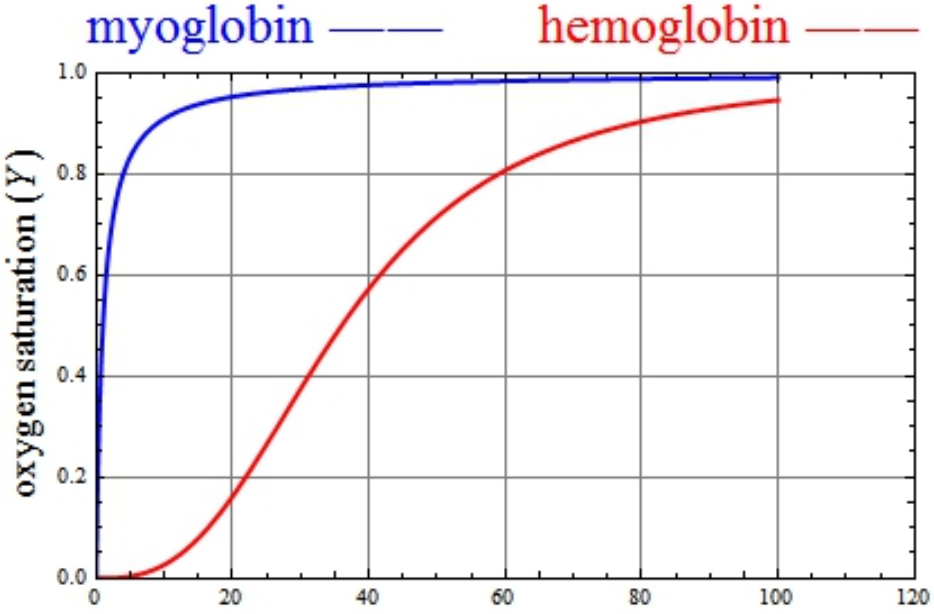
monomer;
MW 16700 dalton



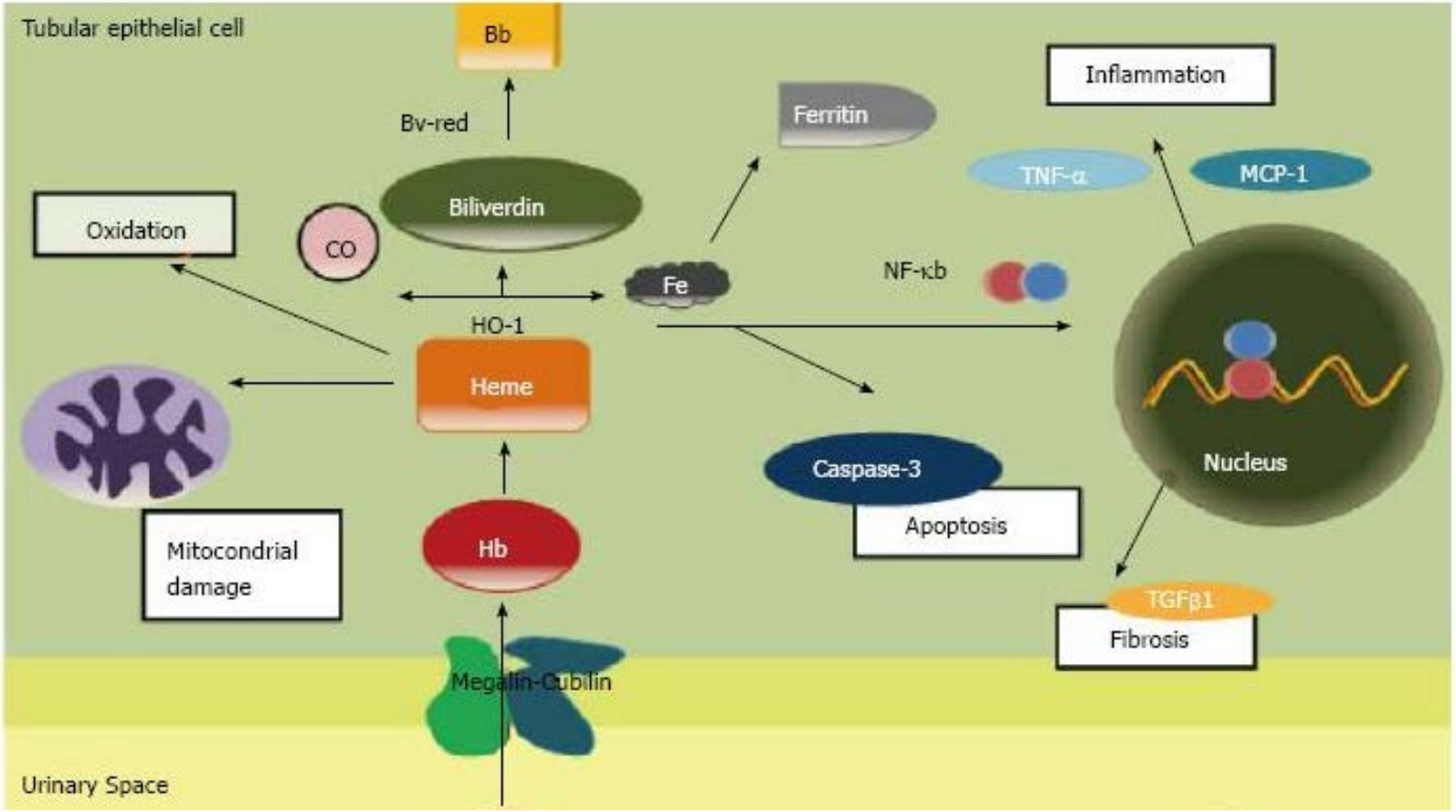
tetramer;
MW 64458 dalton

dissociate into dimer
quickly in vivo

cf. albumin
66500



Direct tubular cell toxicity



myoglobin

Claudia Yuste, et al. World J Nephrol. May 6, 2015; 4(2): 185-195

Tubular cast formation

- Temm-Horsfall protein
  - low isoelectric point due to high sialic acid content
  - remain soluble at low pH (e.g. in urine)

- myoglobin
  - anionic at blood pH
  - cationic in the distal nephron when urine pH <5.5
  - co-precipitation with Tamm-Horsfall protein at this pH

  NB. similar problem with hemoglobin and Bence Jones protein

Clyne DH, et al. Curr Probl Clin Biochem. 1979;(9):299-308..
Hoyer JR, et al. Kidney International, Vol. 16 (1979), pp. 279 -289

Diagnostic criteria

- acute kidney injury
- acute neuromuscular illness or dark urine
- elevated plasma CK level
  - no absolute cut-off value
  - usually >5 times upper limit of normal, or >5000 IU/L

NB. myoglobinuria not necessary

Marc L Miller. UpToDate Topic 5169 Version 17.0.

Can other muscle cause rhabdomyolysis?

myocardial infarct

- complete occlusion of one coronary artery, i.e. acute STEMI, usually result in CK 1000-1500 IU/L
- whole heart broken: CK ~5000 IU/L

gut infarct

- no myoglobin in smooth muscle !

Management

prevention

- recognition of at risk cases
- fluid resuscitation

treatment

- correct hypovolemia / electrolyte disturbance
- renal replacement therapy

recovery

- watch out for rebound hypercalcemia

Crush injury: most readily recognized

3 phases of mortality

- immediate death
- after extrication: hyperkalemia
- delayed: acute kidney injury

pre-hydration for
2 reasons

Early vigorous fluid resuscitation

mechanism of AKI prevention

- rapid correction of hypovolemia
- urine alkalinzation to prevent nephrotoxic effects of myoglobinuria
- reverse inappropriate negative inotropic / vasodilatory effects of hyperkalemia and lactic acidosis

Fluid resuscitation regimen

(find a vein in arm or leg even if the patient is still trapped)

- administer fluid early; start with 1 L before extrication

- preferable fluid combination (for 2 L)
  - 1 L of isotonic saline
  - 1 L of 5% glucose + 100 mmol bicarbonate
- 3 to 6 L/d (in emergencies when supervision is not guaranteed) or up to 10 L/d or more if continuous supervision is available

- add 10 ml 20% mannitol per hour if urine output >20 ml/h

Vanholder R, et al. J Am Soc Nephrol 11: 1553–1561, 2000.

Sodium bicarbonate: what does it do?

- correction of hyperkalemia
  - transcellular shift (if acidosis present)
  - facilitate distal tubule potassium delivery (if HCO3 level high)

- urine alkalization
  $\rightarrow$ prevent myoglobin / Tamm-Horsfall protein precipitation

- direct renal tubular protection
  (from complement mediated injury)

Evidence based ?

study	design	subject	n.	groups	result
Shmazu	retrospective	crush synd	14	late vs early; high vs low vol	early better
Gunal	retrospective	crush synd	16	late vs early	early better
Homsi	retrospective	ICU	24	NS vs NaHCO3 and mannitol	no difference
Brown	retrospective	trauma	2083	NS vs NaHCO3 and mannitol	no difference
Cho	RCT	toxin	28	NS vs Ringer lactate	no difference

Xavier Bosch, et al. N Engl J Med 2009;361:62-72.

Dialysis to remove myoglobin?

- conventional hemodialysis: no effect

- hemofiltration
  - pore size big enough for myoglobin
  - effective in vitro
  - little effect in vivo
    (does not shorten plasma half life of myoglobin)

Xavier Bosch, et al. N Engl J Med 2009;361:62-72.
Mikkelsen TS, et al. Acta Anaesthesiol Scand 2005;49:859-864.

Prognostic indictors

- derivation 1397 patients
- validation 974 patients

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

Gearoid M. McMahon, et al.
JAMA Intern Med. 2013;173:1821-1828.

Conclusion

- statin-induced rhabdomyolysis: usually due to drug interaction
- AKI in rhabdomyolysis is caused by hypovolemia, renal vasoconstriction, direct tubular toxicity, and luminal cast
- early hydration of high risk group, especially in crush injury, is the key measure to prevent AKI