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AD-COR Program inovativ de formare in domeniul cardiologiei pediatrice
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MODUL TEORETIC

SIR in pediatric cardiac surgery

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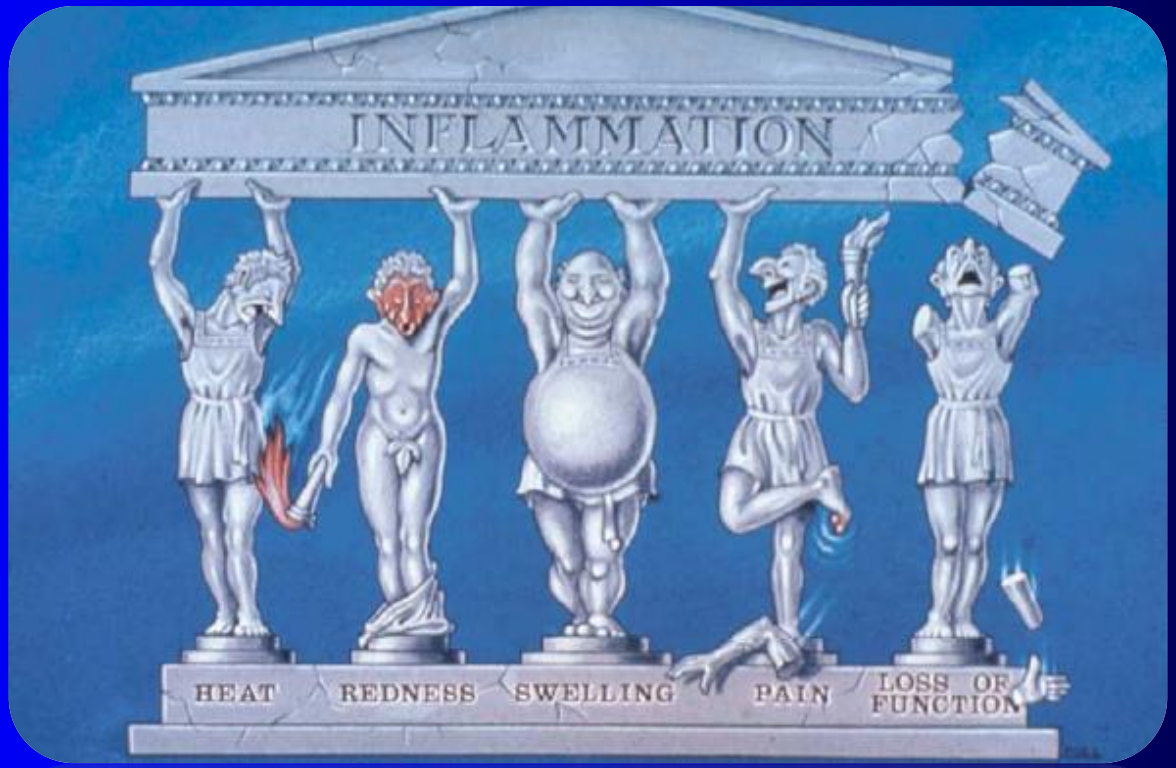
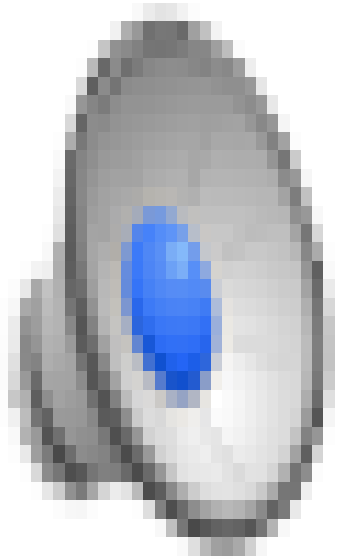
SIR in pediatric cardiac surgery

Minimizing Systemic Inflammation during CPB in the Pediatric Population



SIR in pediatric cardiac surgery



SIR in pediatric cardiac surgery

Definition

The clinical syndrome that results from a deregulated inflammatory response or to a non-infectious insult.

Diagnosis

Core temperature > 38.5°C or < 36°C, plus at least one of the following sign.

Age	Heart Rate	Resp Rate	WBC count
< 1 week	> 180 or < 100	> 50	> 34 k
1 to 4 weeks	> 180 or < 100	> 40	> 19.5 k or < 5.5 k
1 to 24 months	> 180 or < 90	> 34	> 17.5 k or < 5.5 k
2 to 6 years	> 140	> 22	> 15.5 k or < 6 k
6 to 13 years	> 130	> 18	> 13.5 k or < 4.5 k
13 to 18 years	> 110	> 14	> 11k or < 4.5 k

Incidence of SIR in pediatric cardiac surgery is 100%

SIR in pediatric cardiac surgery

An old concept:

Complement and the damaging effects of cardiopulmonary bypass.

Kirklin JK, Westaby S, Blackstone EH, Kirklin JW, Chenoweth DE, Pacifico AD

J Thorac Cardiovasc Surg 1983, 86: 845

This study demonstrates the damaging effects of CPB, relates them in part to complement activation by the foreign surfaces encountered by the blood, and supports the hypothesis that the mechanisms of the damaging effects include a whole-body inflammatory reaction.

Inflammation studies are getting increasingly complex with every year.

SIR in pediatric cardiac surgery

- Systemic inflammation is not always damaging.
- Symptoms of SIR depend on the severity of the reaction: mild (tiredness), moderate (hyperthermia) or severe (hypotension).
- Cardiac surgery provokes a systemic spread of inflammatory mediators which may be related to post-operative organ dysfunction.
- Cardiac surgery causes a rapid release of anti-inflammatory mediators.
- Balance between pro- and anti-inflammatory cytokines is of greater importance than their absolute levels, as it is in coagulation (pro- and anti-thrombotic/coagulation factors).

SIR in pediatric cardiac surgery

SIRS during pediatric cardiac surgery

depends on several acquired factors during CPB:

- ✓ Bypass circuit, open, closed, tubing, oxygenator, arterial filter
- ✓ Blood pumps, occlusive/centrifugal
- ✓ Pulsatile/continuous flow
- ✓ Temperature of perfusion
- ✓ Air-blood contact, suckers
- ✓ Auto transfusion of shed mediastinal blood
- ✓ Hemolysis
- ✓ Transfusion of PRBC, FFP, platelets
- ✓ Ischemia-reperfusion injury
- ✓ Endotoxin
- ✓ Hemofiltration
- ✓ Hemostatic drugs

Most of these factors are modifiable.

SIR in pediatric cardiac surgery

SIRS during pediatric cardiac surgery

- depends on several genetic factors:

✓ Apolipoprotein E,
✓ IL-10 promoter genes,
✓ C4 phenotypes,
✓ TNF NcoI genes

- depends on several anesthetic and surgical factors:

✓ Intubation
✓ Insertion of lines, tubes and catheters
✓ Anesthetic drugs
✓ Surgery: cut down, tissue attrition

Most of these factors are not modifiable.

SIR in pediatric cardiac surgery

CPB is not the sole culprit causing inflammation during pediatric cardiac surgery and the % of its responsibility is unknown.
However, CPB is one of the easiest to modify factors.

SIR in pediatric cardiac surgery

Research Methodology

With so many factors causing

SIR during pediatric cardiac surgery,

- how can we design a controlled study?
- how can we find a control group equivalent to the treated group?

It is unrealistic.

SIR in pediatric cardiac surgery

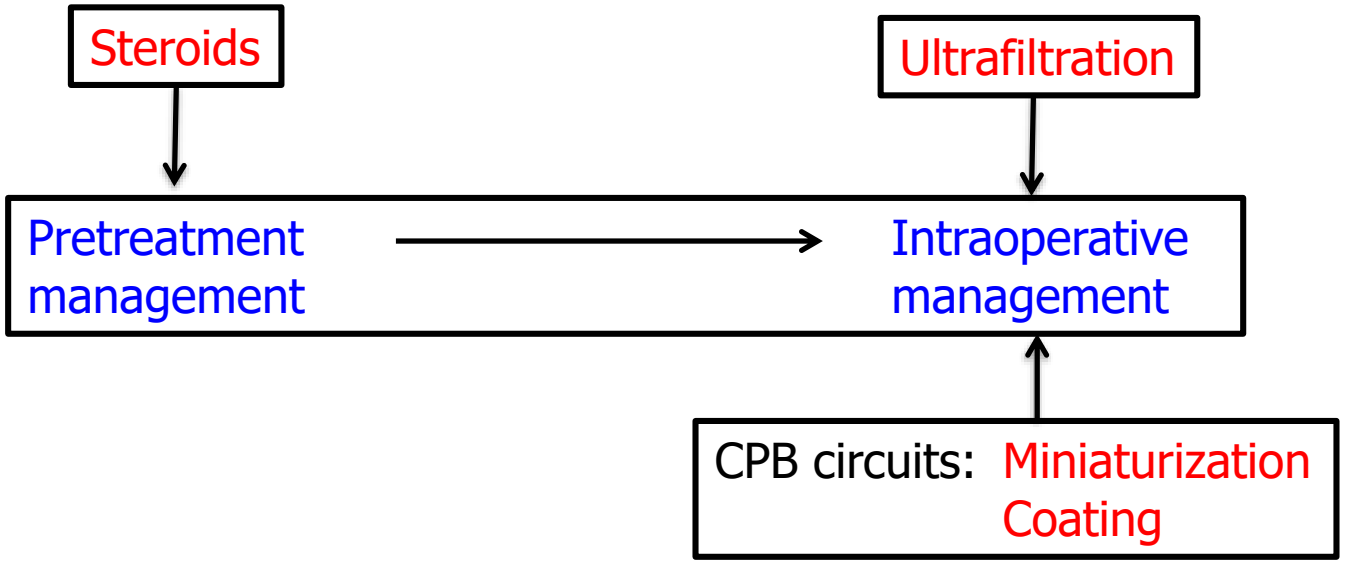
Research Methodology

- The kinetics of SIR during CPB is complex and can be divided into several phases:
  - ✓ The early phase occurs when blood comes into contact with the circuit by activation of F-XII and C3, followed by activation of endothelial cells, platelets and leukocytes, monocytes, macrophages.
  - ✓ The late phase is driven by the ischemia-reperfusion injury and endotoxemia following aortic unclamping.
  - ✓ Complement activation by protamine-heparin interaction.
  - ✓ Inflammatory response to blood products transfusion.
- Activation of coagulation is intricate with inflammation. Thrombin, factors X_a, VII_a exert a pro-inflammatory response directly or indirectly via complement activation.

When are the right time points for blood samples?

SIR in pediatric cardiac surgery

The most widely used strategies to minimize inflammatory response to CPB



SIR in pediatric cardiac surgery

Methylprednisolone administration to ward-off detrimental effects of inflammation

- The standard dose has been 30 mg/kg before and during initiation of bypass since 1982.

Some beneficial effects were demonstrated in the past (1980-2000):

- Alteration in the balance pro/anti-inflammatory biomarkers
- Attenuation in complement activation
- Attenuation in increase of bronchial NO concentration
- Decrease up-regulation of neutrophil CD 11b surface glycoprotein

Clinical benefits were "*suggested*", including:

- ✓ Increase in cardiac index
- ✓ Decrease in pulmonary capillary wedge pressure
- ✓ Decrease in post-operative hyperthermia

SIR in pediatric cardiac surgery

Corticosteroids administration to ward-off detrimental effects of inflammation

Recent works and meta-analysis failed to demonstrate any benefit.

- Prophylactic steroids for pediatric open heart surgery
  Cochrane Database Syst rev 2007; 4: CD005550
  The use of prophylactic steroids is not supported by the existing evidence.
- Preoperative steroid treatment does not improve markers of inflammation after cardiac surgery in neonates: results from a randomized trial
  J Thorac Cardiovasc Surg 2014; 147: 902
  The routine administration of preoperative glucocorticoids in neonatal cardiac surgery should be reconsidered.
- Methylprednisolone in neonatal cardiac surgery: reduced inflammation without improve clinical outcome
  Ann Thorac Surg 2013; 95: 126
  No cardio-protective effect or better clinical outcome was noticed.

SIR in pediatric cardiac surgery

Corticosteroids administration to ward-off detrimental effects of inflammation

Recent works and meta-analysis suggest/demonstrate drawbacks.

- Standardized preoperative corticosteroid treatment in neonates undergoing cardiac surgery: results for a randomized trial
  J Thorac Cardiovasc Surg 2011; 142: 1523
  Combined pre- and intraoperative use of glucocorticoids may exacerbate renal dysfunction.
- Perioperative methylprednisolone and outcome in neonates undergoing heart surgery
  Pediatrics 2012; 129: e385
  This multicenter study suggests increase infection in certain subgroups.
- Cumulative corticosteroid exposure and infection risk after complex pediatric cardiac surgery
  Ann Thorac Surg 2013; 95: 2133
  Cumulative duration of corticosteroid exposure is independently associated with postoperative infection.

SIR in pediatric cardiac surgery

Corticosteroids administration to ward-off detrimental effects of inflammation

Recent works and meta-analysis suggest/demonstrate drawbacks.

- Corticosteroids and outcome in children undergoing congenital heart surgery: analysis of the pediatric health information systems database
  Circulation 2010: 122; 2123

  46 730 patients included, 54% received corticosteroids

✓ No difference in mortality or duration of ventilation

✓ Corticosteroids were associated with
  - longer length of stay
  - greater incidence of infection
  - greater use of insulin

✓ No significant benefit of corticosteroids was seen and the association of corticosteroids with increased morbidity was most prominent in RACHS-1 categories 1 through 3.

SIR in pediatric cardiac surgery

Hemofiltration to ward-off detrimental effects of inflammation

- CUF, MUF and ZBUF were described but only CUF and MUF are commonly used.

- CUF and MUF can reversed hemodilution
  - low hemoglobin level
  - hypoprotidemia
  - dilutional coagulopathy

- CUF and MUF can decrease blood level of some pro- and anti-inflammatory biomarkers

The impact of CUF and MUF on immediate clinical outcome is still debated and the respective role of hemoconcentration and removal of inflammatory products on hemodynamics is unknown.

SIR in pediatric cardiac surgery

Hemofiltration to ward-off detrimental effects of inflammation

Non-exhaustive list of biomarkers found in studies

Bradykinin, Kallikrein, Interleukin: IL-1, IL-4, IL-5, IL-6, IL-8, IL-10, IL-12, IL 13 Nitric oxid synthase, Nuclear Factor-kB, TNF α, Transforming growth factor β,Lipopolysaccharide, Endotoxin, C3, C4, C5, Interferon-η, Platelet activating factor, tPAI-1, C-reactive protein, Adhesion molecules: E selectin, L selectin,, ICAM-1, VCAM, CD11B/CD18 Oxidizing agent, Oxygen-derived free radicals, Elastase, Metalloproteinases, Bactericidal permeability increasing protein (BPI), CRP…

- ✓ Analysis of blood samples obtained at various time points are often limited to short-term period and only demonstrate that filtration is efficient in decreasing some biomarkers blood levels.
- ✓ Kinetics of biomarkers synthesis are not taken into account.

SIR in pediatric cardiac surgery

Hemofiltration to ward-off detrimental effects of inflammation

Inflammatory cytokines in pediatric cardiac surgery and variable effect of the hemofiltration process
Perfusion. 2005; 20: 263

- Hemofiltration reduced TNF-α concentration, but the effect disappeared on the following day.
- Hemofiltration is effective in removal of TNF-α, but its role is debatable for the control of IL-1, IL-6, sIL-6r and IL-8 levels.

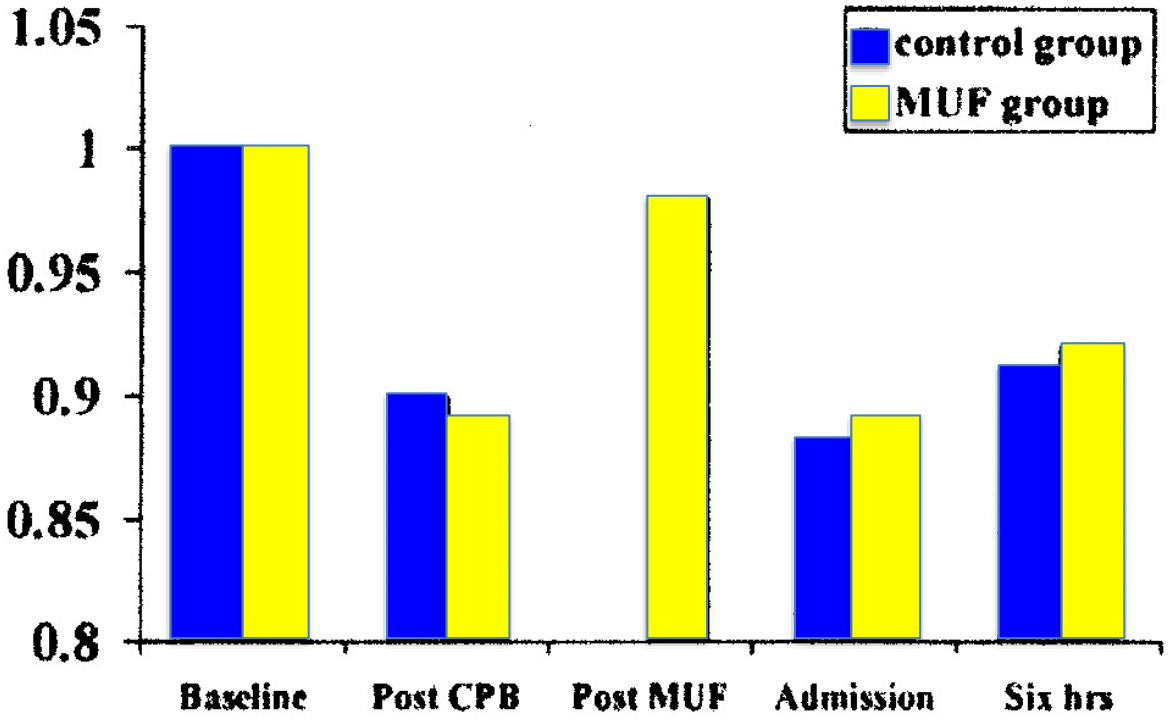
The benefits of continuous ultrafiltration in pediatric cardiac surgery
Scand Cardiovasc J. 2004; 38: 307

- During the early postoperative hours, IL-8 is significantly reduced in patients undergoing MUF, however, the concentrations of IL-8 were similar in both groups at the end of 24 h.

SIR in pediatric cardiac surgery

Effect of modified ultrafiltration on pulmonary function after cardiopulmonary bypass
Mahmoud AB, et al. Chest 2005; 128: 3447-53

Conclusions: The use of MUF after CPB can produce an immediate improvement in lung compliance and gas exchange capacity. However, these improvements are not sustained for the first 6 h postoperatively and do not reduce the duration of postoperative intubation, ICU stay, or total hospital stay.



Static pulmonary compliance

SIR in pediatric cardiac surgery

Hemofiltration to ward-off detrimental effects of inflammation

Many works described a short-time effect of hemofiltration on inflammatory biomarkers and on clinical state.

Filtration treats a consequence of cellular activation, not cellular activation itself.

Do we believe that a short-time decrease in inflammatory biomarkers can significantly modify patient outcome?

SIR in pediatric cardiac surgery

Miniaturized bypass circuit to ward-off detrimental effects of inflammation

Rationale: In pediatric patients blood is exposed to more foreign surface than in adult patients.

But for pediatric patients studies are rare and inconclusive.

Miniaturized cardiopulmonary bypass system in neonates and small infants

Interact Cardiovasc Thorac Surg. 2008; 7: 75

- Introduction:

CPB in children is associated with a capillary leak due to inflammatory response.

- Patients:

Eighty consecutive patients weighing <5 kg were retrospectively reviewed.

The priming volume was reduced from 500 ml to 140 ml.

- Method:

Postoperative peak C-reactive protein (CRP), body weight gain (%BWG) and duration of postoperative mechanical ventilation (MVT) data were collected for each patient.

- Conclusion:

The miniaturized circuit reduced the peri-operative inflammatory response, resulting in reduced postoperative systemic edema, and postoperative mechanical ventilation time.

SIR in pediatric cardiac surgery

Coated by-pass circuit to ward-off detrimental effects of inflammation
Studies are rare and inconclusive

Impact of heparin bonding on pediatric cardiopulmonary bypass:
a prospective randomized study
Ann Thorac Surg. 2000; 70: 191
Heparin-bonded circuits ameliorate the systemic inflammatory response in pediatric patients from cardiopulmonary bypass.

IL-6 and IL-8 levels after cardiopulmonary bypass are not affected by surface coating
Ann Thorac Surg. 1999; 68: 1751
Albumin preprime and heparin-bonding do not attenuate the inflammatory response component attributable to the concentration of these markers.

SIR in pediatric cardiac surgery

Can we learn anything from hemodialysis studies?

Advantages:

- ✓ The same patient with the same genotype can be studied two or three times a week.
- ✓ There is no anesthesia, no surgery, no transfusion, no ischemia- reperfusion no hemolysis, i.e. fewer variables.
- ✓ A dialyzer can be re-used for the same patient.

As a consequence, it is much easier to analyze the effects on inflammation of the extra-corporeal circuit.

- ➢ Reuse of the dialyzer prevents most reactions:
  - dialyzer is likely to be coated with patients proteins
  - circuit biocompatibility is increasing with dialysis time

- ➢ Two dialyzers are worse than one: 100% of intolerance reaction versus 3-5%. Inflammation is related to surface of polymers in contact with blood.

SIR in pediatric cardiac surgery

CONCLUSIONS

After decades of studies we are still unable:

- to have a "decent" definition of SIR during cardiac surgery
- to measure precisely and routinely the balance between pro/anti-inflammatory biomarkers
- to correlate this balance with clinical outcome
- to predict patients at risk of inflammatory-induced end organ dysfunction
- to regulate overexpression of inflammation

But

A non-significant benefit added to one or several non-significant benefits may reach significance threshold.

This may explain part of the progress done in mortality and morbidity incidence during the last decade.

SIR in pediatric cardiac surgery

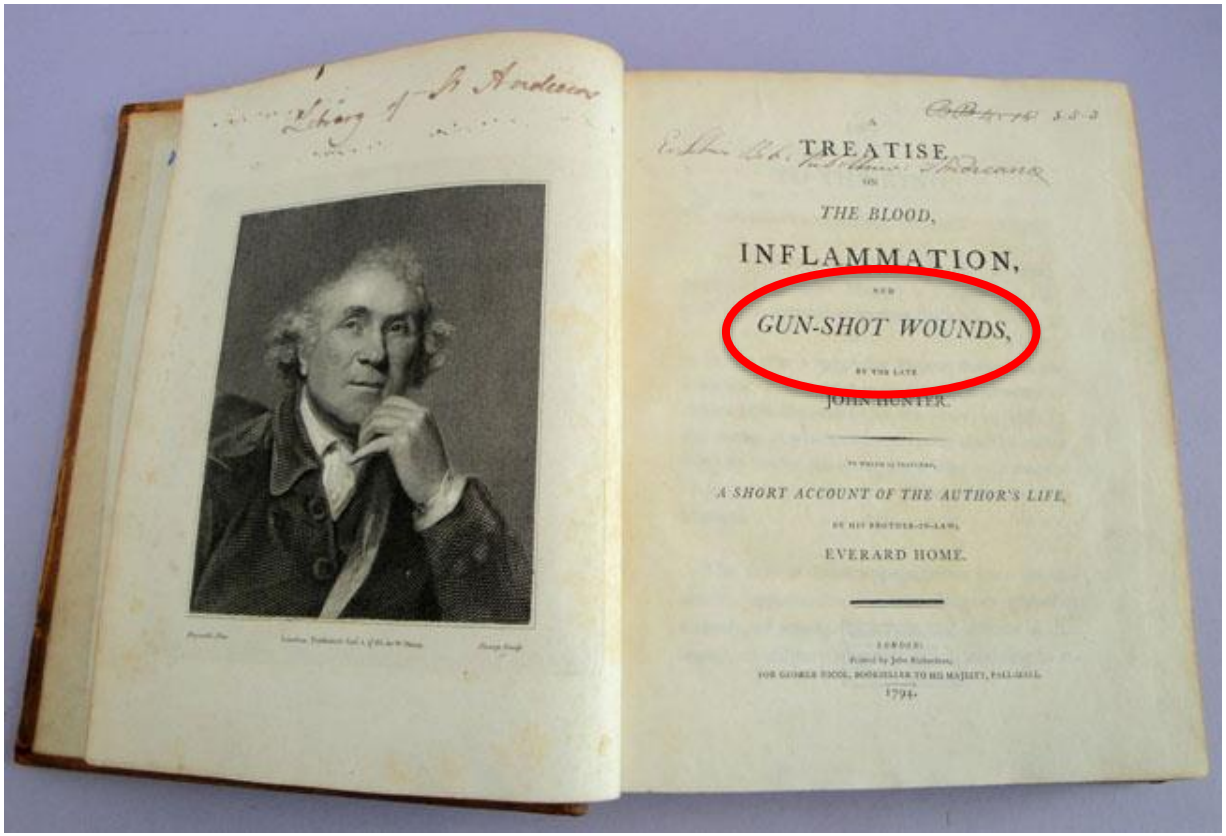
What can we expect in a near future?

- New drugs like Cangrelor,
  a potent platelet inhibitor
  that acts quickly
  and has rapidly reversible effects

- New polymers mimicking natural vascular endothelium i.e. "secreting" nitric oxide and inhibiting platelet activation could be a significant progress.

A Nitric Oxide-Releasing Heparin Conjugate for Delivery of a Combined Antiplatelet/Anticoagulant Agent
Suchyta DJ et al. Mol Pharm. 2014 Jan 24

SIR in pediatric cardiac surgery
CONCLUSION



"Inflammation in itself is not to be considered as a disease…
and in disease, where it can alter the diseased mode of action, it likewise leads to a cure; but where it cannot accomplish that salutary purpose,…it does mischief."

John Hunter 1794