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CytoSorb® Usage in Cardiac Surgery

Systemic Inflammatory Response Syndrome in Heart Surgery: New possibilities for treatment through the use of a cytokine adsorber during ECC?
Born, F., Pichlmaier M, Peterss S, Khaladj N, Hagl C. Kardiotechnik 2014 2/2014

The ECC is still the key technology in the performance of cardiac surgery. Currently used conventional extracorporeal circulation (CECC) systems need to be further optimized [14]. At LMU Munich positive experiences with minimized perfusion were consistently implemented. Minimized/optimized perfusion can reduce the inflammation by advanced perfusion technology [15, 16, 17, 18], but in complex interventions such as re-operations, hypothermic arrest or multiple interventions you reach the limits. Despite the use of modern perfusion technology, it is possible that a post-perfusion syndrome (PPS) can develop during long operations leading to SIRES in 2-10% of all cases. The newly introduced CytoSorb technology is a promising treatment option in patients with SIRS due to cardiopulmonary bypass surgery and increased cytokine values. Procedures involving the aortic arch, selective antegrade cerebral perfusion and hypothermic arrest require extra-long perfusion and ischemic time. It is postulated that the preventative use of a cytokine adsorber during open heart surgery with heart-lung machine has a positive impact on significant clinical and inflammatory parameters. In a retrospective study two patient groups (n=20) were evaluated. The aim of this retrospective observational study is thus to analyze the effect of CytoSorb on the inflammatory response evolving. The IL-6 differs significantly in control and investigatory group during the postoperative course; fibrinogen reacts with significantly lower activation. The leucocyte shows a positive trend in the CytoSorb group. The CRP in the CS group showed a lower rise and a faster normalization. The procalcitonin increased with high significance in the control group.

Acute Kidney Injury and Cardiac Surgery

Predicting Acute Kidney Injury Following Cardiac Surgery: A Systematic Review.
Huen S, and Parikh, CR, Annals Thoracic Surg 2012, 93(1):337-347.

Background—Acute kidney injury (AKI) after cardiac surgery confers a significant increased risk of mortality. Several risk models have been developed to predict postoperative kidney failure after cardiac surgery. The objective of this systematic review is to evaluate the available risk models for AKI after cardiac surgery.

Methods—Literature searches were performed in the Web of Science/Knowledge, Scopus, and MEDLINE databases for articles reporting the primary development of a risk model and articles reporting validation of existing risk models for AKI after cardiac surgery. Data on model variables, internal and/or external validation, measures of discrimination, and measures of calibration were extracted.

Results—Seven articles with a primary development of a prediction score for AKI after cardiac surgery and 8 articles with external validation of established models were included in the systematic review. The models for AKI requiring dialysis are the most robust and externally validated. Among the prediction rules for AKI requiring dialysis after cardiac surgery, the Cleveland Clinic model has been the most widely tested thus far and has shown high discrimination in most of the tested populations. A validated score to predict non-dialysis requiring AKI is lacking.

Conclusions—Further studies are required to develop risk models to predict milder, nondialysis requiring AKI after cardiac surgery. Standardizing risk factor and AKI definitions will facilitate both the development and validation of risk models predicting AKI.

Risk Factors for Perioperative Acute Kidney Injury After Adult Cardiac Surgery: Role of Perioperative Management

Parolari A, Pesce LL, Pacini D,Mazzanti V, Salis S, Sciacovelli C, Rossi F, Alamanni F. For the Monzino Research Group on Cardiac Surgery Outcomes. Ann Thorac Surg 2012, 93:584–91.

Background. The development of acute kidney injury (AKI) after adult cardiac surgery is associated with increased morbidity and mortality. Our aim was to assess the risk factors for postoperative AKI and whether the addition of perioperative management variables can improve AKI prediction.

Methods. We studied 3,219 patients operated from January 2006 to December 2009. The AKI was defined as proposed by the Acute Kidney Injury Network. Patient preoperative characteristics, as well as intraoperative, cardiopulmonary bypass (CPB), and postoperative management variables, were evaluated for association with AKI with logistic regression analysis. The model including all variables was assessed first, then separate models including only preoperative variables followed by the sequential addition of intraoperative, CPB, and postoperative management variables were tested; receiver operating characteristic analysis was used to evaluate and compare models' discriminatory power.

Results. The AKI occurred in 288 of 3,219 patients (8.9%). Logistic regression analysis identified 15 predictors of AKI; 4 were preoperative (age, diabetes, smoking, and serum creatinine), 4 intraoperative (inotropes, erythrocytes transfusion, cross-clamp time, and need of a new pump run), 2 CPB-related (urine output and furosemide administration during CPB), and 5 postoperative (erythrocytes transfusion, administration of vasoconstrictors, inotropes, diuretics, and antiarrhythmics). Model-discrimination performance improved from an area under the curve of 0.830 (95% confidence interval 0.807 to 0.854) for the model including only preoperative variables to an area under the curve of 0.904 (95% confidence interval 0.886 to 0.921) for the model including all variables ($p < 0.001$).

Conclusions. Several factors influence AKI development after cardiac surgery and perioperative patient management significantly affects AKI occurrence. Predictive models can be sensibly improved by the addition of these variables.

Acute kidney injury following cardiac surgery.

Gude, D, Jha R. Annals of Cardiac Anaesthesia 2012, 15(4):279- 286

Acute kidney injury (AKI), a recognized complication of cardiac surgery with cardiopulmonary bypass (CPB) is associated with increased morbidity and mortality (15-30%) with approximately 1% of all the affected patients requiring dialysis. Early detection of AKI would enable intervention before occurrence of irreversible injury and might minimize the morbidity and mortality. Recently developed biomarkers of AKI facilitate its earlier discovery and help assessment of its severity and prognosis. In this article, we review the causes of well-known yet inexplicable association between CPB and AKI, the advances in pathophysiologic basis, the diagnostics and the management options.

Acute Kidney Injury After Cardiac Surgery: Focus on Modifiable Risk Factors

Karkouti, K; Wijeysundera DN; Yau TM, Callum, JL, Cheng DC; Crowther M; Dupuis JY, Fremes SE; Kent B, Laflamme C, Lamy A, Legare JF, Mazer CD, McCluskey SA; Rubens FD, Sawchuk C, Beattie WS. Circulation 2009, 119:495-502.

Background:

Acute kidney injury (AKI) after cardiac surgery is a major health issue. Lacking effective therapies, risk factor modification may offer a means of preventing this complication. The objective of the present study was to identify and determine the prognostic importance of such risk factors.

Methods and Results:

Data from a multicenter cohort of 3500 adult patients who underwent cardiac surgery at 7 hospitals during 2004 were analyzed (using multivariable logistic regression modeling) to determine the independent relationships between 3 thresholds of AKI (_25%, _50%, and _75% decrease in estimated glomerular filtration rate within 1 week of surgery or need for postoperative dialysis) with death rates, as well as to identify modifiable risk factors for AKI. The 3 thresholds of AKI occurred in 24% (n_829), 7% (n_228), and 3% (n_119) of the cohort, respectively. All 3 thresholds were independently associated with a _4-fold increase in the odds of death and could be predicted with several perioperative variables, including preoperative intra-aortic balloon pump use, urgent surgery, and prolonged cardiopulmonary bypass. In particular, 3 potentially modifiable

variables were also independently and strongly associated with AKI. These were preoperative anemia, perioperative red blood cell transfusions, and surgical re-exploration.

Conclusions:
AKI after cardiac surgery is highly prevalent and prognostically important. Therapies aimed at mitigating preoperative anemia, perioperative red blood cell transfusions, and surgical reexploration may offer protection against this complication.

Cardiopulmonary bypass-associated acute kidney injury: a pigment nephropathy?
Haase M, Haase-Fielitz A, Bagshaw SM, Ronco C, Bellomo R. Contrib Nephrol 2007, 156:340-353.

Acute kidney injury (AKI) is a common and serious postoperative complication following exposure to cardiopulmonary bypass (CPB). Several mechanisms have been proposed by which the kidney can be damaged and interventional studies addressing known targets of renal injury have been undertaken in an attempt to prevent or attenuate CPB-associated AKI. However, no definitive strategy appears to protect a broad heterogeneous population of cardiac surgery patients from CPB-associated AKI. Although the association between hemoglobinuria and the development of AKI was recognized many years ago, this idea has not been sufficiently acknowledged in past and current clinical research in the context of cardiac surgery-related AKI. Hemoglobin-induced renal injury may be a major contributor to CPB-associated AKI. Accordingly, we now describe in detail the mechanisms by which hemoglobinuria may induce renal injury and raise the question as to whether CPB-associated AKI may actually be, in a significant part, a form of pigment nephropathy where hemoglobin is the pigment responsible for renal injury. If CPB-associated AKI is a pigment nephropathy, alkalinization of urine with sodium bicarbonate might protect from: (1) tubular cast formation from met-hemoglobin; (2) proximal tubular cell necrosis by reduced endocytotic hemoglobin uptake, and (3) free iron-mediated radical oxygen species production and related injury. Sodium bicarbonate is safe, simple to administer and inexpensive. If part of AKI after CPB is truly secondary to hemoglobin-induced pigment nephropathy, prophylactic sodium bicarbonate infusion might help attenuate it. A trial of such treatment might be a reasonable future investigation in higher risk patients receiving CPB.

Acute Kidney Injury Associated with Cardiac Surgery
Rosner MH and Okusa MD. Clin J Amer Soc Nephrol 2006, 1:19-32.

Acute renal failure (ARF) occurs in up to 30% of patients who undergo cardiac surgery, with dialysis being required in approximately 1% of all patients. The development of ARF is associated with substantial morbidity and mortality independent of all other factors. The pathogenesis of ARF involves multiple pathways. Hemodynamic, inflammatory, and nephrotoxic factors are involved and overlap each other in leading to kidney injury. Clinical studies have identified risk factors for ARF that can be used to determine effectively the risk for ARF in patients who undergo bypass surgery. These high-risk patients then can be targeted for renal protective strategies. Thus far, no single strategy has demonstrated conclusively its ability to prevent renal injury after bypass surgery. Several compounds such as atrial natriuretic peptide and N-acetylcysteine have shown promise, but large-scale trials are needed.

The Role of Plasma Free Hemoglobin in Organ Injury in Cardiac Surgery

Hemolysis during cardiac surgery is associated with increased intravascular nitric oxide consumption and perioperative kidney and intestinal tissue damage

Windsant ICV, de Wit NCJ, Sertorio JTC, van Bijnen AA, Ganushchak YM, Heijmans JH, Tanus-Santos JE, Jacobs MJ, Maessen, JG, Buurman WA. Front Physiol 2014, 5:340

INTRODUCTION: Acute kidney injury (AKI) and intestinal injury negatively impact patient outcome after cardiac surgery. Enhanced nitric oxide (NO) consumption due to intraoperative intravascular hemolysis, may play an important role in this setting. This study investigated the impact of hemolysis on plasma NO consumption, AKI, and intestinal tissue damage, after cardiac surgery.

METHODS: Hemolysis (by plasma extracellular (free) hemoglobin; fHb), plasma NO-consumption, plasma fHb-binding capacity by haptoglobin (Hp), renal tubular injury (using urinary N-Acetyl-β-D-glucosaminidase; NAG), intestinal mucosal injury (through plasma intestinal fatty acid binding protein; IFABP), and AKI were studied in patients undergoing off-pump cardiac surgery (OPCAB, N = 7), on-pump coronary artery bypass grafting (CABG, N = 30), or combined CABG and valve surgery (CABG+Valve, N = 30).

RESULTS: FHb plasma levels and NO-consumption significantly increased, while plasma Hp concentrations significantly decreased in CABG and CABG+Valve patients ($p < 0.0001$) during surgery. The extent of hemolysis and NO-consumption correlated significantly ($r (2) = 0.75$, $p < 0.0001$). Also, NAG and IFABP increased in both groups ($p < 0.0001$, and $p < 0.001$, respectively), and both were significantly associated with hemolysis ($R s = 0.70$, $p < 0.0001$, and $R s = 0.26$, $p = 0.04$, respectively) and NO-consumption ($Rs = 0.55$, $p = 0.002$, and $R s = 0.41$, $p = 0.03$, respectively), also after multivariable logistic regression analysis. OPCAB patients did not show increased fHb, NO-consumption, NAG, or IFABP levels. Patients suffering from AKI (N = 9, 13.4%) displayed significantly higher fHb and NAG levels already during surgery compared to non-AKI patients.

CONCLUSIONS: Hemolysis appears to be an important contributor to postoperative kidney injury and intestinal mucosal damage, potentially by limiting NO-bioavailability. This observation offers a novel diagnostic and therapeutic target to improve patient outcome after cardiothoracic surgery.

Connecting hemolysis and visceral injury during cardiovascular surgery: Studies on the causes, effects, and treatment of hemolysis-induced organ injury

Multiple Articles, Multiple Authors

Cardiovascular disease is the major cause of death worldwide, claiming over 7.2 million lives in 2004 due to coronary heart disease alone.[1] In the Netherlands, the total number of patients diagnosed with coronary heart disease was 730.400 in 2007 (RIVM). In 2008, 16.877 patients required open heart surgery to sufficiently treat coronary and/or cardiac valve disease. The introduction of the cardiopulmonary bypass (CPB) in the early nineteen sixties as a more routine technique during cardiovascular surgery led to a significant increase in treatment options for patients with serious cardiovascular disease, such as patients with multifocal coronary artery disease, cardiac valve disorders or patients with major vascular disease such as (thoracoabdominal) aortic aneurysms. CPB, also called extracorporeal circulation, enabled ongoing organ perfusion and oxygenation during extensive and time-consuming operations of the heart and/or aorta. Nevertheless, despite major technical and medical refinements since its first introduction, CPB assisted surgery is still associated with (relatively) high morbidity and mortality. Principally, major postoperative complications such as renal dysfunction (requiring dialysis), and pulmonary complications such as prolonged mechanical ventilation, ventilation assisted pneumonia or the adult respiratory distress syndrome, are relatively common. Several CPB-related factors, such as ischemia-reperfusion injury, hemodilution, and initiation of a pro-inflammatory response, have been extensively studied for their role in the development of these postoperative complications. Furthermore the impact of intravascular hemolysis caused by mechanical stress within the CPB system, among other factors, has been mentioned in the literature but not related to organ injury or patient outcome. This thesis aimed to elucidate the causes of acute hemolysis and its effects on the development of postoperative complications after (major) cardiovascular surgery.

Effect of Air Exposure and Suction on Blood Cell Activation and Hemolysis in an *In Vitro* Cardiotomy Suction Model

El-Sabba AM, Toomasian CJ, Toomasian JM, Ulysse G, Major T, Bartlett RH. ASAIO Journal 2013; 59:474–479.

Cardiopulmonary bypass (CPB) elicits a systemic inflammatory response. The cause may include surface-induced leukocyte activation and hemolysis. A study was designed to describe the effects of both suction and an air–blood interface independently and in combination on leukocyte and platelet activation, and hemolysis in an *in vitro* model. Fresh human blood was drawn and tested in four different conditions including control (A), 10 minutes of −600 mm Hg suction (B), 10 minutes of blood exposure to room air at 100 ml/min (C), and 10 minutes of simultaneous suction and air flow (D). Samples were analyzed by flow cytometry (platelets and leukocytes) and plasma-free hemoglobin (PFHb). Leukocyte CD11b expression and platelet P-selectin (CD62P) were analyzed by flow cytometry. In comparison with baseline, granulocytes were significantly activated by air (group C, $p = 0.0029$) and combination (group D, $p = 0.0123$) but not by suction alone (group B). Monocytes and platelets were not significantly activated in any group. The PFHb increased significantly in group C ($p < 0.001$) and group D ($p < 0.001$). This study suggests that the inflammatory response and associated hemolysis during CPB may be related to air exposure, which could be reduced by minimizing the air exposure of air to blood during cardiotomy suction.

Hemolysis and cell-free hemoglobin drive an intrinsic mechanism for human disease

Gladwin MT, Kanias T, Kim-Shapiro, DB. J Clin Invest 2012, 122(4):1205-1208.

Blood transfusion represents the first and most prescribed cell-based therapy; however, clinical safety and efficacy trials are lacking. Clinical cohort studies have suggested that massive transfusion and/or transfusion of aged stored blood may contribute to multiorgan dysfunction in susceptible patients. In this issue of the *JCI*, Baek and colleagues report that aged stored blood hemolyzes after massive transfusion in a guinea pig model. Hemolysis led to vascular and kidney injury that was mediated by cell-free plasma hemoglobin and prevented by coinfusion of the specific hemoglobin scavenger protein, haptoglobin. These studies support an expanding body of research indicating that intravascular hemolysis is a pathological mechanism in several human diseases, including multiorgan dysfunction after either massive red blood cell transfusion or hemoglobin-based blood substitute therapy, the hemoglobinopathies, malaria, and other acquired and genetic hemolytic conditions.

Postoperative acute kidney injury is associated with hemoglobinemia and an enhanced oxidative stress response

Billings FT, Ball SK, Roberts LJ, Pretorius M. Free Radical Biol and Med 2011, 50:1480-1487.

Acute kidney injury (AKI) frequently afflicts patients undergoing cardiopulmonary bypass and independently predicts death. Both hemoglobinemia and myoglobinemia are independent predictors of postoperative AKI. Release of free hemeproteins into the circulation is known to cause oxidative injury to the kidneys. This study tested the hypothesis that postoperative AKI is associated with both enhanced intraoperative hemeprotein release and increased lipid peroxidation assessed by measuring F2-isoprostanes and isofurans. In a case–control study nested within an ongoing randomized trial of perioperative statin treatment and AKI, we compared levels of F2-isoprostanes and isofurans with plasma levels of free hemoglobin and myoglobin in 10 cardiac surgery AKI patients to those of 10 risk-matched controls. Peak plasma free hemoglobin concentrations were significantly higher in AKI subjects (289.0±37.8 versus 104.4±36.5 mg/dl, P=0.01), whereas plasma myoglobin concentrations were similar between groups. The change in plasma F2-isoprostane and isofuran levels (repeated-measures ANOVA, P=0.02 and P=0.001, respectively) as well as the change in urine isofuran levels (P=0.04) was significantly greater in AKI subjects. In addition, change in peak plasma isofuran levels correlated not only with peak free plasma hemoglobin concentrations (r2=0.39, P=0.001) but also with peak change in serum creatinine (r2=0.20, P=0.01). Postoperative AKI is associated with both enhanced intraoperative hemeprotein release and enhanced lipid peroxidation. The correlations among hemoglobinemia, lipid peroxidation, and AKI indicate a potential role for hemeprotein-induced oxidative damage in the pathogenesis of postoperative AKI.

Hemolysis is associated with acute kidney injury during major aortic surgery
Windsant ICV, Snoeijs, MG, Hanssen SJ, Altintas S, Heijmans JH, Koeppel TA, Schurink GWH, Buurman WA, Jacobs MJ. Kidney International 2010, 77:913-920.

Hemolysis is an inevitable side effect of cardiopulmonary bypass resulting in increased plasma free hemoglobin that may impair tissue perfusion by scavenging nitric oxide. Acute kidney injury after on-pump cardiovascular surgery arises from a number of causes and severely affects patient morbidity and mortality. Here, we studied the effect of acute hemolysis on renal injury in 35 patients undergoing on-pump surgical repair of thoracic and thoracoabdominal aortic aneurysms of whom 19 experienced acute kidney injury.
During surgery, plasma free hemoglobin increased, as did urinary excretion of the tubular injury marker N-acetyl-b-Dglucosaminidase, in patients with and without acute kidney injury, reaching peak levels at 2 h and 15min, respectively, after reperfusion. Furthermore, plasma free hemoglobin was independently and significantly correlated with the urine biomarker, which, in turn, was independently and significantly associated with the later postoperative increase in serum creatinine. Importantly, peak plasma free hemoglobin and urine N-acetyl-b-D-glucosaminidase concentrations had significant predictive value for postoperative acute kidney injury. Thus, we found an association between increased plasma free hemoglobin and renal injury casting new light on the pathophysiology of acute kidney injury. Therefore, free hemoglobin is a new therapeutic target to improve clinical outcome after on-pump cardiovascular surgery.

Increase in plasma free haemoglobin during cardiopulmonary bypass in heart valve surgery: assessment of renal dysfunction by RIFLE classification
Vanek T, Snircova J, Spegar J, Straka Z, Horak J, Maly M. Perfusion 2009, 24(3):179-183.

Heart valve surgery carries a high risk of renal insufficiency as an independent risk factor due to prolonged cardiopulmonary bypass. Multiple causes of cardiopulmonary bypass-associated renal damage have been described, and haemoglobin-induced renal injury is presently being investigated. Forty-three patients scheduled for heart valve surgery (mostly combined) were enrolled in the prospective study. Plasma free haemoglobin (PFH) levels were evaluated by photocolorimetric measurement at the start of procedures ($t0$) and before the end of extracorporeal circulation ($t1$). A statistically significant increase in PFHlevels during cardiopulmonary bypass was detected [median values (interquartile range) - $t0$: 62.0 (53.4) mg/L, $t1$: 320.4 (352.2) mg/L], $P<0.001$. A significant regression relationship between the duration of cardiopulmonary bypass and the increased PFH was found (Spearman's correlation coefficient 0.628, $P < 0.001$). In some elderly patients, the tendency towards a high release of PFH during cardiopulmonary bypass was more pronounced, but the overall association between age and PFH levels was of borderline significance ($P = 0.077$). The correlation between PFH and post-operative serum creatinine was low and non-significant, but the latter correlated highly with the pre-operative serum creatinine values (Spearman's correlation coefficient reached values of 0.6-0.7, $P < 0.001$). Patients were classified according to the Risk of renal failure, Injury to the kidney, Failure of kidney function, Loss of kidney function and End-stage renal failure (RIFLE) classification for acute renal dysfunction during post-operative days 1 – 4; the influence of PFH levels at $t1$ on the consequent RIFLE classification was not proven ($P=0.648$), but 4 patients in the Injury category had shown a higher median value of PFH (433.6 mg/L) in comparison with the others (29 patients with no acute renal dysfunction - 313.7 mg/L, 10 patients at Risk - 330.1 mg/L).

Hemolysis in Cardiac Surgery Patients Undergoing Cardiopulmonary Bypass: A Review in Search of a Treatment Algorithm
Vercaemst L. J Extracorporeal Technology 2008, 40:257-267.

Abstract: Hemolysis is a fact in all extracorporeal circuits, as shown in various studies by the increasing levels of plasma-free hemoglobin (PfHb) and decreasing levels of haptoglobin during and after cardiopulmonary bypass (CPB). Beside complete red blood cell (RBC) destruction or hemolysis, RBCs can also be damaged on a sublethal level, resulting in altered rheological properties. Increased levels of free RBC constituents together with an exhaust of their scavengers result in a variety of serious clinical sequela, such as increased systemic and pulmonary vascular resistance, altered coagulation profile, platelet dysfunction, renal tubular damage, and increased mortality. Sublethal RBC damage is characterized by decreased microperfusion and hypoxic RBCs, leading to end organ dysfunction caused by cellular ischemia. Isolated extracorporeal circuit components can be considered non-hemolytic if used according to recommendations, but extracorporeal circuit composition and management during CPB can still be optimized, avoiding cell damaging mechanical forces. Although most RBC destruction in standard CPB remains within the capacity of the endogenous clearing mechanisms, in some

cases, levels of PfHb do substantially rise, and precautionary measures need to be taken. Higher degree of hemolysis can be expected in young children, after extensive surgery, and in prolonged support as in patients supported by ventricular assist devices (VADs) or extracorporeal membrane oxygenation (ECMO). These patients are especially susceptible to the toxic influences of unscavenged RBC constituents and the loss of rheologic properties of the RBCs. Considering the high percentage of neurologic and renal sequela in post-cardiotomy patients, all imbalances possibly contributing to these morbidities should be focused on and prevented, if not treated. Considering the severity of the consequences of RBC damage, the high incidence of this complication, and especially the lack of interventional strategies in cases of suspected or confirmed RBC damage, there may be a need for a treatment algorithm for this phenomenon.

The Effect of Time and pH on Hemolysis During Cardiopulmonary Bypass
Bansal A, Hampton C, Badri Z, Savage K, Pohlmann JR, Toomasian JM and Cook KE. UMURD 2008 5:23-25.

Objective: During cardiopulmonary bypass (CPB), the breakage of red blood cell membranes (hemolysis) and activation of humoral components (i.e. enzymes) in the blood can occur. Hemolysis and humoral component activation can lead to multiple post-operative complications (i.e. renal and lung failure). The purpose of this study is to investigate the causes of hemolysis during CPB. We hypothesize that blood damage during CPB is caused primarily by exposure of the blood to air and negative pressure during cardiotomy suction, which is used to collect blood that is lost during the operation.

Methods: An in-vitro model was used to investigate the role of time and pH on hemolysis during the application of negative pressure and an air-blood interface. In the time experiment, ovine blood was exposed to pressure of -600 mmHg and room air-flow of 50 mL/min at increasing times (1, 5, 10, 15, and 30 min). In the pH experiment, ovine blood was exposed to a negative pressure of 600 mmHg, and 50 mL/min of either 25% CO2 or room air-flow (approximately 0.038% CO2) for ten minutes. Twenty-five percent CO2 was used to mimic normal physiological pH. Citrate and heparin anti-coagulants were used to prevent clotting in both experimental groups.

Results: Red blood cell lysis increased linearly with the time that the blood was exposed to negative pressure and air. In the pH experiment, there was no significant difference in hemolysis between the room air group and the 25% CO2 group.

Conclusion: Hemolysis during CPB is time-dependent when exposed to negative pressure and an air-blood interface. Rapid changes in blood pH do not contribute to this hemolysis.

Cardiopulmonary bypass induced inflammation: pathophysiology and treatment. An update
Paparella D, Yaua TM, Young E. European J of Cardio-thoracic Surgery 2002, 21:232-244.

Cardiac surgery with cardiopulmonary bypass (CPB) induces an acute phase reaction that has been implicated in the pathogenesis of several postoperative complications. Recent data indicate that a complex sequence of events leads to the final activation of leukocytes and endothelial cells (EC), which is responsible for cell dysfunction in different organs. Activation of the contact system, endotoxemia, ischemia and reperfusion injury and surgical trauma are all potential triggers of inflammation following CPB. Different pro- and anti-inflammatory mediators (cytokines, adhesion molecules) are involved and their release is mediated by intracellular transcription factors (nuclear factor-kB, NF-kB). In this review, we examine recent advances in the understanding of the pathophysiology of the CPB-induced acute phase reaction and evaluate the different pharmacological, technical and surgical strategies used to reduce its effects. Emphasis is given to the central role of transcription factor NF-kB in the complex mechanism of the inflammatory reaction and to the effects of compounds such as heparin and glycosaminoglycans, phosphodiesterase inhibitors and protease inhibitors whose role as anti-inflammatory agent has only recently been recognized.

Acute Renal Failure after Cardiopulmonary Bypass Is Related to Decreased Serum Ferritin Levels
Davis CL, Kausz AT, Zager RA, Kharasch ED, Cochran RP. J Am Soc Nephrol 1999, 10:2396-2402.

Abstract. Acute renal failure (ARF) requiring dialysis occurs inup to 4% of patients after cardiopulmonary bypass (CPB). CPB leads to the generation of intravascular free hemoglobin, resulting in increased endothelial and renal tubular cell free iron, which is associated with renal injury. Conversely, renoprotection is conferred by processes

that upregulate heme and iron sequestration pathways, such as ferritin. This study evaluates the influence of free hemoglobin generation during CPB and the capacity to sequester free iron on the occurrence of post-CPB renal insufficiency. Thirty consecutive patients undergoing CPB were enrolled in the study. Serum creatinine, free hemoglobin, and ferritin were measured preoperatively, at the end of bypass, and 24 and 48 h after surgery. Renal injury, as determined by an increase in the serum creatinine of $25% (ARF) by 48 h after surgery, occurred in 40% (12 of 30) of patients, and dialysis was necessary in 6.6% (2 of 30). Free hemoglobin levels increased in all patients but did not correlate with postoperative ARF. However, patients with preoperative serum ferritin levels #130 mg/L, the median value for the group, had a sixfold greater likelihood of developing ARF compared to patients with levels above this value (*P* 5 0.03). Lower serum ferritin levels appear to be associated with the development of ARF. Serum ferritin levels may signify intravascular as well as endothelial and renal epithelial cell ability to bind free iron generated during CPB-induced hemolysis, and thus may help provide information regarding the risk for ARF.

The Role of Cytokines and Inflammation in Organ Injury in Cardiac Surgery

Systemic Inflammatory Response Syndrome After Extracorporeal Circulation: A Predictive Algorithm for the Patient at Risk
Litmathe J, Boeken U, Bohlen G, Gursoy D, Sucker C, Feindt P. Hellenic J Cardiol 2011; 52: 493-500.

Introduction: Perioperative systemic inflammatory response syndrome (SIRS) remains a catastrophe in cardiac surgery and adequate patient screening is still lacking. We present a prospective trial starting with preoperative data collection. For the first time, the postoperative outcomes of patients after open-heart surgery are evaluated to predict a hazard-constellation for the patient at risk of developing SIRS.

Methods: Of 2315 patients undergoing cardiac surgery over a 2-year period, 107 were considered likely to develop perioperative SIRS based on a high-risk stratification; 12 of them actually developed SIRS and were recruited for this study. Another 20 uneventful consecutive patients served as controls. Blood samples were collected from before the induction of anaesthesia until the morning of the second postoperative day and were analysed for complement, cytokines, adhesion-molecules, endothelin-1 (ET-1), plasminogen-activator inhibitor (PAI), the coagulation and fibrinolysis cascade and routine laboratory analysis.

Results: Significant preoperative differences were observed in leukocytes, lymphocytes, alkaline phosphatase, ICAM-3 and VCAM-1 ($p<0.05$). Significant positive correlations were found for ET-1 and lactate in the SIRS group. The increase in these parameters was correlated with a prolonged duration of extracorporeal circulation. The best predictive combination for SIRS consisted of alkaline phosphatase, ET-1, ICAM-1, -2, -3, VCAM-1 and ELAM-1.

Conclusions: The results suggest a new theory regarding the development of perioperative SIRS. It is not the extracorporeal circulation itself that represents the main trigger, but rather an *a priori* activation of the endothelial cells, lymphocytes and leukocytes. This activation impairs the microcirculation and finally leads to multi-organ failure. The current data allow the identification of the patient at risk and can thus influence the individual operative schedule.

Systemic Inflammatory Response Syndrome after Cardiac Surgery under Cardiopulmonary Bypass
Hirai S. Ann Thorac Cardiovasc Surg 2003, 9:365-70.

Objective: This prospective study was designed to elucidate the duration of systemic inflammatory response syndrome (SIRS) and the mechanisms that lead to the protraction of SIRS in patients who are operated on under cardiopulmonary bypass (CPB).

Methods: The duration of SIRS in 13 patients with SIRS was studied. Two groups were divided according to the duration to investigate the meaning of the duration of SIRS. The perioperative parameters which significantly correlated with the duration of SIRS, including the kinetics of cytokines and white blood cells (WBC) counts were investigated.

Results: In patients with SIRS extending for a period greater than 12 hours (group A), the duration of CPB, interleukin-6 (IL-6), interleukin-8 (IL-8) and WBC count after aortic declamping were significantly longer and higher than those in patients with SIRS lasting less than 12 hours (group B). The duration of SIRS significantly correlated with the highest level of IL-6 ($r=0.724$, $p=0.0038$) and the duration of CPB ($r=0.626$, $p=0.0201$).

Conclusions: These results suggest that the duration of CPB and cytokinemia, with high IL-6 levels, during this short time frame until just after cardiac surgery might play an important role in the development of the SIRS.

Reduced expression of systemic proinflammatory and myocardial biomarkers after off-pump versus on-pump coronary artery bypass surgery: A prospective randomized study
Serrano CV, Souza JA, Lopes NH, Fernandes JL, Nicolau JC, S.L. Blotta MH, Ramires JAF, Hueb WA. J Crit Care 2010, 24:305-312.

Background: The effects of off-pump (OffPCABG) and on-pump (OnPCABG) coronary artery bypass grafting (CABG) on myocardium and inflammation are unclear.

Objective: Compare the inflammatory response and myocardial injury from patients (pts) submitted to OffPCABG with those that undergo OnPCABG.

Methods: Patients with normal left ventricular function were assigned to OffPCABG (n = 40) and OnPCABG (n = 41). Blood samples were collected before and 24 hours after surgery for determination of creatine kinase (CK)–MB (CK-MB), troponin I (cTnI), interleukin (IL)–6, IL-8, P-selectin, intercellular adhesion molecule (ICAM)-1 and C-reactive protein (CRP). Mortalities were registered at 12 months.

Results: Preoperative CK-MB and cTnI levels were 3.1 ± 0.6 IU and 1.2 ± 0.5 ng/mL for OffPCABG and 3.0 ± 0.5 IU and 1.0 ± 0.2 ng/mL for OnPCABG pts. Postoperative CK-MB and cTnI levels were 13.9 ± 6.5 IU and 19.0 ± 9.0 ng/mL for OffPCABG vs 29.5 ± 11.0 IU and 31.5 ± 10.1 ng/mL for OnPCABG (P b .01). OffPCABG and OnPCABG pts had similar preoperative IL-6 (10 ± 7 and 9 ± 13 pg/mL), IL-8 (19 ± 7 and 17 ± 7 pg/mL), soluble P-selectin (70 ± 21 and 76 ± 23 pg/mL), soluble ICAM–1 (117 ± 50 and 127 ± 52 ng/mL), and CRP (0.09 ± 0.05 and 0.11 ± 0.07 mg/L). At 24 hours, for OffPCABG and OnPCABG: IL-6 was 37 ± 38* and 42 ± 41*,† g/mL; IL-8, 33 ± 31* and 60 ± 15*,† pg/mL; soluble P-selectin, 99 ± 26 and 172 ± 30*,† pg/mL; soluble ICAM-1, 227 ± 47 and 236 ± 87*,† ng/mL; and CRP, 10 ± 11* and 14 ± 13*,† mg/L (*P b.01 vs preoperation; †P b.01 vs OffPCABG).

The Systemic Inflammatory Response Syndrome and Cardiopulmonary Bypass
Day JRS, Taylor KM. Int J Surgery 2005, 3:129-140.

Cardiac surgery using cardiopulmonary bypass (CPB) provokes a systemic inflammatory response. This is mainly triggered by contact activation of blood by artificial surfaces of the extracorporeal circuit. Although often remaining subclinical and resolving promptly at the end of CPB, in its most extreme form this inflammatory response may be associated with the development of the systemic inflammatory response syndrome (SIRS) that can often lead to major organ dysfunction (MODs) and death. Here, we review the pathophysiology behind the development of this ''whole body'' inflammatory response and some of the methods currently used to minimise it.

Cardiopulmonary Bypass Induced Inflammation: Pathophysiology and Treatment. An Update
Paparella D, Yau TM, Young E. Eur J Cardio-thoracic Surg 2002, 21: 232-244.

Cardiac surgery with cardiopulmonary bypass (CPB) induces an acute phase reaction that has been implicated in the pathogenesis of several postoperative complications. Recent data indicate that a complex sequence of events leads to the final activation of leukocytes and endothelial cells (EC), which is responsible for cell dysfunction in different organs. Activation of the contact system, endotoxemia, ischemia and reperfusion injury and surgical trauma are all potential triggers of inflammation following CPB. Different pro- and anti-inflammatory mediators (cytokines, adhesion molecules) are involved and their release is mediated by intracellular transcription factors (nuclear factor-kB, NF-kB). In this review, we examine recent advances in the understanding of the pathophysiology of the CPB-induced acute phase reaction and evaluate the different pharmacological, technical and surgical strategies used to reduce its effects. Emphasis is given to the central role of transcription factor NF-kB in the complex mechanism of the inflammatory reaction and to the effects of compounds such as heparin and glycosaminoglycans, phosphodiesterase inhibitors and protease inhibitors whose role as anti-inflammatory agent has only recently been recognized.

Cytokine responses and myocardial injury in coronary artery bypass grafting
Wei M, Kuukasjarvi P, Laurikka J, Kaukinen S, Iisalo P, Laine S, Laippala P, Metsanoja R, Tarkka M. Scand J Clin Lab Invest 2001, 61:161–166.

Objective: Cardiopulmonary bypass is acknowledged to be one of the major causes of a complex systemic inflammatory response after cardiac surgery, and it may contribute to postoperative complications and even multiple organ dysfunction. We here compared the cytokine responses and the degree of myocardial injury after coronary artery bypass grafting with or without cardiopulmonary bypass.

Methods: Nine patients underwent oOE -pump revascularization and 13 with cardiopulmonary bypass. Plasma levels of tumor necrosis factor-a (TNF-a), interleukin (IL)-6, IL-8 and IL-10 were measured before anesthesia induction, and 5 min, 1, 4, and 20 h after reperfusion to the myocardium. Levels of the MB isoenzyme of creatine kinase (CK-MB) were also measured after the operation.

Results: Levels of TNF-a were low in both groups. A delayed elevation of IL-6 was noted in the oOE -pump group. IL-8 and IL-10 levels were significantly higher in the CPB than in the oOE -pump patients after reperfusion (p=0.006 and 0.001 respectively). Postoperative CK-MB levels were significantly higher in the CPB than in the oOE - pump group (p=0.001). Cytokine levels correlated with CK-MB values.

Conclusion: The results indicated that oOE -pump revascularization was associated with reduced cytokine responses and less severe myocardial injury. The degree of myocardial injury, as defined by CK-MB release, correlated with cytokine release. Intervention designed to reduce cytokine responses in cardiac surgery may be advantageous for patients with severe comorbidity.

Inflammatory Response to Cardiopulmonary Bypass
Edmunds LH. Ann Thorac Surg 1998, 66:S12-16.

This article reviews the roles of the contact and complement systems and of neutrophils and monocytes in the inflammatory response to cardiopulmonary bypass and open heart operation. These blood proteins and cells, together with other blood elements, produce the vasoactive and cytotoxic substances and microemboli that cause the morbidity associated with cardiopulmonary bypass and open heart operation.

Endothelial Cell Injury in Cardiovascular Surgery: The Systemic Inflammatory Response
Boyle EM, Pohlman TH, Johnson MC, Verrier ED. Ann Thorac Surg 1997, 63:277– 84.

Many of the components currently used to perform cardiovascular operations lead to systemic insults that result from cardiopulmonary bypass circuit-induced contact activation, circulatory shock, and resuscitation, and a syndrome similar to endotoxemia. Experimental observations have demonstrated that these events have profound effects on activating endothelial cells to recruit neutrophils from the circulation. Once adherent to the endothelium, neutrophils release cytotoxic proteases and oxygen derived free radicals, which are responsible for much of the end-organ damage seen after cardiovascular operations. Recently the cellular and molecular mechanisms of endothelial cell activation have become increasingly understood. It is conceivable that once the molecular mechanisms of endothelial cell activation are better defined, therapies will be developed allowing the selective or collective inhibition of vascular endothelial activation during the perioperative period.

Systemic Inflammatory Response Syndrome After Cardiac Operations
Cremer J, Martin M, Redl H, Bahrami S, Abraham C, Graeter T, Haverich A, Schlag G, Borst HG. Ann Thorac Surg 1996, 61(6):1714-1720.

BACKGROUND:
A systemic inflammatory response after open heart operation may be responsible for hyperdynamic circulatory instability and organ dysfunction. To what extent mediator release is involved needs to be clarified.

METHODS:
Ten patients with postoperative hyperdynamic circulatory dysregulation (group I) requiring application of alpha-constrictors and 10 patients with routine cardiac procedures and stable postoperative hemodynamic indices

(group II) were analyzed for mediator release and metabolic and hemodynamic changes until the third postoperative day.

RESULTS:
Group I patients showed a significantly increased cardiac index and decreased systemic vascular resistance after bypass (cardiac index, group I: 5.2 +/- 1.2 L.min-1.m-2, group II: 2.5 +/- 1.6 L.min-1.m-2; systemic vascular resistance, group I: 495 +/- 204 dyne.s. cm-5, group II: 1,356 +/- 466 dyne.s.cm-5) and at 3 hours (cardiac index, group I: 4.4 +/- 0.8 L.min-1.m-2, group II: 2.9 +/- 0.6 L.min-1.m-2; systemic vascular resistance, group I: 567 +/- 211 dyne.s.cm-5, group II: 1,053 +/- 273 dyne.s.cm-5). Significantly higher serum levels of interleukin-6 were assessed in group I (postbypass, group I: 6,812 +/- 9,293 pg/mL, group II: 295 +/- 303 pg/mL; 3 hours, group I: 3,474 +/- 5,594 pg/mL, group II: 286 +/- 296 pg/mL). Concentrations of elastase, tumor necrosis factor, soluble tumor necrosis factor receptor, and interleukin-8 were elevated in group I (not significant). Early postoperative levels of soluble E-selectin and soluble intercellular adhesion molecule were also higher in group I (not significant). Continuously increased levels of endotoxin could be detected in only 3 of 10 patients in group I. Severe lactic acidosis (> or = 5 mmol/L) occurred in group I only.

CONCLUSIONS:
Postoperative hyperdynamic instability after open heart operations appears to be associated with a certain pattern of mediator release. In particular, interleukin-6 appears to be involved in circulatory dysregulation and metabolic derangement.

SIRS – The Systemic Inflammatory Response Syndrome After Cardiac Operations
Taylor KM. Ann Thorac Surg 1996, 61:1607-8.

Although Samuel Johnson's observation was addressed to his colleagues, not to SIRS (the acronym for the systemic inflammatory response syndrome), the point he makes is nonetheless relevant. Awareness of this aspect of cardiac surgery pathophysiology is increasing, but real understanding of the mechanisms involved is still sadly lacking. The article by Cremer and colleagues published in this issue attempts to develop our understanding, focusing on the hemodynamic changes and the patterns of cytokine release that are features of this syndrome.

Lung Dysfunction in Cardiac Surgery

Lung Injury and Acute Respiratory Distress Syndrome After Cardiac Surgery
Stephens RS, Shah AS, Whitman GJR. Annals Thoracic Surgery 2013, 95(3):1122-1129.

As many as 20% of patients undergoing cardiac surgery will have acute respiratory distress syndrome during the perioperative period, with a mortality as high as 80%. If patients at risk can be identified, preventative measures can be taken and may improve outcomes. Care for patients with acute respiratory distress syndrome is supportive, with low tidal volume ventilation being the mainstay of therapy. Careful fluid management, minimization of blood product transfusion, appropriate nutrition, and early physical rehabilitation may improve outcomes. In cases of refractory hypoxemia, rescue therapies such as recruitment maneuvers, high-frequency oscillatory ventilation, and extracorporeal membrane oxygenation may preserve life

Lung injury and mechanical ventilation in cardiac surgery: a review
Delgado Alves Rodrigues C, Almeida de Oliveira RAR, de Toledo Piza Soares SM; Castilho de Figueiredo L, Araújo S, Dragosavac D. Rev Bras Ter Intensiva 2010, 22(4):

Respiratory failure after cardiopulmonary bypass heart surgery can result from many pre-, intra- or postoperative respiratory system-related factors.
This review was aimed to discuss some factors related to acute lung injury observed during the postoperative period of cardiac surgery and the mechanical ventilation modalities which should be considered to prevent hypoxemia.

Lung Dysfunction Following Cardiopulmonary Bypass
Apostolakis E, Filos KS, Koletsis E, Dougenis D. Card Surg 2010;25:47-55

Background: It is well known by now that during open heart surgery many detrimental factors are involved in lung injury. The influence mainly of cardiopulmonary bypass (CPB), anesthesia, hypothermia, operation itself, as well as medication and transfusion, can cause a diffuse injury in the lungs, which most often leads to a postoperative pulmonary edema and abnormal gas exchange.

Methods: We performed an unrestricted search of Pubmed Medline and EMBASE from 1966 through 2008. Clinical, experimental, basic science, and review papers were included. Results: The hypothesis that a systemic inflammatory reaction takes place after the use of CPB, could explain most of these effects influences in the lung. On the other hand, the release of various pro-inflammatory cytokines like TNF-´ a, IL-1, IL-2, IL-6, IL-8, and endotoxin during CPB can lead to the entrapment of neutrophils in the pulmonary capillaries. Consequently, the following chain of reactions is likely to occur: an endothelial cell swelling, plasma and protein extravasation into the interstitial tissue, release of proteolytic enzymes, congestion of the alveoli with plasma, erythrocytes and inflammatory debris.

Conclusion: In this review we highlight the possible pathophysiological mechanisms implicated in the observed postoperative lung dysfunction.

Predictors and Early and Late Outcomes of Respiratory Failure in Contemporary Cardiac Surgery
Filsoufi, F, Rahmanian, PB, Castillo, JG, Chikwe J, Adams DH. Chest 2008, 133:713-721.

Background: Respiratory failure (RF) is a serious complication following heart surgery. Theprofile of patients referred for cardiac surgery has changed during the last decade, making prior investigations of RF after cardiac surgery less relevant to the current population. This study was designed to analyze the incidence, predictors of RF, and early and late outcomes following this complication in a large contemporary cardiac surgery population.

Methods: We retrospectively analyzed prospectively collected data from the New York State Department of Health database including 5,798 patients undergoing cardiac surgery between January 1998 and December 2005. Patients with RF (intubation time > 72 h) were compared to patients without RF.

Results: The incidence of RF was 9.1% (n _ 529). The highest incidence of RF was observed following combined valve/coronary artery bypass graft (14.8%) and aortic procedures (13.5%). Multivariate analysis revealed preoperative and operative predictors of RF such as renal failure (odds ratio [OR], 2.3), aortic procedures (OR, 2.6), hemodynamic instability (OR, 3.2), and intraaortic balloon pump (OR, 2.6). The mortality rate following RF was 15.5% (n _ 82), compared to 2.4% (n _ 126) in the no-RF group ($p < 0.001$). Kaplan-Meier survival curves
showed significantly poorer survival among RF patients ($p < 0.001$) compared to the no-RF group.

Conclusion: RF remains a serious and common complication following cardiac surgery, particularly in patients undergoing complex procedures. RF is associated with significant comorbidity, increased hospital mortality, and reduced long-term survival. Future research efforts should focus on a more precise identification of patients at risk and the development of new treatment modalities that would potentially prevent the occurrence of this complication.