Comparison of the frequency and intensity of the systemic inflammatory response in patients undergoing cardiac muscle revascularization surgery with and without the use of extracorporeal blood flow

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COMPARISON OF THE FREQUENCY AND INTENSITY OF THE SYSTEMIC INFLAMMATORY RESPONSE IN PATIENTS UNDERGOING CARDIAC MUSCLE REVASCULARIZATION SURGERY WITH AND WITHOUT THE USE OF EXTRACORPOREAL BLOOD FLOW

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LIST OF ABBREVIATIONs

ACCP - American College of Chest Physicians
ACT – Activated clotting time
AKI – Acute kidney injury
ATP – Adenosine triphosphate
C3a – Complement protein 3a
CABG – Coronary artery bypass graft
CAD – Coronary artery disease
CPB – Cardiopulmonary bypass
CRP – C-reactive protein
CVP – Central venous pressure
DHCA – Deep hypothermic circulatory arrest
ICU – Intensive care unit
IL-1 – Interleukin 1
IL-10 – Interleukin 10
IL-18 – Interleukin 18
IL-1ra - interleukin-1 receptor antagonist
IL-6 – Interleukin 6
IL-8 – Interleukin 8
IκB – Inhibitor of κB
MODS – Multiple organ dysfunction syndrome
MUF – Modified ultrafiltration
NF-κB – Nuclear factor kappa-light-chain-enhancer of activated B cells
NO – Nitric oxide
OPCAB – Off-pump coronary bypass grafting
PCT – Procalcitonin
PVC – Polyvinyl chloride
ROS – Reactive oxygen species
SCCM - Society of Critical Care Medicine
SIRS – Systemic inflammatory response syndrome
SVR – Systemic vascular resistance
TA – Tranexamic acid
TNF-α – Tumor necrosis factor-alpha
TNFsr 1 and 2 - TNF soluble receptors 1 and 2
TOE – Transoesophageal echocardiography
ULN – Upper limit of normal
cNOS – Constitutive NO synthase
ecNOS – Endothelial NO synthase
iNOS – Inducible NO synthase
sIL-2R – Soluble receptors of interleukin-2

1. INTRODUCTION

1.1. Factors that activate the inflammatory response to cardiac surgery

Numerous studies have shown the link between cardiac surgery and the activation of the inflammatory response following such procedure. After all, cardiac surgery, as any other type of major surgery, constitutes a major physiological stress and inducer of inflammation due to the significant surgical trauma that is natural to occur in this type of intervention. In addition to the physical injury, other perioperative and intraoperative factors such as blood loss, the need for fluid resuscitation and transfusions, and hypothermia can, directly or indirectly, potentiate the inflammatory reaction.

Furthermore, evidence suggests that cardiopulmonary bypass (CPB) activates de inflammatory response via three different mechanisms (Figure 1). The first mechanism involves exposure of the blood to foreign surfaces of the CPB circuit with resultant direct contact activation of the immune system (1). The second mechanism, due to aortic cross-clamping, involves ischemia-reperfusion injury to the brain, heart, lungs, kidneys and liver. Activation of the inflammatory response is associated with restauration of organ perfusion after release of the aortic cross-clamping (1). At last, splanchnic hypoperfusion, during and after CPB, may damage the intestinal mucosal barrier, allowing endotoxins to translocate into the bloodstream. The ensuing endotoxemia may indirectly activate the inflammatory cascade (2).

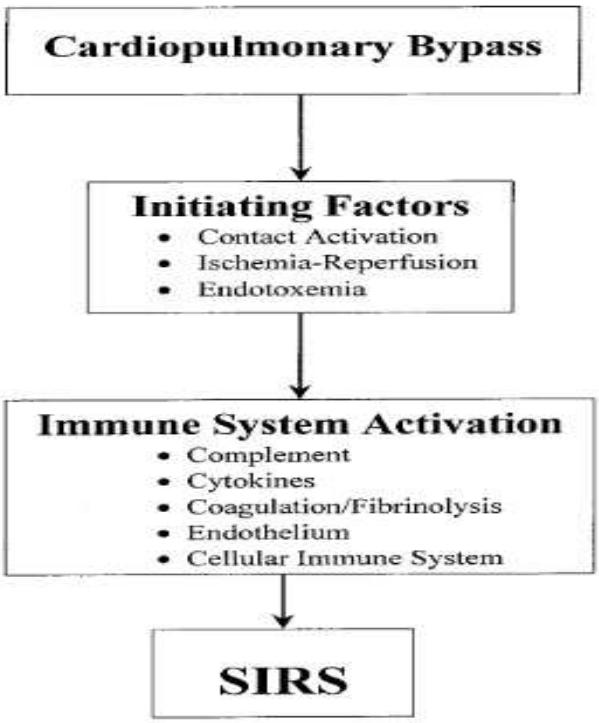

Figure 1. Schematic illustration of how CPB may trigger SIRS (6).

In addition, there are other important factors, which are related to the use of CPB, influencing the inflammatory response, namely the priming solution composition, cardioplegia, involvement of pulsatile or non-pulsatile perfusion, sort of oxygenator and pump, type of extracorporeal circuit, and the temperature throughout CPB and its length (3). Another consideration is the creation of excessive shear stress during CPB due to significant pressure changes around the circuit, which causes damage to blood components and stimulates the inflammatory response (4). Shear stress decreases the deformability of erythrocytes, and increases hemolysis. Leukocyte adhesivity is increased, and mechanical disruption can be seen at high rates of shear stress, with neutrophil degranulation and release of cytotoxic items. Excessive shear stress also increases activation of platelets and may lead to endothelial injury (4).

In short, Cardiac surgery without a doubt incites an overwhelming incendiary reaction, which has significant clinical ramifications and we must accept that the etiology of inflammatory response following cardiac surgery is possibly a combination of dysfunctional hemodynamic peribypass, global myocardial ischemia, suboptimal organ perfusion during CPB, and immune events associated with exposure to extracorporeal circulation that will be present at all times (5).

1.2. SIRS

1.2.1. Definition

The inflammatory response is a rapid, highly amplified, humoral and cellular reaction our body sustains upon tissue injury (6). This biological response, although beneficial, may prove detrimental to the body and result in more damage if prolonged.

In 1992, the American College of Chest Physicians (ACCP) and the Society of Critical Care Medicine (SCCM) introduced definitions for the hierarchical continuum of inflammatory conditions. This continuum was encompased by systemic inflammatory response syndrome (SIRS), sepsis, severe sepsis, septic shock, and multiple organ dysfunction syndrome (MODS) thereby clarifying the differences between them (7).

The idea behind stablishing these concepts lies on the fact that development of any of the forementioned inflammatory conditions has been linked, to different extends, with higher rates of complications, higher morbidity and mortality, and a poorer outcomes in general (6). For example, "sepsis" has classically been utilized to imply a clinical response to infection, and a similar response may arise in the absence of such insult. In fact, patients who appear to have sepsis but have negative microbial cultures have similar morbidity and mortality rates to the respective culture-positive populations (6). The term "systemic inflammatory response syndrome" has been proposed to describe the entry point to this continuum of inflammatory conditins; an entity that overlaps with normal postoperative physiology (8).

To define a clinical response to a nonspecific infectious or noninfectious insult, SIRS was defined as 2 or more of the following variables (7): Fever of more than 38°C (100.4°F) or less than 36°C (96.8°F), heart rate of more than 90 beats per minute, respiratory rate of more than 20 breaths per minute or arterial carbon dioxide tension ($PaCO_2$) of less than 32 mm Hg, and abnormal white blood cell count (>12,000/μL or <4,000/μL) or >10% immature (band) forms (7).

Stablishing the presence or absence of this inflammatory response is important for several reasons. Firstly, although non-specific, it is a sensitive indicator of injury. Secondly, the classification of severity of SIRS into uncomplicated SIRS, sepsis, severe sepsis, and septic shock, based on the existence of documented infection or hypotension, has prognostic significance. Thirdly, organ dysfunction is a frequent complication of SIRS. Finally, long-term survival in patients developing SIRS may also be adversely affected, a phenomenon that is well documented in the context of sepsis, with the risk of death increased for up to 5 yr after the septic episode (6).

1.2.2. Clinical Presentation

1.2.2.1. History

Despite having a fairly common physiological pathway, there are multiple triggers leading to SIRS, and patients may present in different ways. The history should be based on the main symptom, with a pertinent system review being conducted (9). Constitutional symptoms of fever, chills and night sweats should be addressed because this could help differentiate between infectious and non-infectious etiologies (9). Timing of symptoms can also direct the differential diagnosis towards an infectious, traumatic, ischemic or inflammatory cause (9).

Pain may help a physician in differential diagnosis and appropriate evaluation, particularly when it can be localized. Physicians should carefully collect information on the length, location, radiation, intensity, and aggravating factors associated with the pain to help develop a detailed differential diagnostic (9).

In patients for whom a diagnosis cannot be made on the basis of the initial history, a complete systems review is indicated in order to attempt to uncover a possible diagnosis (9).

Prescription drugs, and any other ingested substances, should be reviewed for each patient. Side effects of medication or pharmacological properties may either provoke or mask SIRS (e.g. tachycardia prevented by beta blockers). Recent changes in medications should be discussed to rule out a new side effect or interactions between drugs (9). Information about allergy should be collected and characteristics of the reaction should be obtained (9).

1.2.2.2. Physical examination

In most cases, a focused physical exam based on a patient's symptoms is adequate. In certain instances, a complete physical examination may be indicated if no obvious etiology is obtained during the history or the laboratory evaluation (9). In order to rule out an abscess or gastrointestinal bleeding, patients who can not provide any history should also undergo a complete physical examination including a rectal examination (9).

An integral component of the diagnosis is careful examination of the initial vital signs. It is necessary to reassess the vital signs periodically during the initial evaluation period, as numerous factors (e.g. stress, anxiety, exertion of walking to the exam room) can lead to a false diagnosis (9). With the exception of white blood cell count abnormalities (>12,000/μL or < 4,000/μL or >10% immature [band] forms), the criteria for SIRS is based on vital signs as follows (9):

- Fever above 38 °C (100.4 °F), or below 36 °C (96.8 °F) (9);
- Heart rate is over 90 beats per minute (9);
- Respiratory rate above 20 breaths per minute or arterial tension of carbon dioxide ($PaCO_2$) below 32 mmHg (9).

Other important poins to consider, relating to physical examination, are:

- Respiratory rate is the most sensitive marker of disease severity (9);
- Patients at the extreme of age may not have classic SIRS criteria. Consequently, a high index of clinical suspicion is often needed to diagnose a serious disease (infectious or non-infectious) (9);
- Patients receiving a beta-blocker or calcium channel blocker are frequently unable to raise their heart rate and therefore may not have tachycardia (9);
- While low blood pressure is not a requirement for SIRS, it is still an significant marker; if the blood pressure is low, it is of paramount importance to provide intravenous access and fluid resuscitation. Frank hypotension associated with SIRS is rare unless the patient is septic or severely dehydrated (hypotension may lead to the patient being admitted or transferred to the ICU) (9).

1.3. Markers and tools for detection of SIRS

1.3.1. Approach Considerations

A thorough diagnosis for systemic SIRS includes, at a minimum, a complete blood cell count (CBC) with differential to test for leukocytosis or leukopenia. The criteria for SIRS stablishes that the white blood cell count should be less than 4,000/μL or more than 12,000/μL or the presence of more than 10 percent immature (band) types on the differential (9). An increased percentage of bands is related to increased incidence of infectious causes (10).

Typically, routine tests include a basic metabolic panel as well. Laboratory testing should be individualized based on patient's history and results of physical exam, as it is discouraged to measure every possible measurable marker of inflammation, injury, and infection in all patients. Since infectious etiologies have a high mortality if not effectively treated, and because effective infection treatment also involves bacteriological identification of the offending organism, priority needs to be emphasized for bacteriological cultures in diagnostic workup (9).

Although almost anything can be measured, tests to consider include (9):

- Blood cultures;
- Urinalysis and culture (even in asymptomatic patients);
- Sputum Gram stain and culture (if respiratory symptoms);
- Cardiac enzymes;
- Amylase;
- Lipase;
- Cerebrospinal fluid analysis;
- Liver profiles;
- Lactate;
- Venous or arterial blood gases (for assessment of acid-base status) (9).

1.3.2. Imaging studies

SIRS does not have any specific diagnostic imaging. The selection of imaging studies depends on the etiology which requires admission to hospital and intensive care unit (ICU) (9).

1.3.3. Other laboratory markers

1.3.3.1. Interleukin 6

Patients that have elevated levels of interleukin 6 (IL-6; >300 pg/mL) and meet the criteria for SIRS were found to be at higher risk for complications such as pneumonia, MODS, and demise (11). Moreover, a decrease in IL-6 by the second day of antibiotic therapy has been shown to be a marker of therapy effectiveness and a positive prognostic sign in those patients with an infectious etiology for their SIRS (12).

1.3.3.2. Lactate

Levels of blood lactate are almost always assessed in patients who are critically ill. These are thought to be markers of tissue hypoxia related to anaerobic metabolism (9). Even though a reasonable assumption in patients presenting with circulatory shock and trauma, they represent the inflammatory burden in septic patients more than the level of tissue dysoxia and, therefore, do not commonly decrease in response to fluid resuscitation if elevated (9). Values are commonly raised from enhanced peripheral intraorgan production, decreased hepatic uptake and restricted renal elimination (9). Numerous studies have found a clear link between the lactate rates and mortality (9).

1.3.3.3. Procalcitonin

PCT is increasingly becoming available as a point-of-care test for physicians. The availability of this assay will currently vary according to the medical centre (9).

The use of acute-phase reactants has been evaluated by a significant amount of research to help differentiate infectious from the non-infectious causes of systemic inflammatory response syndrome (9). In this regard, several studies have identified levels of plasma PCT as valuable (13).

Arkader et al. showed in an observational, prospective study in a pediatric ICU that PCT levels could be used to distinguish between infectious and non-infectious SIRS, whereas CRP levels could not. In this study, PCT levels in all 14 patients with bacterial sepsis were increased at admission (median 9.15 ng/mL), while CRP levels were increased in only 11 of the 14 patients. Additionally, the levels of PCT subsequently decreased in most patients who progressed favorably, while CRP levels did not (14).

A review by *Selberg et al* of PCT and CRP, as well as IL-6 and protein complement 3a (C3a), showed that PCT, IL-6, and C3a were more reliable in the differentiation of SIRS from sepsis. Plasma concentrations of PCT, C3a, and IL-6 were significantly higher in septic patients up to 8 hours after clinical onset of sepsis or SIRS; median PCT was 3.0 ng/ml in SIRS patients, compared to 16.8 ng/mL in septic patients (15).

Balci et al. confirmed that PCT in challenging populations, like multiple trauma patients, is a superior predictor of early septic complications than CRP is (16). *Hohn et al.* successfully proved, at the ICU, that sepsis protocols using PCT to determine the use of antibiotics were associated with reduced antibiotic therapy duration without jeopardizing patient outcomes (17).

Caution must be exercised in interpreting the results of PCT in the elderly. *Lai et al.* has shown that PCT is useful in the prediction of bacteremia in elderly patients but is not an independent marker for local infections (18). Currently, acceptable cut-off rates for PCT at which they are relevant are also under debate (9).

1.3.3.4. Leptin

Leptin, an adipocyte-generated hormone that acts centrally on the hypothalamus to regulate body weight and energy expenditure, is an emerging marker that correlates well with serum IL-6 and TNF-α levels (9). Researchers have been able to differentiate sepsis from non-infectious SIRS with a sensitivity of 91.2% and a specificity of 85% using serum leptin levels with a cutoff of 38 μg/L (19, 20).

1.3.3.5. Special concerns

Some group of patients may present with sepsis or other complications without meeting SIRS criteria. These include patients at the extremes of age, patients with immunosuppression, and patients with diabetes (9).

Intensive assessment of pregnant patients is necessary due to the presence of two patients as well as the likelihood of uncontrolled inflammation to lead to preterm labor (9).

1.4. The Coronary artery bypass graft surgery

The most common form of heart disease is Coronary artery disease (CAD). This is the product of atheromatous changes in the supplying heart vessels. It is the main cause of deaths worldwide. A variety of clinical conditions from asymptomatic atherosclerosis and stable angina to acute coronary syndrome (unstable angina, NSTEMI, STEMI) are identified with CAD (21). When coronary artery stenosis reaches a certain degree of occlussion, the need for intervention, either medical or surgical, is indicated to prevent fatal outcome.

From his research at the Cleveland Clinic, René Favaloro is credited with developing the coronary bypass technique. Ever since its introduction in 1967, Coronary artery bypass grafting (CABG) has increased in number until the last decade, with minuscule development, probably from improved percutaneous and medical treatments (22). Despite recent trends, CABG remains one of the most frequent, effective, and well-studied medical procedures (22).

1.4.1. Technique

The concept of the coronary bypass surgery is to restablish natural perfusion to the myocardium by providing alternate routes for blood to enter the territories under attack. This strategy provides several advantages that include the use of large-caliber conduits attached at specific locations, which maximize normal blood flow to the affected region, and their extramyocardial positioning avoids the compressive forces of the heart during systole (22). The most crucial component of the operation is the installation of a bypass graft that is technically sound and well-created strategically (22).

A variety of conduits may be selected; the saphenous vein is the prototype graft and still the most frequently used. This vessel can be easily harvested with minimal morbidity, and a precisize anastomosis is technically simple to create (22). Nowadays, the implementation of minimally invasive endoscopic techniques reduce the impact of the surgery on the patient (22). The use of the saphenous vein does not come without limitations, which are essentially based on its tendency to produce rapid atherosclerotic lesions. The atherosclerotic plaque of the graft has a thinner fibrous cap and a higher predilection for distal embolism (22). At 10 years, the patentability of saphenous vein grafts is around 50 percent (22). Additionally, there may be no suitable vein conduit, either from varicous or sclerotic damage or from lack of harvest material due prior bypass procedures (22).

Another vessel that can be applied as a graft conduit is the left internal mammary artery. This can be moved from its pedicle on the left subclavian artery to create an anastomosis with the anterior or lateral epicardial vessels of the heart, most commonly to the LAD (22). There are several well-described advantages strategy related to the use of the left internal mammary artery, when compared to saphenous vein grafts, mostly related to the improved patency rate of this vessel (22). The right internal mammary artery can also serve as a bypass conduit but harvesting both internal mammary vessels increases the risk of sternal ischemia and complications of surgical wound healing (22).

The main approach to coronary bypass grafting is by a median sternotomy, in which the sternum is separated longitudinally and the heart and great vessels are exposed (22). Alternatively, a left thoracotomy may be used, especially after prior cardiac operation where sternal reentry could risk injuries to adhesed cardiac structures or patent grafts. The targets are identified on the epicardial surface, and the anastomotic reconstruction sites are determined based on information from the native vessel's preoperative cardiac catheterization and suitability (22). An arteriotomy is performed and extended for around 5 mm on the exposed

vessel (22). Conduits are built with an acceptable size of bevel or spatulation, and the anastomosis is made, usually in a running fashion with fine polypropylene sutures. Patency and hemostasis of the conduits are tested. Additionally, they are cut to the appropriate size, in order to avoid tension or kinking (22). The saphenous vein or free arterial ducts are usually connected to the ascending aorta (22). A 4-5 mm circular aortotomy is created with a punch device (22). The anastomoses are established using a polypropylene suture in running fashion (22). When the conduit length is restrictive, Y grafts off of other vein grafts or off of the pedicled internal mammary artery graft are possibilities to create the proximal anastomoses (22).

Once all the anastomoses have been completed, CPB weaning is prepared (22). The patient is warmed up to normothermia, and as this occurs the heart often experiences ventricular fibrillation, which requires cardiac defibrilation (22). Transient abnormalities in carciac electrical conduction may be experienced, requiring temporary pacing (22). Mechanical ventilation is restarted, and the patient can then be weaned gradually from the CPB system (22). Pharmacologic inotropic support may be required, but otherwise unnecessary, if preoperative preservation of ventricular function has been achieved (22). An effective dose of protamine is injected to counteract the heparin effects, and the bypass cannulae are removed (22).

After hemostasis is appropiately achieved, the chest is closed with stainless steel wires (22). Typically, the pericardium is left open as a preventive measure to ensure that there will not be constriction of the atria or kinking of the bypass grafts (22). To protect it from future injury in case of required sternal reentry, the pedicled left internal mammary artery graft is positioned posterior to the left lung's anterior surface (22).

In recent times, attempts have been made to reduce the invasive nature of coronary bypass grafting and potential CPB complications. Techniques for performing bypass grafting without CPB have been improved and promoted. The benefits of Off-pump coronary bypass grafting (OPCAB) are related to the reduction of air- and/or atheroemboli-related neurological complications, in addition to reducing blood transfusion requirements and costs (22). The treatment includes beating heart manipulation and stabilisation to reveal the epicardial targets (22). Hemodynamic instability can result, particularly for vessels on the posterior and posterolateral surfaces, while the heart is elevated and rotated. The anesthesiologist and the surgeon must be able to respond to these rapid changes and immediately relinquish off-pump attempts to institute CPB before substantial organ injury takes place (22). Even though many single-center reports have shown acceptable short-term results and mid-term graft patency rates after OPCAB procedures, randomized multicenter and observation trials have indicated that

these techniques may provide some advantages at the cost of increased incomplete revascularization and lower graft patency rates. As a result, penetrance of OPCAB has not increased significantly (22).

1.4.2. Indications

Recommended indications for CABG surgery from the American Heart Association and the American College of Cardiology are as follows (22):

Asymptomatic patients with:

- Left main or left main equivalent coronary artery disease (CAD; proximal LAD, proximal circumflex) (class I);
- Three-vessel CAD (class I);
- Proximal LAD disease and one- or two-vessel disease (class IIa, especially if the non-invasive study shows decreased LV function or extensive ischemia (22).

Symptomatic patients with:
Stable angina

- Left main or left main equivalent coronary artery disease (class I);
- Three-vessel CAD (class I);
- Proximal LAD disease and one- or two-vessel disease (class IIa, especially if the non-invasive study shows decreased LV function or extensive ischemia);
- One-or two-vessel disease not affecting proximal LAD although with high-risk noninvasive study findings (Class I);
- Disease of one vessel involving the proximal LAD (Class IIa) (22).

Unstable angina/NSTEMI

- Left main or left main equivalent coronary artery disease (class I);
- Three-vessel CAD (class I);
- Illness of one or two vessels with ongoing ischemia; vessels are not suitable for percutaneous therapy (class I);
- One-or two-vessel disease not affecting proximal LAD (class IIa) (22).

STEMI

- Continuous chest pain or hemodynamic instability with lesions unfit for percutaneous procedure (Class I);
- Surgical myocardial infarction complications, like ruptured papillary muscle or post-infarct ventricular septal defect (Class I);
- Cardiogenic shock (class I);
- Recurrent malignant arrhythmias (class I) (22).

Decreased LV function

- Left main, left main equivalent, or three-vessel CAD (class I);
- Two-vessel CAD (class I);
- Proximal LAD disease (class IIa) (22).

Failed Percutaneous intervention

- Continuous ischemia with an adequate distal target (Class I);
- Hemodynamic instability (class I) (22).

1.5. The cardiopulmonary bypass system

Breakthroughs in cardiac surgery were possible due to the development of a cardiopulmonary bypass. CPB is the system used to provide a bloodless field for heart surgery. It integrates an extracorporeal circuit aimed at providing physiological support in which venous blood is drained to a reservoir, oxygenated, and pumped back to the body. For the successful use of this system, team effort between surgeon, perfusionist and anaesthesiologist is paramount. Nevertheless, the procedure may result in complications and strategies to reduce these are part of current research (23).

1.5.1. The CPB circuit

The CPB circuits are composed by pumps, cannulae, tubes, reservoirs, oxygenators, heat exchangers and arterial line filters (Figure 2). Modern CPB devices are capable of monitoring blood pressures, temperature, oxyhemoglobin saturation, blood gases, electrolytes as well as providing safety features such as bubble detectors, oxygen sensors and low-level detection alarms (23).

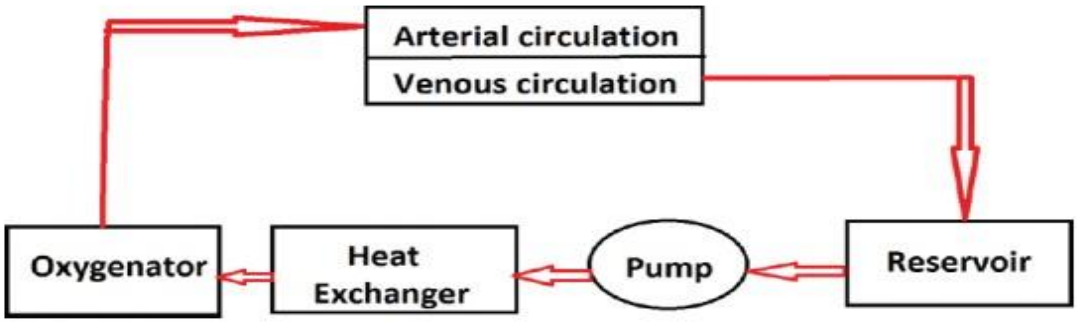

Figure 2. Major components of the CPB circuit. Venous blood travels, with the aid of gravity, into the reservoir. Subsequently, the pump moves blood, from the reservoir, to the heat exchanger and oxygenator in order to deliver warm, oxygenated blood to the arterial circulation (23).

1.5.1.1. The Pump

There are 2 main types of pumps used in CPB systems. The first type, referred to as roller pump, is formed by two rollers placed on a rotating arm that compress the tubing apparatus to produce forward blood flow. Nontheless, compression of a length of tubing may lead to hemolysis and accumulation of tubing debris, the incidence of which increases with time. The use of roller pumps for longer procedures is therefore discouraged (23).

On the other hand, the centrifugal pump consists of impellers within the housing. When rotated quickly, negative pressure is generated at one inlet and positive pressure at the other, thereby driving the blood forward (23). This second type of pump is dependent on afterload, so if there is a rise in SVR, a fall in the cardiac output will occur unless the flow through it is increased (23). In longer cases, centrifugal pumps may improve platelet preservation, renal function and neurological outcomes (24).

1.5.1.2. Cannulae

The patients are connected to the CPB circuit via cannulae. These are made of polyvinylchloride (PVC) and reinforced with wire to avoid blockage due to kinking (23).

In most open-heart surgeries, single-stage cannulae are used, where two cannulae are inserted into the inferior and superior vena cava and joined by a y-piece (23). For most closed-heart operations, dual-stage cannulae are used, where one cannula is inserted into the right atrium (23). Drainage is by gravity (23).

Alternatively, the femoral vein can be used as a site for cannulation in minimally invasive or redo surgeries, in which a long cannula is inserted up to the right atrium (23). Transoesophageal echocardiography (TOE) assists in assessing its proper positioning (23).

1.5.1.3. Oxygenator

In the age of membrane oxygenators, bubble oxygenators have only a historical significance (23).

Hollow microporous polypropylene fibers (internal diameter of 100–200 μm) are used as membrane oxygenators. As gases pass through the fiber, the blood flows outside the fiber, separating blood and gas phases (23). They are less likely to result in air embolism and are more precise in controlling blood gas (23). Newer designs have an integrated filter for the control of emboli and therefore do not need additional arterial filters (23).

The oxygenator is incorporated into, and placed next to, a heat exchanger to decrease emission of air embolism by changes in blood temperature (23).

1.5.1.4. Tubing

Its durability and acceptable rate of hemolysis makes polyvinyl chloride (PVC) the material of choice for the tubes (23). The addition of plasticisers to give flexibility to the tubes, such as di(2-ethylhexyl) phtalate, may be toxic and shows shedding from the tube (25). New plasticisers made of dioctyl adipate, which are currently under study, show less leaching (23).

1.5.1.5. Reservoir

The reservoir has the task of collecting blood suctioned from the heart (23). The most commonly type used are open reservoirs. These allow passive removal of venous air and are capable of applying vacuum to enhance drainage (23). To process drained blood, they require a different cardiotomy along with a defoaming circui (23)t. Once used, a sufficient amount of blood is maintained in the reservoir to avoid the intrusion of air into the arterial circuit (23).

Closed reservoirs, on the other hand, need a separate circuit that will allow them to process the drainage (23). Nevertheless, they posess smaller surface areas that ensure a reduction of blood contact with arteficial surfaces, at the expence of offering limited volume capacity (23). This results in less inflammatory activation, increased sterility and decreased post-operative transfusion (26).

1.5.1.6. Cardioplegia system

Cardioplegia is a strategy of myocardial protection in which the heart is perfused with a solution that causes electromechanical arrest in order to reduce the consumption of myocardial oxygen (23). This is necessary for intracardiac operations where cross-clamping of the aorta renders the myocardium ischaemic (23). In relation to the clamp, the cannula that will deliver the cardioplegic solution is placed proximally, while the aortic cannula is distally (23). The solution is delivered by a separate pump, antegradely or retrogradly, into the aortic root or the coronary sinus, respectively (23). TOE can guide the positioning of the balloon-tipped retrograde cannula within the coronary sinus (23). Retrograde cardioplegia by itself causes inadequate protection of the right ventricle (23). Ostial cardioplegia is performed when severe aortic regurgitation occurs (23).

Cardioplegia may be either crystalloid (cold) or blood-based (warm or cold), and may be administered in a continuous or intermittent manner. Frequently, the solutions are potassium-based (23). Blood cardioplegia is a combination of oxygenated blood and crystalloid (ratio 1:1 to 8:1) (23). Other substances can be added including bicarbonate, mannitol, magnesium , calcium, adenosine, procaine, glucose, and glutamate (23).

A controlled mixture of gas is delivered to the oxygenator via the gas line and blender (23). PaO_2 is determined by the FiO2 set whereas the total flow determines $PaCO_2$ on the CPB system (23). Distal to the pump, the arterial line filter is in charge of removing particulate matter more than 20–40 μm in size (23).

An attempt was made to improve biocompatibility with various materials, minimizing inflammation and thrombus formation on the surface of the circuit (23). Several studies have shown evidence of decreased inflammation and platelet activation resulting in lesser bleeding and transfusion, when covalently-bounded heparin circuits are used (27-30). New coatings include poly-2-methoxyethylacrylate, phosphorylcholine, and trillium but the clinical advantages of one form of coating over another remain contentious (31).

1.5.2. CPB procedure

1.5.2.1. Priming

The de-airing of CPB circuit is carried out through priming solutions that include a combination of crystalloids plus colloids. Priming brings haemodilution that increases flows throughout hypothermia (23). Heparin 3–4 units/ml is included in the solution (23). According to the pre-bypass haemoglobin as well as priming volume, supplement of external blood could be necessary to conserve a goal haematocrit on bypass (21%–24% in adults and 28%–30% in children) (23). The next equations are employed (23):

- Total circulating volume (TCV) = Patient's blood volume + priming volume (23)
- Target haematocrit (Hct) on CPB = Patient's blood volume (PBV) × Hct/TCV (23)
- Blood required on prime = (Target Hct × TCV) – (Pt. Hct × PBV)/Hct of donor blood (23)

Cardiac index of a 70 kg individual with average metabolic rate at 37°C is 2.2–2.4 L/m2/min. For each and every 1°C decline in temperature, the desired cardiac output lowers by 7%, and also pump flow could be lowered by an equivalent factor. Having the body surface area (BSA) from the patient, the desired pump flow is as follows (23):

- Pump flow rate = BSA × Cardiac index (23)

1.5.2.2. Initiation of CPB

Before arterial cannulation, heparin (300 U/kg IV) is administered with a target ACT (evaluated after 3 min) greater than 480 seconds. The systolic pressure should be 90–100 mmHg throughout arterial cannulation to minimize the risk of aortic dissection (23). The aortic cannulation is performed first, in the event of hypotension associated with venous cannulation, to establish fluid resuscitation (23). Upon connection of the aortic cannula to the tubing, line pressure is evaluated to exclude dissection (23). Venous clamping is slowly released after venous cannulation to create complete CPB after which the ventilation is withdrawn (23).

1.5.2.3. Anticoagulation

Clot formation on CPB has life-threatening consequences (23). To determine the appropriateness of heparinisation, Activated clotting time (ACT) is used. Normal ACT varies from 80s to 120 s (32). The haemodilution and hypothermia can also affect it. During bypass ACT must be tracked every 30–40 minutes (23).

In certain patients, distorted heparin response with inability to attain goal ACT could be seen, with response to additional doses of heparin finally accomplishing target ACT (23). Heparin resistance is an inability to meet target ACT even after large doses of heparin (800–1000 U/kg) (33). Risk factors typically involve old age, recent exposure to heparin, infusion of nitroglycerin, thrombocytosis and a deficiency of antithrombin III (34). Therapies include concentrate of antithrombin III (1000 units) or fresh frozen plasma (2–4 units) administration (35).

In patients with heparin-induced thrombocytopenia who require CPB, additional exposure to heparin is a major worry (23). Alternative medications include lepirudin, argatroban, danaparoid, and bivalirudin, all of which are without specific reversal agents (23). Bivalirudin does have the benefit of a short half-life of 24 min owing to bivalirudin-bound thrombin metabolism (36). Consequently, care must be taken to avoid stasis in the circuit as bivalirudin is metabolized in static blood unless it is circulated continuously (23).

1.5.2.4. Anesthesia and monitoring on CPB

Perfusion pressure is often used as a surrogate measure for organ perfusion and therefore should be kept between 50 and 70 mmHg (23). Patients with high blood pressure and those at risk of stroke need greater flows and perfusion pressure to ensure adequate organ perfusion (37). Cerebral oximetry, evoked potentials, and transcranial Doppler are used to determine cerebral blood flow (23). The monitoring of mixed venous oxygen saturation can offer an approximation of the equilibrium between global oxygen delivery and demand. Mixed venous oximetry of 70% or higher is preserved, but this still may not ensure adequate tissue bed perfusion (38).

To prevent an air embolism, blood levels in the reservoir should be monitored (23). A low Central Venous Pressure (CVP) is the aim, as high CVP points to inadequate venous return (23). Surveillance of aortic line pressure, blood temperature and the integrity of the oxygenator gas supply is extremely important. Glucose is kept around 120 and 180 mg/dL (39). Anaesthesia may be sustained by inhalation, or total intravenous anesthesia. Volatile anaesthetics offer preconditioning for cardioprotective effects (23). During CPB, administration of nitrous oxide is avoided to prevent an air emboli from increasing in size (23). Hypothermia helps to reduce anaesthetic needs, but drug pharmacokinetics are also modified due to haemodilution and altered metabolism resulting in varying effects (23).

1.5.2.5. Temperature management

During CPB, hypothermia is used for its supposed protective effects on the heart. With hypothermia, the viscosity of the blood decreases and enables for maintaining a greater perfusion pressure despite haemodilution (23).

Nevertheless, hypothermia results in the reversible suppression of coagulation factors and platelets (23). The data are currently inconclusive concerning the hypothermic dominance over the normothermic bypass (40). Instead of the absolute temperature, it has been shown that the rate of rewarming and cerebral hyperthermia seem to be more important in preventing cerebral injury (41-43).

Locations for monitoring core temperature entail the rectum, urinary bladder, pulmonary artery, and oesophagus (23). An estimate of the cerebral temperature can be provided by obtaining nasopharyngeal temperature (23).

1.5.2.6. Acid-base management

This is especially important in the case of hypothermic CPB and deep hypothermic circulatory arrest (DHCA) (23). With cooling, CO2 is more soluble in the blood (reducing partial pressure), which leads to alkalosis (23). In alpha-stat, the "alpha" corresponds to the histidine alpha-imidazole ring that is a major intracellular buffer. The constancy of this ring's charge state is critical when regulating pH-dependent cellular processes. Through alpha-stat, pH is not corrected and hypothermia will end up causing $PaCO_2$ to drop (23). Blood gasses estimated at 37 ° C are uncorrected (23). By preserving cerebral autoregulation, alpha-stat establishes limits on microemboli (23). The downside of alpha-state regulation is inhomogeneous cerebral cooling (23).

During hypothermia, the pH-stat keeps a constant pH and $PaCO_2$ (23). CO2 is applied to the oxygenator, which induces increased brain blood flow and cooling (23). Prolonged management of the pH-stat may result in severe acidosis, requiring a switch to conventional alpha-stat during the rewarming phase (23).

The alpha-stat is advantageous in adults with moderate hypothermia (44). In infants, brain injury is mostly linked to hypoperfusion, so pH-stat is beneficial (45, 46). If DHCA is used, a cross-over strategy with pH-stat can be used in the initial cooling phase followed by an alpha-stat switch. This optimizes cerebral cooling and prevents severe acidosis with extended pH-stat (47).

1.5.2.7. Ultrafiltration

During and after CPB, ultrafiltration eliminates inflammatory mediators and excess fluid while creating haemoconcentration (23). Conventional ultrafiltration uses a haemofilter built into the bypass circuit (23). Modified ultrafiltration (MUF) is used after the surgical repair is done and before administering protamine, with blood drained from the arterial line and returned to the venous line after moving through the haemofilter (23). It was first described in 1991 by *Naik et al.* (48). Many randomised controlled trials showed reduced blood loss and need for transfusions, particularly in paediatric patients on MUF (49-52).

1.5.2.8. Weaning

Weaning is the method of phasing out extracorporeal assistance as the heart gains control over the circulation. Many steps are necessary to complete the weaning successfully (23).

Using hypothermia requires a rewarming period (23). Cerebral injury is associated with fast rewarming and hyperthermia (23). The nasopharyngeal temperature should not surpass 37 °C, however authors accept 35.5 °C–36.5 °C temperature range (23). The gradient of temperature between the venous blood and the heater should not exceed 10 °C (23). The elevated gradient between core and peripheral temperature could result in temperature after drop (23). Utilizing vasodilators can help to homogenous reheating and raise venous capacitance during transfusion of circuit blood (23). Additional anaesthetic doses are given; acid-base balance, electrolyte levels, PaO_2, $PaCO_2$, blood sugar and haematocrit are maintained within normal ranges (23). Serum potassium level of 4.5–5 mmol/L is aimed to protect from arrhythmias (23).

De-airing of the heart is executed after open-heart surgeries (23). TOE is useful for determining the appropriateness of de-airing (23). Because of its anterior location, air embolism, often affecting the right coronary artery, may exacerbate arrhythmias, ST-elevation and myocardial dysfunction. This is treated by enhancing the perfusion pressure and preserving pulsatile perfusion whilst partially clamping the veinous line (23).

Heart rate, rhythm and contractility shall be evaluated (23). Sinus bradycardia is treated with atropine and/or beta-adrenergic agonists whereas a persistent atrioventricular block is managed with epicardial pacing (23). Aortic cross-clamp removal may be associated with ventricular fibrillation, particularly in conditions that cause left ventricular hypertrophy, such as severe aortic stenosis. Defibrillation with the biphasic energy of 5–20 J is performed using internal paddles (23). With persistent dysrhythmias it is important to add antiarrhythmic drugs such as amiodarone, lidocaine, and magnesium (53).

Weaning problems caused by systemic hypotension may be attributed to hypovolaemia, ventricular dysfunction or low SVR (23). Hypovolaemia is handled through use of controlled blood boluses from the circuit (23). Vasopressors such as phenylephrine, noradrenaline, or vasopressin are used to treat low SVR (23). The need for inotropes must be determined by a visual evaluation of the contractility and with TOE (23). Previous left ventricular dysfunction, severe pulmonary hypertension, inadequate myocardial protection and protracted cross-clamping time are factors that must be considered in determining the use of inotropes after

bypass (23). There are a variety of inotropes available but there is no evidence base for advocating one inotrope over another (23). Inodilators such as milrinone, dobutamine and levosimendan may be used for increased afterload in the setting of ventricular dysfunction (23). Levosimendan use could be associated with a decrease in mortality (54).

1.5.3. Complications

1.5.3.1. Mechanical complications

Bleeding, selective cerebral perfusion from cannula malposition, dislodgement of atherosclerotic plaque, and arterial dissection are associated with arterial cannulation (23). When a patient develops low arterial pressure, high arterial line pressure (> 300 mmHg), loss of venous return and bluish discolouration of vessels, a dissection should be suspected . TOE can be performed to diagnose it. Repair of the dissection requires DHAC (23).

Venous cannulation, as arterial cannulation, may be associated with bleeding and cannula malposition (23). An air lock may develop, causing inadequate return and leading to congestion in the cerebral and splanchnic circulations (23). Pumping from an empty reservoir can result in a massive air embolism, which is treated by pump cessation and starting retrograde cerebral perfusion (23).

Other complications include failure of the oxygenator, malfunction of the pump, circuit coagulation, rupture of the tubing, failure of the gas supply and electrical fault due to which manual cranking must be always available (23).

1.5.3.2. Systemic complications

CPB induces instability of the platelets, both qualitatively and quantitatively (23). The concentration of pro-coagulants is reduced due to haemodilution (23). It activates the inflammatory, coagulation, complement, and fibrinolytic pathways (6,23). Thromboelastography may help in understanding the cause of the disorder of bleeding (23). With prolonged bypass time, redo-surgery and pre-operative use of anticoagulants, bleeding is more prominent (23).

Studies have demonstrated diminished blood loss and transfusion requirements in patients with prophylactic anti-fibrinolytics before cardiac surgery (55,56). Effective inhibition of fibrinolysis requires a loading dose of 10 mg/kg of tranexamic acid (TA) complemented by 1 mg/kg/h or 50 mg/kg of epsilon-aminocaproic acid followed by an infusion of 25 mg/ k/h (57). TA in high doses can increase the risk of seizures by approximatelly 5% – 7% (58).

Hypotension and inflammatory response can lead to acute kidney injury (AKI). Protracted bypass time, sepsis and diabetes are risk factors. Therapy requires high perfusion pressure maintenance, the use of early biomarkers to detect AKI, and dialysis (23).

The spectrum of brain injury varies from cognitive impairment to stroke (23). The management approach includes maintaining higher perfusion pressure, appropriate HCt, and management of alpha stat (23). TOE can be used in conjunction with epiaortic ultrasound to identify calcification/atherosclerosis of the ascending aorta in order to avoid cannulation of such sites (23).

The effects of CPB can cause acute respiratory distress syndrome (23). Atelectasis, induced by anaesthesia and decreased mucociliary clearance, further contributes to acute lung injury (23). As a result, atelectasis and pleural effusions following cardiac surgery are common pulmonary complications (23). Hence, in the pre- and post-operative periods of cardiac surgery, lung protection strategies are required (23).

Vasoplegia is characterized by severe, vasopressor-resistant vasodilation owing to nitric oxide synthase activation, ATP-sensitive potassium channels in the vascular smooth muscle and a relative vasopressin deficiency (23). Treatment involves administration of fluids and vasopressors including phenylephrine, norepinephrine and vasopressin. Methylene blue (1.5 mg/kg IV) acts as a competitive nitric oxide inhibitor used as a rescue therapy (23).

Blood contact with artificial surfaces, ischaemia-reperfusion injury, endotoxemia and surgical trauma may provoke systemic inflammatory reactions after CPB, which is the main focus of this report (23). Acute phase reactions are initiated by release of complement, cytokines, endotoxin and NO leading to increased capillary permeability (23). Rewarming could exacerbate stress reactions and release of inflammatory mediators (23). The function of steroids is questionable, given the lack of adequate benefits and post-operative infection flaring (59, 60).

1.6. Specific components of the pathophysiology of SIRS to cardiac surgery

1.6.1. The Immunological response

1.6.1.1. The complement cascade

The complement system can be activated by one or more of three pathways. Firstly, the classical pathway can be initiated by direct binding of C1q, the first protein in the complement cascade, to the pathogen surface. It may also be activated by binding of C1q to antigen-antibody complexes during an adaptive immune response, and is thus a key link between the effector mechanisms of innate and adaptive immunity. Secondly, The MB-lectin pathway is initiated by binding the mannan-binding lectin, a serum protein, to mannose-containing carbohydrates on bacteria or viruses. Finally, the alternative pathway can be initiated when spontaneously activated complement component binds to the surface of a pathogen (61).

Cardiac surgery is responsible for activation of complement through various pathways, which include the direct binding of C1q and/or mannose-binding lectin, or indirectly by binding to antibodies or C-reactive protein (62-69). Complement activation during CPB is primarily via the alternative pathway (70). Activation by surface contact gives rise to direct activation of the C3 component with generation of C3a and C3b. C3b provides further activation of the complement while being covalently bound to foreign surfaces, which propagates activation through the alternative pathway (Figure 3) (71).

Direct evidence of complement activation is illustrated by the pulmonary sequestration of neutrophils and monocytes during CPB (72). Furthermore, later studies demonstrated that C3a makes it appearance in the plasma at the onset of CPB , and increases until extracorporeal support is terminated (73). Additionally, transpulmonary white-cell gradients indicated neutrophil trapping in the pulmonary circulation (73). Little is understood about the factors inducing and regulating complement excitability on artificial surfaces as opposed to research examining the interaction of complement with biological membranes. Nevertheless, biomaterials have been designed to reduce excessive activation of the complement linked to extracorporeal circulation (74, 75).

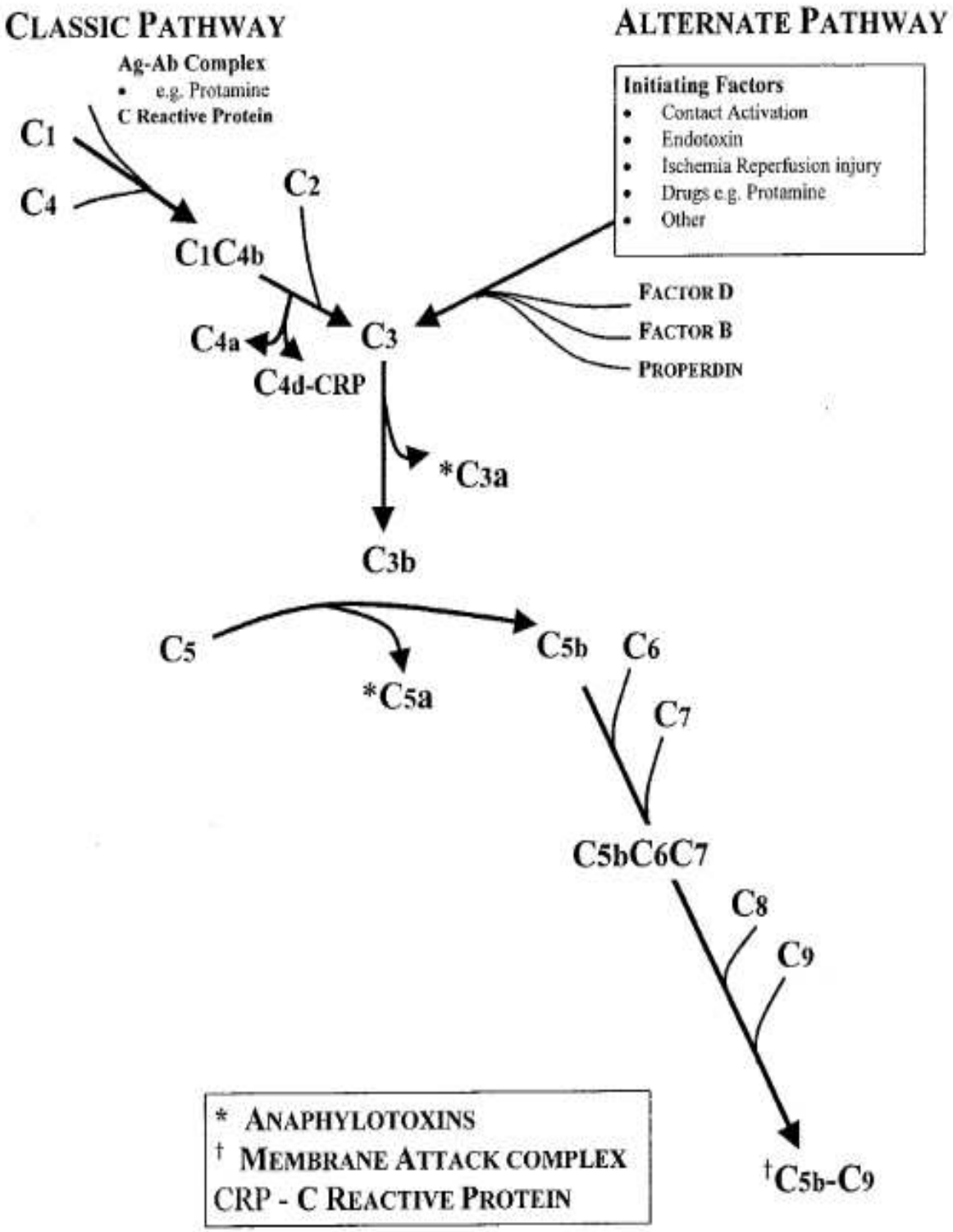

Figure 3. Factors activating complement cascade during cardiac surgery with CPB. The Classic pathway is triggered by Antigen-Antibody (Ag-Ab) complexes or CRP, while the Alternate pathway may be initiated by a series of initiating factors. Note that both pathways lead to the activation of C3 (with generation of C3a and C3b), which ultimately activates the termianl common pathway (with generation of C5a and Membrane attack complex) (6).

Complement activation during cardiac surgery may also develop via non-CPB mediated mechanisms (76, 77). For example, plasmin, produced as part of contact activation initiated by tissue injury, has been implicated in complement activation via direction activation of C3 (78). Further complement activation following CPB is mediated by the administration of protamine for reversal of heparinization (70). When heparin-protamine complexes are formed, the complement classic pathway is triggered (79, 80). A second postponed rise in complement products activation is observed within the first 5 days after cardiac surgery. This delayed complement activation seems to be induced by C reactive protein in response to heparin-protamine complexes (81). Additionally, protamine administration leads to the inhibition of plasma carboxypeptidase N, resulting in more inflammation from greater anaphylatoxin and kinin concentration (82, 83).

CPB-induced complement stimulation leads to a substantial reduction of serum complement levels (71). Depletion of the complement components results in a reduction in the effectiveness of opsonization with subsequent disability to eliminate foreign substances (71). Lower values of serum bactericidal activity are shown after bypass compared to baseline, which are attributable to complement depletion (71). Also, the function of neutrophils is impaired by widespread complement activation. Inactivation of C3a is linked with neutrophil expression of C3b receptors (71). Expression of this receptor leads to neutrophil aggregation, rendering them ineffective for phagocytosis. At the same time, expression of the C3i receptor stimulates degranulation of neutrophils, increasing proteolytic activity in the serum (71). Both, sequestration of neutrophil aggregates within the lung and degranulation within the pulmonary circulation, cause post-CPB pulmonary damage (71).

The complement's crucial role in the inflammatory process to heart surgery was proved by the effects of complement-specific inhibitors. Soluble human complement receptor type 1 dampens lung and myocardial injury (84), while blocking C3a formation inhibits neutrophil, monocyte and platelet activation in CPB models (85). Anti-C5a monoclonal antibodies ameliorate pulmonary, myocardial, mesenteric and microvascular dysfunction as a result of CPB (86-88). Specific blockage of the complement alternative pathway by monoclonal antibodies to properdin leads to almost complete suppression of the emergence of C3a and C5b-9 and greatly reduces thrombocyte and polymorphonuclear leukocyte activation (89). Up-regulation of adhesion molecules required for neutrophils to bind to the CPB circuit and vascular endothelium, a necessary step in the injury process, is prevented by recombinant soluble complement receptor 1, C3-binding cyclic synthetic peptide, and

antihuman C5 monoclonal antibody (90-92). Elevated serum levels of C5b-9, a terminal complex of C5 to C9 complement proteins, are also reported while on CPB. In a simulated extracorporeal circulation model, selective inhibition of the formation of C5b-9 by antihuman monoclonal antibody against C8 prevents platelet activation but not leukocyte activation (93).

The extent of complement activation in patients receiving CPB has clinical relevance. Throughout cardiac surgery, the amplitude of the complement activation tends to be associated with postoperative pulmonary shunting generated by protamine-heparin complexes activation of the classic complement pathway (94). Additionally, after CABG, the C4d-C-reactive protein, a marker for C-reactive protein-mediated complement activation, coincides with postoperative arrhythmias (80, 81). Concentrations of postoperative C3a may predict the likelihood of pulmonary, cardiac, renal, and hemostatic malfunction and the chances of developing MODS in children (76, 95). Techniques that strengthen biocompatibility with the CPB circuit decrease complement activation indices and may reduce postoperative morbidity, especially in high-risk individuals (29). Anti-C5a antibody that minimizes the formation of sC5b-9, lessens myocardial injury, blood loss and cognitive postoperative deficits, substantially, in people exposed to CPB (96).

1.6.1.2. The cytokine cascade

Cytokines are secretory products of various cells that exert effect mainly on the cells around them (71). They are soluble proteins and polypeptides that act as the immune system's paracrine emissaries and are generated by activated monocytes, tissue macrophages, lymphocytes, and endothelial cells (6). Specific cytokines will either exhibit proinflammatory or anti-inflammatory actions (6). Cytokines are usually subject to tight homeostatic regulation and are developed in response to a variety of physiological and pathological stimuli in order to maintain immunological and physiological homeostasis (6).

Proinflammatory cytokines hold an important responsibility in boosting the inflammatory reaction and predicting outcomes, with serum levels of particular cytokines like interleukin-1(IL1) and interleukin-6 (IL-6), in some subgroups of critically ill individuals (97). The term Interleukin has its roots on the fact that this group of cytokines represent the means for communication between leukocytes (6). Cardiac surgery, especially on-pump procedure, induces SIRS with significant cytokine releases (6).

IL-1 is a critical mediator of CPB-related inflammatory reaction, which generates a wide array of clinical and biological effects (71). Maximal IL-1 generation occurs at the same time as increases in body temperature, 24 hours after high CPB levels (71). Twenty hours after the peak in IL-1 production there is a peak in complement activation, recognized by liberation of C3a as well as C5a. Complement polypeptides, together with endotoxins if present, induce monocytes to produce IL-1. IL-1 then acts as a direct modulator of the host inflammatory response by leading to the development of fever, synthesis of acute phase reactants, release of immunoregulatory cytokines and growth factors, endothelial function changes, decreased vascular resistance and increased capillary permeability (71). IL-1 can also stimulate vascular endothelium to produce nitric oxide (endothelium-derived relaxing factor), which can account for the clinically reported CPB vasodilation (71).

Another important modulator of the inflammatory response and antigenic reaction is IL-6. Its participation in the inflammatory processes is illustrated by a study that measured serial changes in serum IL-6 levels in patients undergoing heart transplant, which also compared tissue IL-6 concentration from atrial samples of both donor and recipients (71). Plasma IL-6 concentration remained stable prior to CPB. At the onset of CPB, levels of IL-6 initially experienced a reduction, which by the end of the procedure, in contrast, raised fourfold over control values. Plasma IL-6 remained elevated after CPB for at least 1 hour and returned to control values 24 hours after the operation. These findings indicate that a substantial increase in IL-6 was caused by CPB and/or perfusion of the transplanted heart (71).

Other proinflammatory mediators including IL-8 and tumor necrosis factor alpha (TNF-α) reache maximum values 2-4 hours following CPB and fall to near-normal levels within 24 hours (98). TNF-α and IL-1 are raised early, while IL-6 and IL-8 peak later following cardiac surgery (6).

Although a clear relationship has not been demonstrated, there is a link between poor outcomes postoperatively and the burden of proinflammatory cytokines (99). Patients developing SIRS after heart surgery have shown substantial increases in the concentration of cytokines compared to patients with an uncomplicated course (100). In the subgroup of patients developing SIRS, non-survivors had significantly elevated levels of IL-8 and IL-18 in contrast to survivors (100). Moreover, plasma levels of IL-6 are correlated with mortality in pediatric patients after heart surgery (101).

The proinflammatory cytokine response to cardiac surgery is compensated by an anti-inflammatory cytokine response, with anti-inflammatory cytokines, cytokine receptor antagonists, and soluble cytokine receptors, also generated in large amounts. Main anti-inflammatory cytokines feature interleukin-10 (IL-10), interleukin-1 receptor antagonist (IL-1ra), TNF soluble receptors 1 and 2 (TNFsr 1 and 2), and transforming growth factor (TGF) (6). IL-10 is a powerful inhibitor of TNF-α, IL-1, IL-6 and IL-8 production (6). For example, IL-10 cardioprotects by suppressing neutrophil-endothelial interactions (Figure 4) (102). IL-10 is capable of reducing mortality rates and clinical development of acute lung injury (103). Likewise, IL-10 can inhibit the proliferation of vascular smooth muscle, constituting an endogenous source of protection that is potentially relevant in patients following CABG (104).

Figure 4. Schematic representation of the 3-staged process of neutrophil-endothelium interaction. Each neutrophil represents a major event (from left to right). Firstly, the flowing neutrophil enter the "rolling" state, in which it slows down along the endothelium. Secondly, neutrophils and endothelium express integrins that allow for tighter adherense to the the capillary wall. Finally, after tight binding to the endothelium, the neutrophil migrates from the circulation into tissues, resulting in activation and degranulation with further endothelial injury.

Whereas the precise function of other anti-inflammatory intermediaries continues to remain unclear, the clinical prognosis after CPB could rely on the equilibrium among proinflammatory and anti-inflammatory cytokines (6).

1.6.1.3. The cellular immune response

The cellular immune system is central to the post cardiac surgery inflammatory response (6). Following CPB there is enhanced spontaneous stimulation of both granulocytes and macrophages (6). Furthermore, exposure of patients' plasma to the CPB results in hyperstimulation of naive monocytes and granulocytes (6).

Macrophages are essential components of the innate immune system as they are responsible for the absorption of opsonized material as well as for aiding with the guidance of cell-mediated immune processes. Also, by presenting antigens to T lymphocytes with their major histocompatibility complex class II molecules, and by releasing IL-1, macrophages activate T lymphocytes and stimulate the adaptive immunity (71). CPB stimulates monocytes and macrophages through enhanced development of monocyte chemoattractant, cytokine production and macrophage adhesion molecule expression (105, 106). Limited amount of studies have evaluated the effects of CPB on macrophage function, but a decrease in the ability to clear bacteria has been noted (71). The antigen-presenting function which would impair the activation of cell-mediated immunity is presumably also altered (71).

Neutrophil function includes several synchronized cellular processes, namely chemotaxis, phagocytosis, and intracellular digestion. CPB impairs these normal immunologic functions of neutrophils (71). Chemotaxis, largely directed by C3a and C5a, is depressed postoperatively for 7 days after CPB, with longer procedures producing greater antichemotactic effects (71). During CPB, C5a attenuates cell chemotaxis by eliminating C5a signaling responsiveness, a product of C5a neutrophil receptors internalization (71). The neutrophil–endothelial adhesion process is an important element of the inflammatory process which results in generalized endothelial injury. It is now well understood and known to entail different stages of primary and secondary adhesion, which has been proven by elevated concentrations of leukocyte adhesion molecules (i.e. selectins and integrins) after CPB (107, 108).

Additionally, reticuloendothelial Kupffer cells show significantly elevated phagosomes following CPB that can provoke a relatively "overuse" type of phagocytic activity impairment (109, 110). For example, experiments have shown a reduction in white-cell phagocytic activity after CPB reflected by defective clearance of parenterally administered bacteria (71). Non-specific release of digestive enzymes (N-acetyl-iS-glucosaminidase, is-glucuronidase, lactoferrin, neutrophil elastase, and myeloperoxidase) and oxidative end products, secondary to the inflammatory response triggered by CPB, reduces intracellular digestion of the ingested microbes (71). The premature release of antimicrobial enzymes and oxygen-free radicals not only reduces the efficacy of antimicrobials but also causes tissue damage by these mediators of tissue injury (71).

In summary, several findings highlight the clinical importance of leukocytes in the inflammatory response to CPB (6). Sequestration of pulmonary neutrophils has been reported following CPB and is consistent with evidence of serious histological lung damage (6). Neutrophil suppression of CD11/ CD18 expression or activity increases myocardial function after heart surgery (6). Blocking adherence of neutrophils lessens lung injury following CPB (6). Ultimately, techniques that reduce circulating leukocytes may mitigate injury to the organs and can enhance patient outcome after CPB (6).

1.6.2. Nitric oxide

Nitric oxide (NO) is a ubiquitous biologic mediator that acts as a physiologic regulator and can be responsible for tissue damage. NO is a diffusible short-lived molecule of arginine metabolism with important physiologic regulatory functions including endothelial-mediated vasodilation in both the systemic and pulmonary circulations, potentially significant immunomodulatory functions, as well as protean roles in nociception, memory, and erectile function (6, 111). After CPB, The restored blood flow reintroduces metabolites and oxygen to the cell inducing the release of reactive oxygen species (ROS) in the myocardium, which has the potential to damage cellular proteins, DNA and the plasma membrane, creating a substrate for the cardiac dysfunction (112). ROS lead also to reduce NO bioavailability (6).

Nevertheless, NO's role in the inflammatory process is complex and it has many possible negative outcomes (6). Cytokine-induced myocardial function impairments appear to be associated with increases in inducible NO synthase (iNOS), which is up-regulated by CPB. Consequently, Early detection of up-regulation of myocardial iNOS could well lessen hemodynamic instability after CPB, whereas inactivation of NOS may correct refractory hypotension in shock (6). NO is a highly reactive, strong oxidant that combines with a wide range of in vivo particles. Although the free radical scavenging function of NO is typically protective, NO might still merge with superoxide radicals to form peroxynitrite, a more reactive and harmful free radical (6). At last, NO is a strong cellular toxin potentially predisposing to cell death by directly disabling the enzymatic workforce of glycolysis, the citric acid cycle, and the electron transport chain, with a resultant reduction in the concentrations of intracellular adenosine triphosphate (ATP) and antioxidants (6).

The timing, source, and quantity of NO generated are key to explaining these seemingly contradictory actions. NO is naturally generated in minute amounts by cNOS isozymes, including the vascular endothelial isoform (ecNOS). EcNOS plays an important part in the physiological regulation of basal vascular tone, capillary integrity of the blood flow, and endothelial adhesion of leukocytes and platelets (6). In the early phases of the inflammatory reaction, ecNOS function tends to be impaired, enabling for both unchallenged vasoconstriction and enhanced white lood cell and platelet adhesion to the vascular endothelium. Within 4-8 h, nonetheless, NO starts being produced at much greater amounts as iNOS is generated in a large array of tissues, such as vascular smooth muscle, hepatocytes, and cells of Kupffer (6). Cytokines, especially the IL-1 beta, play a major role in the NO-induced inflammatory dilation process (6). Once fully developed, the proinflammatory response shows a considerable output of NO (6). Even though this has been disputed, exhaled NO after the onset of CPB could actuality represent an indicator of the magnitude of the inflammatory response (6).

1.6.3. The Coagulation-fibrinolytic cascades

Coagulation–fibrinolytic cascades and the inflammatory response, though distinct mechanisms are closely intertwined in many ways, with coagulation activation being a key component of the acute inflammatory response and conversely. In this sense, inflammation and coagulation may be viewed as different aspects of the bodys response to injury (6).

A balance of procoagulant and anticoagulant influences, which usually coexist in a dynamic equilibrium, modulates hemostasis (6). Traditionally, the coagulation system has been separated into intrinsic and extrinsic pathways, both leading to the final common pathway, resulting in the formation of an insoluble fibrin clot via thrombin generation. This cascade consists of dormant circulating coagulation factors, which are consecutively triggered by enzymatic cleavage, creating an active serine protease that catalyzes the hydrolysis of the next component in the cascade (6). Thrombin, the end product, stimulates the creation of fibrinogen-insoluble fibrin that forms the strands that connect the platelet plug (6). Typically, this mechanism is regulated and restricted to injury sites by modulators, namely plasminogen activators, thrombomodulin, C and S proteins, and serine protease inhibitors like antithrombin III (6). Stimulated during coagulation, the fibrinolytic cascade allows the synthesis of plasmin, which separates fibrinogen and fibrin, remodeling the created clot and eventually clearing the thrombus as the endothelium recovers (6).

Coagulation activation following CPB was thought to be primarily produced by the activated intrinsic pathway through the contact mechanism. Plasma factor XII appeared essential to the process in this model, being consumed and activated upon interaction with the CPB circuit (6). That being said, patients with congenital factor XII deficiency still develop thrombin after CPB. This indicates that perhaps the extrinsic pathway could also be implicated, which requires tissue factor expression and activation, maybe in response to inflammatory stimuli and oxidative or shear stress (6).

Several relevant points concerning the dynamic interconnection among coagulation and inflammation, in the scope of CPB, deserve consideration. Endothelium is active in both processes (6). Proinflammatory cytokines carry a major role in launching coagulation, locally at inflammatory sites, by endothelial activation, by inducing tissue factor expression, by stimulating the expression of leukocyte adhesion molecules on intravascular cell surfaces, and by promoting the release of platelet-activating factors (6). At the same time, the coagulation system is influencing the inflammatory response (6). Activation of platelets in tissue damage sites results in the generation of various intermediaries that modify the integrity of the

tissue (6). Some proteins in coagulation, including thrombin and factor Xa, have proinflammatory effects (6). Thrombin, created after the coagulation cascade is activated, induces many other cell chemotaxins and mitogens that are accountable for the expansion of lesion and tissue repair (6).

Heparin and protamine, which are utilized in most patients undergoing cardiac surgery to regulate coagulation, seem to have important immunomodulatory properties (6). Heparin happens to have significant anti-inflammatory properties (6). Heparin-protamine neutralization can lead to multiple cardiovascular effects, such as elevated pulmonary artery pressure and reduced systolic and diastolic blood pressure, systemic vascular resistance, heart rate, cardiac output, and myocardial oxygen consumption (6). While protamine has adverse effects on its own, the complex of heparin-protamine is especially detrimental. This association stimulates the inflammatory reaction by many pathways, through activation of complement, release of histamine, synthesis of thromboxane and nitric oxide, and formation of antibody (6). Thromboxane release can cause serious pulmonary hypertension (6). In a subgroup of patients, the heparin-protamine relationship may lead to serious anaphylactoid reactions (6).

The equilibrium of procoagulants and anticoagulants forces is deeply impaired in CPB patients. Stimulation of procoagulants, like thrombin, requires treatment with anticoagulant medications before CPB to avoid formation of blood clots immediately after contact with the extracorporeal system (6). Additionally, fibrinolysis activation while on CPB likely contributes to the coagulopathy usually seen in these patients postoperatively (6). Rampant vascular injury following CPB may lead to uncontrolled platelet activation, thrombin production, and disseminated intravascular coagulation (6). The resultant widespread accumulation of fibrin in the microvasculature may occlude the blood flow in the microvascular circulation and inflict damage to the end organs, potentially progressing to MODS and death (6).

1.6.4. The Endothelium

As was once assumed, the vascular endothelium is a complex participant in cellular and organ activity instead of a static barrier, which is closely engaged in a number of physiological and pathological processes, and has evolved as the core subject of several of the biochemical activities that influence the heart surgical patient's perioperative course. The endothelium helps to control vascular tone and permeability, coagulation and thrombosis, and directs the passage of leukocytes, through the expression of surface proteins and the secretion of soluble mediators, into areas of inflammation (6).

The inflammatory response to CPB is marked by a generalized activation and dysfunction of the vascular endothelium. Inflammatory mediators, as for TNF-α and IL-1β, attach to the endothelium via different receptors, activating various signaling pathways, which then stimulate a particular number of genes within the endothelial cell nucleus, called activation genes (6). The transcription factor NF-κB plays a crucial role in the process of signal transduction. When stimulated, it separates from the cytosolic inhibitory protein IκB, migrates to the endothelial cell nucleus, attaches to specific DNA sequences, and affects the basal transcriptional apparatus conformation resulting in activation gene transcription (6). This steps results in the translation of proteins, which include adhesion molecules (e.g., E-selectin, intercellularadhesion molecule-1) and cytokines (e.g., IL-8), needed for endothelial activation, a process that takes around 4 h and peaks at 8–24 h depending on the gene (6).

Activated endothelial cells assume a critical function in integrating the processes of inflammation and coagulation by producing proteins that are essential to activate these systems (6). The expression of endothelial cell adhesion molecule mediates the communication between the neutrophil and the endothelium, culminating in adhesion, activation, and degranulation of neutrophils. This therefore harms the endothelium, causing diffuse capillary leaks and edema (6). Tissue factor expression results from injury to the vascular endothelium, further boosted by IL-1β and TNF-α, which stimulates the extrinsic pathway of coagulation and may result in disseminated intravascular coagulation (6). Furthermore, in inflammatory conditions, protein C, a main inhibitory regulator of hemostasis, is antagonized, most likely by TNF-α, further tipping the balance towards a prothrombotic state (6).

Vascular endothelium, as well, plays a key role in the origin of microcirculatory derangement after CPB (6). Endothelial control of the local vascular tone is regulated by a range of relaxing and contracting factors derived from endothelium, including NO, prostacycline, hyperpolarizing factor derived from endothelium, endothelin and thromboxane A2 (6). This is evident by the rise in pulmonary vascular resistance accompanying CPB due to a decrease in NO release from defective pulmonary vasculature, a phenomenon that is reversed by NO administration (6).

Compromised endothelial activity, together with inflammation and atherosclerosis, is involved in the pathogenesis of unfavorable cardiovascular events (6). Of particular concern, the inflammatory response to cardiac surgery could increase the likelihood of a heart event after corrective operation (6). Proinflammatory cytokines and endotoxin might impair dilatation dependent on endothelium, and the endothelium could end up losing its capabilities to react to circulating hormones or autacoids (6). Studies on vasoregulation of the forearm show that IL-1beta, TNF-α, and endotoxin cause long term but reversible dysfunction of vascular endothelium relaxation, named "endothelial stunning" (6). Likewise, proinflammatory cytokines hinder the synthesis of NO and antiplatelet prostanoid vasodilator (6). Absence of NO's vasodilatory and anticoagulant influence can modify myocardial perfusion and risk exposing pre-existing atheroma to unopposed vasospastic and prothrombotic effects (6). This can clarify the link of an acute inflammatory incident with a temporary rise in cardiovascular events (6).

Furthermore, endothelial impairment may restrict the long-term success of cardiac surgery , especially CABG, by assisting in the development of narrowing at anastomotic graft sites as a consequence of medial hyperplasia and by augmenting atherosclerosis development (6). Anomalies of endothelium-dependent vasodilation, including paradoxical vasoconstrictor reactions to exercise, are often noted in early stages of CAD (6). Long-term clinical follow-up studies indicate that this would be related to a higher risk of cardiovascular incidents (6). Endothelial malfunction stimulates inflammation, attracting leukocytes and platelets into the vessel walls that might cause atherosclerotic plaque formation (6). This process is markedly potentiated by hypercholesterolemia, and especially prevalent at locations of disrupted blood circulation such as graft anastomoses (6). Vascular endothelium dysfunction in patients with hypercholesterolemia is largely due to decreased NO bioavailability (6). In this respect, statins, which lower cholesterol, were shown to reestablish endothelial function swiftly, through direct up-regulation of ecNOS (6). This endothelial function restoration leads to enhanced myocardial perfusion, lessened myocardial ischemia and atherosclerosis reversal (6).

2. OBJECTIVES

2.1. Aim

The aim of this study was to investigate and compare the degree of systemic inflammatory response in patients undergoing CABG surgery with and without the use of cardiopulmonary bypass, while the additional goal was to investigate the association between inflammatory indicators of SIRS and postoperative hospitalization length, morbidity, and mortality after cardiac surgery.

2.2. Hypothesis

1. The main hypothesis is that CABG surgery without cardiopulmonary bypass is associated with smaller systemic inflammatory response than CABG surgery with cardiopulmonary bypass.
2. The additional hypothesis is that patients with lower inflammatory indicators after cardiac surgery will have shorter hospital stay, lower morbidity, and lower mortality.

3. SUBJECTS AND METHODS

3.1 Study design

This cohort study (Prospective Observational Study) was conducted at the University of Split School of Medicine and the Department of Anesthesiology and Intensive Medicine at the University Hospital of Split, over a period from March to July 2020. The study protocol was approved by the Ethics Committee of the University of Split School of Medicine and the Ethics Committee of the University Hospital of Split. All participants provided written informed consent and all procedures were carried in accordance with the Declaration of Helsinki.

3.2 Subjects

This study recruited 30 patients with Coronary Artery Disease, scheduled for elective CABG surgery, evaluated at the department of Anesthesiology and Intensive Medicine, University Hospital of Split. We included only coronary patients who underwent cardiac muscle revascularization surgery with or without the use of extracorporeal blood flow. Patients with mixed pathology who also required operation on valves, in addition to CABG surgery, were excluded from the study. Patients were divided into two groups; the first patient group was operated without the use of CPB, while the second patient group was operated with the use of CPB. Allocation of the patients into each group was based on the judgement of the surgical team. All patients were assesed and recorded for comorbidities common to most cardiac patients (e.g. hypertension, hypelipedimia and Diabetes mellitus) and reeived standard medication for their conditians (e.g. Angiotensin-converting-enzyme inhibitors for arterial hypertension; statins for hyperlipidemia). All patients received the same anesthetics (i.e. Midazolam, Fentanyl, and Sevofluran) and perioperative antibiotic treatment (i.e. Cefazolin 2g i.v.). The duration of surgery was monitored for all subjects.

3.3 Assessment of SIRS

Upon surgery, patients were observed for signs of SIRS. Inclusion criteria for SIRS are two or more of the following: temperature >38 °C or <36 °C, heart rate >90 beats/min, respiratoryrate >20 breaths/min or $PaCO_2$ <32 mmHg, white blood cell count >12,000 cells/mm3 or <4,000 cells/mm3. Frequency of SIRS in the two groups of patients, length of hospital stay, morbidity amd mortality rates were analyzed. Measurement of this criteria were repeated at the end of surgery and, at the cardiac ICU, on postoperativedays 1, 2, 3, and 5.

3.4. Sample collection and laboratory analysis

Blood was collected from all patients on the day of admission to the department of cardiac surgery by venipuncture. Moreover, in addition to continous monitoring of the clinical parameters (including SIRS criteria), all patients had blood collected at the end of surgery and on days 1, 2, 3, and 5 postoperatevely, either by venipuncture or from a central venous catheter. Samples were sent to the central laboratory facility of the University Hospital of Split for analysis of leukocyte counts, C-reactive protein (CRP) levels, and procalcitonin (PCT) levels.

3.5. Assesment of secondary outcomes

In addition to recordings of SIRS frequency and levels of inflammatory parameters, both study groups were analysed for lengths of hospital stay, morbidity and mortality rates after surgery.

3.6. Statistical analysis

Statistical software MedCalc (Ostend, Belgium; version 11.5.1.0) for Windows was used for statistical data analysis. Normality of data distribution has been assessed by Kolmogorov-Smirnov test. Data were presented as means ± standard deviation for continuous variables and as whole numbers and percentage for categorical variables. Student t-test or Mann-Whitney U test were used for analysis of continuous data. Chi-square test has been used for comparison of categorical variables. The statistical significance was defined as $P<0.05$.

3.7. Compliance with ethical standards

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institution and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Authors declared that the research was conducted according to the principles of the World Medical Association Declaration of Helsinki “Ethical Principles for Medical Research Involving Human Subjects”. Patients were informed in detail and informed consent was obtained from the parents or legal guardians of the patients to use the data. The study protocol was approved by the Ethics Review Board of University Hospital of Split.

4. RESULTS

Among the eligible patients, 30 patients provided written informed consent and were enrolled in the study. Demographic characteristics, surgical characteristics, diagnoses and comorbidities of subjects included in the study are presented in Table 1. Except for the diagnoses of *St post IM* , which was almost statistically significant ($P = 0.085$), and *St post PCI cum impl. stentis* that was significantly different (OPCAB: 27.8% vs. CABG: 0%, $P=0.049$), there was no difference amongst the forementioned variables between the group undegoing CABG surgery with CPB and the group who was not exposed to CPB.

Table 1. Demographic characteristics, surgical characteristic, diagnoses and comorbidities of patients.

Demographic characteristics	**Total (N=30)**	**OPCAB (N=18)**	**CABG (N=12)**	***P****
Age, mean (SD), yr	66.6 ± 7.8	65.2 ± 8.9	68.7 ± 5.9	0.242
Male sex (%)	27 (90)	16 (88.9)	11 (91.7)	0.805
Surgical characteristics				
1 graft received	7 (23.3)	6 (33.3)	1 (8.3)	0.119
2 grafts received	15 (50)	8 (44.4)	7 (22.2)	0.221
3 grafts received	8 (26.7)	4 (22.2)	4 (33.3)	0.508
Patient diagnosis				
CAD (%)	30 (100)	18 (100)	12 (100)	
AIM (%)	2 (6.7)	1 (5.6)	1 (8.3)	0.775
AIM reg. Ant (%)	1 (3.3)	1 (5.6)	0 (0)	0.412
AIM subendocardialis (%)	5 (16.7)	4 (22.2)	1 (8.3)	0.325
Angina pectoris (%)	1 (3.3)	0 (0)	1 (8.3)	0.222
Atherosclerosis ext inf bill (%)	1 (3.3)	0 (0)	1 (8.3)	0.222
Atrial fibrillation (%)	2 (6.7)	2 (11.1)	0 (0)	0.240
Congestive heart failure (%)	1 (3.3)	1 (5.6)	0 (0)	0.412
Heart Failure (%)	1 (3.3)	1 (5.6)	0 (0)	0.412
Ischemic Cardiomyopathy (%)	12 (40)	7 (38.9)	5 (41.7)	0.880
Left main Coronary aa stenosis (%)	2 (6.7)	1 (5.6)	1 (8.3)	0.775
Pulmonary edema (%)	1 (3.3)	1 (5.6)	0 (0)	0.412
Pulmonary hypertension (%)	2 (6.7)	1 (5.6)	1 (8.3)	0.775
Sick sinus syndrome (%)	1 (3.3)	0 (0)	1 (8.3)	0.222
St post AIM (%)	2 (6.7)	1 (5.6)	1 (8.3)	0.775
St post CPR (%)	1 (3.3)	1 (5.6)	0 (0)	0.412
St post IM (%)	4 (13.3)	4 (22.2)	0 (0)	0.085
St post NSTEMI (%)	3 (10)	2 (11.1)	1 (8.3)	0.805
St post PCI cum impl. stentis(%)	5 (16.7)	5 (27.8)	0 (0)	0.049
St post STEMI (%)	1 (3.3)	1 (5.6)	0 (0)	0.412
Stenosis ACI bill (%)	1 (3.3)	1 (5.6)	0 (0)	0.412
Third degree AV Block (%)	1 (3.3)	1 (5.6)	0 (0)	0.412
Unstable angina (%)	7 (23.3)	3 (16.7)	4 (33.3)	0.301

Patient comorbidities *(Table 1 continued)*

Arterial hypertension (%)	24 (80)	13 (72.2)	11 (91.7)	0.198
Asthma (%)	1 (3.3)	0 (0)	1 (8.3)	0.222
Chronic Gastritis (%)	1 (3.3)	1 (5.6)	0 (0)	0.412
Chronic Pancreatitis (%)	1 (3.3)	0 (0)	1 (8.3)	0.222
Chronic Thyroiditis (%)	1 (3.3)	1 (5.6)	0 (0)	0.412
Chronic renal insufficiency (%)	4 (13.3)	3 (16.7)	1 (8.3)	0.515
Depression (%)	1 (3.3)	1 (5.6)	0 (0)	0.412
Diabetes Mellitus I (%)	3 (10)	2 (11.1)	1 (8.3)	0.805
Diabetes Mellitus II (%)	12 (40)	8 (44.4)	4 (33.3)	0.550
End-stage renal disease (%)	2 (6.7)	2 (11.1)	0 (0)	0.240
Glucose intolerance (%)	1 (3.3)	1 (5.6)	0 (0)	0.412
Hypercholesterolemia (%)	2 (6.7)	1 (5.6)	1 (8.3)	0.775
Hyperlipoproteinemia (%)	12 (40)	7 (38.9)	5 (41.7)	0.880
Hyperuricosuria (%)	2 (6.7)	2 (11.1)	0 (0)	0.240
Hypothyroidism (%)	2 (6.7)	1 (5.6)	1 (8.3)	0.775
Ischemic neuropathy of the optic nerve (%)	1 (3.3)	1 (5.6)	0 (0)	0.412
Nicotinism (%)	1 (3.3)	0 (0)	1 (8.3)	0.222
Prostatic hyperplasia (%)	2 (6.7)	2 (11.1)	0 (0)	
Psoriasis (%)	1 (3.3)	1 (5.6)	0 (0)	0.412
Psychoorganic syndrome (%)	1 (3.3)	1 (5.6)	0 (0)	0.412
Right femoral artery stenosis (%)	1 (3.3)	0 (0)	1 (8.3)	0.222
St post PTA AFS cum impl. stentis (%)	1 (3.3)	0 (0)	1 (8.3)	0.222
St post PTA AFS (%)	1 (3.3)	0 (0)	1 (8.3)	0.222
Stenosis ACI 50% (%)	1 (3.3)	1 (5.6)	0 (0)	0.412
Stenosis ACI dex subtot. (%)	1 (3.3)	1 (5.6)	0 (0)	0.412
Struma gl. thyreoideae nontoxica (%)	1 (3.3)	0 (0)	1 (8.3)	0.222
Urinary Tract Infection (%)	2 (6.7)	1 (5.6)	1 (8.3)	0.775

Data is presented number (percentage), unless otherwise stated

*t-test for independent variables or chi-square test

AIM - Acute myocardial infarction; Atherosclerosis ext inf bill – Bilateral atherosclerosis of the lower extremities; CAD – Coronary artery disease; CPR – Cardiopulmonary resuscitation; IM – Myocardial infarction; NSTEMI – Non-ST elevation myocardial infarction; PCI cum impl. stentis – Percutaneous intervention with stent implant; PTA AFS – Percutaneous transluminal angioplasty; PTA AFS cum impl. stentis – Percutaneous transluminal angioplasty with stent implant; STEMI – ST elevation myocardial infarction; St post – Status after; Stenosis ACI 50% - Internal carotid artery stenosis 50%; Stenosis ACI bill – Bilateral internal carotid artery stenosis; Stenosis ACI dex subtot. – Right subtotal Internal carotid artery stenosis; Struma gl. thyreoideae nontoxica – Nontoxic thyroid goiter; aa – Artery; reg. Ant – Anterior region; subendocardialis – subendocardial.

Perioperative levels of inflammatory parameters (leukocyte count, CRP and PCT levels) of the patients are presented in Table 2. Preoperative leukocyte counts (normal: 4.5-11.0×10^9/L) in both study groups were within the normal range. Moreover, PCT levels (normal: <0,05 ng/ml; mildly eleveted: 0,15-2 ng/ml; elevated: >2 ng/ml) were slightly above the upper limit of normal (ULN) in both subset of patients but without meeting the criteria of elevated values. CRP levels (normal: <5 mg/L) were elevated in both groups even before undergoing the surgical procedure. There was no significant difference in preoperative inflammatory parameters between the patients allocated to the on-pump and off-pump procedures (refer to Table 2 for inflammatory parameters levels and *P* values).

Table 2. Comparison of patients' (N=30) inflammatory parameters preoperatively (day 0) and postoperatively (day 1-5), among those undergoing OPCAB (N=18) and CABG (N=12) procedures.

	Inflammatory parameters	**Mean ± SD**	***P****
Day 0	Leukocyte count overall	7.96 ± 2.43	0.219
	Leukocyte count CABG	8.65 ± 3.00	
	Leukocyte count OPCAB	7.50 ± 2.02	
Day 1-5	Leukocyte count overall	10.93 ± 3.72	0.575
	Leukocyte count CABG	10.46 ± 3.58	
	Leukocyte count OPCAB	11.25 ± 3.83	
Day 0	CRP overall	9.10 ± 9.92	0.667
	CRP CABG	10.19 ± 12.70	
	CRP OPCAB	8.49 ± 8.78	
Day 1-5	CRP overall	110.51 ± 93.45	0.862
	CRP CABG	107.82 ± 91.43	
	CRP OPCAB	113.94 ± 95.22	
Day 0	PCT overall	0.07 ± 0.04	0.200
	PCT CABG	0.06 ± 0.02	
	PCT OPCAB	0.08 ± 0.05	
Day 1-5	PCT overall	1.30 ± 1.87	0.458
	PCT CABG	0.99 ± 1.60	
	PCT OPCAB	1.51 ± 2.00	

Data is presented as Mean±Standard deviation
*t-test for independent variables
CABG – on-pump CABG; CRP – C-reactive protein; OPCAB – off-pump CABG;
PCT – Procalcitonin.

Likewise, postoperative leukocyte counts in all patients, although with a marginal increase, remained in the ULN (Table 2). The levels of CRP in both groups of study subjects showed a marked increase beyond normal levels, while PCT reached mildly elevated values in these groups. As for preoperative levels of inflammatory parameters, there was no significant difference in postoperative leukocyte count (OPCAB: 11.25±3.83 vs. CABG: 10.46±3.58, *P*=0.575), CRP level (OPCAB: 113.94±95.22 vs. CABG: 107.82±91.43, *P*=0.862), and PCT level (OPCAB: 1.51±2.00 vs. CABG: 0.99± 1.60, *P*=0.458) amongst the patients in our study groups.

Regarding SIRS, 12 (40%) out of the 30 subjects met at least one criteria at any point throughout the study (Table 3). The exact number of criteria met by each group, on each day of measurements, is illustrated in Figure 5.

Table 3. Number of SIRS criteria met per patient on each day

Patient	Day 0	Day 1	Day 2	Day 3	Day 5
1*	0	1	0	0	0
2*	0	0	0	0	0
4*	1	1	1	1	0
5*	0	0	0	0	0
6*	0	0	0	0	0
8*	0	0	0	0	0
9*	0	0	0	0	0
10*	0	1	1	2	0
11*	0	0	0	0	0
12*	0	2	1	0	0
15*	0	1	1	1	0
17*	0	1	1	1	0
18*	0	0	0	0	0
19*	0	1	1	1	1
22*	0	0	0	1	0
24*	0	0	0	0	0
25*	0	0	0	0	0
29*	0	1	1	1	1
3†	0	0	0	0	0
7†	0	0	0	0	0
13†	0	0	0	0	0
14†	1	0	1	1	0
16†	0	1	1	1	1
20†	0	0	0	0	0
21†	0	0	0	0	0
23†	0	0	0	0	0
26†	0	0	0	0	0
27†	0	0	1	2	2
28†	0	0	0	1	0
30†	0	0	0	0	0

*OPCAB – off-pump CABG
†CABG – on-pump CABG
0 – None; 1 – Elevated leukocyte count; 2 – Elevated leukocyte count and Temperature <36 °C or >38 °C

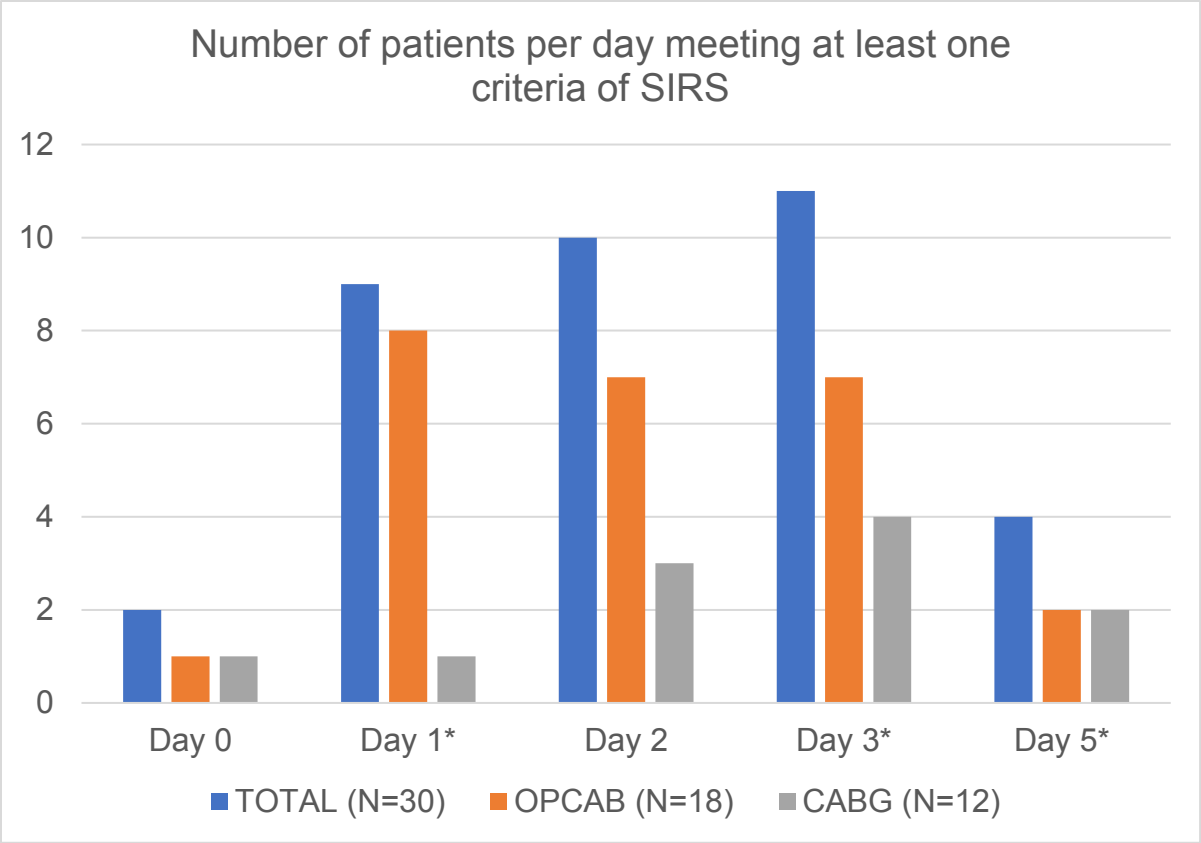

Figure 5. Number of patients per day meeting at least one SIRS criteria
*A patient had positive SIRS (2 or more criteria) on these days
CABG – on-pump CABG; OPCAB – off-pump CABG

All patients who met one SIRS criteria had an elevated leukocyte count, of which 4 and 8 underwent CABG surgery with and without CPB, respectively (Table 4). Only 3 (10%) of those patients filled the required number of criteria (2 or more) in order to confirm the presence of SIRS. In this regards, one of the patients received conventional CABG surgery, and two subjects belonged to the group undergoing CABG surgery without CPB (Table 3, Table 4). Those who fulfilled two criteria, and were found to have SIRS, had a reduced or elevated body temperature. Nevertheless, when SIRS criteria were analyzed, no statistically significant difference between the OPCAB and CABG groups was found for leukocyte counts (OPCAB: 44.4% vs. CABG: 33.3%, P=0.550), temperature (OPCAB: 11.1% vs. CABG: 8.3%, P=0.805), and the presence of the syndrome itself (OPCAB: 11.1% vs. CABG: 8.3%, P=0.805).

Table 4. Number of patients fulfilling SIRS criteria and number of patients diagnosed with SIRS.

Criteria	Total (N=30)	OPCAB (N=18)	CABG (N=12)	*P**
Leukocyte count (>12,000/μL or < 4,000/μL or >10% immature [band] forms)	12 (40)	8 (44.4)	4 (33.3)	0.550
Heart rate (>90 bpm)	0 (0)	0 (0)	0 (0)	
Respiratory rate (>20 breaths/minute) or **$PaCO_2$** (<32 mmHg)	0 (0)	0 (0)	0 (0)	
Temperature (>38 °C or <36 °C)	3 (10)	2 (11.1)	1 (8.3)	0.805
Presence of SIRS (2 or more criteria)	3 (10)	2 (11.1)	1 (8.3)	0.805

Data is presented as number (%)

* chi-square test

CABG – on-pump CABG; OPCAB – off-pump CABG; $PaCO_2$– Partial arterial pressure of carbon dioxide; SIRS – Systemic Inflammatory Response Syndrome

Secondary outcomes of our study (length of hospital stay, morbidity and mortality) are detailed in Table 5. The overall length of hospital stay after surgery was 13±6 days, with both groups showing identical periods of hospitalization postoperatively (OPCAB: 13±6 days vs. CABG: 13±6 days, *P*=1.000). A total of 13 (43.3%) subjects developed complications postoperatively, while only 2 (6.7%) patients developed a fatal end point. In this regards, 7 (38.9%) of the patients in the OPCAB group developed morbid conditions, while this was true for 6 (50%) of the subjects who underwent conventional CABG surgery with CPB. No significant difference in the frequency of posoperative morbidity was shown between these groups (P=0.555). Similarly, there was no difference in postoperative mortality between our test groups, with only one of the patients in each group developing the fatal outcome (OPCAB: 5.6% vs. CABG: 8.3%, *P*=0.775).

Table 5. Length of hospital stay, morbidity and mortality of patients.

Outcome	Total (N=30)	OPCAB (N=18)	CABG (N=12)	*P**
LHS, mean (SD), days	13±5	13±6	13±6	1.000
Morbidity (%)	13 (43.3)	7 (38.9)	6 (50)	0.555
Mortality (%)	2 (6.7)	1 (5.6)	1 (8.3)	0.775

Data is presented as number (%), unless otherwise indicated

*t-test for independent variables or chi-square test

CABG – on-pump CABG; LHS – Lenght of hospital stay; OPCAB – off-pump CABG

5. DISCUSSION

There is little question that cardiac surgery leads to an unprecedented inflammatory reaction with major clinical consequences. We must agree that the pathogenesis of the inflammatory reaction following cardiac surgery may be a mixture of defective hemodynamic peribypass, global myocardial ischemia, inadequate organ perfusion during CPB, and immune reactions correlated with extracorporeal exposure (5). For several decades, coronary artery bypass grafting using cardiopulmonary bypass and cardioplegia has been the gold standard for the revascularization of coronary arteries. Nonetheless, in order to keep a bloodless and motionless field, the patient pays the price of CPB in the shape of activation of the inflammatory response, blood trauma, nonpulsatile blood flow, and potential air or atherosclerotic debris embolization from the aorta. The goal to prevent such negative impacts of CPB contributed to the reemergence of off-pump coronary artery bypass surgery in the late 1990s. Currently, there is ample evidence to consider that outstanding results could be obtained by trying to avoid CPB. Even so, OPCAB is still in the search of an identity because denialists have viewed it as a method affiliated with many flaws, including intraoperative myocardial ischemia, unsatisfactory anastomoses and a prolonged learning curve (113).

The inflammatory response was evidently present in our study, with 40% of the 30 test subjects fulfilling at least one criteria of SIRS at any point throughout the time period. We demonstrated that, although present, this systemic inflammatory response was not different amongst the group of patients receiving conventional CABG surgery with CPB from that of subjects who were treated with the off-pump procedure. This was shown by an insignificant difference in the number of patients who were positive for SIRS between the OPCAB and CABG groups (11.1% vs. 8.3%, P=0.805, respectively).

Furthermore, the increase in leukocyte counts and CRP values, together with the clinical signs of SIRS, speak in favor of the inflammatory response. The overall leukocyte count for both study groups, which were marginally elevated after surgery and not significantly different, remained within the normal range (OPCAB: 11.25±3.83 vs. CABG: 10.46±3.58, P=0.575). These values of leukocytes post surgery could imply the presence of an inflammatory reaction but not to the degree seen in SIRS. Further supporting the presence of inflammation, CRP levels were elevated in all patients but no difference was exhibited between the OPCAB and CABG groups (113.94±95.22 vs. 107.82±91.43, P=0.862, respectively).

As for postoperative leukocyte counts and CRP levels, we did not observe significant differences in postoperative PCT levels regardless of the use of CPB (OPCAB: 1.51±2.00 vs. CABG: 0.99± 1.60, *P*=0.458). In an observational, prospective study performed in a pediatric ICU, *Rajar et al.* showed that PCT levels can be used to differentiate between infectious and non-infectious SIRS, while CRP levels cannot (14). As proved in our study, an increase in PCT value did correlate with the development of bacterial infection (namely, Bronchopneumonia, Pneumonia, Pseudomembranous colitis, Septicemia, and Surgical wound infection) as a postoperative complication if this value was normal before surgery itself. Elevated CRP levels, on the other hand, did not have a direct correlation with the development of an specific complication if any was present.

Unlike our study, significant number of randomized controlled trials have reported that the systemic inflammatory response produced by OPCAB and its related lasting effects are far less serious than those induced by traditional CABG using CPB (Figure 6), despite comparable surgical trauma (113). The positive effects of OPCAB in dulling this systemic inflammatory response could be related to the absence of CPB as well as the prevention of global myocardial ischemia (113).

We also proved that there was no difference regarding the postoperative hospitalization length and the development of morbid conditions irrespective of CPB usage. In fact, the length of hospitalization amongst the OPCAB and CABG groups were identical (13±6 days vs. 13±6 days, *P*=1.000, respectively), as opposed to our hypothesis. The proportion of test subjects who developed morbid conditions, similarly, was no different between our study groups (OPCAB: 38.9% vs. CABG: 50%, *P*=0.555). The majority of postoperative complications our patients developed (namely, Decubitus ulcer, Pericardial and pleural effusions, Pneumothorax, Postoperative cardiac insufficiency, Postoperative cognitive dysfunction, Postoperative tachycardia-bradycardia syndrome, relapsing Paroxysmal ventricular tachycardia, Respiratory insufficiency, Sick sinus syndrome, and Transcient ischemic attack) are known consequences of the surgery and not of the degree of systemic inflammation itself.

Finally, our study also found no difference between groups in terms of development of a fatal outcome (*P*=0.775). Two patients died due to Cardiorespiratory failure, one in each study group, which corresponded to 5.6% of the subjects who received OPCAB surgery and 8.3% of those who underwent the procedure with CPB.

Study	Intervention (n per group)		Main Outcome
	CABG + CPB	OPCAB	
Wan, et al.[9] 2004	19	18	IL-10, IL-6, IL-8, TNF-α, and VCAM-1 significantly higher in the CABG with CPB group.
Velissaris, et al.[10] 2004	26	26	Comparable release of cortisol and vasopressin in low-risk patients after OPCAB or CABG with CPB.
Wehlin, et al.[11] 2004	16	21	Less complement activation in low-risk OPCAB patients.
Dorman, et al.[12] 2004	25	25	Postoperative ET levels were higher in CABG with CPB group (P <0.05).
Johansson-Synnergen, et al.[13] 2004	26	26	OPCAB reduces complement activation but does not significantly affect TNF-α and IL-8 release or endothelial function.
Al-Ruzzeh, et al.[14] 2004	10	10	Less activation of circulating neutrophils in OPCAB patients.
Jemielity, et al.[15] 2003	25	25	Peak IL-6 level significantly lower after OPCAB; CRP higher after CABG; comparable increase in AGP.
Aydin, et al.[16] 2003	15	15	Endotoxin and lactate levels lower in OPCAB patients (P <0.05) except after sternotomy.
Wildhirt, et al.[17] 2001	13	13	Significant reduction in systemic and cardiac adhesion molecule expression after OPCAB.
Schulze, et al.[18] 2000	13	13	Significant increase in the TNF-system and sIL-2r after CABG; no difference in IL-6 levels; CRP and total nitrate/nitrite levels significantly lower after OPCAB.
Czerny, et al.[19] 2000	16	14	Significantly lower IL-10, P-selectin, ICAM-1, myoglobin, and CK-MB concentrations and troponin I release after OPCAB.
Ascione, et al.[20] 2000	30	30	Neutrophil elastase activity (P <0.0001), IL-8 levels (P=0.01), WBC counts (P <0.01) and incidence of postoperative infection (P <0.0001) higher after CABG.
Diegeler, et al.[21a] 2000	10	20[b]	Significantly higher release of C3d, C5a, IL-8 IL-10, and TNF-α receptors p55 and p75 after CABG.
Matata, et al.[22] 2000	10	10	Significant increase in lipid H_2O_2 (190% at 4 h), protein carbonyls (250% at 0.5 h), nitrotyrosine (510% at 0.5 h), IL-8 levels, elastase activity, and C3a, and sE-selectin concentrations after CABG.
Gu, et al.[23] 1998	31	31[c]	Leukocyte elastase activity, platelet β-thromboglobulin concentrations, and C3a levels significantly increased after CABG with CPB.

[a]The type of operative approach did not influence this immune response.
[b]Full sternotomy OPCAB (10) and limited LAT OPCAB (10).
[c]MIDCAB (31).

AGP = acid glycoprotein; C3a, C3d, C5a = complement components; CABG = coronary artery bypass grafting; CK-MB = MB isoenzyme of creatine kinase; CPB = cardiopulmonary bypass; CRP = C-reactive protein; ET = endothelin; H_2O_2 = hydroperoxides; ICAM-1 = intercellular adhesion molecule-1; IL = interleukin; LAT = left anterior thoracotomy; MIDCAB = minimally invasive direct coronary artery bypass; OPCAB = off-pump coronary artery bypass surgery; sE-selectin = soluble E-selectin; sIL-2r = soluble interleukin-2 receptor; TNF = tumor necrosis factor; VCAM-1 = vascular cell adhesion molecule-1; WBC = white blood cell

Figure 6. Impact of OPCAB on Systemic Inflammatory Response (113).

In comparison to our analysis, in the review by *Shahzad et al.,* three major meta-analyses stated that the length of hospital stay in patients undergoing OPCAB is reduced considerably when compared to the similar procedure using CPB. This is due to a reduction in the morbidity rate and lower incidence of complications related to the use of OPCAB (113). Like our study, none of the meta-analyzes showed differences in mortality rate between on-pump and off-pump procedures (113).

Of note, the diagnosis of *St post PCI cum impl. stentis* was significantly different between our study groups (OPCAB: 27.8% vs. CABG: 0%, P=0.049). Studies have found that inflammatory markers rise in the blood after stent placement. *Almagor et al*. demonstrated that values of CRP in patients after coronary stent implantation were persistently high over the medium term, representing a perpetual systemic inflammatory response (114). Further studies proved that there is long-term continuity of the high levels of sanguineous inflammatory mediators in patients with stent implants. Serum levels of the soluble receptors of interleukin-2 (sIL-2R) for activation of T-lymphocytes are still high four months after stent implantation. The pro-inflammatory cytokines and the acute phase proteins are also precociously released in the peripheral circulation, and immunity mediated by cells continues for an indefinite period after stent implantation (114). Such findings of persistently elevated inflammatory markers prove the presence of continuous SIRS following the implantation of coronary stents, which could have led to falsely elevated inflammatory parameters in the group of patients who underwent the off-pump surgery.

This was a small (N=30) prospective single-centre study with a predominately Caucasian population. Multi-centre inclusion would improve external validity. We also only measured the basic inflammatory parameters because other inflammatory markers are complicated and expensive to retrieve.

As this study was observational, and performed on patients who required a vital intervention, subjects were not randomly assigned to the CPB and non-CPB group; it was not possible to match both groups by certain variables such as sex, age, number of grafts required, diagnoses, and comorbidities. Aditionally, patients were exposed to different medications required for each of their specific preexisting comorbidities. This could have introduced bias by affecting the way the systemic inflammatory response developed.

The prospective study design required long durations for follow-up, making it difficult to maintainig adequate recordings and susceptible to withdrawal of patients. This even lead to the change of the original study design, which include measurement of parameters until postoperative day eight, to five days of mesurements postoperatively. Also, measurements were not taken by an specific individual but rather by a staff . In both cases, the origin of missing information can lead to information bias.

Finally, we failed to include a larger number of patients due to the global COVID-19 pandemic ocurring at the time of the study. With an increase sample size, we might have achieved the objectives of our hypothesis.

Even though our study has some limitations like small sample size, cohort design in a single-center, and presence of exposures, this is the first time as far as we know that a data study on the Systemic Inflammatory Response, and its parameters, after CABG surgery with and without the use of CPB has been done in Croatia. Further research and a larger number of patients are needed to clarify the role of CPB on the outcomes following cardiac surgery.

6. CONCLUSION

CABG surgery with and without cardiopulmonary bypass are associated with a similar Systemic Inflammatory Response. Hospital stay, morbidity, and mortality after cardiac surgery is the same regardless of the presence of CPB. Our study failed to demostrate any difference in the frequency and intensity of the Systemic Inflammatory Response in patients undergoing cardiac muscle revascularization surgery with and withou the use of extracorporeal blood flow.

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8. SUMMARY

Objectives: The aim of this study was to investigate and compare the degree of the Systemic Inflammatory Response in patients undergoing CABG surgery with and without the use of cardiopulmonary bypass, with an additional focus on investigating the association between inflammatory indicators of SIRS and postoperative hospitalization length, morbidity, and mortality after cardiac surgery.

Patients and methods: This study enrolled 30 patients, aged between 52 and 83 years, who were scheduled for elective CABG surgery with or without CPB. Allocation of patients into either group was based on the judgement of the surgical team. Patient leukocyte count, CRP level, PCT level, and number of SIRS criteria were determined before surgery and on the 1st, 2nd, 3rd and 5th postoperative days.

Results: Postoperative leukocyte counts were elevated but remained in the ULN. On the contrary, CRP and PCT levels were markedly beyond normal range in the majority of measurements. However, no significant difference in the postoperative leukocyte count, CRP levels, and PCT levels between cardiac surgery with and without CPB was observed. No significant positive correlation was found between higher inflammatory indicators of SIRS and postoperative hospitalization length, morbidity, and mortality.

Conclusion: CABG surgery with and without cardiopulmonary bypass are associated with a similar Systemic Inflammatory Response. Hospital stay, morbidity, and mortality after cardiac surgery is the same regardless of the presence of CPB. Our study failed to demostrate any difference in the frequency and intensity of the Systemic Inflammatory Response in patients undergoing cardiac muscle revascularization surgery with and without the use of extracorporeal blood flow.

9. CROATIAN SUMMARY

Ciljevi: Cilj ove studije bio je istražiti i usporediti intenzitet sistemskog upalnog odgovora kod pacijenata koji su podvrgnuti operaciji revaskularizacije srčanog mišića sa i bez upotrebe izvantjelesnog krvotoka, s dodatnim fokusom na ispitivanje povezanosti između pokazatelja upale SIRS-a i trajanja poslijeoperacijske hospitalizacije, pobola, i smrtnost nakon srčane operacije.

Ispitanici i postupci: Ovo je istraživanje obuhvatilo 30 pacijenata, starih između 52 i 83 godine, kojima je operacija revaskularizacije srčanog mišića sa ili bez CPB-a. Raspodjela pacijenata u bilo koju skupinu temeljila se na prosudbi kirurškog tima. Broj leukocita, razina CRP-a, razina PCT-a i broj prisutnih SIRS kriterija određeni su prije operacije i 1., 2., 3. i 5. postoperativni dan.

Rezultati: Poslijeoperacijski broj leukocita u praćenih pacijenata je bio povišen, ali ostao je u ULN-u. Suprotno tome, u većini mjerenja razina CRP i PCT bila je znatno iznad normalnog raspona. Međutim, nije primijećena značajna razlika u poslijeoperacijskom broju leukocita, razini CRP-a i PCT-u u bolesnika operiranih sa i bez CPB-a. Nije utvrđena značajna pozitivna povezanost između viših upalnih pokazatelja SIRS-a i trajanja hospitalizacije, pobola i smrtnosti.

Zaključak: Operacije revaskularizacije srčanog mišića sa i bez kardiopulmonalnog bajpasa povezane su sa sličnim sistemskim upalnim odgovorom. Boravak u bolnici, pobol i smrtnost nakon kardiološkog zahvata isti su bez obzira na korištenje CPB-a pri izvođenju operacije srca. Dakle, naša studija nije uspjela utvrditi nijednu razliku u učestalosti i intenzitetu sistemskog upalnog odgovora kod pacijenata koji su bili podvrgnuti revaskularizaciji srčanog mišića sa i bez korištenja izvantjelesnog krvotoka.

10. CURRICULUM VITAE

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