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Review

Vitamin C to improve Organ Dysfunction in Cardiac Surgery Patients – Review and Pragmatic Approach

Aileen Hill[1,2,3*], Sebastian Borosch[3,4], Carina Benstöm[1,3], Christina Neubauer[1,3], Patrick Meybohm[5], Pascal Langlois[6], Neill KJ Adhikari[7], Daren K Heyland[8] and Christian Stoppe[1,3*]

[1] Department of Intensive Care Medicine, University Hospital RWTH, D-52074 Aachen, Germany; ahill@ukaachen.de (A.H.), cbenstoem@ukaachen.de (C.B.), cstoppe@ukaachen.de (C.S.)
[2] Department of Anesthesiology, University Hospital RWTH, D-52074 Aachen, Germany, elaaf@ukaachen.de
[3] 3CARE—Cardiovascular Critical Care & Anesthesia Evaluation and Research, D-52074 Aachen
[4] Department of Thoracic, Cardiac and Vascular Surgery, University Hospital RWTH, D-52074 Aachen, Germany; sborosch@ukaachen.de
[5] Department of Anesthesiology and Intensive Care, University Hospital Frankfurt, D-60590 Frankfurt, Germany; patrick.meybohm@kgu.de
[6] Department of Anesthesiology and Reanimation, Faculty of Médecine and Health Sciences, Sherbrooke University Hospital, Sherbrooke, Québec, Canada; Pascal.laferriere-langlois@usherbrooke.ca
[7] Department of Critical Care Medicine, Sunnybrook Health Sciences Centre; Interdepartmental Division of Critical Care Medicine, University of Toronto, Toronto, Canada; Neill.Adhikari@sunnybrook.ca
[8] Clinical Evaluation Research Unit, Kingston General Hospital, K7L 2V7 Kingston, Canada; dkh2@queensu.ca

* Correspondence: ahill@ukaachen.de (A.H.); christian.stoppe@gmail.com, Tel.: +49-241-8036575 (C.S.)

Abstract: The pleiotropic biochemical and antioxidant functions of Vitamin C (Vit C) have recently sparked interest in its application in intensive care. Vit C protects important organ systems such as the cardiovascular, neurologic and renal system during inflammation and oxidative stress. Vit C also influences the systems of coagulation and inflammation and its application might prevent the development of organ damage. The current evidence of Vit C's effect on the pathophysiological reactions during various acute stress events, such as sepsis, shock, trauma, burn and ischemia-reperfusion injury imposes the question, if the application of Vit C might be especially beneficial for cardiac surgery patients, who are routinely exposed to ischemia/reperfusion and subsequent inflammation, systematically affecting different organ systems. This review covers current knowledge about the role of Vit C in cardiac surgery patients with focus on its influence on organ dysfunctions. The relationships between Vit C and clinical health outcomes are reviewed with special emphasis on its application in cardiac surgery. Additionally, this review pragmatically discusses evidence regarding the administration of Vitamin C in every day clinical practice, tackling the issues of safety, monitoring, dosage and most the appropriate application strategy.

Keywords: vitamin C; ascorbic acid; cardiac surgery; antioxidant therapy; nutrient; oxidative stress; organ dysfunction; multi organ failure

1. Introduction

1.1. Pathogenesis of Organ Dysfunction after Cardiac Surgery

Patients undergoing cardiac surgery experience a complex systemic inflammatory response syndrome (SIRS). SIRS after cardiac surgery is induced by surgical trauma [4, 5], foreign surface contact during cardiopulmonary bypass (CPB) [6 – 13], CPB itself [5, 13 – 16], ischemia-reperfusion-injury (I/R) [4, 6, 14, 17], endotoxemia [6, 14, 17], and blood transfusion [14, 18, 19] as shown in Figure

1. Each stimulus triggers both the cellular and the humoral inflammatory response systems. Cellular mechanisms include the activation of leukocytes, platelets and endothelial cells [4, 6, 11, 14, 16, 17]. Humoral reactions are mainly the activation of complement and coagulation systems, as well as the release of inflammatory mediators and reactive oxygen species [4, 8, 11, 14].

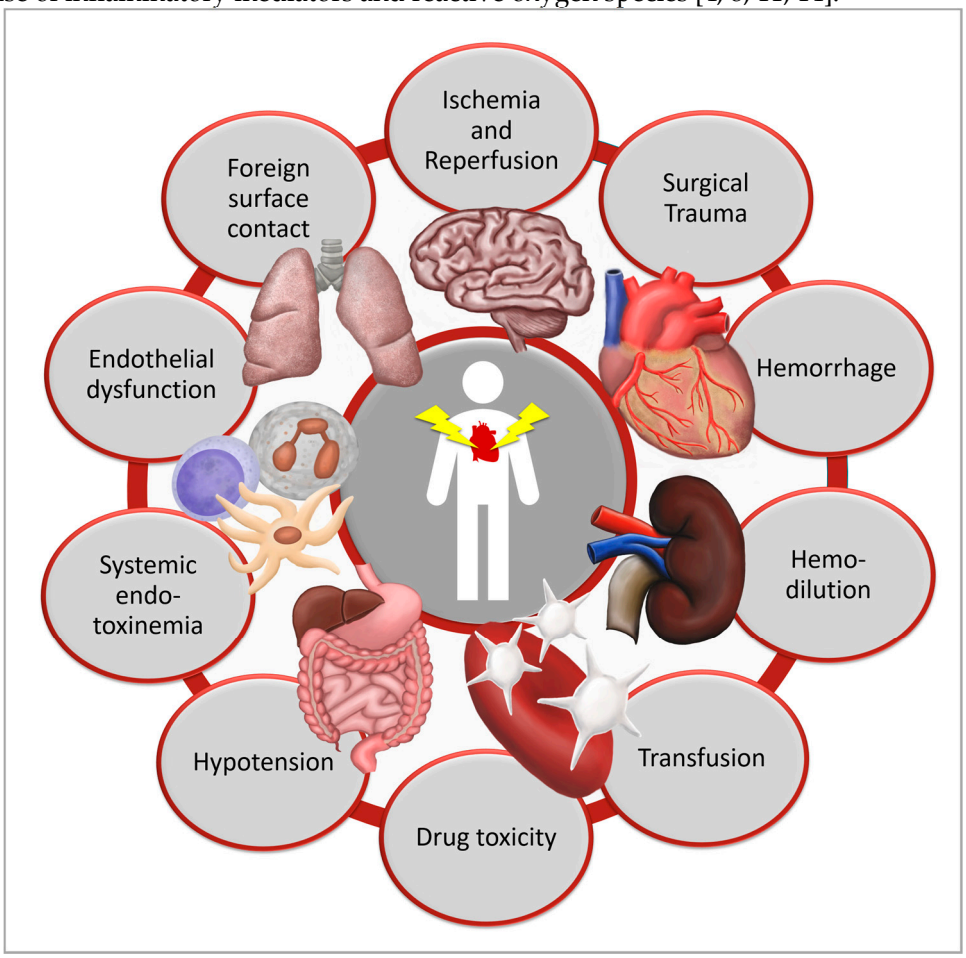

Figure 1. Pathomechanisms of organ damage in cardiac surgery.

Oxidative stress is defined as an imbalance between production of oxidants, mainly free radicals and reactive metabolites, in relation to their elimination by protective mechanisms. In many acute stages of disease, the production of reactive oxygen species (ROS) is initiated by several conditions, for example I/R-injury, activation of the NADPH oxidase, as well as severe alterations in the mitochondrial metabolism [1]. ROS play an essential role in the human biology and regulate different metabolic processes and signaling pathways. In critical illness, such as trauma, surgery, ischemia and reperfusion, shock and sepsis, the ROS production increases and often exceeds the natural antioxidant capacity, leading to damage of the structures of macromolecules. Structural damage of macromolecules, such as proteins, nucleic acids, lipids and carbohydrates impairs their essential biological function and leads to significant damage of cell structure and organ function [20]. The results of the general activation of the inflammatory system and the oxidative stress are leukocyte extravasation, intravascular leukostasis, lipid peroxidation, cell death, vasodilation and capillary fluid leakage in the tissues, which in sum negatively influence patient outcome [2 – 5, 21, 22].

While SIRS is a well-known reaction to cardiac surgery, this syndrome can cause multiple acute and persistent organ dysfunctions, which are explained in greater detail in section 3. Postoperative complications, especially organ failures and infections are major determinants of morbidity and mortality, necessitating a prolonged hospital and intensive care unit (ICU) length-of-stay (LOS), which is further associated with high care related costs and worse quality of life (QOL) after cardiac surgery [4, 6, 11, 14, 15, 17, 23 – 28]. In fact, the development of acute and persistent multiorgan

dysfunction occurs in 15 % of patients and is the most important determinant of mortality, clinical outcome and QOL for patients, who had undergone cardiac surgery [7].

1.2. Basic Metabolism and Functions of Vitamin C

Vitamin C is an essential micronutrient involved in numerous biochemical and biological processes. Two forms of Vit C are present in the plasma: ascorbic acid (AA) and its oxidized form dehydroascorbate (DHA) [30]. The human body is unable to synthesize Vit C due to lack of the last enzyme in the biosynthetic process. An adequate intake of Vit C of 200 mg/d, equaling approximately 5 servings of fruit and vegetables is recommended, though food content varies due to its lability [31]. Vit C is absorbed enterally, remains unbound in the human plasma and is dialyzable. Renal elimination of Vit C follows its glomerular filtration, if the concentration of Vit C in the urine is larger than the capacity of the responsible transport protein, which is achieved by Vit C uptake of 100 mg/d and a plasma concentration of 60 µmol/l [31].

There is no data for true bioavailability of enteral Vit C, but almost complete bioavailability was calculated in several models for dosages of 200 mg/d. A steep sigmoidal relationship between Vit C dose and steady-state plasma concentration was observed, where a dose of 200 mg produces approximately 80 % plasma saturation, while plasma saturation occurs at about 1000 mg of Vit C. However, the saturation of cells occurs at 100 mg/d due to active Vit C transport, which saturates at about 60 – 70 µmol/l. The peak plasma concentration is reached about 2 hours after ingestion, while an exponential drop of plasma levels is observed after intravenous application of Vit C, where a half-life of Vit C in plasma of approximately one hour was observed [31].

Vit C has pleiotropic functions in the human body, acting as an electron donor and thereby being a reducing agent for 8 enzymes and many intra- and extracellular reactions. Enzymatic reactions dependent on Vit C are the synthesis of norepinephrine, collagen and carnitine, amidation of peptide hormones and tyrosine metabolism. The promotion of iron absorption in the small intestine is another function of Vit C. [31]. Based on its redox-potential and powerful antioxidant capacity, Vit C has been called the most important antioxidant countering the influence of free radicals [32, 33]. The functions of Vit C in the various organ systems are explained in greater detail in Section 2.

1.3. The Influence of Vitamin C on Oxidative Stress and Inflammation

Vit C scavenges free radicals through the formation of the ascorbyl radical and thereby prevents damage to macromolecules, such as lipids or the DNA. The dismutation of two ascorbyl radicals produces one molecule of ascorbate and one molecule of DHA [8]. Additionally, Vit C inhibits the expression of intracellular adhesion molecules and thereby inhibits the intake of immune cells into the microcirculation [8]. Furthermore, an increase of the intracellular Vit C concentration inhibits the protein phosphatase type 2A and thereby protects the endothelial barrier from septic shock [9]. Due to its pleiotropic functions in 8 enzymatic processes, Vit C not only mitigates oxidative stress, but restores vascular responsiveness to vasoconstrictors [10], ameliorates microcirculatory blood flow, preserves endothelial barriers [49], prevents apoptosis [11] and augments the bacterial defense [42].

1.4. Current Evidence of Vitamin C in Critically Ill Patients

Sepsis, trauma, burn and surgery are causes of systemic inflammatory responses and can lead to similar pathologies in the human body, including microvascular dysfunction, refractive vasodilatation, endothelial barrier dysfunction and edema and disseminated intravascular coagulation. Vitamin C concentrations are lowered in critical illness [12], in patients recovering from surgery [13, 14], in patients after cardiac surgery [15] and especially in patients going into multiorgan failure [5, 16]. Fowler et al observed a lower rate of organ dysfunction as assessed by the sequential organ failure assessment (SOFA) Score and a reduced 28-day mortality after the application of Vit C in patients with sepsis and multiorgan-failure, whereas an influence on the ICU-LOS was not observed [17]. Zabet et al. demonstrated in 2016 a significantly reduced mean vasopressor demand and shorter duration of vasopressor therapy and reduced mortality in septic patients receiving Vit C

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[18]. In 2002, Nathens et al. observed a decreased risk of pneumonia, acute respiratory distress syndrome (ARDS) and a tendency towards lower alveolar inflammation in a randomized controlled trial (RCT) of antioxidant supplementation in mostly trauma patients, though the results of this RCT did not reach statistical significance [19]. In severe burn patients, ascorbic acid reduced fluid demand and increased urine production in a retrospective review by Kahn et al. [20] and in an RCT by Takada et al. [21]. In fact, the application of Vit C is frequently considered in the treatment of severe burn patients [22]. While an overview of the influence of Vit C on organ dysfunction is summarized in Table 1, Section 2 will take a closer look on each individual organ system.

Table 1: Summary of Vit C´s influence on organ systems

Organ System	Influence of Vitamin C
Nervous system	• Elevated levels (up to 80 times) protect neurons from oxidative damage [15, 34] • Reduces the infarct volume after ischemia [35]
Cardiovascular System	• Attenuates myocardial damage and improves myocardial stunning [15] • Reduces vasopressor demand [18] • Reduces rate of atrial fibrillation [23, 24] • Improves endothelial function [49]
Respiratory System	• Reduces intubation time [25] • Decreases risk of pneumonia and alveolar inflammation [19]
Renal System	• Reduces fluid demand and increases urine production [40]
Gastrointestinal System	• Attenuates drug toxicity, decreases inflammatory reaction [26] • Lowers infiltration of neutrophils [26] • Reduces the expression of apoptosis related genes as well as DNA [11]
Coagulation System	• Restores platelet function and decreases capillary plugging [42] • Attenuates a sepsis-induced drop of thrombocytes [42]
Immune System	• Inhibits bacterial growth [29], enhances microbial killing [43] • Supports endothelial barrier function and promotes antioxidant scavenging [43]

2. Influence of Vitamin C on the Organ Systems in Cardiac Surgery Patients

2.1. Nervous System

2.1.1. Neuropsychological Dysfunction after Cardiac Surgery

Brain tissue is very susceptible to oxidative damage because of its high content of polyunsaturated fatty acids and its high demand for oxygen. Neuropsychological complications are commonly seen in patients undergoing cardiac surgery, leading to a prolonged ICU stay (Figure 2). The American College of Cardiology and the American Heart Association defined two classes of neurological complications after cardiac surgery: Type I neurological deficits include stroke and transient ischemic attack, coma and fatal cerebral injury, Type II include delirium and postoperative cognitive dysfunction (POCD) [27].

Cerebral ischemia due to stroke, microembolization, hypoperfusion, or hypoxemia contributes considerably to cognitive decline. New cerebral lesions occur in about 30 – 50 % of cardiac surgery patients, but most of them are clinically inapparent. The incidence of manifest stroke with clinical deficits is about 1 – 2 % after low-risk heart surgery [28, 29, 30, 31, 32]. Contributing factors are major bleeding and transfusions of red blood cells, preoperative use of unfractionated heparin and use of CPB [28]. Delirium is observed in a quarter and POCD is observed in 25 – 65 % of all patients, while most of these patients recover within the first months [29, 33]. Cognitive function is strongly influenced by the systemic inflammation reaction, leading to increased permeability of the blood-brain barrier and cerebral edema [34]. All neuropsychological complications are associated with decreased QOL, inability to work, loss of independence and increased mortality [32].

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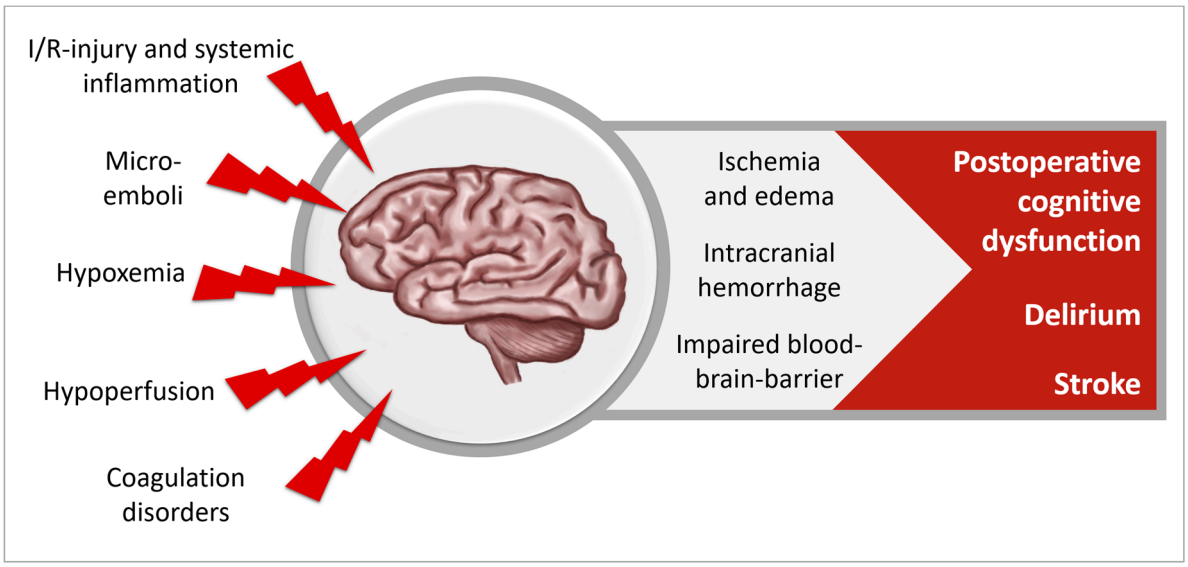

Figure 2. Cerebral dysfunction after cardiac surgery

2.1.2. Role of Vitamin C in the Nervous System

Vit C levels are elevated up to 80 times in the cells of the brain and up to 4 times in the cerebrospinal fluid due to its active transport via the sodium-dependent vitamin C transporter-2 (SVCT2) transporter, protecting neurons and leukocytes from oxidative damage [15]. Vit C is also essential for the myelination of the neurons [35] and a Vit C deficiency through insufficient transporter molecules leads to hypomyelination and collagen-containing extracellular matrix deficits [36]. If oxidized, Vit C can also be taken up by glucose transporters [37]. During I/R injury or stroke, the Vit C is shifted from the intracellular to the extracellular compartment, leading to an intracellular Vit C deficiency and perhaps neuronal damage [15].

While there is evidence that Vit C reduces infarct volume in cerebral ischemia, most evidence is derived from experimental studies inducing stroke or I/R-injury: reduced infarct volumes after experimental stroke models were demonstrated by Henry et al. [38] and Huang et al. [39]. This finding was supported by a recent study demonstrating that Vit C protects from neuronal cell death in a model of ethanol induced damage in early development age [40]. Ethanol thereby induced the development of oxidative stress. Amongst others, the protection was evaluated by reduced activation of caspase-9 and 3 as well as reduced levels of cytochrome c [40]. Lagowska-Lenard et al. found elevated antioxidant levels in the serum after Vit C supplementation in a placebo-controlled RCT in patients with ischemic stroke. However, in this small study, the clinical outcome was unchanged [41].

2.1.3. Vitamin C´s Influence on the Nervous System in Cardiac Surgery Patients

In the meta-analysis of Hu et al. 2017 including eight RCTs and 1,060 patients, Vit C supplementation had no effect on the incidence of stroke (0.8% [Vit C] vs. 2.0% [Control]) in cardiac surgery patients [23]. To our knowledge, until now, no study evaluated the influence of Vit C on cognitive dysfunction or delirium in cardiac surgery patients.

2.2. Cardiovascular System

2.2.1. Cardiovascular Dysfunction after Cardiac Surgery

Surgical trauma, myocardial I/R, the excretion of inflammatory mediators, intraoperative cardioplegic arrest, reduced coronary blood flow and microvascular occlusion lead to a decline of myocardial contractility and a reduction of ventricular compliance and resulting function, as displayed in Figure 3. Vasodilation and decreased systemic vascular resistance contribute to systemic hypotension as well. Therefore, vasopressor treatment is commonly needed to support the circulation

perioperatively in cardiac surgery patients. Although it is associated with increased oxidative stress and endothelial dysfunction and myocardial fibrosis [42].

Myocardial dysfunction and cardiovascular insufficiency after cardiac surgery can cause a mismatch of oxygen delivery and metabolic demand and lead to tissue hypoxia. Ventricular systolic and diastolic dysfunction occurs in up to 70 % of cardiac surgery patients [43, 44]. The low cardiac output syndrome (LCOS) is clinically characterized by hypotension and signs of tissue hypoperfusion and occurs in 5 – 15 % after cardiac surgery [43, 45]. Acute kidney injury (AKI) as well as neurologic and pulmonary complications are the most common consequences of LCOS, leading to a mortality rate of more than 20 % [34, 44, 46]. Arrhythmias are very common after cardiac surgery. Their impact on the clinical outcome depends on the kind of arrhythmia, its duration, ventricular response rate and cardiac function [47]. Arrhythmias might be I/R- and inflammation- induced and result from an increased intracellular calcium concentration due to calcium-influx through the damaged, peroxided lipids in the cell membranes as well as hindered calcium uptake by the sarcoplasmic reticulum [15].

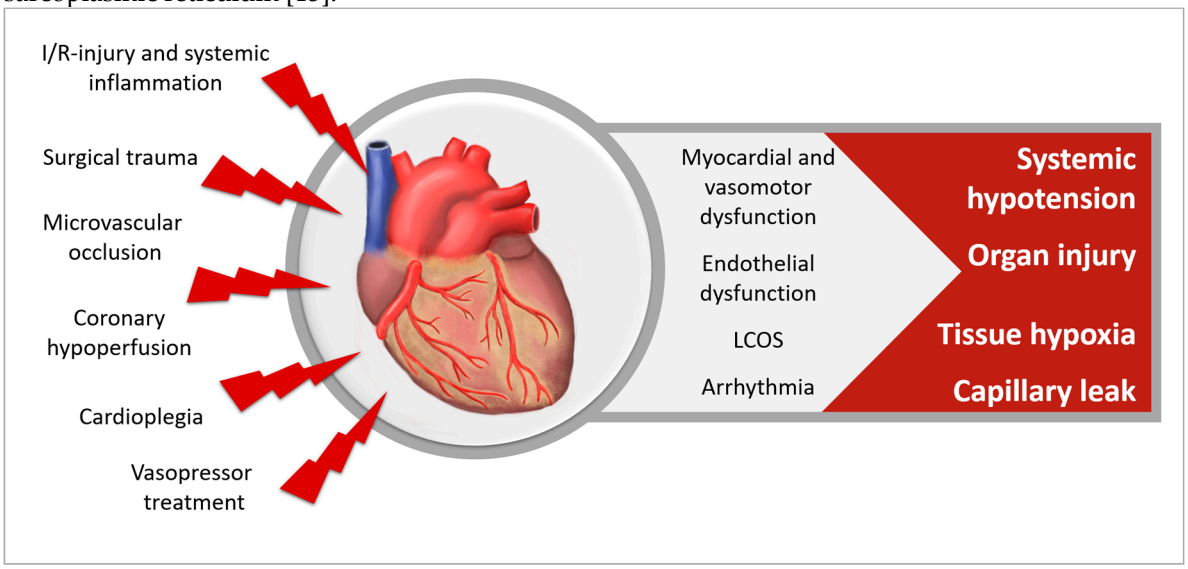

Figure 3. Cardiovascular dysfunction after cardiac surgery

2.2.2. Role of Vitamin C in the Cardiovascular System

The effects of Vit C in the cardiovascular system are tremendous. Despite the capability of scavenging free radicals, Vit C also promotes the differentiation of embryonic and pluripotent stem cells into cardiac myocytes [48, 49]. Vit C has cardioprotective properties, which were demonstrated in rat models, where Vit C reduced oxidative damage in diabetic rats [50] and during I/R-injury [51]. Vitamin C improved myocardial stunning and increased left ventricular function in some animal studies, however, other animal studies showed no effect of Vit C and some only in combination with other antioxidants [15]. Therefore, preclinical data regarding the myocardial protection through Vit C in I/R-injury remains inconclusive, as discussed in detail in a review by Spoelstra-de Man et al. [15].

Vit C inhibits the expression of inducible nitric oxide synthetase (iNOS) in endothelial cells and neuronal nitric oxide synthetase (nNOS) and thereby lowers the plasmatic level of nitric oxide (NO), which is responsible for the activation of the guanylate cyclase, which counteracts the effects of vasoconstrictors. Vit C also prevents the impairment of vasoconstriction [10] and restores inter-endothelial electrical coupling through connexin 37-contaning gap-junctions as well as through protein kinase A-activation required for connexin 40 dephosphorylation [10]. Therefore, Vit C might increase vasopressor-sensitivity. However, in patients with endothelial dysfunction due to cardio-metabolic diseases, such as hypertension, atherosclerosis, diabetes and smokers, Vit C promotes endothelial- and nitric oxide-dependent vasodilation [52]. Overall, Vit C might improve micro-perfusion [10, 13].

In extension, ascorbate also tightens the endothelial permeability barrier [52] and thus might lead to reduced extravasation and edema [53]. A meta-analysis including 44 RCTs and 1129 patients, displayed an overall positive effect of Vit C on endothelial function independently of baseline plasma concentration or route of administration [54]. In the studies included in this meta-analysis, endothelial function was assessed using ultrasound, plethysmography and pulse wave analysis. The effects were significant in patients with cardio-metabolic disorders, especially with heart failure ($p< 0.02$), atherosclerosis ($p< 0.001$) and diabetes ($p< 0.001$).

2.2.3. Vitamin C´s Influence on the Cardiovascular System in Cardiac Surgery Patients

In cardiac surgery with CPB, Vit C levels decrease with the production of ROS and remain low for days after surgery [15] indicating a greater demand of Vit C in the setting of surgery and I/R-induced oxidative stress. Oxidative stress and myocardial damage after cardiac surgery with CPB might be decreased by the administration of Vit C, as demonstrated in an RCT by Dingchao et al. in the 1990ies [55]. In this RCT including 85 patients, the intervention group received a total of 250 mg/kg Vit C before and after CPB. Markers for myocardial injury (creatine kinase (CK) and creatine phosphokinase isoenzyme muscle/brain (CK-MB), as well as malondialdehyde as a marker for oxidative stress were significantly lower in patients receiving Vit C. Clinically, the cardiac index was higher, intervention-group patients were less likely to need defibrillation after weaning from CPB and had shorter ICU- and hospital-LOS [55].

Vit C treatment also improves the ventricular function, reduces vasopressor and fluid demand [55 – 57] and increases the cardiac index (CI). In a systematic review [58] and in 6 different meta-analyses including 8 – 15 RCTs [23 – 25, 59 – 61], Vit C was shown to significantly reduce the occurrence of postoperative cardiac arrhythmia, mainly atrial fibrillation (AF). However, the results of these meta-analyses might be strongly influenced by publication bias, as discussed by Hemilae [62]. While postoperative AF gained increasing attention in the past years, and was investigated by several RCTs and meta-analyses, to our knowledge, no large, multicenter study evaluated the effect of Vit C on other important outcomes, such as myocardial function or vasopressor and fluid-demand.

2.3. Respiratory System

2.3.1. Pulmonary Dysfunction after Cardiac Surgery

Pulmonary dysfunction (Figure 4) occurs in up to 79 % of patients after cardiac surgery, ranging from mild subclinical functional changes to manifest acute respiratory distress syndrome (ARDS) in less than 2 % of patients [63]. Acute lung injury is characterized by inflammation, and tissue damage is dealt mainly through oxidative stress and free radicals [64]. ROS like nitric oxide and superoxide can nitrate and oxidize key amino acids in lung proteins, such as surfactant protein, disturbing their function [65].

Factors contributing to pulmonary dysfunction are poor lung mechanics, increased intrapulmonary shunt and vascular resistance, pulmonary edema, changes in surfactant and alveolar protein accumulation. The underlying pathomechanisms include inflammation and free radicals, I/R-injury, transfusion-associated lung injury and drug toxicity. Pulmonary dysfunction causes prolonged need for mechanical ventilation, increases ICU- and hospital-LOS and mortality, and significantly affects long-term physical and psychological morbidity [34, 66 – 70].

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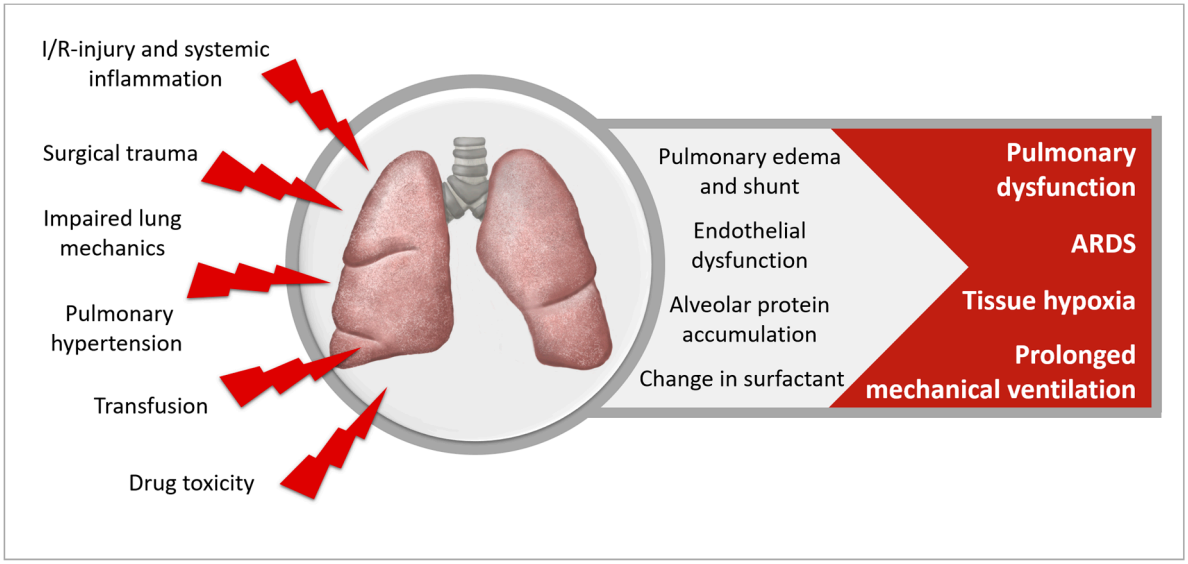

Figure 4. Pulmonary dysfunction after cardiac surgery.

2.3.2. Role of Vitamin C in the Respiratory System

Vit C functions as an antioxidant preventing ROS-induced lung damage and rapid oxidation of ascorbate occurs in during acute inflammation in acute lung injury [65]. In a mouse-model, the supplementation of Vit C preserved lung barrier function and preserves functionality of ion pumps in the alveolar epithelium [71] and decreased the lung pathology in an *in vivo* study of influence virus infected mice [72]. In rats, Vit C attenuated lung injury caused by I/R [73].

A study conducted in 2016 found that Vit C treatment of human bronchial epithelial cells attenuates particulate matter induced ROS damage, IL-6 expression and increased cell viability [74]. Vitamin C additionally attenuated the smoking induced pulmonary emphysema and vascular remolding by reducing ROS induced protein oxidation [75]. In a study by Nathens et al. in 2002, the application of Vit C decreased risk for pneumonia and ARDS with lower alveolar inflammation in a cohort of 270 mostly trauma patients [19]. Even though the results of this RCT did not reach statistical significance, further investigations on that subject were sparked. In the OMEGA study, Rice et al. supplemented antioxidant cocktails to ARDS patients and observed no benefit [76]. However, these cocktails contained many components and the 2g/d Vit C was only a minor component. In an RCT by Gadek at al., a combination of antioxidants, including Vit C decreased pulmonary inflammation and showed beneficial effects on gas exchange and requirement of mechanical ventilation in patients with ARDS [77].

2.3.3. Vitamin C´s Influence on the Respiratory System in Cardiac Surgery Patients

Even if preclinical and clinical data seem promising, only very few studies addressed the effect of Vit C on pulmonary dysfunction in cardiac surgery. To our knowledge, the duration of mechanical ventilation was the only outcome parameter measured in RCTs investigating this matter. Reduced intubation time after cardiac surgery was shown in a meta-analysis including 3 RCTs and 575 patients (mean difference: -2.41, 95% confidence interval -3.82/-0.98, p= 0.001). However, the heterogeneity of the included trials was high (p= 0.74) [25].

2.4. Renal System

2.4.1. Renal Dysfunction after Cardiac Surgery

Acute kidney injury (AKI) is one of the clinically most significant organ dysfunction and occurs in about 28 % of cardiac surgery patients [78], with 2 – 5 % of patients requiring dialysis. Contributing factors are oxidative stress during renal I/R-injury, inflammation, hemolysis, cholesterol emboli, nephrotoxic drugs and toxins resulting in glomerular and tubular damage, reduced glomerular

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filtration rates and impaired creatinine clearance as shown in (Figure 5). AKI is strongly associated with need for renal replacement therapy, increased hospital- and ICU-LOS, mortality and decreased long-term QOL [34, 78 – 84].

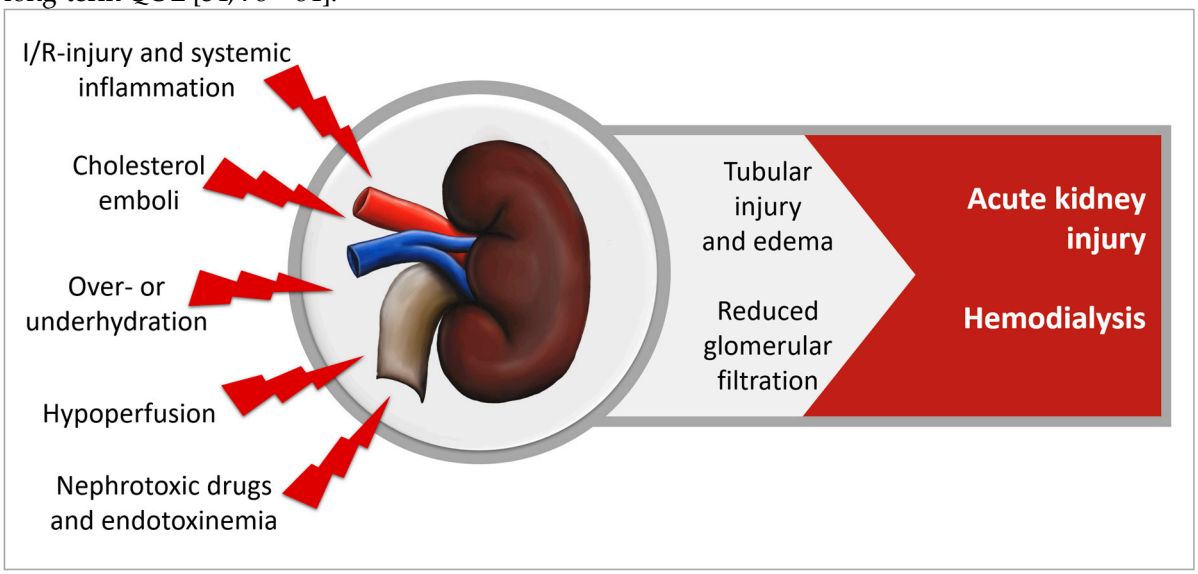

Figure 5. Renal dysfunction in cardiac surgery

2.4.2. Role of Vitamin C in the Renal System

The protective properties of Vit C on the renal system are also attributed to its anti-oxidant capabilities. Vit C administration reduced the serum creatinine levels in patients who experienced contrast-mediated nephropathy after coronary angiography [85]. These findings were supported by a meta-analysis including 1.536 patients in 9 RCTs in 2013 by Sadat et al., decreasing risk for AKI by 33 % (risk ratio 0.672, confidence interval 0.466 – 0.969, p=0.034) [86]. In contrast, excessive and long-term Vit C consumption might lead to oxalate nephropathy. In a case report in 2012 Gurm et al. described a woman who consumed 3 – 6.5 g of Vit C daily [87]. A similar case was reported in 2015. A 96-year-old woman was also diagnosed with oxalate nephropathy resulting from an excessive Vit C intake [88]. The tubular injuries are thereby caused by crystalline deposits of calcium oxalate, which might be metabolized from Vit C. Therefore, the recurring formation of kidney stones, as well chronic renal failure and hyperoxaluria are contraindications for a high-dose long-term Vit C therapy, even though adverse effects seem unlikely in short-term administration [15, 89]. In an RCT study including burn patients, decreased volume requirement for fluid resuscitation, as well as increased urine output were observed [21].

2.4.3. Vitamin C´s Influence on the Renal System in Cardiac Surgery Patients

A pilot study by Antonic et al. in 2017 with 100 on-pump CABG surgery patients was not able to confirm the assumed benefits of Vit C on renal function [90]. Potential causes for the insignificance of the results might be a rather low dosage and oral administration of Vit C (2 x 1 g/d) and the oral administration, as discussed in greater detail in section 4.2. In any case, further research is warranted, to investigate the effect of a high-dosage intravenous Vit C application, to fully achieve the antioxidant and possibly nephroprotective effects.

2.5. Gastrointestinal System

2.5.1. Gastrointestinal Dysfunction after Cardiac Surgery

Gastrointestinal (GI) complications (Figure 6) occur in 0.2 – 4 % [91], while a postoperative gastrointestinal atony is observed in most of cardiac surgery patients [92, 93]. Inflammation and I/R-injury increase gastrointestinal permeability and can lead to bacterial translocation and systemic endotoxemia. The most common GI complications are postoperative ileus and GI hemorrhage, while

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mesenteric ischemia and intestinal perforation are the GI complications with the highest mortality. GI complications increase LOS and mortality [34, 94 – 97].

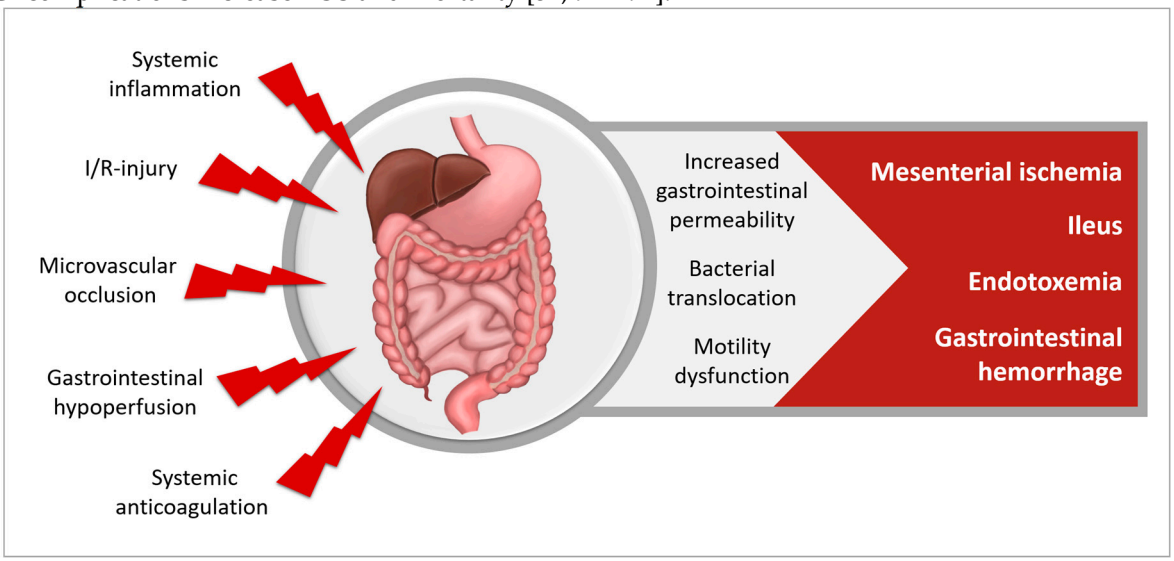

Figure 6. Gastrointestinal dysfunction after cardiac surgery

2.5.2. Role of Vitamin C in the Gastrointestinal System

The few available studies on the interaction of Vit C with the GI system are derived from oncology. Vit C treatment might mitigate GI adverse effects associated with cancer treatment [98], where chemotherapy is often associated with damage to the mucous membrane. Al-Asmari et al. found attenuated toxicity of the antineoplastic drug 5 fluorouracil when Vit C was administered, demonstrated by decreased activation of nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) and COX-2 expression as well as lower infiltration of neutrophils [26]. The authors suggested that the observed benefits were due to the antioxidative effects of Vit C. Similar findings were observed by Yamamoto et al. in 2010, who could show that Vit C treatment attenuated the expression of apoptosis related genes as well as DNA damage in crypt cells caused by radiation [11].

2.5.3. Vitamin C´s Influence on the Gastrointestinal System in Cardiac Surgery Patients

To our knowledge, no study of Vit C in cardiac surgery reported neither beneficial nor adverse effects on the gastrointestinal system.

2.6. Coagulation System

2.6.1. Coagulation Disorders after Cardiac Surgery

Coagulation disorders – both prothrombotic activity and coagulopathy have deleterious effects on patient outcome (Figure 7). I/R induces the production of ROS by platelets and other vascular sources. ROS can alter platelet function and increase platelet aggregation and thrombus formation [99, 100]. In a vicious circle, ROS and platelets augment each other. Therefore, ROS may act prothrombotic. Additionally, reduced nitric oxid (NO) responsiveness of the platelets might promote adhesion of the platelets to the endothelium, which is associated with increased cardiovascular morbidity in patients with acute coronary syndrome [99]. On the other hand, intra- and postoperative coagulopathy commonly observed after cardiac surgery, lead to an increased need for the transfusion of blood products and surgical re-exploration. The definition of bleeding is still debated [101], but mild bleeding occurs in almost one fifth and major bleeding 3 – 12 % of cardiac surgery patients [102]. A mean blood volume of 470 ml is lost during the first 12 hours after cardiac surgery [103]. Contributing factors to coagulopathy are consumption and dilution of platelets and coagulation factors and heparinization during CPB, as well as effects of preoperative drugs and preexisting anemia and low fibrinogen-levels. The transfusion of the allogeneic blood products is associated with

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inflammation, transfusion-associated lung- and kidney injury and increases risk of stroke [28]. Overall, coagulopathy and major bleeding increase the risk of stroke, acute kidney injury, infections, surgical reoperation, LOS and mortality [102 – 104].

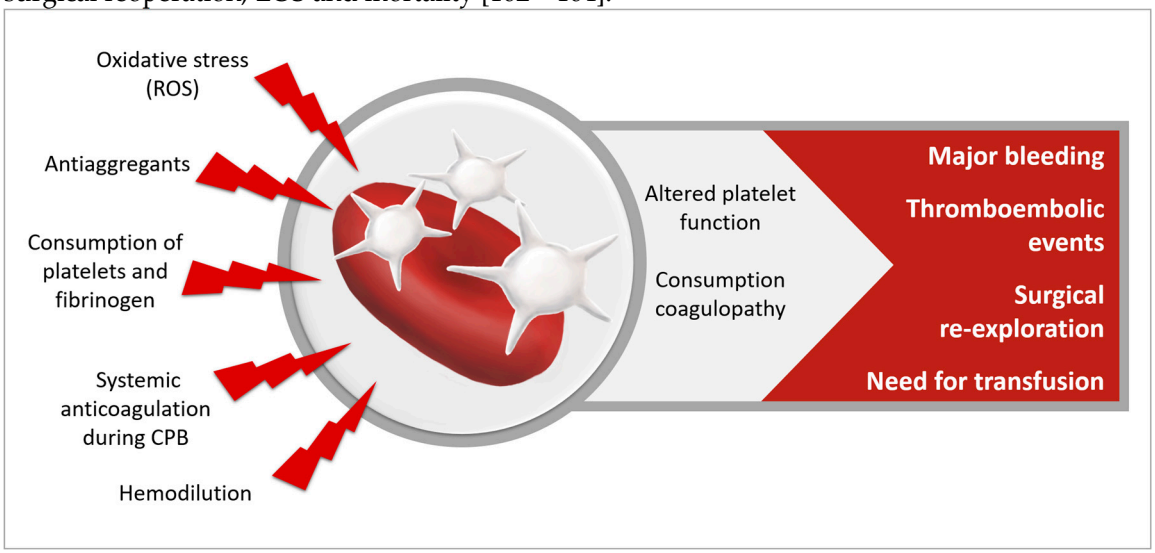

Figure 7. Coagulation disorders after cardiac surgery

2.6.2. Role of Vitamin C in the Coagulation System

Vit C has a tremendous impact on cellular and plasmatic hemostasis in the human body and has both pro- and anticoagulatory effects. The interaction between coagulation and Vit C supplementation was already discussed in the early 1960s by Dayton and Weiner [105].

On a cellular level, antioxidants, such as Vit C may inhibit platelets by scavenging ROS, disrupting the vicious circle of ROS-platelet-activation and restoring normal platelet function [99]. In healthy individuals, prostacyclin and NO prohibit platelet activation and prevent thrombosis. Vit C however, inhibits the expression of inducible nitric oxide synthetase (iNOS) in endothelial cells and neuronal nitric oxide synthetase (nNOS) and thereby lowers the plasmatic level of nitric oxide (NO) [10], hence acting pro-coagulatory. However, Vit C also prevents microthrombus formation through inhibition of thrombin-induced and P-selectin mediated platelet aggregation and platelet-endothelial adhesion [10]. Even after the onset of microthrombus formation, ascorbate injection even reverses capillary plugging and platelet-endothelial adhesion [10]. Ascorbate also inhibits the pH-dependent thrombin-induced release of plasminogen-activator-inhibitor-1 from platelets [10].

The plasmatic coagulation is influenced by Vit C via several pathways. ROS and other stimuli activate NF-κB. The transcription factor NF-κB initiates the expression of cytokines and proteins involved in coagulation, such as tissue factor [106]. This suggests that coagulation via NF-κB can be affected by Vit C [107, 108]. Furthermore, Vit C decreases tissue plasminogen activator and von Willebrand-factor, demonstrating an important link between inflammation, coagulation and Vit C [108, 109]. Vit C is also known to restore the capacity for endogenous, endothelium-dependent fibrinolysis in smokers [110].

On a systemic level, the influence of Vit C on the hemostasis might be dose-dependent. While depleted Vit C levels are associated with gastrointestinal hemorrhage especially in patients undergoing acetylsalicylate-treatment [111], in very high dosages (0.5 – 1 g/kg), Vit C was found to promote the occurrence of thrombosis through pro-coagulant activation of erythrocytes in a rat model [112]. Vit C abolished coagulation abnormalities in septic mouse blood [71] and attenuated a sepsis-induced drop of thrombocytes in the systemic blood in septic patients [10].

2.6.3. Vitamin C´s Influence on the Coagulation System in Cardiac Surgery Patients

To our knowledge, only two studies of Vit C in cardiac surgery have addressed the issue of hemostasis. In one RCT from Sadeghpour et al. (n=290), Vit C reduced chest tube bleeding [113], while no difference was shown in another RCT [57]. Clearly, further research is needed to determine

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the influence of Vitamin C on blood loss, need for transfusion and risk of thromboembolic events and to translate biochemical pathways into clinically relevant outcomes.

2.7. Immune System

2.7.1. Immune dysfunction after Cardiac Surgery

After cardiac surgery, infections are the most common non-cardiac complication [114], (Figure 8). A quarter of all patients undergoing high-risk heart-surgery are diagnosed with a postoperative infection [115], and nearly 5 % experience major infection. Pneumonia is the most frequent nosocomial infection in half of these cases. Surgical site infections and catheter- and device-associated infections each make up 25 % of infections [115, 116]. Major infections have a tremendous effect on subsequent survival and are associated with longer mechanical ventilation, ICU- and hospital stay and a higher morbidity and mortality up to 5 years after the operation [63, 114, 115, 117 – 125].

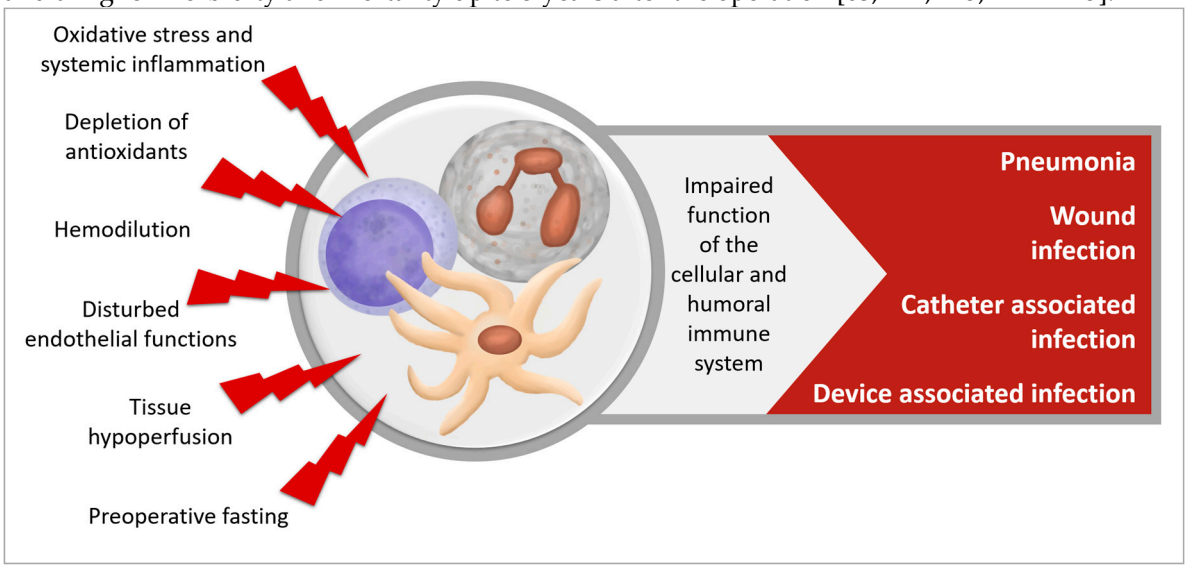

Figure 8. Dysfunction of the immune system after cardiac surgery

2.7.2. Role of Vitamin C in the Immune System

Infections are associated with and accompanied by an increase of oxidative stress. The increased ROS production during infection, and hypermetabolic Vit C requirements are the reasons for the observed Vit C reduction [126, 127].

Vit C is actively accumulated into the dermal cells and neutrophils via the sodium-dependent Vit C transporters (SVCT). Neutrophils further increase their intracellular Vit C concentration through uptake of DHA via glucose transporters (GLUT) and metabolization to ascorbate [127]. The accumulation of Vit C in phagocytotic cells can enhance chemotaxis, phagocytosis, generation of ROS and microbial killing. Vit C is also necessary for apoptosis and the clearing of spent neutrophils from the infected site. Vit C enhances the proliferation and differentiation of B and T-cells. Vit C deficiency results in impaired immunity and thus, higher susceptibility for infections.

Vit C supports endothelial barrier function against pathogens and promotes antioxidant scavenging activity of the skin. Vit C is a known inhibitor of bacterial growth, such as *S. aureus* and intestinal bacteria. One possible mechanism for the antibacterial function of Vit C is the production of hydrogen peroxide during its oxidation [13]. Vit C also shortens time to wound healing through stimulation of proliferation, differentiation and migration of keratinocytes and fibroblasts, as well as through the stimulation of lipid synthesis [127]. Vit C also enhances microbial killing through improved immune cells chemotaxis, motility and phagocytosis and decreases necrosis through facilitation of apoptosis and clearance [127]. Differentiation and proliferation of B and T lymphocytes is stimulated by Vit C as well, enhancing antibody levels.

However, the increased ROS production by the immune system is an important response to invasive pathogens. Therefore, if radical-scavenging role of Vit C is solely beneficial, remains debated and most likely dose-dependent. The systemic effect of Vit C on bacterial and viral infections needs further research, while current evidence demonstrates that Vit C might prevent the development, or ameliorate the clinical course of pneumonia [128, 129]. Vit C deficiency was associated with increased inflammation as measured in CRP and patients with septic shock were deficient in Vit C in 40 % in an observational study by Carr et al. [12]

2.7.3. Vitamin C´s Influence on the Immune System in Cardiac Surgery Patients

Unfortunately, again, there is little knowledge about the influence of Vit C on postoperative immune function and infections in cardiac surgery. Sadeghpour at al reported a significant reduction in the composite outcome "complications", defined as death, infection, impairment in renal function and need for reoperation [113]. Neither the incidence of infection, nor the influence of infection on the whole combined outcome parameter were reported in this study. Jouybar 2012 et al. [130] showed no difference in white blood count and inflammatory mediators using two bolus dosages of 3g of Vit C 12 – 18 h before surgery and during CPB initiation.

3. Influence of Vitamin C on the Overall Clinical Outcome of Cardiac Surgery Patients

Considering the above-mentioned evidence and the data gained from meta-analyses and RCTs, as listed in Table 2 and Table 3, Vit C may have positive effects on many vital functions and organ systems, which overall may have beneficial effects on patients short, mid and longterm outcomes.

- The overall effect is reflected by a reduced ICU-LOS in a meta-analysis of Geng et al. including 12 RCTs and 1584 patients [25] and Baker et al., including 11 RCTs and 1390 patients.
- Reduced hospital LOS was demonstrated in a systematic review 2014 including 5 RCTs [58], as well as the meta-analyses of Geng [25] and Baker [59] and Shi et al., including 13 trials involving 1956 patients [60]. However, in the meta-analysis by Hu et al. including 8 RCTs and 1060 patients, Vit C application was not associated with reductions in ICU or hospital-LOS [23].
- Vitamin C might also reduce intubation time and postoperative complications as found by the meta-analyses of Hu and Shi [25, 60].

However, all meta-analyses observed significant clinical heterogeneity of the included studies. In addition, effects on LOS in unblinded studies are subject to performance bias due to cointerventions or differentially applied policies on discharge. Additionally, none of the available RCTs included in these meta-analyses was adequately powered to detect an influence of Vit C on overall clinical outcomes, such as on LOS or mortality, as discussed by Polymeropoulos et al. [24].

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456 **Table 2.** RCTs investigating the effects of Vitamin C in cardiac surgery. (p.o.= per os, i.v.= intravenous, sign. =
457 significantly, N.A.= not available, WBC= white blood count, preop = before surgery, postop= after surgery)

Author and Year	Patients	Dosage of Vitamin C	p.o/ i.v.	Results
Knodell 1981 [131]	175 + hepatitis	Preop: 4 x 800 mg/d for 2 days Postop: 4 x 800 mg/d for 2 weeks	p.o.	Elevations of plasma Vit C, no influence on the hepatitis
Li 1990 [132]	20	Preop: 250 mg/kg before the start of extracorporeal circulation	N.A.	Sign. reduction in lipid peroxidation
Dingchao 1994 [55]	85 CPB	125 mg/kg 30 minutes before surgery and at the end of CPB	i.v.	Decreased CK/ CKMB, LDH, & rate of defibrillation, ICU- and hospital LOS, improved CI
Carnes 2001 [133]	86 CABG	Preop: 1 x 2 g the night before Postop: 2 x 0.5 g/d for 5 days	N.A.	Lower rate of AF
Demirag 2001 [134]	30 elective	Group 1: 2 x 50 mg/kg Vit C at induction and end of CPB Group 2: Vit C +diltiazem: bolus and 2 µg/kg/min until end of CPB	i.v.	Prevention of lipid peroxidation no difference in myocardial I/R-injury
Eslami 2007 [135]	100 CABG	Preop: 1 x 2 g night before Postop: 2 x 1 g/d for 5 days	p.o.	Lower rate of AF
Colby 2011 [136]	24 CABG and/ or valve	Preop: 1 x 2 g night before Postop: 2 x 0.5 g/d for 4 days	p.o.	No difference in CRP, WBC, fibrinogen, Trend: decreased AF, hospital- and ICU-LOS
Papoulidis 2011 [137]	170 CABG	Preop:1 x 2 g 3 h prior to surgery Postop: 2 x 0.5 mg/d for 5 days	i.v.	Sign. lower rate of AF, hospital- and ICU-LOS
Bjordahl 2012 [138]	185 CABG	Preop: 1 x 2 g night before surgery Postop: 2 x 1 g/d for 5 days	p.o.	No difference in postoperative complications, mortality or AF
Jouybar 2012 [130]	40 CABG	Preop: 2 x 3 g 12 – 18 h before surgery and during CPB initiation	i.v.	No difference in inflammatory cytokines, hemodynamics, blood gases, urea nitrogen, creatinine, WBC, platelet counts & outcomes
Dehghani 2014 [139]	100 CABG	Preop: 1 x 2 g Postop: 2 x 0.5/d g for 5 days	p.o.	Sign. lower rate of AF, hospital- and ICU-LOS
Ebade 2014 [140]	40	Preop: 1 x 2 g Postop: 1 x 1 g 12 h after surgery, 3 x 1 g for 6 days after surgery	i.v.	Lower incidence of AF Shortened ICU- and hospital-LOS
Sama-dikhah 2014 [141]	120 CABG	Preop: 1 x 2 g Postop: 1x 1 g/d for 5 d days Plus atorvastatin 40 mg	p.o.	Sign. lower rate of AF
Sadegh-pour 2015 [113]	290 CABG, valve	Preop: 1 x 2 g before surgery Postop: 1x 1 g/d for 4 days	Preop: i.v. Postop: p.o.	Sign. reductions in AF, hospital-LOS, intubation time, complications (death, renal function, infection) and drainage, unchanged ICU-LOS
Das 2016 [56]	70 elective low risk CABG	Preop: 2 x 0.5 g for 7 days prior to surgery	p.o.	Lower vasopressors-demand, no difference in time to extubation, ICU- and hospital-LOS, mortality or complications
Antonic 2016 [142]	105 CABG	Preop: 2 x 2 g: 24 and 2 h before surgery Postop: 2 x 1 g/d for 4 days	i.v.	Trend: decreased rate of AF, no difference in complications
Antonic 2017 [90]	100 CABG	Preop: 2 x 2 g: 24 and 2 h Postop: 2 x 1 g/d for 5 days	i.v.	No sign. protective effect of ascorbic acid on the incidence of postoperative AKI

458

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4. Vitamin C in Combination with other Antioxidant Therapies

Vitamin C has been combined with other antioxidant substances to minimize oxidative damage, as well as with anti-arrhythmic drugs such as beta-blockers and diltiazem with the objective to reduce the incidence of postoperative cardiac arrhythmia. In combination with beta-blockers, the incidences of AF and ICU-LOS were significantly reduced compared to CABG-patients who only received beta-blocker pre-surgery [57].

Vitamin C also regenerates α-Tocopherol (Vit E), therefore, a combination therapy might offer more benefits compared to a monotherapy [5]. A combination of Vit C and E significantly reduced 28-day mortality and duration of mechanical ventilation in ICU patients in a study by Crimi et al. [143]. Howe et al. observed a reduction of mechanical ventilation and a trend towards reduced all-cause mortality and ICU-LOS in critically ill patients [144]. In cardiac surgery patients, the combined Vit C and E therapy lowered oxidative stress, as demonstrated by lower lipid oxidation and lysosomal enzyme activity [145], improved function of the pulmonary vessels [146] and seemed to have an anti-inflammatory effect as measured in lower CRP levels in a study by Gunes et al. [147], see also Table 3.

Table 3. RCTs investigating antioxidant cocktails in cardiac surgery

Author and Year	N	Treatment	Outcomes
Barta 1991 [145]	20	Preop: 2000 IU Vit E: 12 h before surgery; 2 g Vit C in the morning on the day of surgery	Inhibition of the decrease of catalase Lower lipid oxidation and lysosomal enzymes in intervention group
Westhuyzen 1997 [148]	76	Preoperative (7-10 days): 1g Vit C and 750 IU Vit E	Supplementation of the vitamins prevented depletion, but provided no clinical advantage
Angdin 2003 [146]	22	Preop: 900 mg Vit E for 10-14 days plus 1 x 2 g Vit C and 600 mg allopurinol the evening before surgery, and acetylcysteine during surgery	Reduction of pulmonary vascular endothelial dysfunction in the group treated with antioxidants
Castillo 2011 [149]	95	Preop: for 7 days n-3 PUFA 2g/d Plus, for 2 days preop until discharge Vit C 1g/d and Vit E 400IU/d	Decrease in oxidative stress-related biomarkers in atrial tissue
Gunes 2012 [147]	59	Preop: Vit C 500 mg and Vit E 300 mg Postop: Vit C 500 mg/d and Vit E 300 mg/d for 4 days	Significant reduction of CRP
Rodrigo 2013 [150]	203	Preop: 1 g/d Vit C plus PUFA and Vit E for 2 days preop until discharge	Decrease in oxidative stress-related biomarkers in atrial tissue
Stanger 2014 [151]	75	4 subgroups: control, vitamins, n-3 PUFAs, and a combination of vitamins and n-3 PUFAs Vitamin group: 500 mg Vit C + 45 IE Vit E 30 minutes before reperfusion, postop and 120 minutes after reperfusion	Attenuation of postop oxidative stress, Oxidative stress associated with consumption of antioxidants and onset of AF
Rezk 2017 [57]	100	3 days preoperatively Group 1: ß-blocker: 5 mg bisoprolol and 2g/d Vit C Group 2: ß-blocker only	Significantly lower incidence in Vit C group, ICU-LOS, need for inotropes and mechanical ventilation

5. Practical Approach to Vitamin C Supplementation

5.1. Risks and Side Effects

As demonstrated above, many studies have supplemented Vit C, but significant adverse effects on patients in short term use have not yet been reported [15, 18, 113]. This is true for low, as well as for dosages of 200 mg/kg/d and up to extremely high dosages of 1500 mg/kg three times a week in

cancer patients [15]. Possible adverse effects are related to dosage, enteral route and duration of Vit C supplementation and include:

- Diarrhea and abdominal bloating [89]
- False negative tests for gastrointestinal occult bleeding [89]
- Aggravation of iron overload in patients with hemochromatosis or other diseases requiring frequent blood transfusions, such as thalassemia major and sideroblastic anemia [89]
- Possible adverse pro-oxidative effect in large dosages in case of iron overload [15]
- Possible hyperuricosuria [89]
- Formation of kidney stones through precipitation of calcium oxalate, especially in patients with chronic renal failure, hyperoxaluria and recurring formation of kidney stones [15, 89]
- Hemolysis in patients with hereditary glucose-6-phosphate dehydrogenase (G6DP) deficiency when administered in high dosages of > 4 g/d [89]
- False-high measurements of blood glucose in hand-held devices [152, 153]

5.2. Application Strategies

5.2.1. Dosing

Current literature does not support a specific Vit C dosing strategy in cardiac surgery, in the absence of a definitive trial. The dose typically administered by parenteral and enteral nutrition is 200 mg/d, which is recommended for the healthy population. In a study by Carr et al., standard enteral or parenteral nutritional therapy with a mean of 125 mg/d did not prevent hypovitaminosis C in critically ill patients [12]. Even after less invasive and elective surgery, such as maxilla-facial surgery, higher dosages (500 mg – 2000 mg/d, mean 1150 mg/d) were required to increase plasma Vit C levels and compensate for the observed loss [13, 154, 155]. In patients experiencing significant inflammation and oxidative stress, such as trauma, burn, sepsis and cardiac surgery patients, the Vit C requirement seems to increase dramatically. A dosage of 3 – 4 g/d parenterally seems necessary to normalize the Vit C plasma levels in patients with burns or sepsis [15] or critically ill trauma patients [14]. Probable causes for this high demand are higher consumption due to the antioxidant capacity of Vit C, as well as increased renal clearance during Vit C substitution.

Fowler et al. recently published a phase 1 clinical trial suggesting that 200 mg/kg/day yields higher plasma levels of vitamin C and more favorable Sequential Organ Failure Assessment (SOFA) scores compared to 50 mg/kg/day in severely septic patients [17]. A very high dosage of 66 mg/kg/h for the first 24 hours was used in the study by Tanaka et al. in burn patients, which led to reduced fluid demand and increased urine production [20, 21].

In cardiac surgery patients, the dosing regimen used in the previously mentioned studies are extremely heterogenous. Most studies use a single dose of 2 g once prior to surgery. Postoperatively, a very small dosage of less than 1 g/d was administered [113, 131, 133, 136, 137, 139, 141]. However, single-dosages as high as 150 mg/kg [55] or 250 mg/kg have also been applied [132]. To our knowledge, there is no dose-finding study available in cardiac surgery patients yet.

5.2.2. Timing

The oxidative damage is highest minutes after reperfusion, hence an early administration may be optimal. Logically, preoperative administration might refuel the body´s antioxidant capabilities, preparing for CPB. Application of a dosage before the removal of the aortic cross-clamp and reperfusion might achieve the minimal ROS-scavenging plasma-levels of 1 – 10 mmol/l [15].

In one study, the cardiac index was significantly higher in the first 6 hours after the operation in patients receiving a mega-dose of 125 mg/kg, suggesting that the effect of Vit C might wear off after that period of time [55]. Ruemelin et al. showed a rapid decrease in plasma concentration after the end of the infusion [155]. In the study by Tanaka [21], serum levels of Vit C increased quickly under continuous infusion, remained elevated until 12 hours after infusion and decreased rapidly.

5.2.3. Mode of Administration

One possibility to counteract the rapid metabolic clearance and drop of plasma Vit C levels would be a continuous infusion, which is feasible and effective under UV-protection [21]. However, Vit C´s lability allows for degradation of the vitamin before it enters the patient. Another option might be frequent bolus dosing, as used in the trial by Fowler et al. [17].

Another question not yet answered is the route of administration. Through enteral supplementation, serum Vit C cannot be raised to physiological levels, even if the highest tolerated dosage is administered enterally [12]. When Vit C is supplemented parenterally, supraphysiological dosages can safely be administered and the antioxidant effects of Vit C may be increased. [15]. On the other hand, even an oral application of Vit C has shown to be beneficial in the RCTs by Sadeghpour [113], and Dehghani [139].

5.2.4. Monitoring

As outlined before, Vit C can be measured in its oxidized form DHA. When monitoring DHA in blood samples, it has to be kept in mind that ascorbic acid is sensitive to oxidation and degradation during blood sampling, handling, storage and analysis. Therefore, the handling, storage and following shipment to reference laboratories may be problematic [156]. Factors influencing the stability of DHA in whole blood and serum are temperature, light-exposure, pH, contamination with copper or iron and anticoagulant of the blood sample [157, 158], as well as dissolved oxygen, solvent, ionic strength, trace metals and oxidizing enzymes. In a refrigerator at 4 °C, the degradation of Vit C within 24 hours is 1.8 % in serum tubes and 7.2 % in plasma tubes [159].

Therefore, blood samples should be drawn immediately pushed into crushed ice in a light protected box and be delivered within 2 hours for reliable Vit C measurements [160]. When whole blood is immediately centrifuged, acidified and stored at -70 °C, ascorbic acid degrades very slowly and can be analyzed for at least 6 years. However, due to different degradation rates depending on the acid and anticoagulant used in sampling tubes, a quick analysis seems preferable [157, 161]. High performance liquid chromatography (HPLC) with electrochemical detection is the current gold standard of Vit C measurement, which usually requires the stabilization of Vit C through acid or alcohol precipitation usually combined with a metal chelator [158]. Robitaille and Hoffer showed that the simpler UV light detection is equivalent to the electrochemical detection [156]. A recent study by Pullar et al. demonstrated a good stability of DHA for up to a year at -80°C both as plasma, as well as in extracts with perchloric acid (PCA) containing 100 µmol/l of the metal chelator diethylenetriaminepentaacetic acid (DTPA) extracts, with a loss of 8 % in 12 months [158].

Considering these influencing factors, the measurement of Vit C is elaborate and costly and therefore, not readily accessible in the ICU.

5. Conclusion and Future Directions

The many ways of Vit C to attenuate inflammation and oxidative damage lead to an increasing interest in its clinical application. Preclinical as well as preliminary clinical studies demonstrated beneficial effects of Vit C on the organ function during inflammation and oxidative stress.

Until now, no serious adverse events have been reported in any of the cited studies, highlighting the safety of this pharmaco-nutrient. However, the number of studies investigating the effect of Vit C in cardiac surgery is very small and results are inconclusive, yet. This might be due to the heterogeneity of dosage, route of administration, time points, choice of endpoints and settings. Importantly, neither the specific population, nor dosage and timing of Vit C application have yet to be elucidated in cardiac surgery. Despite the outlined pleiotropic effects on different organ functions, no study investigated the impact of Vit C on clinical outcomes after cardiac surgery. Yet, given the summarized promising evidence, further trials in cardiac surgery patients with complex surgical procedures are encouraged.

Any conclusive evidence of the benefits in cardiac surgery patients would lead to rapid implementation of this promising therapy for four reasons: 1) the overall well safety profile of vitamin

C which may enable a broad use; 2) the feasibility of the Vit C administration without any dose adjustments; 3) familiarity to clinicians and patients as a therapy for cancer and in some burn units; 4) low costs to produce and to administer.

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Appendix A: Abbreviations

AA	Ascorbic Acid
AF	Atrial Fibrillation
AKI	Acute Kidney Injury
CABG	Coronary Artery Bypass Graft
CI	Cardiac Index
CK	Creatine Phosphokinase
CK-MB	Creatine Kinase-Muscle/Brain
CPB	Cardiopulmonary Bypass
CRP	C-reactive Protein
DHA	Dehydroascorbate
DTPA	Diethylenetriaminepentaacetic acid
GI	Gastrointestinal
HPLC	High Performance Liquid Chromatography
ICU	Intensive Care Unit
IL	Interleukin
iNOS	Inducible Nitric Oxide Synthetase
I/R	Ischemia/Reperfusion
i.v.	Intravenous
LCOS	Low Cardiac Output Syndrome
LDH	Lactate Dehydrogenase
LOS	Length of Stay
N.A.	Not Available
NADPH	Nicotinamide Adenine Dinucleotide Phosphate
NFκB	Nuclear Factor kappa-light-chain enhancer of activated B cells
nNOS	Neuronal Nitric Oxide Synthetase
NO	Nitric Oxide
PCA	Perchloric Acid
PCT	Procalcitonin
PN	Parenteral Nutrition
p.o.	Per Os
POCD	Postoperative Cognitive Dysfunction
Postop	Before Surgery
Preop	After Surgery
PUFA	Poly Unsaturated Fatty Acids
QOL	Quality of Life
RCT	Randomized Controlled Trial
ROS	Reactive Oxygen Species
Sign.	Significantly
SIRS	Systemic Inflammatory Response Syndrome
SOFA	Sequential Organ Failure Assessment
SVCT2	Sodium-dependent Vitamin C Transporter-2

TNFα	Tumor Necrosis Factor α
Vit C	Vitamin C
Vit E	Vitamin E / α-Tocopherol
WVC	White Blood Count

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