Review

Preventing Myocardial Injury Following Non-Cardiac Surgery: A Potential Role for Preoperative Antioxidant Therapy with Ubiquinone

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Abstract: Over 240 million non-cardiac operations occur each year and are associated with a 15–20% incidence of adverse perioperative cardiovascular events. Unfortunately, preoperative therapies that have been useful for chronic ischemic heart diseases, such as coronary artery revascularization, antiplatelet agents, and beta-blockers have failed to improve outcomes. In a preclinical swine model of ischemic heart disease, we showed that daily administration of ubiquinone (coenzyme Q10, CoQ10) enhances the antioxidant status of mitochondria within chronically ischemic heart tissue, potentially via a PGC1α-dependent mechanism. In a randomized controlled trial, among high-risk patients undergoing elective vascular surgery, we showed that NT pro-BNP levels are an important means of risk-stratification during the perioperative period and can be lowered with administration of CoQ10 (400 mg/day) for 3 days prior to surgery. The review provides background information for the role of oxidant stress and inflammation during high-risk operations and the potential novel application of ubiquinone as a preoperative antioxidant therapy that might reduce perioperative adverse cardiovascular outcomes.

Keywords: CoQ10; ubiquinone; myocardial injury; troponin; BNP; vascular surgery; outcomes

1. Introduction

It has been estimated that over 240 million major non-cardiac surgical procedures are scheduled each year, with at least 1 in 6 suffering from adverse events that occur during those surgeries including a 30-day risk of either death or significant cardiovascular complication [1,2]. Based on the magnitude of these clinical consequences, numerous studies have been completed to focus on strategies that might modify cardiac risks before scheduling major operations that do not involve the heart [3]. In a randomized controlled study involving over 500 veterans undergoing elective vascular surgery and 20 medical centers within the Veterans Affairs (VA) health care system, we demonstrated that a strategy of preoperative coronary artery revascularization before an elective vascular surgery did not reduce the long-term risk of death at 2.7 years following the operation [4]. Using an additional preoperative strategy with a preconditioning protocol, we also failed to reduce the incidence of postoperative elevations in cardiac troponin [5]. Other randomized controlled trials have tried to reduce adverse perioperative outcomes and have targeted well-accepted risk factors among patients undergoing elective surgery, including pharmacological agents that are known to reduce secondary outcome measures in patients with...
coronary artery disease. Unfortunately, they have not consistently shown that the incidence of postoperative adverse cardiovascular events can be mitigated [6–8]. Clearly, strategies that modify traditional risks of patients with chronic ischemic heart disease have not proven effective in reducing perioperative ischemic events and myocardial injury (MINS) following high-risk surgery. In a sub-study of our trial, termed the coronary artery revascularization prophylaxis (CARP) trial, we showed that the incidence of elevated cardiac troponin following surgery was not reduced with preoperative coronary artery revascularization, yet was a powerful predictor of long-term risk of adverse outcomes [9]. These data are consistent with other trials [10,11] and emphasize the important fact that cardiac troponins provide incremental value in post-operative risk-stratification [12]. There may be value in assessing cardiac biomarkers following surgery because among patients with an elevated troponin who had their medical regimen maximized, rehospitalization rates following discharge were lower than those individuals with an elevated troponin who did not have a change in therapy [13].

An emerging strategy that has been advocated is the use of preoperative cardiac biomarkers as a means of identifying those individuals at risk for postoperative adverse cardiac events [14]. In that regard, measurement of the cardiac biomarker, Brain Natriuretic Peptide (BNP) before non-cardiac operations is considered a Class I indication, as recommended by the Canadian Cardiovascular Society for Perioperative Care [15]. That guideline was based on evidence that BNP levels correlate with postoperative troponin levels and predict risk of complications within 30 days following surgery [16–18]. Of interest, in a randomized controlled trial involving patients with heart failure, these biomarkers were lowered by administration of coenzyme Q10 (CoQ10) [19]. Conceivably, pharmacological interventions that lower BNP might prove effective in reducing postoperative myocardial injury. In the present review, the goal is to review relevant work from perioperative care and outline how a new approach to reducing oxidant stress and inflammatory signals might reduce injury. The focus of our review is to gather relevant references in perioperative medicine as well as on the potential value in the application of ubiquinone by using a search system that encompasses basic and translational sciences, as defined by approaches recommended and outlined by the PRISMA guidelines.

2. Preoperative Risk Assessment and Postoperative Adverse Outcomes

For over four decades, clinical researchers have developed several models to identify high-risk patients prior to elective vascular surgery [3]. In a comprehensive approach, Lee and colleagues validated six clinical risk variables that independently predict adverse postoperative events following surgery [20]. Terted the Revised Cardiac Risk Index, these variables include a history of coronary artery disease, stroke, heart failure, insulin-dependent diabetes, creatinine >2.0 mg%, and high-risk operations that include vascular surgery. In a cohort of the CARP trial, we showed that these variables were highly predictive of either death or myocardial infarction within the first 30 days post-surgery, but the risk of adverse events in those subsets could not be lowered with preoperative coronary artery revascularization [21]. Additional randomized controlled studies that targeted therapies for chronic ischemic heart disease, including beta-blockers, aspirin, clonidine, and statins did not show consistent results in preventing myocardial injury following non-cardiac surgery (MINS) [6–8,22,23]. In a large cohort of patients undergoing surgery [24], BNP was used as a preoperative biomarker for improving risk-stratification [14] and has now been incorporated into Canadian guidelines for the risk-assessment of patients undergoing elective vascular surgery [25]. Considering that BNP level is a modifiable variable, we completed a pilot study to determine whether preoperative administration of CoQ10 might reduce BNP in patients undergoing high-risk vascular surgery. In that regard, the primary results of our randomized controlled trial was that N-terminal pro hormone BNP (NT-proBNP) levels before and after the procedure predicted risk for having myocardial injury as well as having a prolonged post-operative hospitalization period following the elective operation (Figure 1) [2]. These observations are consistent with
those of Canadian investigators in use of perioperative cardiac biomarkers prior to non-cardiac operations [25]. Of interest and important for the development of new approaches in perioperative care, we also showed that preoperative administration of coenzyme Q₁₀ (CoQ₁₀) for 3 days prior to the elective vascular surgical procedure reduced perioperative NT-proBNP levels [2] (Figure 2). These data support the notion that perioperative use of antioxidant therapies may play a critical role in reducing the incidence of cardiac biomarker elevations and possibly improve outcomes following hospital discharge. Clearly, a novel approach to preventing myocardial injury following high-risk surgery is needed. This would require a shift in paradigm, addressing the biological significance of oxidant stress and inflammatory signaling that is incorporated in the pathophysiology of cardiac biomarker release.

Figure 1. Among the entire group of patients undergoing elective vascular surgery (n = 123), an elevated N-terminal pro hormone BNP (NT-proBNP) level predicted those patients who would have myocardial injury (elevated postoperative troponin level) as well as those patients who had a longer postoperative stay in the hospital. These data show the importance of NT-Pro BNP levels before and after the operation for perioperative risk-stratification [2]. Values are expressed as medians, interquartile values, and means. Permission was granted to reproduce the data.

Figure 2. Patients were randomized to either coenzyme Q₁₀ (CoQ₁₀) (n = 62) or placebo (n = 61) for 3 days before elective vascular surgery, and as shown, NT-Pro BNP levels were lower with treatment. The degree of injury, as defined by the change (delta) in troponin I levels from baseline to peak postoperative level, was higher in the placebo compared with that of the CoQ₁₀ treatment group [2]. Values are expressed as medians, interquartile values, and means. Permission was granted to reproduce the data.
3. Oxidant Stress and Cardiovascular Disease

Oxidative stress is a well-known factor involved in cardiovascular diseases including ischemia-reperfusion and heart failure [26]. While a small amount of ROS (reactive oxygen species) may play a physiological role in signaling transduction, uncontrolled ROS formation, especially during early reperfusion, increases oxidative stress and cell injury [26–28]. The burst in ROS generation is a critical factor in the increased opening of mitochondrial permeability transition pores (MPTPs) that increases cell injury during ischemia-reperfusion [29,30]. The MPTP is a non-selective pore that is located in inner mitochondrial membranes [31]. MPTP opening leads to increased permeability of the inner membrane that triggers mitochondrial damage. A permeabilized inner membrane during MPTP opening may augment ROS generation by increasing electron flow into the electron transport chain due to uncoupled respiration [32]. The permeation of the inner membrane leads to decreased ATP generation by depolarizing inner mitochondria membrane potential [31]. MPTP opening also leads to increased permeability of the outer membrane by inducing mitochondrial matrix swelling through accumulation of calcium and H₂O within the matrix [33]. Proteins located within the mitochondrial intermembrane space, including cytochrome c and apoptosis-inducing factor (AIF), are translocated into the cytosol through the leaky outer membrane and increase apoptosis in both a caspase-dependent and caspase-independent manner [34–36]. An increase in ROS generation also impairs cardiac function by oxidizing the proteins involved in cardiac contractile activity [37]. ROS generation impairs mitochondrial quality control mechanisms including inhibition of autophagy, which is a key process for removing dysfunctional mitochondria in the heart [38]. The increased ROS production also increases apoptotic cell death and cardiac hypertrophy by activating signaling transduction [39]. ROS generation also increases ventricular fibrosis, including in aged hearts, by activating cardiac fibroblasts [39,40]. ROS generation can also increase ER (endoplasmic reticulum) stress [41,42] that contributes to mitochondrial dysfunction and cardiac injury during aging [43]. The ER not only plays a critical role in protein folding and lipid synthesis but is a calcium storage site and regulates calcium homeostasis [41,43]. An increase in misfolded proteins within the ER causes ER dysfunction (ER stress) [44]. The initial response to the ER stress is an attempt to restore ER function by slowing down protein synthesis. However, prolonged ER stress increases cell injury. Induction of acute ER stress using thapsigargin increases cell death by impairing mitochondrial function in adult hearts [44–47]. ER stress is increased in the heart with aging [43]. Chronic treatment with 4-phenylbutyrate (4-PBA), which is a chemical chaperone that stabilizes protein conformation within the ER, improves mitochondrial function in aged hearts [43], supporting the notion that ER stress contributes to mitochondrial dysfunction during aging. Although the mechanisms by which aging leads to increased ER stress remains unclear, ROS generation is a potential causative factor. Therefore, future studies should consider whether the attenuation of ROS generation by overexpression of either catalase [48] or CoQ treatment [19] can decrease ER stress in aged hearts.

In addition to the direct damage caused by free radicals, oxidative stress can increase mitochondrial and cell injury by facilitating proteases, including calpain activation [49]. Calpains are a family of calcium-activated cysteine proteases that include 14 isoforms [49]. Ubiquitous calpains, including calpain 1 and calpain 2, exist in cytosol and mitochondria [49,50], and their activation increases tissue injury during myocardial ischemia and reperfusion [34,51–57]. In fact, the activities of calpain 1 and calpain 2 are both increased in isolated hearts following ischemia-reperfusion [49]. Cytosolic calpain 1 activation leads to cleavage of proteins including bid, Na⁺,K⁺-ATPase, Ca²⁺-ATPase, spectrin, and troponin T [49,55–57]. Activation of calpain 1 impairs cardiac function by degrading contractile proteins including junctophilin-2 [58]. Ischemia-reperfusion also leads to increased activities of mitochondrial calpain 1 [34] and calpain 2 [50]. Activation of mitochondrial calpain 1 and calpain 2 leads to a damaged electron transport chain (ETC) and MPTPs that are sensitized to opening [34,50,54,59]. Interestingly, elevated calcium concentrations, even in pathological conditions, are below the threshold to activate calpain 1 and calpain 2 [49].
However, the calcium concentration required to activate calpain 1 and calpain 2 is markedly decreased in the presence of oxidative stress [60,61]. Thus, increased ROS generation may be a key co-factor to activating calpain 1 and calpain 2 during cardiac stress states including catecholamine exposure, ischemia-reperfusion, heart failure, and aging [62]. Thus, ROS generation at the time of a major, high-risk operation can lead to cell injury through direct oxidation of proteins and indirectly facilitate proteases activation.

In cardiac myocytes, most ROS are generated from the electron transport chain (ETC) [26–28]. Superoxide anion (•O₂⁻) is the most abundant ROS in cells [63]. The superoxide anion is formed when O₂ captures an additional electron leaking from the ETC. Superoxide anions are the base for generating other types of ROS, including hydrogen peroxide (H₂O₂), hydroxyl (•OH), and peroxynitrite (ONOO⁻). Since most ROS are generated at the ETC, it is not surprising that the initial target of ROS damage is in the ETC itself [64]. Prevention of electron flow into the ETC leads to decreased ROS generation in control [65] and ischemia-damaged mitochondria [66,67]. Inhibition of proximal electron flow through the ETC reduces cardiac injury during reperfusion by decreasing ROS generation [30,68,69] and calcium overload [69]. Blockade of the electron transport also decreases cardiac injury in aged hearts following ischemia-reperfusion [70,71]. These results indicate that the mitochondrial respiratory chain is a key source of ROS production in cardiac myocytes. ROS generated by the ETC first impairs the ETC itself to further augment ROS generation [66]. Thus, the damaged ETC plays a central role in ROS generation [63] and, in that regard, may be an important pharmacological target during major operations.

Complexes I, II, and III are potential sites for ROS production by the ETC [26,72,73]. Complex I is the first respiratory complex and consists of a membrane arm embedded in the inner membrane and a peripheral arm oriented into the mitochondrial matrix [74,75]. The peripheral arm is responsible for NADH oxidation and subsequent electron transfer through complex I to ubiquinone [74]. The membrane arm is essential for proton pumping across the inner membrane. Although complex I is a key site of ROS generation, the exact sites (subunits) of ROS generation within complex I are poorly defined. Subunits in both the membrane arm, including N2, and the peripheral arm, including flavin mononucleotide (FMN), are proposed to be sites of ROS generation within complex I [76,77]. Complex I generates ROS through two mechanisms: forward (complex I → Q → complex III) or reverse (complex II → Q → complex I) electron flow-mediated ROS generation [78,79]. The forward flow-induced ROS generation requires an almost fully reduced condition within complex I [80]. This situation usually occurs when complex I is severely damaged or in the presence of complex I inhibitors including rotenone [65,68,81]. Ischemia-reperfusion damages complex I at its quinone binding sites, which leads to electron accumulation within complex I and increases forward flow-mediated ROS generation [82]. Inhibition of complex I using rotenone also increases ROS generation from complex I [65]. Blockade of electron transport at the distal site of the ETC including cytochrome oxidase also favors forward flow-induced ROS generation from complex I [62,83].

In addition to blocking electron transport at the individual respiratory complexes, disruption of supercomplexes can contribute to decreased oxidative phosphorylation and increased ROS generation [84]. The supercomplexes are assembled with complexes I, III, and IV in the ratio of 1:2:1 [62]. Formation of the supercomplexes increases the efficiency of electron transport and decreases ROS generation by reducing electron leakage from the ETC [85,86]. Destabilization of supercomplexes increases ROS generation from complex I [87,88]. The content of supercomplexes is decreased in mitochondria from aged or failing hearts [62]. This may lead to increased ROS generation from complex I during aging and heart failure.

Complex I can also produce ROS by inducing the reverse electron flow that occurs when succinate is used as a complex II substrate to provide electron flow from complex II to complex I [79,89]. Mitochondrial membrane potential is a driving force for the electron flow from complex II to complex I [78]. Thus, depolarization of mitochondrial membrane potential using an uncoupler [78,79] is an efficient approach to eliminate the reverse flow-
induced ROS generation. In addition, blockage of electron transport from complex II to I by using complex I [90] or complex II inhibitors also decreases the ROS generation by the reverse electron flow [79,89]. ROS generated by reverse electron flow also increases cell injury during ischemia-reperfusion [91,92].

As discussed above, complex II plays a role in reverse flow-induced ROS generation. The complex II may also directly generate ROS within complex II [93,94]. ROS generation by complex II is dependent on the succinate concentration [79]. High concentration of succinate (>5 mM used in most in vitro analysis) inhibits ROS generation from complex II. ROS generation is increased in complex II when a relatively low concentration of succinate (0.5 mM) is used in the presence of complex II inhibitor (thienyltrifluoroacetone (TTFA)) or a complex III Qo center inhibitor [93]. TTFA blocks electron transport at the terminal part of complex II, which increases electron accumulation within complex II and subsequent ROS generation [93]. In contrast, inhibition of complex II at the succinate-binding site with malonate decreases ROS generation from complex II due to decreased electron flowing into complex II [65].

Complex III is a key source of ROS generation in heart mitochondria [65,72]. ROS is generated in both the complex III Qo center (quinol oxidation site oriented to the mitochondrial intermembrane space) and the Qi center oriented to the mitochondrial matrix space. ROS produced at the Qo center are oriented to the intermembrane space and subsequent cytoplasm through voltage-dependent anion channel (VDAC) in the outer mitochondrial membrane [65,72,95,96]. ROS generated at the Qi center are released into the mitochondrial matrix and detoxified by mitochondrial antioxidants. Antimycin A is a classic complex III inhibitor that inhibits electron transport at the Qi center [65]. Antimycin A predominantly increases ROS generation from the Qo center. Myxothiazol or stigmatellin inhibit electron transport at the complex III Qo center [65,97]. Thus, inhibition of complex III using myxothiazol or stigmatellin leads to decreased ROS generation from complex III. As discussed above, myxothiazol or stigmatellin increases ROS generation from complex I or complex II based on the substrate usage. ROS generated from the complex III Qo center plays a critical role in aging and ischemia-reperfusion injury [97]. Recent study also showed that ROS generated by the Qo site of complex III increases ER (endoplasmic reticulum) stress [42].

The electron transport chain is not the only source of oxidant stress within mitochondria of heart tissue [27,62]. Monoamine oxidase (MAO), p66shc, and NOx4 are potential sources of ROS generation within mitochondria. MAO is located on the outer mitochondrial membrane and functions in the regulation of catecholamines and other biogenic amines [37]. MAO has two isoforms: MAO-A and MAO-B. Both MAO-A and B isoforms are equally expressed in human hearts. However, MAO-A is the major isoform in rat hearts, and the MAO-B is the major isoform in mouse hearts [37]. H2O2 is generated when MAO breaks down neurotransmitters, including norepinephrine, epinephrine, and dopamine [98]. MAO-mediated ROS generation contributes to cardiac injury [99], muscle dystrophy [100], and aging.

Another redox enzyme that exists in the mitochondrial intermembrane space is p66shc. It is one of the isoforms in the ShcA adaptor protein family [62,101] and has a cytochrome c binding region towards the N-terminal side end [101]. The cytochrome c binding domain is the redox center of p66shc [101,102]. In conditions with increased ROS generation, including cardiac ischemia, the cytochrome c binding domain in p66shc binds with cytochrome c leading to electrons transferring from cytochrome c to oxygen to increase ROS generation [101]. Downregulation of p66shc leads to decreased ROS generation and prolonged mouse life span, indicating that ROS generation from p66shc contributes to the aging process [103,104].
4. Antioxidants and Cardioprotection

Cells have antioxidant defenses to detoxify the ROS [63]. The antioxidant enzymes include superoxide dismutase (SOD), catalase, and glutathione peroxidase. SODs are the most effective antioxidant enzymes at converting superoxide anion (\(\bullet O_2^-\)) to hydrogen peroxide (H\(\text{H}_2\text{O}_2\)). SODs also inhibit the formation of peroxynitrite (ONOO\(^-\)) by preventing NO reaction with superoxides via the timely removal of superoxides [105]. SOD has three isoforms: cytosolic SOD1, mitochondrial SOD2, and extracellular SOD3. Since copper (Cu) and zinc (Zn) are required as cofactors for SOD1 and SOD3, these SODs are also called Cu-ZnSOD. SOD2 is also referred to as Mn(manganese)SOD in that the Mn is used as a cofactor in SOD2 [105]. Stimulation of SOD1/2 expression decreases cerebral injury during heart arrest and resuscitation [106]. Genetic disruption of the SOD2 gene increases oxidative stress and cardiac hypertrophy [107], supporting the concept that superoxide anions generated from mitochondria play a critical role in oxidative stress-induced cell injury.

Hydrogen peroxide is detoxified by antioxidants including catalase, glutathione peroxidase (GPX), and peroxiredoxins (PRDX) [63]. Catalase reduces H\(\text{H}_2\text{O}_2\) to H\(\text{H}_2\text{O}\), especially in the presence of high concentrations of hydrogen peroxide, and also functions as a peroxidase in conditions with low concentrations of hydrogen peroxide [108,109]. Aging leads to myocardial hypertrophy and dilatation, cardiac dysfunction, and increased fibrosis. Overexpression of mitochondrial-targeted catalase reverses these defects in aged mice. These results clearly show that increased mitochondrial oxidative stress contributes to cardiac dysfunction during aging [48].

Peroxiredoxins (PRDXs) reduce hydrogen peroxide and peroxynitrite [110]. PRDXs are a family of thiol specific antioxidant proteins including six isoforms in mammalian cells. PRDX 1, 2, 3, and 6 mainly exist in the cytosol. PRDX 4 is found in the endoplasmic reticulum [111]. In addition, PRDX 3 and 5 are present in the mitochondria [90,111]. Ischemia-reperfusion leads to decreased PRDX 3 activity in mouse heart mitochondria [112]. Overexpression of the PRDX3 decreases the development of myocardial infarction-induced heart failure [113]. Genetic inhibition of the PRDX 6 increases cell injury during ischemia-reperfusion by increasing lipid peroxidation [114]. In contrast, overexpression of PRDX 6 decreases cardiac injury during oxidative stress [115]. Interestingly, knockout of p53 leads to increased PRDX3 content in mouse hearts in the basal condition. Knockout of p53 improves mitochondrial function and decreased cardiac injury during ischemia-reperfusion [90], supporting that PRDXs play a critical role in reducing ROS generation from mitochondria during ischemia-reperfusion.

Glutathione peroxidases (Gpx), with six isoforms, are located in the cytoplasm, nuclei, and mitochondria [116]. Glutathione (GSH) is the major intracellular thiol reserve, mainly present in the reduced form. GSSG is glutathione disulfide. The Gpx reduces H\(\text{H}_2\text{O}_2\) to H\(\text{H}_2\text{O}\) and simultaneously oxidizes GSH to GSSG. Then, the GSSG is reduced to GSH by glutathione reductase in the presence of NAPDH. The GSH/GSSG ratio is used as a marker of oxidative stress. Ischemia-reperfusion leads to decreased Gpx4 expression [117]. Resveratrol treatment protects cells exposed to exogenous H\(\text{H}_2\text{O}_2\) by increasing glutathione peroxidase, catalase, and heme oxygenase-1 (HO-1), indicating that resveratrol treatment increases vascular oxidative stress resistance by scavenging H\(\text{H}_2\text{O}_2\) [118]. These results clearly show that glutathione peroxidase plays a critical in deceasing oxidative stress during pathological conditions.

Heme oxygenase (HO) catabolizes heme to produce labile Fe, carbon monoxide (CO), and biliverdin [119]. Free heme increases the production of hydroxyl radicals through the Fenton reaction (4). HOs include two isoforms: HO-1 and HO-2. HO-1 is an inducible form. Heme catabolism by HO-1 extracts Fe from the protoporphyrin IX ring to produce labile Fe that is buried in a multimeric complex to prevent labile Fe from triggering the Fenton reaction [119]. Heme catabolism also produces biliverdin that is converted to bilirubin, having an antioxidant effect. CO (carbon monoxide) is also produced during heme catabolism [119]. Although an increasing amount of evidence indicates that oxidative stress plays a key role in cell damage during heart failure [120], ischemia-reperfusion, and
aging, the effect of administering exogenous antioxidant treatment and reducing cell injury during pathological conditions including aging and heart failure is still controversial [121]. As discussed above, overexpression of catalase improves cardiac function in aged hearts [48], indicating that promotion of endogenous antioxidants may be a proper strategy to decrease oxidative stress. Interestingly, administration of dimethyl fumarate leads to increased Nrf2 and HO-1 expression [122]. Dimethyl fumarate treatment also decreases cell injury during ischemia-reperfusion by increasing HO-1 expression [123,124]. Stimulation of HO-1 expression with dimethyl fumarate treatment may be a novel approach to decrease cell injury during aging because endogenous antioxidants are already impaired [121].

5. Potential Mechanisms of CoQ10 Against Oxidant Stress

Coenzyme Q10 (CoQ10), or ubiquinone, is a lipid-soluble benzoquinone with 10 isoprenyl units in its side chain. It plays a key role as an intracellular antioxidant, protecting membrane phospholipids and mitochondrial membrane proteins from free radical-induced oxidative injury [2]. Functioning within the inner mitochondrial membrane [2], ubiquinone serves as a structural component of complexes I and III and facilitates the transport of electrons to their ultimate reaction with oxygen for water production. In this capacity, the synthesis of adenosine triphosphate within the electron transport chain of myocytes is critical [125,126]. CoQ10 also prevents the leakage of electrons to oxygen that would result in the production and release of reactive oxygen species (ROS) (Figure 3).

In addition to its actions on electron transport, CoQ10 binds to common sites involved with the MPTP, preventing pore formation and membrane depolarization, both of which trigger apoptosis. The mechanism by which CoQ10 inhibits pore formation in mitochondria involves secondary changes in MPTPs’ calcium binding affinity, preventing cytochrome c release and subsequent ATP hydrolysis [127]. The protection of complex I activity during ischemia-reperfusion by inhibiting calpain 1 and 2 leads to a reduction in ROS generation [75]. Additional experimental work from various animal models as well as patients supports the notion that supplementation of CoQ10 has value in reducing oxidant stress [128]. In a rat model of Alzheimer’s disease, cultured cortical neuron induced-damage by exposure to amyloid-beta can be inhibited with the addition of CoQ10 and ROS can be reduced through a mechanism involving activation of the PI3-K/Akt survival pathway [129]. In a swine model, dietary supplementation of CoQ10 (5 mg/kg/day) for 30 days increased the myocardial content of ubiquinone in isolated mitochondria by 30%. When the pig hearts were then placed on cardiopulmonary bypass and subjected to 30 min of regional ischemia-reperfusion, CoQ10 treated hearts showed improved left ventricular (LV) function, lower levels of creatine kinase release, and reduced levels of malonaldehyde (MDA) content, a marker of oxidant stress within post-ischemic tissue [130].
Figure 3. The figure demonstrates a potential mechanism for the addition of CoQ10 in the diet for 4 weeks and how enhanced electron transport chain functioning through complex III (Q-cycle) reduces the generation of reactive oxygen species in the intermembrane space [128].

Similar observations have been shown in patients pretreated with CoQ10 prior to coronary artery bypass graft surgery (CABG) [2], with reduced levels of MDA and protein carbonyls and enhanced glutathione peroxidase activity observed post-CABG [131,132]. Although CoQ10 levels may have a direct effect on reducing oxidant stress, chronic administration may also improve the antioxidant status indirectly at the transcriptional level by the regulation of mitochondrial protein expression. In skeletal muscle tissue, aging reduces the levels of peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1α), the master switch of mitochondrial biogenesis. This reduced PGC-1α level leads to depleted concentrations of glutathione (GSH) with enhanced oxidative stress markers [133]. In studies of isolated C2C12 skeletal muscle cells [128], supplementation of CoQ10 with α-lipoic acid enhanced PGC-1α expression and increased genes that encode proteins involved in glutathione synthesis, recycling, and metabolism [134]. These findings are consistent with observations made in a rat model of pharmacologically-induced seizures, whereby administration of CoQ10 reduced oxidant stress by enhancing PGC-1α nearly 3-fold [135]. These changes were also associated with increased levels of nuclear factor erythroid 2-related factor 2 (Nrf2) and silencing information regulator 1 (Sirt1), both of which improve redox control within the cell, by increasing mitochondrial antioxidants such as superoxide dismutase 2. It has been suggested that CoQ10 increases the expression and activity of PGC-1α by its activation of the cAMP response element binding protein and adenosine monophosphate-activated protein kinase (AMPK) phosphorylation [136]. In our swine model of chronic myocardial ischemia, we administered daily CoQ10 (400 mg/day) for 4 weeks, and compared to placebo-treated animals, we observed an enhanced expression of nuclear-bound PGC1-alpha, indicating activation of mitochondrial biogenesis, as well as increased expression of antioxidant proteins within isolated mitochondria [137] (Figure 4 and Table 1). In addition to its role in mitochondrial biogenesis and protection, CoQ10, the only endogenously produced lipid-soluble antioxidant in the cell, is also present within the Golgi apparatus, and plays a key role in redox control and nitric oxide elaboration by maintaining coupling and normal activity of eNOS [138]. Taken together, these data support the concept that CoQ10 provides a key role as an antioxidant in the heart cell by enhancing ETC exchange within mitochondria as well as increasing expression of antioxidant proteins to reduce the accumulation of oxidant stress within cardiac tissue [128].
Figure 4. In a pre-clinical swine study of chronic myocardial ischemia, administration of CoQ10 (400 mg/day) in the chow for 4 weeks increased the expression of activated PGC1-alpha, the master switch for mitochondrial biogenesis, leading to enhanced expression of mitochondrial antioxidant proteins in the chronically ischemic territory. The data support the concept that CoQ10 is protective by transcriptionally regulating antioxidant proteins in heart tissue. *p < 0.05.

Table 1. Mitochondrial anti-oxidant proteins.

| Antioxidant Protein | Accession ID | p Value |
|---------------------|--------------|---------|
| Glutathione peroxidase | A0A287AG70_PIG | 0.029 |
| Superoxide dismutase | A0A287A4Z2_PIG | 0.001 |
| Aldehyde dehydrogenase 6 | F1S3H1_PIG | 0.002 |
| Superoxide dismutase (Cu-Zn) | SODC_PIG | 0.87 |
| Glutathione S-transferase kappa | F1SRV4_PIG | 0.6 |
| Cluster of aldehyde dehydrogenase | F1SDC7_PIG [4] | 0.54 |
| Alcohol dehydrogenase | F1RTZ1_PIG | 0.62 |
| Thioredoxin reductase 2 | A0A287BQ74_PIG | 0.99 |
| Glutathione-disulfide reductase | F1RX66_PIG | 0.93 |

n = 4/group; Data normalized to healthy animals; Log fold change calculated by Hib + CoQ10/Hibernation. Significance determined by the Permutation test with the Benjamini–Hochberg test; Resulting p value: p < 0.00834.

Reducing oxidant stress in the mitochondria within the myocyte may play a key role in attenuating inflammation within cardiac tissue. In a meta-analysis, CoQ10 administration was shown to significantly decrease plasma C-reactive protein (CRP) levels [139]. A number of cytokines, including interleukin-6 (IL-6) [2], are secondary messengers that activate production and release of CRP in the liver [140] and are reduced following administration of CoQ10 [135]. The greatest effect on CRP reduction with CoQ10 administration is observed among those patients with increased IL-6 levels, providing support for the notion that the hepatic release of CRP is downstream from IL-6 [141]. A reasonable mechanism combining CoQ10's antioxidant effect with mitigation of inflammation is by the inhibition of NF-kB, which transcriptionally regulates the production and elaboration of pro-inflammatory cytokines [142]. Very importantly, this regulation of inflammatory cytokine markers is activated by complex I-generated ROS [143,144], providing additional support for the importance of the Q-cycle within the inner mitochondrial membrane of hearts as a key regulator of inflammation (Figure 5).
6. Administration of CoQ10 and Improved Clinical Outcomes

Among older individuals, the concentration of plasma CoQ10 levels is low, but when increased, inversely correlates with levels of lipid oxidative biproducts [145]. CoQ10 supplementation is well tolerated with doses of at least 2400 mg/day [146] and is protective against oxidative stress with a number of cardiovascular and neurodegenerative diseases [147,148]. In patients scheduled for open heart surgery, CoQ10 administration lowers the requirement for inotropic drugs following surgery, with an observed reduction in the number of arrhythmias [149]. In elderly patients from Sweden, giving CoQ10 (200 mg/day) with selenium (200 μg as selenized yeast) was associated with reduced cardiovascular deaths after 4 years, an observation that was also observed 10 years post-randomization [150]. In addition to the improved outcomes, CoQ10 supplementation reduced elevated cardiac biomarkers in the blood that have been used as identifiers of poor outcomes. In a group of dialysis patients who were randomized to receive daily CoQ10 (1200 mg/day), plasma concentrations of oxidant stress markers, F2-isoprostanes, were lower after 4 months compared with that of placebo-treated patients [151]. Very interestingly, among a prespecified group of individuals, therapy reduced troponin-T and NT pro-BNP levels, providing additional evidence for a critical link between oxidant stress and these commonly used cardiac biomarkers. This observation is important for interpreting the results of the Q-SYMBIO trial, which among patients with stable congestive heart failure tested the benefit of chronic administration of CoQ10 (300 mg/day) versus placebo. The design of the trial was a double-blind, randomized, controlled study and showed that treatment led to a significant long-term reduction in major cardiovascular endpoints [19]. Consistent with other studies, treatment also lowered plasma BNP levels, which is an important cardiac biomarker for predicting adverse outcomes in patients with heart failure. Among healthy elderly patients, serum levels of ubiquinol are correlated with reduced levels of NT pro-BNP [152], and when treatment is provided, it further lowers BNP levels over a period of 5 years [150,153]. The mechanism by which CoQ10 reduces BNP is unclear but may be related to its effects on reducing either oxidant stress or inflammation. In a cohort of 51 patients with stable ischemic heart disease, those patients who were randomized to CoQ10 (300 mg/day) for 4 months had increased activity of antioxidant enzymes, such as superoxide dismutase, catalase, and glutathione peroxidase, and reduced inflammatory
markers TNF-α and IL-6 [154]. The effects of CoQ10 administration on reducing the inflammatory cytokines in heart tissue is critical for the interpretation of the Q-SYMBIO trial results in patients with congestive heart failure [2]. Elaboration of the cytokine IL-6 occurs with cardiac myocytes and with sustained activation of gp130, a member of the signaling pathway, and induces adverse remodeling in the heart, such as hypertrophy. At 6 weeks following transaortic constriction (TAC) in wild type mice, the degree of hypertrophy was activated by a combination of CaMKII and the STAT3 pathways, and this signaling cascade in addition to the ventricular hypertrophy was blocked in those mice with disruption of the IL-6 gene [155]. The degree of BNP expression was also lowered in the IL-6 knock-out mice following TAC, providing additional evidence that the elaboration of BNP in the heart is downstream from cytokine activation of IL-6. Furthermore, among those patients with insulin resistance and rheumatoid arthritis, increased IL-6 levels were the best predictor of increased NT-proBNP levels, further supporting a direct link between inflammation and elevated cardiac biomarkers [156]. These clinical observations are also supported by work in human cardiac fibroblasts, which has shown increased BNP expression following exposure to various inflammatory markers, including the interleukins [2,157].

In summary, traditional therapies that improve outcomes in patients with chronic ischemic heart disease have failed to reduce perioperative adverse outcomes following non-cardiac operations. Use of cardiac biomarkers such as NT-proBNP has become an important means of risk-stratification and can identify those patients who will experience myocardial injury as defined by elevated cardiac troponin following surgery. There is emerging evidence that administration of ubiquinone prior to a major cardiac operation will reduce these elevations in BNP and troponin by mitigating oxidant stress [158]. However, the number of studies that have used rigorous designs involving randomized, controlled, double-blind strategies with treatment of CoQ10 versus placebo prior to major vascular or cardiac operations are limited (Table 2). Clearly, additional studies are needed, particularly related to the proper dosing of ubiquinone relative to plasma levels, as well to understanding the potential benefits in patients with congestive heart failure relative to oxidant stress markers and improved bioenergetics [159]. Hopefully, the community dealing with perioperative care can advance novel, alternative, safe antioxidant therapies prior to and following major vascular operations, particularly among high risk patients defined by either the revised cardiac risk index [20] or an elevated preoperative level of BNP [14] as a means of reducing short-term and potentially long-term postoperative adverse outcomes.

Table 2. Randomized, controlled, double-blind studies testing the effects of preoperative treatment with CoQ10 vs. placebo on postoperative outcome measures.

| Study Results of Treatment | Type of SurgerySample Size | Pre-Op Rx Time | Dose of CoQ10 | Primary End Point Measure | Post-Op Time |
|---------------------------|---------------------------|----------------|--------------|----------------------------|--------------|
| Khan et al. [2]           | Vascular                  | n = 121        | 3 days       | 400 mg/d                   | NT Pro-BNP   | 30 days |
| Orlando et al. [160]      | AVR                       | n = 50         | 7 days       | 400 mg/d                   | Troponin I/CK-MB | 5 days |
| Rosenfeldt et al. [131]   | CABG ± AVR                | n = 121        | 14 days      | 300 mg/d                   | MDA          | 30 days |
| Taggart et al. [161]      | CABG                      | n = 20         | 12 h         | 600 mg                     | Troponin T/CKMB | 30 days |
| Judy et al. [162]         | CABG ± AVR                | n = 20         | 14 days      | 100 mg/d                   | CI/LVEF      | 30 days |

MDA (malondialdehyde); CK-MB (creatine kinase-myocardial band); CI (cardiac index), LVEF (left ventricular ejection fraction), CABG (coronary artery bypass graft), AVR (aortic valve replacement).

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