Practical Prevention of Cardiac Remodeling and Atrial Fibrillation with Full-Spectrum Antioxidant Therapy and Ancillary Strategies

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Abstract

A wealth of research data points to increased oxidative stress as a key driver of the cardiac remodeling triggered by chronic pressure overload, loss of functional myocardial tissue, or atrial fibrillation. Oxidative stress is a mediator of the cardiomyocyte hypertrophy and apoptosis, the cardiac fibrosis, and the deficits in cardiac function which typify this syndrome, and may play a role in initiating and sustaining atrial fibrillation. Nox2- and Nox4-dependent NADPH oxidase activity appears to be a major source of this oxidative stress, and oxidants can induce conformational changes in xanthine dehydrogenase, nitric oxide synthase, and the mitochondrial respiratory chain which increase their capacity to generate superoxide as well. Consistent with these insights, various synthetic antioxidants have been shown to suppress cardiac remodeling in rodents subjected to myocardial infarction, aortic constriction, or rapid atrial pacing. It may prove feasible to achieve comparable benefits in humans through use of a “full-spectrum antioxidant therapy” (FSAT) that features a complementary array of natural antioxidants. Spirulina is a rich source of phycocyanobilin, a derivative and homolog of biliverdin that appears to mimic the potent inhibitory impact of biliverdin and free bilirubin on NADPH oxidase activity. Mega-doses of folate can markedly increase intracellular levels of tetrahydrofolates which have potent and versatile radical-scavenging activities – including efficient quenching of peroxynitrite-derived radicals. Supplemental coenzyme Q10, already shown to improve heart function in clinical congestive failure, can provide important antioxidant protection to mitochondria. Phase 2 inducer nutraceuticals such as lipoic acid, administered in conjunction with N-acetylcysteine, have the potential to blunt the impact of oxidative stress by boosting myocardial levels of glutathione. While taurine can function as an antioxidant for myeloperoxidase-derived radicals, its positive inotropic effect on the failing heart seems more likely to reflect an effect on intracellular calcium dynamics. These measures could aid control of cardiac modeling less directly by lowering elevated blood pressure, or by aiding the perfusion of ischemic cardiac regions through an improvement in coronary endothelial function. Since nitric oxide functions physiologically to oppose cardiomyocyte hypertrophy and cardiac fibrosis, and is also a key regulator of blood pressure and endothelial function, cocoa flavanols – which provoke endothelial release of nitric oxide – might usefully complement the antioxidant measures recommended here.

Oxidative Stress Drives Cardiac Remodeling

Cardiac remodeling is a typical response to chronic pressure overload, as in systemic or pulmonary hypertension, or aortic stenosis. It also commonly occurs after a loss of contractile myocardial tissue – owing to myocardial infarction, severe coronary ischemia, or myocarditis – since this imposes an increased work load on the viable myocardium. Atrial remodeling is typically seen in atrial fibrillation, and appears to be both an effect and a cause of this syndrome. The remodeling process involves hypertrophy and apoptosis of cardiomyocytes, degradation of extracellular matrix via metalloproteinase
activation, as well as a reactive fibrotic response in which fibroblasts convert to myofibroblasts, multiply, and lay down increased amounts of collagen-rich ground substance. A decrease in cardiac contractile efficiency, manifesting as progressive decreases in ejection fraction, reflects impairment of intracellular calcium regulation and mitochondrial function in cardiomyocytes, the stiffness imparted by fibrosis, chamber dilatation, and – especially during the later stages of cardiac failure - continuing apoptotic loss of cardiomyocytes. These structural and functional changes are also associated with systemic endothelial dysfunction\textsuperscript{1} and increased risk for arrhythmias. All too often this syndrome terminates lethally, as cardiac output falls too low to sustain life, or ventricular fibrillation or infarction intervenes.

Increased myocardial oxidative stress is a concomitant of cardiac remodeling, and there is considerable evidence from rodent studies that this stress is a key mediator of most aspects of this syndrome.\textsuperscript{2-4} Oxidant-mediated activation of NF-kappaB and of ASK\textsuperscript{5-11} plays a major role in driving cardiomyocyte hypertrophy and apoptosis, as well as degradation of extracellular matrix – responsible for chamber dilatation - via increased metalloproteinase expression.\textsuperscript{12-25} Oxidants also contribute to the post-translational activation of matrix metalloproteinases,\textsuperscript{26-28} interfere with efficient intracellular calcium control by altering the structure of proteins and channels that bind and transport calcium,\textsuperscript{29} and damage mitochondria in ways that impede electron transport and boost superoxide generation.\textsuperscript{30-33} The latter two effects contribute to reductions in contractile efficiency and ejection fraction, as does evolving cardiac fibrosis. In cardiac (myo)fibroblasts, oxidative stress is required for efficient TGF-beta signaling, apparently because it boosts the activity of the Smad transcription factors activated by this hormone;\textsuperscript{34, 35} TGF-beta is a crucial mediator of cardiac fibrosis, driving the phenotypic transition of cardiac fibroblasts to myofibroblasts, boosting the synthesis of collagen, other matrix proteins, and metalloproteinase inhibitors, and promoting production of the autocrine fibroblast growth factor CTGF;\textsuperscript{36-40} its increased production during cardiac remodeling may be driven, in part, by oxidative stress.\textsuperscript{41} Increased superoxide levels also quench nitric oxide, which, in the moderate physiological concentrations produced by eNOS,\textsuperscript{42} works via cGMP/PKG to oppose both cardiomyocyte hypertrophy and cardiac fibrosis.\textsuperscript{43-48}

In rodent studies, chronic pressure overload boosts the expression and activity of NADPH oxidase in cardiac tissue, including cardiomyocytes; both the Nox2 (gp91phox) and Nox4 isoforms are up-regulated.\textsuperscript{49-52} A similar phenomenon is observed in non-infarcted cardiac tissue following induced infarction.\textsuperscript{53} Furthermore, angiotensin II, endothelin, and alpha-adrenergic agonists – hormones which activate heterotrimeric G proteins via 7-pass receptors, and which play a clinically significant role as amplifiers of the cardiac remodeling process – stimulate the hypertrophy of cardiomyocytes in vitro, while also boosting NADPH oxidase activity.\textsuperscript{54-57} Increased local activity of cytokines, including TNF-alpha and TGF-beta, can also promote NADPH oxidase activation.\textsuperscript{58, 59} Intriguingly, sub-pressor doses of angiotensin II, which precipitate cardiac remodeling in mice, fail to do so in mice that are Nox2 double knockouts. On the other hand, chronic pressure overload induces cardiomyocyte hypertrophy, but not cardiac fibrosis, in Nox2 \textsuperscript{+/-} mice, presumably because Nox4 is induced under these circumstances.\textsuperscript{51} Aldosterone, which appears to mediate the pro-fibrotic effects of angiotensin II in the heart, promotes cardiac induction of Nox2,\textsuperscript{60} the NADPH oxidase inhibitor apocynin prevents cardiac hypertrophy in aldosterone-infused rats.\textsuperscript{61} The hypertrophic response of rat cardiomyocytes to endothelin-1 in vitro is blocked by co-incubation with biliverdin,\textsuperscript{62} which rapidly gives rise intracellularly to bilirubin, now known to function as a potent physiological inhibitor of NADPH oxidase.\textsuperscript{63-65} Biliverdin is generated within cells by heme oxygenase activity; strategies which boost cardiac expression of HO-1 have been
found to prevent cardiac remodeling in rodents subjected to aortic constriction, myocardial infarct, or angiotensin II infusion, as well as in spontaneously hypertensive rats. All of these findings are consistent with the proposition that elevated activity of NADPH oxidase is a key mediator of both cardiac fibrosis and cardiomyocyte hypertrophy in rodent models of cardiac remodeling.

However, the excessive cardiac oxidative stress associated with cardiac remodeling is amplified by other sources, presumably in part because oxidative stress can act in a feed-forward fashion to boost superoxide production by xanthine dehydrogenase, nitric oxide synthase, and the mitochondrial respiratory chain. Thus, oxidative stress can induce a conformational change in xanthine dehydrogenase, such that it functions as a xanthine oxidase capable of generating superoxide; this may explain why allopurinol decreases cardiac remodeling in mice subjected to myocardial infarction or pressure overload. Furthermore, peroxynitrite-derived radicals, by oxidizing the cofactor tetrahydrobiopterin, can induce an “uncoupling” of nitric oxide synthase, such that it produces superoxide rather than anti-hypertrophic nitric oxide. Indeed, administration of tetrahydrobiopterin has an ameliorative impact on cardiac remodeling in mice subjected to aortic constriction or infarction. Finally, oxidative damage to the mitochondrial respiratory chain, as well as to mitochondrial DNA, can lead to an impairment of respiratory chain function that boosts mitochondrial superoxide generation. Tumor necrosis factor-alpha, the cardiac levels of which are typically elevated during cardiac remodeling, also promotes mitochondrial superoxide production via generation of ceramide. These considerations suggest that, whereas selective inhibition of NADPH oxidase would likely have a major impact on the oxidative stress associated with cardiac remodeling, ancillary measures which oppose the production or effects of oxidants would likely improve the clinical impact of such a strategy.

Further evidence that excessive oxidative stress is a central mediating factor in cardiac remodeling is provided by studies demonstrating that the antioxidants N-acetylcysteine, probucol, and N-2-mercaptopropionyl glycine attenuate cardiac remodeling in rodents subjected to aortic banding or myocardial infarction.

Role of Oxidative Stress in Atrial Fibrillation

In regard to atrial fibrillation (AF), atrial NADPH oxidase has been shown to be activated in this disorder; furthermore, induction of atrial fibrillation with rapid atrial pacing in pigs is associated with increased NADPH oxidase activation, owing in part to increased activation of Rac1. Moreover, atrial fibrillation develops spontaneously in mice genetically engineered for cardiac-specific expression of a constitutively active form of Rac1 (which activates NADPH oxidase). Conversely, statins, which down-regulate Rac1 activity by suppressing its isoprenylation, appear to have a favorable impact on risk for atrial fibrillation, while blunting the decrease in atrial effective refractory period induced by rapid atrial pacing. This later finding is consistent with the possibility that oxidant stress promotes and sustains atrial fibrillation by reducing the effective refractory period of atrial myocytes. And oxidative stress may be a trigger for the post-operative atrial fibrillation that is a common complication of cardiac surgery; treatment with oral ascorbate prior to and following surgery significantly reduced the incidence of this complication in patients undergoing cardiac bypass graft surgery. Furthermore, patients who subsequently developed atrial fibrillation following cardiac surgery had higher atrial NADPH oxidase activity than those who did not. Not surprisingly, atrial oxidative stress appears to drive the atrial remodeling that typically
accompanies long-term atrial fibrillation and likely helps to sustain it;\textsuperscript{92} thus, treatment with probucol or ascorbate is reported to inhibit atrial remodeling in dogs subjected to rapid atrial pacing.\textsuperscript{93, 94} Finally, the ability of superoxide to quench endocardial nitric oxide bioactivity might conceivably play a role in the increased risk for atrial mural thrombi and thromboembolic stroke associated with atrial fibrillation.\textsuperscript{96} These considerations suggest that effective antioxidant measures – particularly those which target NADPH oxidase – may have some utility for preventing and possibly controlling atrial fibrillation, and for suppressing the atrial remodeling associated with this condition.

**Full-Spectrum Antioxidant Therapy for Prevention of Remodeling**

Full-spectrum antioxidant therapy (FSAT), as recently defined, refers to a comprehensive antioxidant supplementation program that incorporates, among other things, mega-dose folate and the spirulina – derived phytonutrient phycocyanobilin (PhyCB).\textsuperscript{95} PhyCB, a biliverdin derivative, has been shown to mimic the inhibitory impact of biliverdin on NADPH oxidase activity.\textsuperscript{96} The reason why PhyCB may be of greater practical utility than biliverdin in this regard is that the PhyCB content of spirulina is about 0.6\% of its dry weight – whereas there are no known naturally rich sources of biliverdin, a compound that is difficult to synthesize. The recent discovery that PhyCB can function as an NADPH oxidase inhibitor helps to rationalize the numerous studies showing that orally administered phycocyanin (the spirulina protein which includes PhyCB as a chromophore) has broad-ranging anti-inflammatory and cytoprotective properties in rodents.\textsuperscript{96, 97} Most pertinent to our current discussion, oral phycocyanin has been reported to reduce cardiac superoxide production in cholesterol-fed hamsters – an effect associated with a down-regulation of p22phox expression.\textsuperscript{98}

The remarkable antioxidant potential of high-dose folate stems from the fact that intracellular levels of intracellular reduced folates can be increased very substantially in cells which concentrate folate against a gradient, such as endothelial cells.\textsuperscript{99} Once inside cells, folate is rapidly reduced to tetrahydrofolate compounds which have outstanding antioxidant activity. In particular, they efficiently quench peroxynitrite-derived radicals\textsuperscript{100} – which likely explains why high-dose folate can promote effective coupled activity of nitric oxide synthase in oxidatively-stressed endothelial cells.\textsuperscript{99, 101-104} Folate likely has comparable activity in cardiomyocytes; this can be deduced from a recent study in which pre-treatment with high-dose folate – or acute administration during reperfusion – was shown to markedly reduce the extent of cardiac tissue death induced by a 30-minute occlusion of the left coronary artery in rats.\textsuperscript{105} Moreover, folate pre-treatment also helped to preserve bioenergy status and efficient cardiac function during the ischemic phase – perhaps indicative of an antioxidant effect on cardiac mitochondria. (Mitochondria sustain oxidative damage during hypoxia, despite low oxygen levels.\textsuperscript{106, 107}) This remarkable study may be viewed as suggestive evidence that high-dose folate may have outstanding potential as a myocardial antioxidant in the context of cardiac remodeling.

Measures which boost cellular glutathione levels – phase 2 inducers, melatonin, and the glutathione precursor N-acetylcysteine – also have potential as components of FSAT. (Phase 2 inducers and melatonin increase glutathione levels by increasing the expression of the rate-limiting enzyme for glutathione synthesis, gamma-glutamylcysteine synthase.\textsuperscript{108-110}) The ability of N-acetylcysteine supplementation to prevent ventricular hypertrophy in mice subjected to aortic constriction, has been
The phase 2 inducer epigallocatechin-gallate (EGCG) prevents ventricular hypertrophy in rats rendered hypertensive or subjected to aortic constriction.\textsuperscript{111-113}

Coenzyme Q10, while serving as a crucial cofactor in the mitochondrial respiratory chain, also provides important antioxidant protection for mitochondrial membranes. Perhaps that explains why, in most studies, supplemental coenzyme Q10 has been found to improve cardiac function in patients with congestive failure.\textsuperscript{114-116} Furthermore, there are recent reports that supplemental coenzyme Q10 has a favorable impact on post-infarction myocardial remodeling in rats, and lessens hypertrophy in dogs with tachycardia-induced heart failure.\textsuperscript{117,118}

Taurine, which detoxifies that hypochlorous acid generated by myeloperoxidase, can be included in FSAT, and has been reported to improve cardiac function in congestive failure.\textsuperscript{119-121} However, this may not reflect an antioxidant action, but rather a modulation of intracellular calcium dynamics that produces a positive inotropic effect comparable to that of digitalis.\textsuperscript{123,124} Fortunately, unlike digitalis, taurine does not seem to increase risk for arrhythmias, and indeed has anti-arrhythmic activity in some models.\textsuperscript{125,126} The impact of taurine on cardiac remodeling appears to have received little attention. In cats, for whom taurine is a dietary essential, prolonged taurine deficiency is associated with a potentially fatal dilated cardiomyopathy.\textsuperscript{127,128}

**Boosting Nitric Oxide Production as a Complementary Strategy**

As noted above, moderate concentrations of nitric oxide (NO) antagonize both the hypertrophy of cardiomyocytes and the pro-fibrogenic activity of cardiac fibroblasts. These effects appear to be mediated by cGMP-stimulated protein kinase G activity, and have been demonstrated in numerous cell culture studies. Conversely, chronic inhibition of NO synthase promotes cardiac hypertrophy in rodents, demonstrating that these effects of NO are physiological;\textsuperscript{129,130} the endothelial isoform of NO synthase is found in cardiomyocytes as well as endothelial cells.\textsuperscript{42} The antihypertrophic effects of nitric oxide may reflect, at least in part, reduced transcriptional activation of NFAT, a key mediator of cardiomyocyte hypertrophy.\textsuperscript{43,131} Acting via PKG, NO somehow suppresses calcium-dependent calcineurin activation; a dephosphorylation mediated by calcineurin is required for nuclear translocation of NFAT. In cardiac fibroblasts, NO, likewise acting via PKG, inhibits the ability of TGF-beta to promote transcription by blocking nuclear translocation of Smad2/3.\textsuperscript{46,132}

Supraphysiological concentrations of biotin (roughly 1-2 orders of magnitude higher than the physiological level) boost guanylate cyclase activity by 2-3-fold;\textsuperscript{133,134} the magnitude of this effect – maximized by a biotin concentration of 1 µM - is comparable to that of carbon monoxide, but far lower than that of NO – perhaps explaining why high doses of biotin are well tolerated.\textsuperscript{135} Conceivably, some sufficient dosage schedule of biotin might achieve and sustain a modest systemic increase in cGMP levels; if so, such a regimen could be expected to oppose cardiac remodeling, inasmuch as the protective effects of NO in this regard appear to be mediated by cGMP/PKG. Oral biotin exerts anti-diabetic effects in rodent models which may reflect an increase in cGMP levels.\textsuperscript{136-138}

Alternatively, supplemental tetrahydrobiopterin could be expected to recouple eNOS in oxidant-exposed heart cells, in which oxidation of this cofactor induces eNOS uncoupling. Indeed, oral administration of tetrahydrobiopterin has been found to oppose and even reverse cardiac hypertrophy and fibrosis in rats.
subjected to aortic constriction; however, this benefit seems to have reflected an antioxidant effect rather than an increase in NO production, as cardiac PKG activity was not found to be higher in the tetrahydrobiopterin-treated rats (possibly because hormonal activators of guanylate cyclase activity were higher in the untreated rats). Although tetrahydrobiopterin has direct radical-quenching activity and might be considered as a component of FSAT, it is currently very expensive in the high doses that are likely to be clinically useful; it is currently available as a drug for phenyketonuria, and the average annual cost per patient is estimated at $57,000.

Cocoa flavanols – most notably epicatechin – can act directly on vascular endothelium to provoke NO release; this is thought to explain their vasodilatory/anti-hypertensive effects. Theoretically, they might have the capacity to boost cardiomyocyte exposure to NO, or perhaps even provoke NO release by these cells. It would be of interest to examine the impact, if any, of cocoa flavanols in rodent models of cardiac remodeling.

**Reduction in Elevated Blood Pressure with Antioxidants and Cocoa Flavanols**

Hypertension is often the underlying cause of cardiac remodeling, and it can exacerbate this response in patients who are recovering from an infarction or who suffer from myocarditis. It is thus intriguing to note that many of the antioxidants recommended above have anti-hypertensive potential. Activation of NADPH oxidase, both centrally and peripherally, appears to play a role in essential hypertension. Although the impact of dietary spirulina on hypertension has not yet been formally tested, a recent open study in which mostly normotensive subjects received 4.5 g spirulina daily reported significant reductions in both systolic (10 points) and diastolic (7 points) blood pressure. The ability of high-dose folate to recouple endothelial NO synthase suggests anti-hypertensive potential for this strategy, and indeed, 10 mg folate daily lowered blood pressure in patients who had recently sustained a myocardial infarction. The antihypertensive utility of coenzyme Q10 is well-documented. Taurine supplementation has antihypertensive activity in various rodent models, and a few clinical reports suggest that it might also be useful in this regard in humans. While it is not clear whether cocoa flavanols could aid prevention of cardiac remodeling by boosting NO exposure in cardiac parenchyma, antihypertensive activity for these flavanols has been reported, presumably reflecting increased endothelial release of NO. Moreover, hypertension appears to be unknown among the Kuna Indians of Panama as long as they maintain their traditional practice of consuming several servings of raw cocoa daily. It can thus be predicted with some confidence that FSAT, complemented by cocoa flavanols, could often alleviate cardiac overloading by decreasing elevated blood pressure.

**Improving the Bioenergetics of Ischemic Myocardium**

When cardiac remodeling is associated with cardiac ischemia, measures which improve the perfusion and bioenergetics of ischemic myocardium can be expected to lower the mechanical stress imposed on other regions of the heart, and thus limit the stimulus to remodeling. High-dose folate improves flow-mediated vasodilation in patients recovering from myocardial infarct – an effect which presumably could aid the perfusion of ischemic myocardial regions. Spirulina, by suppressing endothelial superoxide production and thus improving the bioactivity of NO, could be expected to have a similar and complementary effect on endothelial function. Although spirulina has not yet been evaluated clinically in this regard, it has demonstrated favorable effects on endothelial NO production in obese rats, and has a marked anti-
atherogenic impact in cholesterol-fed hamsters. While cocoa flavanols can promote vasodilation acutely by provoking endothelial NO release, they have also been shown to improve flow-mediated endothelium-dependent vasodilation during chronic use. The bioenergetics of ischemic myocardial regions can also be improved by measures which promote selective myocardial use of glucose as fuel, such as ample supplemental intakes of carnitine and a very-low-fat diet. In a double-blind supplementation trial, a regimen incorporating carnitine, coenzyme Q10 and taurine was shown to decrease left-ventricular end-diastolic volume in patients with ischemic coronary diseases and a low ejection fraction.

Complementary Drug Therapy

Therapy with beta blockers and angiotensin antagonists is well known to suppress cardiac remodeling while improving survival in patients with congestive failure or cardiac overload. The utility of beta blockers appears to reflect the fact that chronic overactivation of the beta1-adrenergic receptor, driven by excessive cardiac sympathetic activity (as commonly seen in metabolic syndrome and congestive failure), leads to increased activation of L-type calcium channels in cardiomyocytes; this in turn promotes cardiomyocyte hypertrophy and apoptosis, cardiac fibrosis and an increased risk for arrhythmias, mediated largely by Ca+2/calmodulin-dependent protein kinase II and calcineurin. A cAMP-mediated activation of Epac and Ras (but not PKA) also contributes to the hypertrophic impact of these receptors. (In contrast, activation of the beta2-adrenergic receptor appears to antagonize these effects.) It can be anticipated that concurrent beta-blocker therapy will complement the benefit of the antioxidant measures recommended here. The utility of angiotensin antagonists for prevention of cardiac remodeling is largely a function of their antioxidant activity; as noted above. Statins also have the potential to diminish cardiac NADPH oxidase activity, by lessening the isoprenylation of Rac1, an effect which likely explains the anti-hypertrophic effects of statins in rodent models of cardiac remodeling. Whether tolerable clinical doses of statins can have a worthwhile impact on cardiac remodeling or survival in heart failure is not yet clear, as conflicting findings have been reported, with the largest prospective randomized study to date finding no benefit.
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