The Oxidative Stress Hypothesis of Congestive Heart Failure*

Radical Thoughts

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There is extensive experimental evidence from *in vitro* and animal experiments that congestive heart failure (CHF) is a state of oxidative stress. Moreover, in animal models, the development of CHF is accompanied by changes in the antioxidant defense mechanisms of the myocardium as well as evidence of oxidative myocardial injury. This has led to the hypothesis that oxidative stress may be a mechanism of disease progression in CHF. Indeed, many patients consume antioxidant supplements making the assumption that no harm will result and, possibly, that this therapy will yield some clinical benefits. The focus of this review is to examine the oxidative stress hypothesis of CHF as it pertains to humans. To date, human studies that have sought evidence for a role of oxidative stress in patients with CHF have fallen short of providing strong support for this hypothesis. Studies that have demonstrated an association between oxidant stress and CHF are small and are hindered by methodologic limitations that diminish the impact of their conclusions. Randomized trials of antioxidant supplementation for CHF are scarce, and to our knowledge no study yet convincingly demonstrates any benefit from consuming antioxidant supplements. Therefore, the available evidence is insufficient to support or negate the oxidative stress hypothesis of CHF and the use of antioxidants cannot be recommended as a specific therapy for this condition. ***(CHEST 2001; 120:2035–2046)***

Key words: antioxidants; congestive heart failure; free radicals; oxidative stress

Abbreviations: CHF = congestive heart failure; CoQ_{10} = coenzyme Q_{10}; CuZnSOD = copper zinc superoxide dismutase; eSOD = erythrocyte superoxide dismutase; GCMS = gas chromatography mass spectrometry; GSH = reduced glutathione; GPX = glutathione peroxidase; HPLC = high-performance liquid chromatography; LV = left ventricular; MnSOD = manganese superoxide dismutase; NYHA = New York Heart Association; ROS = reactive oxygen species; SOD = superoxide dismutase; TBARS = thiobarbituric acid-reactive substances

In recent years, many disease states have been associated with excess free-radical activity, and antioxidants have received much attention as a potential therapy for conditions ranging from aging to cancer and coronary heart disease.[1] A free radical is any molecule possessing an unpaired electron. The most important free radicals in biological systems result from the addition of electrons to molecular O_2.[2] The complete reduction of O_2 to water requires four electrons and occurs predominantly (95%) in mitochondria via the cellular respiratory chain without the production of reactive intermediates. However, O_2 reduction also occurs one electron at a time (univalent reduction) in a variety of physiologic as well as potentially pathologic processes. This produces partially reduced intermediates, including the free-radical superoxide anion, the nonradical hydrogen peroxide, and the highly reactive hydroxyl radical. These species are generally highly reactive and are referred to collectively as reactive oxygen species (ROS). Examples of ROS reactions with other biological molecules include the removal of electrons (oxidation) that can result in bond scission as well as the abstraction of hydrogen atoms. The resultant modification of organic molecules by ROS can be referred to as oxidative injury. Because of the reactivity of ROS, several enzymatic and nonenzymatic defenses such as superoxide dismutase (SOD), catalase, glutathione peroxidase (GPX), vitamin E, and vitamin C exist to protect against oxidative damage to other organic molecules.[3] Oxidative stress, which may result in oxidative tissue damage, occurs when there is an imbalance between ROS production and antioxidant defenses, such that either ROS produc-

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tion is increased and/or defense mechanisms are impaired. The purpose of this review is to explore the evidence that oxidative stress exists and contributes to disease progression in patients with congestive heart failure (CHF).

The Oxidative Stress Hypothesis of CHF

CHF is a syndrome characterized by chronic and progressive left ventricular (LV) systolic dysfunction. Despite the success of current therapies, including angiotensin-converting enzyme inhibitors,[4] β-blockers,[5] and aldosterone antagonists,[6] morbidity and mortality from CHF remain high and research into other disease-modifying factors continues. Recently, the role of oxidative stress has been explored as such a mechanism of disease progression. In the setting of CHF, excess free-radical generation may arise from many sources, including vascular nicotinamide adenine dinucleotide oxidases,[7] xanthine oxidases, autooxidation of catecholamines,[8] nitric oxide synthase activation,[9,10] or mitochondrial leakage.[11] Besides excess ROS generation, animal models of CHF have suggested that myocardial antioxidant defenses are also impaired.[12,13] These observations have prompted the formulation of an oxidative stress hypothesis of CHF. This hypothesis states that CHF is characterized by generalized and cardiac-specific oxidative stress, and that chronic oxidant injury contributes to impairment of myocardial function and ultimately clinical progression of the heart failure state.

Extensive evidence in support of this hypothesis comes from *in vitro* research and from experimental *in vivo* animal models of CHF. *In vitro* experiments have demonstrated that excess free-radical generation or impaired antioxidant function adversely affects several myocyte functions,[14–17] depresses myocardial contractility,[18,19] causes myocardial tissue injury,[20] and may also induce myocyte apoptosis.[21] *In vivo* animal models have also demonstrated the significance of oxidative injury to cardiac function; the best-studied example is that of myocardial stunning and injury due to reperfusion after a period of ischemia.[22,23] Several animal models of chronic CHF have also confirmed a role for oxidative stress.[12,13] Anthracycline-mediated cardiomyopathy in animals has been shown[24,25] to result primarily from oxidative injury and antioxidant therapy attenuated myocardial injury in this model. The administration of an antioxidant acutely improved cardiac function in a dog model of tachycardia-induced cardiomyopathy[26] providing evidence that, besides oxidant injury, oxidative stress may also reversibly depress cardiac function in this setting. A detailed examination of the evidence derived from *in vitro* and *in vivo* animal experiments is beyond the scope of this review, and the reader is referred to recent reviews on these topics.[27,28]

Oxidative Stress and CHF in Humans

Based on extensive nonhuman evidence, the biological plausibility of the oxidative stress hypothesis is well established. However, in humans there are only a few specific disorders in which a clear link between oxidative stress and chronic ventricular dysfunction has been established: anthracycline-mediated cardiomyopathy,[29–31] alcoholic cardiomyopathy,[32] and prolonged selenium deficiency or Keshan disease, although the causal role of oxidative stress is less certain in this situation.[33] In these examples, there are clear mechanisms that account for oxidative stress, either due to increased ROS generation, or impaired antioxidant defenses, as likely occurs in Keshan disease.[33] However, whether free-radical processes have a pathophysiologic role in the vast majority of patients with CHF due to ischemic, hypertensive, valvular, or idiopathic causes is unclear. Evidence that oxidative stress exists and/or has a role in humans with either idiopathic or ischemic cardiomyopathy has not been overwhelming. Studies that have explored oxidative stress end points in patients with CHF will be the focus of the remainder of this review.

Studies Demonstrating an Association Between Oxidative Stress and CHF in Humans

Thus far, large observational epidemiologic studies and prospective longitudinal cohort studies linking free-radical activity to CHF in humans are lacking. The evidence is limited to small observational case-control studies[34–41] that have demonstrated an association between markers of oxidative stress and clinical CHF. Although widely referenced, interpretation of these data requires caution, as these studies share some significant limitations that are discussed below.

Study Populations

Previously reported studies[34–38,40,41] for which appropriate control data are available are small and overall include < 200 patients with CHF. Aside from small sample size, a major limitation of many of these studies were confounding factors within the patient population. In some reports,[34,35,37,40,41] evidence of oxidative stress was likely not specific to the heart failure state because of the presence of other condi-

tions in the study population associated with oxidative stress, such as coronary artery disease or risk factors for atherosclerosis. In other studies,[38,39] risk factors for atherosclerosis were not well characterized. Interestingly, Diaz-Velez et al[37] compared patients with CHF to patients with cardiovascular risk factors and normal LV function as well as to healthy control subjects. These investigators found no difference in markers of oxidative stress between the two patient groups. Because aging may be associated with increased oxidative stress,[42] the results of two studies[37,38] were also confounded by the use of healthy control subjects who were significantly younger than the patients with CHF. To address some of these issues, McMurray et al[36] stratified patients with CHF by the presence or absence of coronary artery disease and found that, regardless of etiology, CHF was associated with markers of oxidative stress when compared to age-matched control subjects. We also compared CHF patients to age-matched control subjects with normal LV function and found increased markers of oxidative stress in CHF despite the presence of atherosclerosis in both groups.[41] Overall, the available evidence that oxidative stress is specific to the clinical syndrome of CHF in humans is not robust. A larger study comparing CHF patients with normal coronary arteries, free of any other conditions associated with oxidative stress, to a healthy age-matched control population would still prove valuable.

Biochemical Measures of Oxidative Stress

Free-radical species are highly reactive, short-lived and, as such, cannot be practically measured in human *in vivo* studies.[43] In the absence of a direct measure of free radicals, human studies have quantified the consequences of free-radical reactions employing methods that have significant limitations.

Measuring Lipid Peroxidation: Polyunsaturated lipids are very susceptible to free-radical attack. This process, referred to as lipid peroxidation, eventually yields several relatively stable decomposition products, including aldehyde compounds that can then be measured in plasma as an indirect index of free-radical activity.[43] Malondialdehyde, likely the most commonly measured index of oxidative stress in human studies, is only one of many aldehyde compounds produced by lipid peroxidation. Malondialdehyde is frequently measured in plasma by the thiobarbituric acid-reactive substances (TBARS) assay. Thiobarbituric acid reacts with malondialdehyde to produce a stable adduct that can be quantified using either spectrophotometry or high-performance liquid chromatography (HPLC). Although HPLC measures the thiobarbituric acid-malondialdehyde adduct more specifically that spectrophotometry, several other lipid-peroxide decomposition products and a variety of nonlipid-related materials are also detected.[44] Furthermore, malondialdehyde arises from the degradation of a variety of nonlipid molecules, including proteins, carbohydrates, DNA, and bile pigments.[45] Therefore, although the TBARS assay is accepted as an index of oxidative stress, this method quantitates malondialdehyde-like material and does not specifically measure malondialdehyde or lipid peroxidation. Other indexes that reflect lipid peroxidation include conjugated dienes, lipid hydroperoxides, and exhaled-breath hydrocarbons. These end points are also relatively nonspecific and do not appear to offer any advantage over the TBARS assay.[46]

Several small studies[34–39] have been published demonstrating elevated plasma concentrations of malondialdehyde-like material in patients with CHF (Table 1). The lack of specificity inherent in the TBARS assay is apparent on review of these studies. By spectrophotometry, the measured plasma concentrations of malondialdehyde-like material were approximately fivefold to 50-fold higher than when an HPLC method was employed.[34–39] More recently, malondialdehyde has been measured with greater accuracy using gas chromatography mass spectrometry (GCMS). Using this method, malondialdehyde is detected in human plasma in concentrations up to 100-fold smaller than when malondialdehyde-like material is measured by the TBARS assay,[47,48] and no longer differentiates CHF patients from control subjects.[41] Recently, a method has been developed that employs GCMS for the measurement of multiple aldehydes, including malondialdehyde, simultaneously from a single sample. Besides improved sensitivity and specificity for the measurement of malondialdehyde, this method may better reflect the extent of lipid peroxidation as a broader array of lipid peroxidation products is quantified.[49] These products include both saturated aldehydes, such as malondialdehyde, and unsaturated aldehydes, such as 4-hydroxy-nonenal. The unsaturated aldehydes have a well-documented toxicity to organic molecules and their detection may be of greater biological importance than that of malondialdehyde.[50,51] Using this method, we studied patients with CHF and age-matched control subjects with normal LV function.[41] Many aldehyde products of lipid peroxidation in plasma were significantly elevated in the CHF patients (Fig 1). Interestingly, the concentrations of unsaturated aldehydes in plasma were specifically elevated in the CHF group compared to the control group, while saturated species were either not different or decreased. Given the

Table 1—*Studies of Oxidative Stress in CHF Patients That Reported Malondialdehyde

Source	Study Groups (Participants, No.)	Lipid Peroxidation End Point, μmol/L†		Antioxidant End Point	Comments
McMurray et al[34]	CHF, CAD (29)	MDA (Sp)	~15‡		Control subjects did not have CAD
	Control subjects (15)		~8		
Belch et al[35]	CHF, CAD (45)	MDA (Sp)	9.0 (7.9 to 10.2)	In CHF: plasma thiols ↓	Control subjects matched for smoking
	Control subjects (45)		7.7 (6.9 to 9.2)		
McMurray et al[36]	CHF, CAD (15)	MDA (Sp)	10.0‡	In CHF: plasma thiols ↓	
	CHF, IDCM (15)		9.3‡	eSOD activity ↓	
	Control subjects (15)		7.6	GSH, ceruloplasmin ↑	
Diaz-Velez et al[37]	CHF (30)	MDA (HPLC)	2.65 ± 1.0‡		CAD with or without risk factors group had normal LV function
	CAD with or without risk factors (26)		2.10 ± 0.7‡		
	Control subjects (16)		1.45 ± 0.77		
Keith et al[39]	CHF (58)	MDA (HPLC)	~0.3 to 0.6	Plasma GPX activity ↓ Vitamin E ↔, vitamin C ↓	Lipid peroxides ↑ in CHF
Nishiyama et al[38]	CHF, IDCM (12)	MDA (Sp)	3.7 ± 1.3‡	eSOD ↔	CHF patients mean age 52 yr
	Control subjects (7)		1.9 ± 0.6		Control subjects mean age 23 yr
Mak et al[41]	CHF (8)	Total aldehydes (GCMS)	9.3 ± 0.8‡		Malondialdehyde (GCMS)
	Control subjects (8)		6.6 ± 0.3		CHF: 0.101 ± 0.003 μmol/L Control: 0.096 ± 0.003 μmol/L

*CAD = coronary artery disease; IDCM = idiopathic dilated cardiomyopathy; Sp = spectrophotometric method; MDA = malondialdehyde.
†Data are presented as mean, mean (range), or mean ± SD.
‡$p < 0.05$ vs control group.

known biological toxicity of unsaturated aldehydes, further exploration of the significance of these findings is underway.

Attention has recently focused on the measurement of F_2-isoprostanes as a sensitive and specific index of oxidative stress.[52] F_2-isoprostanes are relatively stable products arising from the free-radical–catalyzed peroxidation of arachidonic acid on phospholipids. Therefore, these compounds represent another index of membrane peroxidation. The utility of F_2-isoprostanes, measured in both plasma and in 24-h urine samples by GCMS, as indicators of oxidative injury in humans has been demonstrated in smokers[53] and after coronary reperfusion.[54] Moreover, this index is sufficiently sensitive to detect changes in oxidative stress; it was possible to demonstrate a decrease in F_2-isoprostanes with either the cessation of smoking or the administration of vitamin C to smokers who were otherwise healthy.[53,55]

In an intriguing report, 8-iso-prostaglandin $F_2\alpha$ was measured in the pericardial fluid of 51 consecutive patients at the time of cardiac surgery for either valvular or ischemic heart disease.[40] These investigators[40] demonstrated a strong correlation between the concentration of pericardial 8-iso-prostaglandin $F_2\alpha$ and LV dimensions measured echocardiographically. A relationship between pericardial 8-iso-prostaglandin $F_2\alpha$ and functional class was also observed. The investigators[40] hypothesized that oxidant stress in the heart may play a role in ventricular remodeling based on the relationship between pericardial 8-iso-prostaglandin $F_2\alpha$ and LV dimensions. However, as the authors[40] point out, it is not possible to identify the cell type of origin for 8-iso-prostaglandin $F_2\alpha$. As well, there is little information concerning the accumulation of markers of CHF in pericardial fluid, their relationship to pathophysiologic processes in the heart, or how such compounds are cleared. A relatively large human study of oxidative stress and CHF has been reported recently by Reilly et al[56] in abstract form. They measured urinary 8,12 isoprostane $F_2\alpha$-VI in 91 patients with CHF and 30 age-matched control subjects using GCMS. No differences in urinary 8,12 isoprostane $F_2\alpha$-VI, or in any of the four classes of F_2-isoprostanes, were detected between the two groups. Furthermore, levels of 8,12 isoprostane $F_2\alpha$-VI did not fall after transplantation or after successful implantation of a ventricular assist device.

In summary, despite methodologic limitations, several studies[34–39,41] have demonstrated an association between human CHF and elevated plasma aldehydes, the most commonly used marker of generalized oxidative stress. However, in one of the largest human studies[56] completed to date, the measurement of F_2-isoprostanes failed to demonstrate evidence of increased oxidant stress. These discordant findings highlight certain limitations that must be addressed in future investigations. Currently, there are no accepted "gold standards" for either the direct measurement of ROS generation or for the measurement of free-radical–mediated injury in hu-

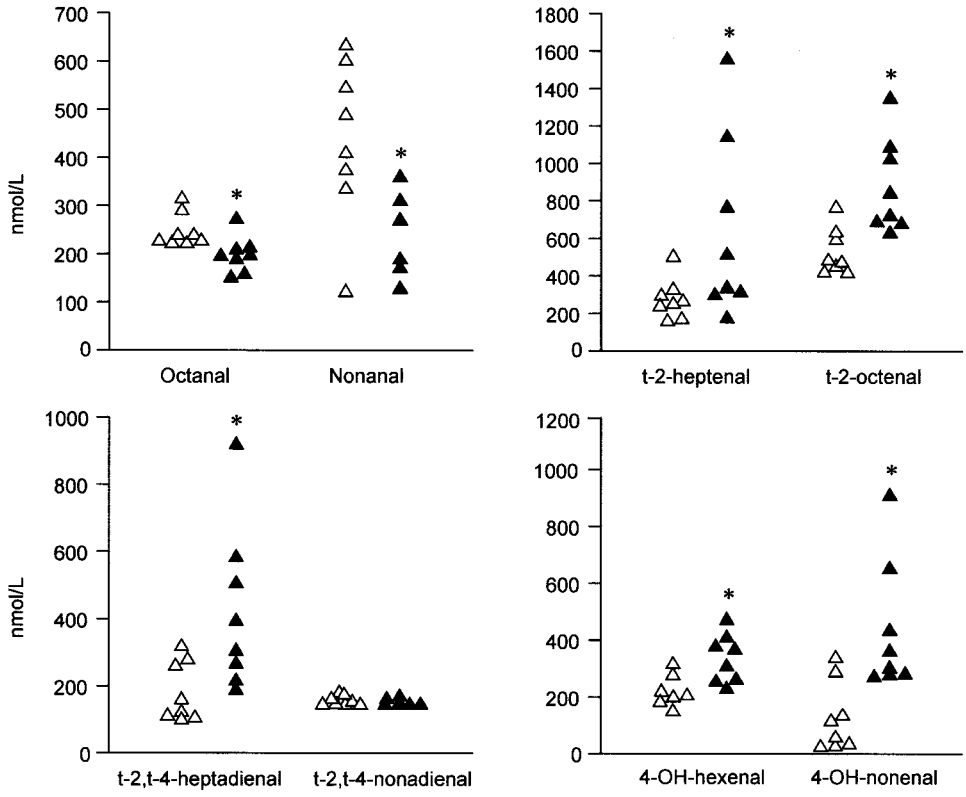

FIGURE 1. Arterial plasma concentration of selected aldehydes in subjects with normal LV function (open triangles) and patients with CHF (closed triangles). Octanal and nonanal are examples of saturated aldehydes. t-2-heptenal, t-2-octenal, t-2,t-4-heptadienal, t-2,t-4-nonadienal, 4-OH-hexenal, and 4-OH-nonenal are examples of unsaturated aldehydes. * = $p < 0.05$ vs normal LV function group. Modified and reprinted with permission from the *Journal of Cardiac Failure*.[41]

mans *in vivo*. Available methods for the direct measurement of ROS utilize agents that trap radical species *ex vivo*.[57,58] Based on the short-lived nature of free-radical species, such measurements reflect free-radical generation in close proximity to the site of collection and possibly *ex vivo*. The best available methods for the measurement of lipid peroxidation are expensive and not widely accessible; therefore, they may not be suitable for use in large-scale clinical trials.

Measuring Antioxidant Defenses: Recognizing the limitations of the methods for measuring products of lipid peroxidation, most investigators[35,36,38,39,59] have attempted to quantify antioxidant defenses as another means of detecting oxidative stress in humans. In patients with CHF, decreased thiol groups in plasma[35,36] as well as those associated with erythrocyte membranes[59] have been consistently demonstrated. The depletion of thiol groups may reflect increased interaction between free radicals and membrane-associated proteins. However, the activities of various antioxidant enzymes have been measured in plasma with less consistent results. Reduced glutathione (GSH) functions as an important part of the antioxidant defense system by scavenging free radicals and regenerating other antioxidants. In CHF, both significant increases of plasma GSH[36] and decreases of whole-blood reduced GSH[59] have been demonstrated. The activity of erythrocyte SOD (eSOD) has been generally found to be depressed, although a single report[38] demonstrated no difference in eSOD activity compared to control. The activity or serum concentrations of a variety of other antioxidants published in small reports include plasma ceruloplasmin (increased in CHF[36]), GPX (decreased in CHF[39]), vitamin E (not different from control in CHF[39]), and vitamin C (decreased[39] and not different from control in CHF[60]). Thus, there is apparently little consensus regarding which plasma index of antioxidant status is most useful, and the data available have been inconsistent.

Free radicals are generated as a part of normal cellular activity, and thus the intracellular enzymatic antioxidant defenses are paramount to the protection of organ function. Since free radicals are extremely

short lived and participate in reactions close to the site of their generation, the assessment of antioxidant enzymes in tissue is likely more meaningful than their measurement in plasma. These enzymes include the copper zinc SOD (CuZnSOD), manganese SOD (MnSOD), catalase, and GPX. In animal models of cardiomyopathy, a decrease in myocardial antioxidant activity has been observed[13,61] and may contribute to cardiac oxidative stress either as a cause or as a result.[62] Recently, two studies[63,64] have examined myocardial gene expression, protein levels, and enzymatic activity of CuZnSOD, MnSOD, catalase, and GPX from the explanted hearts of patients with end-stage CHF as well as nonfailing donor hearts. In both studies,[63,64] expression and activity of CuZnSOD, MnSOD, and GPX were not different in CHF patients compared to control subjects, suggesting intact myocardial superoxide scavenging capability. One study demonstrated significant increases in catalase messenger RNA, protein levels, and activity,[63] while, in contrast, the other study[64] demonstrated significantly depressed catalase activity despite preserved messenger RNA and protein expression. Although both findings can be reconciled independently with increased oxidant stress, together these studies do not clarify whether a change in myocardial antioxidant status is a pathophysiologic mechanism in the progression of CHF in humans. To date, there is minimal information on the status of antioxidant protection by extracellular SOD in humans with CHF.

Relationships Between Oxidative Stress and Indexes of Disease Severity

Many investigators[35,37–41] have attempted to relate biochemical end points of oxidative stress to indexes of disease severity (Table 2). Evidence of a relationship between markers of lipid peroxidation and ejection fraction or LV dimensions may support a link between oxidative stress and ventricular dysfunction; however, the data available are from relatively small studies[35,37,39,40] and have yielded conflicting results. A more consistent relationship has been demonstrated between markers of oxidative stress and functional indexes, including New York Heart Association (NYHA) class and peak exercise oxygen consumption.[38–40] Interestingly, these findings may support the concept that oxidative stress may relate to impairment in peripheral blood flow or skeletal muscle function.

We have demonstrated[41] a relationship between plasma aldehydes and ventricular contractility in a small number of patients (Fig 2). However, we did not administer an antioxidant intervention, and it is plausible that circulating aldehydes, rather than cardiac free-radical activity, may have had a negative inotropic effect. A more compelling demonstration of a functional role of oxidative stress in CHF was reported by Hornig and coworkers.[65] These investigators[65] demonstrated that endothelial dysfunction, which has been observed consistently in patients with CHF, can be reversed by the administration of

Table 2—*Studies of Oxidative Stress in CHF Patients That Reported Associations With Disease Severity

Source	Study Groups (Participants, No.)	Oxidative Stress End Point	Indexes of Disease Severity	Correlation
Belch et al[35]	CHF, CAD (45) Control subjects (45)	MDA (Sp)	LV ejection fraction (radionuclide angiography)	Yes (negative)
Diaz-Velez et al[37]	CHF (30) CAD with or without risk factors (26) Control subjects (16)	MDA (HPLC)	LV ejection fraction (radionuclide angiography)	No
Nishiyama et al[38]	CHF, IDCM (12) Control subjects (7)	MDA (Sp)	Peak exercise oxygen consumption	Yes (negative)
Mallat et al[40]	CHF NYHA II–III (41) NYHA I (10)	Pericardial fluid 8-iso-prostaglandin $F_{2\alpha}$ (GCMS)	NYHA functional class LV diastolic and systolic diameter (echocardiography) LV fractional shortening (echocardiography)	Yes (positive) Yes (positive) No
Keith et al[39]	CHF (58)	Lipid peroxides (Sp) and malondialdehyde (HPLC)	NYHA functional class LV ejection fraction (echocardiography) LV dimensions (echocardiography)	Yes (positive) No No
Mak et al[41]	CHF (8) Control subjects (8)	Total aldehydes (GCMS)	LV contractility (LV + dP/dt)	Yes (negative)

*LV +dP/dt = maximum rate of isovolumic LV pressure rise. See Table 1 for expansion of abbreviations.

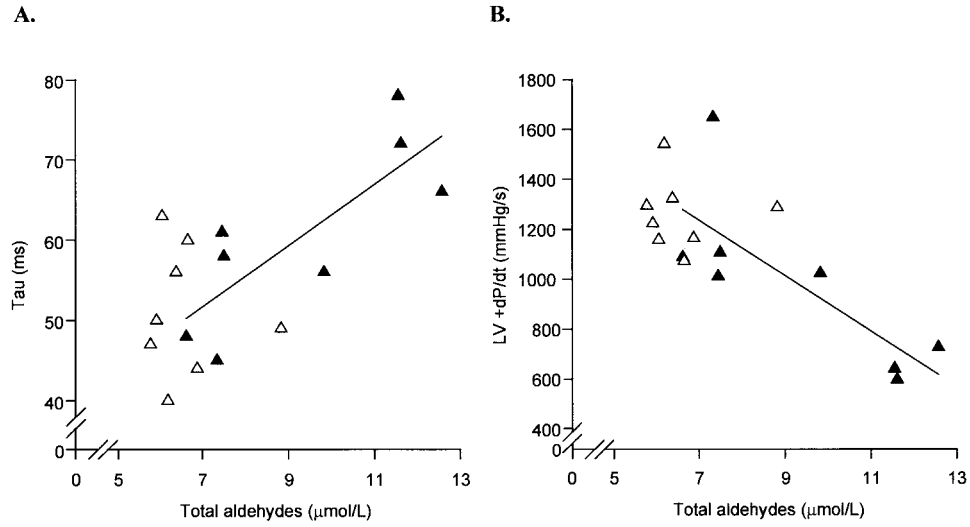

FIGURE 2. The relationship between plasma aldehyde concentration and τ (Tau; *left*, *A*) and isovolumic contractility (LV +dP/dt; *right*, *B*) in subjects with normal LV function (open triangles) and patients with CHF (closed triangles). The regression lines shown are for the relationship between plasma aldehyde concentration and τ ($r = 0.79$, $p < 0.05$) and LV +dP/dt; $r = -0.76$, $p < 0.05$) in the CHF group. Reprinted with permission from the *Journal of Cardiac Failure*.[41]

high-dose intravascular vitamin C, a powerful antioxidant. This effect of vitamin C in CHF patients was consistent with that found in other patient populations where oxidative stress is thought to contribute to endothelial dysfunction.[66,67] The postulated mechanism for endothelial dysfunction relates to the consumption of the endothelium-derived relaxing factor, nitric oxide, by superoxide anion; endothelial function is thus restored by the administration of vitamin C, which quenches excess superoxide. However, the effect of vitamin C in CHF patients was not confirmed in a subsequent report,[60] in which vitamin C had no effect on impaired endothelial function in patients with idiopathic dilated cardiomyopathy. Therefore, the evidence that oxidative stress in patients with CHF contributes to endothelial dysfunction remains uncertain.

THE PROMISE OF ANTIOXIDANT THERAPY?

Despite methodologic issues, an association between oxidative stress and CHF has been generally accepted. Whether free-radical activity has a causal or propagating role in CHF remains unresolved. Evidence of causality such as a "temporal" or "dose-response" relationship may be obscured by the heterogeneous etiology of CHF and the numerous factors involved in disease progression. Indeed, as noted, attempts to relate markers of oxidative stress to ventricular function have not identified a clear relationship. As in the case of the neurohumoral hypothesis, "reversibility" or the success of antioxidant therapy in preventing or retarding disease progression would likely provide the best evidence in support of the oxidative stress hypothesis of CHF. However, to date there is a distinct scarcity of randomized clinical trials investigating the therapeutic potential of antioxidant therapy in patients with CHF.

Antioxidant Vitamins

Vitamin E, vitamin C, and beta carotene remain the most widely studied antioxidants in the setting of large, randomized controlled trials. The largest of these studies[68,69] has investigated the efficacy of antioxidant therapy in the primary prevention of cancer in $> 20{,}000$ subjects. In contrast, to our knowledge only two small trials[70,71] of vitamin E therapy in patients with CHF are available. A nonrandomized, uncontrolled, and unblinded study[70] of vitamin E supplementation for 4 weeks in 20 patients with CHF demonstrated improvement in markers of oxidative stress (malondialdehyde measured by TBARS). The focus of the study[70] was on biochemical rather than clinical end points; among other important limitations, the study cohort was comprised of patients requiring acute admission to the hospital and who received active treatment for decompensated CHF during the study period. Keith et al[71] performed a double-blind, randomized, placebo-controlled trial of vitamin E in 56 CHF patients in which the primary end points were again biochemical. Although plasma vitamin E levels increased, 12 weeks of treatment did not have any

impact on markers of oxidative stress, including malondialdehyde and F_2-isoprostanes.[71] No effect on quality of life was observed.

Without positive evidence from clinical trials, encouraging the use of antioxidants based on the rationale that they are likely to be of no harm may be inappropriate. Large-scale trials of vitamin C, vitamin E, and beta carotene for the primary prevention of cancer[68,69,72,73] and vitamin E in secondary prevention of acute ischemic coronary events[74–77] have raised important questions concerning the utility of antioxidant therapy. Although evidence for the role of oxidative stress in the genesis of both these conditions is more clearly established than it is for CHF, supplementation resulted in minimal or no clinical benefit. This may have related to the inability of available oral supplements to provide adequate antioxidant protection *in vivo* rather than an invalidation of the oxidative stress hypothesis. It may not be possible to attain physiologically effective concentrations in plasma with conventional oral regimens, especially in the case of vitamin C.[78] For malignant disease, it may be necessary to intervene earlier and for a longer period of time. Of importance, the use of beta carotene was not benign and associated with a significant increase in malignant disease.[73] These issues highlight the necessity of accumulating adequate clinical evidence prior to recommending the use of antioxidant vitamins for CHF.

Coenzyme Q_{10}

The therapeutic potential of coenzyme Q_{10} (CoQ_{10}) for CHF has received much attention and is consumed by many patients without a physician's directive. CoQ_{10} is a vital part of the mitochondrial electron transport chain and can function as a potent lipid-soluble antioxidant. It is synthesized endogenously, and deficiency is not an issue in health, although some data[79] suggest a myocardial deficit of CoQ_{10} may exist in CHF. Because of the prominent role of CoQ_{10} in myocardial energetics as well as its antioxidant potential, it has been hypothesized that supplementing the relative deficiency of CoQ_{10} may have therapeutic benefits in patients with CHF. Several CHF trials of CoQ_{10} have demonstrated benefits with respect to subjective clinical end points but are only available as published reports from international symposia.[79] Such trials include a multicenter study,[80] which is the largest, double-blind, randomized controlled trial to date (and to our knowledge). These investigators[80] randomized 641 patients with NYHA class III and IV symptoms to therapy with CoQ_{10} or placebo for at least 12 months. Mortality, a prespecified end point, was surprisingly low overall (approximately 6%) and not different between the two study groups. Objective measures of ejection fraction were not obtained; however, hospitalization for worsening CHF was lower in the treatment group. There are a few randomized controlled trials of CoQ_{10} for CHF published in peer-reviewed journals (Table 3).[81–85] In general, no improvement in ejection fraction measured by radionuclide ventriculography,[82,83,85] or echocardiography[84] has been observed with CoQ_{10} supplementation; a single study[81] demonstrated improved ejection fraction using obsolete methods. A treatment benefit of CoQ_{10} with respect to maximal exercise capacity has not been consistently observed and no benefit has been detected with respect to peak oxygen consumption during exercise or quality of life as measured by the Minnesota "Living with Heart Failure" Questionnaire. To our knowledge no studies have demonstrated a benefit of CoQ_{10} with respect to mortality. Thus, the existing evidence does not warrant the recommendation of CoQ_{10} as a therapy for patients with CHF.

Table 3—*Studies of CoQ_{10} in Patients With CHF

Source	Study Design (Participants, No.)	Dose, mg/d	LVEF (Method of Measurement)	Other Results
Langsjoen et al[81]	Crossover (19)	100	Increased (systolic time intervals)	Stroke volume increased
Permanetter et al[82]	Crossover (25)	100	Unchanged (radionuclide angiography)	Cardiac output unchanged LV dimensions unchanged Exercise capacity unchanged
Hofman-Bang et al[83]	Crossover (79)	100	Unchanged (radionuclide angiography)	Exercise capacity increased Quality of life increased
Watson et al[84]	Parallel (30)	100	Unchanged (echocardiography Simpsons rule)	Cardiac output unchanged PCWP unchanged Quality of life unchanged
Khatta et al[85]	Parallel (55)	200	Unchanged (radionuclide angiography)	Peak oxygen consumption unchanged Exercise capacity unchanged

*PCWP = pulmonary capillary wedge pressure; LVEF = LV ejection traction.

Carvedilol

The utility of both selective and nonselective β-blockers for the treatment of CHF has been definitively established in large clinical trials.[5,86] Carvedilol is a nonselective β-blocker that has generated additional interest because of its purported antioxidant properties *in vitro*.[87] To date, however, it has not been demonstrated that treatment with carvedilol has any benefits with respect to long-term clinical outcomes compared to β-blockers such as metoprolol that are not considered significant antioxidants.[88–90] Carvedilol may reduce cardiac sympathetic activation more than metoprolol, an effect that is attributed to greater adrenergic blockade than to any antioxidant effect.[91] A direct comparison[90] of carvedilol to metoprolol in the treatment of CHF has demonstrated no difference in their effects on malondialdehyde (measured in plasma by the TBARS assay). Both drugs were associated with a similar improvement in ejection fraction and similar decreases in plasma malondialdehyde after 6 months of treatment. These results draw attention to the fact that TBARS may simply be elevated in heart failure because of impaired clearance, and decreased because of the hemodynamic improvement observed with both drugs, rather than any antioxidant effect of carvedilol.

Conclusion

The existing evidence for a role of oxidative stress in the pathophysiology of CHF in humans is not compelling. Measurement of free-radical activity *in vivo* in humans is not straightforward. Studies relating markers of oxidative stress to CHF have been small and have demonstrated an association at best. Attempts to demonstrate a relationship between these markers and the severity of heart failure have been conflicting. Attempts to elucidate the status of antioxidant defenses have also been inconsistent. Finally, clinical trials of antioxidant therapy for CHF are few in number and, thus far, have failed to demonstrate convincing benefits.

In vitro and *in vivo* experiments in animal models consistently provide support for the role of oxidative stress in promulgating LV dysfunction. This extensive body of literature continues to suggest that there is great potential benefit in therapies that can decrease oxidative stress in humans with CHF. However, several issues must be addressed in order for clinical studies in humans to move forward. The absence of a means to reliably measure free-radical activity in humans *in vivo* remains a great limitation. Such information is necessary to evaluate whether specific treatments provide adequate antioxidant protection. Such a tool would also be important to identify subsets of the CHF population that may exhibit particularly elevated levels of oxidative stress and who may reap greater clinical benefit with antioxidant therapy. Without such information, interpretation of clinical trials may yield incorrect conclusions because of inadequate antioxidant agents or because of inclusion of patients less likely to benefit.[92] To date, for a variety of disease states, studies of the commonly available oral antioxidant vitamins have demonstrated marginal therapeutic efficacy. Further study is required to identify treatments, either individually or in combination, that may have more potent antioxidant properties *in vivo*. Besides examining the effects of long-term administration of antioxidant treatment, experiments that explore the effects of acute manipulation of redox environment on cardiac function *in vivo* are also important and ongoing.[26,93]

Although much of the experimental evidence of oxidative stress in humans with CHF remains preliminary, the use of vitamins and other nutraceuticals that purport antioxidant properties receives much publicity in the popular press. Many patients continue to consume vitamin supplements, often without informing their physicians. Unfortunately, the evidence thus far is insufficient to support or negate the oxidative stress hypothesis of CHF and, at present, the use of antioxidants cannot be recommended as a specific therapy for this condition.

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