Angiotensin Type-1 Receptor A1166C Gene Polymorphism Correlates With Oxidative Stress Levels in Human Heart Failure

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Abstract—Oxidative stress plays a critical role in the pathogenesis of cardiovascular disease and diabetes. Studies in vascular cells and experimental animals have demonstrated that the angiotensin type-1 receptor (AT1R) contributes to formation of reactive oxygen species by activating nicotinamide-adenine dinucleotide phosphate oxidases, but the relevance of this pathway to human heart disease has not been established. Here we demonstrate that a polymorphism in the AT1R gene (A1166C), linked to increased receptor activity, is associated with elevated levels of oxidative stress markers in heart failure patients but not in healthy controls. Plasma protein carbonyls (PCs), a marker of oxidative protein modification, were 10-fold higher in heart-failure patients compared with controls [geometric means and 95% CIs for patients, 75 (57 to 100) pmol/mg; controls, 5 (4 to 7) pmol/mg; \( P < 0.001 \)]. Moreover, levels of PCs were 50-fold higher in patients homozygous for the polymorphism (CC) than in controls and significantly higher than the AA and AC genotype patient groups [CC: 273 (135–550); AC: 59 (35–98); AA: 65 (40–106) pmol/mg; \( P < 0.001 \)]. Levels of myeloperoxidase were also modestly increased in heart-failure patients [51 (46–57) ng/mL] compared with controls [37 (32–44) ng/mL; \( P < 0.001 \)], but were especially elevated in patients with a CC genotype [CC: 72 (58–89); AC: 52 (44–61); AA: 39 (34–46) ng/mL; \( P < 0.001 \)]. The AT1R genotype was demonstrated to be an independent predictor of both PCs and myeloperoxidase levels in heart-failure patients. These findings suggest that oxidative stress in human heart failure is regulated via angiotensin signaling and may involve the nicotinamide dinucleotide oxidase pathway. (Hypertension. 2006;47:1155-1161.)

Key Words: heart failure ■ oxidative stress ■ receptors, angiotensin

Oxidative stress contributes to the pathogenic processes underlying atherosclerosis,1 heart failure,2–4 and diabetes,5,6 and the role of oxidative stress in the progression of congestive heart failure (HF) has generated considerable interest. Oxidative stress arises from enhanced generation of free radicals and other reactive oxygen species (ROS) in excess of the antioxidant capability of the tissue to remove them. Oxidative stress can damage tissue constituents directly and may also have more subtle effects on cell regulatory and signaling processes, such as ion transport, adhesion molecule expression, vasodilation, proliferation, and apoptosis.3,7,8 There are several potential sources of ROS in HF, but NAD(P)H oxidases (NOX) seem to be especially relevant to cardiovascular pathology.3,9,10 This family of membrane-associated enzyme complexes is expressed in cardiomyocytes, vascular endothelial cells, and smooth muscle cells.11 The NOX can be activated by angiotensin II (Ang II) to generate superoxide radicals and hydrogen peroxide via the angiotensin type-1 receptor (AT1R), as has been demonstrated in cultured vascular cells12–14 and in experimental animals.10,15,16 However, the role of AT1R activity in generating ROS in the setting of human HF has not yet been established.

It has been well established that increased levels of hormones of the renin–angiotensin system (RAS) also contribute to a poor prognosis in both HF and in diabetic patients by stimulating adverse sodium and water retention, increasing peripheral vascular resistance, and promoting adverse vascular and cardiac remodeling.17 Inhibition of the RAS with angiotensin-converting enzyme blockers, angiotensin receptor inhibitors, or an aldosterone blocker has been shown to be effective in reducing morbidity and mortality in HF.18 The adverse effects of Ang II are primarily mediated through the AT1R.19 A common polymorphism in the AT1R gene (A1166C) has been linked to enhanced physiological responses to Ang II. This AT1R A1166C polymorphism has
been associated with increased vasoconstrictor activity in response to Ang II in hypertensive patients\(^{20}\) and in human arteries.\(^{21,22}\) Whether the generation of reactive oxidants is enhanced in carriers of the \(AT1R\) polymorphism was previously unknown.

Inflammation and endothelial dysfunction are also implicated in the progression of HF,\(^{23}\) and oxidants produced by monocytes or neutrophils may contribute to the disease process. These cells are capable of generating large amounts of superoxide, hydrogen peroxide, and, through the action of myeloperoxidase (MPO), hypochlorous acid, nitrogen dioxide, and other free radicals.\(^{24}\) Interest in MPO in cardiovascular disease has been stimulated by observations that plasma levels are elevated in patients with acute coronary syndromes or chest pain and may provide an independent prognostic indicator for adverse outcomes.\(^{24,25}\) To date, there have been no publications reporting levels of MPO in HF patients.

To determine whether plasma markers provide evidence of elevated oxidative stress levels in HF and whether oxidative stress in human HF is affected by \(AT1R\) genotype, we have measured protein carbonyls (PCs), which have been shown to be a good index of protein oxidation in a range of disease states,\(^{26,27}\) and MPO in patients with HF and age-matched controls. In view of the debate over the role of oxidative stress in the complications of diabetes,\(^{5}\) cohorts of HF patients with and without diabetes were examined. Our objectives were to determine whether plasma PC and MPO concentrations are increased and associated with severity markers in these patient groups and whether \(AT1R\) signaling contributes to oxidative stress in the setting of human HF.

### Methods

#### Patients HF Registry

From December 1, 1997, to August 31, 2000, patients admitted to Christchurch Hospital (Christchurch, New Zealand) considered by the admitting physician to have HF and to meet the Framingham and European Society of Cardiology Criteria\(^{27}\) were included in the Christchurch Heart Failure Registry (\(n=\)2730). All of the Christchurch Heart Failure Registry patients were New York Heart Association class IV at time of hospital admission, and survivors were New York Heart Association class II or III at time of discharge. Nearly 60% of patients had hypertension, 23% had type-2 diabetes, 32% had a previous history of HF, and 34% a previous history of myocardial infarction. A randomly selected subgroup of patients who were considered fit at discharge by the attending medical team were subsequently follow-up to investigate levels of oxidative stress in HF with and without diabetes. Oxidative stress markers were measured in 83 patients with type-2 diabetes, in 82 randomly selected, age- and gender-matched, nondiabetic HF patients, and a control group of 85 age- and gender-matched healthy controls (\(n=\)30; CC: \(n=\)53; AC: \(n=\)45; AA: \(n=\)37) and in 112 age- and gender-matched healthy controls (\(n=\)30; CC: \(n=\)53; AC: \(n=\)45; AA: \(n=\)37). The \(AT1R\) A1166C genotype of HF patients and controls was determined by PCR restriction fragment-length polymorphism assay.\(^{28}\) All of the individuals genotyped as CC were regenotyped, along with an equal number of randomly selected AA and AC patients, and were 100% concordant with the original genotype. The frequencies of the \(AT1R\) genotype in the normal Christchurch population are 50% AA, 42% AC, and 8% CC and are in Hardy–Weinberg equilibrium.

In HF patients, echocardiography was performed at the time of HF admission. Left ventricular (LV) end diastolic and systolic volumes (LVEDV and LVESV), LV mass index, and LV ejection fraction (LVEF) were assessed by standard methods.\(^{29}\) Drug treatment on discharge after the index admission was documented. Clinical events (death and hospital readmission for HF) were recorded over a median follow-up period of 3.9 years (range: 10 days to 6.4 years). Date of death was confirmed by searching the National Health Index linked to the National Register of Deaths. The number of adverse events in this HF cohort over the follow-up period was 93 deaths and 93 readmissions for HF. Patient ethnicity was self-declared. The cohort was predominantly of European ancestry (\(\approx\)87%), with 6.8% identifying as New Zealand Maori or Pacific Islander and the remainder (7.2%) identifying as Asian, Indian, or Middle Eastern ethnicities.

The investigation was approved by the Canterbury Human Ethics Committee (Ethics Approval Reference Number for Heart Failure Study CTY/99/02/014 and for the Study of Healthy Volunteers CTY/01/05/062), and all of the participants provided written, informed consent. The study adhered to the principles of the Declaration of Helsinki and Title 45, US Code of Federal Regulations, Part 46, Protection of Human Subjects, Revised November 13, 2001, effective December 13, 2001. All of the procedures followed were in accordance with institutional guidelines.

#### Hormone, PC, and MPO Assays

Blood samples were taken into EDTA before discharge from the index hospital admission, and plasma concentrations of n-terminal brain natriuretic peptide (N-BNP)\(^{30}\) and Ang II\(^{11}\) were measured by radioimmunoassay as described previously. PCs were analyzed by ELISA after derivatization with 2,4-dinitrophenylhydrazine\(^{31}\) using kits (Zenith Technology). Myeloperoxidase was measured by sandwich ELISA on plasma diluted 1:10 using a monoclonal antibody (Abcam) and a rabbit polyclonal antibody produced in-house. The detection range was 0.3 to 25 ng/mL, and the assay coefficient of variation was 13%.

#### Statistical Analysis

Univariate analysis relating PCs and MPO values to demographic data were performed using ANOVA. Levels of PCs, MPO, and hormones displayed consistently skewed distributions and were, therefore, log transformed before analysis, and geometric means with their 95% CIs were reported. Associations between \(AT1R\) genotype, plasma Ang II, plasma PC, and MPO levels were determined using a general linear model with \(AT1R\) genotype and plasma Ang II as covariates. Multivariate analysis was performed using a step-wise Cox proportional hazards model to determine independent associations between markers of oxidative stress and other risk factors (age, ethnicity, previous HF, diabetes, LVEF, plasma N-BNP, and angiotensin-converting enzyme inhibitor treatment) for survival and HF readmission. Kaplan–Meier survival curves were compared between above/below-median PC levels (high/low-risk groups) using log-rank tests. Potential bivariate correlations were explored between PCs and MPO, levels of circulating N-BNP and Ang II at hospital admission, and with measures of cardiac function, including LV internal diastolic and systolic dimensions, LV mass index, and LVEF. All of the statistical analyses were performed using SPSS version 11 software (SPSS Inc.). A \(P<0.05\) was considered significant.

#### Results

#### Baseline Characteristics

Baseline characteristics of the patient and control groups are given in the Table, demonstrating similar age and gender profiles for the cases and controls. Ethnicity was not significantly associated with levels of PCs \((P=0.436)\) or MPO \((P=0.217)\) and was not independently associated with sur-
vival \( (P = 0.259) \). There was no significant effect of gender on PCs or levels of MPO. There were nonsignificant trends toward an increase in PCs with age in each group, but MPO levels were not significantly correlated with age. Among HF patients, there were no significant differences between those with or without diabetes with regard to drug treatment, history of myocardial infarction, plasma Ang II concentration, plasma N-BNP, or echocardiography data (Table).

PCs and AT1R Genotype in HF

Plasma levels of PCs were significantly elevated in HF patients compared with matched controls \( (P < 0.001; \) Figure 1A and Table), with mean PC levels >10-fold higher in HF patients compared with controls. The PC levels seen in HF patients were marginally elevated compared with the healthy controls \( 10 \)-fold higher in HF patients \( P < 0.001; \) Figure 1B and Table). Plasma MPO levels in the diabetic HF patients compared with the healthy controls were not different from controls. There was, however, a significant correlation between plasma MPO and circulating N-BNP. Regression analysis indicated that both ATIR genotype \( (P < 0.001) \) and plasma Ang II levels \( (P = 0.003) \) independently predicted levels of plasma PCs in these HF patients.

MPO Levels and AT1R Genotype in HF

Plasma levels of MPO were significantly greater in nondiabetic HF patients compared with the healthy controls \( (P < 0.001; \) Figure 1B and Table). Plasma MPO levels in the diabetic HF patients were not different from controls. There was no significant correlation between levels of MPO and PCs \( (r = 0.086; \) Figure 2B). There was also no significant relationship between MPO levels and mortality, either when diabetics were considered separately from nondiabetics or for the HF group as a whole \( (P = 0.836) \). There was, however, a significant correlation between plasma MPO and circulating Ang II \( (r = 0.167; \) Figure 2B), although not with LVEF or N-BNP.

Plasma levels of MPO in HF patients, but not controls, were also significantly associated with ATIR genotype \( [CC: 72 (58 to 89); AC: 52 (44 to 61); AA: 39 (34 to 46) \text{ng/mL}; \) Figure 2B]. In HF patients with an ATIR CC genotype, MPO levels were almost double those of the entire control group \( 37 (32 to 44) \text{ng/mL}; \) Figure 2B]. In HF patients with an ATIR CC genotype, MPO levels were almost double those of the entire control group \( 37 (32 to 44) \text{ng/mL}; \) Figure 2B]. In HF patients with an ATIR CC genotype, MPO levels were almost double those of the entire control group \( 37 (32 to 44) \text{ng/mL}; \) Figure 2B]. In HF patients with an ATIR CC genotype, MPO levels were almost double those of the entire control group \( 37 (32 to 44) \text{ng/mL}; \) Figure 2B]. In HF patients with an ATIR CC genotype, MPO levels were almost double those of the entire control group (Figure 2B). Among the healthy controls, levels of plasma PCs were not significantly different among the ATIR genotype groups \( [CC: 10 (5 to 18); AC: 5 (3 to 10); AA: 6 (3 to 10) \text{pmol/mg}; \) Figure 2A]. Among the healthy controls, levels of plasma PCs were not significantly different among the ATIR genotype groups \( [CC: 10 (5 to 18); AC: 5 (3 to 10); AA: 6 (3 to 10) \text{pmol/mg}; \) Figure 2A]. Among the healthy controls, levels of plasma PCs were not significantly different among the ATIR genotype groups \( [CC: 10 (5 to 18); AC: 5 (3 to 10); AA: 6 (3 to 10) \text{pmol/mg}; \) Figure 2A]. Among the healthy controls, levels of plasma PCs were not significantly different among the ATIR genotype groups \( [CC: 10 (5 to 18); AC: 5 (3 to 10); AA: 6 (3 to 10) \text{pmol/mg}; \) Figure 2A]. Among the healthy controls, levels of plasma PCs were not significantly different among the ATIR genotype groups \( [CC: 10 (5 to 18); AC: 5 (3 to 10); AA: 6 (3 to 10) \text{pmol/mg}; \) Figure 2A]. 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Cox stepwise regression analyses indicated that PC and MPO levels were not independently predictive of death or HF readmission in this model. Nor was AT1R genotype predictive of death in a Cox univariate analysis ($P = 0.432$).

Discussion

We report elevated plasma levels of PCs and MPO in patients with established HF. Intriguingly, both were significantly correlated with circulating Ang II concentrations and were highest in homozygotes for the A1166C polymorphism in the AT1R gene. Moreover, the AT1R genotype was an independent predictor of levels of PCs and MPO activity. This genotype is reported to be associated with increased receptor activity.20–22 These results imply that both PC and MPO levels may be influenced by the activity of the AT1R receptor.

Neither marker was increased in diabetic HF patients in this study, beyond the effect of HF alone, despite the evidence that hyperglycemia leads to the generation of ROS.6 In fact, levels of MPO were slightly higher in nondiabetic HF patients compared with diabetic patients. However, when AT1R genotype was considered, elevated MPO levels were almost entirely confined to HF patients with the CC genotype, of which the majority were in the nondiabetic group.

Our novel finding that PCs are markedly elevated in plasma from HF patients adds weight to the concept that HF is associated with increased reactive oxidant production. The observation that PC levels were, on average, 10-fold higher in HF patients than in controls is far greater than the 2- to 3-fold differences in 8-isoprostan e levels reported by others.33,34 This indicates that plasma PC level is a sensitive index of oxidative stress in HF.

The finding that PCs were positively associated with circulating Ang II and were much higher in AT1R CC patients suggests that they were generated by an Ang II-regulated process, and we postulate that the NOX family of enzymes may contribute to the elevated PC levels. NOX is activated by Ang II via the AT1R to generate superoxide and has already been implicated in the pathophysiology of HF.11,33–35 Oxidants generated by NOX play a pivotal role in Ang II signaling in the vasculature, but excessive oxidant production may contribute to the adverse effects of this hormone, such as hypertension and restenosis.9,36,37 Higher NOX activity has been observed in cardiac tissue of failing human hearts.37,38 A detrimental effect of excessive Ang II-NOX activity is supported by the finding that knockout mice lacking a component of the oxidase have a reduced cardiac hypertrophic response to Ang II.10,39 Furthermore, an association between the beneficial effects of losartan, a selective AT1R inhibitor, and decreased oxidative stress has been reported in a rat MI model.40 Our findings strongly suggest that Ang II–mediated oxidative stress occurs in HF in humans. Treatment of patients with AT1 receptor blocker drugs before coronary artery bypass surgery has been reported to down-regulate expression of the NOX subunit, gp91phox, in mammary artery biopsies.41 Taken together, our findings of high PC levels in AT1R CC HF patients suggest that this genotype may be associated with greater NOX activation and increased generation of reactive oxidants.
Plasma MPO concentrations are increased in patients with chest pain or acute coronary syndromes. It was perhaps surprising, therefore, that only a modest increase in MPO was observed in HF in the present study. Moreover, in contrast to the studies of acute coronary syndromes where high MPO was a prognostic indicator, previous myocardial infarction or history of coronary artery disease was not associated with higher MPO in our study. In fact, if the AT1R genotype patients are excluded, levels were only marginally above control values within this HF cohort. Because increased levels of MPO are associated with inflammation and the activation of neutrophils and monocytes, and inflammation is a feature of atherosclerosis and myocardial ischemia, MPO is likely to prove a more relevant marker in acute coronary syndromes than established HF. MPO activity has been reported in atherosclerotic lesions, and high levels are associated with plaque rupture and endothelial dysfunction. The finding that plasma MPO levels were associated with AT1R genotype in HF patients was unexpected and suggests a hitherto unknown link between the maladaptive effects of the RAS and the pathology of HF. There is no direct relationship between this system and MPO, but it may be that activation of the AT1R, either via NOX products or another route, induces inflammatory cell activity and MPO release.

Whereas survival of individuals with the AT1R CC genotype was not significantly worse despite their extremely high level of oxidative stress as indicated by PC and MPO measurements, a trend for increased mortality in those with elevated PCs was observed. The contribution of oxidative stress to cardiac dysfunction and the transition to HF is becoming established. Reactive oxidants are well known to affect NO signaling and endothelial function, as well as pathways involved in cell proliferation and cardiac remodeling. Matrix metalloproteinases, which are important in LV remodelling, can be activated by oxidants, and a correlation between 8-isoprostane levels and matrix metalloproteinase activity in HF has been shown recently. Oxidative inactivation of plasminogen activator 1 can also lead to LV dilation. Cardiac remodeling is accepted as a determinant of the course of HF, with adverse effects on HF survival. Whether increased oxidative stress levels in AT1R CC patients contribute to HF progression and increase mortality is currently unknown and will require further prospective studies.

**Perspectives**

We report for the first time that 2 markers associated with oxidative stress, plasma PCs and MPO, were significantly elevated in HF patients compared with healthy controls. Particularly high levels of PCs and MPO were observed in HF patients homozygous for a gene polymorphism associated with enhanced AT1R receptor activity. Furthermore, AT1R genotype was shown to be an independent predictor of both oxidative markers in these HF patients. The AT1R CC genotype was not associated with higher mortality or fre-
quency of other adverse clinical outcomes in HF patients, implying that the elevated levels of PCs and MPO observed did not result from a more severe degree of HF in patients of the CC genotype. One possible explanation for these findings is that vascular reduced nicotinamide-adenine dinucleotide phosphate oxidases are a source of circulating oxidative stress in HF. Moreover, because levels of PCs and MPO were both predicted by AT1R genotype, the endogenous AT1R activity seems to modulate levels of markers of oxidative stress originating from different biochemical pathways.

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References


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