

Advanced Glycation Endproducts in Chronic Heart Failure

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Advanced glycation endproducts (AGEs) have been proposed as factors involved in the development and progression of chronic heart failure (CHF). Cross-linking by AGEs results in vascular and myocardial stiffening, which are hallmarks in the pathogenesis of CHF. Additionally, stimulation of receptors by AGEs may affect endothelial function and myocardial calcium uptake and may perpetuate coronary sclerosis in CHF. CHF is common in conditions with AGE accumulation, such as diabetes and renal failure. This review describes in detail the interrelation of plasma AGEs, renal function, and the severity and prognosis in clinical CHF patients with mild to moderate loss of renal function. This association is compared with the relation between tissue AGE accumulation (marked by skin autofluorescence) and diastolic dysfunction in renal failure. The evidence reviewed here provides support for the assumed role of AGEs in determining the severity and prognosis of CHF, but also highlights the differences in this relation between plasma and tissue AGEs and between patients with and without advanced renal failure. Ongoing clinical intervention trials to reduce AGE accumulation in patients with CHF may elucidate the causal role of AGEs in the development and course of CHF.

Key words: heart failure; advanced glycation endproducts; renal function

Introduction

Chronic heart failure (CHF) is a common condition that continues to have a high mortality rate. In contrast to the drop in mortality in acute coronary syndromes, roughly 50% of CHF patients still die within 5 years of diagnosis.¹ CHF is characterized by symptoms of dyspnea at exercise and fatigue, related to an inability of the heart to pump sufficient blood to fulfill the requirements of the body, or to its inability to do so only at elevated filling pressures. Etiologically, 50% of CHF cases are due to ischemic causes, which include those related to preceding acute coronary syndromes or other manifestations of predominantly coronary atherosclerosis. The main cause in the nonischemic group is idiopathic dilatory cardiomyopathy. The increase in the prevalence of CHF is related to the increase in the prevalence of some of the risk factors for CHF: increasing age, diabetes mellitus, and renal failure are important among these and are all conditions well known to be

associated with the accumulation of Maillard reaction products (MRP) and advanced glycation endproducts (AGEs). Although this link was recognized long ago, and AGEs were suggested to be important causes of the development of diabetic cardiomyopathy, it has received surprisingly little attention. One reason may have been that CHF is not recognized as a characteristic chronic complication of diabetes mellitus (or of renal failure for that matter).

The severity of HF is clinically graded according to the New York Heart Association (NYHA) functional classification, but can also be quantified using markers such as ejection fraction (EF) or maximal total body oxygen consumption (VO₂max), or biochemically by levels of NT-pro-BNP. NYHA class and EF are also prominent prognostic factors, but the same holds for renal function, which may reflect the degree of forward failure. However, renal failure may also have an important causative or perpetuator role in the prognosis of CHF, including the mechanism of accelerated AGE accumulation.² Recent data on the prognostic value of AGE in CHF in patients with renal failure will be reviewed here.

CHF is preceded by diastolic dysfunction (DD), which is characterized by reduced relaxation and compliance of the left ventricle (LV). Because cross-linking of the extracellular matrix by AGEs is a classic

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explanation for the deleterious effects of AGEs, increased myocardial AGE accumulation has been related to DD; supportive evidence of this link is discussed below.^{3,4} Interventions with AGE formation inhibitors or breakers in CHF are also discussed.

Reasons for a Link Between AGE Accumulation and CHF

-Epidemiologic: *High prevalence of HF and DD in conditions associated with AGE accumulation, diabetes, and renal failure. Diabetic cardiomyopathy.*

The risk of HF is higher in patients with diabetes, especially in females.⁵ This is partly because of the well-known increase in macrovascular complications, including coronary heart disease (CHD). However, in the absence of CHD, diabetic cardiomyopathy is often invoked as another precursor to CHF. Diabetic cardiomyopathy is common in diabetes mellitus.^{6,7} Originally it was defined by specific pathological abnormalities. Diabetic cardiomyopathy is first manifested by asymptomatic DD that later progresses to systolic dysfunction.^{7,8} Eventually diabetic cardiomyopathy can deteriorate into CHF and sudden cardiac death. Although AGE accumulation has been recognized as one of the possible contributing factors to diabetic cardiomyopathy, this issue has so far received limited attention.^{9,10}

-Pathogenetic: *Cross-linking, secondary to AGE accumulation, in myocardium and vessels, gives compliance loss, a cornerstone in the development of HF. Role of AGE-receptor interaction.*

Accumulation of AGEs results in stiffening of interstitial and vascular tissue, clinically manifested by reduced arterial compliance and increased pulse pressure. AGEs form cross-links among protein fibers, such as matrix collagen, elastin, and laminin, resulting in conformational changes that alter both the structural and functional characteristics of these cross-linked proteins.¹¹ They affect physiological properties of matrix proteins, such as charge, hydrophobicity, turnover, and elasticity.

These pathophysiological changes do not only result from indirect effects of AGEs on endothelial dysfunction, increased thrombogenicity and accelerated atherosclerosis at the (coronary) vascular level, but direct myocardial changes due to cross-linking of proteins in the myocardial matrix also occur. The systemic vascular effects also result in increased afterload for the heart.⁹

Stimulation by AGE of receptors such as the RAGE receptor, leads to prolonged cellular activation and re-

lease of inflammatory cytokines, which may also result in the development and progression of cardiac dysfunction and subsequent CHF.

One receptor-mediated effect of AGEs is the induction of fibrosis via the upregulation of transforming growth factor- β .¹² AGE receptor activation also influences calcium metabolism in cardiac myocytes, causing a significant delay in calcium reuptake and a consequent increase in the duration of the repolarization phase.¹³

-Contribution of renal hypoperfusion and function loss as perpetuator in HF through decreased clearance of circulating and renal MRP and AGE.

A hallmark of clinical CHF is renal hypoperfusion and loss in renal function. Considered a functional consequence of forward failure and thereby systolic HF, it is also an important marker of the severity and the prognosis of CHF.^{14,15} The fall in glomerular filtration rate (GFR) and renal blood flow is associated with a reduced filtration and tubular handling of MRP, such as AGEs and AGE peptides, resulting in accelerated accumulation of AGE. Therefore, reduced clearance and accelerated accumulation of AGE resulting from renal hypoperfusion in CHF may perpetuate the dismal course of CHF.

-Interventional: *CHF chosen as model in AGE-reducing pharmaceutical interventions.*

Preliminary evidence for AGEs in the development of cardiac dysfunction originates from two trials with the AGE cross-link breaker Alagebrium (ALT-711) in patients with HF. In the DIAMOND trial, Little *et al.*¹⁶ treated 23 patients with stable diastolic HF open-label with ALT-711. After 16 weeks, left ventricular mass was reduced and diastolic function improved. The PEDESTAL trial is an open-label study investigating the effects of ALT-711 on diastolic function and left ventricular mass in patients with systolic HF and DD. Preliminary results confirm those of the DIAMOND trial.¹⁷

Clinical Evidence for Link Between AGE and Diastolic Function or Systolic HF?

The role of AGEs in the development of DD has been investigated extensively in animals.^{4,18–20} In such studies, the effect of various AGE-lowering strategies confirms an active role for AGEs in the development of DD. Only limited human studies have been published.^{16,17,20}

Berg *et al.*²¹ analyzed serum AGE levels and LV diastolic function in type 1 diabetes. They found correlations between serum AGEs and both isovolumetric

relaxation time and LV end-diastolic diameter, but did not find correlations between AGEs and other parameters for diastolic function. Notably, tissue velocity imaging was not used to determine diastolic function.

Plasma AGE levels were previously evaluated in CHF by Heidland *et al.*²² in a small group of patients with severe CHF, heart transplant recipients, and normal controls. Paradoxically, a decrease was found in carboxymethyllysine (CML) and AGE fluorescence in patients with CHF. Heart transplant recipients did, however, show an increase in measured AGE data. Unfortunately, data on NYHA functional class, NT-pro-BNP levels, and prognosis were not provided. The authors suggested that the results may have been biased by hypervolemia, lowered plasma protein concentrations, and decreased dietary intake of AGEs in patients with CHF.

Steine *et al.*²³ reported that serum AGEs and duration of diabetes were predictors of systolic strain, assessed by Doppler tissue imaging, in type 1 diabetes (duration 32 ± 5 years). However, no relation existed between serum AGE and other systolic or echocardiographic indices.

Koyama *et al.*²⁴ evaluated the prognostic value of serum AGEs as risk factors in CHF for the first time. Serum pentosidine levels predicted cardiac death and rehospitalization, independent of other risk factors in CHF.

As discussed above, indirect evidence for a role of AGEs in cardiac dysfunction also originates from the DIAMOND and PEDESTAL trials in CHF patients.^{16,17}

Recently, a study in our center on patients with CHF and mild to moderate impairment of renal function assessed whether plasma CML and carboxyethyllysine (CEL), assayed by liquid chromatography–tandem mass spectrometry, are related to the severity and prognosis of CHF; this study focused on the role of renal function and perfusion in this relation.^{9,25} One hundred and two CHF patients with an average LVEF of $28 \pm 9\%$ were followed for 1.4 (1.1–1.9) years. NYHA functional class and NT-pro-BNP were used as estimates of the severity of CHF. GFR and effective renal plasma flow (ERPF) were measured using radiolabeled iothalamate and hippurate infusion. Survival analysis was performed for the combined endpoint of the first occurrence of either death, heart transplantation, or hospitalization for CHF. CML levels were associated with NYHA class and NT-pro-BNP. Furthermore, CML predicted outcome, even after correction for age and gender (hazard ratio [HR] 3.9). In a multivariate analysis, GFR was the only remaining determinant of CML. Regarding the prognostic value of CML, model

correction for GFR, ERPF, and microalbuminuria resulted in an HR for CML of 1 after correction for GFR, and showed that replacing GFR by ERPF in the model led again to a nonsignificant HR. After correction for urinary albumin excretion, the HR was 4.4 (2.2–9). Similar analysis revealed that CEL was again primarily determined by GFR ($B = -0.28$, $P = 0.004$), but was not significantly associated with CHF severity or prognosis.

For comparison, provisional results are discussed from a cross-sectional study in dialysis patients—both hemodialysis and peritoneal dialysis—in which diastolic and systolic function were evaluated by echocardiography (unpublished results). DD was assessed with early diastolic velocity (Em) using tissue velocity imaging. Skin autofluorescence (AF), as a marker of tissue AGE accumulation, was assessed using an AGE reader as described previously.²⁶ Among 43 patients, aged 58 ± 15 years and with a median duration of dialysis of 2.8 (1.3–5.3) years, systolic dysfunction ($LVEF \leq 45\%$) was present in 9 patients (24%), and DD ($Em < 8$ cm/s) was present in 35 patients (81%). No correlations were found between plasma AGE levels and any of the diastolic function parameters. Skin AF revealed high levels (mean 3.7 ± 0.7 a.u.), and was correlated with diastolic filling, including Em, E/A ratio, and E/E' (p all < 0.02). No correlations were found between LVEF, LV and LA diameters, and skin AF. In multivariate regression analysis 45% of the variance of average Em was determined by age and skin AF.

Discussion

Despite reasons summarized in this review for a link between AGE and CHF, and despite experimental support, clinical evidence based on circulating AGE levels remains limited and has provided no convincing proof. This review stresses that the relation between AGE and CHF differs for plasma and tissue AGEs and for patients with and without advanced renal failure. A more complex interaction seems to exist between renal function and the behavior of AGE in circulation and at the tissue level, not only in CHF, but also in other conditions. Plasma AGEs are related to severity and prognosis of CHF. Levels of circulating AGEs are determined to a major extent by metabolism of plasma proteins, which is orders of magnitude faster (days to weeks) than in tissues with long-lived proteins like the skin or the myocardial interstitial tissue (often many years). Because tissue levels of AGE directly reflect the cross-linking of interstitial and intracellular proteins and the receptor interactions, it is not

surprising that tissue function is better represented by tissue AGE markers, such as skin autofluorescence than by circulating AGE levels. Moreover, as for the renal failure group in our center's study, plasma or serum AGE levels are known to be quite variable depending on the dialysis procedures and sampling times in hemodialysis patients.²⁷ Skin AF is independent of hemodialysis sessions (unpublished results) and has been reported to have a day-to-day coefficient of variation of less than 6 percent.²⁵

The prognostic value of AGEs has been studied in populations other than patients with CHF. In patients with renal failure, results vary widely. Although Schwedler *et al.*²⁸ and Busch *et al.*²⁹ reported that circulating AGE levels were not related to prognosis in renal failure, Wagner *et al.*³⁰ and Roberts *et al.*³¹ did find prognostic value in circulating AGEs. Perhaps these discrepancies in the predictive value of circulating AGE levels illustrate again that circulating AGEs are less reliable as prognostic markers, especially in renal failure, because of the reasons given above. Our group demonstrated that AGE accumulation, measured by skin AF, was a strong and independent determinant of total and cardiovascular mortality both in patients on dialysis and in diabetic patients.^{32,33} Kilhovd *et al.*³⁴ showed that high levels of circulating AGEs predicted cardiovascular mortality in nondiabetic women. However, they presented their data uncorrected for renal function; their results may, therefore, be biased. The relation of plasma CML to severity and prognosis in CHF in our patients seems to be restricted to mild and moderate renal failure, and may actually be a mere reflection of the effects of renal function loss, considering the predominant role of GFR on plasma CML in our multivariate analysis. On the other hand, tissue AGE accumulation remains related to DD in advanced renal failure, whereas plasma AGEs are not. Unfortunately, no skin AF or other indices of tissue AGE accumulation were measured in our CHF study.

Because the prognostic value of plasma CML in our CHF group disappeared after correction for GFR or for ERPF, but not with microalbuminuria/proteinuria as a structural renal damage marker, this suggests that the direct functional effects of HF on GFR and ERPF account for the prognostic effects of circulating CML in CHF. Although this may seem to further diminish the clinical value of circulating AGEs as prognostic markers in CHF, it also serves to explain why renal function is such a determining factor for the course and prognosis of CHF in the longer term, independent of actual filling state. Accumulation of AGE and other MRP resulting from impaired renal clearance in CHF with forward failure may serve as a pivotal per-

petuator of myocardial and vascular damage. Thus, AGE accumulation may be a possible explanation for the fact that the prognosis of patients with a history of cardiovascular disease becomes worse as soon as CHF develops, independent of the degree of local cardiac damage.

This mechanism underlying the bleak prognosis supports interventions specifically directed at the reduction of AGE accumulation in CHF patients. Experimental, and still limited clinical, evidence suggests that angiotensin receptor blockers and angiotensin converting enzyme inhibitors may reduce AGE formation, but no studies have addressed this in patients with CHF.³⁵ In conditions other than CHF, attempts to reduce AGE formation, and thereby ameliorate clinical endpoints, with interventions with benfotiamine—and, earlier, pyridoxamine—may serve as examples for another approach. As a follow-up to the DIAMOND and PEDESTAL studies, the BENEFICIAL study, a single-center, double-blind, placebo-controlled, randomized study for 9 months of Alagebrium in addition to conventional medication in patients with CHF with systolic dysfunction (EF < 40%), has recently started (Hartog, personal communication), with the effect on aerobic capacity (VO₂max) and safety as primary endpoints. Secondary endpoints include diastolic/systolic function with echocardiography, NT-pro-BNP, NYHA HF class, AGEs in tissue as assessed by skin AF with an AGE reader, and in blood, and questionnaire scores. Results of such trials to reduce AGE accumulation are needed to elucidate the causal and/or perpetuating role of AGEs in the development and course of HF.

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Conflict of Interest

The authors declare no conflicts of interest.

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