

## Commentary

# Advanced glycation endproducts in sepsis and mechanical ventilation: extra or leading man?

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Published: 14 July 2009

This article is online at <http://ccforum.com/content/13/4/164>

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*Critical Care* 2009, **13**:164 (doi:10.1186/cc7939)

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## Abstract

Advanced glycation endproducts (AGEs) are primarily known as a complication in diabetic patients through their mediation of the inflammatory response. However, a variety of studies have demonstrated enhanced formation of AGEs in cardiovascular disorders. Despite the large number of AGEs produced during the Maillard reaction, recent focus is on the major non-crosslinking AGE N<sup>ε</sup>-carboxymethyllysine. Kneyber and colleagues focused on sepsis-induced cardiac dysfunction and investigated whether myocardial inflammation is associated with enhanced cardiac AGE deposition and whether this is further enhanced by mechanical ventilation. They showed that both conditions are associated with enhanced AGE deposition and myocardial inflammation. Therefore, AGEs may participate in the inflammatory response related to cardiac dysfunction in critically ill patients. Moreover, life-saving ventilation stimulates AGE formation in these patients. This interesting study raises the question of whether AGEs in critically ill patients are a driving force of the disease.

## Advanced glycation endproducts

The advanced glycation endproduct (AGE) N<sup>ε</sup>-carboxymethyllysine (CML), as recently investigated by Kneyber and colleagues [1], can be formed either from glucose via ketoamine or glyoxal or from lipids by oxidation via glyoxal. This may explain why the pathophysiological role of AGEs is not restricted to diabetes, in which condition they have been primarily studied [2].

The enhanced formation of AGEs results in enhanced urinary excretion. In this context, renal-insufficient patients have been associated with CML values several times higher than in healthy controls. Accumulating AGEs can be observed histologically as endothelial depositions in atherosclerotic plaques and tubular cells [3-5]. Their deposition initiates increased NADPH oxidase and nuclear factor κB activity as well as a reduction in endothelial nitric oxide synthase activity [6]. These major effects cause inflammatory changes,

extracellular matrix accumulation and endothelial dysfunction. Therefore, AGE accumulation is a potential target for treating inflammatory diseases.

## AGEs in sepsis and during mechanical ventilation

The new and interesting idea of Kneyber and colleagues was to investigate the association of CML with myocardial inflammation during sepsis and the clinically relevant state of mechanical ventilation, which by itself is known to induce AGE accumulation in the lungs. This is of relevance as sepsis-induced cardiac dysfunction is a frequent complication associated with increased mortality. Therefore, they focused on a situation where AGE accumulation is increased by systemic inflammation and exacerbated by mechanical ventilation. The association of CML with myocardial inflammation in sepsis and mechanical ventilation is intriguing. Indeed, sepsis enhances CML deposition, which is further aggravated by mechanical ventilation. Thus, the myocardial deposition of AGEs is associated with the disease and the therapeutic approach of mechanical ventilation perpetuates AGE formation.

## Opposing AGE effects in cardiovascular animal models

These results raise the question, however, whether the association reflects a relevant pathophysiological mechanism or 'only' reflects the critical disease state. In the former case, interfering with the production or accumulation of AGEs could provide possible treatments. One option is to administer soluble RAGE - the extracellular ligand-binding domain of RAGE, the AGE receptor - which binds AGEs and thereby limits the deleterious effects of AGEs. In animal experiments, treatment with soluble RAGE ameliorated inflammation and significantly reduced the atherosclerotic lesion area in a glycemia- and lipid-independent manner [7].

AGE = advanced glycation endproduct; CML = N<sup>ε</sup>-carboxymethyllysine.

Another pharmacological option is blockade of AGE formation by substances such as aminoguanidine or pyridoxamine. These have also been proven to prevent age-related cardiac hypertrophy in the absence of changes in collagen and elastin content [8] and diabetic complications in animal models [9]. These different approaches to treat AGE accumulation and the pathophysiological relevance of AGE formation in sepsis and mechanical ventilation need to be addressed in future studies using either soluble RAGE or blockers of AGE formation.

### AGEs in human cardiovascular disorders

Several cross-sectional studies have documented that AGE-induced inflammation is also present in human diseases with chronic low-grade inflammation and has also been associated with diabetic microangiopathy [10], endothelial dysfunction [11], atherosclerosis [3] and chronic heart failure [12]. However, in a prospective substudy of the Irbesartan Type 2 Diabetic Nephropathy Trial (IDNT) cohort including 450 patients with nephropathy caused by type 2 diabetes, CML was not predictive for cardiovascular events [13]. Therefore, it remains uncertain whether CML is of cardiovascular relevance in humans.

### Conclusions and outlook

Kneyber and colleagues present an interesting association between a major non-cross-linking AGE and sepsis combined with mechanical ventilation. Whether this association reflects a pathophysiologically relevant characteristic needs to be investigated in future studies. However, if interventional studies demonstrate positive effects in animal models, the availability of safe and cheap agents may offer an opportunity to target myocardial inflammation in sepsis and mechanical ventilation.

### Competing interests

The author declares that they have no competing interests.

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