Chromogranin A in heart failure

Since the initial demonstration of increased circulating norepinephrine in patients with chronic heart failure\[1\], a large number of investigations on neuroendocrine activation in heart failure have followed. It is now clear that persistent activation of neuroendocrine systems, notably the adrenergic system and the renin–angiotensin system is maladaptive in heart failure (reviewed in\[2\]).

In this issue, Ceconi et al. report that serum levels of chromogranin A, the major secretory granule matrix protein in neuroendocrine cells, are elevated in patients with heart failure\[3\]. The increases in chromogranin A serum levels are related to decreasing functional status and provide independent prognostic information, i.e. within a given NYHA class, patients with chromogranin A levels above the median have a worse prognosis than patients with chromogranin A levels below the median. As with many novel observations, the work by Ceconi et al. raises many questions and leaves room for imagination. Therefore, let us take a closer look at chromogranin A from a cardiologist's standpoint.

Chromogranin A, a protein initially described in catecholamine storage vesicles of the adrenal medulla, has a widespread distribution in secretory vesicles throughout the endocrine, neuroendocrine and nervous system, where it is co-localized and co-secreted with the respective peptide or amine hormone\[4\]. Chromogranin A plays a pivotal role in the process of hormone packaging and secretory granule formation\[5\]. Importantly, chromogranin A also functions as a multipurpose prohormone. The primary structure of chromogranin A contains several pairs of basic amino acids that represent proteolytic cleavage sites for the generation of a number of biologically active peptides. Proteolysis of chromogranin A takes place in a tissue-specific manner both within secretory granules and after secretion into the extracellular space. An emerging functional pattern is that such chromogranin A-derived peptides inhibit further hormone release from the (neuro)endocrine cell of origin. For example, in catecholaminergic cells, proteolytic processing of chromogranin A liberates cestatin, a peptide with catecholamine secretion-inhibitory and vasodilating activities\[6–8\]. Among the many chromogranin A-derived peptides, cestatin is certainly the best characterized. However, a wide range of biological effects have been attributed to other chromogranin A-derived peptides, such as vasodilatation\[9\], promotion of cell adhesion and spreading\[10\], induction of apoptosis\[11\] and bactericidal/antifungal activities\[12\].

What are the cellular sources of serum chromogranin A in heart failure? In healthy humans, serum chromogranin A levels are not related to circulating levels of epinephrine and norepinephrine\[13\], which is not surprising as chromogranin A is released from many different (neuro)endocrine cell types. However, in situations where the sympathetic nervous system is activated (e.g. during high-intensity exercise), catecholamine and chromogranin A concentrations are more closely related\[13,14\]. Increases in circulating chromogranin A levels have also been described in patients with catecholamine producing tumours\[15\] and in patients with essential hypertension\[16\]. Accordingly, elevated serum chromogranin A may in part reflect adrenergic activation in heart failure. However, the relationship of chromogranin A and chromogranin A-derived peptides to catecholamines and other neuroendocrine mediators needs to be examined more closely before chromogranin A can be regarded as a marker for neuroendocrine activation in heart failure.

Considering the antiadrenergic and/or vasodilatory effects of cestatin and other chromogranin A-derived peptides, Ceconi et al. speculate that chromogranin A may serve a compensatory role in heart failure. Given the close relation of chromogranin A levels to heart failure severity and prognosis, it is possible that chromogranin A plays a role in the pathophysiology of the disease. The assumption that chromogranin A mediates beneficial effects is premature, however. For example, cestatin has been shown to prevent desensitization of catecholamine release, and might thereby sustain catecholamine release in situations of heightened sympathetic outflow\[17\]. The complex question whether chromogranin A and chromogranin A-derived peptides exert beneficial or detrimental effects in heart failure cannot be answered at the present time.

In any case, the study by Ceconi et al. should stimulate future experimental and clinical research into the cellular sources of chromogranin A, the proteolytic processing of chromogranin A at the tissue level and in the circulation, and the autocrine,
paracrine and possibly endocrine effects of chromogranin A-derived peptides in heart failure. In that way, we might turn imagination into knowledge.

K. C. WOLLERT
H. DREXLER
Department of Cardiology and Angiology, Hannover, Germany

References