Pathophysiological role and clinical relevance of cytokines in hypertensive heart failure

A combined clinical and experimental study

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I. Haugen E, Chen J, Wikström J, Grönros J, Gan LM and Fu LXM. Parallel gene expressions of IL-6 and BNP during cardiac hypertrophy complicated with diastolic dysfunction in spontaneously hypertensive rats. International Journal of Cardiology. 2007; 115: 24-28


III. Haugen E, Gan LM, Isic A, Skommevik T, Fu LXM. Increased IL6 but not TNF-alpha predicts mortality in heart failure population in the very elderly. Experimental & Clinical Cardiology. 2007 (in press)

IV. Haugen E, Furukawa Y, Isic A, Fu LXM. Increased adiponectin levels in parallel with increased NT-pro BNP in patients with severe heart failure in the elderly: a hospital cohort study. Manuscript
Pathophysiological role and clinical relevance of cytokines in hypertensive heart failure
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Abstract
Although mortality due to heart failure has decreased significantly in the last decade since the introduction of ACE-inhibitors and β-adrenergic receptor blockers in the management of heart failure, chronic heart failure is still one of the most important causes of morbidity and mortality and has a very high frequency for readmission to hospitalization because of the aggravation of heart failure. This accounts for a significantly higher health-care expenditure that is twice as much the cost for cancer. One of the most important reasons is that the present heart failure management is mostly directed at the restoration of neurohormonal imbalance, rather than targeting the primary mechanism of the disease. There is an increasing body of evidence showing that inflammation is involved in the pathophysiology of heart failure, particularly in the young. Moreover, one of the most frequently seen sub-sets of heart failure in daily clinical practice is heart failure due to hypertension, particularly in the elderly. Heart failure in the elderly is often characterized by predominance of diastolic dysfunction and comorbidity. Therefore, heart failure is heterogeneous and the underlying mechanism may differ greatly from one cause to another and between the young and the elderly.

The portfolio of cytokines includes at least tumor necrosis factor α and interleukin-6 in the cardiovascular system. These have been referred to as proinflammatory cytokines. These inflammatory mediators are known to be expressed by all nucleated cell types residing in the myocardium including myocytes, suggesting that these molecules may not only orchestrate an inflammatory response but also participate directly in the pathophysiological processes such as remodeling. Thus, it is very likely that the elaboration of cytokines represents not only the mechanism responsible for worsening of heart failure, but also the mechanism of initiating heart failure. In heart failure in younger patients, the circulating level of tumor necrosis factor α has been shown to be elevated. However, whether this is similarly elevated in elderly heart failure patients remains poorly understood. Since majority of heart failure patients are over 65 years old, this issue becomes very important and clinically relevant. Furthermore, recent large randomized clinical trials of tumor necrosis factor antagonists in heart failure patients in the younger population showed disappointing results. Therefore, the significance of cytokine activation in heart failure remains controversial. Is cytokine activation important in heart failure? Is this equally important in heart failure irrespective of age? If so, why was tumor necrosis factor α inhibition not effective in chronic heart failure in recent clinical trials?

We hypothesize that proinflammatory cytokine activation is pathophysiologically important and clinically relevant in hypertensive heart failure. However, cytokine activation may differ between the young and the elderly. Moreover, suppression of a single cytokine in heart failure may not be a rational and effective treatment strategy because it may lead to the upregulation of other proinflammatory cytokines.

In this PhD thesis, we studied cytokine mRNA expressions in myocardium in the early stage of hypertensive heart failure in Spontaneously Hypertensive Rats with or without treatment with tumor necrosis factor α antagonist Etanercept. Moreover, we characterized circulating cytokine profile among heart failure patients in the elderly.

We have shown that there were cardiac hypertrophy in Spontaneously Hypertensive Rats with increased heart/body weight ratio, diastolic heart dysfunction as determined by the tissue Doppler, increased mRNA levels for interleukin 6 and brain natriuretic peptide whereas a decreased mRNA for the β-adrenergic receptor. Chronic treatment with etanercept in Spontaneously Hypertensive Rats resulted in decreased relative wall thickness as well as increased cardiac reserve and higher blood pressure. In addition, interleukin-6 was further upregulated compared with placebo treatment. In human studies, our results have shown increased interleukin-6 and tumor necrosis factor α in heart failure patients compared with those in the control group. Moreover, interleukin-6, tumor necrosis factor α and vascular endothelial growth factor were significantly increased in patients who died within one year. Further logistical regression analyses showed that interleukin-6 is the only significant predictor for one-year mortality. In a subgroup of heart failure with atrial fibrillation there were significant cytokine activations, whereas in subgroups such as those with ischemia or diabetes, cytokines were less activated. Furthermore, we have shown significantly increased adiponectin levels in these elderly heart failure patients.

In conclusion, in hypertensive heart failure, both clinically and experimentally, there is increased cytokine activation. In case of heart failure in the elderly, there is different activated cytokine profile as compared with that in the younger. Moreover, it appears that it is not enough to suppress one single cytokine because the cytokine network is redundant. However, more fundamental studies are needed to understand this complex cytokine network before an appropriate anti-inflammatory therapy emerges.

Key Words: hypertension, cardiac remodelling, heart failure, cytokines, interleukin 6, etanercept, adiponectin, elderly.