A direct link between haemodynamic failure and inflammatory activation in heart failure: the simplified approach to heart failure and to creation of life

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This editorial refers to ‘Peripheral venous congestion causes inflammation, neurohormonal and endothelial cell activation’†, by P.C. Colombo et al. on page 448

“The classical pathophysiological concept of heart failure (HF) is, of course, the failing pumping force of the myocardium leading to poor tissue perfusion and subsequent functional failure of a range of tissues and organs. The logical consequence, to treat this problem by medically enforced stronger myocardial contractility, failed dramatically, however, as mortality in the long run was even increased with treatment by catecholamines or phosphodiesterase inhibitors. The reasoning from these clinical findings together with further studies formed the basis for the paradigm of neuroendocrine activation as a major underlying principle of HF above and beyond haemodynamic failure. The neurohormonal hypothesis of HF as proposed 20 years ago by Milton Packer1 soon became established as a cornerstone of HF pathophysiology. In fact, all of today’s medical treatment concepts in chronic HF with proven benefits on prognosis target neurohormonal activation in some way.

This insight was only the first step that opened an era of huge advances in understanding the complexity of the pathophysiology of heart failure. Beyond the haemodynamic failure and neuroendocrine activation, further paradigms were uncovered as contributing to clinical symptoms, to progression, and to mortality of HF. As one prominent feature, inflammatory immune activation was recognized to occur in HF, adding further complexity by linking haemodynamic, endothelial, and metabolic dysfunction (Figure 1). Moreover, it soon became apparent that it is not only the myocardium itself which is the target and promoter of the disease. On the contrary, multiple systemic effects involve peripheral tissues and organs in feedback loops of disease progression. Clearly, chronic HF should be regarded as a systemic disease with secondary dysfunctions, e.g. of the kidneys, skeletal muscles, bone marrow, intestine, endothelium, and others that contribute to the downward spiral of symptomatic and prognostic deterioration.2

Sound evidence emerged that increased proinflammatory cytokine levels account for a latent systemic immune activation even in stable and compensated ambulatory HF patients. Tumour necrosis factor-α, interleukin-1, and interleukin-6 are the most prominent cytokines implicated in HF progression. A range of cell types have been identified to secrete cytokines under pathological conditions such as HF, with local (autocrine and paracrine) or systemic effects. However, the origin of elevated cytokine plasma levels in HF remained a matter of debate, and several hypotheses are discussed. First, the failing heart itself can express proinflammatory cytokines. Indeed, increased cytokine expression and spillover from the overburdened myocardium into the systemic circulation has been observed.3 Secondly, tissue hypoxia may result in increased cytokine production on a systemic level, as suggested mostly from cell studies and experimental animal models. Thirdly, intestinal hypoxia and/or congestion may result in compromised intestinal barrier function and subsequent increased translocation of gut flora lipopolysaccharides.4,5

Most of today’s insights into the role and mechanisms of cytokines in HF were achieved from intense research during the 1990s. A series of interventional trials tested the convincing concept that lowering cytokines in HF may improve morbidity and/or mortality in CHF patients. Disappointingly, the RECOVER, RENAISSANCE, and ATTACH trials were unable to show a clinical benefit of targeting increased cytokine levels in chronic HF.6,7 A number of

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methodological issues of the trials were discussed to explain the negative results. However, the failure of anticytokine therapies in HF may also be explained by the complexity of the signalling effects that go well beyond the activation of immune cells and that are far from being understood. The fact that cytokines came into action very early in the evolution of multicellular organisms early in the Cambrian period (540 million years ago) suggests that these molecules may confer a significant survival benefit on the organism. Despite such considerations, further research in this field tailed off after the negative treatment trials mentioned above.

Colombo et al. now take up the thread again as they report on a direct link between peripheral venous congestion and local release of inflammatory mediators. Using a simple yet robust clinical model, they could show a direct and mechanistic link between acute venous congestion even without ischaemia and inflammation, with increased cytokine release and modification of key proinflammatory genes. The study, despite its rather simple protocol and plain test setting, nevertheless provides convincing results regarding direct inflammatory activation by increased pressure load. Of course the test settings are a huge simplification of the true pathophysiological conditions since relevant factors such as older age, chronic HF-induced neurohormonal activation, and accumulation of secretory products due to renal impairment were not accounted for. Also the perplexing short period of 75 min of pressure overload compared with the prolonged chronicity in chronic HF for months and the unphysiologically high level of venous pressure increase (+30 mmHg compared with <$10 mmHg above normal in most patients with chronic HF) would by no means realistically mimic the conditions in chronic patients. With this in mind, to find significant activation of inflammatory gene signatures and cytokine secretion in such simplified conditions supports the applicability of the hypothesis even more strongly.

In fact, it is simplification in the setting that is sometimes needed to shed light on highly inter-related and seemingly inextricable conditions. One may be reminded of another fascinating example of a highly simplified experimental setting that resulted in nothing less than the proof of one of nature’s finest hours: the Miller–Urey experiment that proved the abiogenetic creation of life on earth. Searching for the miracle of organic life developing from anorganic precursors, in 1953 Stanley Miller and Harold Urey conducted an experiment that simulated the conditions thought to be present on the early earth. They used as few ingredients as water, methane, ammonia, and hydrogen as presumed components of the early atmosphere, poured all these into a sterile glass flask, and added heat and electric sparks resembling extensive volcanic and thunderstorm activity. Being a student of chemistry at the University of Chicago, Stanley Miller could wait no longer than one night for these ingredients to work on what may have required several hundred millions of years in the original setting. Opening the flask he was nevertheless able to identify as many as three of the 20 proteinogenic amino acids. After this highly simplified initial experiment, of course, multiple repeated tests around the world were performed that uniformly confirmed the principal approach by Miller and Urey. Increasing

![Figure 1](image-url)
complexity of the settings resulted in ever higher organic molecules deriving from anorganic precursors including sugars, purines, porphyrins, and eventually even adenosine triphosphate (ATP). With the drastic simplification of the experimental conditions the scientists were able to prove a principle that was unsuccessfully sought after by a large scientific community with highly complex hypotheses and experiments.

The paradigm of proinflammatory immune activation in HF as reported by Colombo and colleagues may of course not exactly resemble the creation of life on earth. However, the reductive approach of the experiment may help to refocus on a principle of experimental work.

With better understanding of the pathways and the effects of inflammatory activation in HF, novel therapeutic concepts may arise to continue the story that was put to rest after the RECOVER and RENAISSANCE trials. Today’s medical treatment strategies in HF with prognostic improvement rely nearly exclusively on the inhibition of neuroendocrine overactivation. This concept had been developed in the late 1980s. Since then, none of the more recent pathophysiological paradigms that were correctly identified as contributing to HF progression successfully translated into a guideline-relevant therapeutic concept.

Several metabolic strategies to improve energy efficacy are currently pursued and with i.v. therapy a first step towards metabolic interventions in HF has been made. Both metabolic treatments and anti-inflammatory concepts are promising candidates for novel treatment options in HF. More work in these fields is warranted to extend our therapeutic armamentarium beyond the current standards of neuroendocrine inhibition.

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