

Review

<Clinical Science: Heart Failure>

# Heart Failure as a Systemic Disease: Role of Inflammation

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Heart failure is a common disease that can usually affect the other organs. The presence of a common link between heart failure and its comorbidities, such as muscle wasting, renal failure, and major depression, remains to be elucidated. Heart failure leads to activation of the innate and adaptive immune responses. On the other hand, the immune system cascades are important for the development of most comorbidities. Herein, we discussed the hypothesis that activation of the immune system in the early phase of heart failure is relevant in the pathophysiology of the comorbidities that develop in the subsequent course of the disease.

Keywords: heart failure, comorbidities, innate immune system, adaptive immune system

Heart failure (HF) is a common disease worldwide. In Germany, it is the most common reason for hospital admission and is the third most common cause of mortality. The management of HF is complex and is mainly based on medical treatment. HF patients have often a substantial number of comorbidities. In a cross-sectional trial of more than 120,000 patients with HF, >40% had more than five comorbidities; this group accounted for over 80% of the hospitalizations.<sup>1)</sup> One example is major depression, which has a lifetime incidence of 19% in Germany; however, in HF patients, the incidence is 37%.<sup>2)</sup> Mortality rate is increased in HF patients with major depression.<sup>3)</sup> Indeed, comorbidities can influence the need for hospitalization, survival, and quality of life of HF patients. Therefore, management of comorbidities is important.

The reason for the association of HF with several comorbidities is unclear. One explanation could be that comorbidities bring about HF; however, this cannot explain the magnitude of the comorbidities that we encounter. Second, a reduced cardiac function could lead to an incomplete supply of blood and oxygen with secondary organ damage. This could explain the development of comorbidities in the terminal stage of HF, but not in the early stage of HF. Third, even before its late

stage, HF could trigger the development of comorbidities through common pathophysiologic mechanisms. We hypothesize that the latter mechanism is of great importance. One potential mediator for the different organ effects could be activation of the immune system, which we observe in HF.

## Activation of the Innate Immune System in Heart Failure

Activation of the immune system is a well-described mechanism in HF patients. In the early nineties, upregulation of proinflammatory cytokines in patients with HF was first discovered.<sup>4)</sup> In particular, in depth investigation on the role of TNF has discovered that TNF was upregulated in the plasma of humans with HF<sup>4)</sup>; that animals with cardiac overexpression of TNF developed HF<sup>5)</sup>; and that development of HF in animals can be blocked by TNF antagonism.<sup>6)</sup> Despite these findings, the mechanism for immune system activation remained obscure because the etiology of HF, except that which is caused by viral myocarditis, is usually not infection. Subsequently, it was discovered that the initial immune activation happens through the innate immune system,<sup>7)</sup> which is the first line of defense that is evolutionary conserved and recognizes specific pathogenic

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patterns through so-called pattern recognition receptors (PRRs). The PRRs can be activated not only by patterns from pathogens, but also by the so-called danger associated patterns (DAMPs). As the name implies, DAMPs are factors that indicate danger, such as when they are released from dying cells. One example could be the different heat shock proteins that are released from the cytoplasm of dying cells and can subsequently bind to toll-like receptors (TLRs). Therefore, the function of the innate immune system is not limited to infection; it can also be viewed as form of reaction to stress.

The different innate immune system receptors, like the TLRs, are expressed in the heart and are upregulated in patients with HF.<sup>8)</sup> These receptors are of pathophysiologic importance; for example, activation of TLRs subsequently leads to signaling events in the heart. Furthermore, the cellular constituents of the innate immune system, like the neutrophils and macrophages, can be found in the heart upon injury and are necessary for adequate healing response. Macrophages infiltrate the heart within hours after an episode of myocardial infarction (MI) and are necessary for formation of granulation tissue and scar. Depletion of macrophages has been shown to lead to increased mortality and inadequate healing after MI.<sup>9)</sup> These findings indicate that a proinflammatory response after MI is not essentially adverse, but is necessary for an appropriate healing response.

### Activation of the Adaptive Immune System in Heart Failure

Once the innate immune system is activated, mechanisms to downregulate the proinflammatory response have to be launched since a continuous immune activation is maladaptive. Subsequently, the innate immune system activates the adaptive immune system, wherein T-cells have the capability to decrease the innate immune response.<sup>10, 11)</sup> Indeed, we were able to show that after MI, the T-cells, which are the most important cellular parts of the adaptive immune response, were activated and increased in the lymph nodes than drain the heart. Therefore, T-cells are essential for adequate healing. For example, mice lacking CD4<sup>+</sup> T-cells were observed to have healing defects after MI.<sup>12)</sup> In addition, animals without T-cells were observed to have heightened innate immune response.

Regulatory T-cells (T<sub>reg</sub>), in particular, seem to be

important for the above-mentioned process, as demonstrated by the fact that T<sub>reg</sub> depletion increased mortality, whereas activation of T<sub>reg</sub> rescued the phenotype and decreased immune activation. These findings were potentially mediated by an interaction with macrophages. We demonstrated that activated T<sub>reg</sub> can induce the development of M2 macrophages, which are important for adequate healing, a process that may be paracrine mediated (e.g., through TGF).<sup>13)</sup>

In summary, after cardiac injury, such as MI, the initial response of the body is activation of the proinflammatory innate immune system. This is followed by activation of the adaptive immune system, which can, in turn, downregulate the proinflammatory response. This cycle of activation and deactivation of the immune response is necessary for adequate healing.

### Activation of the Immune System is Systemic

Activation of the immune system is not localized to the heart, but it can also be found in different organs. For example, upregulation of cytokines were demonstrated in the muscle of patients with HF.<sup>14)</sup> In such cases, the source of the circulating cytokines is not only cardiac. Moreover, only a small portion of the monocytes/macrophages that are found in the heart after an MI are secreted from the heart itself; rather, these infiltrating inflammatory cells come from other sources, such as the spleen and the bone marrow.<sup>15)</sup> Therefore, in HF, the immune system manages a complex interaction of different organs.

### The Immune System and the Systemic Interactions in Heart Failure

HF patients have a substantial number of comorbidities. We hypothesize that the presence of active comorbidities is, at least, partially mediated by inadequate activation of the immune system. For example, HF patients are often well-known to have muscle wasting, which is induced directly by proinflammatory cytokines.<sup>16)</sup> The above-mentioned association between depression and HF could also be mediated by the immune system. The role of the immune system in the development of depression has already been proven and is independent of HF. In one of our studies on an experimental mice model of HF, activation of the immune system in the brain was shown to produce anxiety.<sup>17)</sup> These data

implied that interaction of the immune system with the other organs is likely to predispose individuals with HF to develop comorbidities.

### Conflicts of Interest

The author has no conflicts of interest to declare.

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