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EDITORIAL

Special Issue "Novel Perspectives on Heart Failure"

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Heart failure is a leading cause of hospitalization in European countries. Approximately 1–2 % of the population has systolic heart failure and another 1–2 % presents with compromised left ventricular systolic function without symptoms eventually undergoing a transition into overt heart failure. Regarding diastolic dysfunction, prevalence may be even much larger [1, 6].

In the previous century, a number of studies have brought tremendous insights into the pathophysiology of heart failure, some of which have been used to develop treatment strategies. This led to the introduction of beta-blockade and blockade of the renin-angiotensin-aldosterone system as efficient therapies in heart failure. However, during the last three decades no new drug treatment strategy has been introduced and all progress in heart failure treatment was made by devices including cardiac resynchronization and prevention of sudden death by implantable cardioverter defibrillators. The only exceptions from this are ivabradine, an inhibitor of the sinus node pacemaker current [10], which like beta-blockers reduces heart rate, and ferric carboxymaltose to treat the heart failure comorbidity of iron deficiency [5].

This article is part of the Topical Collection Novel Perspectives on Heart Failure.

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One potential reason for the lack of successful translation of some obvious targets into patient treatment may be related to the fact that we are neglecting some important aspects of heart failure pathophysiology. One major aspect may be the way heart failure clinically progresses. Usually, clinical progression occurs stepwise by decompensation events requiring hospitalization. These decompensation steps may be called acute heart failure syndrome in analogy to the acute coronary syndrome of coronary artery disease [11]. In general, recovery from acute heart failure syndrome is incomplete resulting in a progressive decline of cardiac function and functional status with each decompensation step.

The current special issue on heart failure addresses important novel pathophysiological mechanisms which may be of crucial relevance for the understanding of stepwise progression of heart failure through repetitive acute heart failure syndromes. One may speculate that acute heart failure syndrome may be triggered by inflammation and prevention of complete recovery may be related to long lasting epigenetic regulation of gene expression. Furthermore, deterioration of cardiac function may be related to metabolic changes which are associated with the production of free radicals and disturbed excitation–contraction coupling.

The review by the group of Stefan Frantz [4] provides important information on inflammatory processes as key pathophysiological trigger mechanisms in heart failure. They suggest that we may have previously addressed wrong aspects of inflammation and that new targets identified may allow to develop novel anti-inflammatory treatment strategies on a more individualized basis. This is supported by the review of Ryozo Nagai's [2] group which covers the interaction of cardiomyocytes, fibroblasts, and immune cells in the process of heart failure deterioration.

On the one hand, immune cells such as T-lymphocytes, monocytes, and macrophages have protective effects to compensate for various stresses to the heart. On the other hand, they may cause harmful inflammation and induction of acute heart failure syndrome and heart failure progression. This review also highlights the important novel recognition that understanding cell–cell interactions in heart failure may dramatically improve our understanding of its pathophysiology.

Triggered by inflammation and immune reactions, heart failure progression occurs through apoptosis, fibrosis and myocyte dysfunction. Three subcellular systems which themselves closely interact may be crucial to these processes: (1) myocardial energy production and metabolism, (2) production and scavenging of free radical species, and (3) excitation–contraction coupling. In this direction, the review on myocardial energetics by the group of Christoph Maack [8] indicates that rather than energy lack, disturbed metabolism may be harmful through generation of radical oxygen species and metabolic intermediates. Radical oxygen species are not only produced by mitochondria, but also by NADPH oxidases which are ubiquitously expressed contributing significantly to physiological and pathophysiological signaling processes. The review by Ajay Shah′s [3] group elegantly explains how compartmentalization of NADPH oxidase isoforms causes free radicals to exert subtle regulatory effects on the one hand and harmful signaling mechanisms on the other. Free radical-mediated signaling mechanisms include processes such as cell–cell interaction, development of hypertrophy, matrix remodelling, apoptosis, and excitation–contraction coupling. The latter topic is addressed by the review of Lars Maier′s group [7]. They focus on the recent findings on sarcoplasmic reticulum calcium leak and sarcolemmal late sodium current, both of which are closely related to activation of calcium-calmodulin-dependent kinase which among other mechanisms is activated by radical oxygen species. Finally, it is tempting to speculate that pathological processes triggered during an acute heart failure syndrome persist through epigenetic mechanisms of gene regulation as elucidated by the group of Gianluigi Condorelli [9]. Such mechanisms include DNA methylation, histone modification, ATP-dependent chromatin remodelling and microRNA-dependent regulation of gene networks.

These state-of-the-art reviews on six important and interconnected mechanisms of cardiac regulatory systems provide important new insights into heart failure pathophysiology. The material presented may not only trigger new mechanistic studies, but also lead to the development of new treatment strategies.

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