Adrenal Signaling in Heart Failure
Something More Than a Distant Ship’s Smoke on the Horizon

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Heart failure (HF) is the leading cause of mortality and morbidity in the Western world.1 The search for therapeutics to cure HF has led investigators to examine the mechanisms underlying HF, paying a particular attention to understanding the role of defects in β-adrenergic receptors (βARs) regulation in the pathophysiology of such a disease. Hence, during HF, enhanced levels of catecholamines resulting from activation of the sympathetic nervous system lead to chronic stimulation of cardiac βARs. This acute fight or flight response ensures an increase in cardiac function, to achieve an adaptation of the cardiac output to the systemic needs and somehow preserve cardiovascular homeostasis. However, long-term stimulation of the BARs becomes harmful, contributing to the progression of failure.2

The heart adapts to the chronically elevated concentration of adrenalin and noradrenalin by blunting the response to agonist stimulation. Such a process, known as desensitization, is essentially mediated by βAR phosphorylation via G-protein–coupled receptor kinases (GRKs),3 followed by translocation and binding to the receptor by the multifunctional protein β-arrestin, targeting the receptor for internalization.4 Two distinct isoforms of β-arrestin are expressed in the heart, namely β-arrestin-1 and β-arrestin-2. Of interest, proteomic analyses revealed that β-arrestins directly interacts with >300 proteins from different families involved in cellular signaling. Thus, arrestin-mediated signaling encompasses manifold pathways, including kinase activation, transcriptional regulation, and receptor transactivation. The importance of β-arrestins is further evidenced by the early embryonic lethality of the double knockout mouse.4 Remarkably, the functional role of each isoform in HF had not been extensively investigated hitherto.

In a noteworthy study reported in this issue of Hypertension, the group led by Dr Lymeropoulos5 elegantly shows in an in vivo model of myocardial infarction that β-arrestin-1 is detrimental for cardiac function. Intriguingly, the authors demonstrate that β-arrestin-1 plays a key role in HF pathophysiology via actions not only in the heart but also in the adrenal gland, where catecholamines are primarily produced. Indeed, genetic deletion of β-arrestin-1 (achieved by a global knockout mouse model) markedly improved cardiac function, adverse remodeling, aldosterone levels, and cardiac βAR function during HF progression.

Mechanistically, the deletion of β-arrestin-1 in the adrenal glands might be responsible for the improvement in the neurohormonal profile described in these animals after myocardial infarction. However, the observed amelioration in the adrenergic and inotropic reserves can be essentially attributed to the absence of β-arrestin-1 in the heart (Figure). The authors demonstrated how to obtain both these advantages at 1 fell swoop, brilliantly exploiting the β-arrestin-1-mediated signaling in the adrenal-cardiac axis.5 Of course, this model represents a streamlined point of view of the whole story because adrenal gland is not the exclusive site of production of catecholamines.6

Likewise, the same group had previously2 shown that turning down via a gene therapy approach the adrenal levels of GRK2, a master regulator of cardiac βAR desensitization alongside with β-arrestins,7 cardiac function after myocardial infarction was substantially improved. Ergo, modulation of βAR signaling via β-arrestin-1 and GRK2 inhibition from both the heart and the adrenal (Figure) seems to lead to a reduced neurohumoral burden, halting the myocardial adverse remodeling and increasing the inotropic reserves.

There are several intriguing unanswered questions arising from this novel discovery; for instance, which is the respective role of β-arrestin-1 and β-arrestin-2, which action and effect have been frequently reported to be counteracting,2,4 in the transactivation of the epidermal growth factor receptor, alongside with its numerous and significant subsequent effects? Besides, which is the consequence of β-arrestin-1 deletion on insulin sensitivity and overall cardiac metabolism, especially in HF setting? Is β-arrestin-1 involved in lipid and glucose homeostasis and in insulin release from the pancreatic beta cell? Which is the functional link between β-arrestin-1 and the modulation of important phenomena undoubtedly evoked by myocardial infarction, including inflammation, angiogenesis, and mobilization of (bone marrow derived) stem cells (all processes intensely involved2 in the response to ischemic injury via cardiac repair and regeneration)? Another mechanism that might take in the GRK2/β-arrestin-mediated cross talk between the adrenal gland and the heart is represented by the regulation of gene expression mediated by noncoding RNAs (in primis microRNAs). Supporting a potential role for β-arrestin-1 in the regulation of these activities, β_AR has been shown recently to partake in all the above-mentioned processes.6,8,9 Equally important, growing evidence indicates that loss or dysfunction of β-arrestin-2 results in profound disturbance of insulin...
signaling, thereby contributing to the development of insulin resistance and progression of diabetes mellitus.10

Further insight into the complex neurohumoral mechanisms underlying HF might be gained in the future using conditional and tissue-specific knockout models (a major limitation of the study, promptly acknowledged by the authors, is actually the use of global knockout mice), focusing on the multifaceted interconnectivity of G-protein–coupled signaling. Nevertheless, this commendable work by Bathgate-Siryk et al5 may unlock the door to novel therapeutic interventions in HF. Indeed, modulation of events regulated by GRKs and β-arrestins signaling, both in the heart and in the adrenal, will certainly represent a more than promising strategy for the development of powerful new therapies to treat patients with failing hearts, with the auspicious potential of complementing β-blocker treatment, hampered by its negative inotropic effect.

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References
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