

Editorial

Progress in the development of a unifying hypothesis on the mechanisms underlying the electrical and mechanical abnormalities of the failing heart: One step backward but two steps forward

The incidence and prevalence of death and disability from heart failure have steadily increased over the last two decades despite the overall decline in the age-adjusted death rates for cardiovascular diseases in general during the same period [1,2]. As of 2003, the incidence of heart failure is estimated at 550,000 new cases per year and the prevalence of heart failure is approximately 5 million patients or 2.3% of the total population [2]. Alarming, the prevalence of some degree of cardiac dysfunction may be considerably higher with a 2003 study of a representative Minnesota population showing a prevalence of systolic dysfunction of 6% and diastolic dysfunction of 28.1% [1]. Based on Framingham Heart Study data, the lifetime risk of developing heart failure in men and women is staggering at 1 in 5 individuals [3]. Of those individuals under the age of 65, 80% of men and 70% of women will die within 8 years and the 1-year mortality is extraordinarily high at 1 in 5 [2]. Consequently, overall deaths from heart failure have increased 20.5% from 1993–2003. The two major causes of death in heart failure patients are mechanical pump failure and electrical abnormalities leading to cardiac arrhythmias with the incidence of sudden cardiac death being 6–9 times greater in heart failure patients compared with the general population. In light of these alarming statistics, it is not surprising that the number of heart failure-related hospital discharges increased by 174% from 1979 to 2003; and that the estimated direct and indirect cost of heart failure in this country for 2006 is \$29.6 billion [2]. Clearly, our current preventive and therapeutic heart failure strategies have failed to reverse this epidemic proportion of heart failure and to lessen the human and economic costs of heart failure on our society.

After decades of intensive clinical and basic science investigations, the precise mechanisms that are responsible for both the contractile and electrical abnormalities characteristic of heart failure remain unclear. Progress has been hindered, in part, by the fact that the mechanical and electrical phenotype of the failing heart represents the “triangulation” of a host of physiological, neurohumoral, and biochemical abnormalities that are the consequence of the interplay of multiple and complex genetic and environmental influences.

Nonetheless, distinct patterns of abnormalities have consistently emerged from recent clinical studies and studies of animal models of heart failure [4]. Heart failure is often associated with abnormalities in cardiac cAMP generation and Ca^{2+} handling, two inter-dependent pathways that determine cardiac contractile function. However, restoration of intracellular cAMP levels to normal through pharmacological means (e.g., β -adrenergic receptor agonists, milrinone) was not associated with successful clinical outcomes, and agents that directly influence Ca^{2+} signaling have not yet been shown to be effective. Consequently, these two tightly linked pathways in the failing heart remain elusive targets in heart failure therapeutics. Therefore, new efforts have been directed in examining the possible beneficial effects of correcting the more downstream effectors.

Indeed, new studies have documented several key differences between the modification of receptor- vs. effector-genes with regard to β -adrenergic receptor (β -AR) signaling in heart failure. At least 9 closely related isoforms of adenylyl cyclase (AC_1 through AC_{IX}), each encoded by a distinct gene, have been cloned and characterized in mammals. Individual AC isoforms may affect selective functions in cardiomyocytes, and AC_V and AC_{VI} are the most abundant isoforms in the heart. Cardiac-directed expression of adenylyl cyclase VI (AC_{VI}) has been intensively studied as a possible means to treat heart failure. When this strategy is applied to a genetic model of dilated cardiomyopathy (G_{α_q} -overexpressing mice), survival and LV function are markedly improved in $G_{\alpha_q}/\text{AC}_{IV}$ mice [5,6]. In contrast, when the same cardiomyopathy model is treated with the overexpression of β -adrenergic receptors, life span is shortened [7]. One possible explanation for this worsening outcome may be related to the fact that this strategy provided sustained global increases of intracellular cAMP. In contrast, it was previously documented that sustained increases in cAMP are not observed in cardiac myocytes expressing AC_{VI} . Clearly, there are marked differences in the effects that are evoked by these two elements in the β -AR- G_s -AC signaling pathway, although both strategies involve cAMP.

In this issue of the *Journal of Molecular and Cellular Cardiology*, Timofeyev et al. tested the hypothesis that the improved survival of $G_{\alpha q}/AC_{IV}$ mice may be attributable to not only the known improvement in contractile function but also to the reversal of the adverse electrical remodeling characteristic of $G_{\alpha q}$ -overexpression-mediated cardiomyopathy [8]. They compared four lines of mice: wild-type controls, AC_{VI} alone, $G_{\alpha q}$ alone, and $G_{\alpha q}/AC_{IV}$ mice with respect to electrophysiological indices of repolarization including surface electrocardiograms (ECG), action potential duration (APD), L-type Ca^{2+} currents, and multiple K^+ currents. As expected, the cardiac-directed overexpression of AC_{IV} on the background of $G_{\alpha q}$ attenuated the development of $G_{\alpha q}$ -related cardiomyopathy and restored normal contractile function. Importantly, compared with $G_{\alpha q}$ mice, the $G_{\alpha q}/AC_{IV}$ mice had normal RR intervals on ECG with no episodes of spontaneous electrical alternans, normal APD, and normal transient outward K^+ currents (I_{to}) and inward rectifier K^+ currents (I_{K1}). In addition, while $G_{\alpha q}/AC_{IV}$ mice had increased basal L-type Ca^{2+} current density, their responsiveness to catecholamines measured as the proportion of current enhancement evoked by β -adrenergic stimulation (i.e., isoproterenol) was the same as the wild-type controls. Therefore, it is quite reasonable to speculate that the improved survival of $G_{\alpha q}/AC_{IV}$ mice may be due, in part, to the correction of the repolarization abnormalities that accompany $G_{\alpha q}$ overexpression alone.

Moreover, this study also supports the notion that β -AR-AC signaling derives its specificity through compartmentalization of specific β -AR subtypes with various G-protein subtypes and AC isoforms, which fine tune intra-cytoplasmic trafficking and compartmentalization of cAMP. The compartmentalization occurs at multiple levels including localization of receptors, G proteins, and ACs at specific membrane domains, as well as localization of phosphodiesterase, protein kinase A, and phosphatases in macromolecular complexes [9–11].

Although ACs are activated by nonselective β -AR agonists such as isoproterenol, recent data suggest that the various AC isoforms may be differentially activated by specific membrane receptors [12]. In addition, there is a unique link between AC, cAMP, and Ca^{2+} that may explain the pivotal effects of ACs in heart failure. Overexpression of the AC_{VI} isoform restores SERCA2a affinity for calcium in murine dilated cardiomyopathy by regulating phospholamban-mediated inhibition of SERCA2a. The current study by Timofeyev et al. [8] further reveals a possible mechanism by which AC_{VI} , compared with other signaling elements associated with increased cAMP generation, has a salutary effect in the failing heart [13].

References

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Ye Chen-Izu

C. William Balke*

*Departments of Medicine and Physiology,
Institute of Molecular Medicine,
University of Kentucky College of Medicine,
Dean's Office MN150, Chandler Medical Center,
800 Rose Street, Lexington,
KY 40536-0298, USA*

E-mail address: b.balke@uky.edu.

*Corresponding author. Tel.: +1 859 323 9093;
fax: +1 859 323 2039.