Advances in Heart Failure

Targeting the β-Adrenergic Receptor System Through G-Protein–Coupled Receptor Kinase 2: A New Paradigm for Therapy and Prognostic Evaluation in Heart Failure
From Bench to Bedside

Giuseppe Rengo, MD, PhD; Pasquale Perrone-Filardi, MD, PhD; Grazia D. Femminella, MD; DanielaLiccardo, MS; CarmelaZincarelli, MD, PhD; Claudio deLucia, MD; GennaroPagano, MD; FabioMarsico, MD; AnastasiosLymeropoulos, PhD; DarioLesoco, MD, PhD

G-protein–coupled receptors (GPCRs) are a superfamily of more than 1000 membrane proteins that respond to a wide spectrum of extracellular signals, modulating various physiopathological processes.1,2 Several GPCRs, such as adrenergic, angiotensin, endothelin, and adenosine receptors, are expressed in cardiovascular (CV) tissues to maintain CV homeostasis. Importantly, GPCR-mediated adrenergic deregulation has been shown to both cause and contribute to the onset and progression of major CV diseases ultimately leading to heart failure (HF). Thus, GPCRs have become salient targets of current pharmacotherapy in CV disorders, and in past decades, many efforts have been made to better clarify their role in the pathophysiology of cardiac disease, focusing not only on receptor functions but also on postreceptor components that mediate or regulate their responses. Among the latter, a relevant role has been attributed to G-protein–coupled receptor kinases (GRKs). In this review, we focus on GRK2, the most abundant and versatile GRK expressed on CV system, tracing the way from initial experimental evidence to more recent data suggesting a potential role for this kinase in the clinical management of HF.1,2

GPCR Signaling and GRK Functions: Pathophysiological Background

On stimulation, GPCRs interact with heterotrimeric G proteins, which in turn dissociate into 2 functional monomers, namely Gα and Gβγ, both of which modulate different effector systems. Agonist binding to GPCR promotes the activation of complex regulatory mechanisms to protect the receptor from both acute and chronic stimulation, a process termed desensitization. As extensively described, GPCR desensitization involves 3 main events in chronological order: receptor phosphorylation and uncoupling from G proteins, internalization of membrane-bound receptors, and downregulation through reduced mRNA and protein synthesis or increased degradation of internalized receptors.1,2

The desensitization process is mediated by 3 families of proteins: second-messenger–dependent protein kinases, GRKs and arrestins. The defining feature of GRKs is that they recognize and phosphorylate only agonist-activated (agonist-bound) GPCRs, thereby promoting the association of cytosolic cofactor proteins called arrestins, which target GPCRs for endocytosis and activate G-protein–independent signal transduction cascades.1,2

The GRKs are a family of cytosolic serine/threonine kinases consisting of 7 isoforms that share structural and functional similarities.1 On the basis of divergent C-terminal domain architecture and membrane-targeting mechanisms, the GRKs are classified into 3 subfamilies: (1) the rhodopsin kinase GRK1 and visual pigment kinase GRK7, (2) the β-adrenergic receptor (βAR) kinases (or GRK2 and 3), and (3) the GRK4 group (GRK4–6). GRK2, GRK3, GRK5, and GRK6 are expressed in a wide variety of tissues, whereas other GRKs display a more restricted expression pattern.1

GRK2 in the CV System: Experimental Evidence

GRK2, initially identified as βARK1 (βAR kinase-1), is the most abundant GRK expressed in the heart.2 On receptor activation, GRK2 translocates to the plasma membrane, as a consequence of its interaction with Gβγ subunits released by agonist binding of the receptor, and initiates receptor desensitization.1,2

During past decades, a key role for GRK2 in the development of myocardial dysfunction as a consequence of various noxious stimuli has been postulated. In 1982, Bristow et al3 observed that in human failing hearts, βAR density and function were significantly reduced compared with normal hearts. Subsequent studies demonstrated that βAR loss is
selective for the β1AR subtype, which accounts for 70% to 80% of total cardiac βARs under normal conditions, whereas remaining β2ARs and β3ARs are desensitized.4 In 1993, the cardiac levels and activity of GRK2 were found to be significantly elevated in end-stage human HF, suggesting a potential mechanism for the observed HF-Lvad mediated βAR downregulation and desensitization.5 Adding to GRK2 relevance in the overall regulation of the normal and compromised hearts are the findings of elevated levels in experimental models of cardiac ischemia, hypertrophy, and hypertension, all ultimately leading to HF.6,7

Because neurohormonal activation occurs early in the course of HF, sympathetic nervous system hyperactivity has been investigated as a plausible early trigger for increasing GRK activity in failing myocardium.8 Iaccarino et al9 demonstrated that normal healthy mice exposed to infusion of βAR agonist isoproterenol develop myocardial hypertrophy and impaired βAR signaling, associated with increased GRK2 levels and activity. In contrast, administration of atenolol and carvedilol decreased GRK2 expression and GRK2 levels and activity. In contrast, administration of a competitive inhibitor of GRK2 binding to Gβ subunits, even though the exact mechanism of action may involve other functions, such as sequestration of Gβ from other signaling pathways and protection from ischemic injury through anti-apoptotic effects.17,18

Further interesting data focusing on βARKct as a potential therapeutic strategy in HF came from studies using adenoviral-mediated gene therapy. Indeed, infection with an adenoviral vector containing βARKct of myocytes isolated from failing rabbit hearts (AdβARKct) resulted in an improvement of defective βAR signaling.19 In vitro gene transfer of AdβARKct to failing human myocytes also induced improvement of contractile dysfunction, providing proof of concept for the feasibility of this approach in human HF.20 The next step was to validate GRK2 inhibition in vivo. To this end, White et al21 administered AdβARKct through the coronaries of rabbits at the time of MI, resulting in prevention of adverse ventricular remodeling, improvement of cardiac contractility, and preservation of βAR function. This study was the first to clearly demonstrate that GRK2 elevation and βAR desensitization are ultimately maladaptive in HF, supporting the hypothesis that its inhibition via AdβARKct gene delivery could have beneficial effects. A subsequent study was conducted in rabbits in which AdβARKct was delivered percutaneously to the heart 3 weeks after MI, when HF was established. βARKct expression resulted in improvement of contractile dysfunction and reversal of βAR desensitization.22 In other studies, βARKct was expressed in a rabbit model of right ventricle (RV) failure, resulting in amelioration of RV function and, notably, improvement of survival.23 Other studies have been performed using AdβARKct delivery to the heart in the setting of acute myocardial injury.24 However, the aforementioned studies were limited to an acute window of observation due to the limitations of Ad vectors (short-term expression and high inflammatory responses in vivo).25 Thus, to establish the long-term effects of βARKct gene therapy and to demonstrate its translational feasibility in chronic conditions as HF, βARKct was cloned into adenov-associated viruses (AAVs). AAV vectors produce stable and long-term transgene expression and have been safely used in gene therapy studies in animals and humans.16 A study was performed in which AAV6-βARKct was administered through direct intramyocardial injection in rats with established HF. The long-term cardiac AAV6-βARKct gene therapy in HF resulted in sustained improvement of cardiac function, reversal of remodeling, and normalization of the neurohormonal signaling axis, proving that βARKct gene therapy can be of long-term therapeutic value in HF.26 The results of some of the most significant studies on βARKct gene therapy are summarized in Table 1.

GRK5, the other GRK abundantly expressed in the myocardium, has also been shown to be upregulated in animal models and human cases of HF.27 However, GRK5 action on βAR signaling appears to be qualitatively different from that of GRK2 in the heart and not directly related to receptor
GRK2 upregulation in chro-
menna is the primary cause of
excessive desensitization of neu-
rohormonal receptors.35

Table 1. Animal and In Vitro Models Supporting the Therapeutic Value of GRK2 Inhibition in HF Through Gene Therapy

<table>
<thead>
<tr>
<th>Model</th>
<th>Molecular Outcome</th>
<th>Functional Outcome</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>AdγARKct in vitro gene transfer to isolated failing rabbit myocytes</td>
<td>Restoration of βAR signaling</td>
<td>NE</td>
<td>19</td>
</tr>
<tr>
<td>AdγARKct gene transfer in ventricular myocytes isolated from end-stage HF patients</td>
<td>Isoproterenol-stimulated increase in adenylyl cyclase activity</td>
<td>Isoproterenol-stimulated increase in contraction and relaxation velocities. Fractional shortening enhancement</td>
<td>20</td>
</tr>
<tr>
<td>In vivo intracoronary AdγARKct gene transfer in rabbits at the time of MI</td>
<td>Prevention of GRK2 upregulation and βAR signaling abnormalities</td>
<td>Reduction in the degree of LV dysfunction and improved contractility</td>
<td>21</td>
</tr>
<tr>
<td>Percutaneous delivery of AdγARKct to rabbit hearts with established HF</td>
<td>Improvement of βAR-stimulated adenylyl cyclase activity in the LV</td>
<td>Improvement of LV systolic performance</td>
<td>22</td>
</tr>
<tr>
<td>AdγARKct delivery in the RV of rabbits in a model of RV failure</td>
<td>NE</td>
<td>Amelioration of RV function and improvement of survival</td>
<td>23</td>
</tr>
<tr>
<td>AdγARKct intracoronary delivery before cardioplegic arrest</td>
<td>Improvement in βAR signaling abnormalities</td>
<td>Enhanced LV function</td>
<td>24</td>
</tr>
<tr>
<td>AAV6-mediated βARKct intramyocardial gene delivery in rats with established HF</td>
<td>Normalized GRK2 levels, βAR density and cAMP production; normalized catecholamine and aldosterone levels</td>
<td>Reduced LV diameters, enhanced basal and isoproterenol-stimulated contractility</td>
<td>26</td>
</tr>
</tbody>
</table>

GRK indicates G-protein–coupled receptor kinase; HF, heart failure; βAR, β-adrenergic receptor; βARK, βAR kinase; NE, not evaluated; MI, myocardial infarction; LV, left ventricular; RV, right ventricular; and AAV, adeno-associated virus.

desensitization.27 Moreover, it has been recently reported that GRK5-mediated βAR phosphorylation results in alternative, G-protein–independent intracellular signaling leading to transactivation of the epidermal growth factor receptor, with cardioprotective effects.28 Finally, it has been shown that enhanced cardiac GRK5 is pathological in the setting of cardiac hypertrophy.29 Therefore, the actions of GRK5 in the heart might be significantly different from those of GRK2, and this is bound to be the subject of intense investigation in the future.

Extracardiac GRK2 Effects in HF

The relevance of GRK2-mediated receptor desensitization in HF is mainly related but not limited to cardiac βARs. Recently, Lymperopoulos et al30,31 have demonstrated an additional role for GRK2 in sympathetic nervous system modulation in HF: the sympatho-inhibitory function of adrenal α2AR was dysregulated in a HF model, contributing to increased catecholamine levels. GRK2 upregulation in chro-
maffin cells of the adrenal medulla was the primary cause of the lack of α2AR-mediated inhibition of catecholamine release; indeed, GRK2 inhibition resulted in the restoration of negative feedback on catecholamine release by α2AR activation. The crucial role for GRK2 in catecholamine secretion modulation in the adrenal gland has been further confirmed by other studies,32–34 indicating that the effects of “pathological” hyperactivation of GRK2 in HF lie not only in impaired cardiac function but also in unbalanced systemic homeostasis/organ cross-talk due to excessive desensitization of neurohormonal receptors.35

GRK2 as a New Biomarker in HF (Human Studies)

The role played by GRK2 in cardiac βAR dysfunction and HF establishment and progression prompted translation of the experimental evidence into the clinic, in particular investigating a potential role of cardiac GRK2 as biomarker of HF functional and neurohormonal status (Table 2). An important aspect of βAR signaling is that activity of the system in solid tissues is mirrored in circulating white blood cells36 (Figure). Thus, lymphocytes represent a valuable and reliable marker of the functional state of cardiac βAR signaling, which may also extend to GRK2 regulation.

In 2002, Dzimir et al37 demonstrated that in patients with left ventricular (LV) volume overload caused by valvular disease, lymphocyte GRK2 and GRK3 mRNA and protein levels were significantly increased compared with healthy control subjects. These changes were also associated with a significant decrease in β2AR mRNA and depression of receptor-stimulated adenylyl cyclase activity. Interestingly, the increase in GRK2 mRNA correlated with the severity of the hemody-
namic impairment. Subsequently, the same authors evaluated the expression of GRK2, GRK3, and GRK5 and the status of adrenergic signaling in the hearts of patients with dilated cardiomyopathy or with LV volume overload and reported intriguing differences between these two pathological conditions.27

The differential cardiac expression of GRK2 and other GRKs in CV diseases from different etiologies holds great value but some issues remained unsolved: first, myocardial samples are not easily available, and patients must undergo invasive procedures to obtain specimens; second, the data derived from these initial translational studies did not provide information on possible correlations between GRK expression/activity and patient clinical and functional status.

In 2005, Iaccarino et al38 demonstrated that in HF patients, myocardial GRK2 expression and activity are mirrored by lymphocyte levels of the kinase. Importantly, these data support the concept that the GRK system in lymphocyte and heart is regulated in a similar manner, and presumably increased circulating catecholamine levels trigger the in-
crease in GRK2 expression in cardiac tissue and in peripheral blood cells. Moreover, the study also showed that lymphocyte GRK2 in HF patients correlates with LV ejection fraction and New York Heart Association (NYHA) class, with patients...
with lower ventricular function or higher functional classes having higher levels of the kinase. Further insight was provided by Hata et al., who demonstrated that mechanical unloading of the failing heart was associated with restored AR signaling. In particular, end-stage HF patients who underwent LV assist device (LVAD) implantation showed restored AR density and signaling to nonfailing levels after LVAD, reduction in GRK2 mRNA and protein levels and correlation between myocardial and lymphocyte GRK2 levels. Overall, this study was the first to demonstrate that GRK2 expression/activity was associated with AR normalization occurring during reverse remodeling. Notably, this study suggests that lymphocyte levels and their changes after HF treatment may be used as a novel biomarker for HF, reflecting patient’s response to treatment.

Table 2. Clinical Studies Supporting the Value of Lymphocyte GRK2 Levels as Biomarker in Chronic HF

<table>
<thead>
<tr>
<th>Clinical Setting</th>
<th>Main Outcomes</th>
<th>Sample</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>LV volume overload disease</td>
<td>Increased GRK2 and GRK3 mRNA and protein levels compared with control subjects. Decrease in βAR mRNA, depression in receptor-stimulated adenyl cyclase activity and increase in β-arrestin2 mRNA in patient group.</td>
<td>Lymphocytes</td>
<td>37</td>
</tr>
<tr>
<td>Dilated cardiomyopathy and LV volume overload</td>
<td>Volume overload: the expression of both GRK2 and GRK5 was evident in all 4 cardiac chambers, with GRK5 particularly expressed in the LV. Dilated cardiomyopathy: greater increase in GRK expression than volume overload in all 4 chambers, particularly evident for GRK2.</td>
<td>Myocardium</td>
<td>27</td>
</tr>
<tr>
<td>HF</td>
<td>Myocardial GRK2 expression and activity are mirrored by lymphocyte levels of the kinase and lymphocyte GRK2 is correlated with LV function and NYHA class.</td>
<td>Myocardium and lymphocytes</td>
<td>38</td>
</tr>
<tr>
<td>HF</td>
<td>GRK2 expression/activity was decreased after mechanical unloading of failing myocardium and associated with βAR normalization during reverse remodeling.</td>
<td>Myocardium and lymphocytes</td>
<td>39</td>
</tr>
<tr>
<td>HF</td>
<td>GRK2 transiently increased at an early stage of HF but decreased to control values in patients in NYHA class III-IV. β-Blockers were able to reduce the early increase in GRK activity.</td>
<td>Myocardium</td>
<td>40</td>
</tr>
<tr>
<td>HF</td>
<td>GRK2 expression/activity was increased in HF patients and normalized to nonfailing control levels after LVAD support.</td>
<td>Myocardium and lymphocytes</td>
<td>41</td>
</tr>
<tr>
<td>Cardiac transplantation</td>
<td>GRK2 levels significantly declined after surgery and remained low over the course of the study period.</td>
<td>Myocardium and lymphocytes</td>
<td>42</td>
</tr>
<tr>
<td>MI</td>
<td>GRK2 levels significantly increased in patients with ST-segment elevation-MI and were associated with worse systolic and diastolic functions; at 2-y follow-up, patients with higher GRK2 levels at admission had worse systolic function and cardiac remodeling.</td>
<td>Lymphocytes</td>
<td>43</td>
</tr>
</tbody>
</table>

GRK indicates G-protein–coupled receptor kinase; HF, heart failure; LV, left ventricular; βAR, β-adrenergic receptor; NYHA, New York Heart Association; LVAD, left ventricular assist device; and MI, myocardial infarction.

Figure. β-Adrenergic receptor (βAR) signaling in the heart and in peripheral lymphocyte under physiological conditions and in heart failure (HF). Physiologically (left panel), β-AR stimulation by catecholamine (CA) results in the dissociation of the stimulatory G-protein α-subunit (Gαs) from Gβγ. Gαs stimulates adenylate cyclase (AC) to produce cAMP, which, by activating protein kinase A (PKA), regulates different intracellular, sarcolemmal and myofibrillar substrates, thus exerting the cellular effects of receptor activation on cardiac chronotropy, inotropy, and lusitropy. In circulating peripheral lymphocyte, CAs activate βAR, which is associated with both Gαs and inhibitory Gαi-subunit (Gai), which appear to negatively and positively regulate T-cell activity, respectively. During HF (right panel), circulating CA levels increase, resulting in βAR hyperstimulation and enhanced G-protein–coupled receptor kinase (GRK)2 protein levels/activity both in the heart and in peripheral lymphocytes. GRK2 induces βAR phosphorylation, thus initiating receptor downregulation and desensitization in the heart and βAR desensitization in lymphocytes.
In another study, Leineweber et al. showed that in patients at different stages of HF treated with βAR blockers or not, myocardial βAR density decreased with increasing disease severity. As for GRKs, the kinase activity transiently increased at an early stage of HF (NYHA classes I and II). β-Blockers were able to reduce the early increase in GRK activity at NYHA I and II to control levels, whereas in those patients who did not have increased GRK activity (NYHA classes III and IV), they had only a marginal effect. Even though these data are somehow in contrast with previous evidence showing progressive GRK2 increase with HF severity (maybe due to evaluation of all GRK activity and not specific GRK2), they suggest that HF treatment can modulate GRK.

More recently, Akhter et al. demonstrated that βAR density was decreased in HF and increased to near normal in LVAD-treated patients, whereas GRK2 expression and activity were increased in HF and returned similar to nonfailing control subjects after LVAD support. Similar results were reported by Bonita et al. in HF patients undergoing heart transplantation. In this study, both cardiac and lymphocyte GRK2 levels significantly declined after surgery, consistent with improved cardiac function in the transplanted heart. Recently, Santulli et al. demonstrated that lymphocyte GRK2 levels significantly increase in patients with ST-segment elevation–MI and are associated with worse systolic and diastolic functions. Moreover, early revascularization and β-blocker therapy influenced GRK2 levels. Of note, at 2-year follow-up, patients with higher GRK2 levels at admission had worse systolic function and cardiac remodeling. Collectively, these data suggest that GRK2 levels reflect hemodynamic impairment and might have a prognostic value after MI.

As for the role of GRK5 in human HF, a recent study has shown a positive correlation between a single-nucleotide polymorphism of GRK5 (Leu41Gln) resulting in increased activity of the kinase and better prognosis and survival in human HF. The authors of that study suggested the Leu41 variant acts as a “genetic” β-blocker due to increased desensitization of the cardiotoxic (in HF) β1AR. Interestingly, a recent study by Lobmeyer et al. characterized single-nucleotide polymorphisms in both GRK2 and GRK5 genes in patients treated with antihypertensive agents, showing that the rs1894111 G>A polymorphism in GRK2 gene was associated with systolic and diastolic blood pressure response to hydrochlorothiazide in whites and the GRK5 Gln41Leu variation decreased the risk of adverse cardiovascular outcomes independent of treatment strategy.

**Future Perspectives**

From basic to clinical research, many advances have been made in the past decades on the physiopathological role of GRKs, and in particular of GRK2, in the CV system. Thus far, the available knowledge on GRK2 functions fosters the need to further explore the role of the kinase from different investigational approaches: (1) “basic research”; (2) “therapeutic potential”; and (3) “biomarker.”

(1) From the “basic research” point of view, many aspects of the cellular functions of GRK2 warrant further exploration. In particular, the so-called “GRK2 interactome” (ie, the complex network of molecules interacting with GRK2 in the modulation of various cellular pathways) has been shown to regulate crucial cellular signals that go beyond the direct adrenergic response in the CV system. In this regard, it has been demonstrated that GRK2, via β-arrestin1, regulates angiotensin II type I receptors and that GRK2 overexpression promotes insulin resistance after MI. Thus, the favorable effects of GRK2 inhibition in cardiac disease can be ascribed not only to the direct improvement of adrenergic response but also to more complex interactions among different and specific systems involved in the pathophysiological response to myocardial injury.

(2) The “therapeutic potential” of GRK2 modulation rises from the availability of the specific inhibitory peptide, βARKct. Preclinical studies pointed out the positive effects of βARKct gene delivery in animal models of HF, hypertension, and myocardial ischemia. Because clinical studies evaluating safety and efficacy of viral-mediated gene therapy in human HF are currently ongoing, βARKct is a feasible and promising candidate for gene therapy–based treatment of cardiac diseases. Importantly, although GRK2 inhibition and β-blocker therapy have been shown to exert similar effects on βAR signaling restoration in HF, the in vivo effects of these therapeutic modalities are quite different. Indeed, whereas β-blockers are able to prevent HF progression, βARKct gene therapy confers a positive inotropic effect. Moreover, the data produced so far have demonstrated that the combination of these 2 treatments results in prolonged survival and all of the beneficial effects of βARKct expression in HF are still present when β-blocker is coadministered. This strongly suggests that these 2 therapeutic strategies are completely compatible with each other, adding to the potential future clinical application of βARKct gene therapy in HF.

(3) A great potential for future application of GRK2 derives from its emerging role as a “biomarker,” as some of the above-mentioned clinical studies have pointed out. Biomarkers provide the potential to enhance diagnostic, therapeutic, and prognostic approaches to the complex treatment of CV diseases. In HF, on top of current biomarkers such as natriuretic peptides, GRK2 may be appealing for several aspects: (1) its levels in circulating lymphocytes mirror those in the myocardium, providing the advantage of noninvasive evaluation; (2) GRK2 levels correlate with the status of cardiac adrenergic system, the most critical pathway in the regulation of cardiac function whose alterations are a key mechanism of HF onset and progression; (3) GRK2 has been shown to correlate with patient functional status, as its levels vary according to hemodynamic status and NYHA class in HF patients and can be predictive of long-term outcomes in the acute setting of MI; and (4) the levels of GRK2 change in response to specific treatments, as it has been shown for β-blockers and LVAD, which can be monitored in peripheral lymphocytes, providing a mechanism to follow changes in myocardial βAR signaling in response to an intervention. However, for an implementation in the clinical arena, 2 major issues must be resolved: a more readily feasible high-
throughout GRK2 quantification method from blood, such as ELISA assay, must be developed, and, more importantly, the evidence of a cost-effective change in disease management and clinical outcome of HF patients should be tested in ad hoc clinical trials.

Conclusions
Cardiac GRK2 protein levels are tightly related to the status of βAR function in the heart. Thus, GRK2 emerges not only as a potential therapeutic target to curb HF-related βAR unresponsiveness but also as a biomarker of HF status and response to treatment, potentially useful in HF clinical practice. As preclinical and clinical research is rapidly moving forward on this challenging pathophysiological pathway, we hope that the ongoing war against HF will win another battle the near future.

Disclosures
None.

References


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