Phosphodiesterase 2 as a Therapeutic Target for Heart Failure
Is Upregulation an Option?

Samuel H.H. Chan, Julie Y.H. Chan

Heart failure (HF) is a chronic progressive cardiac disease with high morbidity and mortality. A key pathophysiological feature of HF is chronic overexcitation of the sympathetic nervous system and release of catecholamines. The subsequent activation of cardiac β-adrenoceptors (β-ARs) results in molecular and structural changes that lead to cardiac hypertrophy, myocardial fibrosis, or electromechanical dysfunction. This cascade of cellular events creates a setting for lethal cardiac arrhythmias and increases the prognostic risks for mortality and detrimental cardiovascular outcome. Accordingly, pharmacological intervention with β-blockers remains a mainstay practice in clinical management of HF. Nevertheless, chronic β-blocker therapy is known to be accompanied by adverse side effects that include bradycardia, heart block, bronchospasm, fatigue, muscle cramps, and sleep disturbances. Furthermore, not all patients experiencing HF benefit from β-blocker treatments or tolerate the doses necessary to achieve disease improvement. These disadvantages prompted the quest for alternative medication against HF with therapeutic targets other than β-ARs.

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From the Institute for Translational Research in Biomedicine, Kaohsiung Chang Gung Memorial Hospital, Taiwan, Republic of China. Correspondence to Dr Julie Y.H. Chan, Institute for Translational Research in Biomedicine, Kaohsiung Chang Gung Memorial Hospital, 133 Ta-Pei Rd, Kaohsiung 83301, Taiwan, Republic of China. E-mail jcham@adm.cgmh.org.tw


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Contrast, cGMP/PKG signaling is considered a form of myocardial brake that reduces maladaptive hypertrophy, enhances cell survival signaling and mitochondrial function, protects against ischemia–reperfusion injury, and blunts the stimulatory effects of catecholamines. These actions of cGMP are believed to be beneficial in HF partly because they may act against cAMP-induced cardiac remodeling. Moreover, enhancement of β2-AR–coupled cGMP signaling may explain, in part, the therapeutic benefit on the preservation of cardiac function when β1-blockers are used in HF.

The level and subcellular distribution (compartmentalization) of cAMP and cGMP are regulated by cyclic nucleotide–hydrolyzing phosphodiesterases (PDEs). At present, 11 different PDE family members (PDE1–11) have been described, of which PDE4, 7, and 8 are selective for the hydrolysis of cAMP and PDE5, 6, and 9 for cGMP; PDE1, 2, 3, 10, and 11 can hydrolyze both cAMP and cGMP. As the sole means of terminating a cyclic nucleotide–dependent signal, PDEs provide a mechanism for controlling intracellular concentrations of cyclic nucleotides. Among the PDE members expressed in the heart, PDE2 exhibits the unique property, after being activated by cGMP, of producing conformational changes of cAMP to increase its hydrolysis by 10- to 30-fold. This unique property of cGMP-activated cAMP eraser stages PDE2 in the center of a negative cGMP/cAMP cross talk. More notably, the observation that myocardial PDE2 is upregulated in human HF implicates its upregulation or activation as a highly attractive new therapeutic option in the management of HF.

In the current issue of Circulation Research, Vettel et al10 provided evidence to argue for a cardioprotective effect of PDE2 under chronic β-AR stress conditions, most likely via a predominant role in heart rate (HR) regulation. The authors found that specific pharmacological inhibition of PDE2 in healthy experimental animals leads to an exclusive increase in HR, whereas overexpression of the phosphodiesterase in heart-specific PDE2 transgenic mice results in HR decrease. Under pathological conditions of chronic β-AR stimulation, PDE2 contributes to myocardial β-AR desensitization and protects the damaged heart from excessive sympathetic stress on inotropy and chronotropy. The initiation of heart beat is known to be based on a mutual interplay between ion channels of the cell membrane clock (membrane clock) and cellular calcium cycling clock (Ca2+ clock).20 In this study, the authors showed that the accumulation of cAMP in response to β-AR stimulation is markedly blunted in PDE2-overexpressed myocytes, and the induced cAMP-dependent Ca2+ signaling, including ion channels of both membrane and Ca2+ clock, is...
attenuated (Figure). Under the condition of HF, chronic over-
excitation of the sympathetic nervous system significantly
increases arrhythmia susceptibility and dampens cardiac
contractile performance after cardiac ischemia–reperfusion
injury. Vettel et al further found that elevated abundance
of myocardial PDE2 protects against ventricular arrhythmia
induced by acute β-AR stimulation and improves ventricular
function in experimental myocardial infarction induced by
left anterior descending artery ligation. In short, PDE2 over-
expression may offer a potential dual protection to the fail-
ing heart by limiting HR without the depression of contractile
performance. As a consequence, an increase in expression or
activity of PDE2 may be beneficial because it lowers arrhyth-
mia susceptibility and preserves cardiac contractile function
during ischemic injury in the failing heart.

The concept of targeting PDEs for therapeutic manage-
ment of HF is not new, although the theoretical basis is in-
hibition of PDE. For example, milrinone, a PDE3-selective
inhibitor, is reported to be effective in increasing cardiac con-
tractility in patients with HF. However, its clinical indication
has been curtailed because it increases cardiac mortality. Other studies evaluated the efficacy of PDE5-selective in-
hibitors, sildenafil and tadalafil, in chronic HF. It is evident
from those clinical investigations that depending on morpho-
functional impairments and staging of HF, as well as dosing
and duration of treatments, the outcome may vary from no
significant changes in HR and systolic or diastolic blood
pressure to significant improvement of hemodynamics and
clinical parameters, even to reversal of maladaptive chamber
remodeling. Treatment with rolipram, a PDE4-selective in-
hibitor, however, has no effect on positive inotropic and lus-
tropic effects of catecholamines in ventricular myocardium of
patients with HF treated with the β-blocker, carvedilol.

In light that none of the currently available PDE inhibi-
tors has yet been shown convincingly to improve the clinical
symptoms of patients with HF, the findings by Vettel et al may
offer an alternative therapeutic approach to the treatment
of HF. However, several issues require further clarification
before this approach can be put into practice. The first issue
concerns the compartmentalization of cyclic nucleotide sig-
naling. In addition to structural segregations of a cell based
on visible membrane-delimited organelles, cellular compart-
mentalization can be described as functional domains that are
temporally and spatially regulated. To this end, the β-agonist
isoproterenol induces cAMP accumulation and PKA activa-
tion in both soluble and particulate subcellular fractions of
rabbit heart. However, prostaglandin E1 increases only the
soluble fraction of cAMP/PKA signaling. Moreover, adenyl-
lyl or guanylyl cyclase is unevenly distributed within the cell
such that cAMP and cGMP concentrations are at their highest

![Figure. The role of phosphodiesterase 2 (PDE2) in the regulation of heart rate in healthy and failing heart.](image)

In healthy heart, the initiation of heart beat is based on a mutual interplay between ion channels of the cell membrane clock (M clock) and cellular calcium cycling clock (Ca²⁺ clock) mediated by a dynamic balance between the stimulatory cAMP/protein kinase A (PKA) system activated by β₁/β₂-ARs and the inhibitory cGMP/PKG cascade activated by β₃-AR. In the failing heart where PDE2 expression is upregulated, heart rate response to chronic β-AR stimulation is restrained. This is attributed to the unique property of PDE2 as a cGMP-activated cAMP eraser that attenuates β-AR–induced accumulation of intracellular cAMP, along with the induced increase in L-type Ca²⁺ channel (Ica,L) current and fractional release of Ca²⁺ from the sarcoplasmic reticulum (SR), key components of the respective M clock and Ca²⁺ clock machineries for the initiation of heart rate. Under the scenario in which the expression of β₃-AR is increased, the Ica,L current is further suppressed via activation of cGMP/PKG signaling. AC indicates adenylate cyclase; β-AR, β-adrenoceptors; GC, guanylyl cyclase; Gi, adenyl cyclase inhibitory G protein; Gs, adenyl cyclase stimulatory G protein; M clock, membrane calcium clock; NOS3, endothelial nitric oxide synthase; PKA, protein kinase A; PKG, protein kinase G; PLB, phospholamban; PyR, ryanodine receptor; SERCA, sarcoendoplasmic reticulum calcium transport ATPase; and SR, sarcoplasmic reticulum.
close to the cyclase enzymes and at their lowest in the areas containing the PDEs. It is, therefore, conceivable that the specific subcellular localization of PDE2 may dictate the local magnitude and duration of cAMP/PKA signaling. A general limitation of transgenic overexpression is the potential spillover of the protein of interest within the subcellular compartments. Although Vettel et al.19 used an elegant heart-specific PDE2 transgenic mouse model, the possibility still exists that PDE2 may not be physiologically located. As a consequence, the subcellular signaling specificity may have been lost, and every PKA subset present in the cell would be affected (in this scenario, it is suppressed). This issue becomes even more critical when PDEs could be redistributed within the cells under pathological conditions.28 Further insights at the subcellular level on the role of PDE2 in local regulation of cAMP/cGMP signals in cardiac myocytes under HF are, therefore, crucial for the development of novel therapeutic interventions that target PDE2.

The second issue concerns cross talk between cGMP and cAMP signaling pathways, which has been appreciated for some time and again demonstrated in cardiomyocytes by Vettel et al.19 Whereas this study posits PDE2 as a central component of the negative cGMP/cAMP cross talk, whether monotherapy targeting this PDE is clinically effective in HF remains to be seen. Moreover, because the cAMP-hydrorylizing activity of PDE2 is increased in the presence of cGMP, strategies to maintain high intracellular cGMP levels would in theory provide additional benefits. In this regard, a randomized double-blind PARADIGM-HF trial (Prospective Comparison of ARNI [Angiotensin Receptor–Neprilysin Inhibitor] With ACEI [Angiotensin-Converting–Enzyme Inhibitor] to Determine Impact on Global Mortality and Morbidity in Heart Failure)29 in patients with HF who exhibit reduced ejection fraction reported that combined use of valsartan, an angiotensin receptor blocker, with sacubitril, a compound that increases cellular cGMP because of inhibition of the natriuretic peptide–degrading enzyme neprilysin, reduces cardiovascular mortality, duration of hospitalization, and all-cause mortality when compared with monotherapy by the use of a proven dose of angiotensin-converting enzyme inhibitor. It is, therefore, likely that combined use of conventional HF therapy with compounds that target PDE2 will generate enthusiasm as our understanding of the role of PDE2 in the crosstalk between cGMP and cAMP signals advances.

The third issue concerns the long-term value of targeting PDE2 for HF therapy. It is well recognized that on prolonged treatment, many beneficial effects against HF of currently available PDE inhibitors are offset by cardiac mortality, most commonly in the form of fatal arrhythmia or sudden cardiac death. Vettel et al.19 reported that cardiac phenotypes in elderly heart-specific PDE2 transgenic mice are well sustained without out cardiac pathology and premature death. Given that the roles played by PDE2 and other PDE isoforms vary among mammalian species, a cautionary note is that results from animal study may not recapitulate in humans. In particular, results from tissue-specific manipulation of protein of interest in animal studies should be viewed solely as proof of principle. In theory, clinical application of PDE2 to the myocardium could be accomplished by gene therapy. Nevertheless, this approach is fraught with technical and ethical problems of its own.

The pathophysiological mechanisms that underlie HF are complex, making the development of effective, rational therapeutic management of its clinical symptoms an arduous task. Although the concept of targeting PDE2 for the treatment of HF is still immature, the findings of Vettel et al.19 do point to a new direction for therapeutic strategy to protect ventricular arrhythmia during excessive sympathetic stress and improve ventricular function after severe cardiac insults via cGMP-activated cAMP inhibition by PDE2. Because the hitherto available therapies against HF and prevention of sudden cardiac death are only moderately efficient, an augmentation of expression or enzyme activity of PDE2 may offer a potentially promising option in the development of new HF therapy.

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References


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