Cyclic Adenosine Monophosphate in Acute Myocardial Infarction With Heart Failure
Slayer or Savior?
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The prevailing notion is that increased myocardial cAMP in settings of acute myocardial ischemia is detrimental. In fact, β-adrenergic agonists that increase cAMP formation disrupt perfusion-contraction matching and promote infarction in controlled animal models of myocardial ischemia, both by increasing myocardial energetic requirements and by an unfavorable flow redistribution away from the ischemic subendocardium. Apart from increasing infarct size, cAMP promotes ventricular tachyarrhythmias in ischemia/reperfusion. Although increased cAMP acutely increases left ventricular function in heart failure, most trials with either β-adrenergic agonists or PDE inhibitors have revealed increased mortality, possibly secondary to tachyarrhythmias.1

The present article by Takahashi et al5 challenges the concept that cAMP in subacute myocardial infarction with heart failure is bad. They subjected transgenic mice with cardiac-directed overexpression of AC VI to permanent coronary ligation and found 17-fold–elevated AC protein content and 4.3-fold–increased cAMP formation, along with reduced mortality, over a 1-week observation period. The reduced mortality in the AC VI–overexpressing mice was associated with a nonsignificant increase in ventricular extra-systoles but reduced bradyarrhythmias. The better conduction properties in the AC VI–overexpressing mice were not mechanistically explained but are possibly related to connexin 43 expression, which is reduced in heart failure and increased by catecholamines in a PKA-dependent manner.9 Reduced mortality is a robust and undisputable end point in mice and humans, and in this respect, the present study definitely challenges the established concepts of the role of cAMP in myocardial infarction with heart failure. Infarct size did not differ between AC VI–overexpressing and wild-type mice. Apoptosis was increased in the peri-infarct zone, but there was no difference between AC VI–overexpressing and wild-type mice. Inotropic responses to β-adrenergic stimulation 3 days after myocardial infarction and left ventricular size and ejection fraction after 7 days were better in AC VI–overexpressing than in wild-type mice. Because in the absence of reperfusion the infarct size was 96% of the area at risk and thus complete, the ejection fraction was improved exclusively through improved contractile function of the nonischemic myocardium. Increased phospholamban phosphorylation and sarcoplasmatic reticulum calcium uptake provided a reasonable explanation for such improved contractile function.

When trying to extrapolate the present experimental data to the clinical setting, we must address a number of serious caveats. First, the choice of species is not fortunate in this context. Although the use of transgenic approaches is limited to a few species and is most feasible in mice, mice are notoriously resistant to ventricular fibrillation,10 and as evident in the present study, they develop bradyarrhythmias during myocardial ischemia. Thus, with respect to the risk of ventricular fibrillation and its promotion by cAMP, mice do not reflect one of the most important complications of myocardial infarction.11 The second serious caveat relates to the use of a permanent coronary occlusion model without reperfusion, in which, even in wild-type mice, 96% of the myocardium at risk was infarcted. Thus, promotion of further
infarction by elevated cAMP, which is of major concern in most clinical scenarios of acute myocardial infarction, cannot be reflected in the present model in which there is no tissue left where elevated cAMP might cause further damage. The third serious caveat is the severe left ventricular dysfunction in conjunction with an observation period of only 1 week. Symptomatic benefit in patients with short-term treatment with either β-adrenergic agonists or PDE inhibitors that increase myocardial cAMP is well established but typically is not sustained. Thus, with a longer observation period, the beneficial effect of AC VI overexpression also might be gone. On the other hand, a longer observation period is relevant only to those individuals who survive the first week after myocardial infarction.

Interestingly, the authors confirm in their model that nonselective β-blockade, which would be expected to reduce myocardial cAMP levels, also is protective in terms of both left ventricular function and mortality, and this finding corresponds to studies in patients with acute myocardial infarction and heart failure. Apoptosis was not different, thus excluding PKA-independent apoptotic pathways of β-adrenergic stimulation that might be antagonized by propranolol and provide a mechanism for its beneficial action. The authors present no other mechanistic data for this subset of the study. Importantly, what did cAMP do in this particular setting? Theoretically, it is possible that β-blockade through reduced PKA activity and attenuation of the above feedback regulation actually resensitized Gas/AC and made it responsive to nonadrenergic receptor stimulation, eg, by histamine and its inotropic action. However, such resensitization of Gas/AC and sensitization to other Gas-coupled receptors than the β-receptors are not observed in AC VI–overexpressing adult rat cardiomyocytes. Clearly, the β-adrenergic receptor/Gas/Gαi system is dynamically regulated. β-Adrenergic receptor occupation renders the receptor susceptible to becoming a substrate for PKA and G-protein–coupled receptor kinase-2 (GRK2), and GRK2 is upregulated in chronic heart failure. In addition, Gαi is upregulated by β-adrenergic stimulation in chronic heart failure. Because these secondary changes have not yet been studied after myocardial infarction, it is an interesting speculation that β-adrenergic receptor–dependent (catecholamine-mediated) and –independent (mediated by AC VI overexpression) increases in cAMP result in different changes in β-adrenergic signal transduction beyond β-receptor occupation. Thus, depending on its source, cAMP can signal via GRK2 or Gαi to mediate different molecular outcomes. Most interestingly, all data on apoptosis and ventricular function in the present study would suggest that overexpression of AC VI and β-blockade may be additive in providing protection, although none of these data were significant because of the small sample size and the underlying cellular mechanisms were not studied.

The most attractive, although somewhat speculative, concept to explain the data of the present study is that it matters through which AC isoform cAMP is formed and through which PDE isoform it is degraded; in addition, its subcellular localization and its accordingly different targets matter. Although not reported in the present study, there is indeed good evidence for AC- and PDE isoform–dependent regulation and differential subcellular localization of cAMP. In particular, there appears to be a compartment of cAMP that is close to the sarcolemma, in close proximity to β-adrenergic receptors and under the control of PDE isoform 2 or 4 in rat cardiomyocytes, whereas PDE 3 is localized to internal membranes and PDE 5 controls a soluble pool of cAMP. A recent study demonstrated colocalization of Gas, AC, PKA, and L-type calcium channels in caveolae of mouse cardiomyocytes. In addition, AC VI is localized to caveolae. Further localization of the action of cAMP is possible by local pools of PKA through their association with PKA–anchoring proteins. Finally, specific PDE isoforms appear to control the cAMP-mediated responses to activation of specific membrane receptors. The PDE 5 inhibitor sildenafil decreases infarct size, and this protection is associated with increased myocardial cyclic guanosine monophosphate and reduced cAMP levels in isolated rat hearts. On the whole, the by-now well-founded concept of localized signaling through cAMP provides an attractive avenue for more specific drug therapy and, in the present study by Takahashi et al, provides a potential explanation for an additive protection by AC overexpression and propranolol.

These mechanistic data and ideas have found their clinical counterpart in a revival of inotropic therapy of heart failure when added to β-blockade. In particular, a case has been made for adding PDE 3 inhibition to β-blockade to eliminate the proapoptotic β1-adrenergic signaling but retain the stimulatory action of cAMP on sarcoplasmic reticulum function. Unfortunately, the recent data of the Studies of Oral Enoximone Therapy in Advanced Heart Failure (ESSENTIAL) on combined enoximone and β-blockade in patients with advanced heart failure revealed no benefit in terms of mortality and hospitalization. Whether there is a role for PDE 5 inhibition with sildenafil in heart failure, apart from its effects on vasomotor tone, is not yet clear.

In conclusion, the article by Takahashi et al is important because it challenges current concepts on cAMP in myocardial infarction and heart failure. Confirmation in other models, rigorous characterization of underlying mechanisms, and long-term observations of outcome are needed to judge the potential value of this novel therapeutic approach.

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Drs Heusch and Böhm have served on speakers’ bureaus for AstraZeneca, Merck, Menarini, Sanofi-Aventis, and Servier. Dr Leineweber reports no conflicts.

References


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