AMP-Dependent Protein Kinase Activators
Not Just for Diabetes?

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A patent inability to properly use glycolytic and fatty acid substrates and progressive insulin resistance characterize non–insulin dependent diabetes mellitus. Curiously, the failing myocardium may also share these unfavorable characteristics. Insights from the clinical arena indicate a significant relationship between insulin resistance and New York Heart Association heart failure classification. In fact, insulin resistance may beget heart failure and heart failure may beget insulin resistance. Fueled by a recent resurgence in studies of the metabolic derangements contributing to cardiovascular disease, we are beginning to comprehend the complexities of metabolism or at least appreciate the bounds of our ignorance.

Our understanding of such issues surrounding diabetes and heart failure is predicated on identifying the proximal regulators of substrate availability, sensing, and utilization. One potentially satisfying candidate appears to be AMP-dependent protein kinase (AMPK) and is the focus of the study by Gundewar et al in this issue of Circulation Research.

AMPK has emerged as a principal figure in the story of metabolic regulation and dysregulation in diabetes, exercise, and, to a lesser extent, myocardial ischemia. AMPK activation appears to be beneficial in the context of myocardial ischemia and reperfusion, at least in terms of infarct size reduction. Such findings are confirmed by the present and previous studies. However, the intriguing element of the present study is the significant effect of chronic, postischemic metformin treatment with the AMPK-activating biguanide metformin in the context of the failing heart (Figure). Despite a prior contraindication for heart failure because of concerns about the generation of lactic acidosis, interest has been renewed (although it actually never waned for some determined investigators) for the potential use of the insulin “sensitizer” metformin in diabetics with heart failure. Such interest is based not simply on the pretext that metformin should mitigate the severity of the diabetic endocrine defect. Again, there may be significant interplay between diabetes and heart failure with common ground in the insulin resistant heart. A recently initiated and ongoing clinical trial (TAYSIDE) is directed at understanding the precise role of metformin treatment in the failing, insulin-resistant heart (ClinicalTrials.gov identifier NCT00473876).

In the present study, the authors evaluate the efficacy of metformin in attenuating the severity of infarct-induced heart failure in reperfused and nonreperfused nondiabetic mouse models.

So, how does metformin promote such beneficial effects during experimental myocardial infarction and heart failure? Metformin exerts an infarct sparing effect, even if given at reperfusion, and seems to require an AMPK–endothelial nitric oxide synthase (eNOS) axis. One might argue that reduction of infarct size would be sufficient to improve long-term cardiac function, but the data of the authors do not support such a contention. First, the data from the nonreperfused model show no difference in infarct size, yet, a significant improvement in survival. Second, the reperfused model shows a significant reduction in infarct size with a single early reperfusion dose of metformin without any functional improvements after four weeks. In additional groups of mice, daily postischemic metformin treatment significantly improved cardiac function at four weeks. This tells us that infarct size reduction in the murine model may not necessarily predict chronic improvements in cardiac function but, more importantly, that metformin can improve cardiac function in a nondiabetic and dysfunctional heart.

One question that remains unanswered is how metformin activates AMPK. Others have demonstrated the pharmacological capacity of metformin to impair complex I in the mitochondria. Such an effect might elevate cytosolic AMP levels and consequently enable activation of AMPK by an upstream kinase, although others have proposed unrelated mechanisms of AMPK activation by metformin. What is clear from the present study is the obligatory nature of intact AMPK activity to generate the benefits of metformin in the failing heart. The specific requirement of cardiac AMPK suggests that the relevant effects of metformin may not be entirely systemic in the present in vivo model. Metformin treatment could improve cardiac metabolism thereby improving cardiac function and potentially do so in the absence of extracardiac effects. Mitochondria isolated from infarcted, metformin-treated hearts respiring on succinate produced more ATP at a lower oxygen cost than vehicle, consistent with improved coupling of oxidative phosphorylation. It is not clear why the metformin mitochondria were more efficient than the vehicle group, but the finding that PGC-1α was elevated yields at least one clue. Based on work from Kelly and colleagues and Spiegelman and colleagues, we know that deficiency of PGC-1α exacerbates the development of heart failure in mice and that PPAR/PGC activities are largely reduced in heart failure. In the study by Gundewar et al, the authors find that chronic metformin therapy boosts PGC-1α levels while improving ventricular function. Although the

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authors did not investigate the activity of PGC or downstream dependent target message levels, the authors did provide a surrogate of one of the effects of PGC: mitochondrial function. One could argue that such beneficial changes resulted from other mechanisms of heart failure attenuation, but most germane is designing appropriate experiments to address this possibility in future studies.

On a related note, AMPK may function as a positive regulator of GLUT4 vesicular trafficking to the sarcolemmal surface. Evaluating expression of GLUT4 is difficult because it typically resides in intracellular vesicles, which on stimulation by AMPK, translocates to the cell surface. In this regard, AMPK is a positive regulator of glucose uptake in the myocardium. Invoking the myocardial insulin resistance hypothesis, one should recall that various models of heart failure (and diabetes) are characterized by suppression of GLUT4 transport activity. For the heart, such negative regulation of glucose transport carries significant consequences because GLUT4 is the primary glucose transporter in the heart. Thus, the effects of AMPK on metabolism may be manifold, particularly in the dynamic and complex setting of heart failure.

Work from Seidmans and colleagues adds another wrinkle and offers the hypothesis that alterations in glycogen storage could potentially explain some of the present protective effects of AMPK activation. It is possible that during heart failure, augmented glycogen stores could serve as a metabolic buffer during acute periods of cardiac dysfunction or increased metabolic demand. Gundewar et al did not measure glycogen levels in the metformin treated group, but this and other questions are worthy of future investigation. This brings up important questions, such as: How narrow is the dosage window for metformin treatment in heart failure? Is there a higher dose that produces excessive/pathological AMPK activation? Although the present study used quite low doses of metformin, such issues are not trivial considering insights from the AMPK-overexpressing mice, which develop pathological glycogen storage disorders and electric abnormalities.

Clinical data exist to suggest improvements in vascular tone in patients treated with metformin. However, it is difficult to separate the effects of the endocrine improvement of diabetes from the tissue specific effects in patients. The use of nondiabetic mice in the present study seemingly rules out the possibility of protection secondary to alterations in the central endocrine disorder of diabetes. To support such a notion, the authors found no alterations in circulating blood glucose, although glucose clamp studies would provide more direct insight. Nevertheless, this emphasizes an important, although seemingly pedestrian, point in the face of complex
metabolic interactions: favorable alterations in vascular tone could be sufficient to explain the protective capacity of chronic metformin therapy. Such hypotheses are particularly worthy of investigation considering the finding of the authors of eNOS phosphorylation at Ser1177, which implies eNOS activation. If this were simply a nitric oxide story, one could invoke the numerable and salubrious effects of nitric oxide in the cardiovascular system.1,4

What happens with the upstream regulators of AMPK, such as LKB1, during heart failure? Although there are some related insights in the acute, isolated heart, little is known about chronic alterations in LKB1 during heart failure. Conventional wisdom holds that changes in LKB1 activity may be unlikely because LKB1 activity is primarily, although indirectly, regulated at the level of AMP. That is, AMP binding to AMPK (α subunit) favors phosphorylation of LKB1 at Thr172 of AMPK and consequent activation, while antagonizing phosphatase activity at the same site. Calcium dysregulation features prominently in the chronically failing heart. Therefore, is it possible that calcium-driven alterations in another AMPK kinase (eg, CaMKK) activity could also influence AMPK activity in the failing heart? Although related questions have been partially addressed by others during acute ischemia of isolated hearts,15 much remains to be discovered regarding the molecular regulation of AMPK, particularly in the chronic context of heart failure.

Clearly, important questions abound. Could AMPK activators represent a novel approach to treating heart failure in the nondiabetic?

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References

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