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Perspective

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Computational/Experimental Interrogation of the Failing Heart—A Perspective on "Impaired Myocardial Energetics Causes Mechanical Dysfunction in Decompensated Failing Hearts"

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The article by Lopez et al. "Impaired Myocardial Energetics Causes Mechanical Dysfunction in Decompensated Failing Hearts"[1] contributes importantly to our understanding both conceptually and experimentally. Using a rodent model of heart failure produced by transverse constriction of the aorta (TAC), the authors have provided strong evidence that with the reduction of adenosine triphosphate (ATP) and adenosine diphosphate (ADP) in the failing heart, there was a compensatory buildup of inorganic phosphate (Pi). Associated with these changes, metabolic substrate switching was observed with a 24% reduction in the ratio of maximal capacity to oxidize fatty acids to the maximal capacity to oxidize carbohydrates. Targeted metabolomic profiling identified pyrimidine and purine metabolism significantly altered in the heart of TAC rats with increase in adenosine and adenine. This is consistent with an increase in the rate of purine nucleotide degradation via the 5'-nucleotidase activity and an increase in uric acid, hypoxanthine, and purine nucleotide degradation via the adenosine monophosphate (AMP) deaminase pathway.

As emphasized by the authors, the mechanistic link between these altered metabolites and the mechanical functions of the heart has remained poorly understood. A major contribution of the present study was the quantitative determination of the effects of these metabolic changes upon the left ventricular power output (LVPO; e.g. external work). A 26% greater work was found to be required by TAC rats to pump blood through the aortic constriction. The resting LVPO was strongly correlated with oxidative ATP synthesis capacity in the TAC rats indicating that myocardial metabolic dysfunction was indeed the cause of the mechanical dysfunction. Previous simulation studies from the Beard group[2,3] and others[4] have predicted that deleterious changes in these phosphate metabolite levels can cause mechanical dysfunction in heart disease. The results of the present study greatly strengthen the credibility of those predictions and fill a gap in our understanding of the relationship between altered metabolism and reduced cardiac contractility in heart failure.

Although the experimental studies alone represent an important contribution to this field, the most distinguishing aspect of this study comes from the sophisticated application of computational modeling upon which the hypothesis was developed, and the experimental studies were designed and analyzed. Given the interdependence of cellular processes, measurement of a change in one or more of these cellular processes in response to a pathological state is not sufficient to predict the impact of this change on overall cell and organ function. Integrated computational modeling provides a mechanistic and quantitative framework to obtain and predict such outcomes. The essential feature of computationally based models is that they enable computation of variables that are difficult or impossible to measure experimentally and allow for prediction of effective intervention outcomes. The application of integrative

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multi-scale simulations to analyze the mechanistic actions of changes in ATP, ADP, and Pi levels on myocyte cross-bridge kinetics, muscle dynamics, and whole-organ pump function in individual animals represents an important contribution to the field.

The accuracy of such predictions of course depends upon the fidelity of the data utilized to parameterize the model equations that are developed. The multi-scale computational modeling carried out as part of this study was developed as modules utilizing data and models published by many laboratories as referenced by the authors[5,6]. This has provided a unique quantitative and mechanistic framework upon which complex relationships can be predicted and experimentally tested. The different components of the overall system illustrated in figure 1 of Lopez et al.[1] were modularly developed and scaled to determine the effects of alterations of myocyte metabolic function upon whole-organ metabolic function, and the computation of these effects drove the module that determined the emergent properties of cardiac ventricular function including the ventricular–ventricular mechanical interactions and the related stress-strain relationships of the intact heart. The modules representing the metabolic functions of the cell were represented in great detail which is the strongest aspect of this analysis. The high-level circulatory module was represented in simplest terms as a closed-loop lumped parameter model containing a heart, lung, and associated arterial and venous resistance and compliance vessels.

As with all models, there are naturally defined limitations which must be clearly recognized. A weakness of the current analysis is the very simplified representation of the pulmonary and systemic circulation. The current model therefore does not enable predictions of sequential cause and effect changes that are dependent upon mass balance of body fluids and electrolytes and the distribution of blood flow and body fluids. Such alterations would drive changes in pre-load of the heart leading to changes in energetics and failure of the right heart. Nevertheless, if used within the context of the limitations of the model presented in this manuscript, many important mechanistic details linking metabolism and cardiac function can be explored.

The utility of this combined experimental-computational approach is nicely demonstrated in figure 8 of Lopez et al.[1] describing data on myocyte phosphate metabolite pools and mitochondrial oxidative capacity which were utilized in the model of myocardial energetics to thereby predict the cytosolic ATP, ADP, and Pi concentrations. By comparing the energetic phenotypes of the sham rats to those of the TAC heart failure rats, the causal relationships underlying these predictions were determined. The relevance of these predictions to the clinical world is apparent as it is shown that in silico restoration of the normal energetic profile of a failing heart resulted in a restoration of normal feedback control of myocardial ATP synthesis which in turn reduced the injurious elevations of [Pi] thereby improving cardiac systolic function. Since, as the authors point out, there are many commonalities between the TAC rat model and the failing human myocardium, it is reasonable to propose that restoration of these depleted metabolite pools in rats may translate to humans. It is predicted that inhibition of AMP deaminases and 5'-nucleotidases to slow the degradation and depletion of adenine nucleotides and increase AMP-mediated signaling would be prime targets. Indeed, it has been found that a polymorphism of AMP deaminase 1 gene (AMPD1), a common variant of the gene may provide benefit to patients with heart failure and ischemic heart disease.[7–10] However, care must always be taken to not extrapolate predictions of a model beyond the data elements upon which it was built. The current model does not contain the element of chronicity and therefore cannot predict possible long-term effects of these metabolic energy pools upon the function of the heart. Although the current evidence from genetic, clinical, and biochemical studies indicate that short-term protection may be provided, it has been found that long-term attenuation of AMP deaminases may be deleterious indicating that more complicated mechanisms become involved in the chronic state that are not included in the model.

Conflict of Interest

None declared.

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