ABSTRACT FACE PAGE

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TRAINEE POSTER AND ORAL PRESENTATION COMPETITONS:

New to the meeting this year, we are holding *both* a trainee poster competition and a trainee oral presentation competition! If the presenting author is a trainee (i.e., a student at any level or a post doctoral trainee), he/she may enter his/her abstract in the trainee poster competition, the trainee oral presentation competition, or both competitions. Trainees may also submit more than one abstract to the meeting and enter more than one abstract in these competitions. Prizes will be given to the presenters of the top-ranked trainee oral presentation and the top-ranked trainee poster (judged during the meeting by the Program Committee).

13. **If the Presenting author is a trainee, would the Presenting Author like to enter his/her abstract in the Trainee Poster Competition*? Yes or No**

*Note: Trainees who enter the poster competition are expected to stand by their poster during the scheduled poster sessions and present them to the judges.

14. **If the Presenting author is a trainee, would the Presenting Author like to enter his/her abstract in the Trainee Oral Presentation Competition**? Yes or No**

**Note: The Program Committee will select the top four abstracts from trainees who elect to enter their abstract into the trainee oral presentation competition, these four trainees will be notified by Feb. 17th, and they will deliver their oral presentations (which will be judged) on the second day of the meeting after lunch.

A COUPLED MULTISCALE ELECTROMECHANICAL MYOCYTE MODEL TO ASSESS THE EFFECTS OF 2-DEOXY-ATP ON CONTRACTILE FUNCTION IN THE HEART

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INTRODUCTION: Heart failure remains a significant cause of morbidity, mortality, and medical costs worldwide. It is characterized by reduced contractile function and inability of the heart to pump sufficient blood to meet the body's demands. 2-deoxy-ATP (dATP), a novel heart failure therapeutic, has been shown to improve contractile function without impairing relaxation when present in elevated levels in the heart [1]. Previous studies have shown that dATP acts on myosin to increase the rate of crossbridge cycling [2]. It has also been shown that dATP increases the rate of Ca^{2+} transient decay [3]. We hypothesized that dATP may act on the sarcoplasmic reticulum ATPase (SERCA), the pump responsible for removing calcium (Ca^{2+}) from the cytosol after contraction, which could explain this increased Ca^{2+} decay. However, the mechanisms of dATP are still not fully understood, and it may have multiple targets in the myocyte. Since it is difficult to fully assess these mechanisms experimentally, we developed a novel multiscale modeling approach to investigate whether the effects of elevated dATP on myosin and SERCA are sufficient to explain its therapeutic effects.

METHODS: The multiscale modeling framework developed in this study includes computational techniques at the atomic, molecular, and whole cell levels. Gaussian Accelerated Molecular Dynamics (GaMD) simulations were utilized to assess the effects of dATP on SERCA conformation. Brownian Dynamics (BD) simulations were then utilized to determine association rates for dATP binding to SERCA and Ca^{2+} binding to dATP-SERCA using the lowest energy structures determined from the GaMD simulations [3]. BD simulations were also used to determine the association rate between ADP-myosin and actin based on previous MD studies [2]. We then utilized a myocyte model containing several ion channels including SERCA to assess the effects of elevated dATP on Ca^{2+} handling [3]. We also coupled the myocyte model to a Markov model of crossbridge cycling, which captures regulation of contraction via Ca^{2+} [2]. Rate constants determined from the BD simulations were input into the SERCA and sarcomere models to simulate dATP treatment.

RESULTS: We found that dATP causes separation of the cytosolic domains of SERCA, which could indicate increased pump speed. We also found that the association rate for dATP binding to SERCA was 80% higher than the association rate for ATP binding to SERCA due to stronger interactions in the nucleotide binding pocket. The association rate for Ca^{2+} binding to SERCA was also increased, which is likely due to altered electrostatic interactions in the transmembrane region. Further, we found that the combined effects of elevated dATP on both SERCA and the sarcomere were necessary to explain both the increase in fractional shortening and time to 50% and 90% decay of the Ca^{2+} transient seen experimentally. However, we were not able to fully predict the experimental dATP Ca^{2+} transient by altering SERCA parameters alone. We were able to more closely match this data by optimizing parameters for the sodium-potassium ATPase and the plasma membrane ATPase, suggesting that dATP may also affect other ATPase pumps.

CONCLUSIONS: This study affirms dATP as a promising treatment for heart failure and suggests that the therapeutic effects of elevated dATP likely depend on its effects on both myosin and SERCA. Our analysis indicates that this occurs via enhanced SERCA pump function and increased rates of dATP and Ca^{2+} association due to altered electrostatic interactions, which leads to faster Ca^{2+} transient decay. This mechanism may be generalizable to other ATPases, and additional work is needed to determine if this is the case. The novel multiscale modeling framework developed in this study allows for assessment of function from the atomic to cellular levels, and extending our model to the tissue and organ levels in the future will allow for investigation of the regional effects of elevated dATP on overall cardiac function.

REFERENCES:

1. Thomson et al. *JACC Basic Transl. Sci.* **1**(7): 666-679, 2016.
2. McCabe et al. *Proceedings of Biophys. Soc. 62nd Annual Meeting*, San Francisco, CA, USA, 2018.
3. McCabe et al. *Proceedings of Biophys. Soc. 64th Annual Meeting*, San Diego, CA, USA, 2020.

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