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Letter by Teerlink et al Regarding Article, "The Myosin Activator Omecamtiv Mecarbil Increases Myocardial Oxygen Consumption and Impairs Cardiac Efficiency Mediated by Resting Myosin ATPase Activity"

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We reviewed the paper, "The Myosin Activator Omecamtiv Mecarbil Increases Myocardial Oxygen Consumption and Impairs Cardiac Efficiency Mediated by Resting Myosin ATPase Activity,"[1] with interest because its conclusions differ from our work published in this same journal[2] and elsewhere.[3] We commend the authors for pursuing an important question related to an investigational drug being studied in patients with systolic heart failure. However, we believe deficiencies in their experimental approach undermine their conclusions.

First, despite the title of the manuscript, there was no statistically significant difference in directly measured myocardial oxygen consumption preceding and following omecamtiv mecarbil administration (Table 2[1]). In contrast to the prior work in a conscious dog model of heart failure,[2] the authors studied animals under acute anesthesia in which 30% of the animals had to be excluded due to hemodynamic collapse. A critical placebo control group to determine effects of change in hemodynamic status over time was not performed. Without such a control, one cannot disentangle the effect of time from the effect of the drug.

Second, to assess the pressure-volume-area oxygen consumption relationship, the investigators reduced preload in a graded manner; in doing so the investigators appeared to reduce cardiac stroke work to near zero. It is difficult to understand how this was achieved,

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and why this maneuver, performed twice during the experimental protocol, would not itself alter energetics. It would seem quite difficult to sustain such marked preload (and thus stroke work) reduction for any time at all without substantial sympathetic activation or inducing ischemic damage. Even prior to performance of these maneuvers in the healthy animals, increases in both heart rate and dP/dt occurred in the first 20 minutes before omecamtiv mecarbil administration. In fact, dP/dt continued to rise during drug administration, something not observed in prior studies. The authors attributed this to the drug, but without a placebo control, this conclusion cannot be made.

Third, the conclusion that omecamtiv mecarbil increases resting myosin ATPase is contradictory to the finding that omecamtiv mecarbil inhibits the non-actin dependent myosin ATPase in purified systems.[3,4] The authors instead use whole hearts subjected to cardioplegia in which the activation state of the sarcomere is not well defined and calcium concentrations in the myocyte are unstable.[5] Even modest changes in basal calcium will result in sarcomere activation by omecamtiv mecarbil rendering measurements of a basal state inaccurate and uninterpretable.

Finally, the authors employed a dose of omecamtiv mecarbil that is 3-fold higher than the highest doses studied in humans. Assuming infusions were administered correctly (dose reported is in mg/kg/min in abstract and mg/kg/h in methods), the selected dose (0.92 mg/kg/20 min) was nearly 3-fold higher than that employed in conscious dogs (0.33 mg/kg/20 min)[2] and the maximum dose-rate studied in humans (~0.33 mg/kg/20 min).[6] Currently, considerably lower doses are being pursued in the ongoing clinical development program. Since plasma concentrations of omecamtiv mecarbil were not measured, the relevance of the dose studied to the doses now being employed in humans cannot be assessed.

Based on these concerns, we believe this study, with its design limitations and absence of necessary controls, could not adequately address the important hypotheses proposed by the authors and thus does not support their main conclusions.

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