Response to Letter Regarding Article, “Myosin Activator Omecamtiv Mecarbil Increases Myocardial Oxygen Consumption and Impairs Cardiac Efficiency Mediated by Resting Myosin ATPase Activity”

We certainly appreciate the swift response1 from the group of scientists who have put so much work into the development of omecamtiv mecarbil. Their joint effort is remarkable.

However, as Malik and Morgan have stated previously “…omecamtiv mecarbil might increase ATP turnover at the level of the sarcomere…”2 this is clearly demonstrated in Figure 4D of their article. Thus, the main aim in our study3 was assessing this aspect’s impact on cardiac efficiency. A study in conscious dogs4 has demonstrated that the advantage of minimizing surgical and pharmacological interventions, but it precludes the ability to decipher the relation between contractile work and energy consumption. In our view, the Suga-model we have used in the pig studies, the isolated heart, and mitochondrial model fills in some of the missing aspects.5 We cannot see that the concerns raised by Teerlink et al would hamper our conclusions.

First, a general statement of increased oxygen consumption from our study6 is supported by the fact that this was measured in the unloaded mouse heart. Also, calculation of unloaded MVO2 in the pig heart (Y-intercept, Table 2) has few assumptions given the downloading protocol used. All exclusion of pigs (ie, sustainable ventricular arrhythmias causing hemodynamic collapse; 3/19=16%) occurred before inclusion in the protocol. After ischemia and stabilization, this model shows remarkably stable hemodynamics.6 This referred study also has the requested placebo controls, demonstrating a stable myocardial energetics for the extent of the study period.

Second, the model tolerates hemodynamic downloading well, as demonstrated,7 probably because of the anesthetic protocol. No significant alterations in heart rate or dP/dt were observed after infusion of omecamtiv in the postischemic pigs.

Third, we can only state that our observation in whole hearts is compatible with a continuous activated myosin ATPase, supported by the 2,3-butanedione monoxime experiment. We appreciate that the authors have split myosin and actin in their in vitro assay, but the integrated effect of omecamtiv seems to be an increased ATPase activity.8

As for the dose used, we did a dose–response study along the lines described by the respondents, aiming at an increased systolic ejection time of 20% that is suggested to be clinically safe.9 Of notice, the drug was used for the first time in pigs. We apologize for the error in the abstract.

We will maintain that our study raises concerns about the energetic effects of omecamtiv mecarbil. In fact, we previously only observed such an extensive energy wastage by blocking NO using L-NG-nitroarginine methyl ester motivated by the TRIUMPH (Tilariginine Acetate Injection in a Randomized International Study in Unstable MI Patients With Cardiogenic Shock) investigation of tilarginine.10

Disclosures

None.

References


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