Response to Letter Regarding Article "Cardiac Energetics in Patients with Aortic Stenosis and Preserved versus Reduced Ejection Fraction"

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We appreciate the interest and comments by Mahmood in regards to our recent article (1). In this study we have shown not only that cardiac energetics are impaired early in the aortic stenosis (AS) disease process, being present in a group of patients with moderate aortic stenosis, but also that transition to systolic failure in severe AS is not dependent on further energetic decline. Whilst Mahmood points out correctly that energetic impairment was not a "necessary correlate of systolic failure as assessed by LV ejection fraction (LVEF)" this does not imply that it is unrelated. We would like to clarify that as ATP demands increase with AS severity, a reduction in the capacity to deliver ATP to the myocardium, as established early in the process of AS, could increase susceptibility to systolic failure when the increasing ATP demand exceeds supply.

We entirely agree that LV strain is a valuable measure in AS, and related to mortality. We would simply point out that this study already presents data showing cardiac magnetic resonance derived global circumferential strain is related to biopsy derived CK capacity ($r = --0.52$, $p = .001$, Figure III in the supplemental data). Whether CK capacity is related to mortality in AS, as it is in heart failure (2) remains unknown.

Whilst Mahmood is also correct that in this study "myocardial energetics assessed by phosphocreatine to adenosine triphosphate ratio were lower in severe AS with reduced LVEF than in the non-pressure loaded heart" but were "not different compared with severe AS with preserved LVEF" we would like to elaborate on two points. Firstly, the PCr/ATP measurement is a reflection of metabolite pool size, and as such a reduced PCr/ATP is, in the absence of heart failure, reflective of decreased PCr pool size. However, as ATP levels are known to be lower in heart failure, (3) a pseudo normalisation of PCr/ATP occurs, making comparison across groups more complex. As flux through the CK system is arguably a more important variable than metabolite pool size alone, this was the rationale for this study measuring both creatine kinase (CK) k_f and CK total unidirectional forward flux, (4) in addition to simply PCr/ATP.

We agree that correlating echocardiography derived strain with energetics is a sound idea, and that investigation of the role of energetics in timing surgical intervention, is also worthy of investigation. We would however highlight that whilst ^{31}P-MR spectroscopy is currently the only non-invasive way of measuring myocardial energetics, it suffers from low sensitivity and signal-to-noise ratio, and currently available techniques lack the sensitivity to reliably discern individual

patient variations. With recent advances in ultra-high field ^{31}P MRS, (5) individual patient assessment of energetics, including Gibbs free energy of ATP hydrolysis and the dynamics of the ATP synthesis and hydrolysis in the human heart *in vivo* are now becoming possible.

Disclosures Statement

The authors have no relationships to disclose.

References

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