Authors response to letter from Koutroulis et al. JASE-8554: Concerning "Left Atrial Function Is Associated with Earlier Need for Cardiac Surgery in Moderate to Severe Mitral Regurgitation: Usefulness in Targeting for Early Surgery"'

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We would like to thank Koutroulis and colleagues[1] for their kind comments regarding our paper[2], and welcome the opportunity to discuss the points they raise. Specifically, they suggest that speckle strain indices of the left atrium are reflective of the degree of tissue remodeling in the stretched left atrium (LA), and propose that the primary abnormality is dilatation of the LA, which subsequently results in impaired LA deformation.

We wonder whether there was a misunderstanding on the part of Koutroulis and colleagues. In our original manuscript, we stated 'contractile and reservoir strain of the left atrium display subtle early alterations that precede the development of clinical or classic echocardiographic features that mandate *intervention'.* We did not state that changes in LA deformation indices preceded *remodeling* of the left atrium, as they appear to be implying in their letter.

In actual fact, we agree entirely with Koutroulis and colleagues: without doubt, abnormal or impaired left atrial deformation is a *consequence* of left atrial remodeling and dilatation. In the context of chronic mitral regurgitation (MR), LA enlargement is itself proportional to the volume of MR, but also likely reflects alterations in left ventricular (LV) compliance.

Whilst we do not disagree with Koutroulis and colleagues in this regard, we would assert that the assessment of LA function provides additional information to the clinician, rendering it superior to an isolated assessment of LA volume when assessing patients with MR.

Fundamentally, we believe this scenario is similar to that which is seen with the left ventricle: patients with reduced LV ejection fraction often have increased left ventricular volumes. However, cardiologists do not make decisions regarding management of heart failure based solely on the LV size, and 'disregard' the ejection fraction. Similarly, an assessment of LA function can provide information above and beyond that which can be garnered from a simple assessment of LA size.

If we were to take the example of athletes, or individuals who participate in competitive sport: it is well recognized that such individuals may have LA volumes that exceed that expected in a normal population[3]. In this situation, there is physiological remodeling of the left atrium, which is *not* associated with reduced LA deformation[4]. In such a scenario speckle strain imaging of the LA provides better differentiation between pathology and physiology.

Even within a non-athletic population, we would suggest that the discriminatory ability of LA volume alone is perhaps not as clear as may be expected. Historic studies have clearly demonstrated that increasing LA size is associated with progressively poorer survival[5]. In an unselected population, Tsang et al demonstrated that individuals with an LA volume greater than 40ml/m^2 (obtained using the biplane area-length method) have the worst survival[6]. Recent data from the Normal Reference Ranges for Echocardiography (NORRE) study (which excluded athletes from data collection) has shown that within a healthy population, the upper reference limit of LA volumes derived using the

biplane area-length method is up to 42ml/m^2[7]. This latter observation would appear challenging to rationalize given the historic Tsang data. We suggest that the likely explanation for this is that there is substantial overlap between physiological and pathophysiological LA remodeling and volumes.

Ultimately, however, it may be considered clinically irrelevant whether LA deformation is a consequence of LA enlargement or *vice versa*. What is most important for clinicians is the discriminatory ability of any echocardiographic measure at identifying patients who are at risk.

To further support the assertion that LA functional indices have superior clinical value to an assessment of LA volume within the MR population, we have taken this opportunity to provide further statistical analysis of our data. Sequential multivariate cox-proportional hazard models were employed to compare the relative discriminatory value of deformation indices over and above assessment of LA volume (Figures 1a and 1b).

The baseline model incorporated univariate predictors of event-free survival as outlined in Table 2 of our manuscript[2], including: left ventricular internal diameter in diastole (LVIDd), pulmonary artery (PA) pressure, average E/e', and effective regurgitation orifice area (EROA).

The baseline model (Chi-squared 37.2) was improved with the addition of maximal LA volume (Chi-squared 44.4), although the difference was not statistically significant, with a p value for the change of 0.159. Adding contractile strain (Chi-squared 50.0; p=0.021) and subsequently reservoir strain (Chi-squared 61.0; p=0.005) both significantly improved the model (Figure 1a).

Interestingly, an assessment of *minimal* LA volume is superior to *maximal* LA volume in identifying patients at risk for surgery with mitral regurgitation. We believe that this observation further supports the value of LA deformation or functional indices, which in essence describe proportional changes in LA size during the cardiac cycle. Even if we were to include minimal LA volume in the sequential model, however, it is evident that deformation indices are still significantly better at identifying individuals at risk (Figure 1b). The baseline model is improved by the addition of minimal LA volume (Chi-squared 47.6; p=0.05), but further significant increments are noted with contractile strain (Chi-squared 51.1; p=0.044) and then reservoir strain (Chi-squared 61.1; p=0.006).

We would again like to thank Koutroulis and colleagues for their comments. We hope that our response acknowledges that whilst fundamentally we agree with their observation that LA dilatation or remodeling is a key determinant of outcomes within a population with chronic MR, our assertion is that LA functional indices are a far superior method of assessing this remodeling in a clinically relevant, discriminatory and useful way.

Images:

Figure 1: Sequential cox-proportional hazard models demonstrating the incremental discriminatory value of differing echocardiographic markers in the identification of patients with mitral regurgitation who are at risk for surgical intervention. Figure 1a, including maximal LA volume; Figure 1b includes minimal LA volume.

Figure 1a

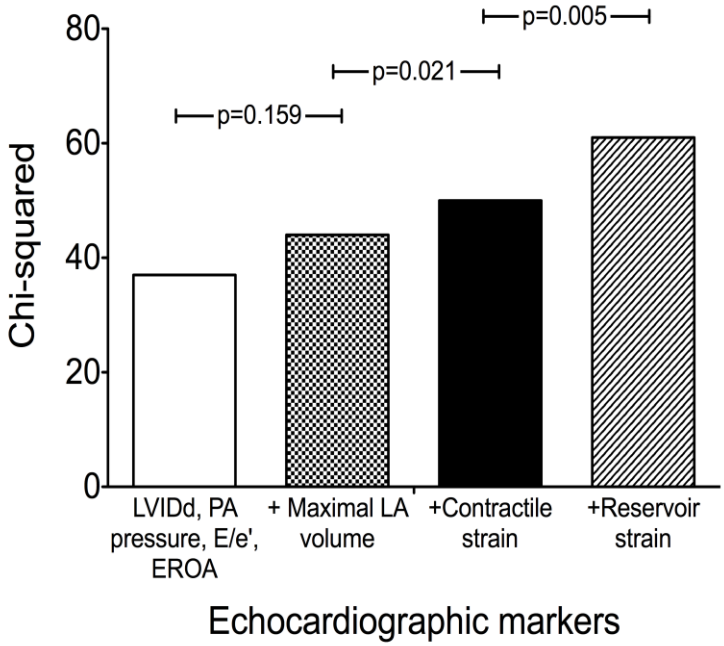
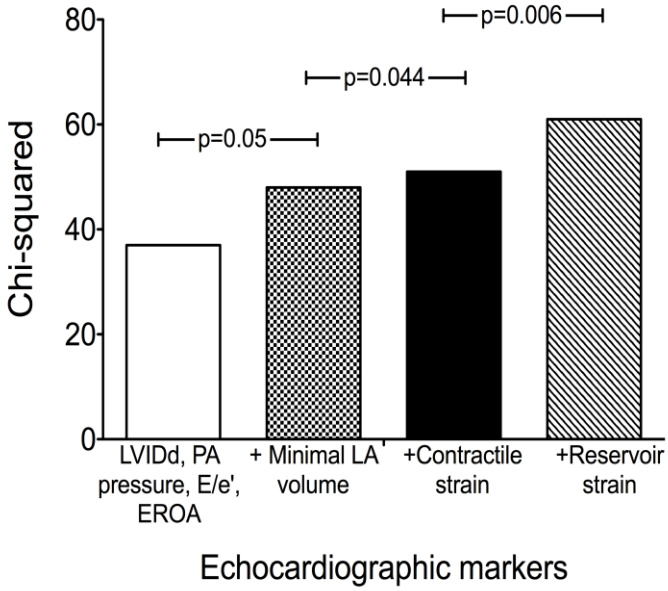


Figure 1b



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