Author’s response to reviews

Title: Regional Myocardial Strain Analysis via 2D Speckle Tracking Echocardiography: [Validation with Sonomicrometry and Correlation with Regional Blood Flow in the Presence of Graded Coronary Stenoses and Dobutamine Stress]

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Author’s response to reviews:

Reviewer #1
1) The clinical impact and contribution of the study appear to be very limited because of the great complexity of the experimental setting.

We acknowledge the complexity of our experimental configuration, but maintain that our unique design provides a more complete evaluation of 2D STE regional strain measurements than previous approaches. In comparison to simpler designs utilizing sonomicrometer pairs or triplets, our sonomicrometer array provides simultaneous, multidirectional strain analysis in multiple regions/vascular territories in the setting of graded stenoses and dobutamine stress. The microsphere flow analysis provides an additional dimension that enriches the physiological and clinical significance of the strain data. As noted on pg. 10 of the manuscript, the 16 crystal sonomicrometer array and associated cardiac and extracardiac reference crystals are designed to reduce sources of error present in simple sonomicrometer configurations by providing substantially greater amounts of data for strain calculations, registration between echocardiographic images and sonomicrometers, and cardiac axis definition. While factors such as instrumentation, mechanical ventilation, and anesthesia can influence strain behavior, we believe these effects are limited and do not impact echocardiographic-
sonomicrometer comparisons because they are equally present in both data sets. In all, we believe that our experimental configuration provides a unique, rigorous, and clinically relevant platform that is highly appropriate for 2D STE software validation as well as investigation of the fundamental interaction between regional myocardial flow and function.

2) The lack of longitudinal strain evaluation in this study could be an important limitation because lower reproducibility and reliability of radial and circumferential strain than longitudinal strain (both global and regional) is just well known, also in human study. We agree that regional longitudinal 2D STE strain data would be useful. However, 2D STE longitudinal strain analysis was not possible in this experimental model because the open chest preparation does not permit standard apical acquisitions for assessment of longitudinal strain. Of note, we did calculate longitudinal strain with the sonomicrometers and intend to apply these data in subsequent analyses of 3D images. Please see below for a discussion of the merits of radial and circumferential strain.

3) The findings of present study could suggest minor clinical usefulness of radial and circumferential 2D STE in the assessment of ischemic heart, given their only moderate correlation with sonomicrometry. We agree that the moderate correlation of regional radial and circumferential 2D STE measurements with sonomicrometer data indicates that these measurements are not optimized for clinical use. This is generally accepted to be true for regional longitudinal strains as well. However, the clinical implications of being able to reliably measure regional strains in any one of the three cardiac directions are substantial and potentially transformative for the field of stress echocardiography. We believe that continuous improvements in acquisition, image processing, and tracking techniques will make regional strain measurements relevant in clinical settings, just as advances in these areas continue to drive the clinical adaptation of global longitudinal strain. At this point, it is premature to conj ect that regional radial and circumferential strains will be less useful clinically than regional longitudinal strains, especially since the current qualitative benchmark of clinical stress echocardiography is wall thickening, an analog of regional radial strain. Preliminary findings from our related, but separate pressure-regional strain analysis of the sonomicrometer data indicate that there are significant differences between ischemic strain patterns in the radial, circumferential, and longitudinal directions. We believe these findings could have important implications in the detection of regional myocardial ischemia and viability, and potentially in other disease processes as well.

4) It could be of interest study finding of non-linear correlation between both radial and circumferential 2D STE and sonomicrometry, and regional myocardial blood flow, measured by microsphere analysis, consistent with previous studies. We agree that the non-linearity of the regional strain-flow relationship is a key finding. This strain-flow relationship was demonstrated in our earlier preclinical work (Am J Physiol. 1992, 262(2 Pt 2):H568-76). It is of general physiologic interest and carries significant clinical implications, especially when considering the relative merits of flow and function measurements in assessments of ischemia and viability. The comprehensive assessment of regional flow and function illustrates the utility of our experimental model and distinguishes it from the majority of other STE strain evaluations, which provide more limited strain information without the benefit of quantitative regional flow analyses.

5) It could be useful for clinically oriented audience that, in discussion, the authors write more considerations about the translation of study results to human clinical scenarios. We agree and have added the following summary of the clinical implications of our findings:
“Our findings contribute to the foundation of knowledge in the developing clinical application of quantitative regional and multidirectional strain analysis. The demonstration of a non-linear relationship between regional myocardial function and blood flow has significant implications when considering the relative virtues of strain and perfusion imaging in clinical assessments of ischemia and viability. In addition, our study provides a rigorous, in-depth evaluation of a clinical 2D STE software package. Our results indicate that 2D STE requires additional refinement before becoming a reliable quantitative clinical technique for measuring regional circumferential and radial strains. Reassessment of FDA-approved clinical software for strain analysis is necessary to determine both clinical merits and limitations.”

Reviewer #2

1) In the methods the authors state that "ED was defined by the peak of the QRS complex on ECG. The systolic cycle length from invasive pressure measurements was used to determine ES". Nevertheless, it is not clear what kind of strain was finally assessed. Did the authors assess end-systolic strain, or peak systolic strain, or peak strain? This should be clarified because it has a pivotal important for data interpretation and also for clinical practice.

End-systolic strain was assessed. This has been clarified throughout the manuscript, including the following additions to the Methods:

Pg. 6:
“End-systolic strains were calculated for each sonomicrometer strain curve.”
“The systolic cycle length from invasive pressure measurements was used to determine ES and aid in the calculation of end-systolic strain.”

2) Previous studies have shown (Voigt JU et al.) have shown that ischemic segments have a particular strain pattern characterized by a delayed strain peak after aortic valve closure. This pattern, called post-systolic shortening, is evident also in your experimental model (Figure 5). The post-systolic shortening phenomenon allows the calculation of the post-systolic index (PSI) that is better correlated to myocardial perfusion/ischemia than peak systolic strain. The authors should assess this parameter and correlate it with myocardial blood flow.

We appreciate the suggestion and have added an analysis of regional PSI and myocardial blood flow, which is summarized in Figure 10, parts e-f. Our data do in fact demonstrate the value of PSI for the detection of regional myocardial ischemia. For both radial and circumferential 2D STE strains in the ischemic region, PSI increased in the presence of moderate stenoses and normalized to lower values with the introduction of low-dose dobutamine.

Pg. 31 (Figure 10): included in attachment

Figure 10, e-f: Comparison of 2D STE post-systolic indices (PSI) and mean regional myocardial blood flow in the ischemic territories: e) radial strains, f) circumferential strains.

3) In the discussion you state that: "The results of the current study and these prior experiments suggest that regional circumferential 2D STE strain measurements correlate and agree with reference sonomicrometer values at levels that are slightly more favorable than regional radial measurements, but inferior to regional longitudinal measurements". Nevertheless, in your study longitudinal strain was not assessed. Please correct this statement accordingly.

We have clarified the statement as noted below:
Pg. 10:
“Longitudinal 2D STE strain analysis was not performed in the current study because the open chest preparation does not permit standard apical acquisitions to assess longitudinal strain. However, the observed correlations between 2D STE and sonomicrometer strains in the radial and circumferential directions were generally less than those reported for longitudinal strains in the other studies.”

4) I think the authors should clarify the clinical utility of their findings and resume them in a specific paragraph.
We agree and have added the following discussion of clinical utility to the text:
Pg. 13:
“Our findings contribute to the foundation of knowledge in the developing clinical application of quantitative regional and multidirectional strain analysis. The demonstration of a non-linear relationship between regional myocardial function and blood flow has significant implications when considering the relative virtues of strain and perfusion imaging in clinical assessments of ischemia and viability. In addition, our study provides a rigorous, in-depth evaluation of a clinical 2D STE software package. Our results indicate that 2D STE requires additional refinement before becoming a reliable quantitative clinical technique for measuring regional circumferential and radial strains. Reassessment of FDA-approved clinical software for strain analysis is necessary to determine both clinical merits and limitations.”

5) In the discussion you state that "Most often, post-systolic deformation related to delayed myocyte contraction and/or passive mechanisms leads to overestimation of ES strain. Actually, in ischemic situation end systolic strain (ESS) is often lower than peak strain (PS) because of the post-systolic shortening phenomenon which is also evident in your pictures. Please amend or explain you statement.
We agree and have clarified the text to more clearly reflect this important point.
Pg. 13:
“Most often, end-systolic strains defined by indirect surrogates of ES tend to be overestimated due to the presence of post-systolic deformation related to delayed myocyte contraction and/or passive mechanisms.”

5) Discussion is redundant and should be shortened of at least one third. Moreover, I advise the authors to divide the discussion in several paragraphs on different topics and to include a paragraph on the clinical utility of their findings as indicated above.
We agree-- we have condensed the Discussion and have partitioned it into subsections with relevant headings. As noted above, we have also added a paragraph that highlights the clinical relevance of our findings.