Author’s response to reviews

Title: Reduced global longitudinal strain in association to increased left ventricular mass in patients with aortic valve stenosis and normal ejection fraction: A hybrid study combining echocardiography and magnetic resonance imaging

Authors:

Wilfried Dinh (wilfried.dinh@helios-kliniken.de)
Werner Nickl (wanickl@yahoo.com)
Jan Smettan (jan.smettan@helios-kliniken.de)
Frank Kramer (frank.kramer@bayer-healthcare.com)
Thomas Krahn (thomas.krahn@bayerhealthcare.com)
Thomas Scheffold (th.scheffold@t-online.de)
Michael Coll Barroso (mail@corovital.de)
Hilmar Brinkmann (hilmar.brinkmann@helios-kliniken.de)
Till Koehler (till.koehler@helios-kliniken.de)
Mark Lankisch (mark.lankisch@helios-kliniken.de)
Reiner Füth (reiner.fueth@helios-kliniken.de)

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Author’s response to reviews: see over
Reduced global longitudinal strain in association to increased left ventricular mass in patients with aortic valve stenosis and normal ejection fraction: A hybrid study combining echocardiography and magnetic resonance imaging

Wilfried Dinh, Werner Nickl, Jan Smettan, Frank Kramer, Thomas Krahn, Thomas Scheffold, Michael Coll Barroso, Hilmar Brinkmann, Till Koehler, Mark Lankisch and Reiner Füth

Comments to reviewers

Reviewer 1

1. **LV mass was appropriately measured by MRI, the gold standard and not subject to inter and intra-observer variability as for echo assessment. However, the categorization that authors used is semi-quantitative whereas they could use quantitative cut-offs.**

   The authors discussed the point of using quantitative cut-offs. We used cut-off values of the left ventricular mass index (LVM) based on current guidelines of the American Society of Cardiology (Lang, 2005 #28). To our knowledge, there is no clear quantitative cut-off value in literature with a clear prognostic implication. Therefore, we preferred the semi quantitative approach according to the recent guidelines.

2. **In line with the previous comment, authors use LVM and not LVMI, which should be preferred.**

   We changes LVM to LVMi in the abstract as well main manuscript. Thank you very much for the recommendation.

3. **Subtle forms of dysfunction are important in patients with aortic stenosis. There are several studies that have demonstrated impaired coronary flow reserve and its normalization after aortic replacement. Please discuss and cite them.**

   We discussed this issue in the main manuscript and cited a paper regarding this issue: “Hildick-Smith et al. showed in a previous study that coronary flow reserve increases after AVR, and this increase occurs in tandem with regression of LV hypertrophy. (Hildick-Smith, 2000 #66)”

4. **Authors do use a control group that is not strictly necessary since they are evaluating GLS before and after valve replacement.**

   We agree with the reviewer that we do not need a control group to compare global longitudinal strain (GLS) before and after aortic valve replacement. Nevertheless, there are no general accepted normal values for GLS available in the literature. Therefore, GLS measurement can change with the echo device used since the ultrasound manufactories may use different technique approached in order to obtain GLS values. Therefore, we used the control group to established normal values in matched patients for our echocardiography laboratory.
5. Patient selection should be detailed. How many patients had concomitant coronary artery disease; how many patients had moderate aortic stenosis.

We included the percentage of patients with concomitant coronary heart disease in table 1. The number of patients with moderate or severe aortic stenosis was already mentioned in the manuscript result sections. Nevertheless, we corrected a type error (6 subjects with moderate AS instead of 4 subjects).

6. Authors should put their results into clinical context

The authors tried to put the results in a clinical context in the discussion section: “These finding justifies the assessment of GLS in patients with AS because GLS helps to identify patients the transition from compensatory hypertrophy to myocardial failure”.

7. It should be reported not only the change of GLS before and after surgery but also the change in LVmass (modify figure 3)

We did not measure LVmass on follow up visits and discussed that issue in the study limitation section. We agree with the reviewer that this is a limitation of our study.

8. There is no mention to the potential role of 3D echocardiography for LV mass assessment. Please address it.

The authors feel that the potential role of 3D echocardiography is not very important in the context of our paper. 3D Echocardiography is not established as a standard method and not widely available. 3D Echocardiography might be a promising tool, but especially 3D strain imaging is a research tool and there are no studies available in subjects with aortic stenosis.

9. You may be interested in citing the following article: Myocardial dysfunction in the periinfarct and remote regions following anterior infarction in rats quantified by 2D radial strain echocardiography: An observational cohort study. Raymond Q Migrino, Xiaoguang Zhu, Mineshkumar Morker, Tejas Brahmbhatt, Megan Bright, Ming Zhao. Cardiovascular Ultrasound 2008, 6:17

We cited this very interesting paper in the discussion section: “In our study, radial strain, as a measurement of radial contraction (Migrino, 2008 #67), was preserved or even increased in subjects with mildly increased LVMi compared to those with normal LVMi or severely increased LVMi. Therefore, in early stages of LV hypertrophy, radial function acts as a compensatory phenomenon to the decrease in longitudinal deformation to maintain a normal LV ejection fraction (Donal, 2009 #68).

10. Please proof read the manuscript because there are a few typos

We proof read the manuscript carefully.

The authors thank the reviewer for the expert opinion of the manuscript.
Reviewer 2

1. The evidence that GLS is reduced in AST patients has been already documented by previous studies. The novelty of this study is the relationship between LVM and the reduction of GLS. However the number of patients with increased LVM is too low. A larger number of these patients should be enrolled to strengthen this result. Another major question is that in the method section, EF < 55% is considered an exclusion criteria. This means that patients with moderate to mild, and thus overt, left ventricular dysfunction have been enrolled. This is in contrast with the goal of the study that is the early, non-overt, detection of left ventricular dysfunction. Please clarify this point and exclude patients with EF < 55%.

We agree with the reviewer that the number of patients included in this study is too small to prove causality. Nevertheless, this is a pilot study and therefore designed to generate a hypothesis, not causality. We did not include any patient with EF < 35%. The recent guidelines of the American Society of Echocardiography have defined a cut of 50%, not 55% to indicate aortic valve replacement in otherwise asymptomatic patients with aortic stenosis. Therefore, we included very few patients with EF < 55% but excluded patients with EF < 35%. In addition, even with MRI techniques there is a inter- and intraobserver- variability of EF measurement. Furthermore, even in subjects with moderately reduced EF is might of of interested if those with increased left ventricular muscle mass have a greater impairment of GLS than those with normal muscle mass. Therefore, we did not exclude patients with EF < 55% from the study, but agree with the reviewer that in a follow up study with the aim to prove causality, one should focus on those with normal EF, defined as EF >55%.

Nevertheless, we carefully reviewed our data and corrected a typo mistake in the MRI EF variables (a subjects was set with a EF of 226, the correct EF was 62. We apologize for this mistake and corrected this in the manuscript table.

2. Radial strain has not been defined in the method. Please define it

We defined radial strain in the method section. “The average peak radial systolic strain values were obtained from the parasternal short axis view at the level of the LV apex.”

3. Follow up should be completed in all the enrolled patients.

We agree with the reviewer and discussed this issue in the study limitations.

4. Was peak radial strain higher in control group than in ATS patients?

The peak radial strain was higher in those with mild increased LVMi compared to those with normal LVMi. We mentioned this in the result section.

5. The evidence that radial strain increased in ATS patients without than in those with increased LVM should be discussed. This may be a compensatory mechanism as documented in other disease with reduced GLS

We discussed the increased radial strain in the discussion and cited a recent paper.

The authors thank the reviewer for the expert opinion of the manuscript.