Author’s response to reviews

Title: 3D Strain Helps Relating LV Function to LV Structure in Athletes

Authors:

Laura Stefani MD (laura.stefani@unifi.it)
Alessio De Luca PhD (deluca.alex@tiscali.it)
Loira Toncelli MD (loiratoncelli@alice.it)
Gianni Pedrizzetti Prof (giannip@dica.units.it)
Giorgio Galanti Prof (giorgio.galanti@unifi.it)

Version: 3
Date: 4 August 2014

Author’s response to reviews:

ANSWER TO REVIEWER #1

We wish to thank the referee for the care he reviewed our work and for having highlighted some relevant aspects that were unclear. We tried to improve manuscript following the suggestions and the comments. Point by point replies to the reviewer’s comments are reported below.

1. When we look at the table 1, we can see that the athletes appear to have the same heart rate as the control group, the same LVEDd and wall thickness. How come?

Indeed, data are very similar between the groups, although non overlapping. The reason is that all the athletes investigated are “non-elite” athletes, they were trained without the excesses of elite athletes; moreover they are from a young population, therefore the myocardial morphological modification is not yet well evident using the standard echo parameters. These are important aspects for a better interpretation of the LV dimension chamber. They have been specifically written in the method section.

2. Table 3. Circumferential strain usually is highest at the apex and lowest at the base in normal subjects. In this work it appears to be highest in mid-ventricular segments in control subjects and in athletes? Please check your calculations.

We understand the reviewers concern: LV strain normally shows a gradient from basal to apical segments. However, values are here averaged on the entire circumference from a 3D endocardial surface, not based on three projections, and the same behavior repeats on the three groups. Moreover, we can hypothesize that apical segments can be considered here as a portion of the medium-apex level where the numbers of the myocardial fibers are normally more represented. This point has been included in the discussion.

3. Interrelationships between principal and secondary strain are based on the interaction between torsion/ twist angle and amplitude of the strain. Rotation, torsion, twist angle can be measured with 2D strain and possible can find differences between athletes and control subjects. The 3D strain that the authors
use appear to have very low frame rate - 20 frames per second and low resolution. Please comment.

The 3D acquisitions have indeed a low frame rate (the number of frames per heartbeat is: average 20.4, standard deviation 5.2), but this looks acceptable for global strain evaluation that is a smoothly varying quantity. The evaluation of torsion from 2D acquisitions gives very variable results for many factors (from the different accuracy of speckles along the circumference –partly along the beam partly transversal-, to the out-of-plane motion of the scan-plane –particularly in the basal section). This motivated us to look for difference in terms of components of the global strain that are statistically more reliable quantities. We agree on the concern and included our perspective about this in the discussion.

4. Why not to try to understand the nature of the differences in the secondary strain? Which measurements performed with speckle tracking can affect secondary strain? For instance, measures of basal/apical rotation and torsion for better investigation of secondary strain – why are they lower in control subjects? Does rotation and torsion affect secondary strain?

We cannot really answer this difficult question through these data. It is clear that principal and secondary strain are computed from longitudinal strain, circumferential strain and torsion. Thus secondary strain depends on the relative value of other strain values and on torsion value relative to them, and there is also a formula relating them. Here, we provide some initial clinical observations but, before getting into observed relationship, we would prefer to have a firmer theoretical ground in support of the possible relationship.

5. Why did you choose to include the subgroup of athletes with bicuspid aortic valve? The main problem in these individuals is the aortic root diameter/significance of the valvular lesion. This group appears not appropriate for the study purpose.

Our Sports Medicine Center is particularly involved in BAV athletes follow-up, with a long experience. BAV population is a special kind of athletes where the eligibility can be permitted exclusively under a periodical assessment of the valve and of the myocardial function. It is important also to specify that the BAV athletes enrolled for the present investigation, have normal function of the valve and of the LV chamber, it is now better clarified by the inclusion criteria. They normally practice sports activity and particularly the Aortic valve does not show any severe stenosis or insufficiency, while the slight increase of the LV diameters is not significant and within the normal range. We also added a brief discussion on the significance of BAV in the discussion.

We would therefore prefer to maintain the data of the BAV group in the manuscript. We think that it does not hide the main results and could rather amplify them. However, if requested by the Editor on the basis of reviewers' proposal, we can accept of adjusting the manuscript removing the results about the group of the BAV athletes.

ANSWER TO REVIEWER #2
We wish to thank the reviewer for his interest of our work and for having commented some relevant aspects that appeared unclear. The manuscript has been improved following the suggestions and the comments raised. Point by point replies to the reviewer’s comments are reported below.

The authors have not made it clear why BAV subjects were included? Is it because of higher prevalence of BAV disease in the population? Moreover, there is no data regarding the gradient across the aortic valve in these subjects.

Our Sports Medicine Center is particularly involved in BAV athletes, and we have indeed a high incidence of BAV young men that are redirected to us for cardiac evaluation in the eligibility to intense sport activity. BAV population is a special kind of athletes where eligibility can be permitted exclusively under a periodical assessment of the valve and of the myocardial function. It is important also to specify that the BAV athletes enrolled for the present investigation, have normal function of the valve and of the LV chamber; they normally practice sports activity and particularly the Aortic valve does not show any severe stenosis or insufficiency, while the slight increase of the LV diameters is not significant and within the normal range. In this context the BAV group can be considered as normal particularly for the LV chamber and aortic valve functioning, in consequence of the selection by the inclusion criteria used. We better clarified these aspects in the inclusion criteria. We also added a paragraph on BAV in the discussion.

Table 1 suggests this group to have highest myocardial mass indexed. Is it due to outflow obstruction (even if mild) or due to aortic regurgitation worsening with exercise

The slight enhancement with not significant value of CMI of BAV group, is a peculiar behavior of this category. It is associated to a larger dimension of the LV chamber, that remains within the normal range and is independent from the aortic valve regurgitation and morphology This aspect was deeply investigated in previous studies and in a large cohort of BAV athletes (Effects of sports activity in athletes with bicuspid aortic valve and mild aortic regurgitation Giorgio Galanti, Laura Stefani, Loira Toncelli, Maria Concetta Robertina Vono Roberto Mercuri and Nicola Maffulli Br. J. Sports Med. published online 3 Jun 2008; doi:10.1136/bjsm.2008.047407; Exercise Training in Athletes with Bicuspid Aortic Valve Does Not Result in Increased Dimensions and Impaired Performance of the Left Ventricle Laura Stefani, Giorgio Galanti, Gabriele Innocenti, RobertoMercuri, and NicolaMaffulli,- Cardiology Research and Practice Volume 2014, Article ID 238694, 8 pages http://dx.doi.org/10.1155/2014/238694)

It was demonstrated that this aspect does not have any relationship with the possible myocardial dysfunction in case of mild aortic insufficiency. The aortic valve regurgitation of the BAV athletes selected is very mild, only a jet at the echo color investigation, none of them had aortic valve obstruction or stenosis. We agree that on the importance of physiological response of the valve insufficiency during exercise. The physiological response to the aerobic exercise is normally characterized of a progressive improvement and of an evident reduction of the valve regurgitation due to the progressive decrease of the
peripheral arterial resistance during exercise. Any possible worsening of the valve occurs only in case of effective valve dysfunction.

This aspect has been now mentioned to improve clarity in the presentation of results.

Also there is no data regarding the pattern of hypertrophy in TAV or BAV athletes. Is it concentric or eccentric? This could affect the pattern of PSA in these subjects, as is shown in table 2 (GCS for BAV athletes is highest).

Thank you very much for raising up this aspect that was not clear enough in the manuscript. We can reasonably exclude the presence of any physiological hypertrophy, in all the groups analyzed. All data are indexed and not compatible with a myocardial hypertrophy. The reason is that all the athletes investigated are "non-elite" and young athletes, therefore the myocardial morphological modification is not yet well evident. For this reason, no classification in eccentric or concentric was possible. This information has been reported with more care in the method section.

There are not TDI parameters for the population under study. This is important to look at LV filling pressures, as this could modify the strain pattern. If possible, diastolic parameters on exercise could be added to the analysis.

We are in completely agreement with the reviewer for the importance in evaluating the diastolic function, especially in case of BAV athletes. Unfortunately this aspect has been considered out of the present investigation. We have inserted in the table and in the text the 2D standard data and the diastolic function is absolutely normal for all the young athletes investigated and therefore, we have not proceeded in evaluating any additional parameters. We respectfully underline also that an eventual reduction of E1, alteration of E/E1 and increase of Left atria area parameters, normally confirm and support the presence of a diastolic dysfunction when the other standard echo parameters are compromised, this is more common in older athletes but was not expected in this young population.

ANSWER TO REVIEWER #3

We wish to thank the reviewer for his appreciation of our work and for having raised some relevant aspects that should need clarifications. The manuscript has been improved following the suggestions and the comments raised. Point by point replies to the reviewer’s comments are reported below.

The authors should better explain their choice of including a group of athletes with BAV.

Our Sports Medicine Center is particularly involved in BAV athletes, and we found a high incidence of BAV young men that are redirected to us for cardiac evaluation in the eligibility to intense sport activity. We have a special interest in that group. We normally allow sports activity in them in presence of substantial normality of the myocardial performance as in the cases selected for the study. However, this is a special kind of athletes where eligibility can be permitted exclusively under a periodical assessment of the valve and of the myocardial
function. We added a paragraph on this aspect in the discussion and provided more information on their selection in the method section.

In the absence of a gold standard the authors have used 2D strain to verify the reliability of their 3D strain results. However, this does not apply for PSA, which is only available in 3D and for which there was no comparator available. As such, the meaning of the difference found is difficult to interpret.

There is a misunderstanding here. All components of 3D strain (both the standard one, long/circ and the new ones principal/secondary) are computed from the same tracking of the 3D endocardial surface. The validation with 2D longitudinal and circumferential strain ensures that the computed endocardial deformation is reliable, then the PSA calculation is simply a change of coordinates from the circumferential-longitudinal. A recent clinical evaluation of the method is provided with a new reference [11].

In the presence of small groups (2 of 15, 1 of 20 subjects, a limitation acknowledged by the authors) the differences noted only in a secondary parameter need to be interpreted with caution. This is particularly important as the difference involves novel parameters about which there is a paucity of data.

We agree with the reviewer, we have further discussed this aspect in the limitation of the study

Issues of validation, reproductibility and normal values particularly related to PS and SS need to be carefully addressed as these are critical to the study results. The potential clinical implications/applications of such parameters in the described setting need to be discussed.

It has been more deeply discussed in the discussion.

Minor comments:

I suggest the authors provide in a separate table all the 2D strain information as well.

We prefer to avoid confusion as the 2D data were used for validation only.

It is not clear why the LVEF was not measured in the standard way, using LV volumes to derive it, particularly since 3D datasets were available. I suggest the authors provide this information. I also believe that providing LA volumes (instead of only linear dimensions) and more data about diastolic function (ie e' values) would help a better description of cardiac structure and function in these groups.

The reviewer is right that EF could be computed by 3D data, however in such a selected population with normal function and regular shape of the cardiac chambers any method is equivalent. Similarly, further information on diastolic function were considered redundant (2D standard data and the diastolic function were normal for all the young subjects investigated).

page 10, line 16 – the expression has been corrected.