

Peer Review File

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Comment 1: In Introduction, you wrote, “However, regardless which atrial switch procedure was used, original pathological states at ventricular level remained uncorrected.”

I suggest to clearly mention that the right ventricle is still functioning as the systemic ventricle after atrial switch.

Reply 1: Thanks for this comment. The sentence has been extended as suggested: “However, regardless which atrial switch procedure was used, original pathological states at ventricular level remained uncorrected with a RV functioning as the systemic ventricle (4-6).”

Comment 2: What is the aim of the study and why do you think assessing the mitral valve in atrial switch patients is important?

Reply 2: Thanks for this important question. dTGA and its correction with atrial switch is associated with volumetric and functional alterations of cardiac chambers including LV and left atrium (LA) remodeling. In most of cases, abnormalities of left (and right) heart chambers are accompanied with dilation and functional impairment of atrioventricular annuli, as demonstrated before in other disorders. The present study aimed non-invasive 3DSTE-derived assessment of mitral annular dimensions and functional properties due to dTGA-associated special pathological state following different kinds of atrial switch procedures. These facts are now mentioned in the Introduction section.

Change in the text: Theoretically, dTGA and its correction with atrial switch is associated with volumetric and functional alterations of cardiac chambers including LV and left atrium (LA) remodeling. In most of cases, abnormalities of left (and right) atria and ventriculi are accompanied with dilation and functional impairment of atrioventricular annuli in between, as demonstrated before in other disorders (12). Due to presence of dTGA-associated special pathological state following atrial switch, the present retrospective cohort study aimed non-invasive assessment of MA dimensions and functional properties by 3DSTE.”

Comment 3: In Method, paragraph 2 (line 93-97): Which parameters were measured with 2D echocardiography?

Reply 3: Thanks for this comment. The text has been extended with the following.

Change in the text: Toshiba Artida™ echocardiographic tool (Toshiba Medical Systems, Tokyo, Japan) attached with a PST-30SBP (1-5 MHz) phased-array transducer was used for 2D Doppler echo. The measured 2D echocardiographic

parameters included LA diameter, thicknesses of interventricular septum (IVS) and LV posterior wall and end-systolic and end-diastolic LV diameters and volumes (all measured in parasternal long-axis view), which were assessed together with visual continuous Doppler evaluation of valvular regurgitations and pulsed Doppler-based exclusion of valvular stenoses (18).”

Comment 4: In Results, two-dimensional echocardiographic data are shown in table 1. But in the particular paragraph (line 138- 144) it is not mentioned that they are shown in table 1.

Reply 4: Thanks for this comment. Now it is obviously mentioned where the 2D data are presented.

Comment 5: In Discussion, why is this study needed and what makes it important? Please discuss.

Reply 5: Thanks for this comment. The study tried to emphasize that dTGA and ‘old-fashioned’ atrial switch operations are accompanied with significant changes not only in myocardial diameters, volumes and functional parameters of atria and ventriculi, but with atrioventricular dimensions and functional properties as well. In earlier studies, strong relationship could be demonstrated between mitral annular dimensions and functional properties and LV/LA parameters in healthy subjects without valvular regurgitations or stenoses, which could partially explain findings in our dTGA patients without significant valvular regurgitations. The followings have been inserted into the text accordingly.

Change in the text: The results demonstrated above are more interesting if we take it into consideration that dTGA patients had no significant MR. It is known that MA itself does not have contractility elements, its motion is highly dependent on the movement of adjacent atrial and ventricular areas as demonstrated before even in healthy subjects without valvular regurgitations or stenoses (25-27). In recent studies, strong associations could be demonstrated between MA dimensions and functional properties and LV/LA parameters even in healthy subjects before valvular abnormalities develop (25-27). LA volumetric and functional abnormalities could be detected in dTGA following atrial switch (17) and compensatory LV morphological and functional changes and LV-RV interactions are theorised to maintain MA function, which could be a topic of future investigations.

In a recent study, Senning-operated subjects showed higher atrial strains as compared to that of Mustard-operated cases, which could be explained by the methodological differences between procedures when autologous native tissue is used during the Senning-procedure, while a synthetic material for the Mustard-procedure making latter theoretically the system more stiff (17). These could lead to MA functional differences, however, the effects of regional LV contractility could not be excluded either. These

results could draw our attention to the late consequences of atrial switch operations for dTGA, comparative studies are warranted with subjects who underwent arterial switch procedures.

25. Kovács Z, Kormányos Á, Domsik P, et al. Left ventricular longitudinal strain is associated with mitral annular fractional area change in healthy subjects-Results from the three-dimensional speckle tracking echocardiographic MAGYAR-Healthy Study. *Quant Imaging Med Surg.* 2019 Feb;9(2):304-311.
26. Domsik P, Kalapos A, Lengyel C, et al. Correlations between mitral annular and left atrial function as assessed by three-dimensional speckle-tracking echocardiography in healthy volunteers. Results from the MAGYAR-Healthy Study. *Orv Hetil* 2014;155:1517-23.
27. Nemes A, Kormányos Á, Ambrus N, et al. Associations between Mitral Annular and Left Atrial Volume Changes in Healthy Adults–Detailed Analysis from the Three-Dimensional Speckle-Tracking Echocardiographic MAGYAR-Healthy Study *Rev Cardiovasc Med* 2022;23:194-203.

Comment 6: Despite the mitral annular dilation, in patients with d-TGA, there did not appear to be increased incidence of mitral regurgitation. In fact, the authors go on to say that there were no patients with Grade 2-4 MR and only 2 patients with Grade 1-2 MR. Additionally the LV did not appear to be dilated as also the LA. How do the authors explain the significant difference in functional parameters as measured by mitral annulus FAC and mitral annulus FS compared to controls, yet have only mild mitral regurgitation? Was there residual shunt at the time of the 3D STE study to explain annular dilation?

Are there normative data for mitral annulus FAC and FS%? Why is the significant decrease not reflected by more than mild regurgitation in these patients?

Reply 6: Thanks for these comments. Residual shunts were excluded in all cases. Normal reference values of 3DSTE-derived MA functional properties have just been published together with their age- and gender-dependency (see new reference 24).

Change in the text: 24. Nemes A, Kormányos Á, Domsik P, et al. Normal reference values of three-dimensional speckle-tracking echocardiography-derived mitral annular dimensions and functional properties in healthy adults: Insights from the MAGYAR-Healthy Study. *J Clin Ultrasound.* 2021;49:234-9.

The results demonstrated above are more interesting if we take it into consideration that dTGA patients had no significant MR. It is known that MA itself does not have contractility elements, its motion is highly dependent on the movement of adjacent atrial and ventricular areas as demonstrated before even in healthy subjects without valvular regurgitations or stenoses. In recent studies, strong associations could be demonstrated between MA dimensions and functional properties and LV/LA

parameters even in healthy subjects before valvular regurgitations or stenoses develop. Although LA volumetric and functional abnormalities could be detected in dTGA, LV rotation proved to increase in a recent study suggesting compensatory effects of LV function in these cases to maintain MA function, which could partially explain findings. The text has been extended with the followings.

Change in the text: The results demonstrated above are more interesting if we take it into consideration that dTGA patients had no significant MR. It is known that MA itself does not have contractility elements, its motion is highly dependent on the movement of adjacent atrial and ventricular areas as demonstrated before even in healthy subjects without valvular regurgitations or stenoses (25-27). In recent studies, strong associations could be demonstrated between MA dimensions and functional properties and LV/LA parameters even in healthy subjects before valvular abnormalities develop (25-27). LA volumetric and functional abnormalities could be detected in dTGA following atrial switch (17) and compensatory LV morphological and functional changes and LV-RV interactions are theorised to maintain MA function, which could be a topic of future investigations.

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Comment 7: Why do patients with Senning procedure have better functional parameters of mitral annulus as opposed to Mustard procedure?

Reply 7: Thanks for this question. MA motion is highly dependent on the movement of adjacent atrial and ventricular areas. In a recent study, Senning-operated subjects showed higher atrial strains as compared to that of Mustard-operated cases, which could be explained by the methodological differences between procedures when autologous native tissue is used during the Senning-procedure, while a synthetic material for the Mustard-procedure making latter theoretically the system more stiff. This train of thought is now mentioned in the text.

Change in the text: In a recent study, Senning-operated subjects showed higher atrial strains as compared to that of Mustard-operated cases, which could be explained by the

methodological differences between procedures when autologous native tissue is used during the Senning-procedure, while a synthetic material for the Mustard-procedure making latter theoretically the system more stiff (17). These could lead to MA functional differences, however, the effects of regional LV contractility could not be excluded either. These results could draw our attention to the late consequences of atrial switch operations for dTGA, comparative studies are warranted with subjects who underwent arterial switch procedures.

Comment 8: Could the authors provide LA strain and LV strain and correlate it with the mitral annular functional parameters?

Reply 8: Thanks for this comment. The followings have been inserted into the text according to the requirements.

Change in the text: Global peak LA longitudinal (LA-LS) and circumferential (LA-CS) strains and LV longitudinal (LV-LS) strain proved to be $11.9 \pm 7.1\%$, $10.8 \pm 9.7\%$ and $-16.1 \pm 5.5\%$, respectively. LA-LS did not show correlation with MAFAC and MAFS ($r = 0.18$, $p = 0.34$ and $r = 0.21$, $p = 0.31$). Similarly, LA-CS did not show correlations with MAFAC and MAFS ($r = 0.16$, $p = 0.32$ and $r = 0.19$, $p = 0.30$). LV-LS did not correlate with MAFAC and MAFS ($r = 0.13$, $p = 0.45$ and $r = 0.19$, $p = 0.30$).

Comment 9: The inter and intraobserver variability is not provided in the paper.

Reply 9: As requested, inter- and intraobserver parameters have been calculated and presented in Results section and in the new Table 3.