Dysfunction of the Systemic Right Ventricle After Atrial Switch: Physiological Implications of Altered Septal Geometry and Load

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Running Head: Septal Dysfunction of the Systemic Right Ventricle

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ABSTRACT

Atrial switch operation in patients with transposition of the great arteries (TGA), leads to leftward shift and changes the geometry of the interventricular septum. By including the implications of regional work and septal curvature, this study investigates if changes in septal function and geometry contribute to reduced function of the systemic right ventricle (RV) in adult TGA patients. Regional myocardial work estimation has been possible by applying a recently developed method for non-invasive work calculation based on echocardiography. In 14 TGA patients (32±6 years, mean±SD) and 14 healthy controls, systemic ventricular systolic strains were measured by speckle tracking echocardiography and regional work was calculated by pressure-strain analysis. In TGA patients septal longitudinal strain was reduced to -14±2% vs -20±2% in controls ($p<0.01$) and septal work was reduced from 2046±318 to 1146±260 mmHg·% ($p<0.01$). Septal circumferential strain measured in a subgroup of patients, was reduced to -11±3% vs. -27±3% in controls ($p<0.01$), and a reduction of septal work (540±273 vs 2663±459 mmHg·%) were seen ($p<0.01$). These reductions were in part attributed to elevated afterload due to increased radius of curvature of the leftward shifted septum. To conclude, in this mechanistic study we demonstrate that septal dysfunction contributes to failure of the systemic RV after atrial switch in TGA patients. This is potentially a long-term response to increased afterload due to a flatter septum and suggests that medical therapy that counteracts septal flattening may improve function of the systemic RV.

New and Noteworthy: We have demonstrated that TGA-patients with systemic right ventricles (RV) have reduced function of the interventricular septum (IVS). Since the IVS is constructed to eject into the systemic circulation, it may seem unexpected that it does not maintain function when being part of the systemic RV. By applying principles of regional work, wall tension and geometry we have identified unfavorable working conditions for the IVS when the RV adapts to systemic pressures.

Keywords: Regional Myocardial Work, Septal Geometry, Echocardiography, Heart Failure, Transposition of the Great Arteries

INTRODUCTION:

The atrial switch operations (Mustard or Senning) on infants with transposition of the great arteries (TGA), represented milestones in the treatment of congenital heart disease (CHD) (17, 25). However, the procedure also introduced severe hemodynamic and physiologic challenges to otherwise normal ventricles as blood flow is redirected in the atria and the right ventricle (RV) remains the systemic ventricle. Over decades a progressive deterioration of systemic RV function may appear, followed by increased heart failure and substantial mortality (7, 22, 27). The mechanisms behind the increased morbidity and mortality in these patients are complex. A number of factors may play a role, but the observed reduction in ventricular function makes an important contribution (4). To target new therapeutic strategies we need better understanding of the mechanisms leading to failure of the systemic RV.

In response to high afterload imposed on the systemic RV, its geometry becomes more similar to a systemic left ventricle (LV), and contraction patterns of the RV free wall changes to increased circumferential and reduced longitudinal shortening (1, 6, 10, 18). Likewise, the subpulmonary LV becomes more similar to the normal RV (1). Additionally, due to reversal of the transseptal pressure gradient which is normally directed from the LV to the RV, the interventricular septum (IVS) is shifted leftwards, and the septal curvature on the RV side reverses from convex to concave (21). Consequently, the septum contracts towards the center of the systemic RV which is opposite of normal systolic motion. Since wall tension is determined in part by local radius of curvature according to the La Place principle, we

hypothesize that septal flattening imposes an additional systolic load on the septum which contributes to reduced myocardial shortening in the septum of the systemic RV.

Strain echocardiography is load dependent, which limits its ability to reflect myocardial contractility (28). Assessment of regional myocardial work is an alternative approach taking into account the effect of afterload. Work assessment is rarely used clinically due to the need for invasive pressure measurement. Our research group has developed a novel method to calculate regional work by a non-invasive approach from myocardial strain and a non-invasive estimate of ventricular pressure (2, 23, 24). Therefore, we explored myocardial function of the septum and free wall of the systemic RV by analyzing regional strain, work and tension. We also performed similar measurements in the systemic LV in healthy controls for comparison.

METHODS:

Study population:

Fourteen TGA patients were included consecutively from the outpatient clinic (Table 1). To test the specific hypothesis that septal flattening contributes to reduced septal function we avoided the confounding influence of associated disorders and therefore excluded patients with ventricular septal defect, paced rhythm, valvular stenosis, severe tricuspid regurgitations or arrhythmias. Clinical examination, electrocardiogram (ECG), echocardiography, brachial artery cuff pressure measurements and blood sampling were performed. Fourteen healthy individuals constituted the control group (Table 1).

The study was approved by the regional ethics committee, and written consent was given by all study participants.

Echocardiography and strain analysis:

A Vivid E9 ultrasound scanner (GE Vingmed, Horten, Norway) was used. Images were acquired from apical 4-chamber and in healthy controls also 2-chamber views. Ventricular diameters of the systemic ventricles were assed from the 4-chamber views. In TGA patients, global function of the systemic ventricle was assessed as right ventricular fraction area change (RVFAC) and tricuspid annular plane systolic excursion (TAPSE). In healthy controls, global function of the systemic ventricle was measured as ejection fraction (EF) by the biplane Simpson method. In addition, typical parasternal short axis (SAX) view at the midventricular level basal to the papillary muscles was possible in a subset of patients.

Average frame rate was 69±12 frames/s. Doppler and color Doppler recordings were carried out for quantification of valvular regurgitations, classified as mild, moderate, moderate to severe and severe.(30)

Strain analysis was performed as speckle tracking echocardiography (Echopac, GE Vingmed, Horten, Norway). Peak strain, defined as maximum shortening, was measured from longitudinal strain curves based on the 4-chamber views. The values given are the average of basal and mid segments of septal and RV free wall (LV lateral wall in controls). In a subset of six patients circumferential strain curves were obtained. Peak septal and free wall strains were calculated as the average of the two segments covering the septum and the free wall region, respectively.

147 **Estimation of regional work derived from pressure-strain relation**

148 Regional work was estimated according to Russell et al (23). Briefly,
149 timing of systemic valvular closure and opening were determined visually from
150 images with a high frame rate (101±35 frames/s). The timing of valvular
151 events was used to adjust the time axis of a standard, average pressure
152 waveform to the patient's heart cycle. The waveform amplitude was scaled by
153 the systemic systolic arterial pressure measured by a brachial cuff. Regional
154 work during systole and isovolumic relaxation was estimated by multiplying
155 strain rate (the derivative of the strain curves) by instantaneous pressure and
156 then integrated over time from end-diastole to systemic atrioventricular valve
157 opening as shown in equation 1:

$$W = -\int_{t_0}^{t_1} P_V(t)\dot{\varepsilon}(t)\,dt \quad (1)$$

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159 $P_V(t)$ is ventricular pressure, and $\dot{\varepsilon}(t)$ is the temporal derivative of strain, both
160 as a function of time (t). The time of peak ECG R-wave is t_0, and t_1 is the time
161 of tricuspid valve opening.

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163 **Geometry and wall tension**

164 Ventricular systolic pressure is a suboptimal measure of ventricular
165 afterload since the influence from radius of curvature is not taken into
166 account. Therefore we calculated wall tension by incorporating the local septal
167 radius of curvature in addition to pressure. We calculated curvature at the
168 midventricular level from SAX images. By using the caliper-function in
169 EchoPac, a chord was drawn in the SAX view in the septal and free wall in the

corresponding segments as the strain analysis. The length of the chord (w) and the height (h) from the chord to mid septum/ free wall was measured. We were then able to estimate local radius (R) of curvature of the two opposing walls by this equation:

$$R = \frac{h}{2} + \frac{w^2}{8h} \quad (2)$$

The radius was calculated at the following events: end-diastole, tricuspid valve closure, aortic valve opening, mid-ejection, aortic valve closure and tricuspid valve opening. Linear interpolation was done between these measurements in order to acquire continuous curvature. The Young-Laplace equation was thereby applied to calculate wall surface tension from RV pressure and curvature as a function of time:

$$\gamma(t) = P_V(t)R(t) \quad (3)$$

Wall surface tension (γ) was then used instead of systemic ventricular pressure for estimation of regional work in equation 1. By proper use of SI units, this gives regional work per unit of wall surface area in units of $J \cdot m^{-2}$.

We also calculated a circularity ratio to be able to compare ventricular geometry in TGA patients and healthy controls. This consisted of the septum to the RV (LV in controls) free wall ratio of radii; i.e. a ratio equal to one is found in a perfect circle, whereas a ratio above one indicates septal flattening.

Reproducibility*:*

Intra- and interobserver reproducibility were assessed in all patients blinded to the initial measurements.

194 **Statistical Analysis:**

195 Values are presented as mean±standard deviation (SD). Comparisons
196 between two groups were performed by using Student´s t test and Chi-square
197 test where appropriate. One-way analysis of variance with post-hoc tests were
198 used for repeated measurements (SPSS 18.0, SPSS Inc., Chicago, IL, USA).
199 Reproducibility analysis was done by Bland-Altman analyses. Pearson r was
200 used for correlation. $P<0.05$ was considered significant.

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RESULTS:

Patient characteristics are given in Table 1. The TGA patients had no or mild symptoms of heart failure as 64% were in NYHA class I and 36% in class II. Arterial blood pressure was similar in patients and healthy controls, but heart rate was slightly lower in the healthy controls. In the systemic RV, global function was reduced as indicated by a reduced RVFAC of (26.5±4.5 %) and TAPSE (1.2±0.3cm) similar to other studies (5). The healthy controls had LVEF of 63±3%. None of the patients had severe systemic tricuspid valve regurgitation (Table 1). The patients had larger end-diastolic and end-systolic diameters of their systemic ventricles than the controls (Table 1).

Regional myocardial function

Myocardial strain analysis revealed that longitudinal shortening were severely reduced in the septum (Figure 1, Table 2). Longitudinal shortening in the systemic ventricular free wall, however, were only slightly reduced within normal values in TGA patients versus healthy controls. From the novel method of non-invasive work calculation we found that regional longitudinal work also was significantly reduced in the septum (Figure 2, Table 2).

To further study the function of the septum we performed measurements in a subset of six patients where short axis echocardiography was possible. We found that the reduced function in the septum was more pronounced measured by circumferential strain (Figure 1, Table 2). This was confirmed by the non-invasive work calculation. To further explore the mechanisms of the reduced septal function we calculated the radius of curvature from the short axis views. A possible explanation of the reduced

septal shortening in TGA patients is that this is a physiological response to increased regional local afterload due to increased septal radius of curvature. To address this potential mechanism we used regional wall tension and estimated regional work from segmental tension-strain loops. Despite the inclusion of curvature in the work calculation, there was still a marked reduction in circumferential septal work compared to the RV free wall (32±16 vs. 83±35 J/m², $p<0.05$). We explored whether curvature compensated for some of the reduction in septal work by calculating the proportion of septal to free wall work for each individual. Without taking into account radius of curvature, septal work constituted on average 33% of the free wall work, however, with incorporation of curvature this proportion increased to 41% ($p<0.01$).This was supported by a correlation between the ratio of septal and RV free wall radii of curvature and peak circumferential strain in TGA patients ($r^2=0.86$, $p<0.01$)(Figure 3).

Ventricular geometry

The geometry of the systemic RV differed from controls due to leftward displacement and flattening of the septum (Figure 4). The ratio between septal and RV free wall circumferential radii of curvature was 1.51±0.19 ($p<0.01$ vs. controls) when measured at end-diastole. This ratio fell through the cardiac cycle as it decreased to 1.22±0.18 ($p<0.05$ vs. end-diastole) at mid-systole, and at end systole the cross-section approached a circular shape with a ratio of 1.08±0.06 ($p<0.01$ vs. end-diastole)(Figure 5). In the healthy hearts circularity was demonstrated as the ratio between septal and LV free wall radii of curvature that was approximately 1 at the end of diastole

Reproducibility*:*

Intra- and interobserver measurements of peak strain correlated well (Figure 6). There were acceptable differences between measurements as seen in the Bland-Altman plot.

DISCUSSION:

Mechanisms of congestive heart failure after atrial switch surgery are complex and include myocardial perfusion anomalies in the systemic RV, progressive tricuspid regurgitation and atrial tachy- and bradyarrhythmias (12, 29). In this study, performed more than thirty years after surgery we found reduced global function in the systemic RV and a marked reduction in septal function. This was most pronounced in the circumferential direction which showed near 60 % reduction in peak strain and 80 % reduction in myocardial work compared to healthy controls. Since the IVS is constructed to eject into the systemic circulation in a normal heart, it may seem unexpected that it does not maintain function when being part of the systemic RV. In the present study, however, changes in septal geometry when the RV adapts to systemic pressures lead to unfavorable working conditions for the IVS.

The reduced RVFAC and TAPSE in the systemic RV were accompanied by dilatation with an increase in end-systolic diameter (Table 1). Despite this, RV free wall function appeared to be relatively preserved since shortening strains were similar to healthy controls. Free wall strains in the normal RV, however, has been shown to be somewhat higher which is expected since it ejects into a low pressure system.(9) Therefore, these results indicate that reduced septal function makes an important contribution

to reduced function of the systemic RV. The increased RV afterload represented by increased end-systolic diameter and increased septal afterload could be stimuli to progressive heart failure in TGA patients.

How to evaluate the systemic RV?

The geometry of the RV is different from the LV, but exposed to a higher afterload as a systemic ventricle it behaves and has geometry more similar to the systemic LV (1, 11, 18). Furthermore, the septum is inverted as it bulges into the LV. This gives a methodological problem when comparing the systemic RV to a normal ventricle. Due to change in geometry and loading it is not appropriate to compare the systemic RV in TGA patients with non-systemic RV in controls. We therefore used the systemic LV as reference to evaluate the regional function in these patients. EF is the most widely used method to evaluate the global LV function, and RVFAC and TAPSE are currently among the recommended methods to measure RV function with variable reproducibility (13). These methods can not be used to compare systemic RV to the systemic LV, in contrast to strain measurements. Moreover, as strain measurements have the ability to measure regional function with acceptable reproducibility (Figure 6) (3, 6) we suggest that strain should be the preferred method in evaluating systolic function in the systemic RV. It has until now, not been recommended to incorporate 3-D in evaluation of the function of the systemic RV (26).

Regional shortening

The strain analysis confirms that there is a change in the deformation pattern of the RV free wall in TGA patients which is consistent with other studies (1, 3, 8, 18). However, there was a depression of septal longitudinal strain (6). Interestingly, when we explored septal function further by analyzing circumferential strain we found even more reduced septal function (Figure 3 and Table 4). In the normal LV, circumferential septal strain exceeds longitudinal strain; however, in the IVS of the systemic RV, we found the opposite.

Regional work

Strain is load dependent and a lower strain is expected with elevated afterload (2, 23). However, when ventricular pressure was accounted for, septal work was still reduced, indicating depression of septal myocardial contractility, potentially a long-term response to high afterload.

We also performed work calculations including estimations of local curvature as an even more precise measure of afterload. The increase in septal afterload in TGA patients was due to a leftward shift and flattening of the septum, which implied a larger radius of curvature and hence increased wall tension according to the Laplace principle. Theoretically, the reduction in septal shortening or work could disappear when curvature was accounted for if this was the only cause of the reduction. Though, our data demonstrated that the difference in regional function between the septum and the free wall was still present, however slightly less when including radius of curvature.

Reduced septal function

The TGA patients are studied 31±5 years after the atrial switch operation, and changes may have appeared in the RV as a result of the increased afterload over time. Perfusion defects, reduced coronary flow reserve and increased fibrosis have been found in these ventricles (15, 16, 19). One may speculate that the reversal of septal curvature could affect myofiber function as the fiber anatomy has evolved specifically for maximal LV function (ref). The reversal and hence abnormal “bending” of these fibers may potentially be a cause of impaired septal function. Some of our observations may also be a result of septal fibers not being orientated to provide maximal RV septal shortening. Thus, our findings indicate that systemic RV function relies more on the RV free wall in order to sustain adequate cardiac output.

LIMITATIONS:

The non-invasive regional work analysis has been validated in patients with normal cardiac anatomy, and not in the systemic RV. The standard waveform was derived from LV pressure recordings in a patient population without CHD. A pressure loaded RV has been shown to have similar pressure-volume loops as the LV (21). Our patients had similar systolic blood pressure compared to controls, and as the peak systolic blood pressure is the most important factor in the regional work calculation we assume that this method is also applicable in this patient group (24).

Fourteen patients included in the study may be considered a small sample size but our main findings are consistent throughout the material. SAX

measurements were only performed in six patients as stringent SAX views are necessary to obtain circumferential strain. These data were used to demonstrate hemodynamic principles and the reduced septal function was seen in both longitudinal and circumferential measurements.

CLINICAL IMPLICATIONS:

Our observations propose that the curvature of the septum, which is a determinant of septal afterload, may be a part of the development of heart failure in TGA patients with systemic RV. Septal position and curvature is determined not only by the material properties of the septum, but also to a large extent by the trans-septal pressure difference (11, 14). If LV pressure is increased (e.g. due to elevated pulmonary artery pressure), the septum will shift rightward and become flatter, while the opposite effect will occur with an isolated rise in RV pressure. The net effect of ventricular pressure changes on RV function is difficult to predict, but the present data suggest these patients will benefit from having a curved septum, especially when septal function is reduced.

Banding the pulmonary artery to increase non-systemic ventricular pressure has been used to treat tricuspid regurgitation and systemic RV failure with various effects on the systemic RV (29). Our findings suggest the unfavorable effect on septal curvature may outweigh the positive impact of the reduced valvular regurgitation in the systemic RV. TGA patients are also at risk for pulmonary hypertension (ref inn her) with probably a similar effect on the septal curvature as the pulmonary banding. Clinical studies should be

performed to evaluate if medical therapy reducing the pulmonary vascular pressure will increase septal curvature and RV function in these patients.

CONCLUSION:

The present study demonstrates that septal dysfunction contributes to systemic RV failure in TGA patients, whereas RV free wall function was maintained. Strain and work analysis showed septal flattening with increased wall tension, suggesting increased regional afterload as mechanism of RV dysfunction in these TGA patients. Studies should be done to determine if medical therapy that counteracts septal flattening may improve function of the systemic RV.

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Table1. Characteristics and echocardiographic findings of TGA patients (n=14) and healthy controls (n=14).

Parameter	Patients	Healthy Controls	p value
Age (years)	32±6	30±7	NS
Male gender no. (%)	9 (64%)	10 (71%)	NS
Senning/ Mustard no. (%)	11 (79%)/3 (21%)	-	
Years since atrial switch procedure	31±5	-	
Systolic/diastolic blood pressure (mmHg)	121±15/ 72±11	121±14/ 68±7	NS
Heart Rate (beats/minute)	71±10	62±9	<0.05
QRS (ms)	109±25	87±12	<0.01
proBNP (pmol/L)	28±12	-	
ACE Inhibitors no. (%)	3 (21%)	-	
Fractional area change, systemic RV (%)	26.5±4.5	-	
Ejection fraction, systemic LV(%)	-	63±3	
End-diastolic diameter, systemic ventricle (cm)	5.6±0.6	5.1±0.4	<0.01
End-systolic diameter systemic ventricle (cm)	4.5±0.5	3.3±0.3	<0.01
Systemic AV valve regurgitation (grade 0/1/2/3/4)	0/7/6/1/0	14/0/0/0/0	<0.01

Values are expressed as mean±SD, otherwise number (percentage).

NS: non-significant, ACE: Angiotensin-converting enzyme, AV valve: atrioventricular valve (tricuspid valve in patients and mitral valve in controls).

Table 2. Longitudinal and circumferential peak strain and work from the systemic right ventricle in TGA patients (longitudinal n=14, circumferential n=6) and the left ventricle in healthy controls (n=14)

Parameter	Patients	Healthy Controls	p value
Longitudinal strain, septum (%)	-14±2	-20±2	<0.01
Longitudinal strain, free wall (%)	-20±3	-22±2	<0.05
p value	<0.01	<0.01	
Longitudinal work septum (mmHg·%)	1146±260	2046±318	<0.01
Longitudinal work free wall (mmHg·%)	1955±373	2239±209	<0.05
p value	<0.01	<0.05	
Circumferential strain, septum (%)	-11±3	-27±3	<0.01
Circumferential strain, free wall (%)	-19±5	-22±3	NS
p value	<0.01	<0.01	
Circumferential work septum (mmHg·%)	540±273	2663±459	<0.01
Circumferential work free wall (mmHg·%)	1753±582	1985±502	NS
p value	<0.01	<0.01	

Values are expressed as mean ± SD.

Figure legends:

Figure 1. Longitudinal and circumferential strain measurements from a TGA patient and a healthy control. The dotted line represents septum, while the continuous line represents the RV free wall in the TGA patient and LV lateral wall in the control. In contrast to the control, the strain measurements were more heterogeneous and the shortening was reduced in the TGA patient, especially in the septum.

Figure 2. Averaged strain curves and pressure-strain loops from all patients. Upper panel: averaged longitudinal (n=14) and circumferential (n=6) strain curves from TGA patients. Lower panel: averaged pressure-strain loops (longitudinal and circumferential) from TGA patients. The loops represent an estimation of regional work. Valvular events are indicated in the figures. Please note the reduced strain and regional work in the septum (red) compared to the RV free wall (blue). This was seen in both longitudinal and circumferential directions. tvc= tricuspid valve closing, avo= aortic valve opening, avc= aortic valve closing, tvo= tricuspid valve opening.

Figure 3. End-diastolic geometry and septal circumferential strain. Short axis views acquired in end-diastole from two TGA patients are shown to the left. The corresponding strain curves from the IVS from the two patients are shown to the upper right. The correlation between septal circumferential strain and end-diastolic geometry is demonstrated at the lower right (n=6). Patient A at

the upper left had a relatively concave interventricular septum and the ratio of septal radius/radius free wall ($R_{septum}/R_{free\ wall}$ – ratio) was 1.32 (blue circle in the scatter plot in the lower right panel). The patient B at the lower left had a flatter interventricular septum with a $R_{septum}/R_{free\ wall}$ - ratio of 1.74 (red circle in the scatter plot). The scatter plot to the lower right shows the correlation between the ratio and peak strain, demonstrating that a flatter septum results in decreased shortening.

Figure 4. Representative examples of ventricular short axis images from a TGA patient and a healthy control at the end of diastole. Circles represent curvature of the septum. In the TGA patient the septal radius of curvature was higher than the control, demonstrating a flatter septum. The septal radius of curvature was also larger than in the free wall. In the control the curvature was similar in the septum and the free wall.

Figure 5. Ratio of curvature ($R_{septum}/R_{free\ wall}$) in TGA patients (mean±SD) throughout systole in relation to RV pressure (schematic). The ratio was obtained at valvular events plus mid-ejection. During systole there was a reduction in the septal radius of curvature as the ventricular pressure increases and the ventricle empties. The ratio was significantly reduced at mid- (*$p<0.05$) and end-systole (†$p<0.01$) compared to end-diastole.

Figure 6. Intra- and interobserver reproducibility of peak strain measurements performed as correlations and Bland-Altman plots. Intraobserver (panel A) and interobserver (panel B) analysis demonstrated excellent reproducibility.

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