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Chapter 3.7

Abnormal left atrial flow patterns in patients after atrioventricular septal defect correction and regurgitation: evaluation with 4DFlow MRI and particle tracing


Submitted
ABSTRACT:

Background
During ventricular systole, a compact recirculating flow pattern forms in the left atrial (LA) blood flow. We aimed to evaluate LA recirculating flow structures in healthy volunteers and patients with corrected atrioventricular septum defect (AVSD) with both none to mild and moderate left atrioventricular valve (LAVV) regurgitation with the use of 4DFlow MRI.

Methods and Results
Data was obtained in eighteen controls (age 24±14 years) and eighteen corrected AVSD patients: nine (24±12 years) with none to mild regurgitation (<9%) and nine (21±13 years) with moderate regurgitation (>17%). In healthy controls, a single recirculating flow structure was visualized in the LA by streamlines (size 4.3±2.9mL) with a similar volume as the lambda2-extracted vortex core (3.9mL, IQR 3.0- 6.8 mL, p=0.27). In patients with regurgitation of the LAVV, two recirculating flow structures were observed in the LA, with opposing circulation direction. Recirculating blood flow contribution originated less frequently from the left pulmonary veins (LPVs) in patients with none to mild regurgitation (27±25%, p=0.023) and moderate regurgitation (6%, IQR 0-23%, p=0.002) compared with controls (49±21%).

Conclusion
Quantitative 3D analysis showed disturbed recirculating LA flow patterns in corrected AVSD patients with decreased contribution to the vortex cores from the LPVs. Furthermore, LAVV regurgitation caused multiple recirculating flow structures and disturbed flow from the LPVs.
INTRODUCTION

The left atrium (LA) has a reservoir function during ventricular systole when blood enters from the right pulmonary veins (RPVs) and left pulmonary veins (LPVs). During diastole, after opening of the left atrioventricular valve (LAVV), the LA serves as a conduit when blood flows from the RPVs and LPVs through the LA into the left ventricle. Efficient filling of the LA, contraction and draining into the ventricle contribute to adequate cardiac function [1].

Recirculating flow patterns and vortex formation are well described in the left ventricle and are known to contribute to efficient blood flow [2]. Recirculating flow in the LA has been described in healthy hearts during systole and mid-diastole based on streamline and pathline analysis from intra-cardiac blood flow velocity data. This phenomenon is suggested to play a role in preventing thrombus formation, preservation of LA flow momentum during ventricular systole and efficient diastolic left ventricular (LV) filling [1;3-5]. Previous studies suggest that the recirculating flow during ventricular systole mainly consist of blood originating from the LPVs. Blood flow from the RPVs was proposed to be directed along the inter-atrial septum towards the ventricle [1].

Regurgitation of the left atrioventricular valve (LAVV) has been a predictor for a poor clinical outcome even in asymptomatic patients [6]. An increase in turbulent kinetic energy in the LA has been described around LAVV regurgitation jets [7]. Patients after atrioventricular septal defect (AVSD) correction often present with LAVV regurgitation [8] and the re-operation rate is as high as 28% [9]. Moreover, the regurgitation direction in corrected AVSD patients is lateral towards the ostia of the LPVs, though the direction varies dynamically during systole [10]. We hypothesize that the dynamic and eccentric regurgitant jet in these patients disturbs formation of normal LA recirculating blood flow patterns.

Novel 4DFlow MRI techniques allow 3D quantification of intra-cardiac flow patterns and vortex analysis [11;12]. Therefore, the aim of this explorative study was to evaluate flow patterns in the LA in healthy subjects and patients after AVSD correction with the use of 4DFlow MRI-based visualization methods. In this study, normal flow behavior in the LA will be evaluated in healthy controls and in patients after correction of an AVSD correction. Furthermore, the effect of LAVV regurgitation on LA flow patterns will be studied by comparing left atrial flow patterns in patients with none-to-mild versus moderate LAVV regurgitation.

METHODS

Twenty healthy controls and twenty patients with a corrected AVSD were included. Patients were selected from a total group of 34 patients who underwent cardiac MRI. Selection was based on regurgitation grade: ten patients were selected with none to mild regurgitation (regurgitation fraction below 9%) and ten patients with moderate regurgitation (regurgitation fraction above
17%). Subjects with aliasing in LA velocity data were excluded. Informed consent was obtained from all patients and controls and/or their parents. Subjects and controls in the current study were also included in previous studies using 4DFlow MRI [10;12;13], but in none of these studies atrial flow patterns were evaluated.

**Magnetic Resonance Imaging**

All subjects underwent whole-heart 4DFlow MRI on a 3T system (Ingenia, Philips Medical Systems, The Netherlands) with maximal amplitude of 45mT/m for each axis and a slew rate of 200T/m/sec. A combination of FlexCoverage Posterior coil in the table top with a dStream Torso coil, providing up to 32 coil elements for signal reception was used, with the following acquisition settings: velocity-encoding of 150cm/s in all three directions, spatial resolution 2.3×2.3×3.0-4.2mm³, flip angle 10°, echo time (TE) 3.2ms, repetition time (TR) 7.7ms, true temporal resolution (4×TR) 31ms, SENSE factor 2 in anterior-posterior direction and Echo Planar Imaging with a factor 5. Retrospective VCG-gating was used with 30 phases reconstructed to represent one average heart cycle and free breathing without motion compensation was allowed. Commercially-available concomitant gradient correction and local phase correction filter were applied from the software available on MRI system (Ingenia 3 T with Software Stream 4.1.3.0). Acquisition time of the 4DFlow scan with a heart beat 60-80bpm was typically 8-10 minutes. Cine 2D left 2-chamber and 4-chamber views were acquired to quantify maximal left atrial volume according to the biplane area-length method \( \frac{8}{3\pi \times \text{Area}(4\text{-chamber}) \times \text{Area}(2\text{-chamber})}{\text{shortest atrial length}} \).

**Streamline evaluation of compact recirculating flow**

As regurgitation occurs during ventricular systole, flow patterns were evaluated during the reservoir function phases of the LA. Streamline display of the velocity field at any instant of time allows visualization of flow structures at a specific time point [14]. Streamline visualization using Mass software (LUMC, Leiden, The Netherlands) was used to assess and quantify compact recirculating flow structures in the LA. A stack of reformatted planes parallel to the 4-chamber view was analyzed with streamlines to visualize the flow pattern in the LA. The number of compact recirculating flow structures (i.e. where streamlines are circular and connected) was visually scored and the rotational direction with respect to the feet-head axis (clockwise or counter-clockwise) was determined (Figure 1A). A previous study showed that the vortex inside the atrium reached its largest volume just before the end of systole [1]. Therefore, the volume of the compact recirculating flow structure was measured two phases before end-systole. The compact recirculating flow structure was manually outlined in each axial slice and the areas were summed and multiplied by the slice thickness to compute the volume of the recirculating flow structure.
Figure 1. Explanation of used methodology.

Streamline visualization shows recirculating flow (dotted line in A) in clockwise direction with respect to the feet-head axis. The lambda2-method is used to extract the vortex core (red in B). Vortex cores are filled with seeds (dots in C). Backwards particle tracing allows the distinction between flow from the right pulmonary veins (RPV) and left pulmonary veins (LPV). RA = right atrium, RV = right atrium, LV = left ventricle.

Figure 2. Differences in left atrial flow between healthy control and patient.

Healthy control (A-C) and a patient with 36% left atrioventricular valve regurgitation (D-F). Streamline visualization shows a single counter-clockwise (with respect to the feet-head axis) recirculating flow structure in the control (arrow in A) compared with multiple recirculating flow structures in the patient (arrows in D). The vortex core in the patient is less compact and nearer to the atrioventricular valve (E). Backward tracing in the healthy control shows predominant contribution of the left pulmonary veins (LPVs) to the vortex core, whereas in the patient only contribution from the right pulmonary veins (RPVs) is observed (F). RA = right atrium, RV = right atrium, LV = left ventricle.
Vortex detection in the left atrium and particle tracing

Three-dimensional (3D) vortex cores can be identified using the gradient properties of the 4DFlow MRI data [12]. Vortex core detection was used to provide a more objective definition of the compact region of recirculating flow in the LA. Backwards particle tracing [15] was then used to distinguish respective contribution of the LPVs and RPVs to the detected vortex core. First, the LA was manually segmented on magnitude images of the 4DFlow scans. Subsequently the lambda2-method [12] was used to detect the vortex core from the velocity field two phases before end-systole. The 3D velocity data of the whole-heart 4DFlow acquisition was used for particle tracing algorithm, using 4th order Runge-Kutta numerical integration to create pathlines. To identify the origin of the recirculating flow, each voxel in the vortex core was designated as a seed point and backward particle tracing was performed until the start of systole. At the first phase of systole the particles were scored as 1) originating from LPVs; 2) originating from RPVs; 3) originating from LV (i.e., regurgitation); 4) particles already present in LA at start of systole (Figure 1). Particles entering the LA from outside the heart and not part of the pulmonary venous flow or LV regurgitation were excluded and considered as tracing errors (i.e., particles crossing the myocardial wall due to the discrete time step or spatial discretization used in the integration algorithm or due to other sources of error such as imaging artifacts). Additionally, to calculate the contribution of particles originating from LPVs and RPVs to the whole LA volume, at the same phase (two phases before systole) the whole atrium was seeded with particles and backwards tracing was performed to the start of systole.

Retrospective flow quantification

Using the same 4DFlow data set, retrospective valve tracking and through-plane flow mapping over the aorta and LAVV was performed. From aortic and LAVV flow-time curves the start and end of systole were determined as well as the regurgitation fraction [16]. Furthermore, the combined flow through the superior and inferior LPVs and the combined flow through the superior and inferior RPVs was quantified by retrospectively placing measurement planes at the ostium of each pulmonary vein, perpendicular to the inflow direction into the LA as visualized with streamlines. A resultant flow-time curve was formed for the summed LPVs and RPVs and peak systolic (S) and peak diastolic (D) flow from the pulmonary veins was defined. Furthermore, the time to peak systolic flow was determined.

Statistical analysis

Data are described as mean ± standard deviation or median (interquartile range) where appropriate. Differences between patients and controls are calculated with an independent t-test or Mann-Whitney U test where appropriate. The within-subject difference were tested with a paired t-test or Wilcoxon signed-rank test where appropriate between 1) volume of the compact recirculating flow structure (defined by streamlines) and vortex core volume (defined using the lambda2-method) 2) the left atrial inflow volume defined with particle tracing and the total
trans-pulmonary vein inflow. Correlation between different flow volumes were evaluated with Pearson’s test.

**RESULTS**

Visual grading of the 4DFlow scans revealed aliasing in the area of the LA in 2 controls and 2 patients (1 with none to mild regurgitation and 1 with moderate regurgitation), who were excluded from further analysis. Characteristics of included subjects are described in Table 1.

<table>
<thead>
<tr>
<th></th>
<th>Controls</th>
<th>Patients with none-mild LAVV regurgitation</th>
<th>Patients with moderate LAVV regurgitation</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Number</strong></td>
<td>18</td>
<td>9</td>
<td>9</td>
</tr>
<tr>
<td><strong>Age (years)</strong></td>
<td>24 ± 14</td>
<td>24 ± 12</td>
<td>21 ± 13</td>
</tr>
<tr>
<td><strong>Male (%)</strong></td>
<td>50</td>
<td>66</td>
<td>6</td>
</tr>
<tr>
<td><strong>Type of AVSD</strong></td>
<td>6 partial, 3 complete/intermediate</td>
<td>5 partial, 4 complete/intermediate</td>
<td></td>
</tr>
<tr>
<td><strong>Age of surgery (months)</strong></td>
<td>58 ± 55</td>
<td>69 ± 110</td>
<td></td>
</tr>
<tr>
<td><strong>Time after surgery (years)</strong></td>
<td>-</td>
<td>19 ± 9</td>
<td>16 ± 8</td>
</tr>
<tr>
<td><strong>Regurgitation fraction (%)</strong></td>
<td>-</td>
<td>5 ± 2</td>
<td>24 ± 6</td>
</tr>
<tr>
<td><strong>Atrial volume (mL)</strong></td>
<td>60 ± 31</td>
<td>74 ± 21</td>
<td>72 ± 24</td>
</tr>
<tr>
<td><strong>Atrial volume / BSA (mL/m²)</strong></td>
<td>34 ± 13</td>
<td>41 ± 8</td>
<td>48 ± 8 *</td>
</tr>
<tr>
<td><strong>LV Ejection fraction (%)</strong></td>
<td>62 ± 4</td>
<td>57 ± 4 *</td>
<td>55 ± 8 *</td>
</tr>
</tbody>
</table>

**Controls**

In the remaining 18 controls, a single counter-clockwise (with respect to the feet-head axis) compact recirculating flow pattern could be detected with streamline visualization during ventricular systole (Figure 2A). The manually segmented compact recirculating flow structure had a median volume of 4.3 ± 2.9mL when measured just before end-systole. These measured volumes showed modest correlation with total LA volume (r = 0.60, p = 0.009), but not with age (p = 0.73). In all controls, a vortex core could be detected with the lambda2-method in the LA. The median volume (3.9mL, IQR 3.0 – 6.8mL) was not different from the volume detected with streamlines (mean difference 0.51mL, p = 0.287 with 95%CI -0.7 – 1.7mL) and correlation between both volumes was r = 0.61 (p = 0.007).

Backward tracing of the vortex core volume revealed a mean of 49 ± 21% of the total vortex volume originating from the LPVs, a median of 7% IQR 3 – 14% originating from the RPVs with a remaining mean of 40 ± 15% of the total vortex volume originating from blood particles already present within the atrium at the start of ventricular systole.
The flow from the four pulmonary veins could be separately detected and quantified in 15 of 18 controls. In the remaining three controls, streamline visualization was not adequate to depict LA inflow at the ostium of all four veins respectively, and to perform retrospective flow mapping. For the remaining 15 controls, the combined flow from the four veins (38 ± 15mL) was comparable to the combined particle volumes of the LPVs and RPVs after seeding the whole atrium and backward tracing (36 ± 15mL) (mean difference -1.8 mL, p = 0.60, 95%CI -9.3 – 6.0 mL). Pulmonary venous flow during ventricular systole in controls showed a right-left volume ratio of 1.2 ± 0.4. Peak velocity was significantly higher in the LPVs (54 ± 14cm/s) as compared with the RPVs (36 ± 11cm/s, p<0.001). Peak systolic flow rate was reached in the LPVs 195 ± 49ms and in the RPV 107ms IQR 87 – 175ms (difference p = 0.003) after the start of ventricular systole.

Patients

All patients were in sinus rhythm, one patient previously underwent a cardioversion because of atrial fibrillation. In patients, the normal LA flow pattern was disturbed. Differences between both patient groups (none to mild regurgitation and moderate regurgitation) and the controls are presented in Table 2.

Of the patients with none to mild regurgitation streamline visualization revealed a single recirculating flow pattern in the LA as seen in controls in 8 (89%) patients and two separate compact recirculating flow structures in 1 (11%) patient, with a regurgitation fraction of 9%. Total volume of compact recirculating flow patterns combined was 3.2 ± 2.0mL in the none to mild regurgitation group, which was not significantly different from the vortex core volume in controls (mean difference patients with none to mild regurgitation to controls 1.0 mL, p = 0.34, 95%CI -1.2 – 3.3 mL). In patients with none to mild regurgitation, particles seeded from inside the vortex core originated less frequently from the LPVs compared with controls (27 ± 25%, p = 0.023). Moreover, an increased contribution to the vortex core of blood already present in the LA at the start of ventricular systole was observed in patients with none to mild regurgitation compared with controls (57 ± 23%, p = 0.03). Using retrospective mapping, detection of flow from four separate pulmonary veins was possible in all patients with none to mild regurgitation and revealed a non-significantly different right-left volume ratio as described in controls (1.1 IQR 0.9 – 1.6, p = 0.61). Peak flow velocity was similar in patient and controls in LPVs and RPVs (Table 2). In patients with none to mild regurgitation, peak flow rate was reached later in the RPVs as compared with controls (mean difference -69ms, 95%CI -121 – -18ms, p = 0.01).

In contrast to the controls, in patients with moderate regurgitation, streamline visualization revealed two or three separate compact recirculating flow structures in the LA in 8 (89%) patients (difference between patient groups p = 0.002) (Figure 2C). In patients with multiple recirculating flow structures, two structures could be detected around the regurgitant jet; one circulating in counter-clockwise direction and one in clockwise direction with respect to the feet-head axis. In 3 out of 9 patients with recirculating flow around the regurgitant jet, another (third) counter-clockwise recirculating flow pattern was seen more cranially in the atrium. Total volume of com-
Left atrial flow patterns combined was 4.7 ± 3.4mL in the moderate regurgitation group, which was not significantly different from the vortex core volume in controls (mean difference patients with moderate regurgitation -0.4mL, p = 0.74, 95%CI -3.0 – 2.1 mL). In patients with moderate regurgitation, particles seeded from inside the vortex core originated less frequently from the LPVs compared with controls (6% IQR 0 – 23%, p = 0.002). A trend towards an increased contribution to the vortex core of blood already present in the LA at the start of ventricular systole was observed in patients with moderate regurgitation (62 ± 27%, p = 0.05) compared with controls. Pulmonary venous flow quantification, possible in five patients with moderate regurgitation, revealed a non-significantly different right-left volume ratio as described in controls (1.3 ± 0.4, p = 0.90). Peak flow velocity was similar in patients and controls in the LPVs and RPVs.

Table 2. Differences between controls and the two patients groups. * indicate p < 0.05 as compared with controls. * pulmonary vein right-left ratio only computed in cases with four pulmonary veins detected. Rotational direction is described with respect to the feet-head axis.

<table>
<thead>
<tr>
<th></th>
<th>Controls</th>
<th>Patients with none-mild LAVV regurgitation</th>
<th>Patients with moderate LAVV regurgitation</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Streamlines</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Volume compact recirculating flow (mL)</td>
<td>4.3 ± 2.9</td>
<td>3.2 ± 2.0</td>
<td>4.7 ± 3.4</td>
</tr>
<tr>
<td>Rotational direction</td>
<td>100% single, counterclockwise</td>
<td>89% single counterclockwise, 11% one counterclockwise and one clockwise</td>
<td>11% single counterclockwise, 11% two counterclockwise structures and 78% one counterclockwise and one clockwise</td>
</tr>
<tr>
<td><strong>Vortex core</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Volume vortex (mL)</td>
<td>3.9 (IQR 3.0 – 6.8)</td>
<td>4.0 (IQR 3.3 – 6.8)</td>
<td>4.2 (IQR 2.3 – 6.7)</td>
</tr>
<tr>
<td>Contribution LPVs (%)</td>
<td>49 ± 21</td>
<td>27 ± 25 *</td>
<td>6 (IQR 0 – 23) *</td>
</tr>
<tr>
<td>Contribution RPVs (%)</td>
<td>7 (IQR 3 – 14)</td>
<td>16 ± 15</td>
<td>17 (IQR 4 – 31)</td>
</tr>
<tr>
<td>Residual in atrium (%)</td>
<td>40 ± 15</td>
<td>57 ± 23 *</td>
<td>62 ± 27 *</td>
</tr>
<tr>
<td><strong>Pulmonary venous flow</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Right-left ratio systolic volume*</td>
<td>1.3 ± 0.3</td>
<td>1.1 (IQR 0.9 – 1.6)</td>
<td>1.3 ± 0.4</td>
</tr>
<tr>
<td>Peak velocity LPVs (cm/s)</td>
<td>54 ± 14</td>
<td>46 ± 12</td>
<td>49 ± 17</td>
</tr>
<tr>
<td>Peak velocity RPVs (cm/s)</td>
<td>36 ± 11</td>
<td>33 ± 12</td>
<td>36 ± 12</td>
</tr>
<tr>
<td>Time to peak LPVs (ms)</td>
<td>195 ± 49</td>
<td>207 ± 53</td>
<td>242 ± 28 *</td>
</tr>
<tr>
<td>Time to peak RPVs (ms)</td>
<td>107 (IQR 87 – 175)</td>
<td>201 ± 74 *</td>
<td>223 ± 61 *</td>
</tr>
</tbody>
</table>
Systolic peak flow rate was reached later in the cardiac cycle in patients with moderate regurgitation compared with controls in both the LPVs (mean difference -48ms, 95%CI -84 – -12ms, p = 0.012) and the RPVs (mean difference -92ms, 95%CI -139 – -44ms, p = 0.001). Time to systolic peak flow rate in the LPVs was moderately correlated with the regurgitation fraction (r = 0.49, p = 0.04) whereas timing of peak flow rate in RPVs was not significantly correlated.

**DISCUSSION**

This explorative study provides new insights in blood flow characteristics in the LA in healthy controls and patients after AVSD correction with recurrent LAVV regurgitation, with the combined use of streamline visualization, semi-automated vortex core detection and particle tracing of pulmonary venous flow of 4DFlow MRI data. Key findings of the study are 1) in controls, on average 49% of volume of the single compact recirculating flow structure in the LA originates from the LPVs, but also on average 7% contribution to the volume originating from the RPVs was observed; 2) in corrected AVSD patients with none to mild regurgitation and with moderate regurgitation, the LPVs contribute less to the vortex core and systolic peak flow was reached later in the RPV; 3) additional differences in corrected AVSD patients with moderate LAVV regurgitation are multiple compact recirculating flow patterns and delayed systolic peak flow in the LPV that was related to regurgitation fraction.

**Vortex formation in the LA in healthy controls**

During ventricular systole the LA is filled and serves as an expanding reservoir. Previous studies observed recirculating blood in the LA [1;3-5], which in some studies is addressed as vortex flow. The recirculating flow conceivably avoids stasis and thrombosis and minimizes static pressure on the atrial wall [17]. Recirculating flow also contributes to the preservation of momentum in blood flow during ventricular systole, when the atrium is filled. Preserved momentum may aid efficient LV filling during early diastole.

Previous MRI studies used vector graphs, streamline analysis and pathline analysis [1;4;18] to visualize recirculating flow in 3D, however quantification of duration and size (area) of recirculating flow was limited to a 2D plane. Park et al. used echocardiography [5], with the advantage of a high frame rate and real-time imaging, but the limitation of analyzing 3D structures on 2D images. Complementing the quantification based on streamlines, the current study used the lambda2-method [12], to allow quantification of atrial vortex flow in 3D. Volumes of streamline-based recirculating flow were comparable to lambda2-detected atrial vortex cores, however, the shape of vortex cores appeared more irregular than the usually compact structures as segmented on streamline representation.

Postulations that flow from the LPVs mainly contributes to the LA recirculating flow formation and that flow from the RPVs is mostly directed along the LA wall with only little contribution to
the vortex, were thus far based on qualitative evaluations only [1]. The current study quantita-
tively showed that flow from LPVs in healthy controls has a substantially higher contribution to
the vortex core than flow from RPVs (on average 49% versus 7%). The higher peak velocities in
the flow from the LPVs compared with the RPVs might be a factor in this difference in contribu-
tion. However, even in healthy volunteers a large variation in venous contribution was observed,
which is possibly caused by diversity in pulmonary vein anatomy [19], which was not assessed
in this study.

**Left atrial flow in patients after AVSD correction**

A recent 4DFlow streamline-based study showed frequent absence of a vortex core in the LA in
patients with a variety of organic heart disease, which was related to pulmonary venous peak
velocity, but not pulmonary vein insertion angle [18]. In studies using computer fluid dynamics
[20], echocardiography [5] and 4DFlow MRI [3], abnormal LA flow was also described in patients
with atrial fibrillation and a relation with thrombus formation was suggested in these patients
[21].

Decreased contribution of blood flow from the LPVs to the vortex core was observed in cor-
crected AVSD patients with moderate as well as none to mild regurgitation. Therefore, the laterally
directed regurgitation (i.e., towards the LPVs) can only partly explain the decreased contribu-
tion of flow from the LPVs to the atrial vortex core in corrected AVSD. Contributing effects may
include the different pulmonary vein and LA anatomy after AVSD correction, possibly caused
by remodeling after surgery. The delayed peak flow rate in the LPVs was predominately present
in patients with moderate LAVV regurgitation and correlated to the regurgitation fraction and
might therefore be a direct result of regurgitation or caused by increased atrial pressure second-
ary to regurgitation.

In the current study, patients after AVSD correction showed a disturbed recirculating flow
pattern. Patients after AVSD correction often develop eccentric and dynamic regurgitation of
LAVV. In patients with regurgitation, two recirculating structures were detected around the
regurgitation jet(s). In an in vitro study, regurgitation jets with a high velocity in the presence of a
prosthetic mechanical heart valve were related to aberrant LA vortex formation and an increase
of shear stress in the blood flow near the wall, which directly activates platelets and has the abil-
ity to damage endothelial cells [22]. If endothelial cells fail to produce enough platelet inhibitors,
this can lead to thrombus formation. The vortex formation observed around the regurgitant
jet(s) in our study may similarly affect the atrial wall. Subsequently, it may contribute to the
LA enlargement, diastolic dysfunction and atrial fibrillation observed in patients with chronic
regurgitation of the LAVV [6]. On the other hand, others have suggested a protective property
of LAVV regurgitation for thrombus formation, due to the increased velocity which may prevent
stasis [23].

The clinical relevance of our preliminary findings comprises the role of disturbed LA flow
patterns on outcome in patients with and without regurgitation. Early correction of moderate-
severe regurgitation is debated even in asymptomatic patients [6] as regurgitation may result in LA dilatation, diastolic dysfunction and atrial fibrillation. Our study showed that LA blood flow in patients after AVSD correction is disturbed, and specifically LAVV regurgitation disturbs normal recirculating flow structures during ventricular systole. The parameters described in this study can be used in future studies to investigate if regurgitation in patients with other congenital or acquired heart disease similarly disturbs LA flow patterns. Further insights in LA flow patterns will help to better understand the effect of regurgitation on the LA and will eventually allow better prediction of the effect of regurgitation, which may be of benefit to optimization of timing of interventions.

**Study limitations**

Current study is a pilot study with small numbers of patients and no patients with severe LAVV regurgitation were available. Compact recirculating flow patterns were manually segmented based on streamline visualization. Streamlines only present the velocity field at an instant in time and therefore cannot represent the true trajectory of recirculating flow. To overcome the limitations of streamlines and the manual segmentation, we have in addition used a semi-automatic method to detect vortex cores, which resulted in similar volumes. Particle tracing resembles the true pathlines of blood flow over time, however changes in velocity magnitude and direction faster than the temporal and spatial resolution allow to detect, cannot be represented in the tracing algorithm. The border between atrium and pulmonary veins was manually segmented, which might have introduced inaccuracies in quantification.

**CONCLUSION**

Using 4DFlow MRI, quantitative 3D analysis of recirculating flow structures and vortex cores in the LA blood flow during ventricular systole showed a higher contribution of blood flow from the LPVs versus RPVs in healthy controls. Furthermore, patients after AVSD correction with and without regurgitation presented a decreased contribution of flow from the LPVs to the vortex cores. Finally, LAVV regurgitation in patients with a corrected AVSD resulted in disturbed LA flow patterns with two recirculating flow structures around the regurgitation jet with an opposed circulation direction. Follow-up studies in patients with disturbed LA flow are needed to further explore the long-term consequences of this disturbed atrial flow on cardiac function.
REFERENCES

