Age, gender, blood pressure, and ventricular geometry influence normal 3D blood flow characteristics in the left heart

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Aims

The aim of this study was to assess the effect of age, gender, physiological, and global cardiac function parameters on differences in normal 3D blood flow in the left ventricle (LV) and atrium (LA) using 4D flow magnetic resonance imaging (MRI).

Methods and results

Four-dimensional flow MRI was acquired in healthy volunteers of two age and gender groups: <30 years (6 women, n = 12) and >50 years (6 women, n = 12). Systolic and early to mid-diastolic vortex flow (number of vortices, duration, area, peak velocity inside the vortex) in the LA and LV was assessed using intra-cardiac flow visualization based on 3D particle traces and velocity vector fields. A larger number of vortices in the LA were found in young compared with older individuals (number of diastolic vortices: 1.6 ± 0.8 vs. 0.7 ± 0.7, P = 0.01) with higher velocities (54 ± 12 cm/s vs. 41 ± 11 cm/s in systole, 47 ± 13 vs. 31 ± 8 cm/s in diastole, P < 0.05). Vortices in the LV base were smaller in women compared with men (369 ± 133 vs. 543 ± 176 mm², P = 0.009), while vortex size was increased in mid-ventricular locations (maximum area: 546 ± 321 vs. 293 ± 174 mm², P < 0.05). Correlation analysis revealed significant relationships (P = 0.005–0.048, correlation coefficients = 0.44–0.84) between LA and LV vortex characteristics (number, size, vortex velocities) and blood pressure as well as end-diastolic volume, LV length, and ejection fraction.

Conclusions

Flow patterns in the left heart demonstrated differences related to age, gender, blood pressure, and ventricular geometry. The findings constitute a prerequisite for the understanding of the impact of cardiac disease on intra-cardiac haemodynamics.

Keywords

Blood flow • 4D flow MRI • Ageing • Gender • Vortex

Introduction

Blood flow through the beating heart is complex and normal physiological as well as pathologically altered blood flow conditions are difficult to assess in vivo. Alterations of blood flow can carry important consequences in congenital or valvular heart disease, in remodelling of the left ventricle (LV) in ischaemic heart disease or in aortic diseases.1,2

To date, a comprehensive analysis of intra-cardiac 3D flow patterns is not performed in clinical routine and only limited data on normal atrial and ventricular flow patterns are available. Blood flow measurements are limited to 2D Doppler echocardiography or phase contrast magnetic resonance imaging (MRI) which acquires flow velocities within a user-selected 2D plane.3,4 Both techniques are limited to measurements at predefined locations and often assess only a single velocity component of the underlying three-directional blood flow. Routinely used phase contrast MRI or Doppler ultrasound do not offer the possibility to measure and visualize the temporal evolution of complex flow patterns within a 3D volume encompassing the beating human heart.

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To overcome these limitations, 4D flow MRI (ECG-synchronized 3D phase contrast MRI with three-directional velocity encoding) has been applied in a number of studies for the analysis of 3D blood flow with full volumetric coverage of the left atrium (LA) and left ventricle (LV). Vortical flow within the cardiac chambers has been described in healthy volunteers as well as in patients with cardiomyopathy, mitral valve insufficiency, and after heart transplantation. Four-dimensional MRI data have been used for the quantification of flow within cardiac chambers, through the heart valves, and in pulmonary arteries in patients with Fontan circulation.

Although it is known that age and gender alter LV myocardial tissue properties and function, a systematic evaluation of normal physiological LA and LV flow formation in relation to age, gender, and other influencing factors such as blood pressure or heart rate is missing. The aim of this study was to test the hypothesis that age, gender, physiological, and global cardiac function parameters correlate with the presence and extent of left atrial and left ventricular systolic and diastolic vortex flow patterns in healthy volunteers.

Methods

Study population

We included 24 healthy volunteers in two age and gender groups: <30 years (n = 12, mean 23.3 ± 1.6 years, 6 women) and ≥50 years (n = 12, 58.3 ± 4.2 years, 6 women). The cut-off age was chosen based on the assumption that a large difference between the age-group cut-offs (20 years) would provide a clear separation of both groups and result in an improved separation of flow characteristics given the small number of individuals in each cohort. All volunteers were without history, symptoms, or medication of cardiovascular or pulmonary disease, diabetes, arterial hypertension, or peripheral arterial disease. All volunteers had a normal echocardiography and ECG findings. Written informed consent was obtained from all participants and the study was approved by our local ethics board. The volunteers’ characteristics are summarized in Table 1.

MR imaging

All examinations were performed using a standard 12-element torso coil (3T, Magnetom TRIO, Siemens, Erlangen, Germany). We employed flow-sensitive MRI with volumetric 3D coverage of the whole heart and three-directional velocity encoding (4D flow MRI) to systematically identify and evaluate the existence and extent of characteristic flow patterns in the left heart. The imaging sequence consisted of a previously described, k-space segmented, rf-spoiled gradient echo sequence with interleaved three-directional velocity encoding. Other imaging parameters were: TE = 2.4 ms, TR = 4.8 ms, flip angle = 7°, field of view = 320 × 240 mm, spatial resolution = 2.5 × 2.5 × 2.8 mm³, temporal resolution = 38.4 ms, scan time ~15–25 min, and parallel imaging with reduction factor R = 2. Magnetic resonance imaging acquisitions were synchronized to the heart and breathing cycle using prospective ECG gating and adaptive diaphragm navigator gating. Prospective ECG gating resulted in 4D flow data covering about 80–90% of the heart cycle, i.e., including systole, early, and mid-diastole.

Data analysis

All 4D flow data underwent pre-processing including noise masking, eddy current correction, Maxwell corrections, and calculation of a 3D phase contrast MR angiogram as described previously. To visually identify and grade intra-cardiac flow patterns, 3D visualization was employed (EnSight v.8.2, CEI, Apex, NC, USA). Flow analysis included the calculation of time-resolved 3D particle traces originating from emitter planes which were manually placed in the pulmonary veins. The resulting traces provide a visual representation of the temporal dynamics and spatial distribution of 3D blood flow (Figure 1). In addition, vector fields in the two- and four-chamber planes were calculated for each time point (Figures 2 and 3). In order to identify and grade intra-atrial and intra-ventricular vortex flow, particle traces were first used to identify vortices and their directions of rotation. In the following, vector graphs were analysed as follows:

- Left atrium (two-chamber and four-chamber view): number, duration, maximum area, and peak velocities inside the vortex. The analysis was performed separately for both systole and early to mid-diastole.
- Left ventricle (two-chamber and four-chamber view): peak diastolic LV in-flow velocity and systolic and early to mid-diastolic vortex formation (number, duration, maximum area, and peak velocity inside the vortex) at base, mid, and apex of the LV.

Vortex duration was defined as the time between the onset of visible vortical flow to its disappearance. Vortical flow in the LA was assessed as viewed from behind, LV flow was evaluated as viewed from above (four-chamber view) or from the left side (two-chamber view). If not stated otherwise, the results given in the text refer to the analysis in two-chamber view.

Statistical analysis

All data are presented as mean ± standard deviation unless stated otherwise. Comparisons between age groups and genders were performed by unpaired Student’s t-test for normally distributed values and the Mann–Whitney U-test for values not normally distributed. Systolic and diastolic vortex formation in the LA and LV (number, duration, maximum area, and peak velocity inside the vortex) were correlated with physiological parameters, such as age, heart rate, and blood pressure and with LV geometry and function. Correlations were calculated by the Pearson Product Moment for values normally distributed, and Spearman’s test was used to calculate correlations for values not normally distributed. The Kolmogorov–Smirnov test was used to test for normality. A. Kruskal–Wallis one-way analysis of variance (‘on Ranks’ for not normally and equally distributed values) followed by the Holm–Sidack (or Dunn’s) procedure for pairwise multiple testing was used for the comparisons between the flow characteristics within the three levels of the LV. Statistical testing was performed using SigmaStat for Windows Version 3.10. Two-tailed tests with P < 0.05 were considered statistically significant.

Results

Study cohort

The clinical characteristics for all subjects are summarized in Tables 1 and 2. Older volunteers had higher systolic blood pressure (P = 0.01) and shorter LV length (P = 0.02). Older men had higher heart rates (P = 0.01), systolic blood pressures (P = 0.04), and higher LV mass (P = 0.02) compared with young men. Women had a higher LVEF and reduced left ventricular end-diastolic volume (LVEDV), LVESV, and LV mass compared with men (P < 0.05, Table 2).
Three-dimensional particle traces

In all volunteers, vortical flow was found in the LA and LV. Systolic and diastolic vortical flow in the LA was evident in 92% of the young and 83% of the older volunteers (Figure 1). Most LA vortices (81% in young and 74% in older subjects) were directed clockwise as viewed from the back. Twenty-eight percent of the vortices in men and only 16% in women were anti-clockwise.

Left atrial flow

In 75% of subjects, systolic and diastolic vortex flow in the LA was evident as shown in Figure 1 and summarized in Tables 3 for vector plot analysis. Compared with early to mid-diastolic vortex flow, systolic vortex flow occurred more frequently (systole vs. diastole: 2.2 ± 1.0 vs. 1.1 ± 0.9, \( P < 0.001 \)), and had longer duration (151 ± 60 vs. 124 ± 74 ms; \( P = 0.055 \) in two-chamber view; 171 ± 90 vs. 96 ± 56 ms in four-chamber view, \( P = 0.005 \)).

Younger individuals showed an increased duration (\( P = 0.023 \)) and higher velocities (\( P = 0.012 \)) inside the vortices in the LA for both systole and diastole compared with the older group. Diastolic LA vortices occurred less frequently in older volunteers (five subjects showed no vortex compared with one subject <30 years) (\( P < 0.013 \)).

Left ventricular flow

The results of LV flow analysis are summarized in Tables 4. The maximum area of vortices decreased from base to apex for both men and women. Larger vortices were found at the base (472 ± 196 vs. 299 ± 112 mm² in mid-ventricular and 214 ±
128 mm² in apical parts of the LV, \( P = 0.002 \)). Peak velocities within the vortices decreased from base to apex (base 6.1 ± 1.7 cm/s, mid 4.5 ± 1.0 cm/s, apex 3.3 ± 0.8 cm/s, \( P < 0.001 \)). The smallest numbers of vortices were found in apical parts of the LV (0.3 ± 0.4 vs. 2.0 ± 0.4 in basal or 2.0 ± 0.7 in mid-ventricular segments, \( P < 0.001 \)). The majority subjects presented with two vortices in the LV base (88%) and mid-ventricular LV (54%) irrespective of age.

Gender-related differences
At the LV base, women revealed smaller vortices (369 ± 133 vs. 543 ± 176 mm², \( P = 0.009 \)) (Figure 3), while vortex size was increased at the mid-ventricular location compared with men (maximum area: 546 ± 321 vs. 293 ± 174 mm², \( P = 0.033 \)). In addition, apical vortices had increased duration in women compared with men (98 ± 38 vs. 48 ± 19 ms; \( P = 0.038 \)).

Correlation with physiological data, LV function, and morphology
There was an inverse relationship between increasing age and systolic vortex velocities [correlation coefficient (CC) = −0.51, \( P = 0.01 \)] and number of diastolic vortices (CC = −0.45, \( P = 0.03 \)) in the LA. Furthermore, age was inversely correlated with the maximum area (CC = −0.49, \( P = 0.02 \)) and velocity (CC = −0.48, \( P = 0.02 \)) of basal LV vortices.

Heart rate did affect the number of diastolic LA vortices (CC = −0.55, \( P = 0.007 \)) and was also correlated with the duration (basal: CC = −0.46, \( P = 0.03 \); mid-LV: CC = −0.57, \( P = 0.005 \)) and area (mid-LV: CC = −0.45, \( P = 0.03 \)) of LV vortices.

Increased systolic blood pressure resulted in a larger size of diastolic LA vortices (CC = 0.50, \( P = 0.046 \)) but reduced vortex peak velocity (CC = −0.54, \( P = 0.03 \)) and less basal LV vortices (CC = −0.44, \( P = 0.048 \)) with lower peak velocities (CC = 0.57, \( P = 0.007 \)). Diastolic blood pressure correlated with mid-ventricular and apical LV vortex velocities (CC = −0.74, \( P < 0.001 \), respectively, CC = −0.84, \( P = 0.03 \)).

Left ventricular end-diastolic volume influenced the number of LA vortices in diastole (CC = 0.49, \( P = 0.03 \)) and LV length correlated with the number of LV vortices (mid-LV: CC = 0.52, \( P = 0.03 \)).

Figure 2 Vector graph visualization of intra-cardiac blood flow in a young (A) and an old (B) healthy volunteer. The formation of diastolic vortex flow in the LA and LV is evident and indicated by the dashed circles. Note the reduced diastolic in-flow velocities (colour coding) and less-prominent vortex flow in the older volunteer. RV, right ventricle; Ao, aorta.
A higher LVEF was associated with a decreased area of basal vortices (CC = −0.49, P = 0.03) and more apical vortices (CC = 0.421, P = 0.05).

**Discussion**

The maintenance of a stable blood flow is fundamental for human life and the ultimate measure of adequate cardio-vascular function.

The results of this study demonstrate the potential of 4D flow MRI with whole heart coverage for the detailed analysis of intra-cardiac vortex flow. The results of our semi-quantitative analysis of flow patterns demonstrated significant age as well as gender-related differences in intra-atrial and intra-ventricular flow patterns.

Flow characteristics in the LA have previously been analysed by others and anti-clockwise vortex formation in the LA has been reported before (as viewed from the front). In our study, previously not described vortex formation in the opposite direction was found in 54% of the individuals mainly from blood flow originating in the upper pulmonary veins. Similar to findings in other
### Table 3  
Cumulative results of vortex analysis in the LA for the young (<30 years) and the older age group (>50 years) analysed in the two-chamber view and in the four-chamber view

<table>
<thead>
<tr>
<th>Analysis based on two-chamber view</th>
<th>Number</th>
<th>Duration (ms)</th>
<th>Area max. (mm²)</th>
<th>$V_{\text{max}}$ (cm/s)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Systole</strong></td>
<td>&lt; 30 years ($n = 12$)</td>
<td>2.2 ± 1.0</td>
<td>178 ± 63*</td>
<td>338 ± 142</td>
</tr>
<tr>
<td>&gt; 50 years ($n = 12$)</td>
<td>2.3 ± 1.1#</td>
<td>124 ± 44</td>
<td>354 ± 268</td>
<td>41 ± 11</td>
</tr>
<tr>
<td><strong>Diastole</strong></td>
<td>&lt; 30 years ($n = 12$)</td>
<td>1.6 ± 0.8b</td>
<td>134 ± 88</td>
<td>319 ± 283</td>
</tr>
<tr>
<td>&gt; 50 years ($n = 12$)</td>
<td>0.7 ± 0.7</td>
<td>110 ± 47</td>
<td>332 ± 164</td>
<td>31 ± 8</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Analysis based on four-chamber view</th>
<th>Number</th>
<th>Duration (ms)</th>
<th>Area max. (mm²)</th>
<th>$V_{\text{max}}$ (cm/s)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Systole</strong></td>
<td>&lt; 30 years ($n = 12$)</td>
<td>1.9 ± 0.9</td>
<td>174 ± 68#</td>
<td>350 ± 279</td>
</tr>
<tr>
<td>&gt; 50 years ($n = 12$)</td>
<td>2.0 ± 1.2</td>
<td>169 ± 112#</td>
<td>259 ± 167</td>
<td>36 ± 12</td>
</tr>
<tr>
<td><strong>Diastole</strong></td>
<td>&lt; 30 years ($n = 12$)</td>
<td>1.7 ± 1.0</td>
<td>111 ± 5</td>
<td>219 ± 194</td>
</tr>
<tr>
<td>&gt; 50 years ($n = 12$)</td>
<td>1.0 ± 1.2</td>
<td>70 ± 50</td>
<td>157 ± 100</td>
<td>27 ± 11</td>
</tr>
</tbody>
</table>

Data represent mean values ± standard deviation. $V_{\text{max}}$, peak velocity; Area max., maximum area.  
*P &lt; 0.05 vs. older age group.  
#P &lt; 0.05 vs. diastole (same age group).

### Table 4  
Cumulative results of vortex analysis in the LV for the young (<30 years) and the older age group (>50 years) analysed in the two-chamber view and in the four-chamber view

<table>
<thead>
<tr>
<th>Analysis based on two-chamber view</th>
<th>Number</th>
<th>Duration (ms)</th>
<th>Area max. (mm²)</th>
<th>$V_{\text{max}}$ (cm/s)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Base</strong></td>
<td>&lt; 30 years ($n = 12$)</td>
<td>2.1 ± 0.3</td>
<td>154 ± 68</td>
<td>538 ± 164</td>
</tr>
<tr>
<td>&gt; 50 years ($n = 12$)</td>
<td>2.0 ± 0.4</td>
<td>116 ± 52</td>
<td>406 ± 206</td>
<td>52 ± 16b</td>
</tr>
<tr>
<td><strong>Mid</strong></td>
<td>&lt; 30 years ($n = 12$)</td>
<td>2.3 ± 0.7</td>
<td>170 ± 81</td>
<td>286 ± 110</td>
</tr>
<tr>
<td>&gt; 50 years ($n = 12$)</td>
<td>1.8 ± 0.6</td>
<td>123 ± 55</td>
<td>312 ± 118</td>
<td>43 ± 14</td>
</tr>
<tr>
<td><strong>Apex</strong></td>
<td>&lt; 30 years ($n = 12$)</td>
<td>0.3 ± 0.4</td>
<td>153 ± 66</td>
<td>149 ± 108</td>
</tr>
<tr>
<td>&gt; 50 years ($n = 12$)</td>
<td>0.3 ± 0.5</td>
<td>89 ± 89</td>
<td>260 ± 152</td>
<td>37 ± 6</td>
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</table>

<table>
<thead>
<tr>
<th>Analysis based on four-chamber view</th>
<th>Number</th>
<th>Duration (ms)</th>
<th>Area max. (mm²)</th>
<th>$V_{\text{max}}$ (cm/s)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Base</strong></td>
<td>&lt; 30 years ($n = 12$)</td>
<td>1.8 ± 0.4</td>
<td>126 ± 37</td>
<td>473 ± 200</td>
</tr>
<tr>
<td>&gt; 50 years ($n = 12$)</td>
<td>1.9 ± 0.3</td>
<td>131 ± 55</td>
<td>438 ± 155</td>
<td>52 ± 10b</td>
</tr>
<tr>
<td><strong>Mid</strong></td>
<td>&lt; 30 years ($n = 12$)</td>
<td>1.7 ± 0.7</td>
<td>155 ± 103</td>
<td>452 ± 333</td>
</tr>
<tr>
<td>&gt; 50 years ($n = 12$)</td>
<td>1.1 ± 0.7#</td>
<td>130 ± 89</td>
<td>381 ± 219</td>
<td>43 ± 14</td>
</tr>
<tr>
<td><strong>Apex</strong></td>
<td>&lt; 30 years ($n = 12$)</td>
<td>0.5 ± 0.7</td>
<td>72 ± 33</td>
<td>152 ± 51</td>
</tr>
<tr>
<td>&gt; 50 years ($n = 12$)</td>
<td>0.5 ± 0.7</td>
<td>84 ± 50</td>
<td>124 ± 55</td>
<td>28 ± 8</td>
</tr>
</tbody>
</table>

Data represent mean values ± standard deviation. $V_{\text{max}}$, peak velocity; Area max., maximum area.  
*Significant differences between both age groups ($P &lt; 0.05$).
studies and probably due to the more cranial location of the left pulmonary veins, vortex formation in flow path ways originating from the left side was more prominent. In contrast to a previous study, we did not find a relationship between LA vortex flow duration and heart rate. In addition, we found shorter durations of LA vortices which might be related to the higher temporal resolution in our study.

As reported by Kilner et al., the heart’s vortical flow characteristics in conjunction with the looped formation of the heart itself seem to be fundamental for a stable blood flow, prevention of energy losses, and optimal atrial–ventricular coupling especially with increased heart rate under exercise. Furthermore, vortex flow is meant to play an important role in the valves’ closure and in preventing blood flow stasis and thromboembolic risk. The asymmetric vortical inflow in the cardiac chambers has been reported in healthy volunteers using phase contrast MRI and ultrasound vectorparticle image velocimetry. Vortices have been described in basal LV locations at the anterior mitral leaflet and near the posterior mitral leaflet. It is assumed that vortices play an important role in redirecting the inflowing blood flow towards the aortic valve.

Previous 4D flow MRI studies have demonstrated that in the healthy heart 30% of the blood in the LVEDV passes the LV directly within one cardiac cycle in the shortest way and with least energy losses, whereas this percentage of ‘direct flow’ in the LV is strongly reduced in the failing heart. Studies with vector particle image velocimetry also revealed altered LV vortices in patients with systolic LV dysfunction, stressing the importance of an undisturbed vortical flow for optimal cardiac function. However, none of these studies based their findings on a systematic age- and gender-related comparison of LA and LV flow characteristics including other influencing factors such as blood pressure or heart rate.

As we could demonstrate, ageing resulted in a reduced number of diastolic LA vortices as well as lower velocities and durations of systolic LA vortices. These findings could not be explained by heart rate or LVEF, which did not differ between the age groups. Shorter LV lengths and higher systolic blood pressures might have contributed to the reduced numbers of mid-ventricular vortices and the reduced diastolic vortical velocities in the LA and LV base but do not explain the other differences of LA vortical flow. It is known that ageing alters LA and LV function due to changes of myocardial structure and differences in Ca channel handling, alterations in the sympathetic nervous system, and a reduction in arterial compliance and endothelial function. In this context, altered Doppler inflow characteristics in the LA and LV have been described with ageing. In line with our finding of reduced LA diastolic vortices, the inflow in the LA decreases in diastole with increased age, whereas inflow in systole increases. Our finding of reduced diastolic vortex formation in the LA and LV in older volunteers might therefore reflect age-related diastolic dysfunction of these individuals.

Women revealed smaller vortices in the LV base and a higher number of vortices in the mid-ventricular LV. In addition, apical vortex formation lasted longer compared with men. Geometric differences such as reduced LVEDV or LV length in women did not explain these gender differences. The higher LVEF in older women might have contributed to smaller vortices in basal parts in women. Similar to our findings, gender differences in LV inflow measured by Doppler echo have been described. However, the increased extent of mid-ventricular vortices in women is a previously unreported finding and might be caused by increased vascular and ventricular stiffness in women as previously reported by Redfield et al.

**Limitations**

A limitation of our study is related to the prospective ECG gating of our 4D flow MR sequence. As a result, only data representing about 80–90% of the heart cycle were acquired within the RR interval. Therefore, atrial contraction with consecutive second filling of the LV could only be visualized in four of the older individuals despite sinus rhythm in all volunteers. It should be noted that, as a result of prospective ECG gating, late diastole is variably included in the results. As a result, the findings of this study need to be interpreted with care and represent flow characteristics during early and mid-diastole only.

A further drawback of the data analysis methodology is related to the use of velocity vector fields from conventional two- and three-chamber views which minimize the ‘three-dimensional’ aspect of our findings, even though these were based on three-directional data.

Another limitation of the study is that we did only perform a semi-quantitative analysis without evaluation of intra- and interobserver variability. In addition, no data on inter-study variability are currently available to provide information on the test-retest reliability of cardiac 4D flow MRI and the analysis methods presented here.

The small size of the study cohort constitutes a major limitation and underlines the feasibility character of this study. In our current study, we have analysed the impact of the haemodynamic state of an individual (heart-rate, blood pressure, etc.) on the resulting cardiac flow characteristics using correlation analysis. The small number of volunteers might explain the significant but moderate correlations (r = 0.4–0.8) found in our cohort between flow characteristics and cardiac function parameters, blood pressure, heart rate, and age. The evaluation of intra-cardiac 3D blood flow in larger cohorts is warranted to confirm our results and clarify the degree of correlation between the haemodynamic state of an individual and the observed flow characteristics.

In addition, further studies with increased sample sizes and including patient data are essential to evaluate the influence of cardiac disease on the flow characteristics of the left heart. Further, an investigating the reproducibility of the flow characteristics indices and semi-quantitative flow pattern grading used in this study are needed. Although we did not evaluate the observer variability of the semi-quantitative flow pattern grading, previous work by our group has demonstrated the reliability of flow pattern grading based on 4D flow MRI data. In a recent study assessing aortic flow patterns in patients with Marfan syndrome using 4D flow MRI, we found substantial inter-observer agreement (kappa = 0.7) for the visual grading of helix and vortex flow in the ascending aorta, the aortic arch, and descending aorta.

A further drawback is related to the relatively long 4D flow MRI acquisition times and the effective averaging of velocity
measures over many heart cycles, only flow characteristics that occur consistently through successive beats are recorded and analysed. The peak local velocities and numbers of vortices identified may underestimate those occurring in real time in any given beat. Nevertheless, our study describes the feasibility of blood flow imaging in the healthy heart and offers new insights into intra-cardiac blood flow characteristics.

**Conclusions**

Cardiac 4D flow MRI in a small cohort of healthy subjects demonstrated that heart rate, blood pressure, LV geometry, age, and gender can affect intracardiac blood flow characteristics. These findings might have the potential to improve our understanding of physiological and pathological processes of cardiovascular function. Future studies including data on reproducibility and larger patient cohorts are needed to assess the impact of intra-cardiac flow patterns on cardiovascular disease and their diagnostic value related to disease progression and therapy monitoring.

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**References**