Adverse outcomes following percutaneous transcatheter interventions

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Citation for published version (APA):

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Chapter 10

Four-dimensional flow MRI in chronic myocardial infarct patients with left ventricular thrombus formation.


Submitted.
Chapter 10

ABSTRACT

Background The formation of left ventricular thrombus (LVT) following myocardial infarction (MI) has been attributed to decreased left ventricular function and/or aneurysmatic apex with resulting stasis of blood flow. Four dimensional (4D) flow cardiovascular magnetic resonance (CMR) allows quantification of kinetic energy (KE) and functional blood flow components that may aid in identifying patients at increased risk for LVT formation.

Objectives In this pilot study, we investigated whether differences in 4D flow-derived parameters could be observed between chronic MI patients with (LVT+) and without an apical LVT (LVT-), and healthy controls.

Methods 4D flow CMR was performed in 19 chronic MI patients (LVT+, n=9 and LVT-, n=10) and 9 age-matched controls. LVT+ and LVT- patients had comparable LVEF. The acquired short-axis cine acquisition was used to segment the LV cavity throughout the complete cardiac cycle. Particle tracing was performed by seeding from the end-diastolic volume to assess functional blood flow components. The LV cavity was divided into 4 levels and the KE of blood was derived for the complete LV and per individual level normalized for LV volume.

Results LVT- and LVT+ patients have an increased delayed ejection flow versus controls (LVT- 20±8 vs. controls 14±5%, P < 0.05 and LVT+ 21± 7 vs. controls 14±5%, P=0.02). Retained flow is significantly decreased in LVT+ versus LVT- patients (19± 5 vs. 24±4%; P=0.03). A lower systolic peak KE was observed in the apex of LVT+ patients versus controls (3.03±1.42μJ/mL vs. 6.81±2.02μJ/mL, P= <0.001). When comparing LVT+ and LVT- group no difference was observed in the maximal KE during systole in the apex (P = 0.11). In vortex core analysis, E-peak longitudinal and orientation parameters are statistically different in LVT+ and LVT- group.

Conclusions LVT patients have an increased residual and delayed blood flow and a decreased peak systolic KE in the apex in comparison to controls. A trend towards a lower KE was observed in LVT+ patients in comparison to LVT-. KE at the apex, as assessed by 4D flow CMR, may be an early indicator of stasis of blood flow. Larger prospective studies are warranted to further evaluate these initial observations.
INTRODUCTION

Left ventricular thrombus (LVT) formation following myocardial infarction (MI) is a well-recognized, but serious complication with an increased risk of thrombo-embolic events.\(^1,2\) In the current era of percutaneous coronary intervention (PCI) and dual antiplatelet therapy, the prevalence of LVT in reperfused MI patients is reported to be 3.5-8.8% as assessed by CMR.\(^3,4\) Major risk factors that have been associated with LVT formation include decreased left ventricular ejection fraction (LVEF) on admission, anterior infarct location, greater percentage of wall motion abnormality and an aneurysmatic apex.\(^2,3,5,6\) Additionally, echocardiography studies have reported abnormal flow patterns in LVT patients, including apical rotating flow and vortex ring formation,\(^7,8\) which may be of importance to identify patients at risk. Although echocardiography is widely available and inexpensive, cardiac magnetic resonance (CMR) has superior diagnostic accuracy for LV thrombus detection.\(^9\)

Recent advances in 4 dimensional (4-D) flow phase contrast CMR allows time-resolved volumetric assessment of the three directional components in the heart during in a single acquisition. The obtained velocity data enables quantification of kinetic energy (KE) and functional blood flow components of intra-cardiac blood flow.\(^10,11\) Assessment of these parameters may be relevant to further understand the complex nature of LVT formation secondary to prior MI.

Therefore, the aim of this pilot study was to assess intra-cardiac flow parameters derived from 4D flow CMR in patients with an apical LVT formation secondary to prior MI. A comparison was made with chronic MI patients with a decreased left ventricular function but without a LVT and healthy age-matched controls.

METHODS

Study population

Nine patients with an apical LV thrombus (LVT+) were prospectively identified either on echocardiographic or CMR imaging. Secondly, we identified a group of chronic MI patients (n=10) who had comparable LVEF but had no LVT formation on CMR (LVT-). Both patient groups were enrolled from the clinical imaging service at Leeds Teaching Hospitals and the University of Leeds (Leeds, United Kingdom). Finally, nine healthy age-matched controls were recruited (Leeds, n=5 and ) and at Leiden University Medical Center (Leiden, the Netherlands, n=4). Controls had no history of cardiovascular disease and were not using any medication.

All included subjects were in sinus rhythm. Exclusion criteria included coronary artery bypass grafting, non-ischemic cardiomyopathy, estimated glomerular filtration rate
<30 mL/min/1.73 m², haemodynamic instability or any contraindication to CMR imaging. Also, for the current analysis we excluded patients with aortic regurgitation and moderate-severe mitral valve insufficiency as this affects intra-cardiac flow.

The study was conducted in accordance with the Declaration of Helsinki and the study protocol was approved by the institutional research ethics committee. All patients provided informed consent prior to inclusion.

**Cardiac Magnetic Resonance imaging acquisition**

All subjects underwent cine and 4D flow imaging on identical clinical 1.5T Philips Ingenia systems (Philips Healthcare, Best, the Netherlands) in Leeds or Leiden using a 28-channel flexible cardiac receiver coil. Cine imaging was performed using a standard steady-state free precession sequence in long axis and short axis orientations covering the left ventricle (30 phases per cardiac cycle). For the acquisition of 4D flow imaging, a 3D time-resolved volume acquisition of the whole heart was performed with velocity encoding in all three directions. Flow encoding was performed by the MPS (measurement, phase, slice) reconstruction method which implies encoding of velocity in three directions sequentially and with respect to the frame of reference, which is the three-dimensional volume. Gradient non-linearity correction and Maxwell correction were compensated by the CMR scanner. Typical imaging parameters were: TE/TR 3.7ms/11 ms, flip angle 10º, VENC 150 cm/s and voxel size 3.0x3.0x3.0mm (30 phases per cardiac cycle).

For the chronic MI patients, we also acquired late gadolinium enhancement (LGE) images at 15 min after administration of a gadolinium-based contrast agent (0.2mmol/kg), using a 2D inversion recovery gradient-echo pulse sequence, in similar imaging orientation as the cine images.12

**Ventricular volume, function and infarct size analysis**

The cine and LGE images were performed to determine left ventricular (LV) volumes, left ventricular ejection fraction (LVEF), infarct size and extent, and the presence of LVT. CMR data was evaluated offline using MASS research software (Version V2017-EXP, Leiden University Medical Center, Leiden, The Netherlands). Analyses were performed (MH, RG, RN) blinded to patient characteristics.

Using standard methods for volumetric CMR assessment,13 manual outlining of endocardial and epicardial borders on the short axis over the entire cardiac cycle was done in order to determine the left ventricular volumes (stroke volume (SV), end-diastolic volume (EDV) and end-systolic volume (ESV)), LV mass and ejection fraction. Stroke volume was defined as the difference in EDV and ESV.

Infarct location and size were assessed on the LGE images using the full-width at half-maximum (FWHM) technique and expressed as a percentage of LV mass.14
LVT was identified as a filling defect within the LV cavity, typically adjacent to regions of abnormal wall motion on cine sequences. This in turn was confirmed on the LGE images in two sequential planes. LVT was differentiated from microvascular obstruction on the LGE images by assessing whether the hypointense structure was located within the hyperenhanced myocardium or located outside the endocardial border in the LV cavity.

The presence of thrombi was scored by two blinded, independent observers (RN and PG), blinded to patient identity.

**Particle tracing quantification and blood flow quantification**

With the 4D flow data we were able to integrate the multidimensional velocity data for particle trace analysis. Particle tracing is a method that allows assessment of the 3D trajectory of a blood volume, illustrated as particles traces, through the LV over the cardiac cycle. A particle trace is the path that an imaginary particle would take through a velocity field from a given time and starting point. The MASS research software was used to interactively place particle trace emitters and region-of-interest planes, and to calculate the particle traces. By using the end-diastolic blood volume in the LV as particle and performing tracing forward and backward in time we were able to perform blood flow component analysis, classified as direct flow, retained inflow, delayed ejection or residual volume and expressed at the proportion of the end-diastolic volume. In the current study, we used the LV outflow tract to evaluate whether a particle has left the LV cavity during systole. Direct flow is defined as the proportion of blood entering the LV during diastole and which is ejected during systole within the same cardiac cycle. Retained inflow is the proportion of blood flow that enters the LV during diastole but remains in the LV at the end of systole within the same cardiac cycle. Delayed ejection is the blood flow that starts and resides inside the LV during diastole and is ejected during systole of the cardiac cycle. Residual volume is the blood that resides within the LV for at least two cardiac cycles and is not a component of the inflow or ejected volume. Figure 1 shows an example of particle tracing with blood flow component analysis in a patient with LVT.

**Kinetic energy analysis**

In order to calculate KE we had to transfer the delineations of the LV endocardial and epicardial borders of the whole cardiac cycle to the 4D data set. Initially, the KE is determined for each individual voxel by using the following formula: \( \frac{1}{2}mv^2 \), in which \( m \) is the mass of blood in one voxel (density of blood assumed to be 1050 kg/m\(^3\))\(^17\), and \( v \) the velocity magnitude in each voxel. Subsequently, total KE of the blood flow in the LV at a certain time point was calculated as the sum of the KE in all voxels inside the LV endocardial delineations (Figure 1). The amount of KE inside the LV for each time point over the entire cycle was illustrated in a KE time curve, and normalized for the LV volume at the concurrent time point. The average systolic and average diastolic KE were
calculated, and the peak KE during systole was determined, since these numbers are primarily affected in patients with impaired cardiac function. Additionally, to determine the differences in KE of the apex, the American Heart Association 17-segments model was used to define the apex (segment 17).\textsuperscript{18}

\textbf{Figure 1.} An example of blood flow component analysis and kinetic energy in a chronic myocardial infarct patient with a left ventricular thrombus. The left panel demonstrates blood flow component analysis in a LVT\textsuperscript{+} patient with the following color encoding: red = residual, yellow = retained, blue = delayed and green = direct flow. The right panel demonstrates kinetic energy with the following color encoding: blue being the lowest value of kinetic energy and red the highest kinetic energy.

\textbf{Vortex core analysis}

Vortex structures are compact regions of swirling blood flow and their detection is based on the physical fluid dynamic properties. A prior study reported the formation of vortex core ring structure in healthy subjects, which was located at the tip of the mitral valve leaflets over the diastolic phase.\textsuperscript{19} For the vortex core analysis we used the Lambda2-method, which is considered the most accepted vortex detection technique. The analysis workflow used was previously described.\textsuperscript{19}

If a vortex ring core was detected during early (E) and late (A) peak filling, its location in the LV and the shape were also quantitatively analyzed. We used a standardized 3D local cardiac (cylindrical) coordinate system. The circumferential (C), longitudinal (L) and radial (R) coordinates and the orientation of the vortex ring core relative to the LV was analyzed (Figure 2). This was done for the vortex core formation during the E- and A- peak filling. Moreover, the shape of the vortex core was quantified by assessing the
circulatory index (CI). The CI is defined as the ratio between the vortex’s short (D1) to long (D2) diameters by using the formula: CI = D1/D2.

Figure 2. Definition of the local cardiac coordinate system (C,L,R) relative to the left ventricle. A 3-dimensional vortex ring core and its quantitative parameters. The cylindrical position of the center of the vortex ring core *asterisk) was defined according to its position in the LV. Longitudinal (L) and radial were normalized relative to the LV long-axis length and the radius of the LV endocardial cavity. The orientation angle was defined relative to the long-axis ®. The circularity index was defined as the ratio between the longest (D1) and shortest (D2) diameter.

We also performed a qualitative visual inspection of the shape of detected vortex cores. This was performed by one observer (MH). The vortices were described as a vortex ring core or a complex vortical structure. Complex vortical shape we defined as not having a clear ring like structure and being more dispersed.

Finally, the vortex formation time (VFT) was calculated to quantify the process of vortex progression during early filling.20 This was determined using the formula: VFT = (Vavg×Eduration) / D. It is based on the average speed of the blood flow during the early filling period (Vavg), the duration of the E-filling (Eduration) and the maximum diameter (D).

Statistical analysis
Normally distributed data are expressed as mean ± SD and for non-normal distributed data the median value (25th to 75th percentile) is provided. Moreover, categorical variables are presented as number (%) and compared by the chi-square test. The instanta-
neous, mean and integrated values of the flow parameters were calculated for each flow subsets’ traces and expressed as a population average (SD). A Student t test or a 1-way analysis of variance was used to compare data with a normal distribution of continuous variables and an independent Mann-Whitney U test for non-normal distributed continuous variables. A P value <0.05 was considered statistically significant. All statistical analysis was performed using SPSS software (version 23.0; SPSS Inc., Chicago, Illinois).

**RESULTS**

Baseline characteristics of all three groups are shown in Table 1. In total we included 9 healthy controls and 19 chronic MI patients of which 9 had a LVT. Healthy controls were age-matched with chronic MI patients (57±8 vs. 65±14 years; P = 0.16). In the LVT+ group, 3 patients received a vitamin K antagonist in addition to antiplatelet treatment and one patient was treated with a novel oral anticoagulant in combination with clopidogrel. All patients in the LVT- group were treated with dual antiplatelet therapy and none with additional oral anticoagulants.

**Table 1. Baseline characteristics**

<table>
<thead>
<tr>
<th></th>
<th>Controls (n=9)</th>
<th>Chronic MI (n=19)</th>
<th>P-value</th>
<th>LVT- (n=10)</th>
<th>LVT+ (n=9)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>57 (8)</td>
<td>65 (14)</td>
<td>0.16</td>
<td>62 (14)</td>
<td>68 (15)</td>
<td>0.36</td>
</tr>
<tr>
<td>Male</td>
<td>5 (55.6)</td>
<td>19 (100)</td>
<td>&lt;0.05</td>
<td>10 (100)</td>
<td>9 (100)</td>
<td>1.0</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>23.2 (2.2)</td>
<td>28.2 (4.0)</td>
<td>&lt;0.05</td>
<td>30.2 (4)</td>
<td>25.9 (2.7)</td>
<td>0.02</td>
</tr>
<tr>
<td>Risk factors</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>0</td>
<td>4 (21.1)</td>
<td>0.14</td>
<td>1 (10)</td>
<td>3 (33)</td>
<td>0.21</td>
</tr>
<tr>
<td>Hypertension</td>
<td>0</td>
<td>6 (31.6)</td>
<td>0.06</td>
<td>3 (33)</td>
<td>3 (33)</td>
<td>0.88</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>0</td>
<td>5 (26.3)</td>
<td>0.09</td>
<td>3 (30)</td>
<td>2 (22)</td>
<td>0.70</td>
</tr>
<tr>
<td>Current smoking</td>
<td>0</td>
<td>10 (52.6)</td>
<td>&lt;0.05</td>
<td>6 (60)</td>
<td>4 (44)</td>
<td>0.50</td>
</tr>
<tr>
<td>Prior infarct related artery</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LAD</td>
<td>-</td>
<td>11 (57.9)</td>
<td>-</td>
<td>5 (50)</td>
<td>6 (67)</td>
<td>0.46</td>
</tr>
<tr>
<td>LCX</td>
<td>-</td>
<td>1 (5.3)</td>
<td>-</td>
<td>1 (10)</td>
<td>-</td>
<td>0.33</td>
</tr>
<tr>
<td>RCA</td>
<td>-</td>
<td>4 (21.1)</td>
<td>-</td>
<td>4 (40)</td>
<td>-</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Anticoagulation</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DAPT</td>
<td>-</td>
<td>14 (73.7)</td>
<td>-</td>
<td>10 (100)</td>
<td>4 (44)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>VKA + antiplatelet</td>
<td>-</td>
<td>3 (15.8)</td>
<td>-</td>
<td>0</td>
<td>3 (33)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>NOAC + antiplatelet</td>
<td>-</td>
<td>1 (5.3)</td>
<td>-</td>
<td>0</td>
<td>1 (11.1)</td>
<td>0.28</td>
</tr>
</tbody>
</table>

* Values are presented as number (%) or mean ± standard deviation.

BMI, Body Mass Index; LAD, left anterior descending artery; LCX, left circumflex artery; RCA, right coronary artery; DAPT, dual antiplatelet therapy; VKA, vitamin K antagonist; NOAC, novel oral anticoagulants
As anticipated, a higher baseline LVEF was observed in the healthy controls compared to the chronic MI group (Table 2). In the chronic MI group, no statistically significant difference was observed in LVEF between the LVT+ and LVT- group. Also, no difference in infarct size (as % LV) was observed between LVT- and LVT+ group.

**Table 2**. Cardiac Magnetic Resonance characteristics

<table>
<thead>
<tr>
<th></th>
<th>Controls (n=9)</th>
<th>Chronic MI (n=10)</th>
<th>P-value</th>
<th>LVT- (n=9)</th>
<th>LVT+ (n=19)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate (bpm)</td>
<td>63 ± 13</td>
<td>63 ± 12</td>
<td>0.91</td>
<td>62 ±11</td>
<td>63 ±13</td>
<td>0.84</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>60.4 ± 6.1</td>
<td>44.8 ± 10.7</td>
<td>&lt; 0.001</td>
<td>49 ± 3.7</td>
<td>40.3 ± 14.1</td>
<td>0.11</td>
</tr>
<tr>
<td>LVEDV (ml)</td>
<td>135.2 ± 33.0</td>
<td>194.5 ± 41.3</td>
<td>&lt; 0.05</td>
<td>186.6 ± 32.7</td>
<td>203.2 ± 49.6</td>
<td>0.40</td>
</tr>
<tr>
<td>LVESV (ml)</td>
<td>53.7 ± 16.5</td>
<td>110.3 ± 45.1</td>
<td>&lt; 0.05</td>
<td>95.4 ± 18.8</td>
<td>126.8 ± 59.9</td>
<td>0.17</td>
</tr>
<tr>
<td>Stroke volume (ml)</td>
<td>81.6 ± 20.4</td>
<td>84.2 ± 19.5</td>
<td>0.74</td>
<td>91.2 ± 16.6</td>
<td>76.4 ± 20.4</td>
<td>0.10</td>
</tr>
<tr>
<td>Infarct size (% of LV)</td>
<td>-</td>
<td>16.6 (11.0-20.0)</td>
<td>0.46</td>
<td>14.4 (10.1-19.6)</td>
<td>18.9 (8.2-36.8)</td>
<td></td>
</tr>
</tbody>
</table>

**E-filing parameters**

<table>
<thead>
<tr>
<th></th>
<th>Controls (n=9)</th>
<th>Chronic MI (n=10)</th>
<th>P-value</th>
<th>LVT- (n=9)</th>
<th>LVT+ (n=19)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peak velocity (cm/sec)</td>
<td>26.2 (23.6-38.8)</td>
<td>41.1 (28.6-47.2)</td>
<td>0.03</td>
<td>39.9 (28.4-46.5)</td>
<td>45.3 (26.9-50.7)</td>
<td>0.81</td>
</tr>
<tr>
<td>Peak time (sec)</td>
<td>0.477 ± 0.050</td>
<td>0.506 ± 0.057</td>
<td>0.20</td>
<td>0.506 ± 0.045</td>
<td>0.505 ± 0.071</td>
<td>0.97</td>
</tr>
<tr>
<td>Duration (sec)</td>
<td>0.345 (0.289-0.399)</td>
<td>0.334 (0.259-0.400)</td>
<td>0.94</td>
<td>0.299 (0.256-0.382)</td>
<td>0.351 (0.267-0.492)</td>
<td>0.57</td>
</tr>
</tbody>
</table>

LVEF, left ventricular ejection fraction; LVEDV, left ventricular end-diastolic volume; LVESV, left ventricular end-systolic volume; E-filing, early filing;

**Blood flow components**

The relative size of the different blood flow components for all three groups is illustrated in Figure 3. In the control group, blood flow is mainly composed by direct flow (mean 42% ± 6). On the contrary, in patients with LVT+ blood flow is primarily composed by residual flow (median 31%; IQR 27-55). Direct flow is decreased in both the LVT- group (P= 0.001) and the LVT+ group (P<0.001) compared to the control group, whereas delayed flow is increased in both the LVT- and LVT+ group (P< 0.05). LVT+ patients have a decreased retained flow in comparison to LVT- patients (19±5 vs. 24±4%, P=0.03).

**Kinetic energy analysis**

First, we assessed the average systolic and diastolic KE in the total LV. Chronic MI patients had a significantly lower average systolic KE in comparison to the controls (9.81 ±2.86 μJ/mL vs. 12.64 ± 2.30 μJ/mL, P = 0.02). No difference was observed in the average diastolic KE between both groups (chronic MI vs. controls: 8.10 ±2.75μJ/mL vs. 9.22±2.87μJ/ mL, P = 0.33).
When considering the KE peak in the different segments of the LV, a trend towards a lower systolic peak KE was observed in the apex of chronic MI patients versus controls (Figure 4; 4.41±3.60 μJ/mL vs. 6.81±2.02μJ/mL, P = 0.08). LVT+ patients had a significantly lower systolic peak KE in the apex in comparison to controls (3.03±1.42μJ/mL vs. 6.81±2.02μJ/mL, P= <0.001). However, when comparing LVT+ and LVT- group no difference was observed in the maximal KE during systole in the apex (P = 0.11).

![Figure 3. Relative proportions of the components of the end diastolic left ventricular blood volume in all three patient groups.](image)

**Figure 3.** Relative proportions of the components of the end diastolic left ventricular blood volume in all three patient groups.

When considering the KE peak in the different segments of the LV, a trend towards a lower systolic peak KE was observed in the apex of chronic MI patients versus controls (Figure 4; 4.41±3.60 μJ/mL vs. 6.81±2.02μJ/mL, P = 0.08). LVT+ patients had a significantly lower systolic peak KE in the apex in comparison to controls (3.03±1.42μJ/mL vs. 6.81±2.02μJ/mL, P= <0.001). However, when comparing LVT+ and LVT- group no difference was observed in the maximal KE during systole in the apex (P = 0.11).

![Figure 4. Peak systolic kinetic energy in apex](image)

**Figure 4.** Peak systolic kinetic energy in apex
KE, kinetic energy; mJ, millijoule, mL, milliliter

### 3D vortex cores analysis

3D vortex ring cores were both qualitatively and quantitatively analyzed. Vortex core analysis was not possible in 5 patients due to the absence of a vortex structure (LVT+ n=3, LVT- n=1, control n=1). In all three groups we observed either a vortex ring core or a complex vortical structure (Table 3). No differences in vortex structure during E- or A filling were observed between the groups.
Table 3. Qualitative vortex core characteristics

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Controls (n=9)</th>
<th>Chronic MI (n=19)</th>
<th>P-value</th>
<th>LVT - (n=10)</th>
<th>LVT + (n=9)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>E-filling</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vortex ring core</td>
<td>3 (33)</td>
<td>11 (58)</td>
<td>0.23</td>
<td>7 (70)</td>
<td>4 (44)</td>
<td>0.26</td>
</tr>
<tr>
<td>Complex vortical structure</td>
<td>5 (62.5)</td>
<td>8 (42.1)</td>
<td>0.51</td>
<td>3 (30)</td>
<td>5 (55.6)</td>
<td>0.26</td>
</tr>
<tr>
<td>No vortex core ring present</td>
<td>0</td>
<td>0</td>
<td></td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>A-filling</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vortex ring core</td>
<td>6 (67)</td>
<td>9 (47)</td>
<td>0.34</td>
<td>6 (67)</td>
<td>3 (33)</td>
<td>0.25</td>
</tr>
<tr>
<td>Complex vortical structure</td>
<td>2 (25)</td>
<td>7 (38.9)</td>
<td>0.44</td>
<td>3 (33.3)</td>
<td>4 (44.4)</td>
<td>0.52</td>
</tr>
<tr>
<td>No vortex core ring present</td>
<td>0</td>
<td>2 (11.1)</td>
<td>0.31</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>

E-peak, early-peak filling, A-peak, late-peak filling. In one healthy control vortex ring analysis was not possible. In 3 STEMI+LVT patients vortex core analysis was not possible during the A-peak filling. Also in one patient (LVT+) there was no late filling.

The quantified parameters on the orientation and shape of vortex core ring are presented in Table 4. In the chronic MI group, the vortex ring core observed during E-filing was positioned more anteriorly (lower circumferential value) in comparison to the control group. During the A-filling the vortex ring core is positioned closer to the septum in comparison to the controls.

Table 4. Qualitative vortex core characteristics

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Controls (n=9)</th>
<th>Chronic MI (n=19)</th>
<th>P-value</th>
<th>LVT - (n=10)</th>
<th>LVT + (n=9)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>E-peak</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Circumferential</td>
<td>115 ± 44°</td>
<td>68 ± 45°</td>
<td>0.02</td>
<td>58 ± 36°</td>
<td>79 ± 53°</td>
<td>0.34</td>
</tr>
<tr>
<td>Longitudinal</td>
<td>0.19 [0.18-0.23]</td>
<td>0.19 [0.17-0.21]</td>
<td>0.90</td>
<td>0.21 [0.19-0.24]</td>
<td>0.17 [0.14-0.20]</td>
<td>0.04</td>
</tr>
<tr>
<td>Radial</td>
<td>0.23 ± 0.10</td>
<td>0.20 ± 0.10</td>
<td>0.54</td>
<td>0.21 ± 0.09</td>
<td>0.19 ± 0.12</td>
<td>0.75</td>
</tr>
<tr>
<td>Orientation</td>
<td>70° (62-77)</td>
<td>68° (56-81)</td>
<td>0.90</td>
<td>62° (53-67)</td>
<td>81° (71-97)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Circularity index (au)</td>
<td>0.76 ± 0.13</td>
<td>0.77 ± 0.10</td>
<td>0.78</td>
<td>0.76 ± 0.09</td>
<td>0.78 ± 0.11</td>
<td>0.78</td>
</tr>
<tr>
<td>A-peak</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Circumferential</td>
<td>106 ± 36°</td>
<td>71 ± 45°</td>
<td>0.08</td>
<td>75 ± 40°</td>
<td>65 ± 55°</td>
<td>0.70</td>
</tr>
<tr>
<td>Longitudinal</td>
<td>0.21 [0.13-0.26]</td>
<td>0.16 [0.14-0.20]</td>
<td>0.22</td>
<td>0.19 [0.15-0.21]</td>
<td>0.14 [0.11-0.17]</td>
<td>0.07</td>
</tr>
<tr>
<td>Radial</td>
<td>0.19 ± 0.06</td>
<td>0.13 ± 0.04</td>
<td>0.02</td>
<td>0.13 ± 0.06</td>
<td>0.13 ± 0.03</td>
<td>0.99</td>
</tr>
<tr>
<td>Orientation</td>
<td>68° (63-70)</td>
<td>65° (56-74)</td>
<td>0.71</td>
<td>64° (57-68)</td>
<td>71° (56-91)</td>
<td>0.41</td>
</tr>
<tr>
<td>Circularity index (au)</td>
<td>0.68 ± 0.09</td>
<td>0.66 ± 0.11</td>
<td>0.59</td>
<td>0.61 ± 0.05</td>
<td>0.72 ± 0.14</td>
<td>0.05</td>
</tr>
<tr>
<td>VFT index</td>
<td>1.31 (0.85-1.85)</td>
<td>1.36 (1.15-1.90)</td>
<td>0.48</td>
<td>1.44 (1.15-1.86)</td>
<td>1.34 (1.04-1.34)</td>
<td>1.0</td>
</tr>
</tbody>
</table>

*Values are presented as mean ± standard deviation or median (25th – 75th percentile)

E-peak, early-peak filling, A-peak, late-peak filling. In one healthy control vortex ring analysis was not possible. In 3 STEMI+LVT patients vortex core analysis was not possible during the A-peak filling. Also in one patient (LVT+) there was no late filling.
In chronic MI, the following differences were observed between patients with and without LVT: In the LVT+ group, the vortex ring core during E-filing is located more towards the annulus (lower longitudinal value) and in a more tilted position (increased orientation value) compared to the LVT- group. During A-filing a more circular ring core (increased circularity index) was observed in the LVT+ group.

Finally, we quantified the process of vortex progression during E-filling by assessing the VFT. There were no differences in VFT observed between the controls and the chronic MI, or between patients with/without LVT.

**DISCUSSION**

This study is the first to perform 4D flow CMR in patients with an apical LVT. The main findings of the current study are as follows: first, a decreased direct and an increased delayed flow was observed in both the LVT+ and LVT- patients in comparison to the healthy controls. LVT patients had an increased delayed and residual blood flow in comparison to controls, indicating less outflow of blood and increased blood volume residing in the LV during systole. Second, patients with an LVT had an increased retained flow in comparison to the LVT- group. Third, patients with a LVT had a significantly lower systolic peak KE in the apex in comparison to controls. Finally, in LVT patients the vortex ring core during E-filing is located more towards the annulus (lower longitudinal value) and in a more tilted position (increased orientation value) compared to the LVT- group. During A-filing a more circular ring core (increased circularity index) was observed.

These observed differences in blood flow components and KE indicate increased blood stasis in the apex of LVT patients, that has been suggested as the pathophysiological etiology of thrombus formation. Previously identified risk factors for LVT following MI are an increased infarct size as observed in anterior infarcts, a lower ejection fraction, hypercoagulability and altered geometry (e.g. aneurysmatic apex). These identified risk factors are thought to increase the risk of thrombosis by reduced blood flow and subsequent stasis. Stagnation of blood in turn results in decreased dilution of activated clotting factors by fresh flowing blood and retarded inflow of clotting factor inhibitors that ultimately results in buildup of thrombi. 4D flow CMR enables in-vivo assessment of complex blood flow transport in the LV in a qualitative and quantitative manner.

**Blood flow component analysis**

Blood flow component analysis allows the investigation of blood transportation efficiency. A higher percentage of direct flow is assumed to be associated with efficient blood transportation as it is the component of flow that has the most direct route and fastest transit through the LV, allowing it to preserve KE. In the current study, LVT pa-
tients had a reduced blood flow efficiency as measured by a decreased direct flow and increased residual and delayed flow. Although there have been no prior studies on blood flow component analysis in LVT patients, a comparison can be made with 4D flow CMR in patients with chronic ischemic heart disease. More severe remodeling of the LV in these patients was associated with a decreased direct flow and increased non-injecting volume (combined retained and residual volume) in comparison to the control group. Similar observations were reported in patients with dilated cardiomyopathy. These results are in concordance with our observation in chronic MI patients, including both the LVT+ and LVT- group.

**Kinetic energy**

KE of blood flow in the LV is dependent on the blood flow velocity and can be derived from 4D flow CMR. In the current study, LVT patients had a decreased systolic peak KE in the apex in comparison to controls. Although not statistically significant, a trend towards a lower systolic peak KE was observed in the apex of LVT+ versus LVT- patients. Similar observations were made in a study on echocardiographic flow characteristics in dilated cardiomyopathy patients with LVT formation. A decreased inflow velocity at the ventricular apex was observed in the patients that had developed a thrombus in comparison to the no thrombus group. Although this study was published in 1989, the observations made at that time support our findings. Also, in patients with non-ischemic dilated cardiomyopathy without any LVT formation, lower values of KE were observed in apically located residual volume. These observations were also considered hallmarks of blood stasis and were suggested to be possible markers of intraventricular thrombosis risk. In a 4D flow CMR study on KE in heart failure patients, a lower average systolic KE was observed in the total LV when indexed to end-diastolic volume. However, this study included both patients with ischemic heart disease and dilated cardiomyopathy.

**Vortex core**

LVT is frequently observed in patients with adverse remodeling of the LV with subsequent LV dilatation. This in turn may contribute to abnormal filling with divergence of the blood flow away from the longitudinal axis of the ventricle with altered vortices. Vortex ring cores result from blood flowing into the LV during diastole and is a prominent feature of intracardiac flow during E- and A- filling. Altered vortex ring formation during LV fillings has been associated with increased viscous energy loss and increased energy loss is most often seen in patients without a ring-shaped vortex during E-filling.

In the current study, no differences in vortex structures were observed during E- or A-filling between the groups. However, differences in its position and orientation in the LV were observed during A-filling. In LVT patients the vortex ring core was located more towards the annulus and more in a tilted position in comparison to the LVT- group.
previous studies on vortex formation were based on 2-dimensional analysis using echo-cardiography, whereas in the current study we investigated 3D vortex ring formation with 4D flow CMR. The shape of the vortex ring core has been shown to correlate with the mitral valve annulus and leaflet tips,\textsuperscript{19} and its orientation has been associated with the LV size as measured by LVEDV.\textsuperscript{31}

Differences in the orientation and location of the vortex core ring in LVT+ and LVT- patients cannot be explained by the LVEDV, as there were no observed differences between the two groups. Therefore, 4D flow analysis offers a unique tool to identify patients with abnormal flow, and hence, potentially increased risk of LVT formation.

Clinical perspectives
Despite a lower occurrence of LVT after the introduction of primary percutaneous coronary intervention and the use of more aggressive anticoagulation therapies, its prevalence is still reported in 3.5-9.1\% MI patients as assessed by CMR.\textsuperscript{3, 4, 32} In addition to an increased risk of thromboembolism, LVT formation is associated with progressive LV enlargement\textsuperscript{2} and independently associated with major adverse cardiac events at 12 months.\textsuperscript{3} Therefore, it is an adverse outcome that is still of clinical importance and assessment of predictive parameters for its formation is relevant. In the current study we observed differences in 4-D flow parameters that may prove to be useful as subclinical markers of intraventricular thrombosis. Future studies will be needed to assess whether KE and blood flow component analysis can be used as predictive subclinical markers. Early prediction of intraventricular thrombosis could result in more intensified monitoring and treatment. Treatment with additional anticoagulants should only be considered if the benefits of anticoagulation counterbalance the increased bleeding risk.

Limitations
Several limitations of the current study should be acknowledged. First, a relatively small number patients were included in each group. Second, 4D flow CMR was performed at one point in time and no conclusions can be made on the predictive value of 4D flow parameters for LVT formation. However, the differences observed in blood flow components and KE, indicate that these 4D flow parameters may be potential important parameters for LVT formation.

CONCLUSION
Chronic MI patients with LVT have an increased delayed and residual blood flow, lower systolic peak KE in the apex, and an abnormal vortex ring core position as assessed by 4D flow CMR. Contrary to the LVT- group, LVT+ had a decreased retained flow. These
observations suggest increased blood stasis and thrombogenicity. Therefore, analysis of KE and blood flow component analysis with 4D flow CMR may be useful subclinical markers of intraventricular thrombus formation. Future larger studies appear warranted.
REFERENCES


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