Differentiation Between Fresh and Old Left Ventricular Thrombi by Deformation Imaging

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Background—Noninvasive echocardiographic differentiation between old and fresh left ventricular thrombi after myocardial infarction would be of clinical importance to estimate the risk for embolization and the necessity of anticoagulation.

Methods and Results—Fifty-two patients, aged 41 to 87 years, with a thrombus after myocardial infarction were included in this 2-part study: In substudy-I, 20 patients, 10 each with a definite diagnosis of fresh or old thrombus, were included. In the subsequent prospective substudy-II, 32 consecutive patients with an incident thrombus after myocardial infarction but unknown thrombus age were started on phenprocoumon and followed for 6 months. Data on medical history, standard echocardiography, strain-rate (SR) imaging and magnetic resonance tomography were analyzed. In substudy-I, analysis of thrombus deformation revealed the most rapid change in SR during the isovolumetric relaxation period when cavity pressure decreases rapidly. Fresh (range: 5–27 days) and old thrombi (4–26 months) could be discriminated without overlap by peak SR during the isovolumetric relaxation period, using a cutoff value of 1 s⁻¹. Applying this threshold value in substudy-II, 17 thrombi were echocardiographically classified as fresh (=SR ≥1 s⁻¹) and 15 as old. After 6 months in the fresh thrombus group, 16 of 17 thrombi had disappeared (94%), and in 1 patient the thrombus size was diminished by ≥50% (now presenting an old thrombus SR pattern). In contrast, 14 of the 15 old thrombi remained unchanged in size and deformation (1 thrombus disappeared).

Conclusions—Fresh and old intracavitary thrombi can be reliably differentiated by deformation imaging. In fresh thrombi, anticoagulation with phenprocoumon results in thrombus resolution in most patients. (Circ Cardiovasc Imaging. 2012;5:667-675.)

Key Words: echocardiography • thrombus • strain rate imaging

Clinical Perspective on p 675

Myocardial deformation can be assessed by tissue Doppler imaging (TDI) using strain-rate (SR) techniques. Since its first evaluation in the 1990s, deformation imaging improved and nowadays even semiautomatic systems using gray-scale loops are available to assess regional myocardial deformation. We conceptualized a study to transfer the knowledge of myocardial deformation imaging to analyze the deformation of LV thrombi. We hypothesized that older thrombi should be more collagen rich than fresh thrombi, therefore better structurally organized and

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Circ Cardiovasc Imaging is available at http://circimaging.ahajournals.org DOI: 10.1161/CIRCIMAGING.112.974964
stiffer, thus exhibiting lower deformation values because of the changing intraventricular pressure. Aims of this study were: (1) to investigate whether fresh and old LV intracavitary thrombi can be reliably differentiated using deformation imaging, (2) to estimate thrombus stiffness by noninvasive imaging, and (3) to monitor the effects of anticoagulation on fresh and old thrombi defined by deformation imaging.

Methods

Study Population
Between 2007 and 2009, a total of 52 patients (43 male, 9 female; mean age 66 ± 13 years, range 41–87 years) with LV thrombi after myocardial infarction were included in the study. Patients were examined in the echocardiography laboratory of the University of Würzburg. The study was performed in 2 parts.

In the first part of the study, 20 patients were included: the first 10 patients were allocated consecutively over a period of 6.5 months (May–November 2007) from the complete sample of patients referred to the University Hospital Würzburg due to acute myocardial infarction. All these 10 patients presented the same course of disease: after hospital admission, patients underwent standard care procedure with immediate coronary angiography and intervention. A ventriculography or an echocardiogram was performed immediately after hospitalization, with an exclusion of LV thrombus. However, these 10 patients showed an LV thrombus in a re-echocardiogram performed before discharge (mean time between initial event and date of the second echocardiogram: 9 ± 6 days, range 5–27 days). These patients were the ones with a definite fresh thrombus. While screening for these patients with acute myocardial infarction, we contacted 10 patients formerly presenting at our hospital with the definite diagnosis of an old thrombus. In all of these patients, echocardiograms or patient history information of the former presence of the thrombus >3 months were available (mean time 17 ± 8 months, range 4–26 months). These patients were the ones with a definite old thrombus.

The second part of the study was prospective and included 32 consecutive patients with a thrombus detected by echocardiography and a history of acute or chronic myocardial infarction. In all patients of study part II, a 6-month follow-up was done. In all patients of substudy I and in all patients of substudy II at baseline, medical history, physical examination and cardiac assessment, including echocardiography, SR-imaging, and MRT, was performed. In the follow-up studies, after 6 months, the same investigations were performed, except MRT. All patients of substudy II were started on phenprocoumon with an international normalized ratio goal of 2.0 to 3.0 during the complete follow-up. Phenprocoumon is a derivative of coumarin with a longer half-life than warfarin inhibiting coagulation by blocking synthesis of coagulation factors II, VII, IX, and X. The study conformed to the principles outlined in the Declaration of Helsinki, and the locally appointed ethics committee had approved the research protocol. Informed consent was obtained from all patients.

Standard Echocardiographic Measurements
LV septal diastolic and LV posterior wall thickness diastolic, LV systolic and diastolic diameters, fractional shortening, and ejection fraction were measured using standard echocardiography (GE Vingmed Vivid 7, Horten, Norway; 3.5 MHZ), as described elsewhere. Moreover, E/A ratio and the deceleration time as well as E/E’ ratio were calculated according to actual guidelines. Time markers for aortic and mitral valve opening and closure were positioned as described before.

If mitral insufficiency was present, the dP/dtMAX was measured. For this, the tangent of the profile of mitral regurgitation velocity curve during its deceleration (isovolumetric relaxation time [IVRT]), between 3 and 1 m/s, was calculated.

Tissue Doppler Imaging
All thrombi were investigated by TDI using apical 4-, 2- and 3-chamber views. The region of interest was placed in and adjusted to the size of the LV thrombus. The region of interest was continuously tracked and followed throughout 3 cardiac cycles, and all measurements were averaged over these 3 cycles. The strain rate and strain curves of the thrombus region were extracted from the apical views and the following parameters were measured: peak systolic SR, peak SR of the isovolumetric contraction period, peak SR of the IVRT, peak systolic strain, end-systolic strain, and postsystolic strain. All analyses were performed using dedicated software (EchoPAC™, GE Ultrasound, Version 10, Horten, Norway). Analysis was done blinded to the knowledge of fresh versus old thrombus. In addition, in the follow-up study, analysis was also blinded to the time point of data acquisition (baseline or follow-up).

Method Limitations
Nowadays 2-dimensional speckle tracking offers an alternative for tissue Doppler strain analysis. It was shown to be more reproducible (less inter- and intraobserver variability) and easier to use for nontrained experts. Additionally, it was suggested to be angle independent, or at least less angle dependent compared with TDI (because the lateral resolution in sector scanning is inherently less compared with the axial one). However, this technique also has some limitations. The main limitation of speckle tracking imaging is the temporal resolution because speckle tracking works typically with frame rates of 50 to 90 Hz whereas TDI is done with >150 Hz. This more limited temporal resolution makes that speckle tracking deformation analysis is currently mainly used to quantify maximal or end-systolic strain in the majority of publications, and SR is rarely reported because of problems with quantification and reproducibility (mainly related to the limited temporal resolution). Additionally, in literature on deformation assessed by TDI and microcrystals in various settings, it was suggested that SR better describes tissue mechanics compared with strain. When estimating the elasticity of thrombi, because of their noncontractile nature and being within the ventricular cavity, one has to look at the deformation induced by changes in the force experienced on their surface. This implies that only the isovolumetric periods can be used, where there is a sudden change in the cavity pressure. The elasticity can be assessed either by measuring the strain and the absolute pressure difference in 2 time points during pressure change or by measuring SR and the time derivative of the pressure simultaneously. Because absolute pressure measurements during the isovolumetric periods are difficult noninvasively and the slope of the mitral regurgitation trace is easily accessible as a surrogate of dP/dt, we had to work with SR to quantify elasticity. The isovolumetric periods only last for some tens of milliseconds. Because the temporal resolution of speckle tracking is 1 data point every 15 to 20 ms, it is quasi impossible to extract either the SR or the strain of the thrombus during the isovolumetric periods. TDI, with a temporal resolution twice or 3 times, better provides a more robust method. Additionally, TDI strain-rate imaging of the thrombi is much easier compared with myocardial assessment. This is because of the following reasons: (1) the angle was no problem, (2) most of the thrombi were quite large and the region of interest in the postprocessing tool could be easily placed in the examined thrombus; and (3) the tracking of the thrombus through the heart cycle was not difficult as most of the apical thrombi were stable in the apex of the left ventricle.

Thrombus Stiffness
The relation between the force exerted on an object and its resulting deformation is described by Hooke law of elasticity. This law states that the force per unit of area (σ) is equal to the elasticity (E—also referred to as elastic modulus) multiplied by the deformation (ε—strain).

The elastic modulus is thus the mathematical description of an object’s tendency to be deformed elastically (ie, nonpermanently) when a force is applied to it and is thus a measure of the stiffness of an elastic material. Thus, E can be calculated as:

\[
\frac{\text{Force}}{\text{Area}} = E \times \text{Deformation}
\]
or $\sigma = E \times \varepsilon$. When the forces on the object are time dependent, this will be reflected in changes in deformation. Therefore, \[ \frac{d\sigma}{dt} = E \times \frac{d\varepsilon}{dt} \] with $\frac{d\varepsilon}{dt}$ corresponding to the SR. Thus \[ \frac{d\sigma}{dt} = E \times \text{SR}(t) \] (formula 1), implying that when forces on the object remain the same, but the elasticity is different, these objects can be discriminated by their different SR and the elasticity can be calculated as \[ E = \frac{\frac{d\sigma}{dt}}{\text{SR}(t)}. \] For 3-dimensional, nonisotropic objects, this relationship is a tensor equation (showing differences in different directions) and can be nonlinear. As it can be expected (and we show it in our results) that fresh and old thrombi are roughly similar in size, and that the forces from pressure and walls are comparable, formula 1 shows that SR has to differ between thrombi with different elasticity.

Thrombi are objects, present in the LV cavity, partially attached to the wall. Thrombi are solid bodies, not volatile formations. Therefore, a force applied to a thrombus must lead to spatial rearrangement of the thrombus mass demanding the same amount of space. This means that thrombi are deformable but incompressible. Thus, when a thrombus is compressed from one side, it should expand at another side, or material (e.g., blood) has to be pressed out from its volume. Thrombi are subjected to the intraventricular pressure (P) at their surface (acting as mechanical stress) and are thus also exposed to pressure variations during the cardiac cycle (dP/dt). In a first approximation, the changing stress on the thrombus surface can be described by the changing pressure in the ventricle \[ \frac{d\text{P}(t)}{dt} = \frac{d\text{P}(t)}{dt}, \] and thus \[ E = \frac{\frac{d\text{P}(t)}{dt}}{\text{SR}(t)}. \] It is thus expected that thrombi will deform most during the periods of biggest changes in P, namely the isovolumetric contraction and relaxation periods. Because, during the IVRT, pressure change is the highest, thrombus stiffness can thus be approximated by \[ E \sim \text{stiffness} = \frac{d\text{P}}{dt_{\text{min}}}/\text{SR}_{\text{IVRT}} \] (formula 2). dP/dt_{min} can be estimated from the slope of the mitral regurgitation velocities and SR_{IVRT} can be calculated from tissue Doppler information (Figure 1).

**Magnetic Resonance Tomography**
MRT was performed to confirm the diagnosis of LV thrombi in all our patients of substudy I and II at baseline. MRT was performed on a 1.5 T scanner (Magnetom Symphony Quantum, Siemens Medical Systems, Erlangen, Germany).

**Statistics**
Data are presented as mean±SD. Differences between groups were compared using nonparametric tests (Mann-Whitney U test, Fisher exact test), as appropriate. Differences between baseline and follow-up in study II were tested using the paired Wilcoxon test. As both substudies I and II are explorative in nature, we applied Bonferroni adjustments to multiple tests reported in Tables 1–4. Otherwise, a 2-sided $P<0.05$ was considered statistically significant. Correlations were computed by the Spearman coefficient. Intra- and interobserver variability for thrombus strain rate IVRT was determined in 10 randomly selected patients and was 6% and 9%, respectively. Statistica (Version 8; STATISTICA, Tulsa, Oklahoma) and SPSS (Version 20; SPSS Inc, Chicago, IL) were used.

**Results**
Clinical data of the substudies I and II are presented in Table 1. No major differences between both study groups were observed, apart from a significant difference in heart rate and prevalence of arterial hypertension (Table 1). In both groups, the burden of cardiovascular risk factors such as hypertension, smoking, hyperlipidemia, and diabetes mellitus, was high.

**Substudy I**
The echocardiographic data of the fresh and old thrombus is presented in Table 2, and the clinical data of the 2 groups is provided in the online-only Data Supplement Table 1. No significant difference was observed in any of the standard echocardiographic parameters to differentiate fresh from old LV thrombi. New thrombi showed a mean 2-dimensional size of 18±9 mm×18±12 mm, similar to old thrombi that exhibited a size of 24±10 mm×17±12 mm ($P=0.17$ for the lateral and $P=0.91$ for the axial dimensions). Three of the new thrombi were rather circular and 7 of them were more...
ellipsoid, whereas 4 of the old thrombi were rather circular and 6 ellipsoid.

The strain and SR values of the fresh and old thrombi in substudy I are presented in Table 3. In general, deformation assessed by SR and strain was lower in old thrombi (Table 3). When analyzing the strain and SR curves, a typical pattern in fresh thrombi was observed: an early peak in the isovolumetric contraction period, followed by a rapid fall baseline: 12 ± 4 mm at baseline. After 6 months follow-up, thrombi disappeared in 16 of the 17 patients with fresh thrombi (94%; Figure 4). The thrombus in the last patient that did not disappear, diminished >50% (thrombus size at baseline: 12 × 13 mm²; follow-up: 4 × 4 mm²) and the SR in the IVRT was now <1 s⁻¹, thus showing the deformation

Substudy II

The patients were grouped according to their SR in the IVRT. Thrombi with an SR ≥1 s⁻¹ were classified as echocardiographically fresh, the ones with an SR <1 s⁻¹ were classified as echocardiographically old. The echocardiographic data of the 2 groups are presented in Table 4. Similar to substudy I, no major differences emerged regarding standard echocardiographic parameters. The clinical data of the 2 groups is provided as online-only Data Supplement (online-only Data Supplement Table II).

Fresh thrombi showed an average 2-dimensional size of 16 ± 8 mm×11 ± 4 mm at baseline. After 6 months follow-up, thrombi disappeared in 16 of the 17 patients with fresh thrombi (94%; Figure 4). The thrombus in the last patient that did not disappear, diminished >50% (thrombus size at baseline: 12 × 13 mm²; follow-up: 4 × 4 mm²) and the SR in the IVRT was now <1 s⁻¹, thus showing the deformation

Table 1. Clinical Characteristics of the Patients in Substudy I and Substudy II

<table>
<thead>
<tr>
<th></th>
<th>Substudy I (n=20)</th>
<th>Substudy II (n=32)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex (M/F)</td>
<td>17/3</td>
<td>26/6</td>
<td>0.99</td>
</tr>
<tr>
<td>Age, y</td>
<td>65 ± 15</td>
<td>64 ± 12</td>
<td>0.61</td>
</tr>
<tr>
<td>Height, cm</td>
<td>172 ± 5</td>
<td>170 ± 9</td>
<td>0.70</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>79 ± 16</td>
<td>83 ± 18</td>
<td>0.45</td>
</tr>
<tr>
<td>Systolic BP, mm Hg</td>
<td>133 ± 16</td>
<td>129 ± 20</td>
<td>0.45</td>
</tr>
<tr>
<td>Diastolic BP, mm Hg</td>
<td>76 ± 7</td>
<td>76 ± 12</td>
<td>0.58</td>
</tr>
<tr>
<td>Heart rate, 1/min</td>
<td>89 ± 19</td>
<td>79 ± 13</td>
<td>0.07</td>
</tr>
</tbody>
</table>

NYHA

| Class I, n             | 7                 | 12                 | 0.99 |
| Class II, n            | 9                 | 15                 | 0.99 |
| Class III, n           | 4                 | 5                  | 0.72 |
| Class IV, n            | 0                 | 0                  | 0.99 |
| Atrial fibrillation, n | 7                 | 4                  | 0.08 |
| COPD, n                | 2                 | 5                  | 0.69 |
| Smoking, n             | 7                 | 20                 | 0.09 |
| Diabetes mellitus type II, n | 5             | 11                 | 0.55 |
| Hyperlipidemia, n      | 13                | 27                 | 0.18 |
| Arterial hypertension, n | 11              | 28                 | 0.02 |
| GFR <90 mL/min/1.73 m², n | 5             | 7                  | 0.99 |

ACE indicates angiotensin-converting enzyme; AT, angiotensin; BP, blood pressure; COPD, chronic obstructive pulmonary disease; GFR, glomerular filtration rate; and NYHA, New York Heart Association.

P values refer to nonparametric tests comparing both study groups (Mann-Whitney U test, Fisher exact test, and χ² test, as appropriate). A Bonferroni-adjusted P<0.0033 was considered statistically significant.

Table 2. Echocardiographic Parameters of the Patients With Fresh and Old Thrombi in Substudy I

<table>
<thead>
<tr>
<th></th>
<th>Fresh Thrombi (n=10)</th>
<th>Old Thrombi (n=10)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>LVEDD, mm</td>
<td>50.3 ± 5.1</td>
<td>54.7 ± 8.6</td>
<td>0.09</td>
</tr>
<tr>
<td>LVEDS, mm</td>
<td>38.1 ± 8.1</td>
<td>44.7 ± 12.0</td>
<td>0.32</td>
</tr>
<tr>
<td>LVEF, %</td>
<td>34.1 ± 9.9</td>
<td>33.4 ± 13.7</td>
<td>0.45</td>
</tr>
<tr>
<td>IVSD, mm</td>
<td>9.9 ± 1.2</td>
<td>10.1 ± 2.7</td>
<td>0.86</td>
</tr>
<tr>
<td>LVPWd, mm</td>
<td>10.0 ± 1.3</td>
<td>9.5 ± 2.1</td>
<td>0.48</td>
</tr>
<tr>
<td>LA, mm</td>
<td>41.5 ± 3.1</td>
<td>44.1 ± 9.2</td>
<td>0.32</td>
</tr>
<tr>
<td>MV-E, m/s</td>
<td>0.7 ± 0.2</td>
<td>0.6 ± 0.2</td>
<td>0.55</td>
</tr>
<tr>
<td>MV-A, m/s</td>
<td>0.7 ± 0.2</td>
<td>0.7 ± 0.3</td>
<td>0.91</td>
</tr>
<tr>
<td>MV E/A</td>
<td>1.3 ± 0.9</td>
<td>1.3 ± 0.9</td>
<td>0.99</td>
</tr>
<tr>
<td>DT, ms</td>
<td>147 ± 39</td>
<td>124 ± 83</td>
<td>0.31</td>
</tr>
<tr>
<td>E′ sept, m/s</td>
<td>0.1 ± 0.1</td>
<td>0.4 ± 0.9</td>
<td>0.76</td>
</tr>
<tr>
<td>E′/E′ sept</td>
<td>18.6 ± 15.9</td>
<td>12.2 ± 2.3</td>
<td>0.99</td>
</tr>
<tr>
<td>E′ lat, m/s</td>
<td>0.1 ± 0.0</td>
<td>0.1 ± 0.0</td>
<td>0.57</td>
</tr>
<tr>
<td>E′/E lat</td>
<td>7.4 ± 2.2</td>
<td>10.4 ± 4.0</td>
<td>0.53</td>
</tr>
<tr>
<td>WMS</td>
<td>2.1 ± 0.2</td>
<td>2.4 ± 0.4</td>
<td>0.02</td>
</tr>
</tbody>
</table>

DT indicates deceleration time; IVSD, interventricular septal diastolic diameter; LA, left atrium; LVEDD, left ventricular end-diastolic diameter; LVEF, left ventricular ejection fraction; LVEDS, left ventricular end-systolic diameter; LVPWd, left ventricular posterior wall diastolic; MV, mitral valve; TI, tricuspid insufficiency; Vmax, maximum velocity; and WMS, wall motion score.

Groups were compared using the Mann-Whitney U test. A Bonferroni-adjusted P<0.0023 was considered statistically significant.

Table 3. Strain Rate Imaging Parameters of the Patients With Fresh and Old Thrombi in Substudy I

<table>
<thead>
<tr>
<th></th>
<th>Fresh Thrombi (n=10)</th>
<th>Old Thrombi (n=10)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maximal systolic strain, %</td>
<td>8.1 ± 11.8</td>
<td>2.4 ± 1.4</td>
<td>0.11</td>
</tr>
<tr>
<td>End-systolic strain, %</td>
<td>2.3 ± 3.8</td>
<td>0.7 ± 1.1</td>
<td>0.58</td>
</tr>
<tr>
<td>Postsystolic strain, %</td>
<td>8.5 ± 5.6</td>
<td>1.8 ± 1.6</td>
<td>0.003</td>
</tr>
<tr>
<td>Maximal strain-rate IVC, s⁻¹</td>
<td>1.30 ± 0.74</td>
<td>0.5 ± 0.19</td>
<td>0.0002</td>
</tr>
<tr>
<td>Maximal strain-rate ejection, s⁻¹</td>
<td>0.20 ± 0.18</td>
<td>0.12 ± 0.11</td>
<td>0.39</td>
</tr>
<tr>
<td>Maximal strain-rate IVR, s⁻¹</td>
<td>1.61 ± 0.46</td>
<td>0.44 ± 0.11</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

IVC indicates isovolumetric contraction time; and IVR, isovolumetric relaxation time.

Groups were compared using the Mann-Whitney U test. A Bonferroni-adjusted P<0.0023 was considered statistically significant.
Table 4. Echocardiographic Parameters of the Patients With Strain rate ≥1 s⁻¹ and Strain Rate <1 s⁻¹ in Substudy II

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Fresh (n=17)</th>
<th>Old (n=15)</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td>LVEDD, mm</td>
<td>54.5±1.7</td>
<td>52.1±13.4</td>
<td>0.50</td>
</tr>
<tr>
<td>LVEDs, mm</td>
<td>40.9±11.4</td>
<td>41.9±9.7</td>
<td>0.87</td>
</tr>
<tr>
<td>LVES, %</td>
<td>39.0±12.6</td>
<td>41.6±12.9</td>
<td>0.55</td>
</tr>
<tr>
<td>IVSd, mm</td>
<td>12.5±6.1</td>
<td>9.0±3.1</td>
<td>0.01</td>
</tr>
<tr>
<td>LVPWd, mm</td>
<td>10.4±1.4</td>
<td>10.1±1.6</td>
<td>0.60</td>
</tr>
<tr>
<td>LA, mm</td>
<td>41.1±5.5</td>
<td>43.6±8.6</td>
<td>0.86</td>
</tr>
<tr>
<td>MV-E, m/s</td>
<td>0.7±0.2</td>
<td>0.7±0.2</td>
<td>0.50</td>
</tr>
<tr>
<td>MV-A, m/s</td>
<td>0.7±0.2</td>
<td>0.7±0.2</td>
<td>0.67</td>
</tr>
<tr>
<td>MV E/A</td>
<td>1.3±1.0</td>
<td>0.9±0.5</td>
<td>0.42</td>
</tr>
<tr>
<td>DT, ms</td>
<td>216±69</td>
<td>254±68</td>
<td>0.27</td>
</tr>
<tr>
<td>E’ sept, m/s</td>
<td>0.5±1.2</td>
<td>0.1±0.2</td>
<td>0.32</td>
</tr>
<tr>
<td>E/E’ sept</td>
<td>16.0±8.2</td>
<td>12.4±8.0</td>
<td>0.40</td>
</tr>
<tr>
<td>E’ lat, m/s</td>
<td>0.2±0.3</td>
<td>0.1±0.0</td>
<td>0.55</td>
</tr>
<tr>
<td>E/E’ lat</td>
<td>8.8±6.3</td>
<td>7.8±1.3</td>
<td>0.71</td>
</tr>
<tr>
<td>WMS</td>
<td>2.2±0.3</td>
<td>2.3±0.4</td>
<td>0.60</td>
</tr>
<tr>
<td>Postystolic strain, %</td>
<td>8.6±8.1</td>
<td>5.0±3.6</td>
<td>0.12</td>
</tr>
<tr>
<td>Maximal</td>
<td>2.0±0.8</td>
<td>0.5±0.1</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

DT indicates deceleration time; IVR, isovolumetric relaxation time; IVSD, interventricular septal diastolic diameter; LA, left atrium; LVEDD, left ventricular end-diastolic diameter; LVEF, left ventricular ejection fraction; LVEDS, left ventricular end-systolic diameter; LVPWd, left ventricular posterior wall diastolic; MV, mitral valve; TI, tricuspid insufficiency; Vmax, maximum velocity; and WMS, wall motion score.

Groups were compared using the Mann-Whitney U test. A Bonferroni-adjusted \( P<0.0023 \) was considered statistically significant.

Figure 2. Left. Gray-scale and tissue Doppler samples of a fresh (top) and old thrombus (bottom). Right. Corresponding strain-rate curves of a fresh and old intracavitary thrombus. The x-axis displays 1 cardiac cycle; the y-axis displays the strain-rate in s⁻¹. The yellow curve is the strain-rate curve of a fresh thrombus, the red, curve of an old thrombus. The dashed lines display the time markers of aortic and mitral valve opening and closure. Note that the largest change in deformation takes place during the isovolumetric relaxation period when cavity pressure decreases rapidly and that the fresh thrombus clearly shows a higher deformation velocity. AVO indicates aortic valve opening; AVC, aortic valve closure; MVC, mitral valve closure; and MVO, mitral valve opening.

Thrombus Stiffness

Mitral regurgitation with an adequate continuous Doppler profile showing the acceleration and the deceleration of the regurgitation jet was present in 16 patients (7 with fresh thrombi and 9 patients with old thrombi). \( \frac{dP}{dt}_{\text{min}} \) was estimated from the slope of the mitral regurgitation velocities, as described in the Methods section. The \( \frac{dP}{dt}_{\text{min}} \) did not differ between fresh and old thrombi: 594±196 mm Hg/s versus 568±138 mm Hg/s, respectively; \( P=0.87 \). Calculation of thrombus stiffness with formula 2 showed that new thrombi (478±246 hPa) had a significant lower stiffness than old thrombi (1711±518 hPa; \( P=0.001 \)). There was good correlation between calculated thrombus stiffness and age of the thrombus (\( r=0.73; P=0.002; \) Figure 5).

Discussion

The current 2-part study focused on echocardiographic age determination of LV thrombi after myocardial infarction. In
the first part of this single-center study, a typical age-related deformation pattern was detected and a threshold value discriminating old from fresh thrombi was derived. In the second prospective longitudinal part of the study, this threshold was validated prospectively. The main findings of our study with 52 patients are:

(1) Compared with the old thrombi, the fresh ones show significantly more deformation with the highest change of deformation during the isovolumetric relaxation period.

(2) Fresh and old intracavitary thrombi can be reliably differentiated by noninvasive deformation imaging.

(3) By the use of Hooke’s law, an approximate calculation of the thrombus stiffness is possible using noninvasive imaging.

(4) Treatment with phenprocoumon results in thrombus resolution only in fresh thrombi.

LV Thrombus After Myocardial Infarction

The development of LV thrombi is one of the common complications after myocardial infarction.6-8 Because of the risk of serious embolic complications, including stroke, they have a high clinical relevance. It is commonly acknowledged that LV thrombus formation is the major source of embolic stroke after ST-elevated myocardial infarction.1-2 Thus, the intrinsic properties of the thrombus change with aging: the older thrombus is more fixed to the LV wall and less fragile because of its collagen-rich organization.30 Although echocardiography plays a major role in the detection of LV thrombus after myocardial infarction, it is not possible to differentiate reliably between fresh and old intracavitary thrombi by standard echocardiography. Some criteria for age determination of LV thrombi by echocardiographic appearance have been suggested: reports state that fresh thrombi are highly mobile and tend to protrude to the LV cavity.4,5,27-31 Older thrombi seem to have in general a smoother surface. However, these characteristics might be misleading in small thrombi, with insufficient image quality, and when parts of the thrombus have already been embolized. Consistent with these observations, no major differences in thrombus appearance of fresh and old thrombi were detected in our patient sample. In contrast, by the use of deformation imaging we were able to differentiate fresh from old intracavitary thrombi, which likely corresponds to different material elasticity and thus might reflect different thrombus structure and organization. Fresh thrombi, which are still in the development and expansion stage, consist mainly of blood material and are not yet organized by collagen.30 Thus, these fresh thrombi are more elastic, which leads to a higher degree of passive deformation during changes in cavity pressure (assessed by deformation imaging) and a lower stiffness. In contrast, old thrombi are highly organized mostly by collagen, which results in a very rigid structure in this perpetuation stage.
Therefore, it is logical to assume that deformation differences, namely the peak velocity of deformation, in old and fresh intracavitary thrombi are related to thrombus density, which results in different stiffness of fresh and old thrombi. It is interesting to note that both fresh and old thrombi showed the highest velocity of deformation during the IVRT, indicating that the pressure change and the induced pressure gradients (due to blood flow and vortices) over the thrombus were the most important mechanical forces on the thrombus surface, whereas the passive deformation induced by the (attached) ventricular wall was much less pronounced. Overall, the total amount of deformation was low (even in fresh thrombi <9%). This is easily explained by the fact that thrombi are incompressible, and the observed deformation thus has to be related to different stress levels across the thrombus surface. However, as a result of the rapidly changing forces (pressures) on the thrombus, the peak velocity of the passive deformation of the thrombi was quite high and comparable in magnitude with actively contracting myocardium.

**Thrombus Resolution With Phenprocoumon**

Observational studies provide support for the hypothesis that anticoagulation reduces the risk of embolization. A report of 43 patients with LV thrombus after myocardial infarction who were followed for a mean of 15 months states no embolic event in the 25 patients treated with anticoagulation, in comparison with 7 reports of embolic events in the untreated patients—all occurring within the first 4 months. Thus, in the 2006 American Heart Association/American Stroke Association guidelines for prevention of ischemic stroke full anticoagulation was recommended for 3 months up to 1 year in patients with myocardial infarction and consecutive LV thrombi.

Various studies suggested that echocardiography can be used to monitor the resolution of thrombi with anticoagulation. However, the predictors of thrombus resolution are not well defined. In a systematic longitudinal study over 12 months, the only independent predictor of thrombus resolution was the absence of apical dyskinesia 6 weeks after myocardial infarction. It is surprising that although full anticoagulation therapy appears to reduce the rate of embolization, studies could not document thrombus resolution by anticoagulation. However, this might be a study setting problem, when the detection of LV thrombi is an incidental finding without definite knowledge of thrombus age and accordingly with no information about onset of thrombus formation. This implies that a lot of the patients in the mentioned studies had an old organized thrombus—where thrombus resolution with full anticoagulation was impossible. In contrast, our data clearly document that under anticoagulation in the course of 6 months fresh thrombi dissolve, or at least substantially decrease in size, whereas old thrombi remain unchanged in morphology, localization, and passive deformation.

**Limitations**

Concerning the thrombus age, only very fresh thrombi and quite old thrombi were investigated in substudy I. This is also the explanation for presenting this very clear cutoff value (1 s⁻¹) without any overlap between old and fresh thrombi. However, this spectrum of thrombus age was also present in the second part of the prospective study. Thus, a study with a large cohort and a multicenter setting covering a wider range of thrombus ages would be needed to confirm our data.

The screening for LV thrombi in the second part of the prospective study was done by echocardiography, although the reference standard for the detection is MRT and problems like foreshortening in echocardiography are well known. However, the aim of this study was not to test for sensitivity and specificity of echocardiographic thrombi detection, but to analyze the deformation of an already detected thrombus. The calculated elasticity is not a direct measure of the true material property of the thrombus because the stress used in the calculation (dP/dt) is not the absolute resulting force that is inducing the deformation, but is merely directly related to it.

The well known disadvantage of the angle dependency of SR-imaging plays no role in the current study as the direction of compression of the thrombus is not important. Thus, especially for the assessment of thrombus deformation SR-imaging is the perfect technique. This is even more emphasized by the results of reanalysis of all thrombi by speckle tracking imaging (online-only Data Supplement Figure I), where it can be seen that a differentiation of fresh and old LV thrombi is not possible with speckle tracking, as explained in the Methods section under Method Limitations.

**Conclusions**

This pilot echocardiographic study of 52 patients has demonstrated that deformation imaging can be used to differentiate fresh and old intracavitary LV thrombi after myocardial infarction and has shown a correlation between thrombus stiffness and thrombus age. This study has potentially significant clinical implications that should be explored in a larger, prospective study.
Sources of Funding

This work was supported by grants from the Bundesministerium für Bildung und Forschung (BMBF: project 01EO1004).

Disclosures

None.

References


20. Lang RM, Bierig M, Devereux RB, Flachskaamp FA, Foster E, Pellikka PA, Picard MH, Roman MJ, Seward J, Shanewise JS, Solomon SD, Spencer KT, Sutton MS, Stewart WJ; Chamber Quantification Writing Group; American Society of Echocardiography's Guidelines and Standards Committee; European Association of Echocardiography. Recommendations for chamber quantification: a report from the American Society of Echocardiography’s Guidelines and Standards Committee and the Chamber Quantification Writing Group, developed in conjunction with the European Association of Echocardiography, a branch of the European Society of Cardiology. J Am Soc Echocardiogr. 2005;18:1440–1463.


Left ventricular thrombi after myocardial infarction are linked with a risk of systemic embolization. The majority of these events occur within the initial 4 months after myocardial infarction. Thus, the ability to differentiate between old and fresh left ventricular thrombi is of clinical importance. This study applied the technique of echocardiographic myocardial deformation imaging to the analysis of left ventricular thrombi. The 2-part study proposes an echocardiographic method to reliably differentiate fresh from old intracavitary thrombi, easy to implement in everyday routine. In this prospective study, sufficient anticoagulation not only diminished the risk of systemic embolization—a well-known fact—but also resulted in fresh thrombus resolution, whereas in patients with old thrombi, anticoagulation had no effect on thrombus resolution. This study has potentially significant clinical implications that should be explored in a larger, prospective study. Such a study might provide new insights concerning the identification of patients with fresh left ventricular thrombus in whom unfavorable consequences might be more likely and who therefore might benefit from anticoagulation.
Differentiation Between Fresh and Old Left Ventricular Thrombi by Deformation Imaging
Markus Niemann, Philipp Daniel Gaudron, Bart Bijnens, Stefan Störk, Meinrad Beer, Hanns Hillenbrand, Maja Cikes, Sebastian Herrmann, Kai Hu, Georg Ertl and Frank Weidemann

Circ Cardiovasc Imaging. 2012;5:667-675; originally published online July 5, 2012;
doi: 10.1161/CIRCIMAGING.112.974964

The online version of this article, along with updated information and services, is located on the World Wide Web at:
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Data Supplement (unedited) at:
http://circimaging.ahajournals.org/content/suppl/2012/07/05/CIRCIMAGING.112.974964.DC1

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http://circimaging.ahajournals.org//subscriptions/
## Supplemental Table 1: Clinical characteristics of the patients with fresh and old thrombi in sub-study I

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<thead>
<tr>
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<th>Old thrombi</th>
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<tbody>
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<td>Gender (m/f)</td>
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<td>Age (years)</td>
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<td>Height (cm)</td>
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<td>76±4</td>
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<td>Heart rate (l/min)</td>
<td>84±15</td>
<td>96±23</td>
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### NYHA

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<td>Nicotin abusus (n)</td>
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<td>Digitalis (n)</td>
<td>1</td>
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ACE, angiotensin converting enzyme; AT, angiotensin; BP, blood pressure; COPD, chronic obstructive pulmonary disease; GFR, glomerular filtration rate; NYHA, New York Heart Association
Supplemental Table 2: Clinical characteristics of the patients with strain rate $\geq 1$ s$^{-1}$ and strain rate $<1$ s$^{-1}$ in sub-study II

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<tr>
<td>Age (years)</td>
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<td>64±12</td>
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<td>Height (cm)</td>
<td>169±10</td>
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<tr>
<td>Weight (kg)</td>
<td>77±18</td>
<td>90±16</td>
<td>0.09</td>
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<td>Systolic BP (mmHg)</td>
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<td>0.17</td>
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<tr>
<td>Diastolic BP (mmHg)</td>
<td>71±8</td>
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<tr>
<td>Heart rate (1/min)</td>
<td>78±12</td>
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**NYHA**

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ACE, angiotensin converting enzyme; AT, angiotensin; BP, blood pressure; COPD, chronic obstructive pulmonary disease; GFR, glomerular filtration rate; NYHA, New York Heart Association
Box-and-whisker plot of old and fresh intracavitary thrombi analysed with 2D speckle tracking. The strain-rate during the isovolumetric relaxation period (s⁻¹) is displayed on the y-axis. Please note that a differentiation of fresh and old thrombi is not possible with speckle tracking.