Percutaneous coronary intervention in acute myocardial infarction: from procedural considerations to long term outcomes
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Citation for published version (APA):

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Chapter 7

Left ventricular thrombus formation after acute myocardial infarction as assessed by cardiovascular magnetic resonance imaging


ABSTRACT

Introduction Left ventricular (LV) thrombus formation is a feared complication of myocardial infarction (MI). We assessed the prevalence of LV thrombus in ST-segment elevated MI patients treated with percutaneous coronary intervention (PCI) and compared the diagnostic accuracy of transthoracic echocardiography (TTE) to cardiovascular magnetic resonance imaging (CMR). Also, we evaluated the course of LV thrombi in the modern era of primary PCI.

Methods Two hundred patients with primary PCI underwent TTE and CMR, at baseline and at 4 months follow up. Studies were analyzed by two blinded examiners. Patients were seen at 1, 4, 12, and 24 months for assessment of clinical status and adverse events.

Results On CMR at baseline, a thrombus was found in 17 of 194 (8.8%) patients. LV thrombus resolution occurred in 15 patients. Two patients had persistence of LV thrombus on follow-up CMR. On CMR at four months, a thrombus was found in an additional 12 patients. In multivariate analysis, thrombus formation on baseline CMR was independently associated with, baseline infarct size (g) (B = 0.02, SE = 0.02, p < 0.001). Routine TTE had a sensitivity of 21–24% and a specificity of 95–98% compared to CMR for the detection of LV thrombi. Intra- and interobserver variation for detection of LV thrombus were lower for CMR (κ=0.91 and κ=0.96) compared to TTE (κ=0.74 and κ=0.53).

Conclusion LV thrombus still occurs in a substantial amount of patients after PCI-treated MI, especially in larger infarct sizes. Routine TTE had a low sensitivity for the detection of LV thrombi and the interobserver variation of TTE was large.
INTRODUCTION

Mortality due to acute myocardial infarction (MI) has decreased since the introduction of primary percutaneous coronary intervention (PCI). Nevertheless, post infarct complications are still a major cause of morbidity and mortality. One of the most feared complications is the occurrence of thrombo-embolic events in patients with left ventricular (LV) thrombus. To date, no randomized trials have evaluated the efficacy of anticoagulation therapy in preventing embolization in this group of patients. However, observational studies conducted in the pre-thrombolytic and thrombolytic era, provide support for long term anticoagulation with vitamin K antagonist. This is reflected in the ESC and ACC/AHA guidelines recommending vitamin K antagonist therapy in patients with LV thrombus after MI for at least 3-6 months and even indefinitely in patients without increased risk of bleeding.

Nowadays, ST-segment elevated myocardial infarction (STEMI) patients undergo primary PCI and receive long term dual anti-platelet therapy (including aspirin and a P2Y12 inhibitor). Consequently, patients with LV thrombus or at increased risk of LV thrombus formation after an MI are frequently treated with vitamin K antagonist in addition to dual anti-platelet therapy and therefore subjected to an increased bleeding risk. Adequate diagnosis and follow-up of LV formation is therefore essential.

We performed a study to address the following issues: (1) assess the prevalence of LV thrombus in patients after STEMI treated with primary PCI and dual anti-platelet therapy (2) compare the diagnostic accuracy of 2D-echocardiography versus cardiovascular magnetic resonance (CMR) (3) evaluate the course of LV thrombi in the modern era of primary PCI.

METHODS

The present study is a substudy of the HEBE-trial, which evaluated the effects of injection of intracoronary bone-marrow cells. A total of 200 patients presenting with a first STEMI was enrolled in this multicenter study involving 8 high volume primary PCI centers located in the Netherlands. All patients had undergone primary PCI with stent implantation within 12 h of symptom onset. Exclusion criteria were: unsuccessful PCI, hemodynamic instability, elevation of creatine kinase (CK) or CK-myocardial band < 10 times the local laboratory upper limit of normal, and contraindications for CMR. The regional committees for medical research ethics approved the study protocol and all patients gave informed consent. All patients underwent transthoracic echocardiography (TTE) and CMR at baseline and at 4 months follow-up.
Cardiovascular magnetic resonance

CMR examinations were performed between 2 and 7 days and repeated at 4 months after primary PCI. The studies were performed on a clinical 1.5 Tesla scanner as previously described. (10) Whole LV coverage was achieved on cine CMR with contiguous short axis slices using a segmented steady-state free-precession pulse sequence. Typical in-plane resolution was 1.6 x 1.9 mm, with slice thickness 5.0 to 6.0 mm (repetition time/echo time 3.2/1.6 ms, flip angle 60º, matrix 256 x 156, temporal resolution 35 to 60 ms). Late gadolinium enhancement images were obtained to examine infarct size, 10 to 15 minutes after administration of a gadolinium-based contrast agent (Dotarem, Guerbet; 0.2 mmol/kg) using a 2D segmented inversion recovery gradient-echo pulse sequence, with slice position identical to the cine images. Typical in-plane resolution was 1.4 x 1.7 mm, with slice thickness 5.0 to 6.0 mm (repetition time/echo time=9.6/4.4 ms, flip angle 25º, triggering to every other heartbeat). The CMR data was analyzed using a dedicated software package (Mass 2008beta, Leiden). Observers were blinded to echocardiographic results and patient identity. After endocardial and epicardial borders were outlined manually on short axis end-diastolic and end-systolic cine images, left ventricular end-systolic volume (LVESV) and left ventricular end-diastolic volume (LVEDV) were determined, after which left ventricular ejection fraction (LVEF) and myocardial mass were calculated. Microvascular obstruction (MVO) was defined as any region of hypoenhancement within the hyperenhanced infarcted area and was included in the calculation of total MI size.

LV thrombi on CMR were defined as filling defects within the LV cavity, typically adherent to regions of abnormal wall motion (hypokinesis, akinesis or dyskinesis) on cine sequences and had to be confirmed by late gadolinium enhancement (see Figure 1 and supplementary materials). Thrombi were carefully differentiated from regions of MVO which appear on (late gadolinium enhancement) LGE as dark areas within the core, and thus completely surrounded, by the hyper intense acute myocardial infarct. The presence or absence of LV thrombus on CMR was scored by two blinded, independent, experienced examiners, blinded to patient identity and TTE results. A consensus was reached in case of disagreement.

Transthoracic echocardiography

TTE was performed within one day of the CMR study. Parasternal, apical and subcostal views were obtained, with special focus on the apical views, since thrombi are most frequent, although not exclusively, located at the apex. On TTE, thrombus was defined as a discrete echo dense structure in the LV cavity with well-defined margins, distinct from the endocardial border, visible in both systole and diastole in at least two views and located adjacent to a hypokinetic or akinetic area of the LV wall. TTE studies were independently analyzed from CMR results. The presence or absence of LV thrombus
LV thrombus as assessed by CMR

on echocardiography was scored by two blinded, independent, experienced examiners, blinded to patient identity and CMR results. A consensus was reached in case of disagreement.

Follow-up

All patients were treated with a loading dose of clopidogrel 300 or 600 mg and thereafter 75 mg/day in addition to an initial loading dose of aspirin followed by 80-100 mg/day. Patients were treated with vitamin K antagonist at the discretion of the treating physician with a target international normalized ratio of 2.0-3.0 for ≥3 to 6 months. Patients were seen at the outpatient clinic at 1, 4, 12 and 24 months after primary PCI, for assessment of clinical status and adverse events. Stroke was defined as the new onset of focal or global neurological deficit caused by ischemia or hemorrhage assessed by appropriate imaging e.g. computerized axial tomography or magnetic resonance imaging, within or around the brain and lasting for more than 24 hours or leading to death. Bleeding was defined according to the criteria of the Thrombolysis In Myocardial Infarction trial. Major bleeding was defined as a decrease in the hemoglobin level of >5 g/dl, intracranial hemorrhage or a >15% absolute decrease in hematocrit, or cardiac tamponade. Minor bleeding was defined as a decrease in the hemoglobin level of 3 g/dl decrease in hemoglobin concentration or >10% decrease in hematocrit from an identified site or: >4 g/dl decrease in the hemoglobin concentration or >12% decrease in hematocrit when bleeding site is not identified or spontaneous gross hematuria, hematemesis, or hemoptysis. A clinical event committee independently adjudicated all potential clinical events.

Figure 1. Left ventricular thrombus formation on late gadolinium enhancement cardiac magnetic resonance imaging (A); Cine cardiovascular magnetic resonance of a thrombus (asterisk) in the apex of the left ventricle (B); Late gadolinium enhancement imaging neatly confirms the avascular non-enhancing thrombus (asterisk) close to the transmural infarcted myocardium with areas of microvascular obstruction.
Statistical analysis

Values are reported as mean ± SD or median (25th to 75th percentile) for continuous variables and as frequency with percentage for categorical variables. Unpaired Student’s t-test and a Fisher’s exact test were used to compare differences between groups of continuous and categorical variables, respectively. To assess intraobserver variation, a kappa statistic was calculated for both CMR and TTE for diagnosing LV thrombus. For inter-observer variation, a kappa statistic was calculated from the results from the first examination. Covariates of interest as predictors of LV thrombus formation were investigated using multivariable logistic regression. Baseline variables that were significant at P ≤ 0.10 on univariate analysis were entered into a multivariate model. Clinical events were presented for descriptive purposes only.

All statistical tests were 2-tailed, and a value of p<0.05 was considered statistically significant. Calculations were generated by SPSS software (version 17.0 for Windows, SPSS, Inc., Chicago, Illinois).

RESULTS

A total of 6 patients were excluded from this sub-analysis due to a non-evaluable CMR. In the remaining 194 patients, mean age was 56±9 years, 85% of the patients were men, mean baseline LV ejection fraction was 42±9 % and 90% had TIMI flow grade 3 after primary PCI. CMR was performed 4±2 days and TTE 3±2 days after primary PCI. During the 24-month of clinical observation, 10 patients were lost to follow-up (all without LV thrombus on baseline CMR).

Incidence of LV thrombus at baseline and at follow-up

On CMR at baseline, a thrombus was found in 17 of 194 (8.8%) patients. LV thrombus resolution occurred in 15 patients. Two patients had persistence of LV thrombus on follow-up CMR. On CMR at four months, a thrombus was found in an additional 12 patients, making a total of 14 of 190 (7.3%) patients with LV thrombus (see Figure 1). Clinical, angiographic characteristics and CMR results stratified according to the absence or presence of LV thrombus at baseline and at 4 months are described in Table 1. All LV thrombi were seen in patients with anterior infarctions. Patients with both early and late LV thrombus had more often microvascular obstruction on baseline CMR and larger infarct sizes than patients without LV thrombus formation (see Table 1) In multivariate analysis, thrombus formation on baseline LGE was independently associated with, baseline infarct size (g) (B=0.02, SE=0.02, p<0.001) and anterior infarction (B=19.47, SE 4900, p<0.001). At 4 months, LV thrombus formation was also independently associated with, baseline infarct size (g) (B=0.06, SE=0.02, p<0.001).
LV thrombus as assessed by CMR

Table 1. Baseline demographics and characteristics stratified according to the early, late, or absence of left ventricular thrombus at cardiovascular magnetic resonance (CMR) in patients after acute myocardial infarction

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Early LV thrombus</th>
<th>Late LV thrombus*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Presence (n=17)</td>
<td>Absence (n=177)</td>
</tr>
<tr>
<td>Age (years)</td>
<td>57 ± 8</td>
<td>56 ± 10</td>
</tr>
<tr>
<td>Male gender</td>
<td>14 (82%)</td>
<td>151 (85%)</td>
</tr>
<tr>
<td>Risk factors</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>0 (0%)</td>
<td>12 (6.7%)</td>
</tr>
<tr>
<td>Known hypertension</td>
<td>4 (24%)</td>
<td>50 (28%)</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>1 (6%)</td>
<td>37 (21%)</td>
</tr>
<tr>
<td>Current cigarette smoking</td>
<td>6 (35%)</td>
<td>95 (54%)</td>
</tr>
<tr>
<td>Angiography and infarct treatment</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time from symptom onset to PCI (hours)</td>
<td>2.8 (2.1–5.1)</td>
<td>3.4 (2.3–4.6)</td>
</tr>
<tr>
<td>Anterior infarction</td>
<td>17 (100%)</td>
<td>106 (60%)</td>
</tr>
<tr>
<td>Medication at discharge</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aspirin</td>
<td>17 (100%)</td>
<td>170 (96%)</td>
</tr>
<tr>
<td>Clopidogrel</td>
<td>17 (100%)</td>
<td>177 (100%)</td>
</tr>
<tr>
<td>Coumarin derivate</td>
<td>8 (47%)</td>
<td>23 (13%)</td>
</tr>
<tr>
<td>Medication at 4 months follow-up</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aspirin</td>
<td>17 (100%)</td>
<td>162 (92%)</td>
</tr>
<tr>
<td>Clopidogrel</td>
<td>17 (100%)</td>
<td>150 (85%)</td>
</tr>
<tr>
<td>Coumarin derivate</td>
<td>8 (47%)</td>
<td>27 (15%)</td>
</tr>
<tr>
<td>Magnetic Resonance Imaging (day 3-5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Presence of microvascular obstruction†</td>
<td>15 (88%)</td>
<td>96 (56%)</td>
</tr>
<tr>
<td>LVEF (%) †</td>
<td>37 ± 10</td>
<td>43 ± 9</td>
</tr>
<tr>
<td>Infarct size (g) ‡</td>
<td>28 ± 12</td>
<td>22 ± 12</td>
</tr>
<tr>
<td>Magnetic Resonance Imaging (4 months)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LVEF (%) †</td>
<td>43 ± 9</td>
<td>47 ± 9</td>
</tr>
<tr>
<td>Infarct size (g) ‡</td>
<td>17 ± 9</td>
<td>14 ± 8</td>
</tr>
</tbody>
</table>

Data are number (%), mean±SD or median (25th–75th percentile). LVEF = Left Ventricular Ejection Fraction; PCI=percutaneous coronary intervention. † The analysis included 189 patients. ‡ The analysis included 167 patients. * 4 follow-up CMR were excluded from this analysis due to poor quality.

**CMR vs. TTE for the detection of LV thrombus**

Of the 17 thrombi visualized on CMR, 4 were visible also on TTE. In 9 patients, TTE suggested an apical thrombus, which could not be confirmed on CMR. Sensitivity and specificity of baseline TTE compared to baseline CMR was respectively 21-24% and 95-98% (see Table 2). CMR intra- and interobserver variation for the detection of LV thrombus was κ 0.91 and κ 0.96 respectively. TTE intra and interobserver variation for the detection of LV thrombus was κ 0.74 and κ 0.53 respectively.
\textbf{Table 2.} Sensitivity, specificity, and predictive value of transthoracic echocardiography (TTE) compared to cardiovascular magnetic resonance (CMR)

<table>
<thead>
<tr>
<th>TTE (baseline)</th>
<th>CMR (baseline)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Presence</td>
<td>Absence</td>
</tr>
<tr>
<td>Presence</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>Absence</td>
<td>13</td>
<td>172</td>
</tr>
</tbody>
</table>

Sensitivity= 24%
Specificity= 95%

<table>
<thead>
<tr>
<th>TTE (4 months)</th>
<th>CMR (4 months)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Presence</td>
<td>Absence</td>
</tr>
<tr>
<td>Presence</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Absence</td>
<td>11</td>
<td>172</td>
</tr>
</tbody>
</table>

Sensitivity= 21%
Specificity= 98%

CMR=cardiovascular magnetic resonance imaging; TTE= transthoracic echocardiography

\textit{Clinical course of LV thrombi}

In 8 of the 17 patients with LV thrombus at baseline (figure 2), the treating physician started vitamin K antagonist on top of aspirin and clopidogrel. The other 9 patients were treated with dual anti-platelet therapy. In 15 of these 17 patients (vitamin K antagonist therapy: n=7, no vitamin K antagonist therapy: n=8), no thrombus was present at 4 months follow-up (see figure 1). Of the two patients with persisting LV thrombus, one was treated with vitamin K antagonist therapy. In an additional 12 patients (6.2%) LV thrombus was absent at baseline CMR but occurred at 4 months follow-up. Four of these patients were on triple-antithrombotic therapy for other indications; eight patients were on dual anti-platelet therapy.

\textit{Clinical events}

One of the 194 patients had clinical evidence of ischemic stroke, however this patient did not have evidence of LV thrombus formation on either CMR or TTE or any other known risk factors for systemic embolism. In three other patients, gastro-intestinal bleedings were documented; all of them received triple anti-thrombotic therapy.

\textbf{DISCUSSION}

Our study demonstrates an LV thrombus prevalence of 8.8% as assessed by CMR among a population of patients with a first large STEMI treated by primary PCI (mean LVEF 42 ±9%). Routine TTE had a sensitivity of 21-24% and a specificity of 95%- 98% compared to CMR for the detection of LV thrombi and the interobserver variation of TTE was large (\(\kappa=0.53\)). Finally, LV thrombi documented in the modern era of primary PCI
LV thrombus as assessed by CMR

and its concomitant dual anti-platelet therapy, appear to have a relatively benign course, irrespective of anti-thrombotic therapy.

**Left ventricular thrombus and incidence**

Early data from the pre- and thrombolytic era suggest that in the setting of acute MI, LV thrombus may be present in 7-46% of patients, most frequently in acute anterior or apical myocardial infarction. In the era of primary PCI and dual anti-platelet therapy, there is limited data concerning the frequency of LV thrombus in AMI. In our study, the incidence of LV thrombus was 8.8% in a selected group of first STEMI patients treated by primary PCI as detected on DE-CMR. Solheim et al., reported a higher incidence of 15% in the first 3 months, Zielinska et al., found LV thrombi formation in 68 of 1,251 patients (5.4%) with acute anterior wall myocardial infarctions and only in 0.3% in those with non–anterior wall MI. Patients with LV thrombus had larger infarct sizes and were more often anterior MI, confirming earlier observations.
**Left ventricular thrombus and diagnosis**

Among the 17 patients with LV thrombus identified by CMR in the current study, 4 were visible also on TTE. Sensitivity and specificity of baseline TTE compared to baseline CMR was respectively 21-24% and 95-98%. No independent gold-standard (e.g. histopathology or surgery) was reachable to determine the better diagnostics accuracy. However, this discrepancy has been reported in two prior studies. One study compared CMR and LGE with echocardiography in a cohort of patients undergoing LV reconstruction surgery in whom surgical and/or pathology verification of thrombus was uniformly performed.\(^{18}\) This study reported that the sensitivity of TTE was 40%, compared with 88% for CMR, showing the superiority of CMR. Another study reported an echo sensitivity and specificity of 33% and 91% in a heterogeneous population of patients with LV systolic dysfunction.\(^{16}\) Intravenous echo contrast during TTE may improve the diagnostic assessment of LV thrombus.\(^{19, 20}\) However, only one compound (SonoVue, Bracco, Milan, Italy) is approved in the Netherlands and its use is contraindicated by the European Medicines Agency in cardiac patients with acute coronary syndrome, recent percutaneous coronary intervention, acute or chronic severe heart failure or severe cardiac arrhythmias.

**Left ventricular thrombus and management**

Previous studies performed in the pre-thrombolytic and thrombolytic era reported varying data concerning the risk of future embolic events.\(^{3-6}\) A 1992 meta-analysis included 11 studies of 856 patients who had an anterior MI; the odds ratio for an embolic event was 5.5 (95% CI 3.0-9.8).\(^6\) In clinically stable patients with chronic heart failure, the risk of thromboembolism seems low (1-3% per year), even in those with very impaired LV function and echocardiographic evidence of intracardiac thrombi.\(^{21, 22, 23}\) Our analysis also indicates that documented LV thrombus (by CMR or TTE) is accompanied by a relative benign course since none of these patients, irrespective of type of anti-thrombotic regimen, experienced a major thrombo-embolic event up to 2 years after myocardial infarction.

Whether management of LV thrombus requires vitamin K antagonist therapy on top of dual anti-platelet therapy cannot be concluded from this observational study and requires the conduction of a randomized trial in acute MI patients with LV thrombus.

**Fundings**

This work was supported by a grant by the Dutch Heart Foundation and National Health Insurance Board/ZON MW, the Netherlands to RD.
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