Angiographically evident thrombus following fibrinolytic therapy is associated with impaired myocardial perfusion in STEMI: a CLARITY-TIMI 28 substudy

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Aims The presence of residual thrombus following fibrinolytic therapy for ST-segment elevation myocardial infarction (STEMI) may predispose to greater embolization and microvascular dysfunction. Methods and results We hypothesized that even in the presence of a patent epicardial artery, residual thrombus would be associated with worsened TIMI myocardial perfusion grades (TMPG), independent of epicardial flow. Data were analysed from the angiograms of 2684 patients enrolled in the CLARITY-TIMI 28 trial, with angiographically patent arteries (TIMI 2/3 flow) at a median of 88 h following fibrinolytic therapy. Thrombus in a patent epicardial artery was observed more frequently among patients with shorter times from randomization to angiography, among patients with non-left anterior descending infarctions, and among patients treated with placebo (vs. clopidogrel). Thrombus was associated with more frequent TIMI 2 flow (35.1 vs. 22.1%, \(P_{<0.001}\)), higher corrected TIMI frame counts (CTFC) (42 vs. 33 frames, \(P_{<0.001}\)), and a lower incidence of normal TMPG 3 (48.7 vs. 63.9%, \(P_{<0.001}\)), irrespective of treatment with clopidogrel or placebo. In multivariable analyses, thrombus remained associated with higher CTFC (\(P_{<0.001}\)) and worse TMPG (OR 1.6 for TMPG 0/1/2, \(P_{<0.001}\)) after adjustment for baseline covariates as well as known correlates of TMPG. The association between thrombus and impaired TMPG remained even after further adjustment for CTFC or TIMI flow grade. Conclusion Residual angiographic thrombus following fibrinolytic therapy in STEMI patients is associated with impaired myocardial perfusion, independent of epicardial flow. This finding emphasizes the roles of platelet aggregation and distal embolization in the pathogenesis of microvascular dysfunction in STEMI.

Introduction

The goal of reperfusion therapy for ST-segment elevation myocardial infarction (STEMI) is to achieve early, full, and sustained perfusion of the myocardium in the distribution of the infarct-related artery. Despite the restoration of epicardial artery patency and normal epicardial flow following reperfusion therapy, patients frequently have abnormalities of myocardial perfusion. Abnormal myocardial perfusion in STEMI has been associated with larger infarct sizes, worsened myocardial salvage, and increased mortality following treatment with fibrinolytic therapy or with primary percutaneous coronary intervention (PCI).

Angiographically evident residual thrombus within the culprit coronary artery has been independently linked to impaired myocardial perfusion following fibrinolytic therapy for STEMI at 60 and 90 min angiography. Similarly, among patients with non-ST segment elevation acute coronary syndromes, angiographic thrombus has been associated with both greater troponin release and impaired myocardial perfusion. However, whether angiographic thrombus is associated with impaired myocardial perfusion on late angiography following reperfusion therapy for STEMI and in the context of modern anti-platelet therapies, including clopidogrel, is unknown. We sought to examine the association of angiographically evident thrombus and myocardial perfusion among a large cohort of patients treated with fibrinolytic therapy and either aspirin plus placebo or aspirin plus clopidogrel. We hypothesized that residual thrombus following fibrinolytic therapy would be associated with worsened TIMI myocardial perfusion grades (TMPG) and slower epicardial flow, independent of treatment with adjunctive clopidogrel.

Methods

CLARITY-TIMI 28 was a multicentre, international, randomized, double-blind, placebo-controlled trial of aspirin vs. aspirin plus
Angiographic analysis

In CLARITY-TIMI 28, all angiograms were analysed offline and blinded to treatment assignment at the TIMI Angiographic Core Laboratory (Boston, MA). For this study, analyses were restricted to the 2684 patients who underwent angiography during the index hospitalization, who demonstrated a patent culprit artery (TIMI grade 2 or 3 flow), and in whom the TMPG and presence or absence of thrombus could be ascertained by the core laboratory. Quantitative coronary angiography and assessments of TIMI flow grade, corrected TIMI frame count (CTFC), and TMPG were measured as previously described by Gibson.

Thrombus was categorized and defined as the presence of an angiographically apparent luminal filling defect, as described previously by Gibson. For this analysis, a patient was considered to have thrombus if grades 2–4 were present (grades 5 and 6 were not applicable to this analysis, restricted to patent arteries): grade 0: no cineangiographic characteristics of thrombus present; grade 1: hazy, possible thrombus present with angiography demonstrating characteristics such as reduced contrast density, haziness, irregular lesion contour, or a smooth convex ‘meniscus’ at the site of total occlusion suggestive but not diagnostic of thrombus; grade 2: thrombus present—small size: definite thrombus with greatest dimensions less than or equal to half the vessel diameter; grade 3: thrombus present—moderate size: definite thrombus but with the greatest linear dimension greater than half but less than two vessel diameters; grade 4: thrombus present—large size: as in Grade 3 but with the largest dimension greater than or equal to two vessel diameters.

Table 1 Baseline characteristics

<table>
<thead>
<tr>
<th></th>
<th>No thrombus (n = 2302)</th>
<th>Thrombus (n = 382)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>57.1 ± 10.3</td>
<td>57.6 ± 9.8</td>
<td>0.33</td>
</tr>
<tr>
<td>Current smoker, n (%)</td>
<td>1185 (51.5)</td>
<td>192 (50.4)</td>
<td>0.68</td>
</tr>
<tr>
<td>History of hypertension, n (%)</td>
<td>974 (42.8)</td>
<td>153 (40.5)</td>
<td>0.39</td>
</tr>
<tr>
<td>History of hyperlipidaemia, n (%)</td>
<td>771 (39.8)</td>
<td>105 (31.3)</td>
<td>0.003</td>
</tr>
<tr>
<td>History of diabetes mellitus, n (%)</td>
<td>373 (16.5)</td>
<td>59 (15.7)</td>
<td>0.70</td>
</tr>
<tr>
<td>Prior myocardial infarction, n (%)</td>
<td>195 (8.5)</td>
<td>24 (6.3)</td>
<td>0.14</td>
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<tr>
<td>History of angina, n (%)</td>
<td>529 (23.3)</td>
<td>78 (20.6)</td>
<td>0.26</td>
</tr>
<tr>
<td>History of prior PCI, n (%)</td>
<td>108 (4.7)</td>
<td>17 (4.5)</td>
<td>0.83</td>
</tr>
<tr>
<td>History of peripheral arterial disease, n (%)</td>
<td>90 (3.9)</td>
<td>19 (5.0)</td>
<td>0.34</td>
</tr>
<tr>
<td>Aspirin use within prior week, n (%)</td>
<td>345 (15.0)</td>
<td>51 (13.4)</td>
<td>0.40</td>
</tr>
<tr>
<td>Body mass index</td>
<td>27.3 ± 4.3</td>
<td>27.7 ± 4.1</td>
<td>0.12</td>
</tr>
<tr>
<td>Anterior infarction, n (%)</td>
<td>42.2</td>
<td>30.6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>TIMI risk index</td>
<td>19.0 ± 8.3</td>
<td>19.0 ± 8.0</td>
<td>0.98</td>
</tr>
<tr>
<td>Time from symptom onset to randomization (h)</td>
<td>2.7 (1.8-4.1)</td>
<td>2.6 (1.7-3.7)</td>
<td>0.046</td>
</tr>
<tr>
<td>Time from randomization to angiography (h)</td>
<td>90.4 (61.8-127.4)</td>
<td>73.1 (12.4-114.8)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Predominant heparin</td>
<td>398 (17.3)</td>
<td>51 (13.3)</td>
<td>0.13</td>
</tr>
<tr>
<td>Unfractionated heparin, n (%)</td>
<td>901 (39.1)</td>
<td>163 (42.7)</td>
<td></td>
</tr>
<tr>
<td>Low-molecular weight heparin, n (%)</td>
<td>1003 (43.6)</td>
<td>168 (44.0)</td>
<td></td>
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<tr>
<td>Creatinine clearance (mL/min)</td>
<td>90.9 ± 30.1</td>
<td>92.1 ± 32.8</td>
<td>0.48</td>
</tr>
<tr>
<td>White blood cell count (×10^3/L)</td>
<td>11.1 ± 3.5</td>
<td>11.2 ± 3.6</td>
<td>0.38</td>
</tr>
<tr>
<td>Platelet count</td>
<td>227.3 ± 65.9</td>
<td>231.4 ± 62.9</td>
<td>0.28</td>
</tr>
<tr>
<td>Haemoglobin</td>
<td>14.0 ± 5.6</td>
<td>14.2 ± 5.0</td>
<td>0.48</td>
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*Patients who received more than one type of heparin were categorized on the basis of the predominant heparin they received, which was prospectively defined as the type of heparin the patients received for the majority of time while awaiting angiography.
less likely to have a history of hyperlipidaemia (P = 0.003), less likely to have an anterior infarction (P < 0.001), had shorter times from randomization to angiography (P < 0.001), and had slightly shorter times from symptom onset to randomization. There were no significant differences in age, creatinine clearance, complete blood count parameters, or TIMI risk index between the two groups. Randomization to treatment with clopidogrel was associated with a lower incidence of thrombus (12.6% vs. 16.0%, P = 0.014, Figure 1). There was also a strong trend for thrombus to be observed more frequently among patients with a recurrent MI prior to angiography [23.7% incidence of thrombus among patients with recurrent MI (n = 59) vs. 14.1% among patients without recurrent MI (n = 2625), P = 0.06].

The associations of thrombus with other angiographic lesions and flow characteristics are shown in Table 2. In stratified analyses, irrespective of treatment with clopidogrel or placebo, the presence of thrombus was associated with less frequent TIMI grade 3 flow (overall rates 64.9% vs. 77.9%, P < 0.001, Figure 2) and higher (slower) TIMI frame counts (Figure 3). Thrombus was also associated with a lower frequency of normal TMPG (48.7% vs. 63.9%, P < 0.001), irrespective of treatment assignment (Figure 4). Thrombus was additionally associated with smaller minimum lumen diameters (0.84 vs. 0.95 mm, P < 0.001) and a greater percent diameter stenosis (69 vs. 63%, P < 0.001). A greater overall thrombus burden also was associated with a stepwise reduction in normal TMPG (Figure 5).

In multivariable analyses, thrombus remained associated with higher TFC (additional seven frames with thrombus, P < 0.001) and worse TMPG (OR 1.6 for TMPG 0/1/2, P < 0.001; Table 3). The independent association between thrombus and worse TMPG remained after further adjustment for CTFC (for thrombus: OR 1.4 for TMPG 0/1/2, P = 0.010) and TIMI grade 3 flow (for thrombus: OR 1.4 for TMPG 0/1/2, P = 0.009). Thrombus was also associated with a greater incidence of revascularization following the protocol angiogram (53.4% vs. 42.6%, P < 0.001).

**Discussion**

This study demonstrates that among patients in whom epicardial patency is successfully restored with fibrinolytic therapy, residual thrombus observed on late angiography is associated with impaired myocardial perfusion, independent of epicardial flow and luminal geometry. These observations validate prior findings in a much larger cohort of 2684 patients and extend these findings to patients who are additionally treated with adjunctive clopidogrel, an agent associated with a lower frequency of residual thrombus following fibrinolytic therapy.

The pathophysiological basis for impaired myocardial perfusion in STEMI is multifactorial and may involve a combination of factors including distal embolization, myocardial oedema and cell swelling, inflammation, reperfusion injury, and vasoconstriction. Initial thrombus formation and ongoing thrombosis appear to be central in many of these processes by serving as a nidus for distal embolization, as well as a mediator of vasoconstrictor release. In patients with STEMI, thrombus can result in distal embolization of microthrombi and platelet-fibrin aggregates into the coronary microcirculation. The authors and others have demonstrated that the administration of potent antiplatelet agents such as glycoprotein IIb/IIIa inhibitors is associated with improvements in both angiographic thrombus as well as myocardial perfusion. Distal microembolization of thrombus is also, however, increasingly being implicated as a cause of...
ongoing inflammation and microvascular dysfunction. Microembolization has been linked to the release of vasoactive mediators such as adenosine and inflammatory cytokines.

A major difference between this study and our prior report of pooled 60 min angiographic data from four prior fibrinolytic trials is that in CLARITY TIMI-28, angiographic analyses were performed later, or at a median of 88 h following fibrinolytic administration. The continued association between thrombus in the culprit artery and impaired myocardial perfusion, even after acute changes in microvascular vasomotor function have to a large extent resolved, is notable and re-emphasizes that thrombosis and embolization may be ongoing processes that continue in the short-term period after successful fibrinolysis.

One pathophysiological explanation for our findings is that residual thrombus may reflect a larger overall thrombotic burden, which may predispose to greater microembolization and microvascular dysfunction. However, it is also possible that residual thrombus may be a marker of thromboresistance, or may even be a surrogate of a more intense prothrombotic and inflammatory process with associated microcirculatory dysfunction. In addition, activation of the coagulation system may also be involved in the persistence and/or recurrence of intracoronary thrombus following the administration of fibrinolytic therapy. Thus, causality or the directionality of the association between thrombus and impaired myocardial perfusion cannot be proved by this analysis, and thus these findings should be considered to be hypothesis-generating.

It is notable that although the association between thrombus and impaired myocardial perfusion was independent of treatment with adjunctive clopidogrel, the co-administration of clopidogrel with fibrinolytic therapy was associated with a lower incidence of observed thrombus even among the patients with patent infarct-related arteries. Despite a reduction in the incidence of thrombus in this subset of patients with patent arteries from CLARITY-TIMI, clopidogrel was not independently associated with improved TMPG. Nonetheless, in the primary trial analysis (including all patients enrolled, irrespective of artery patency on initial angiography), clopidogrel was associated with significant improvements in epicardial patency, TIMI flow grade, and TMPG.

Limitations

The true prevalence of intracoronary thrombus exceeds that observed by angiography, and it is possible that patients...
categorized as having no thrombus actually had a thrombus burden that was below the detection threshold of conventional coronary angiography, although this would have minimized the observed differences between groups. This is a non-randomized analysis of a clinical trial population, and despite efforts to control for confounding, unmeasured confounders may have affected or influenced our observed results.

Conclusions

The presence of residual angiographic thrombus following the administration of fibrinolytic therapy in patients with STEMI is associated with impaired indices of epicardial flow and myocardial perfusion, irrespective of treatment with clopidogrel.

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References

Clinical vignette

Cardiovascular findings in arterial tortuosity syndrome

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A boy presented at birth with an axial diaphragmatic hernia, hyperelastic skin, hyperextensible joints, and arachnodactyly. During infancy, he developed bilateral inguinal herniae and generalized muscular hypotonia. Echocardiography showed an anomalous tortuous course of the pulmonary arteries with suspected stenosis of the left pulmonary artery. Magnetic resonance (MR) imaging demonstrated elongation and tortuosity of the aortic arch and its branches (Panels A and B) and severe tortuosity of the pulmonary arteries (Panels B and C), leading to a significant obstruction of the left branch pulmonary artery that was subsequently stented. At coronarangiography, both coronary arteries presented with a tortuous course without aneurysm or stenosis.

Connective tissue diseases including Ehlers-Danlos syndrome, Marfan syndrome, cutis laxa, and Menkes disease present typical features consisting of hyperelastic or lax skin, laxity of joints, chest and spine deformities, inguinal, umbilical and/or diaphragmatic herniae, and cardiovascular anomalies. Careful clinical assessment, ultrastructural analysis of the skin, molecular studies of the genes involved, analysis of the collagens produced in cultured fibroblasts, and quantification of the plasma levels of copper and coeuloplasmin may help differentiate among the different forms of the disease. However, severe vascular involvement with tortuosity, elongation, aneurysms, or stenosis of the mid-size and large vessels is suggestive of the rare arterial tortuosity syndrome.

In conclusion, echocardiographic screening is recommended for all patients with connective tissue disease, as early detection and treatment of vascular lesions may have a major influence on prognosis.

Panel A. Contrast-enhanced MR angiography demonstrating an elongation of the aortic arch, with the descending aorta located too far left within the thorax.

Panel B. The 3D reconstruction of MR angiography shows the tortuous course of the aortic branches (asterisk, brachiocephalic trunk; double asterisks, left carotic artery). Ao, aorta; MPA, main pulmonary artery.

Panel C. Tortuosity of both pulmonary arteries. The right pulmonary artery makes a loop (asterisk) before its branching.

Panel D. Kinking of the left pulmonary artery owing to a significant stenosis of the origin of the left pulmonary artery (arrow). This stenosis required catheter-guided stenting.