Comparison of direct PCI and front-loaded tissue plasminogen activator for the treatment of patients with right ventricular infarction - a matched-pairs analysis on 174 patients

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Comparison of Direct PCI and Front-Loaded Tissue Plasminogen Activator for the Treatment of Patients with Right Ventricular Infarction – a Matched-Pairs Analysis on 174 Patients

E. Giannitsis, S. Lehrke, U. Wiegand, H. A. Katus, G. Richardt

Patients with inferior acute myocardial infarction (AMI) and concomitant right ventricular infarction (RVI) represent a high-risk population despite early thrombolytic reperfusion. There is accumulating evidence that mechanical reperfusion by means of direct PCI might reverse RV dysfunction and improve prognosis in these patients. Given the lack of randomized trials, we sought to compare the efficiency of a thrombolytic regimen with 100 mg front-loaded recombinant tissue plasminogen activator (rt-PA) versus direct PCI using matched pairs of patients with and without RVI. We enrolled 87 aged and sex-matched pairs of patients presenting within 6 hours after onset of symptoms and assessed prospectively the rates of in-hospital cardiac events (reinfarction, re-ischaemia, death) and predischarge patency of the infarct-related artery (IRA). 30 of 87 pairs (34.5 %) had RVI complicating inferior AMI. These patients had more often systemic hypotension on admission (16.7 vs 40 %, p < 0.01), and suffered more frequently from complete atrioventricular block (35 vs 4 %, p < 0.01). In-hospital mortality rates were insignificantly higher in patients with RVI (15 vs 9 %). Moreover, in-hospital mortality rates were comparable in patients with RVI and non-RVI-AMI regardless whether rt-PA (13 vs 7 %) or direct PCI (16.6 vs 10.5 %) were administered. In the entire cohort, predischarge patency rates of IRA were significantly lower following rt-PA as compared to direct PCI (58.8 vs 93.9 %, p < 0.0001) and particularly among patients with RVI (31.8 vs 96.2 %, p < 0.0001). In addition rates of recurrent ischaemia were significantly higher after rt-PA in patients with RVI (30 vs 3 %, p = 0.012).

In conclusion despite lower predischarge patency rates of the IRA, in-hospital mortality rates were comparable after rt-PA and direct PCI both in the entire cohort and among patients with RVI. Further prospective trials are mandatory to clarify the prognostic impact of lower arterial patency rates after thrombolysis in patients with RVI.

Key words: thrombolysis, direct PCI, right ventricular infarction, outcome

Reperfusion therapy has been shown to improve the clinical course and survival of patients with anterior myocardial infarction, while the benefits of reperfusion therapy in inferior acute myocardial infarction (AMI) and particularly among high risk subgroups like right ventricular infarction (RVI) are less clear [1]. RVI complicating inferior AMI are less clear [1]. RVI complicating inferior AMI is associated with a substantially higher in-hospital mortality and morbidity [2–5]. There is increasing evidence that early mechanical reperfusion may reverse right ventricular (RV) dysfunction and may improve right heart function and survival [6–10].

Theoretically, direct percutaneous coronary intervention (PCI) may be more effective in patients with RVI where the clinical course is more often complicated by severe prolonged hypotension and cardiogenic shock [11, 12]. The question, however, whether direct PCI is superior to fibrinolytic therapy has never been addressed in the setting of RVI infarction.

Methods

Patient population
From April 1993 to May 1995 and from April 1996 to May 1998 two series of consecutive unselected patients with inferior AMI were recruited. During the first period, patients received exclusively a thrombolytic therapy regimen which consisted of 100 mg front-loaded recombinant tissue type plasminogen activator (rt-PA). Patients were excluded for active bleeding, history of stroke or haemorrhagic diathesis, severe trauma within six months, prolonged resuscitation, major surgical procedure within two weeks, uncontrolled hypertension, neoplasm and lack of informed consent, but not for uncomplicated cardiopulmonary resuscitation, bundle branch block or older age.

During the second period, all patients presenting with inferior AMI received exclusively a direct PCI regimen. Patients who were admitted for rescue PCI after failed thrombolytic therapy were excluded to avoid selection bias.

In order to compare the effect of either reperfusion strategy on in-hospital outcome and patency of the infarct-related coronary artery (IRA) before discharge, patients from both series who presented within six hours after onset of symptoms and received reperfusion therapy were matched for age, sex and infarct location, ie, presence or absence of RVI.

In both series, diagnosis of inferior AMI was based on (1) the presence of typical chest pain lasting at least 30 minutes, (2) a 12-lead electrocardiogram depicting ST-segment elevations of at least 1 mm in two or more of the leads II, III, and aVF, or an R/S ratio greater than 1 in lead V1 or V2, and (3) an increase of creatine kinase activity of more than twice the upper limit of normal. In patients with bundle branch block or pacemaker rhythm the diagnosis was based on echocardiographic and angiographic criteria. RVI was diagnosed if ST segment elevation of at least 1 mm was present in right chest lead V4R on admission.

Patient management
Thrombolytic therapy was given with an accelerated dose regimen of 100 mg tissue-type plasminogen activator (rt-PA). Acetylsalicylic acid (500 mg) was administered as soon...
as possible and then in a daily oral dose of 100 mg. All patients received a bolus dose of 5,000 U of heparin intravenously, followed by an infusion of 1,200 U per hour adjusted for activated partial thromboplastin time for at least 48 hours.

Patients who underwent direct PCI received an additional bolus of 7,500 U of heparin after sheath placement. After successful angioplasty, heparin was discontinued to allow early removal of the sheath and was switched to a daily dose of unfractonated low molecular weight heparin given subcutaneously for at least 48 hours. Patients in whom provisional stenting was necessary, received 250 mg ticlopidine immediately after the procedure and then twice daily for 4 weeks. Other medications, including beta-blockers and nitrates were given at the discretion of the physicians and following the recommendations of the ACC/AHA task force [13].

Benefits of reperfusion therapy
Benefits of either reperfusion therapy were assessed in terms of in-hospital mortality and among patients who underwent follow-up coronary angiography before discharge by arterial patency of the IRA. Arterial patency was estimated using the Thrombolysis in Myocardial Infarction (TIMI) classification (TIMI grade 3 flow signifies normal coronary flow [14]). Successful PCI was defined as TIMI grade 3 flow in conjunct with residual stenosis of less than 50%.

Clinical Course and Complications
Clinical data were collected prospectively from admission until discharge. Peak creatine kinase and MB isoenzyme levels were registered to estimate infarct size. In patients who died before having reached peak enzyme levels, the highest value was regarded as peak level.

Adverse clinical events were recorded, including in-hospital death, recurrent ischaemia, reinfarction, or need for CABG during hospitalization. Recurrent ischaemia was defined as chest pain attributable to ischaemia of less than 30 minutes duration and responsive to nitroglycerine, and reversible ST segment change in at least two electrocardiographic leads. Recurrent infarction was defined as prolonged anginal symptoms unresponsive to nitroglycerine with new ST segment elevations and myonecrosis as indicated by enzyme tests.

In addition, patients were followed for complete atrioventricular block, cardiogenic shock, ventricular tacharyrhythmias, need for atropine, or a temporary pacemaker.

Cardiogenic shock was defined as systemic hypotension with peripheral signs of systemic hypoperfusion of more than 15 minutes duration requiring either inotropic support or aortic balloon counterpulsation. Patients who recovered after fluid administration, atropine or pacemaker stimulation for atroventricular block or bradyarrhythmias and did not require inotropic support were not classified as cardiogenic shock.

Statistical analysis
Continuous variables are expressed as means ± SD, and discrete variables are given as frequencies. Differences in continuous variables between groups were examined by a t-test. Differences in discrete variables were calculated with the use of chi-square test or Fisher’s exact test. Odds ratios and 95% confidence intervals were calculated in the standard manner. All tests of significance were two-tailed and used a significance level of p < 0.05. Statistical analysis was performed with a commercially available package (SPSS for Windows, 5.0.1).

Results
Patients
A total of 87 patients who received front-loaded rt-PA within 6 hours from onset of symptoms was compared to an age- and sex matched cohort of patients who received primary PCI. Both treatment groups compared favourably with respect to baseline clinical characteristics (Table 1). Within treatment groups patients with RVI had more often systemic hypotension, experienced more frequently complete atrioventricular block than patients without RVI.

**Defined as systolic blood pressure below 100 mm Hg with clinical signs of systemic hypoperfusion not responsive to fluid administration or requirement of positive inotropic drugs or intraaortic balloon counterpulsation.

* Significant difference (p < 0.05) within treatment group between patients with and without RVI.

Table 1. Clinical findings

<table>
<thead>
<tr>
<th></th>
<th>All patients</th>
<th>Thrombolytic therapy</th>
<th>Direct PTCA</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age (years)</td>
<td></td>
<td>64.5</td>
<td>64.5</td>
<td>ns</td>
</tr>
<tr>
<td>Males (%)</td>
<td></td>
<td>120 (68.9)</td>
<td>60</td>
<td>60</td>
</tr>
<tr>
<td>Elevated ST-segment ≥ 0.1mV in V4R</td>
<td></td>
<td>60 (34.5)</td>
<td>30</td>
<td>30</td>
</tr>
<tr>
<td>Peak creatine kinase (U/l)</td>
<td></td>
<td>897 ± 785</td>
<td>925 ± 620</td>
<td>868 ± 926</td>
</tr>
<tr>
<td>MB-isoenzyme (U/l)</td>
<td></td>
<td>98 ± 67</td>
<td>92 ± 63</td>
<td>103 ± 107</td>
</tr>
<tr>
<td>Heart rate on admission (bpm)</td>
<td></td>
<td>75 ± 23</td>
<td>75 ± 24</td>
<td>75 ± 22</td>
</tr>
<tr>
<td>Systolic blood pressure on admission (mm Hg)</td>
<td></td>
<td>124 ± 36</td>
<td>124 ± 32</td>
<td>124 ± 41</td>
</tr>
<tr>
<td>Latency to treatment (min)</td>
<td></td>
<td>897 ± 785</td>
<td>178 ± 80</td>
<td>191 ± 95</td>
</tr>
</tbody>
</table>

Data are given as absolute counts with relative frequencies in parenthesis or as means ± SD.

Table 2. Clinical features and in-hospital complications by infarct location

<table>
<thead>
<tr>
<th></th>
<th>Thrombolytic therapy n = 87</th>
<th>Direct PTCA n = 87</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Non-RVI n = 57</td>
<td>RVI n = 30</td>
</tr>
<tr>
<td>Systolic blood pressure on admission &lt; 100 mm Hg</td>
<td>7 (12)</td>
<td>9 (30)</td>
</tr>
<tr>
<td>Cardiogenic shock**</td>
<td>8 (14)</td>
<td>8 (27)</td>
</tr>
<tr>
<td>Complete atroventricular block</td>
<td>3 (5)</td>
<td>12 (40)*</td>
</tr>
<tr>
<td>Need of atropine</td>
<td>13 (23)</td>
<td>18 (60)*</td>
</tr>
<tr>
<td>Need of temporary pacing</td>
<td>2 (4)</td>
<td>4 (13)</td>
</tr>
<tr>
<td>Ventricular tachycardia</td>
<td>12 (21)</td>
<td>7 (23)</td>
</tr>
<tr>
<td>Ventricular fibrillation</td>
<td>6 (11)</td>
<td>5 (17)</td>
</tr>
</tbody>
</table>

Data given as absolute counts with relative frequencies in parenthesis.

** Defined as systolic blood pressure below 100 mm Hg with clinical signs of systemic hypoperfusion not responsive to fluid administration or requirement of positive inotropic drugs or intraaortic balloon counterpulsation.

* Significant difference (p < 0.05) within treatment group between patients with and without RVI.
block and needed more often atropin to overcome sinus bradycardia or high-degree atrioventricular block (Table 2). Treatment groups compared favourably with respect to angiographic variables, including severity of coronary artery disease and left ventricular ejection fraction (Table 3). Predischarge coronary angiography was performed in 66 of 87 patients following initially successful primary PCI and in all patients following rt-PA. As displayed in Figure 1 predischarge patency of the IRA (TIMI 3 flow) was seen significantly more often with primary PCI as compared to rt-PA (OR [95% CI]: 10.9 [3.54–33.3], p < 0.0001). With respect to infarct locations, patency rates were significantly higher after primary PCI in both non-RVI-AMI (OR [95% CI]: 4.73 [1.24–18.1], p = 0.02) and RVI-AMI (OR [95% CI]: 55.7 [6.24–497.6], p < 0.00001). Among patients who received rt-PA those with RVI-AMI were more likely to disclose occluded or severely compromised TIMI flow (TIMI < 3) compared to non-RVI-AMI patients (OR [95% CI]: 5.44 [1.8–16.4], p = 0.0033).

Rates of major cardiac events during in-hospital follow-up are listed in Table 4. Although in-hospital mortality rates were higher among patients with RVI (15 vs 9%), this difference did not reach statistical significance. Moreover, mortality rates were comparable between rt-PA and primary PCI both in non-RVI (7 vs 10.5%) and RVI-AMI patients (13 vs 16.6%). Rates of major cardiac events were comparable within and between groups except for myocardial re-ischaemia which occurred significantly more often in patients with RVI who received rt-PA as compared to primary PCI (OR [95% CI]: 12.4 [1.3–105.7], p=0.012).

### Discussion

Among patients with inferior AMI and the high risk subgroup of those complicated by RVI, direct PCI proved superior to front-loaded rt-PA with respect to predischarge patency of the IRA. With respect to clinical events, patients with RVI had a higher rate of recurrent myocardial ischaemia during hospitalization after thrombolytic therapy.

Interestingly, differences in patency rates did not translate into short-term prognosis neither in the entire group nor in the high risk subgroup of RVI. This finding supports the hypothesis that prognosis of RVI is substantially improved following reperfusion-related reversal of RV dysfunction in the early clinical course, and remains excellent regardless of the patency status of the infarcted coronary artery.

The results of this study confirm very recent findings from nonrandomized studies that early reperfusion therapy may reverse RV dysfunction and may improve the clinical course and survival of patients with ischaemic RV dysfunction [6–8].

There is accumulating evidence that direct PCI is very effective for the treatment of RVI. In contrast, available data regarding the salutary effects of timely thrombolytic therapy on RV function and survival are conflicting [9–11, 15–18, 26]. However, these two reperfusion therapies have not been compared, yet.

In some reports, early thrombolytic therapy has been shown to lower in-hospital complications and to improve survival almost exclusively among patients with RVI [9, 10]. Other authors report on spontaneous improvement of right heart function and excellent survival independent of early thrombolytic therapy [15, 16], while even spontaneous improvement of right heart function has been reported for patients who were excluded from thrombolytic therapy.

### Table 3. Angiographic data

<table>
<thead>
<tr>
<th>Severity of CAD*</th>
<th>Thrombolytic therapy n = 68</th>
<th>Direct PTCA n = 66</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Insignificant (~70% stenosis)</td>
<td>2 (3)</td>
<td>–</td>
<td>ns</td>
</tr>
<tr>
<td>1 VD</td>
<td>29 (42.6)</td>
<td>29 (33.3)</td>
<td>ns</td>
</tr>
<tr>
<td>2 VD</td>
<td>18 (26.5)</td>
<td>24 (27.6)</td>
<td>ns</td>
</tr>
<tr>
<td>3 VD</td>
<td>19 (27.9)</td>
<td>34 (39.1)</td>
<td>ns</td>
</tr>
<tr>
<td>LV-EF (%) ± SD</td>
<td>49 ± 10</td>
<td>54 ± 11</td>
<td>ns</td>
</tr>
<tr>
<td>Latency to follow-up angiography (days)</td>
<td>11.8</td>
<td>9.8</td>
<td>ns</td>
</tr>
<tr>
<td>Number of patients at follow-up</td>
<td>n = 68</td>
<td>n = 66</td>
<td></td>
</tr>
<tr>
<td>TIMI flow</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade 0–2</td>
<td>28 (41.2)</td>
<td>4 (6.1)</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Grade 3</td>
<td>40 (58.0)</td>
<td>62 (93.9)</td>
<td>&lt; 0.0001</td>
</tr>
</tbody>
</table>

Data given as absolute counts and relative frequencies in parentheses unless noted otherwise.

* As assessed during initial coronary angiography in patients who received early angiography (prior to direct PTCA) or predischarge angiography (following thrombolytic therapy), respectively.

### Table 4. In-hospital outcome and cardiac events by infarct location

<table>
<thead>
<tr>
<th>Thrombolytic Therapy n = 87</th>
<th>Direct PTCA n = 87</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-RVI n = 57</td>
<td>RVI n = 30</td>
</tr>
<tr>
<td>In-hospital death</td>
<td>4 (7)</td>
</tr>
<tr>
<td>Reinfarction</td>
<td>3 (5)</td>
</tr>
<tr>
<td>Recurrent myocardial ischaemia</td>
<td>14 (24.6)</td>
</tr>
<tr>
<td>Restenosis*</td>
<td>No data</td>
</tr>
<tr>
<td>CABG</td>
<td>8 (14)</td>
</tr>
</tbody>
</table>

Data given as absolute counts with relative frequencies in parentheses.

* Angiographically verified

+ Significant difference (p < 0.05) between treatment groups among patients with right ventricular involvement.
The spontaneous recovery of right ventricular function has been observed regardless of the patency status of the infarct-related artery [11, 17, 18], possibly facilitated by lower oxygen demand and a more favourable oxygen supply of the right ventricle [12], may in part explain the discrepancy between the favourable prognosis of patients with RVI once they have overcome the acute phase and antegrade flow has been restored following reperfusion therapy or spontaneously.

Unfortunately, most available thrombotic studies are limited by a small number of patients and study design and do not provide information regarding the efficacy of early thrombolytic therapy with respect to reperfusion rate and arterial patency in this particular high risk category. The largest available study evaluating the impact of timely reperfusion on arterial patency and survival was performed by the TIMI investigators on 1100 patients with inferior AMI [19]. The authors found that patients with predomi-

nantly RVI as seen with predischarge radionuclide ventriculography had an occluded infarct-related right coronary artery a few hours after thrombolytic therapy and claimed that successful reperfusion may prevent RVI. However, in this study, the diagnosis of RVI was not made before thrombolytic therapy was administered, and thus the cause-effect relation in this setting remains speculative. In experimental models [20, 21] and in patients with sustained hypotension [22, 23] and cardiogenic shock [24], thrombolysis has been found less effective, probably due to impaired flow mediated delivery of the fibrinolytic agent. Both sustained hypotension and low cardiac output due to cardiogenic shock or ativoventricular desynchronization and bradyarrhythmias are more frequently seen with RVI [2, 11, 25]. Thus, cardiogenic shock-like haemodynamic deterioration could affect early reperfusion of the infarcted vessel or may cause subsequent early reocclusion after initial successful restoration of antegrade blood flow. In support, a previous examination of our study group demonstrated unexpectedly low short-term arterial patency of the IRA despite early treatment with an accelerated dose regimen of recombinant tissue type plasminogen activator [26]. However, none of the available studies including our study is able to provide data on whether unsuccessful thrombolysis is due rather to failed reperfusion or to reocclusion of the initially reperfused vessel.

**Limitations**

Given the lack of a randomized study design, comparison of treatment strategies was made by use of matched pairs to control for age and sex. In order to avoid selection bias by inclusion of more severely haemodynamically compromised patients diagnosis of RVI was based on ECG criteria which are reliable for identification of RVI [2, 3, 26]. Echocardiographic and haemodynamic measurement were not performed on a routine basis and were commonly restricted to more severely diseased patients. Although, in this study, mortality rates were comparable after reperfusion therapy, overall mortality rates of patients with RVI may be higher in non-invasive facilities since more patients have contra-

indications to thrombolysis and thus represent a subgroup of patients at even higher risk of death.

**Conclusion**

Among patients with inferior AMI and particularly among those with RVI, direct PCI is more effective than early thrombolytic therapy with respect to patency of the IRA as assessed shortly before discharge. Nevertheless, this difference does not translate into a poorer short-term prognosis of RVI. Whether a subgroup of patients with RVI may incur long-term prognosis of patients with RVI remains undetermined and requires further evaluation.

**References**


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