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Impact of multivessel disease on infarct size among STEMI patients undergoing primary angioplasty



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ABSTRACT

Background: Although primary angioplasty achieves Thrombolysis In Myocardial Infarction (TIMI) 3 flow in most patients with ST-elevation myocardial infarction, epicardial recanalization does not guarantee optimal perfusion in a large proportion of patients. Multivessel disease has been demonstrated to be associated with impaired survival, however its impact on infarct size has not been largely investigated, that therefore is the aim of the current study.

Methods: Our population is represented by 827 STEMI patients undergoing primary PCI. Infarct size was evaluated at 30 days by technetium-99m-sestamibi.

Results: Multivessel disease was observed in 343 patients (41.5%). It was associated with older age (65 [57–74] vs 63 [53–71], $p < 0.001$), higher rate of previous MI (6.4% vs 2.5%, $p = 0.005$), longer ischemia time evaluated as continuous variable (210 [155–280] min vs 196 [145–270] min, $p = 0.065$) or percentage of patients with ischemia time >3 h (63.7% vs 56.4%, $p = 0.038$), and a trend in more cardiogenic shock (5.5% vs 2.9%, $p = 0.055$). Patients with multivessel disease received more often Abciximab (92.1% vs 88.4%, $p < 0.001$), Intra-aortic balloon pump (6.4% vs 1.9%, $p < 0.001$). No differences were observed in other clinical or angiographic characteristics. In particular, multivessel disease did not affect the rate of postprocedural TIMI 3 flow (90.9% vs 93.4%, $p = 0.18$) and ST-segment resolution (52.4% vs 54.9%, $p = 0.48$). Multivessel disease did not affect infarct size (12.7% [4.5%–24.9%] vs 12.3% [4%–24.1%], $p = 0.58$). Similar results were observed in subanalyses without any significant interaction for each variable (anterior infarct location (p int = 0.23), gender (p int = 0.9), age (p int = 0.7), diabetes (p int = 0.15)). The absence of any impact of multivessel disease on infarct size was confirmed when the analysis was conducted according to the percentage of patients with infarct size above the median, even after correction for baseline characteristics, such as age, previous MI, ischemia time, use of Gp IIb–IIIa inhibitors, cardiogenic shock, ischemia time (OR [95% CI] = 1.09 [0.82–1.45], $p = 0.58$).

Conclusions: This study shows that among STEMI patients undergoing primary PCI multivessel disease does not affect infarct size.

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1. Introduction

In patients presenting with acute myocardial infarction primary angioplasty improves survival compared with thrombolysis, due mainly to a large percentage of restoration of TIMI 3 flow [1,2], with further improvement in clinical outcomes observed with the use

of new antithrombotic therapies and devices [3–7]. However, epicardial recanalization does not guarantee optimal myocardial perfusion, which remains suboptimal in a relatively large proportion of patients [8,9]. In addition, concomitant atherosclerosis in coronary vessels other than the infarct-related artery (IRA) is observed in a notable proportion of patients undergoing primary percutaneous coronary intervention (PCI), ranging from 40% to 50% [10–12]. The prognostic impact of multivessel coronary artery disease (CAD) in patients undergoing primary angioplasty has not been extensively investigated [10–14]. Furthermore, few data exist

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on the impact of multivessel disease on infarct size as evaluated by well-refined techniques such as nuclear imaging techniques. Therefore, this is the aim of the current study.

2. Materials and methods

This is a prospective study with the initial population represented by 894 STEMI patients treated by primary angioplasty, who were included in randomized trials conducted between 2001 and 2009 that aimed at the evaluation of infarct size at 30 days after intervention [4,15,16]. A total of 64 patients [16 women (8.7%) and 48 men (7.4%)] were excluded because of death ($n = 16$), reinfarction ($n = 7$), or target vessel revascularization ($n = 11$) within 30 days from revascularization, or refusal to undergo scintigraphy ($n = 30$) and 3 patients undergoing complete revascularization at the time of primary PCI. Therefore, our final population was represented by 827 patients.

All patients were admitted within 12 h from symptom onset, and received at the time of diagnosis aspirin (500 mg intravenously) and heparin (60 IU/kg intravenously), as much as beta-blockers and nitroglycerine intravenously if not contraindicated, whereas the decision to provide glycoprotein IIb–IIIa inhibitors was left at the discretion of the operator at the time of intervention. All patients were on dual oral antiplatelet therapy (aspirin and clopidogrel or ticlopidine) for at least 4 weeks after stent implantation. All demographic, clinical, procedural and in-hospital and follow-up data were collected in a database. Baseline and 30-min post-procedure, a 12-lead electrocardiogram was recorded using the same electrocardiograph. The ST-segment elevation was measured to the nearest 0.5 mm at 60 ms after the J point with the aid of hand-held calipers. The STR was defined as a reduction in ST-segment elevation $\geq 50\%$ at 30 min after infarct artery recanalization.

2.1. Coronary angiography and mechanical revascularization

Selective coronary angiography was performed in multiple projections before mechanical reperfusion. Immediately after diagnostic angiography, percutaneous coronary intervention with stenting of the infarct-related vessel was performed using standard material. Multivessel disease was defined as a visually assessed $>70\%$ diameter stenosis of at least one major epicardial artery beyond the infarct related artery. Successful primary percutaneous coronary intervention was defined as Thrombolysis In Myocardial Infarction (TIMI) grade 3 coronary flow in the treated vessel with a residual stenosis $<20\%$ [17]. Angiographic collaterals were evaluated according to Rentrop classification [18].

2.2. Infarct size assessment

Patients underwent evaluation of infarct size at 30 days from the intervention. As previously described [16], gated single-photon emission computed tomography (SPECT) acquisition began 60 min after technetium-99m-sestamibi injection (740 MBq), using a double-head gamma-camera equipped with high-resolution collimators, 180° rotation arc, 32 projections, 60 s/projection, 8 frames/heart cycle and 64×64 matrices. The studies were reconstructed using filtered back-projection without attenuation or scatter correction and realigned along the heart axis. Perfusion defects were quantified as percentage of LV wall, with the defect threshold set at 60% of peak uptake [19].

2.3. Statistical analysis

Statistical analysis was performed with the SPSS 17.0 statistical package. Continuous data were expressed as median [25–75th

Table 1
Demographic and clinical characteristics according to multivessel disease.

Variable	Single vessel disease ($n = 484$)	Multivessel disease ($n = 343$)	<i>p</i> Value
Age	63 [53–71]	65 [57–74]	<0.001
Age > 75 ys (%)	17.1	24.2	0.013
Female gender (%)	80.4	77.6	0.325
Smoking (%)	49.6	46.4	0.36
Dyslipidemia (%)	33.5	35.0	0.651
Diabetes (%)	12.8	15.5	0.28
Previous MI (%)	2.5	6.4	0.005
Previous CABG (%)	0.6	1.2	0.398
Previous PTCA (%)	3.1	4.4	0.331
Ischemia time (min)	196 [145–270]	210 [155–280]	0.065
Ischemia time >3 h (%)	56.4	63.7	0.038
Anterior MI (%)	41.5	38.5	0.38
Cardiogenic shock (%)	2.9	5.5	0.055

MI = Myocardial Infarction, CABG = Coronary Artery Bypass Grafting, PTCA = Percutaneous Transluminal Coronary Angioplasty.

percentiles] and categorical data as percentage. The analysis of variance test (ANOVA) or Mann–Whitney *U* test was appropriately used for continuous variables, according to the normality of distribution, as evaluated by the Shapiro–Wilk test [20]. The chi-square test or the Fisher's exact test was used for categorical variables. Multiple logistic regression analysis was used to evaluate the impact of multivessel disease on infarct size after adjustment for significant ($p < 0.1$) confounding baseline characteristics.

3. Results

Multivessel disease was observed in 343 patients (41.5%). Patients' characteristics are shown in Tables 1 and 2. Multivessel disease was associated with older age ($p < 0.001$), higher rate of previous MI ($p = 0.005$), longer ischemia time evaluated as continuous variable ($p = 0.065$) or percentage of patients with ischemia time >3 h ($p = 0.038$), a trend in more cardiogenic shock ($p = 0.055$). Patients with multivessel disease received more often Abciximab ($p < 0.001$), Intra-aortic balloon pump ($p < 0.001$). No differences were observed in other clinical or angiographic variables. In particular, multivessel disease did not affect post-procedural TIMI 3 flow (90.9% vs 93.4%, $p = 0.18$) and ST-segment resolution (52.4% vs 54.9%, $p = 0.48$).

Table 2
Angiographic and procedural characteristics according to multivessel disease.

Variable	Single vessel disease ($n = 484$)	Multivessel disease ($n = 343$)	<i>p</i> Value
Collateral circulation			0.991
RENTROP 0 (%)	87.9	91	
RENTROP 1 (%)	9.3	4.2	
RENTROP 2 (%)	2.8	3.6	
RENTROP 3 (%)	0	1.2	
Preprocedural TIMI 3 flow (%)	7.9	8.5	0.765
IRA			0.31
RCA (%)	45.7	44.9	
CX (%)	12.8	16.0	
Graft (%)	0	0.3	
LAD (%)	41.5	38.5	
LM (%)	0	0.3	
Abciximab (%)	88.4	92.1	<0.001
Stenting (%)	98.3	99.2	0.51
IABP (%)	1.9	6.4	0.001
Postprocedural TIMI 3 flow (%)	93.4	90.9	0.184
Complete ST resolution	54.9	52.4	0.481
DES stenting	7.2	5.3	0.42

TIMI = Thrombolysis in Myocardial Infarction, IRA = Infarct-Related Artery, RCA = Right Coronary Artery, CX = Circumflex, LAD = Left Anterior Descending Artery, IABP = Intra-Aortic Balloon Pump, DES = Drug-Eluting Stent.

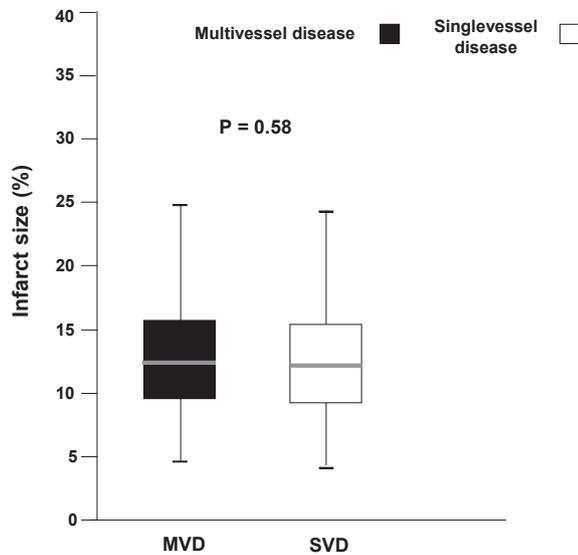


Fig. 1. Bar graphs show the impact of multivessel disease on infarct size. Data are presented as median [25th–75th percentile]. SVD = Single Vessel Disease; MVD = Multivessel Disease.

As shown in Fig. 1, multivessel disease did not affect infarct size (12.7% [4.5%–24.9%] vs 12.3% [4%–24.1%], $p = 0.58$). The absence of any impact of multivessel disease on infarct size was confirmed in subgroup analyses according to infarct location (anterior STEMI: 15.2% [6%–29.4%] vs 16.1% [5.5%–22.7%], $p = 0.81$; non-anterior STEMI: 12.7% [3.3%–21.7%] vs 10.7% [3.1%–21.0%], $p = 0.24$; $p_{int} = 0.23$), gender (female gender: 6.9% [0%–20.8%] vs 5.6% [0%–19.1%], $p = 0.89$; male gender: 14.0% [5.7%–24.8%], $p = 0.48$; $p_{int} = 0.9$), age, (≥ 65 years 13.9% [3.2%–25.3%] vs 15.3% [6.5%–28%], $p = 0.76$; < 65 years: 12.6% [5.6–24.2%] vs 11.8% [4.0–24.6%], $p = 0.63$; $p_{int} = 0.7$), diabetes (yes: 14.5% [4.0%–22.5%] vs 9.2% [3.9%–24.9%], $p = 0.49$; no: 12.7% [4.6%–25.1%] vs 12.8% [4.5%–24%], $p = 0.79$; $p_{int} = 0.15$), without any significant interaction for each variable. The results were confirmed after the exclusion of patients with previous MI (12.6% [4.4%–24.9%] vs 12.2% [3.9%–24.2%], $p = 0.56$).

The absence of any impact of multivessel disease on infarct size was confirmed when the analysis was performed according to the percentage of patients with infarct size above the median (Fig. 2),

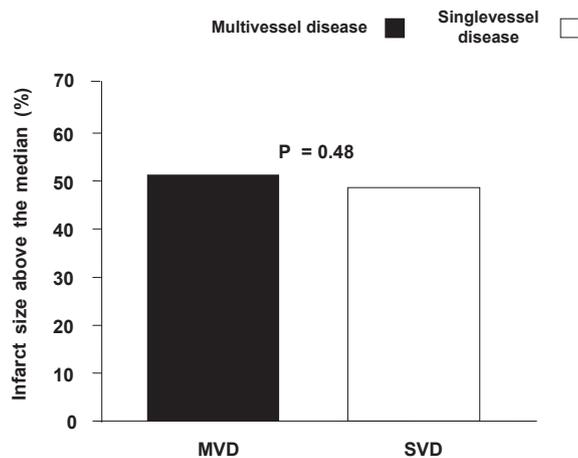


Fig. 2. Bar graphs show the impact of multivessel disease on infarct size (as percentage of patients above the median). SVD = Single Vessel Disease; MVD = Multivessel Disease.

Table 3

Multiple logistic regression analysis to investigate the relationship between multivessel disease and infarct size after adjustment for baseline confounding factors, that were included in block into the model.

Variable	Beta	SE	OR [95% CI]	p Value
Age	0.006	−0.008	0.99 [0.98–1.01]	0.2
Previous myocardial infarction	0.37	0.44	1.55 [0.75–3.2]	0.23
Cardiogenic shock	0.36	−0.32	0.73 [0.36–1.48]	0.38
Gp IIb–IIIa inhibitors	0.24	−0.3	0.74 [0.46–1.18]	0.2
Ischemia time >3 h	0.59	0.15	1.8 [1.36–2.4]	<0.001
Multivessel disease	0.15	0.11	1.09 [0.82–1.45]	0.58

even after correction for baseline characteristics, such as age, previous MI, ischemia time, use of Gp IIb–IIIa inhibitors, Cardiogenic shock (OR [95% CI] = 1.09 [0.82–1.45], $p = 0.58$) (Table 3).

We finally investigated the impact of concomitant presence of chronic occlusion on infarct size. As shown in Fig. 3 a non-significant trend in larger infarct size was observed in patients with multivessel disease and concomitant presence of chronic occlusion.

4. Discussion

This is the largest prospective study conducted to date investigating the impact of multivessel disease on infarct size as evaluated by nuclear technique among STEMI patients undergoing mechanical reperfusion. We did not find any impact of multivessel disease on myocardial perfusion and scintigraphic infarct size.

Mechanical reperfusion has been demonstrated to improve survival as compared with thrombolysis in patients with STEMI. However, clinical outcome remains unsatisfactory in some subgroups [21–23]. Multivessel disease is observed in approximately

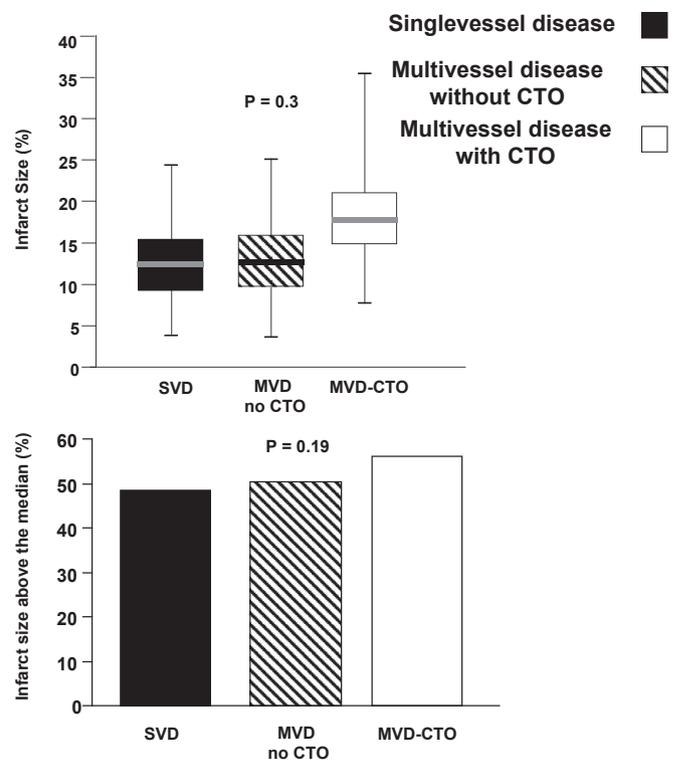


Fig. 3. Bar graphs show the impact of concomitant presence of chronic occlusion in patients with multivessel disease on infarct size. SVD = Single Vessel Disease; MVD = Multivessel Disease; CTO = Chronic Total Occlusion.

50% of patients undergoing primary PCI and has been associated with poorer clinical outcomes [10–14].

In a report from the CADILLAC trial [24], Sorajja et al. reported that the presence of multivessel disease was a powerful independent predictor of mortality, even after adjustment for differences in baseline clinical and angiographic variables. Moreover, the negative prognostic impact of multivessel disease was not impacted by the use of stents or glycoprotein IIb/IIIa inhibitors. A significantly better outcome was observed among patients who received adjunctive revascularization of the non-IRA. Confirming these findings, data from the EGYPT cooperation, including patients treated with GP IIb/IIIa inhibitor and coronary stenting, showed that multivessel disease was independently associated with impaired myocardial perfusion and mortality [25]. Similar findings were observed by Dudek et al. [26]. Few studies have investigated so far the impact of multivessel disease on infarct size as evaluated by refined imaging techniques. Tarantini et al. [27] in a population of 288 STEMI patients undergoing primary angioplasty found that multivessel disease did not impact myocardial reperfusion and infarct size and microvascular obstruction as evaluated by the delayed enhancement of cardiac magnetic resonance. The authors found that the prognostic impact at follow-up was mainly related to a higher occurrence of reinfarction and coronary revascularization.

This is the largest study conducted so far in order to investigate the impact of multivessel disease on infarct size as evaluated by technetium scintigraphy. Confirming the findings by Tarantini et al. [27], in a population of 827 patients we did not observe any impact of multivessel disease on infarct size.

Several factors may certainly contribute to explain our findings. In accordance with previous studies, we found that patients with multivessel disease have a greater incidence of high-risk baseline features that may contribute to an adverse prognosis, mainly due to non-IRA ischemic events. Furthermore, as observed by Eitel et al. [28], the relation of severe microvascular injury (MVO) to the extent of infarct expansion (MVO/infarct size) but not infarct size seems to be a major determinant of prognosis. In fact, MVO/infarct size is a more powerful predictor for long-term outcome after STEMI than either parameter alone reflecting a broader degree of myocardial injury [29]. The extent of infarct size and the development of MVO are influenced by diverging parameters, because MVO is known to be associated with factors beyond the ischemic damage itself, such as reperfusion injury [29,30].

Despite its high prevalence, few randomized data have been reported so far on the optimal management of patients with acute myocardial infarction and multivessel disease, that have not led to a clear consensus. A small randomized trial was stopped prematurely due to slow recruitment [31]. In a recent randomized trial [32], 214 consecutive patients with STEMI and multivessel CAD undergoing primary angioplasty were randomized before the first angioplasty to one of three strategies: 1) culprit vessel angioplasty only; 2) staged revascularization; and 3) simultaneous treatment of non-IRAs. During a mean follow-up of 2.5 years, 42 (50.0%) patients in the 'culprit vessel angioplasty only' group experienced at least one major adverse cardiac event, 13 (20.0%) had an event in the staged revascularization group, and 15 (23.1%) in the simultaneous treatment of non-IRAs group ($p < 0.001$). In-hospital death, repeat revascularization and rehospitalization occurred more frequently in the culprit vessel angioplasty only group (all $p < 0.05$), while there was no significant difference in reinfarction among the three groups.

A subsequent meta-analysis of randomized and non-randomized studies [33] showed that complete revascularization in STEMI is safe and associated with a reduced occurrence of ischemic event mainly due to less revascularization procedures, without any impact on mortality.

Still controversial is the exact timing of complete revascularization. A retrospective analysis from the Horizons study [34] showed that single strategy vs staged PCI was associated with higher 1-year mortality (9.2% vs 2.3%; $p < 0.0001$), definite/probable stent thrombosis (5.7% vs 2.3%; $p = 0.02$), and a trend toward greater major adverse cardiovascular events (18.1% vs 13.4%; $p = 0.08$).

Recently, a relatively small randomized trial [35] including 465 patients, showed that among STEMI patients with multivessel disease, complete one step revascularization was associated with improved outcome, with a trend in reduction in mortality. However, no data were reported on myocardial perfusion and infarct size. Our study showing no impact of multivessel disease on infarct size, does not certainly support one step complete revascularization. Furthermore, it may be argued that more complex procedures, such as chronic occlusion, may significantly increase the amount of contrast media and increase periprocedural complications. Future randomized trials are certainly needed to evaluate if a complete revascularization during hospitalization is associated with improved survival, and to establish the right timing (one step or staged revascularization).

4.1. Study limitations

We assessed infarct size at 1 month after the index infarction instead of at hospital discharge, as in the majority of previously published studies. On the other hand, this circumstance should be more effective in preventing interference of myocardial stunning with the extent of perfusion defects [36]. The execution of a coronary angiographic control before gated SPECT would have allowed the exclusion of infarct-related vessel restenosis. Unfortunately, it was not routinely performed. The availability of outcome data at 1 year follow-up would have improved our results. Unfortunately, data were not available from all patients and therefore not included. However, this is a relatively selected cohort of patients, being included in randomized trials and being 30-day survivors. Due to the small number of patients ($n = 26$), we cannot certainly exclude a potential impact of the presence of a chronic occlusion on infarct size among patients with multivessel disease. SPECT may potentially have problems to discriminate older infarcts in boundary regions. In our study, a higher occurrence of previous NSTEMI was observed among patients with multivessel disease. However, due to the small proportion (4.1%), this issue is not expected to have relevant impact on our results, as confirmed by the analysis after the exclusion of these patients. The absence of a significant association between multivessel disease and cardiogenic shock at admission may be due to a potential selection bias, as much as to the relatively small sample size [37,38]. Finally, we classified our population according to the number of diseased vessels. However, we did not take into account the potential difference in extension of jeopardized areas.

5. Conclusions

This study showed that among STEMI patients undergoing primary angioplasty, smoking does not affect scintigraphic infarct size.

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