Pulse Infusion Thrombolysis (PIT) for Large Intracoronary Thrombus

— Preventive Effect Against the ‘No Flow’ Phenomenon in Revascularization Therapy for Acute Myocardial Infarction —

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Because large thrombus is a limitation for revascularization in acute myocardial infarction (AMI), the present study evaluated the effectiveness of pulse infusion thrombolysis (PIT) in patients with an AMI with a large (>15 mm) coronary thrombus, focusing on the occurrence of the ‘no flow’ phenomenon. The retrospective study compared patients treated before (1988–95; Group A, n=74) and after (1996–99; Group B, n=40) the use of PIT, using the following parameters: lesion success (<50% stenosis during 30-min observation), procedural success (lesion success plus TIMI grade 3 flow), procedural no flow (TIMI grade 0 flow during the procedure with ‘back and forth movement’ of contrast dye after lesion success), persistent no flow (consistent no flow without any flow improvement at the final visualization despite intensive treatment), reocclusion rate and in-hospital death. Group B was significantly better than Group A in procedural success (90% vs 66%; $p=0.005$), procedural ‘no flow’ (51% vs 15%; $p<0.001$), and persistent ‘no flow’ (34% vs 10%; $p<0.05$). Subgroup comparison was performed among the following groups: Direct-BA group (n=44): treated with mechanical angioplasty alone; ICT-BA group (n=40): treated with prior intracoronary thrombolysis and angioplasty; and PIT-BA group (n=30): treated with PIT and angioplasty. There were no differences in thrombus length and lesion success among these 3 groups. Procedural success was best achieved in PIT-BA: 97% vs 52% for Direct-BA ($p=0.003$) and 68% for ICT-BA ($p=0.009$). Procedural ‘no flow’ was least in PIT-BA: 50% vs 3.3% for Direct-BA ($p=0.003$) and 25% vs 3.3% for ICT-BA ($p=0.042$). Persistent ‘no flow’ was less frequent in PIT-BA than Direct-BA: 32% vs 3.3% ($p=0.009$). However, the difference between ICT-BA and Direct-BA was insignificant: 13% vs 3.3% ($p=0.53$). There were no differences in reocclusion rate and in-hospital death among the 3 subgroups. And there were no differences between Direct-BA and ICT-BA in any parameters. PIT was effective in preventing ‘no flow’ in the mechanical revascularization for AMI especially those cases with a large thrombus. (*Jpn Circ J* 2001; 65: 94–98)

Key Words: Angioplasty; Myocardial infarction; Thrombus

It is well known that an intracoronary thrombus triggered by disrupted atheromatous plaques is the major occlusive mechanism of an infarct-related artery (IRA)! The thrombus burden in IRA, especially in cases of massive thrombus, is a limitation to systemic intravenous thrombolysis. Thromboembolism after mechanical angioplasty can potentially induce the ‘no flow’ phenomenon in the distal circulation^{2,3}

Pulse Infusion Thrombolysis (PIT) is a sophisticated thrombolytic method, first applied to peripheral artery and shunt thrombotic occlusion by Bookstein et al^{4,5} and reported by us to be effective in coronary artery disease as well⁶. In this study, we investigated its effectiveness in patients with acute myocardial infarction (AMI), by compar-

ing patients who received PIT prior to mechanical revascularization and those who did not, focusing on cases of large thrombus and the incidence of the ‘no flow’ phenomenon.

Methods

Patient Population

Patients admitted to Kumamoto Central Hospital during the period 1988 to June 1999 under the diagnosis of AMI and who received mechanical revascularization therapy for TIMI grade 0/1 coronary flow (n=708) were examined in this retrospective study. Because the PIT technique started in 1996, the patients were categorized into 2 groups: Group A (1988–95) and Group B (1996–99). Acute phase patients (ie, <24 h from onset) were enrolled, and among the 98 patients who received PIT for AMI, only those with a large thrombus (>15 mm) were selected. Patients who had received systemic thrombolysis treatment, had active gastrointestinal bleeding, or who had a history of cerebral bleeding or other diseases with bleeding diathesis were excluded. Thus the final numbers of enrolled patients having a large thrombus treated

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Table 1 Patient Baseline Characteristics

	Group A (n=74)	Group B (n=40)	p value
Age (years)	63±13	64±10	NS
Gender (male)	53 (72%)	32 (80%)	NS
Hypertension	46 (62%)	26 (65%)	NS
Diabetes mellitus	26 (35%)	12 (30%)	NS
Hyperlipidemia	28 (38%)	13 (33%)	NS
Stroke history	1 (1.4%)	0	NS
Vessel disease			NS
I	46 (62%)	24 (60%)	
II	27 (36%)	13 (33%)	
III	1 (1.4%)	3 (7.5%)	
IRA			NS
RCA	41 (55%)	24 (60%)	
LCX	6 (9%)	4 (10%)	
LAD	27 (36%)	12 (30%)	
Time from onset			NS
<6 h	65 (88%)	35 (88%)	
<12 h	6 (8%)	2 (5%)	
<24 h	3 (4%)	3 (7%)	
Shock	10 (14%)	8 (20%)	NS

Group A, patients treated during 1988–95; Group B, patients treated during 1996–99; IRA, infarct-related artery; AMI, acute myocardial infarction; RCA, right coronary artery; LCX, left circumflex artery; LAD, left anterior descending artery; Shock, systolic blood pressure <80 mmHg after volume expansion therapy.

within 24 h of onset were 74 for Group A and 40 for Group B (Table 1).

In Group A, 36 patients were treated by direct balloon angioplasty (Direct-BA) and 38 patients were treated by intracoronary thrombolysis followed by balloon angioplasty (ICT-BA). In Group B, 2 patients were treated by ICT-BA because of initial guidewire cross failure, and 8 were treated by Direct-BA.

Written informed consent for revascularization and the potential use of the PIT technique was obtained in the early phase of admission. The study protocol was in agreement with the guidelines of the Human Ethics Committee of the institution.

PIT System and Method

Details of the PIT system are described elsewhere.⁶ Briefly, the PIT pump (Nemoto Kyorindo, Tokyo, Japan; Fig 1) allows intermittent spray-like drug delivery through a custom PIT Ultrafuse catheter (SciMed/Boston-Scientific, Maple Grove, MN, USA; Fig 2) with various settings to customize the treatment of the particular thrombus according to its size, age and instability. The side-holes of the catheter are placed into the center of the thrombus and the PIT pump allows constant forceful direct delivery of urokinase into the thrombus, which is macerated and thus increases the drug contact surface and accelerates the lytic process.

PIT was performed in all patients with TIMI grade 0/1 flow in the main coronary artery even after the guidewire cross and multiple passes with a non-inflated balloon.

Urokinase was used as the fibrinolytic drug at a concentration of 4,800–9,600 U/ml in saline. In most cases, PIT was performed as follows: 10 times/min, 0.5 ml/bolus and 1.5–2 ml/s of compulsive force in the first 10 min and followed by the attenuating condition of 3–5 times/min, 0.3–0.5 ml/bolus and 1.5 ml/s of compulsive force. Angiography was performed every 10 min and thus the time and the dose of urokinase to achieve TIMI grade 3 flow was determined. When a significant volume of thrombus remained after flow recovery, PIT was continued until most of the thrombus dissolved, which was indicated by observing the

Fig 1. The compact, electrically powered pump attached to a 5-ml syringe. The T-shaped, one-way valve allows aspiration of the lytic drug solution and forceful propulsion into the PIT catheter. Drug delivery can be changed by times/min, volume/bolus and compulsive force/s in response to the clot's age, size and stability.

Fig 2. Custom-made Ultrafuse Catheter (SciMed/Boston Scientific) for PIT. The shaft size is 3.6Fr proximal, 2.9Fr distal and 1.9Fr at the tip. (A) Spray-like injection through the spirally placed side-holes. (B) Schema of PIT. The thrombolytic drug penetrates deeply into the thrombus and macerates it, resulting in an increase in the drug contact interface and accelerating the lytic process.

Table 2 Procedural Outcomes

	Group A (n=74)	Group B (n=40)	p value
<i>Treatment</i>			
Direct-BA	36 (49%)	8 (20%)	<0.001
ICT-BA	38 (51%)	2 (5%)	<0.001
PIT-BA	—	30 (75%)	
Thrombus (mm)	27.7±0.8	28.8±0.74	NS
Lesion success	65 (88%)	38 (95%)	NS
Procedural success	49 (66%)	36 (90%)	0.005
No-flow during procedure	38 (51%)	6 (15%)	<0.001
Persistent no flow	25 (34%)	4 (10%)	<0.05
UK (10,000 units)	63±28/ICT-BA	57±27/PIT-BA	NS
TIMI 3 UK dose (10,000 units)	—	30±9	—
TIMI 3 time (min)	—	15.6±7.4	—
IABP	22 (30%)	11 (28%)	NS
Stent	10 (14%)	16 (35%)	<0.05

BA, balloon angioplasty; ICT, intracoronary thrombolysis; PIT, pulse infusion thrombolysis; TIMI, Thrombolysis in Myocardial Infarction (TIMI Trial); IABP, intra-aortic balloon pump; UK, urokinase.

Table 3 In-Hospital Outcomes

	Group A (n=74)	Group B (n=40)	p value
Death	8 (11%)	2 (5.0%)	NS
Emergent CABG	0	0	—
Massive bleeding	2 (2.7%)	2 (5%)	NS
Hospital stay (days)	27.5±10.1	19.9±7.6	<0.001
Reocclusion	6/61 (9.8%)	0/34 (0%)	NS

CABG, coronary artery bypass graft; Massive bleeding, huge hematoma necessitating blood transfusion; Reocclusion, symptomatic and/or asymptomatic occlusion confirmed by angiography.

plaque ulcer and/or disappearance of hazy space-occupying lesion.

The urokinase dose did not exceed 960,000 units. Angioplasty was performed subsequent to the PIT procedure.

Angioplasty Protocol

Angiography and angioplasty were performed using routine methods.

In order to assess the thrombus size, angiography was performed after the guidewire cross and multiple passes with a non-inflated balloon. When the thrombus was large enough to warrant pretreatment, the operator administered an appropriate dose of urokinase (240,000–960,000 U) via the guiding catheter prior to balloon inflation. If the thrombus was not large or if urgent revascularization was required, this pretreatment was omitted and the occluded site was dilated immediately after the guidewire cross. Once 'no flow' or high-grade slow flow occurred, additional treatment with intracoronary urokinase, inotropics, verapamil, nicorandil⁷ and intra-aortic balloon pump (IABP) was begun and a stent was also placed in most cases.

Definitions

Patients with a serum creatine kinase more than twice normal, chest pain lasting more than 30 min, and ST-segmental elevation and/or depression were considered to have had an AMI. Shock was defined as systolic blood pressure was less than 80 mmHg, despite volume expansion therapy. Lesion success was defined as persistent patency at the target site with less than 50% residual stenosis without severe dissection or spasm. Procedural success was defined as lesion success plus TIMI grade 3 flow lasting for more than 30 min of observation. Procedural 'no flow' was defined when the 'no flow' phenomenon occurred after

balloon dilatation and was improved by extensive additional treatment during the procedure; in contrast, persistent 'no flow' was defined when flow improvement was not obtained despite the additional treatment.

In the initial screening, a visually estimated thrombus length exceeding 2 cm of balloon length were defined as a large thrombus and measured by digital caliper method using either a balloon catheter with a known length (usually 2 cm) or a PIT catheter (2 or 3 cm in length) as a reference. As the minimum clot length of the selected cases was 15 mm, a large thrombus was longer than 15 mm. Two experienced physicians independently measured the thrombi and the mean length was determined as the thrombus length. 'No flow' was defined as cessation of antegrade coronary flow with back-and-forth movement of a dye stream and lack of contrast dye clearance into the distal circulation (TIMI grade 0), without any evidence of spiral dissection or spasm.

Data Collection and Statistical Analysis

Patient characteristics, angiographic findings, procedural outcomes and in-hospital outcomes were examined. Frequencies of lesion success, procedural success, procedural 'no flow', persistent 'no flow', reocclusion and in-hospital death were compared between the following groups: Group A vs Group B, Direct-BA vs ICT-BA, Direct-BA vs PIT-BA, ICT-BA vs PIT-BA.

Results are expressed as proportions or as mean value ± SD. Differences in categorical variables were analyzed by chi-square analysis in Group A and Group B comparisons and Bonferroni analysis was performed in subgroup comparisons. Differences in continuous variables were analyzed by unpaired Student's t test. A p value less than 0.05 was considered significant.

Table 4 Subgroup Comparisons

	Direct-BA (n=44)	ICT-BA (n=40)	PIT-BA (n=30)	Uniformity ¹	ICT-BA ² vs PIT-BA	Direct-BA ² vs PIT-BA	Direct-BA ² vs ICT-BA
Thrombus (mm)	25.6±0.1	27.8±0.2	28.7±0.3	p=0.383	p=0.982	p=0.721	p=0.981
Lesion success	38 (84%)	35 (88%)	30 (100%)	p=0.112	p=0.132	p=0.105	p=1.000
Procedural success	23 (52%)	27 (68%)	29 (97%)	p=0.001	p=0.009*	p=0.003*	p=0.468
Procedural no flow	22 (50%)	10 (25%)	1 (3.3%)	p=0.001	p=0.042*	p=0.003*	p=0.054
Persistent no flow	14 (32%)	5 (13%)	1 (3.3%)	p=0.004	p=0.525	p=0.009*	p=0.105
Reocclusion	4/36 (11%)	4/31 (13%)	0/29 (0%)	p=0.145	p=0.135	p=0.192	p=1.000
Stent	6 (14%)	11 (28%)	9 (30%)	p=0.175	p=1.000	p=0.258	p=0.342
In-hospital death	5 (11%)	2 (5%)	1 (3%)	p=0.342	p=1.000	p=0.642	p=0.876

¹Chi-square analysis; ²Chi-square analysis by Bonferroni method. BA, balloon angioplasty; ICT, intracoronary thrombolysis; PIT, pulse infusion thrombolysis; *Statistically significant difference; procedural success, procedural no flow and persistent no flow was less frequent in PIT-BA in (Direct-BA vs PIT-BA); procedural success and procedural no flow was less frequent in PIT-BA in (ICT-BA vs PIT-BA); no difference was observed in Direct-BA vs ICT-BA.

Results

Procedural and In-Hospital Outcomes of Pre-PIT Era and PIT Era

There were no significant differences in the baseline characteristics among the 2 groups (Table 1). The right coronary artery was the predominant IRA in both groups.

Table 2 shows the procedural outcomes. Group B included 10 non-PIT cases. Procedural success was more frequently achieved in Group B than Group A. Procedural 'no flow' and persistent 'no flow' were significantly less frequent in Group B than in Group A. Six cases in Group B with procedural 'no flow' (Direct-BA: 5 cases; PIT-BA: 1 case) had been stented and 4 cases maintained persistent 'no flow'.

In Group B, average time to achieve TIMI grade 3 flow was within 15 min with an average dose of 300,000 U of urokinase.

Patient in-hospital outcomes are listed in Table 3. In Group A, of the 5 deaths, 3 were patients with persistent 'no flow'. In Group B, 1 patient who underwent PIT-BA obtained TIMI grade 3 flow with 240,000 U of urokinase for a massive thrombus, but the operator did not perform further thrombolysis despite significant thrombus remaining, because this patient was scheduled for bladder carcinoma surgery. Balloon dilatation immediately resulted in persistent 'no flow'. The patient died 1 week later from low-output syndrome. Another patient was treated by direct percutaneous transluminal coronary angioplasty (PTCA), resulting in immediate persistent 'no flow' and died from low-output syndrome.

There were 2 other patients with persistent 'no flow' in Group B: one underwent ICT-BA and the other Direct-BA. They survived with severe right ventricular dysfunction.

Hospital stay was longer in Group A than in Group B ($p<0.001$).

Subgroup Analysis

Table 4 shows the subgroup data. There was no difference in lesion success, reocclusion rate or in-hospital death. As chi-square analysis confirmed that there was no uniformity in procedural success, procedural 'no flow' and persistent 'no flow' among the 3 groups, differences between each group was analyzed by Bonferroni method. Procedural success was best achieved with PIT-BA. The 'no flow' phenomenon with PIT-BA was less frequent compared with the other 2 groups. Persistent 'no flow' was significantly less in the PIT-BA group compared with Direct-BA. Differences between ICT-BA and Direct-BA were statistically insignificant.

Discussion

The clinical impact of the 'no flow' phenomenon on short-term outcomes is mostly unfavorable^{8,9} and the recent trend of a direct approach with a balloon and/or stent combined with high-pressure dilatation performed blind to the basic lesion anatomy and thrombus volume may increase the incidence of this phenomenon.¹⁰ Although stenting is effective in keeping vessels patent, it is not only lesion success, but effective flow restoration (TIMI grade 3) that is the goal of revascularization therapy.^{11,12} Kaul et al recently reported the adverse effect of slow flow in a series of 68 consecutive patients who received primary stenting for AMI?

The revascularization mechanism of PIT is twofold: the mechanical maceration of the thrombus by direct delivery of a fibrinolytic drug into the thrombus and persistence of the drug within the thrombus to accelerate the lytic process. The PIT pump provides constant forceful drug delivery and controls the delivery pattern in order to balance the mechanical and lytic mechanisms. Our results strongly indicated the meritorious effect of the PIT technique over Direct-BA in preventing the 'no flow' phenomenon. Although there was no significant difference in persistent 'no flow' between the PIT-BA and ICT-BA groups or between the ICT-BA

Fig 3. (A) Angiogram showing occlusion of the mid-anterior descending artery with an acute anterior myocardial infarction. (B) A 3-cm Ultrafuse catheter was placed and PIT started. (C) Angiogram taken 10 min later reveals that the true culprit lesion is located at a distal site and the thrombus has extended proximally. (D) Thrombolysis was continued until the thrombus disappeared and a stent was placed only in the stenotic lesion.

and Direct-BA groups, its incidence was less frequent in PIT-BA, followed by ICT-BA and Direct-BA. This may indicate that performing ICT before angioplasty was partially effective in flow improvement after the onset of 'no flow' with the supportive treatment of IABP, additional thrombolysis, and other drugs.

Another advantage of PIT over direct PTCA is that the operator can optimize the strategy according to the lesion's anatomy, because this procedure is confirmed by visualizing the culprit lesion after the thrombus has disappeared on angiography. Therefore, PIT enables a sequential procedure from thrombolysis to PTCA and/or stent (Fig 3).

Other solutions for large intracoronary thrombus have been introduced recently. The 'Angiojet', a rheolytic thrombectomy device, is an effective solution for large thrombus, especially in vein graft disease.^{13,14} The IIb/IIIa blockade regimen has also been reported as a strong potential solution for the treatment of high-risk thrombus-containing lesions.¹⁵ This blockade of platelet activation is effective in reducing 'slow flow' or 'no flow', but its effect on the thrombus itself, especially large ones like the present cases is unknown.

Study Limitations

As this study was retrospective and there was no rigid study design, there is a possibility that operator bias may influence the final results; for instance, the urokinase dose used in ICT and the technique to treat 'no flow' and/or slow flow may have differed among operators. Initially the study was designed as a multicenter randomized prospective comparison between Direct-BA and PIT-BA; however, most participants rejected randomization after some patients assigned to Direct-BA died because of persistent 'no flow'.

In order to minimize the bias factors, we evaluated the effect of the PIT technique by 2 methods: (1) comparison between the pre-PIT and PIT eras and (2) comparison between subgroups. We only tested urokinase in this study; however, tissue plasminogen activator is also effective in ex vivo and in vivo experiments.⁴ In terms of thrombus examination, we only measured its length, which may not have been enough for accurate thrombus size determination.

As the 'no flow' phenomenon appears to be a multifactorial mechanism, further investigations are necessary to clarify the potential of PIT.

Conclusion

In the mechanical revascularization of patients with AMI, pretreatment of the thrombus with the PIT technique was beneficial in reducing the incidence of the 'no flow' phenomenon, especially for cases with a large thrombus.

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