INTERVENTIONAL CARDIOLOGY AND SURGERY

Relation between the TIMI frame count and the degree of microvascular injury after primary coronary angioplasty in patients with acute anterior myocardial infarction

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Objective: To investigate the relation between thrombolysis in myocardial infarction (TIMI) frame count (TFC) and coronary blood flow velocity (CBFV) parameters reflecting the degree of microvascular injury in patients with acute myocardial infarction.
Results: TFC and CBFV were measured after primary coronary angioplasty in 103 consecutive patients with their first anterior wall acute myocardial infarction. TFC correlated inversely with the averaged peak velocity ($r = -0.43$, $p < 0.0001$). However, TFC did not correlate significantly with diastolic deceleration time and with the averaged systolic peak velocity ($r = -0.16$, $p = 0.22$, and $r = -0.23$, $p = 0.16$, respectively). The patients were divided into two groups according to presence (35 patients) or absence (68 patients) of systolic flow reversal. There was no significant difference in TFC between the two groups (29 (16) *v* 25 (13), p = 0.20).
Conclusions: These findings suggest that the TFC reflects epicardial CBFV. However, it is not accurate enough to assess the degree of microvascular injury after primary coronary angioplasty.

The thrombolysis in myocardial infarction (TIMI) frame count (TFC) was developed as a simple, objective, quantitative, and reproducible method to assess coronary blood flow.[1–3] This method counts the number of cineangiographic frames required for radio-opaque contrast to reach specified distal landmarks in each coronary artery. However, in the setting of acute myocardial infarction (AMI), establishing epicardial coronary blood flow does not necessarily result in microvascular perfusion at the tissue level. In one myocardial contrast echocardiography study, there was evidence of myocardial no reflow in 16% of patients with TIMI grade 3 flow, which implies a lack of microvascular perfusion due to capillary damage.[4] Furthermore, even among patients with TIMI grade 3 flow, left ventricular functional recovery was worse in patients with myocardial no reflow than in those with myocardial reflow.[4 5]

The recently developed Doppler guidewire allows us to evaluate the coronary blood flow velocity (CBFV) and the state of microvascular perfusion in patients with AMI. A distinctive CBFV pattern, characterised by the appearance of systolic flow reversal (SFR), diminished systolic antegrade flow, and rapid deceleration of diastolic flow, is thought to reflect the degree of microvascular injury in the risk area (fig 1).[6 7] In this study, we investigated the relation between TFC and CBFV parameters reflecting the degree of microvascular injury in patients with their first anterior AMI.

METHODS
Study population
The study population comprised 115 consecutive patients with their first anterior AMI who underwent primary coronary angioplasty within 12 hours after the onset of AMI between November 2000 and May 2002. The diagnosis of AMI was defined as (1) chest pain continuing for > 30 minutes; (2) ST elevation > 2.0 mm in two or more contiguous ECG leads; (3) an increase in serum creatine kinase more than threefold the normal concentration; and (4) TIMI grade 0, 1, or 2 flow at the time of the initial coronary angioplasty. Twelve patients were excluded because of inadequate cineangiography for evaluation of the TFC (three patients), inadequate Doppler recording (five patients), or significant stenosis distal to the culprit lesion (four patients). The remaining 103 patients were enrolled in this study. Informed consent for primary coronary angioplasty was obtained from all patients or their families before the procedure.

Procedure
Coronary angiography was performed in the standard femoral approach by Judkin's technique. Cinefilms were recorded at a speed of 15 frames/s. All patients received an intravenous injection of heparin (5000 U) and glyceryl trinitrate (0.3 mg) before coronary angiography. After an additional intravenous or intra-arterial bolus of heparin (5000 U), all patients underwent initial balloon angioplasty followed by stenting. The end point for the coronary angioplasty procedure was defined as a residual stenosis < 25% based on visual assessment. No patients were treated with glycoprotein IIb/IIIa inhibitors.

Analysis of the CBFV pattern
After successful angioplasty, the guidewire was exchanged for a 0.014 inch Doppler guidewire (FloWire, Endosonics, Rancho Cordova, California, USA). The tip of the Doppler guidewire was placed distal to the second diagonal branch in the left anterior descending coronary artery (LAD) after intracoronary injection of glyceryl trinitrate (0.3 mg). CBFV was recorded on videotape and digitised on an offline computer. The following parameters were measured from

Abbreviations: AMI, acute myocardial infarction; APV, averaged peak velocity; ASV, averaged systolic peak velocity; CBFV, coronary blood flow velocity; DDT, diastolic deceleration time; LAD, left anterior descending coronary artery; SFR, systolic flow reversal; TFC, TIMI frame count; TIMI, thrombolysis in myocardial infarction

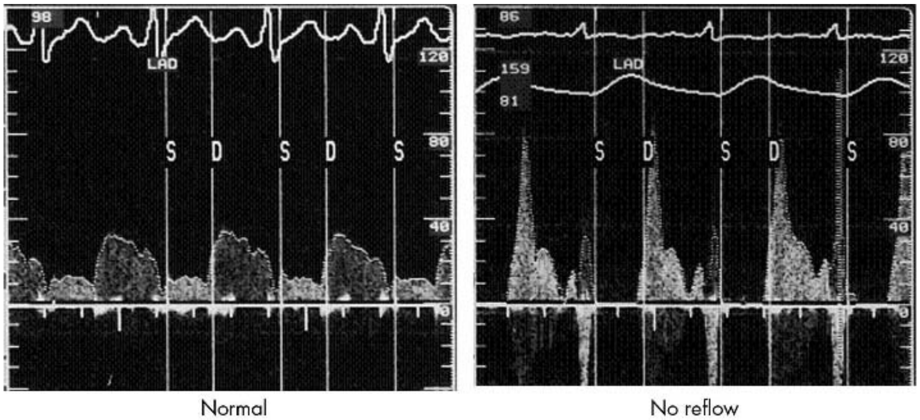

Figure 1 Coronary blood flow velocity patterns in patients with reperfused acute myocardial infarction. (Left) Coronary blood spectrum immediately after angioplasty in a patient without microvascular injury. Antegrade flow is dominant during systole (S). The diastolic (D) peak velocity deceleration is normal. (Right) Coronary blood spectrum immediately after angioplasty in a patient with microvascular injury. Systolic flow reversal and rapid deceleration of diastolic flow are observed.

the CBFV spectrum: time averaged peak velocity (APV), averaged systolic peak velocity (ASV), averaged diastolic peak velocity, diastolic to systolic APV ratio, and diastolic deceleration time (DDT). DDT was measured from the peak diastolic velocity to the point where the extrapolated line intersected the baseline. SFR was defined as rapid reverse flow during early systole (peak velocity $\geqslant$ 10 cm/s and duration $\geqslant$ 60 ms). Two independent observers measured these CBFV parameters in 10 randomly selected patients. The interobserver and intraobserver variability were both $\leqslant$ 5%.

Analysis of coronary angiograms
Collateral flow was graded according to the Rentrop classification from the initial coronary angiograms.[8] The TIMI flow grade and TFC were evaluated from the final coronary angiogram after intracoronary injection of glyceryl trinitrate (0.3 mg). The diameter of the reference vessel and the minimum lumen diameter of the culprit lesion were measured with the automated edge detection system (Cardio 500, Kontron, Munich, Germany) and the residual percentage diameter stenosis was calculated.

TIMI frame count
On the basis of the method described by Gibson and colleagues[1] the number of frames required for dye to reach the distal bifurcation of the LAD (that is, the moustache, pitchfork, or whale's tail) was counted with a cine projector equipped with a frame counter. Because the images were acquired at 15 frames/s, frame counts were multiplied by a factor of two. A single observer blinded to the CBFV measurements assessed the TFC. Intraobserver variability was 0.85 frames.

Table 1 Baseline characteristics of patients

Characteristic	Mean (SD) or n (%)
Age (years)	61 (9)
Men	84 (82%)
Risk factors	
Hypertension	46 (45%)
Diabetes mellitus	30 (29%)
Hyperlipidaemia	50 (49%)
Smoking	74 (72%)
Onset to reperfusion time (h)	3.8 (1.9)
Segment 6	75 (73%)
Rentrop grade $\leqslant$1	100 (97%)
Diameter of stenosis after angioplasty (%)	14 (8)
TFC	45 (25)
Peak creatine kinase (IU/l)	4484 (2700)

TFC, TIMI frame count.

Statistical analysis
Data are expressed as mean (SD). The two groups were compared by Student's t test for continuous variables or χ^2 test for categorical variables. The correlation between TFC and CBFV parameters was assessed by simple linear regression analysis. For all analyses, $p < 0.05$ was considered significant.

RESULTS
Baseline characteristics and CBFV parameters
Table 1 lists the baseline clinical and angiographic characteristics of the patients. Table 2 summarises CBFV measurements. DDT had a significant positive correlation with ASV (r = 0.59, $p < 0.0001$), as fig 2 shows. However, there was no significant correlation between DDT and APV (r = 0.10, p = 0.30).

Relation between TFC and CBFV parameters
As fig 3 shows, TFC correlated inversely with APV (r = −0.43, $p < 0.0001$). However, TFC did not correlate significantly with DDT or with ASV (r = −0.16, p = 0.22, r = −0.23, p = 0.16, respectively). The patients were divided into two groups based on the presence (SFR group, 35 patients) or absence of SFR (non-SFR group, 68 patients). ASV was lower and DDT was shorter in the SFR group than in the non-SFR group (–6.7 (9.7) *v* 11 (6.1) cm/s, $p < 0.0001$, and 289 (130) *v* 767 (347), $p < 0.0001$, respectively), as table 3 shows. However, there was no significant difference in TFC between the two groups (29 (16) *v* 25 (13), p = 0.20) (fig 4).

DISCUSSION
In the present study, TFC correlated significantly with epicardial CBFV, expressed as APV. However, it was not

Table 2 Intracoronary flow velocity measurements

Measure	Mean (SD) or n (%)
APV (cm/s)	18.1 (8.3)
ADV (cm/s)	24.3 (12.3)
ASV (cm/s)	9.7 (7.1)
DSVR	5.4 (5.6)
DDT (ms)	606 (369)
SFR	35 (34%)

ADV, averaged diastolic peak velocity; APV, averaged peak velocity; ASV, averaged systolic peak velocity; DDT, diastolic deceleration time; DSVR, diastolic to systolic velocity ratio; SFR, systolic flow reversal.

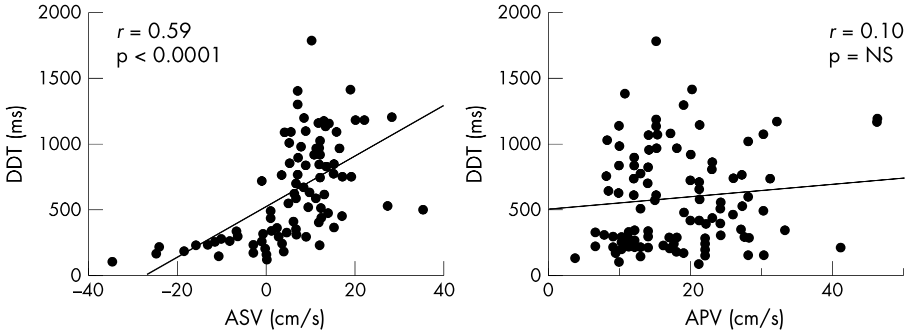

Figure 2 Correlations between diastolic deceleration time (DDT) and (left) averaged systolic peak velocity (ASV) and (right) averaged peak velocity (APV). DDT correlated positively with ASV but there was no significant correlation between DDT and APV. NS, not significant.

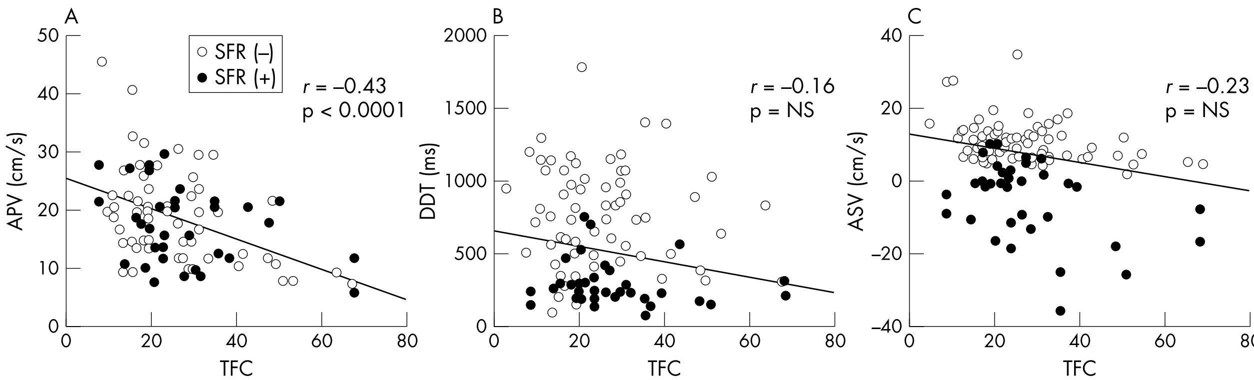

Figure 3 Correlation between TIMI frame count (TFC) and coronary blood flow velocity (CBFV) parameters. (A) TFC correlated inversely with APV but (B) TFC did not correlate significantly with DDT or (C) with ASV. Patients were divided into two groups with (+) and without (–) systolic flow reversal (SFR).

accurate enough to assess the degree of microvascular injury evaluated by CBFV parameters.

Kern and colleagues[9] showed that TFC correlates with APV in patients with TIMI grade 3 flow after primary coronary angioplasty ($r = -0.45$, $p = 0.024$). In addition, Tanedo and colleagues[10] reported a similar correlation between corrected TFC and APV ($r = -0.42$, $p = 0.004$) in heart transplant recipients. The correlation between TFC and APV in this study is compatible with these previous results ($r = -0.43$, $p < 0.0001$), indicating that TFC reflects epicardial CBFV.

It has been reported that SFR, low ASV, and a short DDT are sensitive and specific markers of the no reflow phenomenon in patients with AMI after successful recanalisation.[6,7] In the present study, CBFV data showed that ASV was significantly lower and DDT shorter in the SFR group than in the non-SFR group. Iwakura and colleagues[6] hypothesised that injured coronary microvasculature may increase microvascular impedance and decrease the intramyocardial blood pool, which results in this distinctive CBFV pattern. In addition, recent studies have shown that this distinctive CBFV pattern is also associated with poorer functional recovery and poorer prognosis.[7,11,12] In the present study, although TFC tended to be higher in the SFR group than in the non-SFR group, the difference was not significant. In addition, neither DDT nor ASV, reflecting the degree of microvascular injury, correlated significantly with TFC. These findings suggest that TFC may not be accurate enough to assess microvascular injury after primary coronary angioplasty.

Several studies have shown that APV is significantly higher in patients with TIMI grade 3 flow than in patients with TIMI grade 2 flow.[9,13] APV may not reflect the status of microvascular perfusion in comparison with SFR, ASV, and

Table 3 Comparison between groups based on presence of systolic flow reversal (SFR)

	SFR (n = 35)	Non-SFR (n = 68)	p Value
Age (years)	62 (8)	60 (10)	NS
Men	33 (84%)	56 (82%)	NS
Systolic aortic pressure (mm Hg)	121 (24.5)	117 (22.8)	NS
Diastolic aortic pressure (mm Hg)	75 (13)	74 (15)	NS
Heart rate (beats/min)	73 (15)	73 (14)	NS
Onset to reperfusion time (h)	4.5 (2.2)	3.7 (2.9)	NS
Peak creatine kinase (IU/l)	6571 (2313)	3441 (2245)	<0.0001
APV (cm/s)	16 (7.1)	19 (8.8)	NS
ASV (cm/s)	−6.7 (9.7)	11 (6.1)	<0.0001
ADV (cm/s)	22 (9.5)	25 (13.5)	NS
DSVR	9.9 (16.1)	2.8 (3.8)	<0.001
DDT (ms)	289 (130)	767 (347)	<0.0001

NS, not significant.

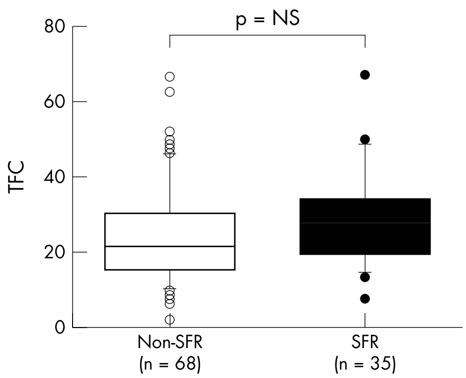

Figure 4 TIMI frame count (TFC) in the systolic flow reversal (SFR) and non-SFR groups. There was no significant difference in TFC between the two groups.

DDT, especially in patients with TIMI grade 3 flow. Consequently, TFC, an angiographic parameter of APV, may not accurately assess the degree of microvascular injury in the modern era of primary coronary angioplasty.

Clinical implications
The intracoronary Doppler guidewire is a sophisticated and expensive tool whose use is not always feasible. In contrast, TFC is determined by a simple quantitative method and can be measured immediately after angioplasty in all catheterisation laboratories. In previous studies, TFC predicted clinical and functional outcome in patients with reperfused AMI.[14,15] However, in our study, TFC did not accurately reflect the status of microvascular perfusion. Considering that the goal of coronary reperfusion is to achieve microvascular perfusion and to salvage the myocardium in the risk area, it is important to assess accurately the degree of microvascular injury after reperfusion. It has been reported that microvascular perfusion can be assessed simply through the use of angiographic techniques such as the myocardial blush grade.[16–18] This method may overcome the imprecision of TFC and characterise the degree of microvascular injury more accurately.

Study limitations
Firstly, the number of patients in this study was relatively small and the study was limited to patients with anterior AMI. Therefore, the results of this study have not been established in patients with inferior or posterior AMI. Secondly, residual stenosis may alter the CBFV pattern. However, in this study, all patients were treated by stenting and the average percentage diameter stenosis assessed by quantitative coronary angiography was 14%. In addition, none of the patients had significant stenosis distal to the culprit lesion. Therefore, the influence of residual stenosis may have been minimal. Thirdly, in this study, myocardial contrast and dobutamine stress echocardiography were not performed. These methods are useful to assess the degree of microvascular injury after reperfusion. However, because of technical limitations, these methods cannot be applied to all acute cases. Fourthly, the value of APV is dependent on positioning of the guidewire. However, we carefully positioned the tip of the guidewire to obtain an optimal signal for CBFV and measured CBFV in the distal LAD. Satisfactory CBFV signals were obtained in 95% of the patients. Lastly, several factors are thought to significantly affect TFC, such as heart rate, the cardiac cycle in which dye is injected, and the size of the coronary artery.[18,19] These factors may have caused the substantial scatter in plots of the TFC and CBFV parameters in fig 3.

Conclusion
Although TFC reflects epicardial CBFV, it is not accurate enough to assess the degree of microvascular injury after primary coronary angioplasty.

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