Effect of Potential Confounding Factors on the Thrombolysis in Myocardial Infarction (TIMI) Trial Frame Count and Its Reproducibility

Adnan Abacı, MD; Abdurrahman Oguzhan, MD; Namik Kemal Eryol, MD; Ali Ergin, MD

Background—The potential factors that introduce variability into TIMI frame count (TFC) have not been systematically investigated. The goal of this study was to determine if nitrate use, dye injection rate, catheter size, the phase of the cardiac cycle in which dye is injected, or heart rate affect the TFC and to investigate the reproducibility of the TFC.

Methods and Results—The dye injection rate was increased 1 mL/s, and angiography was repeated. A coronary angiogram was taken first with an 8F catheter and then with a 6F catheter. After taking angiograms, intracoronary nitrate was given to the patient, and the second angiography was performed. Basal heart rate was increased 20 beats/min, and angiography was repeated. Dye injection was performed at the beginning of systole and diastole. The TFC was not significantly changed by increasing the dye injection rate ($P=0.467$) or by changing catheter size ($P=0.693$). Nitrate administration significantly increased the TFC from $26.4\pm11.9$ to $32.8\pm13.3$ frames ($P<0.001$). Dye injection at the beginning of diastole significantly decreased the TFC from $30.1\pm8.8$ to $24.4\pm7.9$ frames ($P<0.001$) for the left coronary artery and from $24.16\pm4.49$ to $21.24\pm4.45$ frames ($P<0.001$) for the right coronary artery. Increasing heart rate significantly decreased the TFC from $30.4\pm6.1$ to $25.3\pm7.2$ frames ($P<0.001$). Intraobserver and interobserver reproducibility of the TFC was good (mean difference, $1.33\pm1.24$ and $2.57\pm1.72$ frames, respectively).

Conclusions—Nitrate use, heart rate, and the phase of the cardiac cycle in which dye is injected had significant effects on the TFC. Therefore, studies comparing TFC need to consider these factors, and the use of nitrates should be either standardized or randomized. (Circulation. 1999;100:2219-2223.)

Key Words: angiography ■ blood flow ■ coronary disease ■ nitroglycerin

The Thrombolysis in Myocardial Infarction (TIMI) flow-grading system is a valuable and widely used qualitative measure in angiographic trials. Its reproducibility was recently evaluated by a retrospective core angiographic laboratory assessment of the TIMI-4 trial.1 Gibson et al1 showed important differences between the angiographic core laboratory and local investigator judgment of TIMI flow grade. Therefore, to enhance reproducibility, these investigators described a more quantitative assessment of coronary flow, the corrected TIMI frame count (TFC), which counts the number of cineangiographic frames required for dye to travel from the ostium to standardized distal landmarks of the coronary artery. Although the variability between 2 consecutive injections seemed low at the core laboratory, the potential factors that introduce variability into the TFC were not systematically investigated. We investigated the intraobserver and interobserver reproducibility of the TFC and determined if nitrate use, the dye injection rate, the caliber of catheter used, the phase of the cardiac cycle in which dye is injected, or heart rate affect the TFC.

Methods

The study protocol was approved by the Human Research Committee of our institution. Participating patients, after giving informed consent, underwent selective coronary arteriography and left ventriculography, when clinically indicated. Standard technique multiple-view arteriography was done using a cineangiography unit (Infinix CS, Toshiba). Patients were excluded if they had a history of coronary artery bypass graft surgery, left main coronary artery disease, or significant proximal coronary artery disease (>50% stenosis of the diameter of the proximal left anterior coronary artery before the first septal branch, >50% stenosis of the diameter of the circumflex coronary artery before the first obtuse marginal branch, or >50% stenosis of the diameter of the proximal right coronary artery before the first acute marginal branch).

Coronary Angiography

Lorazepam (1 mg) was orally administered before the procedure. A 5000-U intravenous bolus of heparin was administered after access was obtained. No patients received nitrates immediately before the coronary angiography. Nitroglycerin was only given for coronary artery spasm, and patients who received it were excluded from the study. A mechanical electrocardiographic-gated power injector (Angiomat 6000, Liebel-Flarsheim Company) was used to inject contrast dye at rates of 3 to 4 mL/s in the left coronary artery and 2 to 3 mL/s...
in the right coronary artery. Iopromide contrast (Ultravist-370, Schering AG) was used in all of the patients. All injections were performed with electrocardiographic R-wave synchronization, except in the last 50 patients in whom the effect of systole and diastole was investigated. One of the single-plane projections that best identified the distal landmark was chosen for the second coronary angiogram.

In the first 25 patients (injection rate group), the injection rate of the dye was increased by 1 mL/s, and the angiography was repeated. In the second 25 patients (catheter group), the coronary angiogram was taken first with an 8F Judkins catheter; after replacing the catheter with a 6F Judkins diagnostic catheter, the angiography was repeated using the same dye injection rate. In the third 25 patients (nitrate group), 300 mg of intracoronary nitrate was given via the coronary artery after taking the first angiogram, and coronary angiography was repeated using the same catheter size and dye injection rate. In another 25 patients (heart rate group), after the angiogram was taken in the basal condition, the heart rate was increased 20 beats/min over the base rate with a temporary pacemaker, and angiography was repeated using the same catheter size and dye injection rate. In the last 50 patients (25 patients for the left coronary artery and 25 for the right coronary artery), dye injection was performed at the beginning of systole and then repeated at the beginning of diastole with the same injection rate (cardiac cycle group). In these patients, synchronization of the injections with the beginning of systole or diastole was done electrocardiographically.

The angle of the cinecamera did not vary between repeated studies. Also, care was taken to have the catheter in the same position in the coronary ostium between repeated studies. If the left anterior descending or left circumflex coronary artery was subselectively engaged, the patient was not included in the study. In each instance, no contrast was administrated during the 90 s before the coronary injections. All arteriography was recorded on 35-mm cinefilm at 25 frames/s (Kodak). Immediately after each injection, the actual volume, rate, pressure, and duration were recorded. No untoward reactions occurred in any of the patients studied.

TFC

The numbers of cineframes were measured using a frame counter on the ELK Cap-35 B II cineviewer. The first frame used for TFC was defined by a column of contrast extending across 70% of the arterial lumen with anterograde motion, as reported previously. The last frame counted was that in which contrast first appears in the distal predefined landmark branch, but full opacification of the branch is not necessary. These landmarks, as defined by Gibson et al, are as follows: the distal bifurcation of the left anterior descending artery (ie, the mustache, pitchfork, or whale’s tail), the circumflex artery, the distal branch of the lateral left ventricular wall artery with the longest total distance from the coronary ostium, and the first branch of the posterolateral artery in the right coronary artery. If 1 of these landmarks was not well visualized, another well-visualized landmark close to these landmarks was chosen. The frame count of the left anterior descending artery was not corrected because the purpose of the study was to analyze the effects of various factors on TFC. The TFC was measured by 2 experienced observers blinded to the identity and the order of the angiograms. Any disagreements were resolved by a third observer.

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TFC

The numbers of cineframes were measured using a frame counter on the ELK Cap-35 B II cineviewer. The first frame used for TFC was defined by a column of contrast extending across >70% of the arterial lumen with anterograde motion, as reported previously. The last frame counted was that in which contrast first appears in the distal predefined landmark branch, but full opacification of the branch is not necessary. These landmarks, as defined by Gibson et al, are as follows: the distal bifurcation of the left anterior descending artery (ie, the mustache, pitchfork, or whale’s tail), the circumflex artery, the distal branch of the lateral left ventricular wall artery with the longest total distance from the coronary ostium, and the first branch of the posterolateral artery in the right coronary artery. If 1 of these landmarks was not well visualized, another well-visualized landmark close to these landmarks was chosen. The frame count of the left anterior descending artery was not corrected because the purpose of the study was to analyze the effects of various factors on TFC. The TFC was measured by 2 experienced observers blinded to the identity and the order of the angiograms. Any disagreements were resolved by a third observer.

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TABLE 3. Heart Rate and Systolic and Diastolic Aorta Pressure in the Groups

<table>
<thead>
<tr>
<th>Patient Group</th>
<th>No. of Patients</th>
<th>Heart Rate, beats/min</th>
<th>Diastolic Aorta Pressure, mm Hg</th>
<th>Systolic Aorta Pressure, mm Hg</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>First Injection</td>
<td>Second Injection</td>
<td>First Injection</td>
</tr>
<tr>
<td>Injection rate group</td>
<td>25</td>
<td>72±11</td>
<td>72±10</td>
<td>82±9</td>
</tr>
<tr>
<td>Catheter group</td>
<td>25</td>
<td>71±10</td>
<td>72±9</td>
<td>87±11</td>
</tr>
<tr>
<td>Nitrate group</td>
<td>25</td>
<td>70±10</td>
<td>75±11*</td>
<td>88±10</td>
</tr>
<tr>
<td>Heart rate group</td>
<td>25</td>
<td>68±8</td>
<td>89±9*</td>
<td>84±12</td>
</tr>
<tr>
<td>Cardiac cycle group</td>
<td>25</td>
<td>77±13</td>
<td>77±12</td>
<td>91±13</td>
</tr>
<tr>
<td>(left coronary)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiac cycle group</td>
<td>25</td>
<td>69±11</td>
<td>69±10</td>
<td>85±14</td>
</tr>
<tr>
<td>(right coronary)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Data are presented as mean±SD. *P<0.001.

Statistical Analysis
Continuous variables were expressed as mean±SD. The relationship between the continuous variables was evaluated using a paired Student’s t test or Wilcoxon sign rank test, when appropriate. In the nitrate group, ANCOVA was used to assess the confounding effects of heart rate and systolic and diastolic aorta pressure on TFC. In 30 randomly selected studies, 2 observers independently measured the TFC, and interobserver agreement was assessed by linear regression with Bland-Altman analysis.3 These same studies were also reexamined by 1 observer at a separate time to determine intraobserver agreement. If A and B are the repeat measurements, A minus B is the absolute error. Mean absolute error was calculated by ignoring the direction of the error; for this calculation, the absolute value of each error was used. The relative errors were calculated according to the following formula: (A−B)/((A+B)/2), where A and B are the repeated values of the same measurement. The bias is the difference between the mean measurements of A and B. The repeatability coefficient is the expected value below which 95% of the differences will fall for intraobserver and interobserver reproducibility.

For all tests, a value of P<0.05 was considered statistically significant. The SPSS statistical software package (version 5.0) was used to perform all statistical calculations.

Results
A total of 150 patients (mean age, 59 years) were included in the study. Table 1 describes the baseline characteristics of study patients before coronary angiography. Intraobserver and interobserver measurements of the average TFC were closely correlated (r=0.98, SEE=1.8 frames, P<0.0001 and r=0.94, SEE=3 frames, P<0.0001, respectively). By Bland-Altman analysis, the mean difference in TFC measurements between 2 different observers was 2.57±1.72 frames. Similarly, the mean intraobserver difference in TFC measurements was within 1.33±1.24 frames. Mean absolute errors, relative errors, and repeatability coefficients or limits of agreement for TFC are shown for intrasubject and interobserver variability in Table 2. Figures 1 and 2 show Bland-Altman plots for interobserver and intraobserver errors of TFC.

Heart rate and diastolic and systolic aorta pressure changes between the first and second dye injections are shown in Table 3. With nitrate administration, heart rate significantly increased, and diastolic-systolic aorta pressures significantly decreased. In other groups, no differences were found between first and second injection with regard to heart rate and systolic and diastolic aorta pressures, except in the heart rate group, the one in which heart rate was intentionally increased.

The mechanical injector successfully delivered contrast dye at volumes and rates approximating the targeted values in 150 patients undergoing elective diagnostic catheterization. In left coronary arteries, 7.3±0.9 mL was delivered at 3.4±0.6 mL/s. In right coronary arteries, 5.2±0.7 mL was delivered at 2.6±0.5 mL/s. The injected volume was significantly increased in those patients in whom the effect of injection rate was assessed. With the use of a smaller lumen catheter or an increase in the dye injection rate, the injection

TABLE 4. Injection Rate, Injected Volume, and Injection Pressure of the Groups

<table>
<thead>
<tr>
<th>Patient Group</th>
<th>No. of Patients</th>
<th>Injection Rate, mL/s</th>
<th>Injected Volume, mL</th>
<th>Injection Pressure, Psi</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>First Injection</td>
<td>Second Injection</td>
<td>First Injection</td>
</tr>
<tr>
<td>Injection rate group</td>
<td>25</td>
<td>2.7±0.5</td>
<td>3.7±0.4*</td>
<td>5.6±0.4</td>
</tr>
<tr>
<td>Catheter group</td>
<td>25</td>
<td>3.7±0.4</td>
<td>3.7±0.6</td>
<td>7.4±0.8</td>
</tr>
<tr>
<td>Nitrate group</td>
<td>25</td>
<td>3.6±0.5</td>
<td>3.6±0.6</td>
<td>6.7±1.3</td>
</tr>
<tr>
<td>Heart rate group</td>
<td>25</td>
<td>3.8±0.4</td>
<td>3.8±0.4</td>
<td>7.3±1</td>
</tr>
<tr>
<td>Cardiac cycle group</td>
<td>25</td>
<td>3.7±0.3</td>
<td>3.8±0.4</td>
<td>7.4±0.8</td>
</tr>
<tr>
<td>(left coronary)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiac cycle group</td>
<td>25</td>
<td>2.4±0.5</td>
<td>2.4±0.4</td>
<td>5.3±0.8</td>
</tr>
<tr>
<td>(right coronary)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Data are presented as mean±SD. *P<0.001; †P=0.01.
angiographic endpoints between trials. Gibson et al found a mean absolute difference in TFC of 4.7 and quantitative method to assess coronary blood flow. It has been proposed as a simple, reproducible, objective, and quantitative method to assess coronary blood flow. Recently, Doppler measurements are extremely space-dependent and may be affected by the geometry of the stenosis and the position of the wire. In addition, the sampling volume can be rather limited, and it does not necessarily represent the mean velocity of the bloodstream. In contrast, Doppler measurements are extremely space-dependent and may be affected by the geometry of the stenosis and the position of the wire. Therefore, the effect of dye injection at the beginning of systole. However, the differences between diastolic and systolic injections were less marked in right coronary arteries than in left coronary arteries.

**Discussion**

Although various quantitative techniques to measure coronary blood flow have been proposed, the TIMI flow grade is the qualitative measure used in most angiographic trials. The reproducibility of TIMI flow grade was recently evaluated, and significant discrepancies existed between the angiographic core laboratory and local investigator assessment of the grade of coronary blood flow, especially for TIMI 2 flow. Intracoronary Doppler is another way to determine absolute velocity in coronary arteries; however, it also has several limitations. Doppler measurements are extremely space-dependent and may be affected by the geometry of the stenosis and the position of the wire. In addition, the sampling volume can be rather limited, and it does not necessarily represent the mean velocity of the bloodstream. Recently, TFC has been proposed as a simple, reproducible, objective, and quantitative method to assess coronary blood flow. It has been claimed that TFC use could facilitate the comparison of angiographic end points between trials. Gibson et al found a mean absolute difference in TFC of 4.7 ± 3.9 frames between 2 consecutive hand injections, which suggested good reproducibility. We further demonstrated that intraobserver and interobserver errors were low and that intraobserver and interobserver reproducibility was good. French et al also found that TFC measurement was highly reproducible with experienced observers (0.75 ± 4.3 frames).

As expected, the 1.0 mL/s increase in injection rate significantly increased the injection pressure of dye and the volume injected. We showed that the 1.0 mL/s increase in injection rate did not significantly change the TFC. Our study agrees with a previous report showing that the 1.0 mL/s increase in injection rate is associated with only a minor decrease of <2 frames (<7% of the mean TFC). The main effect of changing the catheter from 8F (larger lumen) to 6F (smaller lumen) was on the injection pressure of dye. With the use of a smaller catheter, the injection pressure significantly increased. However, this increase did not have any significant effect on the TFC. From these observations, we thought that the injection pressure and the injected volume were not important factors affecting the TFC and, hence, coronary blood flow.

Nitroglycerin had a significant effect on the TFC. It is well known that nitroglycerin causes dilatation of coronary arteries. The diameters of the coronary arteries increase by dilatation. A wide artery will have larger blood volumes than a narrow artery, and more time (ie, a higher TFC) may be required for a constant volume of contrast agent to travel through the larger blood volume to reach the distal anatomic landmark.

The blood flow in coronary arteries is pulsatile, and it is higher in diastole and lower in systole. All 3 coronary arteries show a diastolic-predominant flow pattern in both proximal and distal arterial segments. Large differences, however, are present between the flow patterns in the left and right coronary arteries. This normal velocity pattern with diastolic predominance was less marked in the right coronary artery, which had a significantly lower peak diastolic/systolic flow-velocity ratio compared with the left anterior descending and left circumflex arteries. Therefore, the effect of dye injection at the beginning of systole and diastole on the TFC was separately investigated in the left and right coronary arteries. We showed that when the contrast agent was injected at the beginning of systole, more time (ie, a higher TFC) was required for a constant volume of dye to reach the distal anatomic landmark than when the dye was injected at the beginning of diastole. However, this may not be true if the number (or time period) of systole and diastole are equal during the time needed for the dye to reach the distal landmark. It may further be speculated that it will be hard to inject the dye at the same point in the cardiac cycle in repeated injections during coronary angiography because

### Table 5. The First and Second Injection Values of the TFC

<table>
<thead>
<tr>
<th>Patient Group</th>
<th>No. of Patients</th>
<th>First Injection</th>
<th>Second Injection</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Injection rate group</td>
<td>25</td>
<td>28.2 ± 11.4 (24)</td>
<td>27.2 ± 11.5 (24)</td>
<td>0.467</td>
</tr>
<tr>
<td>Catheter group</td>
<td>25</td>
<td>25.1 ± 8.7 (26)</td>
<td>25.7 ± 12.4 (26)</td>
<td>0.693</td>
</tr>
<tr>
<td>Nitrate group</td>
<td>25</td>
<td>26.4 ± 11.9 (24)</td>
<td>32.8 ± 13.3 (31)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Heart rate group</td>
<td>25</td>
<td>30.4 ± 6.1 (29)</td>
<td>25.3 ± 7.2 (24)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Cardiac cycle group (left coronary)</td>
<td>25</td>
<td>30.1 ± 8.8 (29)</td>
<td>24.4 ± 7.9 (23)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Cardiac cycle group (right coronary)</td>
<td>25</td>
<td>24.2 ± 4.5 (25)</td>
<td>21.2 ± 4.4 (20)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Data are presented as mean ± SD (median).
hand injection is frequently used. In the right coronary artery, with the injection of dye at the beginning of systole, the TFC was also higher compared with the injection of dye at the beginning of diastole. However, the difference was less marked than that in the left coronary artery. This is related to the less marked diastolic-predominant flow pattern in the right coronary artery.

The ratio of systole to diastole required for the contrast to first reach the distal coronary landmark will change with heart rate. Therefore, the significant effect of heart rate on the TFC may be due to the relative time of systole and diastole during the time it takes the dye to reach the distal landmark.

Another important methodological consideration is the initial effect of selective contrast medium injection on intracoronary flow. The selective intracoronary injection of contrast induces a series of changes in coronary blood flow. Initially, a slight increase in coronary blood flow during the injection can be detected. This is followed by a decrease in blood flow, with a nadir at 1.9 s in the proximal artery at 45% of baseline flow. Finally, hyperemia follows, which peaks between 5 and 10 s at 153% of baseline flow. Coronary blood flow returns to baseline levels within 60 s in almost all patients. This is why no contrast was administrated during the time it takes the dye to reach the distal landmark.

Important variables exist that significantly affect TFC. Therefore, studies comparing the TFC need to consider these factors.

Conclusions
Some important practical recommendations result from this study. The measurement of TFC from coronary angiograms is a bit operator-dependent. Important variables exist that significantly affect the TFC. The dye injection rate and catheter size have no effect on TFC. However, nitrate use, heart rate, and the phase of the cardiac cycle in which dye is injected have a significant effect on TFC. Therefore, studies comparing the TFC need to consider these factors.

References
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