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±11.9 to 32.8±13.3 frames (P<0.001). Dye injection at the beginning of diastole significantly decreased the TFC from 30.1±8.8 to 24.4±7.9 frames (P<0.001) for the left coronary artery and from 24.16±4.49 to 21.24±4.45 frames (P<0.001) for the right coronary artery. Increasing heart rate significantly decreased the TFC from 30.4±6.1 to 25.3±7.2 frames (P<0.001). Intraobserver and interobserver reproducibility of the TFC was good (mean difference, 1.33±1.24 and 2.57±1.72 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 al2 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. Nitroglycerine 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...
TABLE 1. Baseline Characteristics of Study Patients

<table>
<thead>
<tr>
<th>Variable</th>
<th>All Patients (n=150)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>59±13</td>
</tr>
<tr>
<td>Male sex</td>
<td>102 (68)</td>
</tr>
<tr>
<td>Risk factors</td>
<td></td>
</tr>
<tr>
<td>Smoking</td>
<td>92 (61)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>87 (58)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>33 (22)</td>
</tr>
<tr>
<td>Elevated cholesterol</td>
<td>44 (29)</td>
</tr>
<tr>
<td>Stable angina pectoris</td>
<td>139 (93)</td>
</tr>
<tr>
<td>Unstable angina pectoris</td>
<td>11 (7)</td>
</tr>
<tr>
<td>Previous myocardial infarction</td>
<td>30 (20)</td>
</tr>
<tr>
<td>Medications</td>
<td></td>
</tr>
<tr>
<td>Oral nitrates</td>
<td>111 (74)</td>
</tr>
<tr>
<td>Calcium antagonists</td>
<td>68 (45)</td>
</tr>
<tr>
<td>β-Blockers</td>
<td>55 (37)</td>
</tr>
<tr>
<td>ACE inhibitors</td>
<td>92 (61)</td>
</tr>
<tr>
<td>Aspirin</td>
<td>144 (96)</td>
</tr>
</tbody>
</table>

Data are presented as No. of patients (%) or mean±SD.

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. 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 administered 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.

Figure 1. Bland-Altman plots for intraobserver reproducibility of TFC.

Figure 2. Bland-Altman plots for interobserver reproducibility of TFC.

TABLE 2. Intraobserver and Interobserver Errors of the TFC

<table>
<thead>
<tr>
<th></th>
<th>Intraobserver Measurements (Observation 1 minus Observation 2)</th>
<th>Interobserver Measurements (Observer 1 minus Observer 2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bias, frames</td>
<td>−0.47</td>
<td>−1.44</td>
</tr>
<tr>
<td>Mean absolute difference, frames</td>
<td>1.33±1.24</td>
<td>2.57±1.72</td>
</tr>
<tr>
<td>Relative differences, %</td>
<td>4.4±3.9</td>
<td>8.8±6.1</td>
</tr>
<tr>
<td>Coefficient of repeatability, frames</td>
<td>2.48</td>
<td>3.44</td>
</tr>
</tbody>
</table>

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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></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></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 Student’s t test or Wilcoxon 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. Similarly, the mean intraobserver 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>128±54</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>125±27</td>
</tr>
</tbody>
</table>

Data are presented as mean±SD. *P<0.001; †P=0.01.
angiographic end points between trials. Gibson et al\(^1\) found a
been claimed that TFC use could facilitate the comparison of
and quantitative method to assess coronary blood flow.\(^1\) It has
TFC has been proposed as a simple, reproducible, objective,
volume can be rather limited, and it does not necessarily
stenosis and the position of the wire. In addition, the sampling
space-dependent and may be affected by the geometry of the
Intracoronary Doppler is an another way to determine
the grade of coronary blood flow, especially for TIMI 2
graphic core laboratory and local investigator assessment of
The reproducibility of TIMI flow grade was recently evalu-
ated, and significant discrepancies existed between the angio-
ographic blood flow have been proposed,\(^4\)–\(^6\) the TIMI flow grade
Although various quantitative techniques to measure coro-
nary arteries, the dye injection at the beginning of diastole signif-
ically decreased TFC compared with the 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 coro-
nary blood flow have been proposed,\(^4\)–\(^6\) the TIMI flow grade
is the qualitative measure used in most angiographic trials.\(^7\)
The reproducibility of TIMI flow grade was recently evalu-
ated, and significant discrepancies existed between the angi-
graphic core laboratory and local investigator assessment of
the grade of coronary blood flow, especially for TIMI 2
flow.\(^1\) Intracoronary Doppler is an another way to determine
absolute velocity in coronary arteries; however, it also has
several limitations.\(^8\)–\(^11\) 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.\(^1\) It has
been claimed that TFC use could facilitate the comparison of
angiographic end points between trials. Gibson et al\(^1\) found a
mean absolute difference in TFC of 4.7±3.9 frames between 2
consecutive hand injections, which suggested good repro-
ducibility. We further demonstrated that intraobserver and
interobserver errors were low and that intraobserver and
interobserver reproducibility was good. French et al\(^12\) 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\(^2\) 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 arter-
ies. 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.\(^13\) 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.\(^14\) 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 descend-

*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.\textsuperscript{4,15} 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.\textsuperscript{16} 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.\textsuperscript{17} This is why no contrast was administered during the 90 s before coronary injections. Therefore, these flow changes did not influence our frame counts.

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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