Association of a Pulsatile Blood Flow Pattern on Coronary Arteriography and Short-Term Clinical Outcomes in Acute Myocardial Infarction

C. Michael Gibson, MS, MD,* Juhana Karha, MD,* Sabina A. Murphy, MPH,* James A. de Lemos, MD,† David A. Morrow, MD,* Robert P. Giugliano, MD, SM,* Mathew T. Roe, MD, MHS,‡ Robert A. Harrington, MD,‡ Christopher P. Cannon, MD,* Elliott M. Antman, MD,* Robert M. Califf, MD,‡ Eugene Braunwald, MD,* for the TIMI Study Group

Boston, Massachusetts; Dallas, Texas; and Durham, North Carolina

OBJECTIVES
We hypothesized that recognition of systolic flow reversal (pulsatile flow) after thrombolytic administration on coronary angiography is associated with angiographic and electrocardiogram findings reflecting impaired myocardial perfusion, as well as poorer clinical outcomes.

BACKGROUND
Reversal of systolic flow on Doppler velocity wire recordings has been associated with impaired tissue perfusion on myocardial contrast echocardiography in the setting of myocardial infarction (MI).

METHODS
Patients (n = 1,062) with a patent infarct-related artery were drawn from the Thrombolysis In Myocardial Infarction (TIMI) 10, TIMI 14, and Integrillin and Tenecteplase acute MI trials.

RESULTS
Pulsatile flow (systolic flow reversal with cessation of antegrade contrast-dye motion or frank reversal of contrast-dye motion during systole) at 60 min after fibrinolytic administration was present in 11.0% of patients. Pulsatile flow was associated with higher corrected TIMI frame counts (slower epicardial flow) (median 40.1 frames, IQ 30 of 63 vs. 30 frames, interquartile 22 of 42, p < 0.0001), a closed microvasculature (TIMI myocardial perfusion grades 0 of 1, 57.1% vs. 37.8%, p = 0.03) and less complete (>70%) ST-segment resolution (23.5% vs. 58.9%, p = 0.008). Patients with pulsatile flow had a higher risk of death or reinfarction at 30 days (10.3% vs. 5.0%, p = 0.019). After controlling for age, pulse, blood pressure, anterior MI location, epicardial flow, and creatine kinase, pulsatile flow remained associated with an increased risk of death/MI (odds ratio 3.1, p = 0.006).

CONCLUSIONS
A pulsatile pattern of flow is associated with impaired myocardial perfusion and poorer clinical outcomes independent of the velocity of antegrade flow in the epicardial artery. This simple and easily identifiable angiographic flow pattern may be useful in clinical risk stratification.
nonculprit artery is also associated with slower flow in the nonculprit artery (5).

The association of pulsatile flow in the epicardial artery and tissue perfusion on the angiogram has not been evaluated. We hypothesized that pulsatile flow after thrombolytic administration would be associated with impaired myocardial tissue-level perfusion on coronary angiography, poorer electrocardiographic ST-segment resolution, and its detection could be used as an adjunct in clinical risk stratification.

**METHODS**

Patients with suitable coronary angiograms and a patent epicardial culprit artery (TFG 2 of 3) \(n = 1,062\) were drawn from a total of 2,600 patients enrolled in the trials. Patients included were from TIMI 10A \(n = 23\), TIMI 10B \(n = 361\), TIMI 14 \(n = 369\), and Integrimi and Tenecteplase (INTEGRITI) \(n = 309\) acute MI trials. The TIMI 10A trial was a nonrandomized, open-label, dose escalation study of eight ascending doses of tenecteplase (TNK) (6). Thrombolysis in Myocardial Infarction 10B was a randomized trial comparing various doses of TNK with front-loaded rt-PA (7). The TIMI 14 trial compared abciximab plus reduced-dose thrombolytic agent versus full-dose thrombolytic agent (8,9). The INTEGRITI trial randomized acute ST-elevation MI patients prospectively to a combination of epifibatide and reduced dose tenecteplase (TNK) versus full dose TNK (10).

The presence of a pulsatile flow pattern on the angiogram at 60 min (range, 55 to 75 min) after study drug administration was assessed visually by a single experienced observer (C.M.G.) blinded to treatment assignment and clinical outcomes. A pulsatile flow pattern was defined as cessation of antegrade contrast-dye motion or frank reversal of contrast-dye motion during systole. The presence or absence of a pulsatile flow pattern was also assessed on the angiogram after PCI. The TFG, CTFC, and TIMI myocardial perfusion grade (TMPG) were assessed (1,11,12).

The magnitude of ST-segment resolution and the frequency of complete \(\geq 70\%\) ST-segment resolution on the 12-lead electrocardiogram (ECG) at 60 min compared with the baseline ECG were determined by the TIMI Electrocardiographic Core Laboratory (Boston, Massachusetts), blinded to treatment assignment and clinical and angiographic findings, using previously established techniques (13). Recurrent MI was diagnosed by local investigators, except in TIMI 14 where it was adjudicated by a clinical events committee. Recurrent MI was defined as previously described (6–10). Cardiac biomarker determination was performed at each site’s local laboratory, and the data are reported as multiples of the upper reference limit of the particular laboratory that analyzed the sample. All studies were approved by each participating center’s institutional review board, and the trials were conducted according to the principles of the Declaration of Helsinki.

**Statistical analysis.** All analyses were performed using Stata version 7.0 (Stata Corp., College Station, Texas). All continuous variable values are reported as the mean \(\pm\) SD or median where appropriate. Student \(t\) test was used for the analysis of continuous variables. The nonparametric Wilcoxon rank sum test was used for the CTFC analysis because a value of 100 was imputed to an occluded vessel. The chi-square test was used for the analysis of categorical variables when sample size was \(\geq 5\) for all cells in a table. When the sample size was <5 in a given cell of a table, Fisher exact test was used. A multivariate logistic regression model was used for the analysis of death or MI by 30 days. A Kaplan-Meier curve was generated for recurrent MI through 30-day follow-up by pulsatile flow pattern. The log-rank test was used to test the equality of the survivor function by pulsatile flow pattern.

**RESULTS**

A total of 1,062 patients with an open epicardial culprit artery (TFG 2 or 3) on the angiogram 60 min after study drug administration were included in the analysis. Pulsatile flow was present in 117 patients (11.0%), and the remainder (945, 89.0%) had normal antegrade culprit coronary artery flow during the entire cardiac cycle. Patients with pulsatile flow were younger and had a higher heart rate on presentation (Table 1). Pulsatile flow was more frequent if the culprit artery was the left anterior descending (LAD) artery and if angiographically apparent thrombus was present. Patients treated with combination therapy of platelet glycoprotein IIb/IIIa inhibitor plus reduced dose fibrinolytic agent tended to less frequently have pulsatile flow compared with patients treated with fibrinolytic monotherapy (9.5%, 47 of 494 vs. 12.4%, 70 of 567, \(p = 0.14\)). Patients with pulsatile flow tended to have higher median peak creatine kinase values compared with patients with nonpulsatile flow (Table 1).

The incidence of TIMI grade 2 flow was increased among patients with pulsatile flow on the 60-min angiogram (Fig. 1). Likewise, the median CTFC among patients with pulsatile flow pattern was higher (slower flow) compared with patients with nonpulsatile flow pattern (Fig. 2). Furthermore, the presence of pulsatile flow was associated...
with a higher incidence of closed microvasculature compared with nonpulsatile flow (TMPG 0 of 1, 57.1%, 20 of 35 vs. 37.8%, 113 of 299, \( p < 0.03 \), Fig. 3). All angiographic analyses (TFG, CTFC, TMPG) were similar for both LAD and non-LAD culprit arteries. Pulsatile flow resolved in 66.7% (24 of 36) patients after the performance of PCI. On the other hand, 4.1% (12 of 296) of the patients who had nonpulsatile flow before PCI developed new pulsatile flow after PCI.

The incidence of complete (\( \geq 70\% \)) ST-segment resolution on a static 12-lead ECG 60 min after study drug administration was reduced among patients with pulsatile flow (23.5%, 4 of 17 vs. 58.9%, 86 of 146, \( p = 0.008 \) by Fisher exact test, Fig. 4). Likewise, the median extent of ST-segment resolution at 60 min was lower among patients with pulsatile flow (median 55.7%, IQ range 40/68%, \( n = 17 \) vs. median 79.1%, IQ 56/93%, \( n = 146 \), \( p = 0.011 \), Fig. 4).

A pulsatile pattern of coronary blood flow on the 60-min angiogram was associated with a higher incidence of death or recurrent MI at 30 days compared with patients with nonpulsatile flow: 10.3% (12 to 117) versus 5.0% (47 of 942), \( p = 0.019 \) (Fig. 5). A nonsignificant trend for this association persisted even among patients who subsequently underwent a PCI (7.1%, 3 of 42 vs. 3.0%, 10 of 334, \( p = 0.17 \) by Fisher exact test). The presence of a pulsatile flow pattern on the 60-min angiogram remained independently associated with a higher incidence of 30-day death or recurrent MI (odds ratio, 3.1, \( p = 0.006 \)) after adjusting for age, heart rate, systolic blood pressure, LAD culprit location, TFG 3 epicardial blood flow, and peak creatine kinase. This composite end point was driven largely by the risk of recurrent MI, which differed significantly by pulsatile pattern (pulsatile 7.8%, 9 of 116 vs. nonpulsatile 2.8%, 26 of 925, \( p = 0.005 \); Fig. 6) rather than by death (pulsatile 2.6%, 3 of 117 vs. nonpulsatile 2.4%, 23 of 941, \( p = 1.0 \) by Fisher exact). In a multivariate model adjusting for previously identified correlates of angiographic reocclusion (TFG, LAD, thrombus, percent diameter stenosis, eccentric lesion, ulcerated lesion, and collaterals) (14) and clinical reinfarc-

### Table 1. Baseline Clinical and Angiographic Characteristics

<table>
<thead>
<tr>
<th>Variables</th>
<th>Pulsatile Flow (( n = 117 ))</th>
<th>Nonpulsatile Flow (( n = 945 ))</th>
<th>( p ) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yrs</td>
<td>54.9 (± 10.9)</td>
<td>58.7 (± 10.7)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Male gender, %</td>
<td>84.6</td>
<td>76.8</td>
<td>0.056</td>
</tr>
<tr>
<td>Hypertension, %</td>
<td>31.6</td>
<td>32.3</td>
<td>0.88</td>
</tr>
<tr>
<td>Diabetes, %</td>
<td>13.7</td>
<td>13.6</td>
<td>0.98</td>
</tr>
<tr>
<td>Current smoker, %</td>
<td>50.4</td>
<td>50.5</td>
<td>0.98</td>
</tr>
<tr>
<td>Prior MI, %</td>
<td>9.4</td>
<td>13.4</td>
<td>0.22</td>
</tr>
<tr>
<td>Heart rate, beats/min</td>
<td>78.9 (± 16.9)</td>
<td>75.3 (± 17.2)</td>
<td>0.03</td>
</tr>
<tr>
<td>SBP, mm Hg</td>
<td>138.4 (± 22.1)</td>
<td>140.0 (± 21.5)</td>
<td>0.44</td>
</tr>
<tr>
<td>Time to therapy, h</td>
<td>3.3 (± 1.8)</td>
<td>3.5 (± 3.1)</td>
<td>0.82</td>
</tr>
<tr>
<td>Thrombus, %</td>
<td>29.8</td>
<td>20.8</td>
<td>0.027</td>
</tr>
<tr>
<td>LAD location, %</td>
<td>69.2</td>
<td>32.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Multivessel disease, %</td>
<td>41.4</td>
<td>55.3</td>
<td>0.005</td>
</tr>
<tr>
<td>Median peak CK/ULN</td>
<td>9.4 (2.9, 20.5)</td>
<td>7.2 (3.5, 13.4)</td>
<td>0.12</td>
</tr>
<tr>
<td>LVEF, %</td>
<td>56.8 (± 15.2)</td>
<td>58.2 (± 15.4)</td>
<td>0.47</td>
</tr>
</tbody>
</table>

Age, heart rate, SBP, time to therapy, and LVEF values are reported as mean (± SD). Median peak CK values are reported as median (25th percentile, 75th percentile).

CK = creatine kinase; LAD = left anterior descending; LVEF = left ventricular ejection fraction; MI = myocardial infarction; SBP = systolic blood pressure; ULN = upper limit of normal.

Figure 1. (A) Incidence of 60-min Thrombolysis In Myocardial Infarction (TIMI) grade 2 flow among patients with pulsatile versus nonpulsatile flow pattern. (B) Incidence of pulsatile flow among patients with TIMI flow grade (TFG) 2 and grade 3 at 60 min. PCI = percutaneous coronary intervention.

Figure 2. (A) Incidence of 60-min Thrombolysis In Myocardial Infarction (TIMI) grade 2 flow among patients with pulsatile versus nonpulsatile flow pattern. (B) Incidence of pulsatile flow among patients with TIMI flow grade (TFG) 2 and grade 3 at 60 min. PCI = percutaneous coronary intervention.
tion (age and performance of adjunctive PCI) (15), a pulsatile flow pattern remained associated with recurrent MI by 30 days (odds ratio, 5.2; \( p = 0.001 \)). Similar results for pulsatile flow were observed when CTFC was included in the model instead of TFG 3 (odds ratio, 2.8; \( p = 0.017 \) for death/MI and odds ratio, 3.7; \( p = 0.015 \) for MI).

**DISCUSSION**

This study demonstrates that a pulsatile pattern of coronary blood flow is associated with impaired myocardial perfusion and poorer clinical outcomes. Prior studies have demonstrated that impaired epicardial blood flow, LAD culprit artery location, and multivessel or left main disease are all angiographic variables that are associated with poorer clinical outcomes after fibrinolytic administration for acute STEMI (1,14–18). This study extends these observations to demonstrate that a pulsatile pattern of epicardial blood flow is also associated with adverse clinical outcomes. A pulsatile flow pattern was associated with higher incidence of death or recurrent MI at 30 days even after adjusting for other confounding variables. In a multivariate model adjusting for previously identified correlates of angiographic reocclusion (14) (TFG, LAD, thrombus, percent diameter stenosis, eccentric lesion, ulcerated lesion, or collaterals) and clinical reinfarction (15) (PCI and age), the presence of pulsatile flow was associated with a highly significant fivefold increase in the risk of reinfarction. This simple and easily identifiable angiographic flow pattern may be useful in clinical risk stratification.

Pulsatile flow was associated with impaired myocardial perfusion as assessed by the TMPG on the angiogram and by reduced ST-segment resolution. Distal embolization and the release of vasoconstrictors may explain, at least in part, the impairment in myocardial perfusion. Indeed, visible intracoronary thrombus was more commonly present among arteries with a pulsatile flow pattern. Combination therapy

**Figure 2.** (A) Median 60-min corrected Thrombolysis In Myocardial Infarction (TIMI) frame count (CTFC) with interquartile range for patients with pulsatile versus nonpulsatile flow pattern. \( p \) value from Wilcoxon rank-sum test. (B) Incidence of pulsatile flow among patients with above versus below median (30.6 frames) (CTFC) at 60 min.
with platelet glycoprotein IIb/IIIa inhibitors and reduced-dose thrombolytic agents have been associated with a reduction in thrombus burden (19), and it is notable that the administration of glycoprotein IIb/IIIa inhibitors tended to be associated with a reduced incidence of pulsatile flow on the 60-min angiogram.

Pulsatile flow was also observed more frequently among patients in whom the LAD was the culprit vessel. The infarcts in these patients are characterized by a greater volume of myocardium distal to the stenosis (4), a thicker myocardium compared with the right coronary artery, and higher left ventricular filling pressures compared with right ventricular filling pressures. As a result of this, it could be speculated that the greater myocardial edema and consequent extrinsic compression of the capillary network as well as the higher left ventricular filling pressures that develop among patients with anterior infarction may play a role in pulsatile flow. Indeed, systolic flow reversal occurs when the downstream microvascular pressure during systole exceeds the upstream epicardial artery pressure. While pulsatile flow is associated with larger infarct sizes (larger peak creatine kinase levels), the directionality of the causal relationship is unknown; it is not clear if larger myocardial infarctions cause pulsatile flow, or if pulsatile flow (a surrogate for heightened downstream microvascular resistance), in turn, causes larger myocardial infarctions.

Figure 3. (A) Incidence of TIMI myocardial perfusion grade (TMPG) 0 to 1 at 60 min among patients with pulsatile versus nonpulsatile flow pattern. (B) Incidence of pulsatile flow among patients with TMPG 0 to 1 versus TMPG 2 to 3 at 60 min.

Figure 4. (A) Incidence of complete (≥70%) ST-segment resolution (ST Res) at 60 min among patients with pulsatile versus nonpulsatile flow pattern. p value from Fisher exact test. (B) Incidence of pulsatile flow among patients with complete (≥70%) versus incomplete ST Res at 60 min. p value from Fisher exact test. (C) Median ST Res with interquartile range at 60 min among patients with pulsatile versus nonpulsatile flow pattern.
Among patients with pulsatile flow before PCI, flow reversal was resolved in 66.7% of patients after the performance of PCI. Previously we have reported that flow in the nonculprit artery improves after PCI of the culprit artery. There may be shared abnormalities in the downstream microvasculature, some of which may be mediated by heightened neuroadrenergic tone to maintain perfusion pressure. This tone is relieved after dilation of the stenosis. Finally, if the pressure beyond the stenosis is low, heightened pressure during systole may cause flow to reverse in this low pressure system.

**Study limitations.** This is a retrospective analysis, and unidentified confounders may have contributed to the findings. Strict enrollment criteria are used in clinical trials, and the results observed here might not be applicable to all patients in clinical practice.

**Conclusions.** Independent of the velocity of antegrade flow in the epicardial artery, a pulsatile pattern of flow with retrograde or reversed flow during systole is associated with impaired myocardial perfusion and poorer clinical outcome. This simple and easily identifiable angiographic flow pattern may be useful in clinical risk stratification.

**Reprint requests and correspondence:** Dr. C. Michael Gibson, Director TIMI Data Coordinating Center, 350 Longwood Avenue, 1st Floor, Boston, Massachusetts 02115. E-mail: mgibson@perfsue.org.

**REFERENCES**


