RELATIONSHIPS OF THE THROMBOLYSIS IN MYOCARDIAL INFARCTION FRAME COUNT WITH CLINICAL, HEMODYNAMIC AND MEDICINE VARIABLES IN SYNDROME X PATIENTS

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SUMMARY

Background: The thrombolysis in myocardial infarction (TIMI) frame count was reported to reflect coronary blood flow and have prognostic value. However, such data in syndrome X was lacking. The purpose of this study was to examine the prognostic value of the TIMI frame count in syndrome X patients, compared with the normal population.

Methods: The TIMI frame count was measured in 2,049 consecutive patients referred for coronary angiography from March 2003 to February 2005.

Results: Among 308 patients with normal coronary angiograms, 44 undergoing the procedure for electrophysiologic studies or valvular heart disease surveys other than angina were designated normal controls. Another 155 patients with positive stress test results were diagnosed as syndrome X. Comparisons of the two groups showed that the syndrome X patients had higher frame counts in the left anterior descending artery (40.9±15.7 vs. 47.8±25.4; p<0.05) and left circumflex artery (35.2±11.7 vs. 42.0±18.7; p<0.05). A similar trend was found in the right coronary artery (29.3±13.5 vs. 31.9±15.9; p=0.2). The TIMI frame count in each artery of the syndrome X group was related to the patients’ variables (sex, age, and body mass index), clinical variables (medication use, diabetes, hypertension, hypercholesterolemia, smoking, and family history), and hemodynamic variables (aortic systolic blood pressure and left ventricular end-diastolic pressure). By multivariate analysis, the TIMI frame counts in all arteries were significantly higher in women and lower with angiotensin-converting enzyme inhibitor (ACEI) use (both p<0.05). The frame count in the left anterior descending was associated with diuretics use (p<0.05).

Conclusion: Our TIMI frame count data confirm the presence of slow coronary flow in syndrome X patients, especially women. ACEI use shortens the counts in these patients, suggesting that ACEIs have the potential to correct the underlying hemodynamic defects in such patients. [International Journal of Gerontology 2008; 2(3): 109–114]

Key Words: microvascular dysfunction, syndrome X, TIMI frame count

Introduction

Although the thrombolysis in myocardial infarction (TIMI) flow grade is a widely used qualitative measurement in angiographic trials, it is limited by its subjective and categorical nature. In contrast, the TIMI frame count (TFC) is a reproducible, objective and quantitative index of coronary flow1,2. The TFC is derived by counting the number of cineangiographic frames that elapse between the leading edge of the contrast injection entering the proximal portion of a coronary artery and arriving at a predetermined distal landmark1. Recent reports showed that the TFC is correlated with coronary flow reserve3, endothelial function4, stenosis severity in the infarct artery after infarction, infarct zone regional wall motion5, and adverse clinical outcomes6–8. In addition,
technical factors, such as the contrast injection rate and catheter size, were reported to have minimal effects on the TFC. Therefore, the TFC is useful for risk stratification and decision making for patients with coronary artery disease.

Among patients undergoing coronary angiographic examination, cardiac syndrome X (triad of angina-like chest pain, positive stress test, and angiographically normal coronary arteries) is quite commonly seen. This disorder has been linked to endothelial dysfunction of the coronary microvasculature. Although the TFC has been used to assess microvascular dysfunction, such data were limited for syndrome X. Therefore, the aim of this study was to examine the TFC in patients with syndrome X and evaluate its relationships with clinical, angiographic, and hemodynamic variables.

Patients and Methods

Patient population
From March 2003 to February 2005, 2,049 patients underwent coronary angiography in the catheterization laboratory of Mackay Memorial Hospital. Coronary angiography was performed using a Philips Integris BH 5000 (Philips, Hamburg, Germany) equipped with a cardiovascular angiography analysis system (CAAS II). Patients were included in this study if they had a normal coronary angiogram, i.e., no evidence of any obstructive coronary artery disease, coronary ectasia or major coronary spasm. Among the 318 patients with normal coronary angiograms, 44 patients who underwent the procedure for electrophysiologic studies (34 patients) or valvular heart disease surveys (10 patients) other than angina were designated normal controls. Another 119 patients were excluded for a lack of angina symptoms or negative stress tests. The remaining 155 patients with positive stress tests (transient perfusion defect in a thallium 201 myocardial perfusion scan, transient >1-mm ST-segment depression during an exercise treadmill test, or both) and clinical angina or angina-like chest pain were designated the syndrome X group. All case records were reviewed for a detailed history, physical examination, biochemistry parameters, and findings of electrocardiograms and/or echocardiographic examination.

TIMI frame counts
The numbers of cineframes were measured using a frame counter on the cineviewer. The numbers of cineangiographic frames were recorded at 30 frames per second. In general, the TFCs in the left anterior descending artery (LAD) and left circumflex artery (LCX) were assessed in a right anterior oblique projection with caudal angulation while that in the right coronary artery (RCA) was assessed in a left anterior oblique projection with cranial angulation. The first frame used for evaluating each TFC was the first frame in which the dye fully entered the artery with antegrade motion and the last frame was defined as the frame when the dye first entered the distal landmark branch as reported previously. The landmarks included the distal bifurcation of the LAD (i.e., the mustache, pitchfork or whale’s tail), the distal branch of the lateral left ventricular (LV) wall artery with the longest distance from the coronary ostium of the LCX, and the first branch of the posterolateral artery of the RCA.

Definitions of variables
The clinical variables analyzed included age, sex, body mass index (BMI), hypertension (documented hypertension, all with medical control), diabetes mellitus (hemoglobin A1c >7% or postprandial sugar >200 mg/dL), hyperlipidemia (serum total cholesterol >230 mg/dL or triglyceride >165 mg/dL), family history of premature cardiovascular disease, and smoking. The hemodynamic variables examined were LV end-diastolic pressure (LVEDP), LV ejection fraction, and systolic and diastolic blood pressure. Medicine use included β-blockers, statins, calcium channel blockers (CCBs), nitrate, angiotensin-converting enzyme inhibitors (ACEIs), and diuretics.

Statistical analysis
The TFCs were compared in each artery between the groups using a t test and in the syndrome X group by analysis of variance. Univariate analysis of all independent variables with the TFC in each artery was performed using the F distribution and curve regression (either logarithmic or logistic regression), primarily to determine which variables should enter into the multivariable curve regression.

Results

Clinical characteristics
As shown in Table 1, the clinical variables of sex, age, BMI, diabetes mellitus, smoking, family history of
premature cardiovascular disease, elevated cholesterol, angiographic variables of aortic systolic and diastolic pressure, LVEDP, LV ejection fraction, and other medicine use were similar between the study groups except for hypertension, which was more common in the syndrome X group.

**TIMI frame counts**

Table 2 shows the TFCs in the three major coronary arteries. Comparisons of the two groups demonstrated that the syndrome X patients had higher TFCs in the LAD (47.8 ± 25.4 vs. 40.9 ± 15.7; \( p < 0.05 \)) and LCX (42.0 ± 18.7 vs. 35.2 ± 11.7; \( p < 0.05 \)) compared with the controls. A similar trend was found in the RCA (31.9 ± 15.9 vs. 29.3 ± 13.5; \( p = 0.2 \)).

**Univariate analysis**

Table 3 shows the results of the univariate analysis for each of the three major epicardial arteries in the syndrome X patients. The TFC in each artery of the syndrome X group was related to the patients’ variables (sex, age, and BMI), clinical variables (medication use, diabetes, hypertension, hypercholesterolemia, smoking, and family history), and hemodynamic variables (aortic systolic blood pressure and LVEDP), except for aortic diastolic pressure and CCB use. The crucial variables that differed significantly for all three arteries were sex, hypertension, BMI, and use of either ACEIs or diuretics.

**Multivariate analysis**

The results of the multivariable curve regression analysis are shown in Table 4. In all three major epicardial
coronary arteries, sex and ACEIs use were significantly associated with the TFC in syndrome X patients (both \( p < 0.05 \)). In the LAD, the TFC was also associated with diuretics use \( (p < 0.05) \).

**Discussion**

The results of this study revealed that patients with syndrome X had higher TFCs in all three coronary arteries. In addition, in patients with syndrome X, the TFCs were even higher in females, and decreased by treatment with ACEIs or diuretics. These interesting findings indicate the presence of slow coronary flow in patients with syndrome X and suggest that the underlying pathophysiology of syndrome X involves elevation of microvascular resistance.

Although TFC data were initially used for evaluating both acute and stable coronary artery disease\(^ {16} \), recent reports have shown that the TFC may be an index of coronary microvascular behavior, which reflects vascular resistance\(^ {17} \). It is established that a large proportion of patients with syndrome X have both abnormal vasodilatory coronary blood flow responses and increased sensitivity of the coronary microcirculation to vasoconstrictor stimuli (so-called microvascular angina)\(^ {18,19} \). The higher TFCs in patients with syndrome X observed in the present study are consistent with the idea that coronary microcirculation dysfunction contributes to the development of syndrome X.

Endothelial dysfunction in syndrome X appears to be multifactorial and linked to risk factors such as smoking, obesity, hypercholesterolemia, and inflammation\(^ {11} \). In the present study, univariate analysis showed that hypertension, BMI, and use of ACEIs or diuretics were powerful predictors of coronary flow in patients with syndrome X. These findings suggest that many metabolic, neurohumoral and hemodynamic factors can affect coronary vascular resistance and, thus, alter the TFC\(^ {17,20,21} \). Multivariate analysis showed that the use of ACEIs in patients with syndrome X was associated with lower TFCs, consistent with current concepts that ACEIs are beneficial for patients with this disorder\(^ {15} \). However, we did not observe similar effects with CCBs, \( \beta \)-blockers, nitrate, and statins, which were also reported to be beneficial\(^ {13} \). Our findings that the TFCs in all arteries were higher in female syndrome X patients may help to explain why women are more vulnerable to this disorder.

### Table 3. Univariate analysis of the three major epicardial arteries

<table>
<thead>
<tr>
<th>Variable</th>
<th>LAD</th>
<th>LCX</th>
<th>RCA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
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<td>&lt;0.05</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Age</td>
<td>NS</td>
<td>&lt;0.05</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Hypertension</td>
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<td>&lt;0.05</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Aortic systolic pressure</td>
<td>&lt;0.05</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Smoking</td>
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<td>&lt;0.05</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Diabetics mellitus</td>
<td>NS</td>
<td>&lt;0.05</td>
<td>NS</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>NS</td>
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<td>&lt;0.05</td>
</tr>
<tr>
<td>Family history of premature cardiovascular disease</td>
<td>&lt;0.05</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Body mass index</td>
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<td>&lt;0.05</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>LV end-diastolic pressure</td>
<td>NS</td>
<td>NS</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Medication</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>( \beta )-blockers</td>
<td>NS</td>
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<td>&lt;0.05</td>
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<tr>
<td>CCBs</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Statins</td>
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<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>ACEIs</td>
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<td>&lt;0.05</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Diuretics</td>
<td>&lt;0.05</td>
<td>&lt;0.05</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>

LAD = left anterior descending artery; LCX = left circumflex artery; RCA = right coronary artery; NS = not significant; CCB = calcium channel blocker; ACEI = angiotensin-converting enzyme inhibitor.

### Table 4. Multivariate analysis of the thrombolysis in myocardial infarction frame counts in the three major epicardial arteries

<table>
<thead>
<tr>
<th>Variable</th>
<th>( R )</th>
<th>( p )</th>
</tr>
</thead>
<tbody>
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<td>LAD</td>
<td></td>
<td></td>
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<tr>
<td>Sex</td>
<td>0.339</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Diuretics</td>
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<tr>
<td>ACEIs</td>
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<td>&lt;0.05</td>
</tr>
<tr>
<td>LCA</td>
<td></td>
<td></td>
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<tr>
<td>Sex</td>
<td>0.315</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>ACEIs</td>
<td>0.118</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>RCA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td>0.057</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>ACEIs</td>
<td>0.391</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>

*Variables entered into the multivariate analysis were sex, hypertension, smoking, aortic systolic pressure, diabetes mellitus, hyperlipidemia, age, premature family history of premature cardiovascular disease, left ventricular end-diastolic pressure, \( \beta \)-blockers, statins, ACEIs, calcium channel blockers, and diuretics. LAD = left anterior descending artery; ACEIs = angiotensin-converting enzyme inhibitors; LCX = left circumflex artery; RCA = right coronary artery."
**Normal TFCs in Taiwan**

Our data for the TFCs in three coronary arteries were higher than prior values reported by Gibson et al.\(^1\) To the best of our knowledge, no such data have previously been reported for Taiwan. In the report by Gibson et al.\(^1\), the TFCs for the LAD were corrected by dividing by 1.7 to account for its longer length. This ratio is similar to the mean ratio of 1.55 predicted using a three-dimensional vector algebra method\(^2\). In our study, the equivalent ratio was lower than previously reported ratios.

One possibility for the discrepancy may be the difference in age, because the patients in the present study were older than those in the previous reports. Another possibility is the relatively small numbers of patients, and the fact that a substantial portion of the normal control patients had underlying diseases and were taking medication. For example, over 30% of the patients in the normal control group were being treated with ACEIs or diuretics, or statins for concomitant hypertension or hyperlipidemia, respectively. These concomitant diseases and the medications may affect the TFCs. Because the TFCs of the three coronary arteries varied widely in the present study, we did not use corrected TFCs. Further large-scale trials are necessary to clarify the normal corrected TFCs in Taiwan.

**Sex differences in TFCs of patients with syndrome X**

Our findings that female syndrome X patients had higher TFCs in all three coronary arteries than male syndrome X patients are consistent with the prevalence of this syndrome, because it is more prevalent in females. Furthermore, these findings may explain why women are more vulnerable to this disorder. In postmenopausal women with syndrome X, estrogen deficiency has been suggested as a pathogenic agent, and acting via endothelium-dependent and -independent mechanisms\(^3\). This idea is supported by a report that impaired endothelial function in postmenopausal women with syndrome X is improved by administration of 17β-estradiol\(^4\).

**Effects of medicines on the TFCs of syndrome X patients**

Recent evidence suggests that impaired endothelial nitric oxide bioavailability may exist in a significant portion of patients with syndrome X\(^21,25,26\). ACEIs were reported to clinically improve myocardial ischemia in syndrome X patients\(^21,25\). However, conventional anti-ischemic treatments, such as β-blockers and nitrate, were found to have poor effectiveness in syndrome X patients\(^26\). A recent report from Taiwan showed that treatment with enalapril, an ACEI, improved coronary microvascular function by balancing endothelial nitric oxide metabolism in syndrome X patients\(^21\). In the present study, we also found that ACEI use was beneficial for patients with syndrome X. In contrast, although statin therapy was reported to be beneficial in patients with syndrome X\(^27\), treatment with statins was not found to achieve the same beneficial effects in the present study. Regarding diuretics, the TFC in the LAD was higher with diuretic use in the present study. Diuretics are known to alter ventricular preload, which is reported to affect coronary flow reserve, therefore suggesting that diuretics may affect the TFC\(^20\).

In conclusion, our TFC data confirm the presence of slow coronary flow in syndrome X patients, especially women. In addition, use of ACEIs shortens the TFCs in these patients, suggesting that ACEIs can be prescribed for such patients.

**Acknowledgments**

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**References**


