Prognostic Value of Noninvasive Markers of Coronary Reperfusion Compared to TIMI 3 Flow in Patients Treated With Primary Angioplasty

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Introduction and objectives. The aim of this study was to compare the prognostic value of TIMI 3 flow versus noninvasive markers of coronary artery reperfusion on the outcome of patients with a recent acute myocardial infarction (AMI) treated with primary angioplasty.

Patients and method. We analyzed 172 consecutive patients with AMI and ST-segment elevation, who were treated with primary angioplasty within 12 hours of admission. Mean age was 61±13 years, 77% were men, and 56% had a history of previous AMI.

Results. In-hospital mortality was 3.6%; 16.6% developed heart failure, and 11.1% had complex arrhythmias during their hospital stay. The noninvasive criterion for successful reperfusion was the presence of two or more markers of reperfusion based on ECG changes or CK levels after angioplasty. Reperfusion was successful in 87.7% of the patients, and TIMI 3 flow was achieved in 87%. There was no significant concordance between the two methods (kappa index =0.012). Multivariate analysis showed that both successful reperfusion (OR=0.028; 95% CI, 0.003-0.268) and TIMI 3 flow (OR=0.104; 95% CI, 0.019-0.563) were protective for in-hospital mortality. However, in the multivariate analysis only successful reperfusion was a protective factor for heart failure and complex arrhythmias.

Conclusion. Our findings confirm that both TIMI 3 flow and successful coronary reperfusion evaluated noninvasively show independent prognostic value in patients with AMI treated with primary angioplasty. Noninvasive markers of coronary reperfusion should be used as complementary to angiography in these patients.

Key words: Myocardial infarction. Coronary angioplasty. Reperfusion.
Palabras clave: Infarto de miocardio. Angioplastia coronaria. Reperfusión.

INTRODUCTION

Primary angioplasty has proven to be the best therapeutic option for acute myocardial infarction (AMI), providing early, optimal reestablishment of coronary flow and resulting in a significant reduction in mortality as compared to thrombolytic treatment. The success of primary angioplasty is attributed to its ability to promptly restore optimal coronary flow (TIMI grade 3) after arterial recanalization, which is associated with a better immediate and mid-term prognosis. Nevertheless, several investigators using noninvasive techniques have demonstrated that restoration of coronary flow does not guarantee optimal tissue reperfusion. This may be a consequence of injury to the microcirculation caused by arterial embolization and occlusion with particles of fragmented thrombus, or a result of alterations in tissue metabolism due to prolonged ischemia. Failed myocardial reperfusion because of microvascular obstruction could, in turn, lead to failed recovery of contractile function in the infarcted region and a poorer prognosis.

In an earlier study we reported that satisfactory myocardial reperfusion, as assessed by noninvasive markers, such as resolution of ST-segment elevation, early T-wave inversion, and time to peak enzyme levels, is associated with a significantly lower risk for death and in-hospital or mid-term mortality in patients with myocardial infarction treated with thrombolysis and primary angioplasty.

In this study we prospectively compared the prognostic value of noninvasive indicators of coronary perfusion with TIMI grade 3 flow for the appearance of complications at short- and mid-term in patients with AMI treated by primary angioplasty.

PATIENTS AND METHODS

Patients

The study included 172 patients consecutively admitted for AMI within 12 hours of onset and undergoing primary angioplasty at the Hospital Clínico de la Universidad Católica de Chile, during the period of June 1997 to December 2000. All the patients studied had anginal chest pain of more than 30 minutes’ duration and ST-segment elevation ≥1 mm in two or more contiguous electrocardiograph leads. Patients with complete bundle branch block or cardiogenic shock were excluded. At emergency room admission, all patients received 500 mg of aspirin and were intravenously treated with heparin to reach an activated coagulation time of approximately 300 s during angioplasty. In patients receiving an intracoronary stent, clopidogrel, or ticlopidine was continued for 4 weeks. Beta-blockers and angiotensin-converting enzyme were used in the postinfarction period following the criteria of evidence-based medicine.

Clinical Variables

The following variables were analyzed in all patients: a) coronary risk factors: hypertension, dyslipidemia, diabetes mellitus, smoking, and family history of coronary disease, which was considered positive in cases of myocardial infarction before the age of 55 in a direct family member; b) clinical and demographic characteristics: age, sex, personal history of coronary disease, location, and time of evolution of the infarction, heart rate and systolic blood pressure on admission; c) markers of myocardial injury: total creatine kinase (CK) on admission and at 6, 12, and 24 h; d) angiographic characteristics: culprit coronary artery, post-angioplasty TIMI flow, number of vessels with ≥70% stenosis, and stent use.

Noninvasive Indicators of Myocardial Reperfusion

At hospital admission, all patients underwent electrocardiography and determinations of CK and CK MB fraction (CK-MB). The electrocardiogram was recorded at baseline and repeated at 90 min. after angioplasty. Further electrocardiograms were performed and blood samples were taken for cardiac enzyme determinations at 6, 12, and 24 h of evolution. The electrocardiogram on admission was used as a reference to estimate the magnitude of maximum ST-segment elevation. This was calculated to eight-hundredths of a second after the J point in the lead with the most prominent elevation. T-wave inversion in the leads related to the infarction was defined as a tracing >1 mm below the isoelectric line (TP segment). Timing to peak CK value was assessed. Following previously

ratio [OR] = 0,028; intervalo de confianza [IC] del 95%, 0,003-0,268, y OR = 0,104; IC del 95%, 0,019-0,563, respectivamente). Sin embargo, sólo la reperfusión exitosa resultó ser protectora frente a la insuficiencia cardíaca y las arritmias complejas en la evolución intrahospitalaria y en la mortalidad a medio plazo al ajustar por ambos criterios en el análisis multivariado.

Conclusion. Se confirma que tanto el flujo TIMI 3 como la reperfusión coronaria exitosa evaluada a través de indicadores no invasivos tienen un valor pronóstico independiente en pacientes con IAM tratados con angioplastia primaria. Sin embargo, la reperfusión coronaria exitosa resultó ser un indicador de pronóstico independiente para la mortalidad intrahospitalaria y a medio plazo, el desarrollo de insuficiencia cardíaca y arritmias complejas. Los indicadores no invasivos de reperfusión coronaria debieran emplearse en forma complementaria a la angiografía en estos pacientes.

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published criteria, the patients were classified into two groups: a) successful myocardial reperfusion, when at least two of the following three criteria were met: a decrease of more than 50% of the pretreatment ST-segment elevation within the first 90 min, T-wave inversion in the infarct-related echocardiograph leads within the first 24 h, and peak CK values within the first 12 hours after the procedure, b) failed myocardial reperfusion, when at least 2 of the following 3 criteria were met: persistent ST-segment elevation, positive T-wave in the infarct-related leads, and peak CK value more than 12 hours after angioplasty. Asymptomatic ST-segment re-elevation and positive T-wave within 24 hours after the procedure were also considered criteria of failed reperfusion.

**Criteria of Successful Angioplasty and TIMI Coronary Flow**

In keeping with the TIMI group classification, post-angioplasty coronary flow was classified into grade 0, absence of flow beyond the occlusion, grade 1, contrast opacification of the coronary artery, but without distal filling, grade 2, slow opacification of the entire coronary artery and grade 3, normal coronary flow. Angioplasty was considered successful when TIMI 3 flow was obtained and residual stenosis was less than 30%.

**Analysis of Post-AMI Events**

1. In-hospital cardiovascular events: death, development of heart failure (Killip class ≥2), and presence of complex cardiac arrhythmias (atrial fibrillation, ventricular tachycardia, ventricular fibrillation, new bundle branch blocks, and second- or third-degree atrioventricular block) since admission.

2. Cardiovascular events at 6 months’ evolution (follow-up by direct clinical visits, consultation with attending physicians or by telephone): death, development of heart failure, rehospitalization due to heart failure, and recurrent angina.

**Statistical Analysis**

Data are presented as mean ± standard deviation (SD) and percentage. For the univariate analysis we used the chi-square test and the Fisher exact test to compare categorical variables. Continuous variables were analyzed with the Student t test. Agreement between noninvasive reperfusion and successful angioplasty was analyzed using the Kappa index. The multivariate analysis of in-hospital events (death, heart failure, atrial fibrillation, atrioventricular block, or ventricular tachycardia) and mid-term complications (development of heart failure, hospitalization for heart failure, or recurrent angina) was carried out by logistic regression. The multivariate analysis included all the clinically relevant variables (age, sex, coronary risk factors, location of the infarct, time of evolution, heart rate, arterial pressure at admission, CK at admission, number of vessels with ≥70% stenosis, post-angioplasty TIMI flow, total CK peak value, successful or failed reperfusion) that had a P-value of ≤0.05 in the univariate analysis. In addition, a multivariate analysis was performed to independently analyze only TIMI 3 flow or only successful reperfusion with the other confounding variables. The Cox proportional hazards model was used for the analysis of mid-term mortality.

**RESULTS**

Primary angioplasty was performed in the 172 patients in this series and TIMI 3 flow was achieved in 150 (87%). Successful reperfusion according to the noninvasive markers was present in 151 (87.7%) patients and failed reperfusion in the remaining 21 patients. Table 1 shows the demographic, clinical and angiographic characteristics of the patients. A total of 139 patients had both TIMI 3 flow and successful reperfusion, but the Kappa index was only 0.012 (nonsignificant), indicating that there was no agreement between the 2 methods.

Tables 2 and 3 show the characteristics of the patients according to TIMI 3 flow or successful reperfusion. There was a significantly higher percentage of cases of anterior infarction among the patients with failed perfusion.

**Analysis of In-Hospital Events**

In-hospital mortality. In-hospital mortality was 3.65% overall, 0.79% in the group of patients with successful reperfusion and 22.2% in the group with failed perfusion (P<.001).

The conditions associated with a significantly higher risk of in-hospital mortality in the univariate logistic regression analysis included advancing age, age over 70 years and total CK peak level (P=.05). In the multivariate analysis the factors significantly protective against in-hospital mortality were post-angioplasty TIMI 3 flow (OR=0.104; 95% CI, 0.019-0.563) and successful reperfusion (OR=0.028; 95% CI, 0.003-0.268) (Table 2). When the 2 reperfusion indicators, TIMI 3 flow and noninvasive markers, were introduced in the same model adjusted for confounding variables, both TIMI 3 flow (OR=0.062; 95% CI, 0.004-0.846) and noninvasive markers (OR=0.026; 95% CI, 0.02-0.373) continued to be associated with a lower risk of in-hospital death. Advancing age persisted as a risk factor at the limit of significance (OR=1.0004; 95% CI, 1.000-1.611). Table 4 shows the results of the independent analysis of TIMI 3 flow and...
successful reperfusion; both criteria are confirmed to be significant protectors against in-hospital mortality.

**In-hospital heart failure.** Among the total, 16.6% of patients developed in-hospital heart failure. In the univariate logistic regression analysis, the significant predictive factors for in-hospital heart failure included age (OR=1.05; 95% CI, 1.014-1.087), age over 70 years (OR=5.11; 95% CI, 2.11-12.36) and total CK peak value (OR=1.000; 95% CI, 1.0001-1.0004). The significant protective factors against in-hospital heart failure included successful reperfusion (OR=0.315; 95% CI, 0.128-0.774) and post-angioplasty TIMI 3 flow (OR=0.316; 95% CI, 0.105-0.952).

In the multivariate analysis, only successful reperfusion was a significant protective factor against in-hospital heart failure (OR=0.234; 95% CI, 0.079-0.691). The significant risk variables that remained in the model were age over 70 years (OR=7.032; 95% CI, 2.298-21.532) and total CK peak value (OR=1.003; 95% CI, 1.001-1.005). When TIMI 3 flow and successful reperfusion were analyzed independently, the significant protection by the latter was confirmed (Table 4).
In-hospital development of atrial fibrillation, ventricular tachycardia, or second- or third-degree atrioventricular block. The incidence of these alterations was 11.1%. Only age over 70 years (OR=4.008; 95% CI, 1.465-10.963) and advancing age (OR=1.058; 95% CI, 1.014-1.104) were significant risk factors in the univariate regression analysis. Successful reperfusion (OR=0.269; 95% CI, 0.095-0.763) and post-angioplasty TIMI 3 flow (OR=0.176; 95% CI, 0.055-0.56) were significant protective factors.

In the multivariate analysis only successful reperfusion was a significant protective factor against these arrhythmias (OR=0.257; 95% CI, 0.086-0.796) and age over 70 years remained in the model as a significant risk factor. Nevertheless, when the two variables were introduced independently in the multivariate analysis, we found that both TIMI 3 flow and noninvasive indicators were significantly protective against the development of these complications.

FOLLOW-UP

A mean follow-up period of 13 months (range, 0-39 months) was obtained in 86% of the surviving patients. There were no differences in the clinical characteristics of the patients who completed their follow-up and those in whom this information was not obtained because of a loss of contact with our institution.

Mid-Term Mortality

Overall mortality at mid-term was 7.2%. In the univariate analysis, age over 70 years was a risk factor for mid-term mortality (OR=5.69; 95% CI, 1.470-22.033; P<.05). The only protective factor against mid-term mortality was successful reperfusion (OR=0.012; 95% CI, 0.001-0.100; P<.01). Post-angioplasty TIMI 3 flow did not modify the risk of death at mid-term. In the multivariate analysis successful reperfusion remained as a protective factor (OR=0.09; 95% CI, 0.020-0.411; P<.01) and age over 70 years as a risk factor (OR=8.089; 95% CI, 1.630-40.176; P<.05). This was confirmed when TIMI 3 flow and the noninvasive indicators were independently analyzed with the other confounding variables (Table 4).

Development of Heart Failure, Hospitalization Due to Heart Failure or Recurrent Angina

All together, these events presented in 20.5% of patients in the mid-term follow-up. Age over 70 years was a risk factor in the univariate analysis (OR=2.875; 95% CI, 1.14-7.252; P<.05). In the multivariate analysis, a personal history of coronary disease was found to be a significant risk factor for the development of heart failure, hospitalization due to heart failure or recurrent angina (P<.05). Successful reperfusion and TIMI 3 flow did not have an impact on the development of these complications at long-term.

DISCUSSION

In the present series of 172 patients with AMI treated by primary angioplasty, TIMI 3 flow was achieved in 87% of the cases, and successful myocardial reperfusion as assessed by noninvasive indicators in 87.7%. These results were associated with low mortality, a finding that is consistent with the results reported in other series of patients treated with primary angioplasty. In addition, it was demonstrated that optimum post-angioplasty coronary flow resulted in significantly better mortality rates and a lower risk of developing in-hospital heart failure, associated with a smaller infarct size. Most interesting was the confirmation that successful reperfusion and TIMI 3 coronary flow were related with lower in-hospital mortality. Nevertheless, only successful myocardial reperfusion was found to be protective against the development of heart failure, complex cardiac arrhythmias, and mortality at mid-term.

Various clinical studies have demonstrated that successful reestablishment of coronary circulation, whether by thrombolysis or angioplasty, depends on achieving optimum coronary tissue reperfusion and microcirculation. The first study to highlight the importance of coronary reperfusion was done by Ito et al., who used contrast echocardiography in patients with anterior wall infarction treated by angioplasty. The authors demonstrated that in 25% of the cases in which normal anterograde flow had been achieved, reperfusion was not restored. In later studies using other noninvasive methods, such as magnetic resonance imaging and myocardial 99Tc-sestamibi single-photon emission computed tomography, in addition to contrast echocardiography, various authors have confirmed this finding. This lack of tissue perfusion was first described by Klomer et al. in an experimental model, and is known in the literature as the “no reflow” phenomenon. The proposed causes of this phenomenon include microvascular dysfunction produced by endothelial injury, capillary obstruction by the neutrophils, arteriolar spasm and platelet microembolisms.

The noninvasive method most often used to assess myocardial reperfusion has been evaluation of the decrease in ST-segment elevation in the electrocardiographic leads corresponding to the area of the infarction. Using this method in patients treated with thrombolysis, Schroeder et al. reported that patients showing more than 70% resolution of ST-segment elevation had much lower mortality than those showing less than 30% resolution. Because of the simplicity of the method, ST resolution has been incorporated in
routine clinical practice as a relevant part of the evaluation of outcome in multicenter clinical trials. Rapid resolution of ST-segment elevation 30 to 60 minutes after successful coronary angioplasty (with TIMI 3 flow) predicts improved ejection fraction, reduced infarct size and better reperfusion compared with delayed ST-segment resolution.

ST-segment resolution assessed by electrocardiograms performed within a fixed period has limitations. Shah et al described ST-segment fluctuations after thrombolysis, and these findings were later confirmed by Krucoff et al using continuous monitoring by digital echocardiography. In addition, the assigned cutoff values of 30% and 70% of ST-segment resolution leave a population with an intermediate prognosis that encompasses more than 40% of treated cases. It is for this reason that the use of other noninvasive markers, such as early elevation of cardiac enzymes or early T-wave inversion, offers additional advantages and allows establishment of a simple method that is more sensitive and specific. Evaluation of this method in a series of 967 patients treated with thrombolysis showed that each of the indicators used (when present) was associated with a better prognosis. Nevertheless, in the logistic regression analysis including all the noninvasive markers, only T-wave inversion and early enzyme elevation were associated with lower mortality. In a series of 110 patients treated with primary angioplasty and achieving TIMI 3 flow, we found that 11% had failed reperfusion, a lower rate than has been reported in other series in which the only criterion used was ST resolution. Our current results are consistent regarding the low percentage of failed reperfusion after primary angioplasty and they also demonstrate that this method is significantly better than TIMI 3 flow for estimating the short- and mid-term prognosis.

Among the limitations of the method proposed is the fact that the diagnosis of successful or failed perfusion is established late relative to the implementation of primary angioplasty. In this regard, it might be useful to monitor the resolution of ST-segment elevation sequentially in order to assess its stability and to determine whether it is followed by cardiac enzyme and T-wave changes. An attractive but more sophisticated technique has been proposed by Krucoff et al who used continuous ST-segment monitoring by digital echocardiography. This method achieved a high degree of sensitivity and specificity when establishing myocardial reperfusion and the prognosis.

Another limitation of our study is that the only angiographic variable assessed was TIMI 3 flow. It is likely that if other variables such as the TIMI frame count and myocardial blush grade had been incorporated into the analysis, a higher degree of agreement with noninvasive methods would have been achieved.

CONCLUSION

In summary, noninvasive methods derived from the echocardiogram and enzyme panel allowed establishment of the short- and mid-term prognosis in patients treated with primary angioplasty. Moreover, this method was superior and complementary to the degree of coronary recanalization determined on coronary arteriography by TIMI 3 flow. The use of noninvasive markers of myocardial reperfusion has greater prognostic value than TIMI 3 flow in patients undergoing coronary angioplasty, and should be used together with the angiographic method to provide additional data.

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