Acute Release of Plasminogen Activator Inhibitor-1 in ST-Segment Elevation Myocardial Infarction Predicts Mortality

J.P. Collet, MD, PhD; G. Montalescot, MD, PhD; E. Vicaut, MD, PhD; A. Ankri, MD; F. Walylo, MD; C. Lesty, PhD; R. Choussat, MD; F. Beygui, MD; M. Borentain, MD; N. Vignolles, BSc; D. Thomas, MD

Background—A few studies have suggested that von Willebrand factor (vWF) or plasminogen activator inhibitor-1 (PAI-1) can be associated with outcomes of acute coronary syndromes. The present study was designed to assess the acute release of these markers in ST-segment elevation myocardial infarction (STEMI) and their relations to death.

Methods and Results—In 153 consecutive patients with STEMI, vWF and PAI-1 antigens were measured on admission (H0) and 24 hours later (H24). At 30 days, the death rate was 7.2%. Heart failure (Killip stage ≥3) on admission was present in 13.7% of patients. The acute release of PAI-1 (H24−H0, in ng/mL) and of vWF (H24−H0, in %) was dramatically higher in patients who died than in those who survived (46.9±26.3 versus −0.6±2.8 ng/mL, $P=0.0001$ and 65.8±20.0% versus 10.0±5.1%, $P=0.004$ for PAI-1 and vWF, respectively) and in patients developing heart failure compared with those without (24.8±10.1 versus −1.1±3.3 ng/mL, $P=0.004$ and 47.3±11.0% versus 8.1±5.6%, $P=0.005$ for PAI-1 and vWF, respectively). The release of PAI-1 correlated weakly with the left ventricular ejection fraction ($R=-0.195$, $P=0.01$) and the peak of troponin ($R=0.149$, $P=0.045$). Postangioplasty TIMI-3 flow and the acute release of PAI-1 were the only 2 independent predictors of death at 30 days.

Conclusions—The acute release of vWF and PAI-1 over the first 24 hours of STEMI is associated with death and heart failure. The acute rise of PAI-1 is also a strong independent predictor of death at 30 days. **(*Circulation*. 2003;108:391-394.)**

Key Words: myocardial infarction ■ platelets ■ inflammation

High plasma concentrations of plasminogen activator inhibitor type 1 (PAI-1) and von Willebrand (vWF) factor have been associated with the development of coronary artery disease and appear to predict subsequent ischemic events.[1] Previous reports have also shown that the release of these acute phase reactant proteins within the first hours of non–ST-elevation acute coronary syndromes predicts adverse clinical outcomes.[2,3] However, limited and incomplete information is available about these 2 markers in ST-elevation myocardial infarction (STEMI). Raised plasma levels of vWF and PAI-1 have been reported during the acute phase of STEMI, and some drug treatments have been shown to blunt the release of these markers.[4–6] However, the precise relations of vWF and PAI-1 release to myocardial injury and clinical outcomes remain unknown. The present study measured the acute release of these 2 markers during the first hours of STEMI and determined their relations to 1-month mortality.

See p 376

Methods

Patient Population

A total of 153 consecutive patients with an evolving STEMI (<12 hours of symptom onset) or a recent Q-wave myocardial infarction (<48 hours) were enrolled. There were no exclusion criteria. The global risk profile of the patients on admission was assessed with the TIMI (Thrombolysis In Myocardial Infarction) risk score.[7] Heart failure was defined as Killip stage ≥3.

Treatments

All patients received a loading dose of aspirin (500 mg IV) and β-blockers unless contraindicated. Our strategy was to perform primary percutaneous coronary intervention with the combination of stent and abciximab in patients with STEMI <12 hours. All patients who received a stent were also treated with either ticlopidine (500 mg/d) or clopidogrel (300 mg loading dose followed by 75 mg/d) for a period of 4 weeks.

Received November 22, 2002; de novo received March 26, 2003; revision received May 22, 2003; accepted June 6, 2003.

From the Institut de Cardiologie (J.P.C., G.M., F.W., R.C., F.B., M.B., N.V., D.T.) and Laboratory of Haemostasis (A.A., C.L.), Pitié-Salpêtrière Hospital, and the Department of Biostatistics (E.V.), Fernand Vidal Hospital, Paris, France.

Presented in part at the 75th Scientific Sessions of the American Heart Association, November 17–20, 2002, Atlanta, Ga, and published in abstract form (*Circulation*. 2002;106(suppl II):II-533.

Correspondence to Dr G. Montalescot, Institut de Cardiologie, Centre Hospitalier Universitaire Pitié-Salpêtrière (AP-HP), Bureau 2-236, 47, Boulevard de l'Hôpital, 75013 Paris, France. E-mail gilles.montalescot@psl.ap-hop-paris.fr

Circulation **is available at http://www.circulationaha.org** **DOI: 10.1161/01.CIR.0000083471.33820.3C**

Patient Characteristics

		Time From Symptom Onset to Admission	
	Whole Population	STEMI <12 h (n=124)	Q-Wave MI <48 h (n=29)
Age, y	63±15	62±14	64±15
Age >80 y, %	14.4	13.2	18.7
% Males	78.3	80.9	71.8
Risk factors, %			
Diabetes	18.9	16.6	28.1
Hypertension	32.7	28.9	46.9
Dyslipidemia	40.5	47.1	25.0
Smoking	49.7	52.9	32.5
Prior aspirin use	16.3	18.2	9.4
Familial history of CAD	17.6	16.5	21.9
Prior history of CAD, %			
Prior history of MI	9.8	9.1	12.5
Prior revascularization (PCI or CABG)	6.6	6.6	3.1
Clinical parameters			
BMI, kg/m^2	25±4	25±4	24±6
Heart rate, bpm	77.2±18.5	77.7±17.2	80.3±23.5
Systolic blood pressure, mm Hg	122.7±24.5	121.1±22.3	126.3±28.2
Killip stage ≥3, %	13.7	14.0	18.75
TIMI score	5.0±2.7	4.8±2.5	6.3±2.9*
Location of MI, %			
Anterior	43.9	42.1	48.4
Inferior	50.3	52.8	45.2
Lateral	5.8	4.1	3.2
LVEF, %	49.1±11.6	50.6±11.2	48.1±12.2
Creatinine clearance <30 mL/min	9.9	5.1	12.5
No. of diseased coronary arteries, %			
1	43.5	47.7	22.2*
2	32.6	32.4	33.3
3	23.9	19.8	40.7*

CAD indicates coronary artery disease; PCI, percutaneous coronary intervention; BMI, body mass index; and LVEF, left ventricular ejection fraction.

*P<0.05 between evolving and recent MI.

Clinical Follow-Up

In-hospital follow-up was based on physical examination, ECG, creatine kinase, and troponin I (TnI) levels. All patients were followed up at 1 month through written questionnaires and telephone interviews. The primary end point was death of any cause at 30 days of follow-up.

Laboratory Assays

Plasma samples obtained on admission and after 24 hours were used for the determination of vWF antigen and PAI-1 antigen levels with commercially available ELISA kits (Asserachrom). TnI levels were also determined by ELISA. The acute release of vWF and PAI-1 was defined as the difference between their plasma concentrations at 24 hours and baseline (H24−H0).

Statistical Analysis

Categorical variables were expressed as frequencies and percentages and continuous variables as mean±SEM. Depending on the type of the variable considered, t test, χ^2 analysis, or Fisher's exact test was used to identify the potential link between clinical or biological variables and mortality. Then, multivariate analysis was performed with stepwise logistic regression (Biomedical Data Processing Package, University of California, Los Angeles). To avoid overestimating the number of predictive variables, we selected these variables with conservative criteria as follows: limits to enter or remove variables in regression equation must have had a 5% probability value; the ratio between the corresponding regression coefficient and its standard error must have been greater than 2; and results were verified by 2 numerical procedures, an asymptotic covariance estimate and the maximum-likelihood method. Multivariate ORs and their 95% CIs were calculated from the model.

Results

Population Characteristics

The characteristics of the present study population were those of all patients with acute or recent MI (Table). Patients with recent Q-wave MI had a higher risk profile than those with an evolving STEMI (<12 hours), which may account for both their late presentation and higher death rate at 30 days (17.2%

versus 4.8%, respectively; $P=0.019$). Most of the patients (n=118, 77.1%) underwent revascularization during the first 12 hours of symptom onset and 55% within the first 6 hours. The reasons for no immediate revascularization on admission were late presentation (n=19); poor clinical status with severe comorbidities, including dementia or recent stroke (n=9); and TIMI 3 flow without significant culprit stenosis on the coronary angiogram (n=7). Abciximab was used in 81.5% of patients undergoing primary percutaneous coronary intervention. On admission, 100% and 74% of patients received aspirin and β-blockers, respectively. ACE inhibitors were given in 5% and 58% within 24 hours of admission and at discharge, respectively. Deaths occurred in 11 patients at 30 days; all were of cardiovascular origin. Most of the deaths occurred during the initial hospital stay (n=9) and were related to the lack of reperfusion strategy, reperfusion failure, or heart failure. There was no recurrent MI within 30 days.

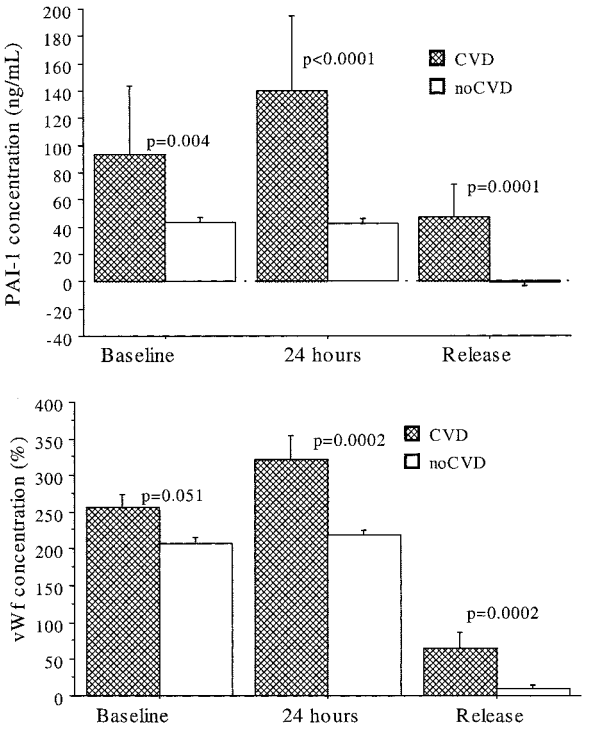
PAI-1 and vWF Plasma Concentrations

Average PAI-1 concentrations remained stable between admission and 24 hours (47.1±4.6 versus 49.7±5.1 ng/mL, respectively; P=NS) in the global population. The time interval between symptom onset and admission affected neither the absolute values of PAI-1 nor PAI-1 acute release. PAI-1 release was dramatically higher in patients developing heart failure than in those without (24.8±10.1 versus −1.1±3.3 ng/mL; $P=0.004$). Weak correlations were found between PAI-1 release and the peak of Tn I ($r=0.149$, $P=0.045$) or left ventricular ejection fraction ($r=-0.195$, $P=0.01$). PAI-1 release did not correlate with the extent of coronary artery disease or with any other baseline characteristics. In contrast, baseline/24-hour concentrations and PAI-1 release were significantly associated with death at 30 days (Figure). This relationship between PAI-1 and death was similar in both subgroups of evolving STEMI and recent Q-wave MI.

There was a significant rise of vWF concentrations from baseline to 24 hours (from 211.5±6.5% to 226.2±7.4%, respectively; $P=0.0066$). Patients presenting late after symptom onset (>12 hours) had higher levels of both H24 vWF and vWF release than patients presenting with an evolving STEMI. The release of vWF was also associated with heart failure (8.2±5.5% versus 47.3±11.0% without and with heart failure, respectively; $P=0.005$). There was no correlation with the peak of TnI or with the ejection fraction. Like PAI-1, baseline/24-hour concentrations of vWF and vWF release correlated significantly with 30-day mortality (Figure). The release of vWF and PAI-1 correlated weakly ($r=0.176$, $P=0.031$), whereas a stronger correlation between 24-hour concentrations of these proteins was obtained ($r=0.38$, $P<0.0001$).

Predictors of Death at 30 Days

After univariate analysis, the baseline characteristics associated with death at 30 days were heart failure, PAI-1 and vWF release, creatinine clearance, age, TIMI score, the use of a reperfusion strategy, postprocedural TIMI 3 flow, and left ventricular ejection fraction. In the multivariate model, TIMI 3 flow after reperfusion strategy ($P=0.03$) and the acute release of PAI-1 ($P=0.01$) were the only independent predictors of 30-day mortality. PAI-1 release remained a significant predictor of death when TnI was forced into the model or when TIMI 3 flow was removed. In addition, when PAI-1 release was removed from the statistical model, vWF release and creatinine clearance were 2 strong independent predictors of death.



Baseline and 24-hour concentrations and release (H24-H0) of PAI-1 antigen (top) and of vWF antigen (bottom) according to cardiovascular death (CVD) at 30 days.

Discussion

The present study demonstrates that both PAI-1 and vWF are released acutely during the first hours of STEMI with a poor prognosis. A dramatic release of these 2 biomarkers occurs in the vast majority of patients developing heart failure and in those dying within the first month. An important finding of the present study is that PAI-1 release is the strongest independent predictor of death at 30 days in this data set.

vWF is a multimeric protein of the acute phase reaction. It is stored in endothelial cells and in platelets and can be released rapidly at the local site of the injured vessel. It is a critical factor for platelet adhesion to exposed subendothelium and for platelet aggregation. PAI-1, by neutralizing tissue-type plasminogen activator, effectively inhibits fibrinolysis and protects clots from early lysis. It is released by activated platelets and endothelial cells but requires a de novo synthesis.

Early and effective reperfusion may not only limit the infarct size but also attenuate the hemodynamic stress, inflammation, and neurohormonal activation related to the ongoing myonecrosis, leading to a reduced release of PAI-1 and vWF from activated platelets and endothelial cells.[4] In contrast to previous studies, we included all patients with an

acute STEMI, of whom only 55% underwent a reperfusion strategy within 6 hours of symptom onset. The delayed myocardial reperfusion in some patients may have minimized the predictive effect of vWF release. Indeed, vWF stored in Weibel-Palade bodies of endothelial cells and in platelet α-granules is released rapidly, whereas PAI-1 requires de novo synthesis with a lag phase of several hours between cell activation and its release.

Multivariate regression analysis identifies the most relevant parameters to predict a clinical event and is not designed to draw mechanistic explanations on the pathogenesis of such events. In the present study, PAI-1 release was the most efficient biological marker to predict death at 30 days. PAI-1 release was linked to vWF release, as shown by the strong predictive value of vWF release when PAI-1 was removed from the multivariate model. Additional investigations are now needed to determine whether PAI-1 and vWF are primarily inflammatory markers of the necrotic myocardium, indexes of the ischemic insult, markers of reperfusion, or markers of the endothelium-platelet interaction.

In conclusion, the present study supports the hypothesis that vWF and PAI-1 release is linked to prognosis of STEMI patients. These markers may represent potential new pharmacological targets. Indeed, previous intervention trials with ACE inhibitors have suggested a benefit of this class of drugs on the fibrinolytic system, blunting the early rise of PAI-1 and leading to better clinical outcome.[5,6] Similarly, various anticoagulant drugs have shown different abilities with regard to vWF release.[3,8] These observations suggest that these drugs may have multiple mechanisms of action to explain their clinical benefit.

Acknowledgment

This study was supported by a grant from the Fondation de France.

References

1. Juhan-Vague I, Pyke SD, Alessi MC, et al. Fibrinolytic factors and the risk of myocardial infarction or sudden death in patients with angina pectoris: ECAT Study Group: European Concerted Action on Thrombosis and Disabilities. *Circulation*. 1996;94:2057–2063.
2. Montalescot G, Philippe P, Ankri A, et al. Early increase of von Willebrand factor predicts adverse outcome in unstable coronary artery disease: beneficial effects of enoxaparin. *Circulation*. 1998;98:294–299.
3. Montalescot G, Collet JP, Lison L, et al. Effects of various anticoagulant treatments on von Willebrand factor release in unstable angina. *J Am Coll Cardiol*. 2000;36:110–114.
4. Andreotti F, Roncaglioni MC, Hackett DR, et al. Early coronary reperfusion blunts the procoagulant response of plasminogen activator-1 and von Willebrand factor in acute myocardial infarction. *J Am Coll Cardiol*. 1990;16:239–243.
5. Wagner A, Herkner H, Schreiber W, et al. Ramipril prior to thrombolysis attenuates the early increase of PAI-1 in patients with acute myocardial infarction. *Thromb Haemost*. 2002;88:180–185.
6. Vaughan DE, Rouleau JL, Ridker PM, et al. Effects of ramipril on plasma fibrinolytic balance in patients with acute anterior myocardial infarction. *Circulation*. 1997;96:442–447.
7. Morrow DA, Antman EM, Charlesworth A, et al. TIMI risk score for ST-elevation myocardial infarction: a convenient, bedside, clinical score for risk assessment at presentation. *Circulation*. 2000;102:2031–2037.
8. Montalescot G, Bal-dit-Sollier C, Chibedi D, et al. Comparison of effects on markers of blood cell activation of enoxaparin, dalteparin, and unfractionated heparin in patients with unstable angina pectoris or non-ST-segment elevation acute myocardial infarction (the ARMADA study). *Am J Cardiol*. 2003;91:925–930.