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# Prolonged pain to hospital time is associated with increased plasma advanced oxidation protein products and poor prognosis in patients with percutaneous coronary intervention for ST-elevation myocardial infarction

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**Abstract** Plasma advanced oxidation protein products (AOPP) are a biomarker for increased production of reactive oxygen species. We examined the possible association between pain to hospital time, plasma AOPP, and outcome of patients receiving percutaneous coronary intervention (PCI) for ST-elevation acute myocardial infarction (STEMI). Plasma AOPP was determined at hospitalization as well as 24 and 48 h after PCI in 79 patients with suspected STEMI. Patients were stratified into a control group (Group I, $n = 21$) after exclusion of coronary artery disease, Group II ($n = 46$) with pain to hospital time <12 h, and Group III ($n = 33$) with pain to hospital time >12 h. Associations between pain to hospital time and AOPP as well as incidence of major adverse cardiac events (MACE) during 6 months of follow-up were analyzed. Plasma AOPP at admission was significantly higher in patients of Group II (97.58 ± 23.41 μmol/l) and Group III (184.52 ± 30.41 μmol/l) in comparison with Group I (57.41 ± 13.60 μmol/l, all $P < 0.001$). Plasma AOPP concentration was positively correlated with pain to hospital time and associated with an increased incidence of MACE during the 6-month follow-up period. Prolonged ischemia is associated with increased oxidative stress and poor prognosis in patients treated with PCI for STEMI.

**Key words** Advanced oxidation protein products · Coronary artery disease · Oxidative stress · Percutaneous coronary intervention

## Introduction

Increased production of reactive oxygen species (ROS) by endothelial, vascular smooth muscle, and adventitial cells is closely associated with the pathogenesis of atherosclerosis.[1,2] Reactive oxygen species are highly reactive molecules, and ROS accumulation could result in DNA damage as well as protein and lipid peroxidation. Under normal aerobic conditions, ROS are produced by the cellular metabolism and are promptly inactivated by counteracting enzymes. The short half-life of ROS makes its direct measurement difficult. Therefore, various molecular markers including advanced oxidation protein products (AOPP) have been proposed to evaluate increased oxidative stress. Increased AOPP was found under oxidative and carbonyl stresses as well as in cases of increased global inflammatory activity. Witko-Sarsat et al. proposed AOPP as a marker of oxidative stress in various body fluids.[3] Tovbin et al. demonstrated increased plasma AOPP levels in patients with renal dysfunction; moreover, the plasma AOPP level was positively correlated to the severity of the renal impairment, the highest plasma AOPP levels being found in patients on hemodialysis and the lowest plasma AOPP levels in healthy subjects.[4] It is speculated that increased AOPP might be a stimulating factor for aggravated renal dysfunction in patients with chronic kidney disease (CKD) owing to its proinflammatory activity and its ability to activate monocytes.[4,5]

Previous studies have shown an association between plasma AOPP with carotid arteriosclerosis in hemodialysis patients.[6] In the general population, plasma AOPP is an independent risk factor for coronary artery disease,[7] whereas high plasma AOPP is related with atherosclerotic cardiovascular events in nondiabetic patients with CKD.[5] Accordingly, Skvarilova et al. observed increased plasma AOPP levels in patients with acute coronary syndromes (ACS).[8] The close association between oxidative stress and plaque instability[2,9,10] led us to test the hypothesis that plasma AOPP levels could monitor oxidative stress and predict the long-term prognosis in patients with ACS. In the present study, we compared plasma AOPP levels at admission, then 24 and 48 h post percutaneous coronary intervention (PCI) in patients with STEMI. We analyzed the association between plasma AOPP and incidence of major adverse cardiac events (MACE) and heart function during 6 months of follow-up post discharge.

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## Patients and methods

A total of 79 patients admitted to our coronary care unit with the diagnosis of STEMI during a time frame of 27 months (June 2005 to October 2007) were included in this study. Diagnosis was confirmed by enzyme tests, electrocardiography, and coronary angiography. There were 46 patients with pain to hospital time less than 12 h (Group II) and 33 patients with pain to hospital time longer than 12 h (Group III). Emergency PCI was performed in all STEMI patients in order to eliminate the possible effects of "closed" and "opened" coronary vessels on AOPP post admission. Twenty-one patients with chest pain who were admitted to our coronary care unit and with normal coronary angiography during the above-mentioned time frame served as control (Group I). All STEMI patients were followed up for 6 months after PCI. The study was approved by the institutional ethics committee for human subjects. Informed consent was obtained from all patients. Exclusion criteria included renal dysfunction and infectious disease. All patients had at least one-vessel occlusion or severe stenosis (>75% of lumen). Balloon angioplasty and stent implantation were performed by the radial or femoral approach according to standard clinical practice. Coronary angiography results before and after PCI were evaluated with on-line quantitative coronary angiography. All patients received aspirin, clopidogrel (Sanofi Winthrop, Gentilly Cedex, France), and/or nitrate before the procedure. Heparin (10000 IU) was administered intravenously at the beginning of the procedure and additional heparin (bolus) was given as indicated to maintain a clotting time of 300 s. ST-segment was monitored before PCI and during the whole procedure. A 12-lead electrocardiogram was taken before, immediately after, and on the following day after PCI.

Blood samples were drawn using a plasma separator tube immediately after hospitalization, 24 and 48 h after PCI in patients with STEMI and at comparable time points in the control patients. Before centrifugation (1000×*g* for 10 min), samples were allowed to clot for 30 min. The plasma was stored at −70°C until analysis. Plasma AOPP was determined by measuring optical density at 340 nm under acidic conditions. The concentrations are expressed as μmol/l of chloramine-T equivalents as described by Witko-Sarsat et al.[3] The intra-assay coefficient of variation was <5% and the interassay variability was <7%. The lower limit of detection was 0.01 μmol/l.

### Biochemical markers of myocardial infarction and echocardiographic determination of left ventricular ejection fraction

Cardiac troponin I (cTnI) and creatine kinase (CK)-MB were measured at admission and 24 h after admission in all STEMI patients by immunoassay using a Dimension RxL system (Dade Behring; Deerfield, IL, USA) in the central laboratory of our hospital. The left ventricular ejection fraction was determined echocardiographically (HP-7500) at discharge and 6 months post discharge.

### Follow-up

All patients were followed up by clinical visit for 6 months after discharge.

### Statistical analysis

Continuous variables are expressed as mean ± SD. Continuous parameters were compared among groups by one-way or two-way analysis of variance followed by post hoc Bonferroni test (SPSS 12.0; SPSS, Chicago, IL, USA). Fisher's exact test and bivariate correlation analysis were also performed as indicated. A $P$ value of less than 0.05 was considered statistically significant.

## Results

### Baseline characteristics

Successful coronary angiogram and reperfusion were achieved in all STEMI patients without major complications. Table 1 summarizes the clinical characteristics of all patients. Age and sex distribution were similar among groups. Incidences of risk factors and current medications (with the exception of β-blocker use) were significantly higher in Groups II and III than in Group I (all $P < 0.05$). The number of treated lesions, lesion length, stent segment, and percent of implanted drug-eluting stent or bare metal stent as well as mean lumen diameter before and after stent implantation were all comparable between Groups II and III (Table 2).

### Plasma AOPP level

AOPP levels at admission and at 24 and 48 h post PCI or equivalent times (Group I) are summarized in Fig. 1 and Table 4. Plasma AOPP in Groups II and III were significantly higher than in group I at all time points, and plasma AOPP in Group III was also significantly higher than that in Group II at all time points (all $P < 0.05$). Plasma AOPP levels remained unchanged in Group I over time. Plasma AOPP was significantly higher at 48 h post PCI than at admission or at 24 h post PCI in patients of Groups II and III. There was a significant correlation between plasma AOPP and pain to hospital time at all examined time points. At admission: AOPP = 116.148 + (2.175 × pain to hospital time), $r = 0.618$, $P < 0.001$; at 24 h post PCI: AOPP = 107.885 + (1.930 × pain to hospital time), $r = 0.576$, $P < 0.001$; and at 48 h post PCI: AOPP = 129.635 + (1.900 × pain to hospital time), $r = 0.570$, $P < 0.001$.

Plasma cTnI and CK-MB levels were significantly higher in patients of Group III than those of Group II at admission (all $P < 0.01$) and at 24 h after admission than those at

**Table 1.** Clinical characteristics

| | Group I ($n$ = 21) | Group II ($n$ = 46) | Group III ($n$ = 33) |
|---|---|---|---|
| Age (years) | 51 ± 11 | 56 ± 13 | 59 ± 13 |
| Sex (male/female) | 12/9 | 34/12 | 21/12 |
| Risk factors | | | |
| Smoking | 4 (19%) | 28 (61%)* | 27 (82%)* |
| Diabetes mellitus | 0 (0%) | 16 (35%)* | 18 (55%)* |
| Hypertension | 3 (14%) | 22 (48%)* | 19 (58%)* |
| Hyperlipidemia | 0 (0%) | 21 (46%)* | 21 (64%)* |
| Medications | | | |
| Nitrates | 0 (0%) | 11 (24%)* | 14 (42%)* |
| ACE inhibitors | 2 (9%) | 26 (57%)* | 18 (55%)* |
| β-Blockers | 6 (27%) | 24 (52%) | 17 (52%) |
| Calcium antagonists | 2 (9%) | 22 (48%)* | 15 (45%)* |
| Aspirin | 3 (14%) | 8 (17%) | 19 (58%)*† |
| History of IHD | | | |
| History of MI | | 2 (4%) | 1 (3%) |
| Angina pectoris | | 3 (5%) | 2 (6%) |
| Congestive heart failure | | 0 (0%) | 1 (3%) |
| Previous PTCA | | 0 (0%) | 1 (3%) |
| Previous CABG | | 0 (0%) | 0 (0%) |
| Kidney disease, creatinine (>2 mg/dl) | | 0 (0%) | 0 (0%) |
| Pain to hospital (h) | | 4.8 ± 2.6 | 37.6 ± 28.4** |
| Pain to cath (h) | | 5.3 ± 2.2 | 52.8 ± 31.1** |

ACE, angiotensin-converting enzyme; IHD, ischemic heart disease; MI, myocardial infarction; PTCA, percutaneous transluminal coronary angioplasty; CABG, coronary artery bypass graft
* $P < 0.05$ vs group I; ** $P < 0.05$ vs group II

**Table 2.** Angiographic demographics and PCI procedure

| | Group II ($n$ = 46) | Group III ($n$ = 33) |
|---|---|---|
| No. of lesions treated | 51 | 47 |
| Lesion length (mm) | 15 ± 1.5 | 17 ± 1.8 |
| Stent segment | | |
| LAD (%) | 29 (57) | 28 (60) |
| LCx (%) | 7 (15) | 11 (23) |
| RCA (%) | 15 (28) | 8 (17) |
| BMS or DES | | |
| BMS (%) | 5 (11) | 1 (3) |
| DES (%) | 41 (89) | 32 (97) |
| Mean lumen diameter (mm) | | |
| Before | 0.11 ± 0.12 | 0.15 ± 0.13 |
| After | 3.22 ± 0.23 | 3.18 ± 0.20 |

PCI, percutaneous coronary intervention; LAD, left anterior descending artery; LCx, left circumflex artery; RCA, right coronary artery; BMS, bare metal stent; DES, drug-eluting stent
* $P < 0.05$ vs Group II

**Table 3.** Biochemical markers of myocardial infarction

| | Group II ($n$ = 46) | Group III ($n$ = 33) |
|---|---|---|
| cTnI (ng/ml) | | |
| Admission | 5.52 ± 4.72 | 11.25 ± 6.62* |
| 24 h post admission | 32.00 ± 13.35† | 36.26 ± 12.33† |
| CK-MB (U/l) | | |
| Admission | 26.09 ± 10.71 | 42.09 ± 10.92* |
| 24 h post admission | 48.17 ± 10.29† | 51.88 ± 12.90† |

cTnI, cardiac troponin I; CK, creatine kinase
* $P < 0.05$ vs Group II; † $P < 0.05$ vs Admission

admission in the same group (all $P < 0.01$, Table 3). Both cTnI and CK-MB levels at admission were positively correlated to pain to hospital time: pain to hospital time = 8.81 + (1.002 × cTnI at admission), $r = 0.305$, $P < 0.01$; pain to hospital time = −1.04 + (0.543 × CK-MB at admission), $r = 0.354$, $P < 0.01$. There were also significant positive correlations between plasma AOPP and cTnI (AOPP = 121.177 + 3.965 × cTnI, $r = 0.343$, $P < 0.001$) and CK-MB (AOPP = 56.732 + 2.924 × CK-MB, $r = 0.542$, $P < 0.001$) at admission, but there were no correlations between plasma AOPP and cTnI or plasma AOPP and CK-MB at 24 h post PCI (all $P > 0.05$).

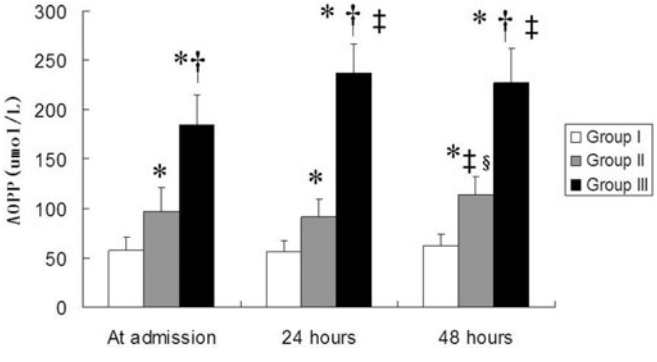


**Fig. 1.** Serial changes in advanced oxidation protein products (*AOPP*) levels among control patients (Group I, *open bar*), patients with pain to hospital time within 12 h (Group II, *gray bar*), and patients with pain to hospital time >12 h (Group III, *black bar*). * $P < 0.05$ vs Group I; † $P < 0.05$ vs Group II; ‡ $P < 0.05$ vs 0 hour in the same group; § $P < 0.05$ vs 24 h in the same group

**Table 4.** The serial change of AOPP (μmol/l) in each group (mean ± SD)

| | 0 h | 24 h | 48 h |
|---|---|---|---|
| Group I ($n$ = 21) | 57.41 ± 13.17 | 56.12 ± 10.42 | 61.75 ± 11.42 |
| Group II ($n$ = 46) | 97.58 ± 11.58* | 91.78 ± 11.38* | 113.78 ± 28.0* |
| Group III ($n$ = 33) | 184.52 ± 30.41*† | 237.26 ± 29.50*†‡ | 227.13 ± 35.18*†‡ |

AOPP, advanced oxidation protein products
* $P < 0.05$ vs Group I; † $P < 0.05$ vs Group II; ‡ $P < 0.05$ vs. 0 h in the same group

Follow-up results

Six-month follow-up data were available in all patients. The left ventricular ejection fraction at discharge was similar between Groups II and III (48% vs 46%, $P > 0.05$) and was significantly lower at 6 months post discharge in patients of Group III compared with that of Group II (41% vs 52%, $P < 0.05$). The hospitalization time for patients in Group III was also significantly longer than that in Group II (8.3 ± 3.5 vs 11.6 ± 4.7 days, $P < 0.01$). The incidence of MACE was significantly higher in Group III (11/33, 7 rehospitalizations, 2 bypass surgery, and 2 deaths) than that in Group II (3/46, 1 rehospitalization and 2 deaths, $P < 0.05$ vs Group III).

## Discussion

Heart failure is considered to be a complex clinical syndrome associated with alterations in the multiple neurohumoral systems and subcellular cardiac structures leading to abnormal cardiac function. Oxidative stress plays a major role in the pathogenesis of heart failure, and previous studies showed that prolonged increased oxidative stress was related to an impaired prognosis in heart failure patients.[1,11,12] The present study shows that plasma AOPP levels at admission, similar to cTnI and CK-MB, were significantly elevated in patients with STEMI compared to control patients and positively correlated to pain to hospital time, cTnI, and CK-MB at admission. Moreover, higher AOPP levels were also associated with an increased incidence of MACE and a reduced left ventricular ejection fraction during 6 months of follow-up. Our results are in line with previous studies[7,8] showing increased plasma AOPP levels in patients with coronary artery disease. We showed for the first time that plasma AOPP was positively correlated with pain to hospital time in patients with STEMI. The present study also demonstrated that plasma AOPP was significantly higher in patients with longer pain to hospital time compared with patients with shorter pain to hospital time. Our data supported the hypothesis that prolonged ischemic time was associated with higher oxidative stress and unfavorable prognosis in these patients despite emergency PCI procedures. Therefore, increased AOPP at admission could be viewed as a significant risk factor for poor prognosis in STEMI patients. Delayed reperfusion might be one of the key factors responsible for poor prognosis due to prolonged increased oxidative stress in patients of Group III in this small patient cohort.[10,11,13,14] These observations need to be verified in future studies with a larger patient cohort.

In conclusion, plasma AOPP is increased in patients with STEMI and positively associated with pain to hospital time, cTnI, and CK-MB at admission. Prolonged ischemic time might be one of the key factors responsible for poor prognosis due to prolonged increased oxidative stress in patients with STEMI despite emergency PCI.

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