Increased serum adiponectin predicts improved coronary flow and clinical outcomes in patients with ST-segment elevation myocardial infarction treated by primary percutaneous coronary intervention

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Background: Previous studies suggested that adiponectin (APN) could ameliorate ischemia/reperfusion injury and endothelial dysfunction in patients with acute myocardial infarction. However, the relationship between serum APN level and coronary flow after primary percutaneous coronary intervention (PPCI) in patients with ST-segment elevation myocardial infarction (STEMI) is unclear.

Methods: A total of 144 patients with STEMI treated by PPCI were enrolled and divided into two groups based on the mean serum APN level on admission. The data on coronary angiograms and laboratory examinations were collected and compared between groups. The incidence of major adverse cardiac events (MACE) was evaluated in all enrolled patients.

Results: The prevalence of Thrombolysis In Myocardial Infarction (TIMI) flow grade <3 after PPCI and corrected TIMI frame count were lower in the high-APN group (P = 0.032 and P = 0.029, respectively). Logistic regression analysis demonstrated that APN was an independent negative predictor of poor coronary flow after PPCI (odds ratio = 0.72, 95% CI: 0.56-0.93, P = 0.011). Kaplan-Meier curves showed that a higher APN level correlated with a better MACE-free survival rate, and multivariate Cox hazard regression analysis indicated that high APN was a significant negative predictor of MACE (hazard ratio = 0.54, 95% CI: 0.29-1.00, P = 0.048).

Conclusion: Elevated serum levels of APN on admission are associated with improved myocardial blood flow and clinical outcomes in STEMI patients treated with PPCI.

Keywords
acute myocardial infarction, adiponectin, major adverse cardiac event, myocardial blood flow, primary percutaneous coronary intervention
Adiponectin (APN), a type of adipocytokine, is secreted from the adipose tissue. Previous studies have demonstrated a significant association of hypoadiponectinemia with the occurrence of acute myocardial infarction (AMI). However, the relationship between plasma APN level and prognosis of AMI remains controversial. Several clinical trials have suggested an inverse correlation of circulating APN level with adverse outcomes in patients with AMI. However, the results of other studies are contradictory. Animal studies showed that myocardial ischemia/reperfusion (MI/R) injury was severe in the APN knockout mice, which was ameliorated by administering exogenous APN. Also, APN could improve vascular endothelial function via its ability to increase nitric oxide production. However, it is still unclear whether APN could protect the cardiomyocytes and improve coronary flow in patients with ST-segment elevation myocardial infarction (STEMI) treated with primary percutaneous coronary intervention (PPCI).

The no-reflow/slow-flow phenomenon is common in patients with STEMI after reperfusion therapies, and it is associated with major adverse cardiac events (MACE). The pathophysiology of no reflow or slow flow involves microembolization, microvascular spasm, microcirculation disturbance, and MI/R injury. The cardioprotective effect of APN might be related to good myocardial perfusion and clinical outcomes in patients treated with PPCI.

The present study investigated the association between APN on admission and the related indicators of myocardial damage and coronary blood flow in STEMI patients undergoing PPCI. We also aimed to observe the relationship between APN and prognosis in these patients.

2 | MATERIALS AND METHODS

2.1 | Participants
A total of 144 patients (114 males and 30 females aged 61.2 ± 12.8 years) with STEMI admitted at Beijing Friendship Hospital from March 2014 to March 2015 were enrolled in this study. The inclusion criteria were STEMI within 12 hours after the onset of symptoms and receiving emergency coronary angiography and PPCI. The exclusion criteria were serious diseases affecting prognosis (renal and hepatic failure, severe anemia, cancer, and acute infectious and inflammatory diseases), active hemorrhage, autoimmune diseases, significant valvular diseases, and AMI with severe stenosis unsuitable for PCI or without significant stenosis. This protocol was approved by the Ethical Committee of Beijing Friendship Hospital, and all patients provided written informed consent.

2.2 | Coronary angiography and PPCI
All participants received the standard therapies of STEMI before and after PPCI. Once a diagnosis of STEMI was confirmed, PPCI was performed immediately by experienced interventional cardiologists after the administration of 300 mg aspirin and 600 mg clopidogrel as loading doses. At least one drug-eluting stent was implanted in the culprit lesion of infarct-related artery (IRA). Dual antiplatelet therapy (100 mg aspirin and 75 mg clopidogrel per day) was continued for 12 months, and then, single antiplatelet therapy (100 mg aspirin per day) was maintained.

Coronary angiograms were interpreted by two independent cardiologists in the catheterization laboratory. Thrombolysis In Myocardial Infarction (TIMI) flow grade (TFG) was defined as complete coronary flow within three cardiac cycles. The corrected TIMI frame count (CTFC) was calculated using the method previously described in which the frames were counted according to the contrast that flowed from the ostium of the target vessel to the distal landmark branch. In addition, the ST-segment elevation myocardial infarction (STEMI) treated with primary percutaneous coronary intervention (PPCI).

2.3 | Blood sampling
Venous blood samples were obtained from peripheral veins before the PPCI procedure. The serum APN level was determined using the enzyme-linked immunosorbent assay, and other biomarkers, such as interleukin-6 (IL-6), leptin, and high-sensitive C-reactive protein (Hs-CRP), were measured simultaneously. The results of laboratory examinations, including routine blood parameters, renal function, uric acid, lipid, glucose, albumin, creatine kinase (CK)-MB, and N-terminal pro-brain natriuretic peptide (NT-proBNP), were also compared in this study.

2.4 | Clinical follow-up
Major adverse cardiac events, defined as death, nonfatal reinfarction, and requirement of hospitalization for unstable angina pectoris (UAP) or decompensated heart failure (HF), were observed during the follow-up period that lasted until March 2018. All patients were followed up for at least 3 years or until an endpoint occurred. The follow-up data were collected from the medical records, patients, and/or their families by telephone interviews and/or outpatient visits.

2.5 | Statistical analysis
Normally distributed continuous variables were expressed as mean ± SD, whereas those with non-Gaussian distribution were presented as median with interquartile interval. Categorical variables were recorded with counts and percentages. Baseline characteristics, concomitant medications, and observational indicators were compared using the Student’s t test or Mann-Whitney U test for continuous variables and using the chi-square or Fisher's exact test for categorical variables. The predictors of poor coronary flow after PPCI were assessed using the multivariate logistic regression analysis including variables with \( P < 0.15 \) in univariate analysis.
Results were expressed as odds ratio (OR) and confidence interval (CI). Univariate and multivariate Cox proportional hazards regression analyses were used to find out the factors associated with MACE by calculating hazard ratios (HRs) and 95% CI. All variables with P < 0.15 on the univariate analysis were entered into the multivariate model using the step-wise backward selection method, and a P value <0.05 was set for inclusion in the multivariate model. The log-rank test for Kaplan-Meier survival curves was used to evaluate the difference in MACE-free survival time between groups. A P value <0.05 was considered statistically significant (2-sided). All statistical analyses were performed with SPSS 26.0 software (IBM, Armonk, NY, USA).

### 3 | RESULTS

#### 3.1 | Comparison of baseline characteristics

In this study, data of APN on admission displayed a normal distribution, and the mean serum APN level was 13.56 ± 2.14 μg/mL. The patients were divided into two groups based on the average APN level on admission: low-APN group (n = 77, APN <13.56 μg/mL) and high-APN group (n = 67, APN ≥13.56 μg/mL).

The baseline clinical characteristics and concomitant medications of the two groups are shown in Table 1. No significant differences were found in baseline characteristics, including age, sex, coronary risk factors, obesity indexes, blood pressure, and heart rate on admission, between groups. The prevalences of HF and anterior myocardial infarction, as well as the time of symptom to admission and door to balloon, were similar in the two groups. All patients received dual antiplatelet therapy and other conventional medications according to the individual condition. No differences in concomitant medications were observed between the two groups.

#### 3.2 | Comparison of laboratory parameters and circulating biomarkers

The laboratory parameters and circulating biomarkers were measured and compared; the results are shown in Table 2. The levels of peak CK-MB and IL-6 on admission were significantly lower in the high-APN group compared with the low-APN group (P = 0.032 and P = 0.003, respectively). In addition, no significant differences were observed in other laboratory indicators between groups, including Hs-CRP, leptin, and peak NT-proBNP.

#### 3.3 | Comparison of coronary imaging characteristics

Table 3 summarizes the angiographic characteristics of the two groups. All patients enrolled in this study underwent PPCI, and the mean number of stents implanted in IRA was 1.15 ± 0.49. No significant differences were noted in the location of IRA and the severity of coronary artery disease between groups. Neither the proportions of using single stent and thrombus aspiration nor the prevalence of initial TFG 0 was obviously different in the two groups. In the high-APN group, the prevalence of TFG 3 after the procedure was higher (P = 0.032), whereas the CTFC after PPCI was lower (P = 0.029), compared with the low-APN group.

#### 3.4 | Predictor of poor coronary flow after PPCI

As shown in Table 4, variables that might affect the coronary flow were brought into the logistic regression analyses. Through the univariate regression analysis, Gensini score, door-to-balloon time ≥90 minutes, and APN on admission were entered into the multivariate model. The final model of multivariable regression analysis
demonstrated that APN was an independent negative predictor of poor coronary flow after reperfusion therapy (OR = 0.72, 95% CI: 0.56-0.93, P = 0.011).

### Table 2: Baseline laboratory parameters and biomarkers

| Variables                        | Low-APN group (n = 77) | High-APN group (n = 67) | P value |
|----------------------------------|------------------------|-------------------------|---------|
| WBC count, ×10^9/L               | 9.69 ± 2.72            | 10.03 ± 2.81            | 0.466   |
| Hemoglobin, g/L                  | 138.43 ± 16.83         | 134.07 ± 17.33          | 0.129   |
| Platelet count, ×10^9/L          | 230.03 ± 62.89         | 216.04 ± 54.51          | 0.159   |
| Creatinine, µmol/L               | 76.04 ± 16.92          | 81.48 ± 22.49           | 0.101   |
| Blood urea nitrogen, mmol/L      | 5.71 ± 1.91            | 5.79 ± 1.74             | 0.786   |
| eGFR, mL/min per 1.73 m²         | 94.57 ± 25.52          | 90.75 ± 28.53           | 0.398   |
| Uric acid, µmol/L                | 321.56 ± 74.39         | 331.22 ± 98.55          | 0.513   |
| Total cholesterol, mmol/L        | 4.33 ± 0.87            | 4.26 ± 1.06             | 0.669   |
| Triglycerides, mmol/L            | 1.54 ± 0.81            | 1.72 ± 1.07             | 0.236   |
| HDL cholesterol, mmol/L          | 1.15 ± 0.25            | 1.08 ± 0.24             | 0.078   |
| LDL cholesterol, mmol/L          | 2.50 ± 0.69            | 2.55 ± 0.87             | 0.698   |
| Albumin, g/L                     | 41.05 ± 3.68           | 41.31 ± 4.21            | 0.696   |
| Admission blood glucose, mmol/L  | 9.28 ± 3.54            | 10.18 ± 5.13            | 0.227   |
| Hemoglobin A1c, %                | 5.90 (5.50-6.90)       | 5.80 (5.40-6.75)        | 0.564   |
| Peak CK-MB, ng/mL                | 122.00 (57.30-261.00)  | 88.40 (45.90-181.60)    | 0.037   |
| Peak NT-proBNP, pg/mL            | 2033 (924-4883)        | 1696 (696-4299)         | 0.437   |
| Hs-CRP, mg/L                     | 7.24 (3.19-14.38)      | 4.00 (1.71-14.79)       | 0.226   |
| IL-6, pg/mL                      | 53.37 (33.32-89.60)    | 36.25 (22.65-60.92)     | 0.003   |
| Leptin, pg/mL                    | 7.19 ± 0.95            | 7.28 ± 0.98             | 0.588   |

APN, adiponectin; CK-MB, MB fraction of creatine kinase; eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein; Hs-CRP, high-sensitive C-reactive protein; IL-6, interleukin-6; LDL, low-density lipoprotein; NT-proBNP, N-terminal pro-brain natriuretic peptide; WBC, white blood cell.

### Table 3: Coronary angiographic profile and PCI procedure

| Characteristics                        | Low-APN group (n = 77) | High-APN group (n = 67) | P value |
|----------------------------------------|------------------------|-------------------------|---------|
| Infarct-related artery                 |                        |                         |         |
| LAD, n (%)                             | 39 (50.6)              | 31 (46.3)               | 0.426   |
| LCX, n (%)                             | 12 (15.6)              | 7 (10.4)                |         |
| RCA, n (%)                             | 26 (33.8)              | 29 (43.3)               |         |
| Multivessel disease, n (%)             | 63 (81.8)              | 56 (83.6)               | 0.780   |
| Gensini score                          | 77.7 ± 36.0            | 72.3 ± 33.5             | 0.348   |
| Single stent implantation, n (%)       | 68 (88.3)              | 61 (91.0)               | 0.592   |
| Using thrombus aspiration devices, n (%)| 25 (32.5)              | 22 (32.8)               | 0.963   |
| Initial TFG 0, n (%)                    | 63 (81.8)              | 54 (80.6)               | 0.851   |
| TFG 3 after PCI, n (%)                  | 60 (77.9)              | 61 (91.0)               | 0.032   |
| CTFC after PCI, n (%)                   | 36.1 ± 16.9            | 30.8 ± 11.8             | 0.029   |

APN, adiponectin; CTFC, corrected TIMI frame count; LAD, left anterior descending coronary artery; LCX, left circumflex coronary artery; PCI, percutaneous coronary intervention; RCA, right coronary artery; TFG, TIMI flow grade.

### 3.5 MACE

The median follow-up time was 41 months (interquartile range 39-45). Altogether, eight patients, four in each group, died in the 3-year follow-up period. Of these, two patients died during hospitalization. No significant differences were observed in the rates of death and nonfatal reinfarction between groups. However, the incidences of rehospitalization for UAP or HF and total MACE were significantly lower in the high-APN group than those in the low-APN group during the 3-year follow-up (P = 0.017 and P = 0.019, respectively; Table 5). Kaplan-Meier curves indicated that the patients in the high-APN group had a better MACE-free survival rate (P = 0.043; Figure 1).

### 3.6 Predictors of MACE

Table 6 shows the results of univariate and multivariate Cox hazard regression analyses for factors associated with MACE. APN and conventional risk factors (age, gender, hypertension, diabetes, estimated glomerular filtration rate, door-to-balloon time, Killip class, multivessel disease, and TFG) were assessed together. Multivariate Cox hazard regression analysis indicated that the increased serum APN level was a negative predictor of MACE (HR = 0.54, 95% CI: 0.29-1.00, P = 0.048), whereas age ≥70 years positively correlated with MACE (HR = 2.23, 95% CI: 1.23-4.06, P = 0.008).

### 4 DISCUSSION

ST-segment elevation myocardial infarction is a severe cardiovascular disease causing high mortality. In addition, patients with STEMI tend to suffer from HF. However, currently available
therapies cannot effectively improve the prognosis of STEMI, despite an increase in the use of PPCI.\textsuperscript{18,22} A retrospective analysis of hospital data in China from 2001 to 2011 revealed that the in-hospital mortality of STEMI did not decrease while the intensity of testing and treatment increased.\textsuperscript{18} Further efforts are needed to improve the clinical outcomes of patients with STEMI.

Better coronary flow and less myocardial necrosis are associated with better clinical outcomes for patients with STEMI. This study showed that the elevated APN level on admission was related to improved myocardial reperfusion evaluated by TFG and CTFC. And we found that APN was an independent negative predictor of poor coronary flow after PPCI. Experimental data confirmed the cardiovascular protective effects of APN,\textsuperscript{23-25} which could stabilize artery plaques and protect against myocardial damage.\textsuperscript{26,28} Several studies demonstrated that APN could also reduce MI/R injury and improve coronary blood flow in both animal models and humans.\textsuperscript{10,11,24-26} Trifunovic et al.\textsuperscript{29} reported that the plasma APN level on admission significantly positively correlated with coronary flow reserve.

### TABLE 4
Univariate and multivariate logistic regression analyses for the predictors of poor coronary flow after PPCI

| Variables                  | Univariate analysis | Multivariate analysis |
|----------------------------|---------------------|-----------------------|
|                            | OR                  | 95% CI                | P value | OR                  | 95% CI                | P value |
| Age                        | 1.01                | 0.97-1.04             | 0.752   | 1.01                | 0.99-1.02             | 0.308   |
| Male sex                   | 0.54                | 0.20-1.46             | 0.221   | 1.00                | 0.99-1.02             | 0.810   |
| Hypertension               | 0.89                | 0.36-2.18             | 0.790   |                     |                      |         |
| Diabetes                   | 0.98                | 0.36-2.71             | 0.971   |                     |                      |         |
| Gensini score              | 1.01                | 1.00-1.02             | 0.103   | 1.01                | 0.99-1.02             | 0.308   |
| eGFR                       | 1.00                | 0.99-1.02             | 0.810   |                     |                      |         |
| Door-to-balloon time ≥90 min| 2.11               | 0.83-5.33             | 0.116   | 0.92                | 0.36-2.35             | 0.866   |
| Killip class II-IV         | 0.56                | 0.18-1.77             | 0.325   |                     |                      |         |
| Initial TFG 0              | 0.80                | 0.27-2.39             | 0.689   |                     |                      |         |
| APN                        | 0.70                | 0.54-0.90             | 0.006   | 0.72                | 0.56-0.93             | 0.011   |

APN, adiponectin; CI, confidence interval; eGFR, estimated glomerular filtration rate; OR, odds ratio; PPCI, primary percutaneous coronary intervention; TFG, TIMI flow grade.

### TABLE 5
Clinical outcomes of 3-y follow-up

| Variables                  | Low-APN group (n = 77) | High-APN group (n = 67) | P value |
|----------------------------|------------------------|-------------------------|---------|
| Death, n (%)               | 4 (5.2)                | 4 (6.0)                 | 1.000   |
| Nonfatal reinfarction, n (%)| 6 (7.8)                | 3 (4.5)                 | 0.635   |
| Rehospitalization for UAP or HF, n (%) | 20 (26.0) | 7 (10.4) | 0.017   |
| Total MACE, n (%)          | 30 (39.0)              | 14 (20.9)               | 0.019   |

APN, adiponectin; HF, heart failure; MACE, major adverse cardiac events; UAP, unstable angina pectoris.

### FIGURE 1
Kaplan-Meier curves for MACE-free survival of the two groups. APN, adiponectin; MACE, major adverse cardiac events.
Multivariate analysis of peak CK-MB and IL-6 positively correlated with the myocardial infarct size. In addition, increased CK-MB and IL-6 levels represented poor clinical outcomes in STEMI patients after reperfusion therapies. Natsukawa et al. showed that the serum APN level on admission was significantly associated with the serum area under the curve of CK-MB. Also, Radwan et al. reported that APN negatively correlated with IL-6. Moreover, animal experiments demonstrated that intracoronary administration of APN could reduce the extent of myocardial infarction. Therefore, the elevated APN level might lead to a reduction of infarct sizes and adverse cardiovascular events.

The relationship between APN and the severity of coronary artery disease is still unclear, especially in patients with AMI. A few studies showed that the reduced APN level was associated with severe coronary stenosis and high atherosclerotic burden. However, their findings were not confirmed in other studies. Similarly, no obvious correlation between the APN level and the severity of coronary lesions was seen in our research by measuring the Gensini score and the prevalence of multivessel disease. It was suggested that the role of APN in predicting the severity of lesions in STEMI patients might be insignificant.

Lindberg et al. revealed that increased plasma APN could predict all-cause and cardiovascular mortality in patients with STEMI undergoing PPCI. The present study did not support their findings.
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