Original Article

Level of von Willebrand factor to assess the occurrence and prognosis of acute myocardial infarction

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Background: To observe and compare the differences in von Willebrand factor antigen (vWF:Ag) levels between patients with acute myocardial infarction (AMI) and healthy residents, and to determine whether this measure can be used to evaluate the incidence of AMI and whether or not to undertake cardiac bypass surgery.

Methods: A retrospective analysis was conducted using the clinical data of 110 patients with acute cardiovascular disease without bypass (no bypass group), 351 patients with AMI and bypass (bypass group), and 60 healthy volunteers (healthy group) who underwent physical examination between July 2018 and May 2019 in Tianjin Chest Hospital. The plasma vWF:Ag was measured and the receiver operating characteristic (ROC) curve was utilized to critically assess its efficacy in determining the occurrence and prognosis of AMI, and the Chi-square test was used to evaluate the correlation between vWF:Ag and clinicopathological factors.

Results: The plasma vWF:Ag was 201% (139%, 250%) in the bypass group, 118% (107%, 134%) in the non-bypass group, and 95.5% (85.25%, 102.75%) in the control group, and the differences were statistically significant (P<0.05). The component status of the plasma vWF:Ag used in the bypass group was greater as compared to that of the normal group (P<0.05) and the non-bypass group (P<0.05). The area under the ROC curve of plasma vWF:Ag level was 0.797 (95% CI: 0.749–0.845). When the medical decision level of plasma vWF:Ag was set at 155.5%, the sensitivity and specificity of predicting AMI were 68.9% and 86.7%, respectively. The levels of plasma vWF:Ag in patients with AMI were correlated with hypertension, diabetes, age, and history of cerebral infarction (P<0.05).

Conclusions: The plasma vWF level can predict the occurrence of AMI and provides guidance for cardiac bypass surgery.

Keywords: Von Willebrand factor (vWF); acute myocardial infarction (AMI); biomarkers

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Introduction

Acute myocardial infarction (AMI) involves extensive myocardial necrosis caused by acute and sustained coronary ischemia and hypoxia, with characteristic changes due to the occluded duration and reperfusion time, the degree of occlusion, and the chance of collateral circulation (1). Clinically, patients with AMI are subject to persistent retrosternal pain, progressive electrocardiographic changes, elevated serum markers of myocardial necrosis, and other characteristic changes (2,3). As a disease with high morbidity and mortality rates worldwide, AMI seriously threatens the health and safety of a large population in China (4-8). Currently, cTn has been regarded as the clinical "gold standard" for the diagnosis of AMI. However, due to its low

specificity, cTn may elevate in chronic renal insufficiency, stroke, heart failure, severe infections, cachexia, and other diseases (9-11), which can complicate a specific diagnosis. With the update of detection techniques, the potential for von Willebrand factor antigen (vWF:Ag) to play a role in the diagnosis of AMI (12) has been increasingly recognized, due to it participating in the inflammatory response to myocardial ischemia-reperfusion injury and promoting complement activation to exacerbate ischemia-reperfusion injury (13-15).

von Willebrand factor (vWF) is known as a large adhesive and multimeric glycoprotein that is incorporated within the vascular endothelial cells, and is encrypted on a portion of chromosome 12. A 250-kDa protein which builds up monomers is encoded by the vWF gene. Upon reaching its maturity stage, a molecule will then consist of 50 to 100 monomers that can develop a size up to 20 MDa. vWF subunits contains binding sites for the following elements: factor VIII, platelet glycoprotein Ib (GPIb), GPIIb/IIIa, heparin, and collagen, in which some are reliant to shear-induced conformational change (16) that is active in blood plasma and essential in the course of thrombosis (17). It is being kept in the a-granules of platelets and the Weibel-Palade bodies of endothelial cells, as represented by an ultra-large vWF (UL-vWF). Substances such as metalloprotease with thrombospondin type 1 repeats, member 13 (ADAMTS13), and a disintegrin transform UL-vWF into inert, smaller pieces (18). A damaged vessel membrane may lead to an extreme shear stress, which can instigate vWF to concurrently merge with the platelet receptor GPIB-IX-V complex (via A1 domain) and the endothelial collagen (via A1 and A3 domain). For this reason, vWF plays an important role in creating a bond between the platelets and subendothelial matrix.

According to the past researches, patients with AMI who received greater contents of vWF:Ag, and persisted for 1 week after reperfusion therapy (19) but also had a definite increase of UL-vWF multimers (20). Subsequently, they indicated that coronary plaque burden is actually connected with the vWF:Ag levels in patients who have stable angina pectoris, while plasma levels of vWF were remarkably higher in patients with angiographic no-reflow, excluding those with electrocardiographic no-reflow (21).

In addition, these analyses predominantly paid attention on the probability of occurrence and prognosis value of plasma vWF and AMI. However, the efficiency of using this parameter to predict the occurrence of AMI, and the difference of the vWF levels between AMI patients who underwent bypass surgery and those who didn't remains unclear. We present the following article in accordance with the STARD reporting checklist (available at https://dx.doi.org/10.21037/apm-21-2162).

Methods

Participants

The participants in this study were 60 healthy volunteers (healthy group) and 461 AMI patients receiving coronary angiography (CAG) in the Tianjin Chest Hospital between July 2018 and May 2019. Participants were divided into two groups based on whether they underwent bypass surgery, comprising a no bypass group (n=110) and bypass group (n=351). All enrolled individuals had imaging data and were not treated with anticoagulants, and the gender, age, imaging results, stent status, and vWF results of both groups were recorded separately. AMI patients were diagnosed in accordance with the global definition of myocardial infarction [2018], along with clinical evidence.

Specimen collection

Two mL of fasting blood was collected in the early morning with 0.105 mol/L vacuum blood collection tubes with sodium citrate anticoagulant, which was centrifuged at 3,000 ×g for 15 min within 2 hours, and the upper layer platelet-poor plasma immediately frozen at –20 ℃ until testing. All the patients attended the study voluntarily. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). Patients and their families signed informed consent documents. The study was approved by the ethics committee of Tianjin Chest Hospital.

Main instruments and reagents

These were a Stago automated coagulation analyzer (Stago) test kit, and a vWF:Ag test kit (nephelometry).

Assay method

The frozen specimen was re-dissolved at room temperature and then placed on the Stago analyzer for the determination

Table 1 Basic clinical data

Groups	Age	Male/female
No bypass group (n=110)	60.93±12.31	56/54
By pass group (n=351)	60.84±10.76	218/133
Healthy group (n=60)	60.03±11.11	30/30
P	>0.05	>0.05

Table 2 Comparison of plasma vWF:Ag level between bypass, no bypass, and healthy groups

Groups	vWF
Bypass	201% (139%, 250%)[a,b]
No bypass	118% (107%, 134%)
Healthy	95.5% (85.25%, 102.75%)

In comparison to the healthy group, [a], P<0.05; in comparison to the no-bypass group, [b], P<0.05; no bypass group in contrary to the healthy group, P>0.05.

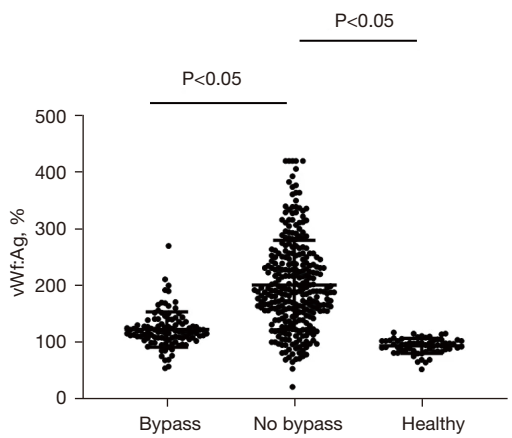

Figure 1 Comparison of plasma vWF:Ag level among three groups. vWF:Ag, von Willebrand factor antigen.

of vWF:Ag.

Statistical analysis

VSPSS 22.0 was used for statistical analysis. Data with normal distribution were expressed as mean and standard deviation, and data with normal distribution were expressed as median and interquartile spacing for pairwise comparisons and comparison between groups with the Kruskal Wallis rank sum test between the bypass, no bypass, and control groups, with statistical significance at P<0.05. Pairwise comparisons was conducted among the three groups using Mann-Whitney U test, showing a statistical significance of P<0.05, and receiver operating characteristic (ROC) curve laid out in order to examine the diagnostic performance of vWF:Ag. Chi-square test was used to evaluate the correlation between vWF:Ag and clinicopathological factors in AMI patients.

Results

Basic clinical data

Gender and age between the bypass group and control group were not statistically significant (P>0.05) but comparable (see *Table 1*).

Comparison of plasma vWF:Ag level

The level of plasma vWF:Ag among the bypass group was higher as compared to that of the healthy group and no-bypass group, showing a statistical significance (P<0.05). While, the level of plasma vWF among the no-bypass group was significantly higher than the healthy group, showing no statistical significance (P>0.05) (see *Table 2* and *Figure 1*).

Performance of plasma vWF:Ag levels in AMI

The performance of plasma vWF:Ag levels in the AMI diagnosis was evaluated by the ROC curve with the bypass group being the positive case and no bypass group being the negative case, and the area under ROC curve of plasma vWF:Ag level was 0.797 (95% CI: 0.749–0.845) as shown in *Figure 2*.

Correlation between the levels of plasma vWF:Ag of AMI patients and clinicopathological factors

The levels of plasma vWF:Ag in AMI patients correlated with hypertension, diabetes, age, and a history of cerebral infarction but not gender (P<0.05), as shown in *Table 3*.

Discussion

First discovered by Erik Avon Willebrane in 1926, vWF is a polysaccharide protein synthesized mainly by endothelial cells and plays a key role in regulating impaired platelet adhesion to endothelia. Endothelial cell damage is the

causative factor for the development of AMI, and vWF levels are an important predictor of AMI and an important indicator for assessing its extent of damage, development, and prognosis (15).

Some clinical prediction scores indicate both short-term and long-term risks such as recurrent ischemic events and death subsequent to myocardial infarction. In comparison, the TIMI risk score is the most convenient type, yet GRACE is reported to be more precise, extensive, and applicable to both NSTEMI and STEMI. Moreover, some biomarkers, including C-reactive protein and B-type natriuretic peptide, can contribute in assigning and classifying patients to a particular risk status. Although, these biomarkers must still be improved and integrated into strategy-based researches. Further, cTn is the only current guideline-approved treatment pathway as seen on any biomarker (22). A substantial relationship between vWF levels and the possible occurrence of MI in vascular disease patients is formed. vWF is commonly degraded by the enzymes ADAMTS13–proteolytically speaking. With that, ADAMTS13 activity is reckoned to be abnormal in relation to ischemic cardiovascular disease. In the context of ACS, it is still indeterminate what the real role of this vWF cleaving protease is. ADAMTS13 levels were apparently minimized in patients with AMI (23). However, some published case-control study showed a significant increase of MI risk in those patients who have higher ADAMTS-13 levels (24). This inconsistency is still unexplained and deserves a supplemental analysis. As reported and seen on ST-elevation

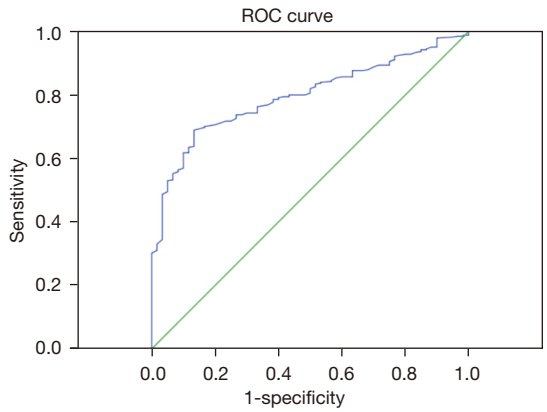

Figure 2 ROC curve of plasma vWF:Ag levels in the diagnosis of AMI. ROC, receiver operating characteristic curve; vWF:Ag, von Willebrand factor antigen; AMI, acute myocardial infarction.

Table 3 Analysis of the correlation between the levels of plasma vWF:Ag of AMI patients and clinicopathological factors

Clinicopathological factors	N	Levels of plasma vWF:Ag		Chi-square value	P value
		≤155.5%	>155.5%		
High blood pressure				50.175	<0.01
No	131	37	94		
Yes	220	148	72		
Diabetes				11.009	<0.01
No	143	75	68		
Yes	208	134	74		
Age				1.513	<0.05
≥65	149	41	108		
<65	202	68	134		
Gender				0.125	>0.05
Male	263	83	180		
Female	88	26	62		
Cerebral infarction				7.231	<0.01
No	275	95	180		
Yes	76	14	62		

MI (STEMI), vWF levels tend to increase within 24 hours, and make its peak in between 48 to 72 hours before it comes back to the baseline some time around day 14 (25).

In this study, the plasma vWF:Ag level among the bypass group was higher as compared to the no-bypass group, and the level in no-bypass group was higher than the control group, showing no statistical significance (P>0.05). While the level of plasma vWF:Ag in our study showed no correlation with the number of bypasses and location of coronary artery stenosis, some studies have found it correlated with atherosclerotic plaques (6), and could sensitively reflect the damage status of vascular endothelial cells in patients with atrial fibrillation (13). The risk of atheroembolic events (3,4) and stroke in patients with new onset atrial fibrillation (26) has also been shown to increase dramatically when vWF levels remain elevated in patients with coronary artery disease after treatment. Patients with coronary artery disease and elevated vWF levels should have their hospitalization periods prolonged, and further imaging should be performed to examine the degree of obstruction.

In the current study, we found that the area under the ROC curve of plasma vWF:Ag level evaluating the incidence of AMI exceeded 0.7, indicating the diagnosis and prediction value of vWF:Ag factor in AMI. The levels of plasma vWF:Ag can well predict the occurrence of AMI and can sensitively reflect the damage status of vascular endothelial cells in AMI patients, providing an important clinical resource for cardiac bypass surgery.

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Footnote

Reporting Checklist: The authors have completed the STARD reporting checklist. Available at https://dx.doi.org/10.21037/apm-21-2162

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://dx.doi.org/10.21037/apm-21-2162). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the ethics committee of Tianjin Chest Hospital. All the patients attended the study voluntarily. Patients and their families signed informed consent documents.

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