AB0 blood types: impact on development of prosthetic mechanical valve thrombosis

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ABSTRACT

Objective: The non-O alleles of the ABO genotype have been associated with an increased risk of thrombosis. We aimed to assess the association between blood group status and prosthetic valve thrombosis.

Methods: The association between AB0 blood group status and prosthetic valve thrombosis was assessed in this retrospective study. Transesophageal echocardiography was performed in 149 patients with a diagnosis of prosthetic valve thrombosis and in 192 control subjects.

Results: Non-0 blood group type (p<0.001), presence of NYHA class III-IV status (p<0.001), and central nervous system (p<0.001) and non-central nervous system (p<0.001) emboli were significantly more prevalent in prosthetic valve thrombosis patients than in the control subjects. The incidence of ineffective anticoagulation was higher in patients with prosthetic valve thrombosis than in controls (p<0.001), as was the presence of moderate to severe left atrial spontaneous echo contrast (p<0.001). The non-0 blood prosthetic valve thrombosis subgroup had a higher incidence of obstructive thrombi and central nervous system thrombotic events than having 0 blood prosthetic valve thrombosis subgroup. Non-0 blood group, ineffective anticoagulation, left atrial spontaneous echo contrast, and a poor NYHA functional capacity were identified to be the predictors of prosthetic valve thrombosis.

Conclusion: Our data demonstrate that patients with non-0 compared with 0 blood groups have higher incidence of prosthetic valve thrombosis and central nervous system embolism and similar rates of non-central nervous system embolism at presentation compared with 0 blood group type. Thus, non-0 blood group may be a risk factor that may be prone to the development of prosthetic valve thrombosis in patients with prosthetic heart valves. (Anatol J Cardiol 2016; 16: 820-3)

Keywords: prosthetic valve thrombosis, ABO blood group status, transesophageal echocardiography

Introduction

AB0 antigens are expressed on red blood cells and a variety of plasma proteins, including von Willebrand factor (vWF), which is a carrier protein for coagulation factor VIII (FVIII) (1). The clearance of vWF is associated with the AB0 antigen type. Proteolysis is significantly faster for group 0 compared with non-0 blood group (0>B>A>AB). VWF-FVIII levels are 25% higher in non-0 blood group compared with group 0 individuals (2). Accumulating evidence indicates an increased risk of thrombosis associated with the non-0 blood group (3-5).

Prosthetic valve thrombosis (PVT) is a potentially life-threatening complication associated with high morbidity and mortality. Ineffective anticoagulation, surgical technique, endocardial fibrosis, pannus formation, foreign body reaction to the prosthetic valve and suture, atrial fibrillation, left atrial enlargement, ventricular dysfunction, pregnancy, and traumatic replacement of the prosthetic valve may lead to an increased development of PVT (6). We hypothesized that the non-0 individuals with mechanical prosthetic valve could be associated with an increased risk of thrombosis compared with the 0 individuals. We also explored the association of AB0 blood group status and PVT related thrombotic events on admission in patients with mechanical prosthetic.

Methods

Between 2009 and 2014, 5,120 patients with mechanical prostheses were examined by two dimensional (2-D) and real-time three dimensional (RT 3-D) transesophageal echocardiography (TEE) at our institution. In total, 149 patients were diagnosed with PVT. The first 192 patients with normally func-
tioning mechanical prosthesis upon TEE examination were selected as the controls. ABO and Rh blood group status were available in all patients. The assessment of ABO blood group has been described in detail elsewhere (7). Patients who had prosthetic valve obstruction without a thrombus/mass/pannus formation in the echocardiographic study and normal prosthetic valve leaflet motion were considered as patient–prosthesis mismatch and were excluded from the study. The study was approved by the local ethics board. All participants were informed about the study, and their informed consents were obtained.

Transthoracic echocardiographic (TTE), 2-D TEE, and RT 3-D TEE studies were performed by the same cardiologist team for each patient. The TEE studies were performed using the X7-2t transducer on an iE33 ultrasound machine (Philips Medical Systems, Andover, MA, USA). Thrombus was recognized as a homogeneous, mobile, or fixed mass with similar echo density to the myocardium located at the valve occluder and/or valve struts and was visualized in all patients with PVT using echocardiography (8). Differentiation of thrombus from pannus overgrowth was based upon echocardiographic and clinical findings, as previously reported (9–11). The cross-sectional area and the largest diameter of the thrombus were measured on TEE as recently described (12). Transmirtal gradients and effective orifice area were measured both with 2-D TTE and TEE according to the current guidelines (13). Left ventricle ejection fraction and left atrium diameter were also noted.

The patient demographic characteristics, blood group type, medical history, and rhythm disorders at the time of admission were entered into a database. We compared the outcomes of PVT and PVT-related thromboembolic events (central and non-central nervous system emboli) with regard to ABO blood groups in this retrospective monocentric study.

Statistical methods

Data are presented as mean±SD for continuous variables and as proportions for categorical variables. Differences between proportions were assessed using the chi-square test and replaced by the Fisher exact test when the expected cell count was <5. Differences between mean values were assessed using the student t-test. Variables with a p value ≤0.1 were selected for logistic regression analysis. A logistic regression analysis was performed in order to identify any independent associates of PVT. Statistical analyses were performed using SPSS version 13.0 (SPSS Inc., Chicago, Illinois). A two-tailed p value of <0.05 was considered significant for all analyses.

Results

The study population (n=341; 29.6% male) included patients with aortic and mitral mechanical PVT (n=149) versus control group (n=192) with a normally functioning mechanical prosthesis. Blood group 0 was the most common phenotype (29%) followed by blood group A (26.6%), B (22.5%), and AB (21.9%). The majority of patients (77.4%) were Rh (D) positive, whereas 22.6% were Rh (D) negative. The most common valve type was St. Jude Medical (St. Jude Medical Inc., St. Paul, Minnesota) bileaflet valve. Among 149 PVT patients, 50 had obstructive and 99 had nonobstructive PVT. The baseline demographic, clinical, and blood group status characteristics of the study patients are presented in Table 1. Presence of non-0 blood group (p<0.001), New York Heart Association class III–IV status (p<0.01), and central nervous system (p<0.001) and non-central nervous system (p<0.001) emboli were significantly more prevalent in PVT patients than in the control subjects. The incidence of subtherapeutic anticoagulation was higher in patients with PVT than in the control subjects (p<0.001), as well as the presence of moderate to severe left atrial spontaneous echo contrast (p<0.001).

The echocardiographic parameters and clinical characteristics of PVT subgroup patients (non-0 versus 0 blood groups)
are listed in Table 2. No significant difference was observed between these subgroups in terms of non-central nervous system embolism, mobile thrombus, left atrial spontaneous echo contrast, and left atrium diameters. There was a significant difference among the two groups with regard to the mitral valve area (p<0.001), mean transvalvular gradient (p<0.001), and mean thrombus area (p<0.001); the PVT patients with non-0 blood group had lower valve area, higher mean transvalvular gradient, and higher thrombus area compared with 0 blood group PVT patients. The non-0 blood PVT subgroup had a higher incidence of obstructive thrombus (p=0.02) and central nervous system thromboembolic events (p=0.02) than 0 blood PVT subgroup.

Blood group type, subtherapeutic anticoagulation, left atrial spontaneous echo contrast, and a poor New York Heart Association functional capacity were all predictors of PVT on multiple regression analysis (p<0.001, OR: 1.35, CI: 1.14–1.58; p<0.001, OR: 28.67, CI: 13.31–93.09; p=0.026, OR: 3.20, CI: 1.12–7.94; p=0.032, OR: 3.55, CI: 1.24–11.23, respectively) (Table 3). The incidence of PVT did not differ between two Rh (D) groups. Rh (D) status did not influence PVT and PVT related thrombotic events.

### Table 2. The characteristics of PVT in blood types

| Echocardiographic and clinical parameters | Non-0 blood type | 0 blood type | P   |
|------------------------------------------|------------------|--------------|-----|
| LVEF, %                                  | 48.5±7.3         | 49.2±7.8     | 0.40|
| OT/NOT                                   | 47/77            | 3/22         | 0.02|
| Mobile thrombus                          | 11               | 3            | 0.71|
| Mitral valve area, cm²                   | 1.2±0.2          | 2.3±0.2      | <0.001|
| Mean transvalvular gradient, mm Hg      | 11.3±1.5         | 4.0±0.9      | <0.001|
| Mean thrombus area, cm²                  | 1.57±0.46        | 1.0±0.52     | <0.001|
| LA diameter, mm                          | 44±5             | 42±8         | 0.09|
| Stroke or TIA                            | 17               | 9            | 0.02|
| Non-CNS embolism                         | 3                | 1            | 0.71|

Data are presented as mean±SD. CNS - central nervous system; LA - left atrium; LVEF - left ventricle ejection fraction; NOT - non-obstructive thrombus; OT - obstructive thrombus; TIA - transient ischemic attack.

### Table 3. The predictors of thrombosis in patients with PVT

| Variable                     | Univariate OR (95% CI) | Multivariate OR (95% CI) |
|------------------------------|------------------------|-------------------------|
| Non-0 blood group            | <0.001                 | <0.001                  | 1.35 (1.14–1.58) |
| Subtherapeutic anticoagulation| <0.001                 | <0.001                  | 28.67 (13.31–93.09) |
| NYHA class                   | <0.001                 | 0.032                   | 3.55 (1.24–11.23) |
| Left atrial SEC              | <0.001                 | 0.026                   | 3.20 (1.12–7.94) |

CI - confidence interval; NYHA - New York heart association; OR - odds ratio; SEC - spontaneous echo contrast.

### Discussion

This is the first study that has evaluated the potential relationship between PVT and PVT-related thromboembolic events and ABO blood groups in patients with mechanical prosthesis. The main finding of this report is that mechanical prosthesis patients with non-0 blood group types has a higher risk for development of PVT and central nervous system embolism compared with 0 blood group patients.

Several previous studies reported that individuals with non-0 blood group had increased risk of thrombosis compared with group 0 individuals; they had higher rates of cardiovascular events (14), increased risk for venous thromboembolism (5, 15, 16), peripheral vascular disease (17), pulmonary embolism (5), and cerebral ischemia (18). In contrast, blood group 0 individuals are consistently over-represented in patients with inherited bleeding tendency (19). Later studies showed higher incidence of bleeding ulcers in group 0 patients (20).

The increased risk of thrombosis associated with non-0 blood groups has been attributed to higher plasma vWF and FVIII levels in these patients. vWF levels are 25% higher in non-0 compared with group 0 individuals (2). One possible explanation is that ABO blood group may influence vWF proteolysis by ADAMTS13 (a disintegrin and metalloproteinase with thrombospondin type 1 repeats-13). Proteolysis of vWF differed according to ABO blood group (0 ≥ B ≥ A ≥ AB), suggesting an effect of the A antigen, and possibly the B antigen (2). In addition to ABO blood group status, vWF levels are influenced by a variety of conditions, including age, diabetes, metabolic syndrome, pregnancy, and chronic inflammatory states (21–23).

Our results show that patients with non-0 blood group had higher incidence of PVT, central nervous system thromboembolic events, obstructive thrombus, mean thrombus area, and mean transvalvular gradients than in patients with 0 blood groups. These findings are consistent with previously reported elevated levels of vWF, a contributor to platelet-mediated thrombotic events with non-0 blood group individuals. Non-0 blood group was found to be significantly higher in patients with PVT compared with control group. Furthermore, it was an independent predictor of PVT in patients with mechanical prosthesis. Therefore, we can suggest that non-0 blood group may be associated with the development of thrombosis in patients with mechanical prosthesis. In this study, the risk factors that could be involved in the thrombotic process of valve prosthesis, such as atrial fibrillation, left ventricle ejection fraction, and left atrium dimensions, did not differ between the groups, which may make the findings more reliable.

### Study limitations

This study has several limitations. We did not measure vWF or Factor VIII levels, which may have prognostic value independent of ABO groups. Another limitation is that histopathological confirmation has not been provided from the patients with PVT to
make the exact diagnosis of thrombus formation. However, evolution of thrombus morphology under medical treatment, which is demonstrated with the utility of RT-3D TEE (8), from atrial side of view, mostly favors the diagnosis of thrombosis. Furthermore, all cases in whom the diagnosis could not be interpreted easily and/or concurrent pannus overgrowth was also suspected were excluded from the study to increase the reliability of the findings.

**Conclusion**

In addition to the well-known risk factors of PVT that include subtherapeutic anticoagulation, the presence of left atrial spontaneous echo contrast, and poor New York Heart Association functional capacity, blood group types may also serve as an important predictor for the development of PVT.

**Conflict of interest:** None declared.

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