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REVIEW

Is ABO blood group truly a risk factor for thrombosis and adverse outcomes?

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Abstract

ABO blood type is one of the most readily available laboratory tests, and serves as a vital determinant in blood transfusion and organ transplantation. The ABO antigens are expressed not only on red blood cell membranes, determining the compatibility of transfusion, but also on the surface of other human cells, including epithelium, platelet and vascular endothelium, therefore extending the research into other involvements of cardiovascular disease and postoperative outcomes. ABO blood group has been recognized as a risk factor of venous thrombosis embolism since the 1960's, effects now understood to be related to ABO dependent variations are procoagulant factor Ⅷ (FⅧ) and von Willebrand factor (vWF) levels. Levels of vWF, mostly genetically determined, are strongly associated with venous thromboembolism (VTE). It mediates platelet adhesion aggregation and stabilizes FⅧ in plasma. Moreover, many studies have tried to identify the relationship between ABO blood types and ischemic heart disease. Unlike the clear and convincing associations between VTE and ABO blood type, the link between ABO blood type and ischemic heart disease is less consistent and may be confusing. Other than genetic factors, ischemic heart disease is strongly related to diet, race, lipid metabolism and economic status. In this review, we'll summarize the data relating race and genetics, including ABO blood type, to VTE, ischemic heart disease and postoperative bleeding after cardiac surgery.

Key words: ABO blood group; Venous thrombosis; Ischemia disease; Cardiac surgery; Outcomes

Core tip: In this review, we updated the reports regarding the associations between ABO blood groups and venous thrombosis, ischemic heart disease as well as postoperative outcomes after cardiac surgery. ABO blood group is clearly associated with venous thromboembolism whereas critical review of the literature reveals a more controversial relationship with atherosclerosis, arterial thrombosis and postoperative outcomes.

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INTRODUCTION

The ABO group of human red cell antigens was discovered by Karl Landsteiner in 1900. ABO antigens are carbohydrate molecules that are the major determinants of the compatibility of red cell transfusions. Naturally occurring, complement fixing IgM antibodies are formed against the A and B antigens in individuals that do not express them on their red cell surfaces and therefore recognize them as foreign antigens. Each individual inherits

Table 1 The incidence of ABO phenotypes in populations from different racial backgrounds

Race	Blood group phenotype	Blood group genotypes				
	O^1 (O^2 rare)	A^1	A^2	B	A^1B	A^2B
Caucasian	44%	33%	10%	9%	3%	1%
Asian	43%	27%	Rare	25%	5%	Rare
African	49%	19%	8%	20%	3%	1%

Illustrations: Sub-group A2 expresses less A antigen on the red cell surface and has been referred to as "weak" A.

Table 2 The association of ABO genotype with von Willebrand factor and factor Ⅷ levels is presented with categorization by von Willebrand factor levels

	Genotype	Median value	
		vWF	FⅧ
Low	O^1O^1	69%	75%
Medium	A^1O, A^2O, BO	89%	96%
High	AA, BB, A^1B	120%	117%
Highest	A^2B	169%	112%

vWF: Von Willebrand factor; FⅧ: Factor Ⅷ.

two ABO alleles. The A and B alleles encode separate glycosyltransferase that add N-acetylgalactosamine and D-galactose of the "H" antigen (group O determinant), converting it into A and B antigens respectively. However, as the O allele does not express either A or B transferase enzymes, continued expression of the unaltered H antigen is the phenotypic marker of the O blood group[1]. The ABO antigens are expressed not only on red blood cell membranes, determining the compatibility of transfusion, but also on the surface of other human cells, including epithelium, platelet and vascular endothelium[2], therefore extending potential pathophysiology into other areas of cardiovascular disease and postoperative outcomes.

Expression of the different ABO phenotypes is partially dependent on racial origin as shown in Table 1, with Group O generally being the most common blood group[3]. Blood groups are basically described by phenotypes, because historically blood groups are determined by commercial antibodies that recognize A and B antigens. By this detection method, both AO and AA genotypes ($A^{1(2)}O^1$, A^1A^2) will be identified as group A, while BO and BB genotypes as group B. In this review, we updated the reports regarding the associations between ABO blood groups and venous thrombosis, ischemic heart disease as well as postoperative outcomes in terms of both ABO phenotype and genotype.

ABO AND VON WILLEBRAND FACTOR

Von Willebrand factor (vWF) has two major biological forms and the high molecular weight vWF (HMW vWF) is hemostatically more active than the low molecular weight vWF (LMW vWF)[4]. HMW vWF mediates the interaction between platelets and damaged areas of the blood vessel wall, while LMW vWF acts as a specific carrier molecule for procoagulant factor Ⅷ (FⅧ), thereby localizing FⅧ to the site of any vascular injury. Both are essential for normal hemostasis[5,6].

Plasma vWF levels are generally reported to be approximately 25% higher in non-O blood individuals[7]. Synthesized in endothelial cells and megakaryocytes, the HMW vWF, enters the plasma from platelet granules following platelet activation and degranulation at the site of tissue injury, or alternatively being stored in endothelial cell Weibel-Palade bodies, then secreted in response to thrombin, fibrin or histamine stimulation[8]. vWF molecular has three binding sites, platelet glycoprotein 1b binds to A1 domain, while collagen binds to A3 domain, forming the primary hemostatic clot[9,10]. The A2 domain binds to ADAMTS13 and is responsible for vWF cleavage (Figure 1).

Clinical observations that the severity of bleeding in mild von Willebrand's disease was exaggerated for group O patients led to the recognition of an ABO dependent variation in vWF levels[11-13]. A formal linkage analysis showed the effect of ABO blood type on von Willebrand factor is a direct functional effect of the ABO locus, rather than linkage disequilibrium between the ABO locus and another unidentified VWF regulation locus[14]. vWF levels can also influence procoagulant FⅧ levels since vWF is a carrier molecule that protects FⅧ from proteolysis in plasma.

Moeller *et al*[15] compared vWF and FⅧ levels in individuals of different ABO phenotype and found ascending order O < A < B < AB for vWF level and O < A < AB < B for FⅧ level. This effect becomes more nuanced when considering the specific genotypes that result in ABO phenotypes, as illustrated in Table 2. Within A and B phenotypes, vWF concentrations in AA or BB are slightly higher than AO or BO[16] and A^1 and B alleles are found to be associated with higher vWF and FVIII levels, while A^2 is comparable to O allele[6,11,13,17].

MECHANISM FOR ABO RELATED VARIABILITY IN VWF LEVELS

There is no direct evidence demonstrating that the ABO locus is associated with vWF synthesis[8], therefore efforts to elucidate the association between ABO and vWF have focused on vWF metabolism and cleavage. ADAMTS13 cleavages HMW vWF to LMW vWF[8,15,18,19], thereby modulating the tendency of vWf to cause platelet aggregation and thrombus formulation[20]. The biological importance of this is exemplified by thrombotic thrombocytopenic purpura (TTP). In TTP, autoantibodies neutralize ADAMTS13 leading to diffuse microvascular thrombosis from the unregulated action of HMW vWF. This extreme example leads to a proposed mechanism for the ABO group related modulation of vWF levels and therefore tendency to thrombosis. While A, B and H antigens are more commonly known to be expressed on the cell surfaces of erythrocytes and various exocrine cells, they are also expressed on the vWF molecule. The

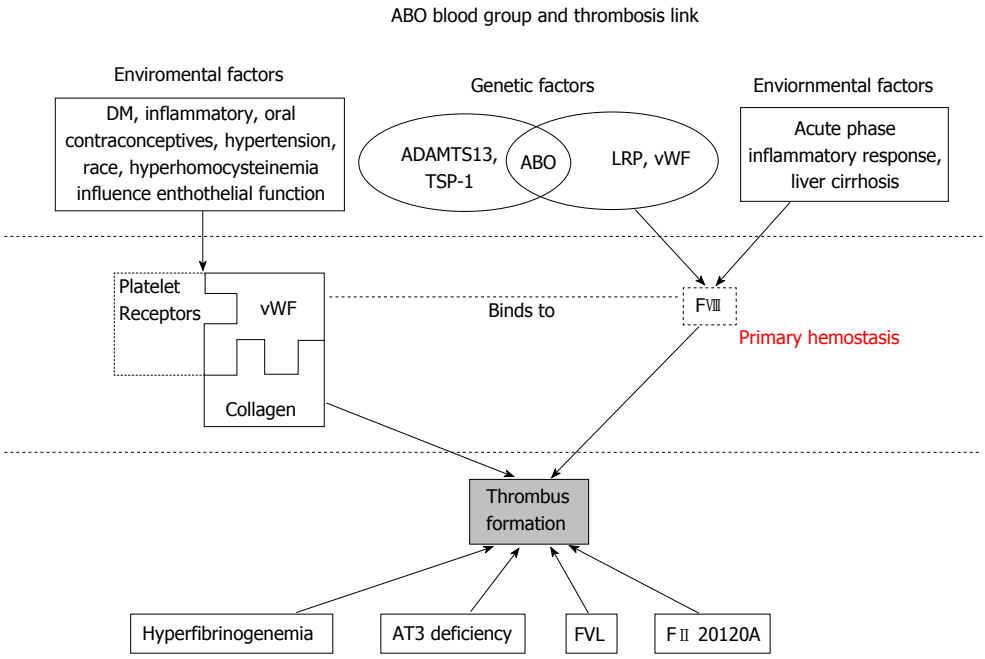

Figure 1 Genetic and environmental factors that contribute to increased levels of von Willebrand factor and factor Ⅷ and risk of thrombus formation. ADAMTS13: A disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13; AT3: Antithrombin Ⅲ; DM: Diabetes mellitus; FⅡ: Prothrombin gene mutation 20210A; FⅧ: Factor Ⅷ; FVL: Factor V leiden; LRP: Lipoprotein receptor-related protein; TSP-1: Thrombospondin-1; vWF: Von Willebrand factor.

location of the A, B and H antigens on the vWF molecule is thought to be close to the A2 domain binding site for ADAMTS13 and that A and B antigens reduce ADAMTS13 binding and, therefore, cleavage[8,21]. Some studies confirmed this hypothesis by providing evidence that the proteolytic effect of ADAMTS13 on vWF was significantly faster in O group (only H antigen expression) than in non-O groups with A and B antigen expression[22,23] . Factors other than ABO group can also modify vWF metabolism which may limit the direct association of ABO group with vWF levels and thrombosis, explaining some inconsistencies in the various studies we report. For example, thrombospondin-1 (TSP-1) has been reported to control vWF multimer size by both directly cleavage and indirectly, competing with ADAMTS13[24,25]. Thus, any genetic factors influence cleavage (ABO blood type, ADAMTS13 and TSP-1) and environmental risk factors that affect endothelial cell function, such as age, diabetes mellitus, hypertension, inflammatory and oral contraceptive drugs, all contribute to the complex risk factors leading to clinical thrombosis. This concept is illustrated in Figure 1.

The link between ABO blood group, H antigen expression and lower vWF levels has been well established above. How this translates into a clinically relevant risk of thromboembolism manifesting either as venous thromboembolism or coronary artery thrombosis is discussed in detail below.

VENOUS THROMBOEMBOLISM

Venous thromboembolism (VTE) includes deep vein thrombosis and pulmonary embolism and is a serious medical condition with a historical mortality rate of 10% and 15% respectively[26]. ABO blood group has been recognized as a risk factor since the 1960's, effects now understood to be related to ABO dependent variations are procoagulant FⅧ and vWF levels. Levels of vWF, mostly genetically determined, are strongly associated with VTE. It mediates platelet adhesion aggregation and stabilizes F Ⅷ in plasma. In a healthy state, twin studies showed 75% of variance in plasma vWF levels result from genetic determinants[27], 30% of which are associated with ABO blood type[28]. Other non-genetic factors, such as aging, diabetes, free radical formation and inflammation, may have a more important role during acute illnesses or during the perioperative period[29]. As shown in Figure 1, environmental causes of endothelial dysfunction can greatly affect vWF levels.

Numerous studies have reported that individuals with non-O blood types had a higher risk of VTE compared to their O counterparts[30-34]. According to Wiggins, compared to O^1O^1 group, AB diplotype category has the highest VTE rate, followed by B allele and A^1 allele[13]. Other rare genotypes like A^3, A^x, A^a, B^3, B^a were less amenable to statistically meaningful comparison in this study. These observations were supported by genotype association studies that showed H-antigen rich genotypes (O^1O^1, O^1O^2, O^1A^2) have a lower incidence of VTE than H-antigen poor genotypes (A^1B, O^1A^1, O^1B)[17,35,36], establishing ABO blood type as an important risk factor for VTE[37].

In Figure 1, various genetic and environmental factors affecting vWF levels are presented. What's more, FⅧ, circulating bound to vWF, also plays a crucial and independent role in the propagation phase of coagulation

Table 3 Outline of the main studies describing the association of ABO blood type and manifestations of atherosclerotic heart disease

Ref.	Population	Sample size	Outcome(s)	Findings
Garrison *et al*[44]	United States		"Cardiovascular disease"	O showed the lowest incidence
Whincup *et al*[45]	United Kingdom (men only)	7662	CAD	Individuals with A blood type has higher incidence of CAD (RR = 1.21, CI: 1.01-1.46)
Rosenberg *et al*[46]	United States (young women)	225 MI *vs* 802 controls	MI	Blood group A was associated with MI
Lee *et al*[47]	Taiwan (young patients)	136 CAD *vs* 129 without CAD	CAD and MI	Group A was associated with increased risk of CAD (OR = 2.61, CI: 1.11-6.14) and MI (OR = 3.53, CI: 1.21-10.29)
Sari *et al*[48]	Turkish	476 MI *vs* 203 healthy control	MI	ABO blood type is not associated with development of MI
Carpeggiani *et al*[49]	Italy	4901	MI and CAD	Group non-O is associated with increased mortality in patients with CAD, groups A and B prevail in MI
Nydegger *et al*[50]		177 patients *vs* 89 control	MI	B allele carriers had higher MI (OR = 2.7, CI: 1.1-6.8)
Stakisaitis *et al*[51]	Lithuania	441	CAD	B blood group can be related with CAD in women
Meade *et al*[52]	United Kingdom	1393 men with 178 IHDs	CAD and MI	Incidence was significantly higher in blood group AB
Mitchell *et al*[53]	United Kingdom		"Cardiovascular disease"	Towns with higher prevalence of group O have higher rate of cardiovascular mortality
Biswas *et al*[54]	India	250 CAD *vs* 250 controls	CAD	Group O increases the risk of CAD
Amirzadegan *et al*[55]	Iran	2016 patients	CAD	No correlation
Biancari *et al*[56]	Finland	1152 CABG patients	MI	No correlation
He *et al*[57]	United States	89501	Coronary heart disease	AB group has highest CAD risk, followed by groups B, A and O

CAD: Coronary artery disease; MI: Myocardial infarction.

activation[6]. Since vWF is the plasma co-carrier of FⅧ, ABO blood type, by altering vWF levels, also exerts an effect on FⅧ levels. Tirado *et al*[34] demonstrated that genetic factors explain 40% of the variance of FⅧ levels; other studies further identified a quantitative trait locus and the ABO locus as two major genetic factors underlining the variability of FⅧ levels[14,38]. Unconnected to ABO group, lipoprotein receptor-related protein has also been identified to be associated with degradation of FⅧ, another consideration when evaluating variance in FⅧ levels[39]. In summary, while ABO blood type and vWF levels are two important factors commonly known to modulate FⅧ plasma level, the biology determining FⅧ is a complex interaction of genetic and environmental factors as illustrated in Figure 1.

However, FⅧ may have some effect independent of vWF. Some studies demonstrated that a high FⅧ level is persistent beyond the acute phase state[40,41], representing a potential risk factor for delayed or recurrent thrombosis. In addition, Morange *et al*[17] described a residual statistical effect of ABO blood group on FⅧ levels after adjustment for vWF levels, postulating that FⅧ is an independent VTE risk factor[29,34] Additionally, FⅧ was reported to be associated with recurrent disease[34], consistent with reports that non-O carriers had a higher incidence of VTE recurrence than O carriers[42,43].

ISCHEMIC HEART DISEASE

Unlike the clear and convincing associations between VTE and ABO blood type, the link between ABO blood type and ischemic heart disease is less consistent and may be confusing. In part this can be due to the inclusion of different end-points that may represent different disease processes, such as angina/atherosclerosis (less likely ABO/vWF related) or myocardial infarction (MI)/coronary thrombosis (more likely ABO/vWF related). The pathogenesis of coronary artery disease (CAD) involves the progression of an atherosclerotic disease process, whereas MI (or acute coronary syndrome) results from a platelet rich thrombus forming on abnormal endothelium diseased by the atherosclerotic process. Platelet rich thrombi (MI) are reliant on primary hemostasis, whereas the mechanism linking ABO group to CAD is less obvious. However, it is important to evaluate ABO group as a risk factor for both these devastating conditions: CAD and MI.

Many studies show that non-O group have higher incidence of ischemic heart disease (Table 3). The Framingham Heart study, and others, suggested A blood type has increased risk of CAD[44-46] and MI[47]; more specifically, A blood group seems to be related to early CAD detection[47,48] and predominates in patients with MI[49]. Other studies noted groups B[50,51] or AB[52] have higher incidence of CAD. Conversely, Mitchell[53] reported that towns with a higher prevalence of group O have higher rates of cardiovascular mortality and an Indian study with moderate sample size also showed O blood group is more frequent in CAD and increased the risk of CAD[54]. Further studies do not identify any association between blood type and CAD[55,56]. Based on these inconsistent results and relative small sample sizes. He[57] conducted a meta-analysis of two large, prospective studies consisting of 89501 participants, and found the highest risk of CAD was observed in blood group AB, followed by group B, A and O. This is consistent with what we know about ABO related vWF/FⅧ levels with the highest in group AB, followed by group B, A and O According to

this meta-analysis, non-O group has an 11% increased risk of CAD, an association not altered by adjusting for other co-morbidities. There was, however, no difference in survival and, paradoxically, a trend towards increased mortality and/or non-fatal myocardial infarction in O blood type patients.

The relationship between ABO genotype and CAD has also been investigated. Wiggins *et al*[13] reported an 18% increased MI risk associated with A^{11} allele carriers compared to O^1O^1 homozygotes, but no other associations were found between B or AB alleles and MI, possibly due to underpowering as B and AB groups are relatively rare. An investigation of postmenopausal women suggested A or B allele carriers almost had two-fold incidence of acute ischemic heart disease compared to OO[58]. Similarly, Nydegger *et al*[50] showed a three-fold risk of MI with the presence of B allele (genotype AB, BB or BO) compared to non B allele (genotype OO, AO, AA) in a smaller case-control study. Another study[59] with angiography showed O^1 allele carriers had a 39% decreased risk of MI compared to non O^1. More obviously, von Beckerath *et al*[59] found a dose-dependent effect with carriage of one or two O^1 alleles being associated with decreased risks of acute MI. However, a recently published study by Reilly *et al*[60] argued that ABO locus did not predict MI in patients with known CAD, but was strongly associated with the presence of CAD in two large genome wide association studies. Whether ABO alleles are associated with the development of MI or only the presence of CAD is not yet clearly defined. It is much easier to investigate the risk factors for CAD prevalence in a cross-sectional study than to evaluate the incidence of MI with a prospective design, as the latter requires a stable cohort with years of detailed follow-up. Currently, the association of MI and ABO blood group has only been well reported in survivors of MI events. This introduces bias, as patients may suffer an asymptomatic MI, not present at hospital, or die before diagnosis.

There are some mechanisms proposed to explain the association between ABO blood type and CAD, but a unifying theory remains elusive. Along with fibrinogen, vWF may play a role in the progression of atherosclerosis by promoting platelet aggregation and adhesion[21]. On the other hand, blood group A has been noted to have higher levels of cholesterol and low density lipoprotein[61], which may partly explain the association with an increased risk of CAD. Additionally, the ABO locus was recently reported to be associated with CAD related inflammatory makers, including intercellular adhesion molecule-1, soluble P-selectin[62], soluble E selectin[63] and tumor necrosis factor-α[53]. Still, the interactions among genetic factors (known genes increasing susceptibly to CAD and the ABO locus) and environmental factors conferring risk for CAD and MI are complicated. It is unclear which ABO phenotypes or genotypes increase CAD and/or MI risk; this risk may differ for the incidence of CAD or MI and survival following MI.

CARDIAC SURGERY

Our group performed a retrospective study to evaluate the relationship between ABO blood types and postoperative bleeding in cardiac surgical patients. This was based on the hypothesis that lower circulating vWF levels seen with group O may reduce primary hemostasis resulting in increased postoperative bleeding. While group O did have impaired baseline measures of primary hemostasis and required less heparin and protamine for perioperative anticoagulation, the result showed no difference of postoperative bleeding between different blood groups[20]. Limitations of such perioperative studies are the lack of intermediate, mechanistic measures of factor levels and the confounding effects of the acute phase response that may drown out an ABO effect. Also, the classification by phenotype is limited. For example, the A^2O genotype with low vWF levels and the A^1A^1 genotype with high vWF levels are both classified as group A. In addition, the statistically convenient categorization into O and non-O phenotype is flawed for the same reason, blurring comparison between H antigen rich and H antigen poor genotypes that have been shown to drive the association between ABO blood type and outcome. As an alternative approach, we have preliminary results suggesting that the AB phenotype (no H antigen) requires less perioperative transfusion than non-AB phenotypes and this is associated with better postoperative survival for the rare AB group. These findings require confirmation with prospective study.

CONCLUSION

In summary, ABO blood group is an important determinant of vWF and FⅧ levels which in turn confer a clear risk of increased VTE with the higher levels seen in the non-O blood types. The associations are far less clear for CAD and MI but a similar pattern emerges with most studies finding group O to be at lower risk. In terms of perioperative bleeding and transfusion, a possible reciprocal for thrombosis, further work needs to be done to determine a consistent ABO effect.

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