The association between blood group and the risk of vascular disease in Quebec blood donors

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Background. The association between antigens A and B and arterial thrombosis, such as coronary heart disease, cerebrovascular disease or peripheral vascular disease, is still unclear. We evaluated the association between blood groups and thrombotic events in a cohort of blood donors from the province of Quebec, Canada.

Material and methods. Among all whole blood donors aged ≥18 years in Quebec between June 1990 and March 2009, a study sample with known blood groups was linked with the provincial hospitalisation and death records to count vascular events. All hospital admissions and deaths with codes for primary and relevant secondary diagnoses of coronary, cerebrovascular or peripheral diseases, including coronary heart disease interventions, were included. Cox regression was used to evaluate the hazard ratio associated between blood groups and these events adjusted for other baseline characteristics.

Results. Among the blood donors, 64,686 had a known blood group and were linked with the provincial health databases. The mean age of these donors was 38 years. The Cox multivariate adjusted hazard ratio for coronary, cerebrovascular or peripheral diseases was 1.19 (95% confidence interval: 1.01-1.40) for subjects with blood group AB compared to those with blood group O. There were no statistically significant associations with other blood groups. Only among women aged ≥40 years did those with blood group A have a higher hazard ratio for coronary heart disease (1.40 [1.01-1.92]) than those with blood group O, after adjusting for other characteristics.

Discussion. When compared to blood group O, only blood group AB was associated with a higher risk of hospitalisation or death because of thrombotic events such as coronary, cerebrovascular or peripheral diseases. However, the associations differed according to age and sex because only females aged ≥40 years with blood group A had a higher risk of coronary heart disease.

Keywords: coronary disease, cerebrovascular disorders, peripheral vascular disease, blood donors, ABO blood-group system.

Introduction

Antigens A and B have a major influence on haemostasis and venous thromboembolism[1,2]. However, the association with arterial thrombosis, coronary heart disease[3] (CHD) or cerebrovascular disease (CVD)[4,5] is less documented and is the subject of controversy. Three meta-analyses have shown conflicting results. The results of Wu *et al*.[6] are quite inconclusive while He *et al*.[7] clearly demonstrated that subjects with blood group O have a moderately lower risk of developing CHD and Dentali *et al*.[8] found significant associations only for myocardial infarction.

Since the frequencies of the ABO system blood groups vary between populations[9], and since no studies had been performed in Canada on severe arterial events (CHD, CVD and peripheral vascular disease [PVD]) resulting in hospitalisation or death, we performed this study to determine whether "healthy" blood donors in the province of Quebec with a non-O blood group have a higher risk of any arterial thrombosis (or combination of thromboses) than donors with O blood group.

Materials and methods

Study population

The sample was selected from all blood donors aged ≥18 years who made a whole blood donation in the province of Quebec between June 1990 and March 2009, excluding autologous donations. The study sample and the linkage with provincial health care registries (hospitalisation and death records) have already been described[10]. In that previous study, we compared donors who were permanently deferred from donation, to donors who remained eligible, after matching the two groups for baseline characteristics. In this study, the cohort

included these two groups. We excluded donors with an unknown blood group and we counted vascular events starting from their inclusion in the cohort.

Thrombotic events (hospitalisations or deaths)

All hospital admissions for a primary or secondary diagnosis coded in the 9th or 10th International Classification of Diseases (ICD) of CHD (ICD-9: 410-414; ICD-10: I20-I25), CVD (ICD-9: 431, 433 to 435 and 437; ICD-10: I61, I63 to I67, I69.1, I69.3, I69.4 and I69.8) and PVD (ICD-9: 440, 441 and 445; ICD-10: I70, I71 and I73.9) between the index donation and March 2009 were included. CHD-associated interventions were also considered (Canadian Classification of Diagnostic, Therapeutic and Surgical Procedures and Canadian Classification of Health Interventions codes 48.0-48.2 and 1IJxx and 1ILxx). Deaths attributable to these ICD-9 and ICD-10 codes were also considered. Only secondary hospital diagnoses and secondary causes of death deemed relevant by the physicians (MG and GD) were included.

Statistical analyses

Rate ratios were calculated to compare the occurrence of CHD, CVD or PVD, alone or combined, between the blood groups. Cox regression was used to evaluate possible confounding of the association between blood groups and CHD, CVD or PVD, alone or combined. Age, number of previous donations and year of entry in the study were modelled as continuous variables; sex, region of residence and Rh factor were defined as categorical variables. The possible confounding effect of each baseline characteristic was individually and collectively assessed and the final models included all variables that meaningfully changed the unadjusted rate ratios. All comparisons were made at the 95% confidence level (two-sided) using SAS Enterprise Guide version 4.1 (SAS Institute, Cary, NC, USA). Héma-Québec's ethical review board approved the study and the authorised government agency (Commission d'accès à l'information du Québec) gave permission to link databases.

Results

Baseline characteristics according to events and blood group

Within the provincial health care registry we successfully traced 66,449 blood donors of whom 64,868 had a known blood group. Their mean age was 38 years. As shown in Table I, the overall rate of events (hospitalisations or deaths) for CHD, CVD or PVD was 3.94 per 1,000 person-years and was higher for subjects with blood group A and AB (p=0.0461 and p=0.0039, respectively). Being an older male, living in regions other than Montreal and having made a large number of previous blood donations were the other characteristics associated with a higher rate of CHD, CVD or PVD in the univariate analysis.

As the proportion of males was higher among blood donors (59.2%), the distribution of sexes according to blood group was always higher for men (A: 59.9%, B: 58.8%, AB: 58.3% and O: 58.7%, χ^2=9.8, p=0.0201). The mean age of donors was nearly the same for all blood groups (38 years for blood group B and O; 39 years for A and AB, p=0.0522). The blood group distribution in people who had thrombotic events was different from that of people who did not have such events (A: 44.3% *vs* 42.4%, B: 9.6% *vs* 10.3%, AB: 5.5% *vs* 4.4% and O: 40.6% *vs* 42.8%, respectively) (χ^2=14.1, p=0.0028).

Multivariate analyses

As the number and the rate of PVD events (0.32) was very low, in Table II we present two multivariate Cox regression models, one with all three categories of diseases and the other one with CHD and CVD without PVD. Only subjects with blood group AB had a statistically higher adjusted hazard ratio (HR) for CHD, CVD and PVD of 1.19 (95% confidence interval [CI]: 1.01-1.40). The hazard ratios for the second model, with CHD and CVD, were almost the same and only that for subjects with blood group AB was statistically higher (HR 1.23 [95% CI: 1.04-1.45]). Being an older male, having entered the cohort earlier, and living in regions other than Montreal were the other characteristics associated with a higher rate of CHD or CVD with or without PVD, in the multivariate analysis. It should be noted that the multivariate analyses yielded the same hazard ratios with or without the inclusion of Rh status (*data not shown*). Our results were not statistically significant for blood group AB in the multivariate analyses for CHD alone, but approached significance (HR 1.18 [95% CI: 0.99-1.42], p=0.068) (*data not shown*).

When the analysis was restricted to older women (≥40 years), those with blood group A had a statistically significant 40% higher risk of CHD events, compared to those with group O (HR 1.40 [95% CI: 1.01-1.92]), after adjusting for other baseline characteristics (Table III). Older age, living in regions outside Montreal and Quebec City and being Rh positive were also significant. No blood group was associated with a statistically higher adjusted hazard ratio for CVD in females aged ≥40 years. Again, these multivariate analyses yielded the same hazard ratios with or without the inclusion of Rh status (*data not shown*).

Discussion

Among our healthy young blood donors, only those with blood group AB had a higher hazard ratio of hospitalisation or death because of CHD or CVD,

Table I - Hospital admissions or deaths attributable to a combination of coronary heart disease, cerebrovascular disease or peripheral vascular disease according to the baseline characteristics of the blood donors.

Baseline characteristics	Number (%)	Person-years	Number of hospitalisations or deaths	Rate*	Unadjusted rate ratio (95% CI)	p
Overall	64,868 (100)	741,290	2,921	3.94		
Sex						
Female	26,492 (40.8)	295,144	331	1.12	Ref.	
Male	38,376 (59.2)	446,145	2,590	5.81	5.176† (4.617 to 5.804)	<0.0001
Age (years)						
18-29	16,760 (25.8)	196,383	52	0.26	Ref.	
30-39	17,814 (27.5)	227,854	368	1.62	6.100† (4.562 to 8.155)	<0.0001
40-49	17,194 (26.5)	192,727	1,013	5.26	19.85† (15.02 to 26.23)	<0.0001
50-59	10,286 (15.9)	99,584	1,036	10.40	39.29† (29.74 to 51.91)	<0.0001
≥60	2,814 (4.3)	24,741	452	18.27	69.00† (51.78 to 91.93)	<0.0001
Blood Group						
A	27,576 (42.5)	316,377	1,294	4.09	1.084† (1.001 to 1.172)	0.0461
B	6,674 (10.3)	77,236	280	3.63	0.960† (0.843 to 1.094)	0.5425
AB	2,892 (4.5)	33,236	160	4.81	1.275† (1.081 to 1.504)	0.0039
O	27,726 (42.7)	314,440	1,187	3.77	Ref.	
Rh factor						
Positive	52,480 (80.9)	600,201	2,369	3.95	1.009† (0.920 to 1.107)	0.8523
Negative	12,388 (19.1)	141,089	552	3.91	Ref.	
Region						
Montreal	30,348 (46.8)	358,187	1,245	3.48	Ref.	
Quebec	9,714 (15.0)	107,694	465	4.32	1.242† (1.169 to 1.369)	<0.0001
Other	24,806 (38.2)	275,409	1,211	4.40	1.265† (1.117 to 1.382)	<0.0001
Previous donations						
None	18,707 (28.8)	207,748	559	2.69	Ref.	
1-3	26,972 (41.6)	319,072	1,170	3.67	1.363† (1.232 to 1.507)	<0.0001
4-6	9,588 (14.8)	115,229	592	5.14	1.909† (1.701 to 2.143)	<0.0001
≥7	9,601 (14.8)	99,240	600	6.05	2.247† (2.002 to 2.521)	<0.0001
Coronary heart disease	64,868	741,290	2,431	3.28		
Cerebrovascular disease	64,868	741,290	451	0.61		
Peripheral vascular disease	64,868	741,290	238	0.32		

*Per 1,000 person-years, hospital admissions and deaths combined. †Crude (unadjusted) rate ratio, comparing the rate of CHD/CVD/PVD with the reference group of that baseline characteristic. CI: confidence interval.

with our without PVD, compared to people with blood group O. However, among people aged ≥40 years, only females with blood group A had a higher risk of CHD.

Our results confirm those of He *et al.*[7] who demonstrated a higher risk of incident CHD in subjects with blood group AB using two large prospective cohorts, the Nurses' Health Study (NHS) and the Health Professionals Follow-up Study (HPFS). However, He *et al.* also concluded that blood groups B and A were associated, to a lesser extent, with higher risk. These findings are probably due to a higher number of incident cases (4,070 cases of CHD in the analysis by He *et al*. *vs* 2,431 cases in our study) which are related to a longer follow-up (26 years in the NHS and 24 years in the HPFS *vs* 19 years in our study) and older age (46 years in the NHS and 53 years in the HPFS *vs* 38 years in our study). The increased risk of CVD among people with blood group AB has also been shown[5]. Nevertheless, the risk of CVD alone was not associated with any blood group in our study but this is also probably due to a limited number of events (n=451).

The association of blood group A with CHD has been known since its demonstration in 1976 in the Framingham Heart study[11]. Other studies found this relationship and this seems to be related to early detection of CHD[12]. The association of only blood group A and CHD can be linked to an allele located upstream of the ABO gene that correlates with blood group A and has been independently associated with recurrent myocardial

Table II - Multivariate Cox regression models for risk of the combination of coronary heart disease, cerebrovascular disease or peripheral vascular disease among blood donors with different blood groups and for the combination of coronary heart disease or cerebrovascular disease.

	Combination of coronary heart disease, cerebrovascular disease or peripheral vascular disease			Combination of coronary heart disease or cerebrovascular disease		
	HR	*95% CI*	*p*	*HR*	*95% CI*	*p*
Sex, Male	3.64	3.24-4.08	<0.0001	3.67	3.26-4.13	<0.0001
Age, per 1 year	1.09	1.09-1.09	<0.0001	1.09	1.09-1.09	<0.0001
Year of entry in cohort	0.98	0.97-1.00	0.0043	0.99	0.97-1.00	0.0077
Region						
Quebec *vs* Montreal	1.21	1.09-1.35	0.0004	1.20	1.08-1.34	0.0009
Others *vs* Montreal	1.14	1.06-1.24	0.0011	1.14	1.05-1.24	0.0015
Number of previous donations, per 1 donation	1.00	0.99-1.00	0.4793	1.00	0.99-1.01	0.7099
Eligible donors *vs* disqualified donors	1.04	0.95-1.14	0.4165	1.05	0.95-1.15	0.3231
Blood group						
A *vs* O	1.06	0.98-1.14	0.1864	1.06	0.98-1.15	0.1733
B *vs* O	0.96	0.84-1.09	0.5350	0.95	0.83-1.08	0.4157
AB *vs* O	1.19	1.01-1.40	0.0385	1.23	1.04-1.45	0.0168
Rh, positive	1.01	0.92-1.11	0.8212	1.01	0.92-1.11	0.8054

HR: hazard ratio; CI: confidence interval.

Table III - Multivariate Cox regression models for risk of coronary heart disease and cerebrovascular disease among female blood donors aged ≥40 years with different blood groups.

	Coronary heart disease			Cerebrovascular disease		
	HR	*95% CI*	*p*	*HR*	*95% CI*	*p*
Age, per 1 year	1.08	1.06-1.11	<0.0001	1.10	1.07-1.14	<0.0001
Year of entry in cohort	1.02	0.98-1.07	0.2886	0.94	0.88-1.01	0.0953
Region						
Quebec *vs* Montreal	0.89	0.55-1.46	0.6508	0.66	0.30-1.41	0.2793
Others *vs* Montreal	1.58	1.16-2.16	0.0039	1.00	0.61-1.61	0.9824
Number of previous donations, per 1 donation	0.96	0.93-1.00	0.0695	0.97	0.91-1.03	0.3494
Eligible donors *vs* disqualified donors	0.78	0.54-1.11	0.1635	1.13	0.60-2.15	0.7051
Blood group						
A *vs* O	1.40	1.01-1.92	0.0406	0.86	0.52-1.43	0.5700
B *vs* O	1.05	0.62-1.76	0.8669	0.92	0.42-1.99	0.8275
AB *vs* O	1.53	0.83-2.84	0.1744	1.73	0.76-3.93	0.1898
Rh, positive	1.73	1.13-2.65	0.0125	1.35	0.73-2.50	0.3456

HR: hazard ratio; CI: confidence interval.

infarction or cardiac death[13]. Other mechanisms have been proposed to explain the association between blood group and CHD, but a unifying theory remains elusive as discussed by Zhou *et al*. in their recent review[14]. However, in another review, one explanation for the association of ABO blood group and CHD was directed towards elevated levels of von Willebrand factor (VWF) and consequently, of factor VIII in the plasma, as a risk factor for CHD and also towards variants at ABO loci associated with increased levels of plasma lipid and inflammatory markers[15]. Other studies have found contradictory results[16,17], one potential explication being the various designs of the studies. Some were cross-sectional studies[17], investigating the risk factors

for CHD prevalence, others studied CHD deaths in patients with CHD[3], while others evaluated the incidence of CHD using a prospective design[2,7]. Besides these, a recent prospective cohort study demonstrated that cardiovascular mortality was significantly increased in subjects with non-O blood groups[18]. In a subgroup of this cohort it was found that subjects with blood group A had higher plasma levels of total cholesterol and low-density lipoprotein.

Our study has several limitations, some of which have been previously described[10], such as the possible bias according to successful traceability of subjects within the provincial health care registry. The lack of information on risk factors and clinical data is the most important limit. However, as these people are successful blood donors, we can hypothesise that the prevalence of risk factors for cardiovascular diseases in this cohort was quite low. Moreover, the linkage with health administrative data ensures that we did not miss any important events. The hospital database has been demonstrated to be reliable, especially with regards to cardiac outcomes[19]. The exclusion of outpatient CHD, CVD or PVD diagnoses could be seen as a limitation but these are included in other health administrative databases that have their own limitations[20]. Finally, we did not include the analysis of subjects with A1 and A2 subtypes, which could have further expanded our results since they are associated with distinct thrombotic risks according to their particular level of VWF.

Conclusions

In conclusion, our results suggest that associations between AB or A blood groups and arterial thrombosis exist, especially in older women, but should be further investigated, as suggested by Franchini *et al*., in other large prospective studies[21] as these diseases are the results of complex interactions between genetic, behavioural, metabolic, psychological, social and environmental risk factors.

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Authorship contributions

All of the Authors contributed to the conception and design of the study, and analysed and interpreted the data. All of the Authors critically revised the manuscript for important intellectual content and approved the final version submitted for publication. CB: literature review, drafting of manuscript; MG and GD: contextualisation of the results; YG: acquisition of data, statistical analyses.

The Authors declare no conflicts of interest.

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