sciendo

CLINICAL RESEARCH

Blood pressure in haemophilia and its relation to clotting factor usage

Srila Gopal, Richard FW Barnes, Doris V Quon, Hao Wei (Linda) Sun, Shannon Jackson, Annette von Drygalski

Background: Patients with haemophilia have a higher prevalence of hypertension than the general population that cannot be explained by traditional cardiovascular risk factors such as age, race, diabetes or obesity. Patients with severe haemophilia, who are on clotting factor prophylaxis, have a higher prevalence of hypertension compared to patients with milder forms of haemophilia, who infuse clotting factor less frequently. This raises the question of whether there is a link between clotting factor usage and blood pressure in haemophilia patients. **Methods:** Data was collected from 193 patients with severe haemophilia presenting to three haemophilia treatment centres in the United States and Canada, including age, body mass index (BMI), blood pressure (BP), Hepatitis C (HCV) and Human Immunodeficiency Virus (HIV) infection status, and clotting factor usage from pharmacy prescriptions (units/kg/year). The correlation between BP and factor usage was examined using quantile regression models. **Results:** Systolic and diastolic BP plotted against factor use showed a cone-shaped scatter of points. There was no association between clotting factor usage and higher systolic or diastolic BP. **Conclusion:** Our observations provide no evidence for an association between increased clotting factor usage and high BP.

Keywords: *Haemophilia, hypertension, clotting factor use, blood pressure*

© Shutterstock

Hypertension is an increasingly recognised problem in haemophilia and is currently not explained by the usual risk factors. Coagulation factors may play a role in blood pressure control.

SRILA GOPAL
Fellow, Hemostasis and Thrombosis, Department of Medicine, University of California San Diego, San Diego, CA, USA. Email: srgopal@ucsd.edu

RICHARD FW BARNES
Statistician, Hemophilia and Thrombosis Treatment Center, Department of Medicine, University of California San Diego, San Diego, CA, USA

DORIS V QUON
Medical Director, Orthopaedic Hemophilia Treatment Center, Orthopaedic Institute for Children, Los Angeles, CA, USA

HAO WEI (LINDA) SUN
Assistant Professor, Division of Hematology, Department of Medicine, University of Alberta, Edmonton, Canada

SHANNON JACKSON
Clinical Associate Professor, Division of Hematology, Department of Medicine, St. Paul's Hospital and University of British Columbia, Vancouver, Canada

ANNETTE VON DRYGALSKI
Associate Professor of Medicine and Director of the Hemophilia and Thrombosis Treatment Center, Department of Medicine, University of California San Diego, San Diego, CA, USA; Department of Molecular Medicine, The Scripps Research Institute, Department of Molecular Medicine, La Jolla, USA

Haemophilia A and B are rare X-linked inherited bleeding disorders, caused by deficiency of coagulation factors VIII and IX, respectively. The availability of clotting factor concentrates has revolutionised the treatment of haemophilia, with the life spans of people with haemophilia (PWH) nearing that of the general population [1]. PWH are now faced with diseases of the ageing general population, such as cardiovascular disorders. It has been shown that haemophilia patients have a higher prevalence of hypertension, and also higher blood pressure (BP) when compared to age- and gender-matched controls in the general population [2-4]. Of note, hypertension can be apparent in young adulthood, and often remains unnoticed and untreated [2]. Uncontrolled BP is an independent risk factor for intracranial haemorrhage (ICH) [5], which is of particular concern in haemophilia, where patients are predisposed to bleeding. ICH is 20-50 times more frequent in patients with haemophilia compared to the general male population and carries a mortality rate of around 20% [6].

Risk factors for hypertension, such as age, obesity, renal dysfunction, diabetes mellitus and smoking, are similar in PWH and the general population [2,7] and do not explain the increased prevalence of hypertension seen in PWH [7]. In fact, PWH have better cardiovascular risk profiles, with lower body mass index (BMI), more favourable cholesterol, better renal function, and less smoking or diabetes [7 8]. Subsequent examination of haemophilia-specific factors, such as urogenital bleeding/renal dysfunction [9] or joint-specific alterations [10] have shown that abnormal synovial vascular remodelling in association with joint bleeding is associated with higher BP [11]. These vascular changes are most pronounced in the arthropathic joints of patients with (moderately) severe haemophilia (plasma Factor VIII or Factor IX activity levels ≤ 2%), who administer clotting factor concentrates for prevention or treatment of bleeding. In contrast, patients with moderate and mild haemophilia (plasma factor activity level > 2%) have less frequent bleeding episodes, use clotting factor concentrates only sporadically, and have lower odds of hypertension [2,3]. This, therefore, raises the question of whether clotting factor usage could be involved in raising BP, since such an association would have direct implications for patient management. Here, we report the results from a study investigating the relationship between BP and clotting factor consumption in a cohort of around 200 patients with severe haemophilia from three haemophilia treatment centres (HTCs) in North America.

METHODS

Patient selection

Data was collected retrospectively for patients with severe haemophilia (factor level < 1%), ≥ 18 years of age seen regularly at three HTCs in the United States and Canada: the University of California San Diego (2012–2013), the Hemophilia Program of British Columbia, Vancouver (2012–2014), and the Los Angeles Orthopedic Hospital (2003–2012). Patient confidentiality safeguards and data acquisition methods were approved by the Institutional Review Boards of all three institutions. Data extracted included demographic information on age and ethnicity, weight, height, haemophilia type and severity, HCV (by serology) or HIV status or reported history thereof, and medication history. For each patient, the most recent information on factor use was extracted from pharmacy prescriptions, or in Canada, the amount distributed to outpatients from the hospital, and presented as units per kilogram per year. Details on the exact clotting factor product were collected where available. Patients with mild and moderate haemophilia were excluded, as were patients taking anti-hypertensive medications, those with no record of factor use, and those using very large amounts of factor (> 20,000 units/kg/year). Patients with current inhibitory antibodies against Factor VIII or Factor IX were excluded from analysis. BP measurements were taken for the three clinic visits closest to the prescription date. BP in all clinics was measured in accordance with the recommendations of the American Heart Association (AHA) [12].

Statistical methods

Preliminary exploratory analysis showed that the rate of change of BP in relation to factor use varied with the level of BP, and that quantile regression would therefore be appropriate [13,14]. Quantile regression estimates the association between quantiles of the response variable (in the case the BP), for example the 10th, 50th or 90th percentile (the 0.1, 0.5 and 0.9 quantiles, respectively) and the independent variable (in this case factor use). The regression for the 50th percentile (0.5 quantile) is analogous to ordinary linear regression, the difference being that it estimates the median instead of the mean. The 0.1 quantile regression is a model fitted to the 10th percentile, and similarly the 0.9 quantile regression is fitted to the 90th percentile.

Confidence intervals and p-values for the regression coefficients were calculated by the rank and rank score methods, respectively [15]. Measures of fit were

calculated by means of an SAS macro for calculating goodness-of-fit statistics for quantile regression, [16] using the R1, "a local measure of goodness of fit for a particular quantile" [17] ranging in value from 0 to 1.

Each patient's BP value comprised either his single value, if only one measurement had been made, or was calculated as the mean of two or three measurements. Since there was evidence from previous analyses that single measurements gave higher BP values than the average of two or three measurements, we took this into account by creating a binary variable (BPnum), where 0 is 2 or 3 measurements, and 1 is a single measurement.

Models were run separately for systolic BP (SBP) and diastolic BP (DBP). First, the model was run with only factor use as a predictor, followed by each of the potential covariates in turn: logBMI, age, quadratic age (that is, age + age^2), BPnum, haemophilia type (Haemophilia B vs A), ethnicity (Caucasian or non-Caucasian), HCV and HIV. Three quantiles were considered (the 0.1, 0.5 and 0.9 quantiles), and there were consequently three regression equations. In this sample there was a complication: each quantile regression was affected differently by each covariate. The variable that made the best overall contribution to explaining the variation in blood pressure was selected. This step was then repeated until adding another covariate made no further improvement to the model.

RESULTS

Patient characteristics

Information was collected from a total of 583 PWH, with a median age of 41 years and BMI of 26.1 kg/m^2. After exclusion of patients who did not meet the study criteria, the final cohort presented in this analysis includes 193 patients with severe haemophilia. Congruent with the reported overall incidence of haemophilia A and B (≈5:1), the majority of patients had haemophilia A, and 15% had haemophilia B. The median ages were 30 and 37 years for those on prophylaxis and on demand respectively (Table 1). The majority of the patients (63%, n=122) were positive for HCV viral infection (by serology) and 25% (n=48) were positive for HIV infection. Two or three BP

Table 1: Demographic characteristics of patients by factor use category

	MEDIAN (IQR)			COMPARISON OF PROPHYLAXIS AND ON-DEMAND PATIENTS, WILCOXON W (P)
	ALL PATIENTS	PROPHYLAXIS	ON DEMAND	
Age (years)	30 (25, 41)	30 (25, 38)	37 (26, 49)	4510 (0.010)
Systolic BP (mmHg)	125 (118, 133)	124 (118, 132)	125 (115, 134)	3706 (0.953)
Diastolic BP (mmHg)	76 (71, 82)	76 (71, 81)	78 (71, 85)	3950 (0.462)
BMI (kg/m^2)	24.5 (22.0, 27.8)	24.5 (22.4, 27.8)	24.4 (21.4, 28.7)	2878 (0.995)
Factor usage (units/kg/year)	3651 (1705, 5771)	4179 (2889, 6551)	818 (485, 1409)	1341 (<0.001)
	ALL PATIENTS	PROPHYLAXIS	ON DEMAND	COMPARISON OF PROPHYLAXIS AND ON-DEMAND PATIENTS, X^2 (P)
Number	193	151	39	
Single BP reading 2 or 3 BP readings	33 160	24 127	9 30	0.670 (0.413)
Haemophilia type: A B	162 30	129 22	31 7	0.114 (0.736)
Non-Caucasian Caucasian	87 103	69 80	17 21	0.000 1.000
HCV: HCV- HCV+	64 125	54 95	10 27	0.744 0.388
HIV: HIV- HIV+	143 50	118 33	24 15	3.691 0.055

The upper half of the table shows median and inter-quartile ranges (IQR) for continuous variables, while the lower half shows frequencies of each categorical variable.

readings were available for 81% of patients (n=157), while the others had a single reading. Median annual clotting factor usage was five times greater for patients on prophylaxis compared to those using factor on demand (Table 1). Based on the AHA 2017 criteria for diagnosis of hypertension [18], 45% of patients had either stage 1 or 2 hypertension (Table 2). All patients used standard half-life factor replacement formulations as this study was performed before extended half-life formulations were routinely used in clinical practice.

Six patients who used high doses of clotting factor (between 10,000 and 20,000 units/kg/year) were excluded from regression analysis for disproportionate leverage. Their data points lay outside of the main cloud of data points, and therefore formed a completely different distribution; however, their data are shown in the graphs.

Table 2: Hypertension categories based on American Heart Association guidelines, 2017

CATEGORY	BP RANGE (MM HG)	NUMBER	%
Normal	< 120/ 80 mm Hg	54	28
Elevated	SBP 12-129 mm Hg	53	27
Hypertension Stage 1	SBP 130-139 or DBP 80-89 mm Hg	58	30
Hypertension Stage 2	SBP > 139 mm Hg or DBP> 90 mm Hg	28	15

Association between clotting factor use and systolic blood pressure

Systolic BP plotted against factor use showed an unusual configuration of points. The scatter of points could be described as a cone or fan, with a wide range of BP values to the left-hand side of the graph. The cloud of points tapers off to a few closely spaced values at the right corresponding to patients using large doses of factor. There was no difference in systolic BP between patients on prophylaxis and those using factor on demand (Table 1, Figure 1A).

For patients on prophylaxis, the quantile regression of systolic BP on factor use is shown in Figure 1B and Table 3A. Of note, the upper quantile, represented by the uppermost line, showed a slight negative correlation between higher BP and factor use. However, the confidence interval for the regression coefficient included zero, indicating that the slope was not different from a flat line. In addition, the R1 values show the model to be a very poor fit (Table 3A). The slopes for the lower and median quantiles, which represent BP readings in the normal range, were even shallower.

Testing for covariates showed that only logBMI improved the model for systolic BP (Table 3B, Figure 1C). The effect of adjusting for logBMI was to reduce the slopes so that all three lines were flat (Figure 1C). Taken together, these observations show no association between systolic BP and factor usage.

Figure 1. Plots of systolic BP values in relation to factor use in PWH

Systolic BP readings are plotted against factor use for all patients (Figure 1A), patients on prophylaxis only (Figure 1B), and patients on prophylaxis after adjusting for log BMI (Figure 1C). The quantile regression models were calculated for values of factor usage up to 10,000 units/kg/year, but the regression lines are projected forward to cover all points. Regression lines for three quantiles are shown: 0.1 or lower (green), 0.5 or median (dark blue), and 0.9 or upper (red).

Figure 1A. Patients on demand (green) and on prophylaxis (blue) shown together

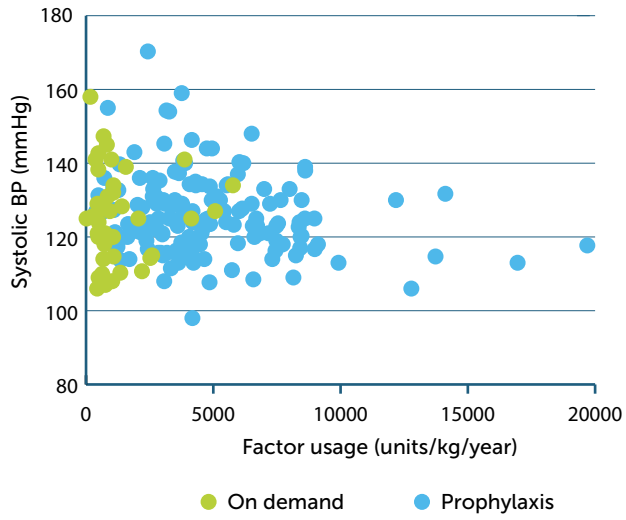


Figure 1B. Quantile regression of systolic BP on factor usage for patients on prophylaxis

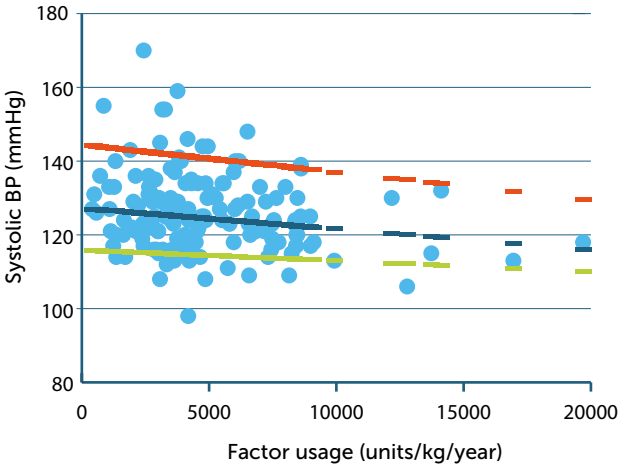
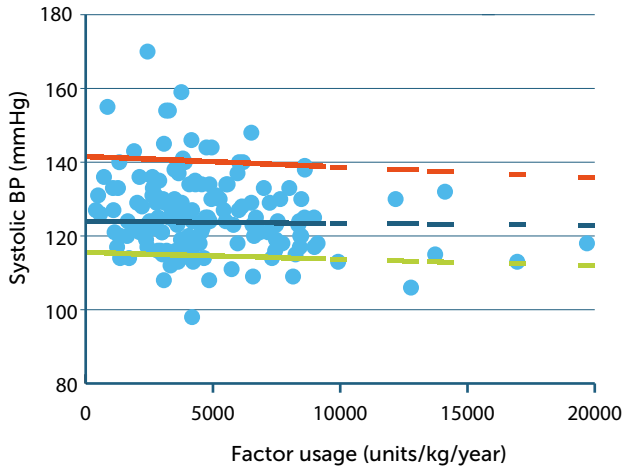


Figure 1C. Quantile regression of systolic BP on factor usage, adjusted for logBMI, for patients on prophylaxis



Association between clotting factor use and diastolic blood pressure

Diastolic BP plotted against factor use showed a similar scatter of points, again resembling a cone or fan (Figure 2A). For patients on prophylaxis, the quantile regression of diastolic BP on factor use is shown in Figure 2B and Table 3C.The lower quantile showed a marked negative slope (Table 3C).

Examining each covariate in turn revealed that the best model for diastolic BP included logBMI and HCV (Table 3D, Figure 2C). After adjusting for logBMI and HCV the negative slope for the lower quantile remained, but with a confidence interval that covered zero. The slopes for the median and upper quantiles were effectively flat (Table 3D). In summary, there was no association between elevated diastolic BP and increased factor use, but rather a weak indication that the lowest blood pressure levels might be associated with higher doses of factor.

Figure 2. Plots of diastolic BP values in relation to factor use in PWH

Diastolic BP readings are plotted against factor use for all patients (Figure 2A), patients on prophylaxis only (Figure 2B), and patients on prophylaxis after adjusting for log BMI and HCV status (Figure 2C). The quantile regression models were calculated for values of factor usage up to 10,000 units/kg/year, but the regression lines are projected forward to cover all points. Regression lines for three quantiles are shown: 0.1 or lower (green), 0.5 or median (dark blue), and 0.9 or upper (red).

Figure 2A. Patients on demand (green circles) and on prophylaxis (blue circles) shown together

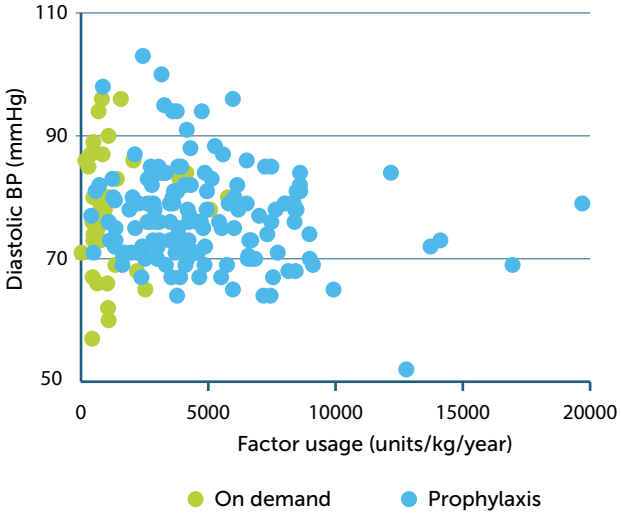


Figure 2B. Quantile regression of diastolic BP on factor usage for patients on prophylaxis

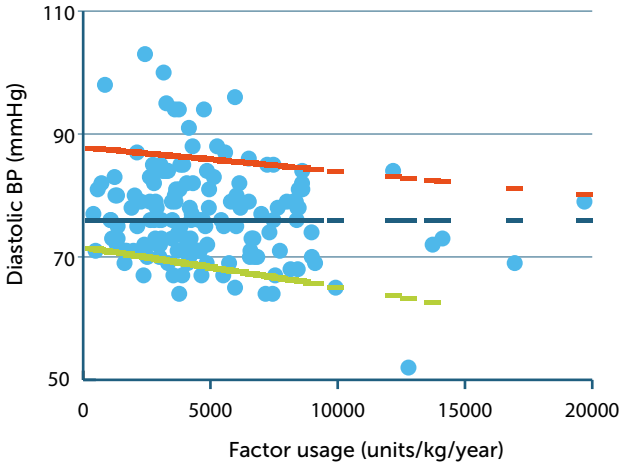
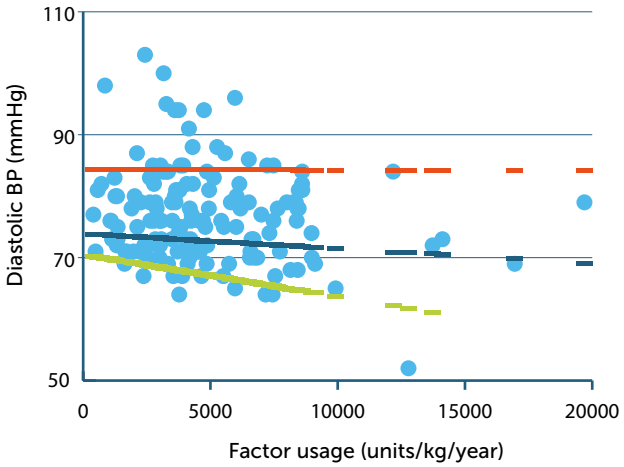


Figure 2C. Quantile regression of diastolic BP on factor usage, adjusted for logBMI and HCV, for patients on prophylaxis



J Haem Pract 2019; 6(1). doi: 10.17225/jhp00147

Table 3. Quantile regression for systolic and diastolic blood pressure on factor usage for patients on prophylaxis

The regression coefficients for the 0.1 (lower), 0.5 (median) and 0.9 (upper) quantiles are shown.

3A. Regression coefficients for systolic blood pressure (unadjusted)

QUANTILE	REGRESSION COEFFICIENT X 10^{-3}	95% CI X 10^{-3}	R1	P
0.1 Lower	-0.29	-1.68, 0.38	0.004	0.366
0.5 Median	-0.57	-1.43, 0.13	0.012	0.146
0.9 Upper	-0.75	-3.43, 0.75	0.001	0.378

3B. Regression coefficients for systolic blood pressure, adjusted for logBMI

QUANTILE	REGRESSION COEFFICIENT X 10^{-3}	95% CI X 10^{-3}	R1	P
0.1 Lower	-0.19	-1.45, 0.70	0.236	0.634
0.5 Median	-0.05	-0.89, 1.30	0.235	0.704
0.9 Upper	-0.29	-3.05, 2.63	0.213	0.672

3C. Regression coefficients for diastolic blood pressure (unadjusted)

QUANTILE	REGRESSION COEFFICIENT X 10^{-3}	95% CI X 10^{-3}	R1	P
0.1 Lower	-0.65	-1.26, -0.21	0.044	0.002
0.5 Median	0.00	-1.31, 0.70	0.000	0.523
0.9 Upper	-0.39	-2.19, 1.29	0.009	0.596

3D. Regression coefficients for diastolic blood pressure, adjusted for logBMI and HCV

QUANTILE	REGRESSION COEFFICIENT X 10^{-3}	95% CI X 10^{-3}	R1	P
0.1 Lower	-0.67	-1.33, -0.19	0.254	0.061
0.5 Median	-0.24	-0.65, 0.51	0.261	0.914
0.9 Upper	-0.01	-2.59, 2.18	0.266	0.698

DISCUSSION

Our observations suggest that clotting factor usage does not adversely affect BP. We note that all the regression slopes in Table 2 were either flat or negative, and none were positive.

The weak negative association between the highest quantile of systolic BP and factor usage, and the negative association between the lowest quantile diastolic BP and factor usage, intrigued us from a biologic standpoint and enables us to speculate around hypocoagulability associated with congenital clotting factor deficiencies and BP regulation. Factor VIII and Factor IX are critical components of the intrinsic pathway of coagulation and are necessary for thrombin generation. In addition to clot formation, thrombin also plays a role in regulating fibrinolysis by both stabilising clot structure via activation of Factor XIII [19], and inhibiting fibrinolysis via thrombin activatable fibrinolysis inhibitor (TAFI) [20]. This appears relevant since patients with hypertension have abnormalities in fibrinolysis pathways [21]. For instance, abnormal Factor XIII activity may contribute to hypertension, although the evidence is conflicting. While some reports suggest a role for activated Factor XIII in increasing blood pressure [22], others suggest that the lack of Factor XIII could be pro-inflammatory and activate the innate immune system [23], which in turn is linked to hypertension [24]. Another notable player is TAFI, which is not only a potent inhibitor of fibrinolysis, but also has anti-inflammatory properties modulated by bradykinin [25]. TAFI activation is impaired in haemophilia due to a lack of thrombin generation [26,27] and may influence bradykinin, which is important for regulating BP by modulating critical pathways including the renin-angiotensin system, as well as vasodilators including prostaglandin, prostacyclin, and nitric oxide. Bradykinin also regulates sodium and water balance in the kidneys. Reduced activity of bradykinin has been associated with hypertension in various animal models and human studies [28]. Thrombin is also necessary for inactivation of plasminogen activator inhibitor (PAI-1) [29]. PAI-1, in addition to its anti-fibrinolytic function, is an acute phase reactant, implicated in inflammatory processes [30], and has been demonstrated to be associated with elevated systolic and diastolic BP in large cardiovascular cohort studies [21]. Taken together, it is therefore plausible that abnormal thrombin generation as a result of Factor VIII or Factor IX deficiency may alter activation of thrombin-dependent molecules that serve dual roles in coagulation and inflammation, thereby influencing molecular pathways of blood pressure regulation.

Unlike other coagulation factors that are synthesised in hepatocytes, Factor VIII is synthesised in vascular endothelial cells [31,32]. Therefore, it is possible that Factor VIII contributes to maintaining vascular endothelial integrity. In support of this concept, it has been described that PWH have abnormal endothelial cell function when compared to healthy controls [33,34]. Endothelial dysfunction has been associated with hypertension [35], particularly in the ageing population.

Another important factor to consider is whether the timing of clotting factor initiation has any bearing on

BP in haemophilia. Primary prophylaxis with clotting factor in haemophilia begins in early childhood, prior to any documented joint disease and before the age of three years [36]. Primary prophylaxis became a realistic therapeutic strategy only recently [37], and our study only evaluated adult PWH who were unlikely to have had access to primary prophylaxis in their childhood.

In summary, there is evidence in the literature to suggest a role for coagulation factors in BP control. We believe that some of the observations presented here align with this concept, and provide motivation for new studies to improve our understanding of the role of specific coagulation factors in BP regulation.

LIMITATIONS

Haemophilia is a rare disease and our observations are limited to a large extent by sample size. Patients already on anti-hypertensive medications were excluded from our analysis and this could be a potential limitation to our data. The reason for their exclusion was due to the relatively small number of patients identified in this category [39], which was not enough to conduct a multivariate analysis to elucidate trends in blood pressure. Patients with high factor usage were excluded from the regression analysis; using a larger sample of patients in this range would also be beneficial in order to examine the association with factor use further. Lack of data pertaining to physical activity and exercise, joint health status, HIV medication history, active HCV infection status, all of which have been known to influence BP, is a further limitation to our study. We also acknowledge that the lack of data pertaining to pain and pain management are limitations. The PWH included in the study used, almost exclusively, a wide variety of recombinant clotting factor brands, and the described effects are most likely a class effect and not attributable to a single product. However, results may not apply to plasma-derived products, or to extended half-life products, which were introduced after data collection for this study was completed. We were unable to examine for differences or similarities in the relationship between BP and factor use in haemophilia A vs. haemophilia B patients due to the very small number of haemophilia B patients in the study.

CONCLUSIONS AND FUTURE DIRECTIONS

Hypertension is an increasingly recognised problem in haemophilia and is currently not explained by the usual risk factors. In searching for haemophilia-specific associations, we examined the effects of clotting factor replacement therapy on BP. There were no associations to suggest that clotting factors could be associated with elevated BPs in our study cohort of PWH. The aetiology of hypertension in haemophilia remains elusive, and will require further study. Factors to consider in future studies would include pain due to joint disease, lack of physical activity due to advanced joint disease, the effect of HCV or HIV infection status, or medications used to treat these disorders.

AUTHORSHIP CONTRIBUTIONS

RFWB and AvD designed the study and RFWB analysed the data. SG contributed to the data analysis and data interpretation, and wrote the first draft of the manuscript. AvD, DVQ, HWS and SJ contributed clinical data sets and critically reviewed the manuscript. AvD provided the study concept and oversight, and contributed to manuscript writing.

ACKNOWLEDGEMENTS

This work was funded by Health Resources and Services Administration (HRSA) H30MC24045 awarded to Annette von Drygalski.

The authors have advised no interests that might be perceived as posing a conflict or bias.

This article reports a retrospective study in which no human participants or animals are directly involved.

ORCID

Srila Gopal https://orcid.org/0000-0003-2732-3216
Richard FW Barnes https://orcid.org/0000-0002-2721-4151
Doris V Quon https://orcid.org/0000-0002-9148-3268
Annette von Drygalski https://orcid.org/0000-0002-9426-6322

REFERENCES

1. Darby SC, Kan SW, Spooner RJ, *et al.* Mortality rates, life expectancy, and causes of death in people with hemophilia A or B in the United Kingdom who were not infected with HIV. *Blood* 2007; 110: 815–25. doi: 10.1182/*blood*-2006-10-050435.
2. von Drygalski A, Kolaitis NA, Bettencourt R, *et al.* Prevalence and risk factors for hypertension in hemophilia. *Hypertension* 2013; 62: 209–15. doi: 10.1161/HYPERTENSIONAHA.113.01174.
3. Fransen van de Putte DE, Fischer K, Makris M, *et al.* Increased prevalence of hypertension in haemophilia patients. *Thromb Haemost* 2012; 108: 750–5. doi: 10.1160/TH12-05-0313.
4. Minuk L, Jackson S, Iorio A, *et al.* Cardiovascular disease (CVD) in Canadians with haemophilia: Age-Related CVD in Haemophilia Epidemiological Research (ARCHER study). *Haemophilia* 2015; 21: 736–41. doi: 10.1111/hae.12768.
5. Ariesen MJ, Claus SP, Rinkel GJ, Algra A. Risk factors for intracerebral hemorrhage in the general population: a systematic review. *Stroke* 2003; 34: 2060–5. doi: 10.1161/01.STR.0000080678.09344.8D.

6. Stieltjes N, Calvez T, Demiguel V, *et al.*; French ICH Study Group. Intracranial haemorrhages in French haemophilia patients (1991-2001): clinical presentation, management and prognosis factors for death. *Haemophilia* 2005; 11: 452–8. doi: 10.1111/j.1365-2516.2005.01090.x.
7. Barnes RF, Cramer TJ, Sait AS, Kruse-Jarres R, Quon DV, von Drygalski A. The hypertension of hemophilia is not explained by the usual cardiovascular risk factors: results of a cohort study. *Int J Hypertens* 2016; 2016: 2014201. doi: 10.1155/2016/2014201.
8. Sait AS, Kuo A, Bettencourt R, Bergstrom J, Allison M, von Drygalski A. Risk assessment for coronary heart disease in patients with haemophilia: a single centre study in the United States. *Haemophilia* 2014; 20: 763–70. doi: 10.1111/hae.12472.
9. Sun HL, Yang M, Sait AS, von Drygalski A, Jackson S. Haematuria is not a risk factor of hypertension or renal impairment in patients with haemophilia. *Haemophilia* 2016; 22: 549–55. doi: 10.1111/hae.12921.
10. Bhat V, Olmer M, Joshi S, *et al.* Vascular remodeling underlies rebleeding in hemophilic arthropathy. *Am J Hematol* 2015; 90: 1027–35. doi: 10.1002/ajh.24133.
11. Barnes RFW, Cramer TJ, Hughes TH, von Drygalski A. The hypertension of hemophilia is associated with vascular remodeling in the joint. *Microcirculation* 2017; 24. doi: 10.1111/micc.12387.
12. Pickering TG, Hall JE, Appel LJ, *et al.* Recommendations for blood pressure measurement in humans and experimental animals: part 1: blood pressure measurement in humans: a statement for professionals from the Subcommittee of Professional and Public Education of the American Heart Association Council on High Blood Pressure Research. *Circulation* 2005; 111: 697–716. doi: 10.1161/01.CIR.0000154900.76284.F6.
13. Koenker R. *Quantile regression.* 2005. New York: Cambridge University Press.
14. Hao L, Naiman D. *Quantile regression.* 2007. Thousand Oaks, CA: Sage Publications.
15. SAS. SAS/STAT 9.22 *User's Guide.* 2010. Cary, NC: SAS Institute Inc. Available from *https://support.sas.com/documentation/cdl/en/statug/63347/HTML/default/viewer.htm* (accessed 26 August 2019).
16. Statcompute. SAS macro calculating goodness-of-fit statistics for quantile regression. 15 April 2017. Available from *https://statcompute.wordpress.com/2017/04/15/sas-macro-calculating-goodness-of-fit-statistics-for-quantile-regression/* (accessed 29 August 2019).
17. Koenker R, Machado J. Goodness of fit and related inference processes for quantile regression. *J Am Stat Assoc* 1999; 94: 1296–310.
18. Whelton PK, Carey RM, Aronow WS, *et al.* 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults: Executive Summary: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Circulation* 2018; 138: e426-e83. doi: 10.1161/CIR.0000000000000597.
19. Schroeder V, Kohler HP. New developments in the area of factor XIII. *J Thromb Haemost* 2013; 11: 234–44. doi: 10.1111/jth.12074.
20. Bouma BN, Mosnier LO. Thrombin activatable fibrinolysis inhibitor (TAFI) – how does thrombin regulate fibrinolysis? *Ann Med* 2006; 38: 378–88. doi: 10.1080/07853890600852898.
21. Poli KA, Tofler GH, Larson MG, *et al.* Association of blood pressure with fibrinolytic potential in the Framingham offspring population. *Circulation* 2000; 101: 264–9. doi: 10.1161/01.CIR.101.3.264.
22. Sane DC, Kontos JL, Greenberg CS. Roles of transglutaminases in cardiac and vascular diseases. *Front Biosci.* 2007; 12: 2530-45.
23. Loof TG, Mörgelin M, Johansson L, *et al.* Coagulation, an ancestral serine protease cascade, exerts a novel function in early immune defense. *Blood* 2011; 118: 2589–98. doi: 10.1182/blood-2011-02-337568.
24. Mian MO, Paradis P, Schiffrin EL. Innate immunity in hypertension. *Curr Hypertens* Rep 2014; 16: 413. doi: 10.1007/s11906-013-0413-9.
25. Myles T, Nishimura T, Yun TH, *et al.* Thrombin activatable fibrinolysis inhibitor, a potential regulator of vascular inflammation. *J Biol Chem* 2003; 278: 51059–67. doi: 10.1074/jbc.M306977200.
26. Mosnier LO, Lisman T, van den Berg HM, *et al.* The defective down regulation of fibrinolysis in haemophilia A can be restored by increasing the TAFI plasma concentration. *Thromb Haemost* 2001; 86: 1035–9.
27. Wyseure T, Cooke EJ, Declerck PJ, *et al.* Defective TAFI activation in hemophilia A mice is a major contributor to joint bleeding. *Blood* 2018; 132: 1593–603. doi: 10.1182/blood-2018-01-828434.
28. Sharma JN. Hypertension and the bradykinin system. *Curr Hypertens Rep* 2009; 11: 178–81.
29. Urano T, Ihara H, Suzuki Y, Takada Y, Takada A. Coagulation-associated enhancement of fibrinolytic activity via a neutralization of PAI-1 activity. *Semin Thromb Hemost* 2000; 26: 39–42.
30. Levi M, Keller TT, van Gorp E, ten Cate H. Infection and inflammation and the coagulation system. *Cardiovasc Res* 2003; 60: 26–39.
31. Fahs SA, Hille MT, Shi Q, Weiler H, Montgomery RR. A conditional knockout mouse model reveals endothelial cells as the principal and possibly exclusive source of plasma factor VIII. *Blood* 2014; 123: 3706–13. doi: 10.1182/blood-2014-02-555151.
32. Everett LA, Cleuren AC, Khoriaty RN, Ginsburg D. Murine coagulation factor VIII is synthesized in endothelial cells. *Blood* 2014; 123: 3697–705. doi: 10.1182/blood-2014-02-554501.
33. Sun H, Yang M, Fung M, *et al.* Adult males with haemophilia have a different macrovascular and microvascular endothelial function profile compared with healthy controls. *Haemophilia* 2017; 23: 777–83. doi: 10.1111/hae.13278.
34. Sartori MT, Bilora F, Zanon E, *et al.* Endothelial dysfunction in haemophilia patients. *Haemophilia* 2008; 14: 1055–62. doi: 10.1111/j.1365-2516.2008.01808.x.
35. Higashi Y, Kihara Y, Noma K. Endothelial dysfunction and hypertension in aging. *Hypertens Res* 2012; 35: 1039–47. doi: 10.1038/hr.2012.138.
36. Srivastava A, Brewer AK, Mauser-Bunschoten EP, *et al.*; Hemophilia Treatment Guidelines Working Group on Behalf of the World Federation of Hemophilia. Guidelines for the management of hemophilia. *Haemophilia* 2013; 19: e1–47. doi: 10.1111/j.1365-2516.2012.02909.x.

37. Manco-Johnson MJ, Abshire TC, Shapiro AD, *et al.* Prophylaxis versus episodic treatment to prevent joint disease in boys with severe hemophilia. *N Engl J Med* 2007; 357: 535–44. doi: 10.1056/NEJMoa067659.

HOW TO CITE THIS ARTICLE:
Gopal S, Barnes RFW, Quon DV, Sun HW, Jackson S, von Drygalski A. Blood pressure in haemophilia and its relation to clotting factor usage. *J Haem Pract* 2019; 6(1): 42-50. *https://doi.org/10.17225/jhp00147*.