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Journal

Microcirculation (New York, N.Y. : 1994), 24(7)

ISSN

1073-9688

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Publication Date

2017-10-01

DOI

10.1111/micc.12387

Received: 9 March 2017 | Accepted: 12 June 2017

DOI: 10.1111/micc.12387

ORIGINAL ARTICLE

WILEY Microcirculation

The hypertension of hemophilia is associated with vascular remodeling in the joint

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Funding information
Biogen, Grant/Award Number: Prevalence and Etiology of Subclinical Joint Bleed; National Hemophilia Foundation/Novo Nordisk, Grant/Award Number: Career Development Award; Health Resources and Services Administration, Grant/Award Number: HRSA service grant H30MC24045

Abstract

Objective: Hemophilic arthropathy is associated with pronounced vascular joint remodeling. Also, compared to the general population, PWH have a higher prevalence of hypertension not explained by usual risk factors. As vascular remodeling in various vascular beds is a hallmark of hypertension, we hypothesized that vascular joint remodeling is associated with elevated blood pressures and hypertension.

Methods: Elbows, knees, and ankles of 28 adult PWH were evaluated for vascular abnormalities with MSKUS/PD, as well as for radiographic and clinical status and pain. Logistic and linear regression models were fitted to examine associations between hypertension, blood pressure, and PD score.

Results: The extent of vascular abnormalities was associated with hypertension and blood pressures. Hypertensive patients had a higher PD score compared to nonhypertensive patients, and the risk of hypertension increased steeply with PD score. SBP was also strongly associated with PD score, while DBP was only weakly associated.

Conclusions: Vascular remodeling in hemophilic joints is associated with hypertension and elevated blood pressures. As hypertension is a grave risk factor for intracranial hemorrhage, a prominent cause of mortality in hemophilia patients, future studies are needed to address the causal pathways between vascular joint remodeling and blood pressure.

KEYWORDS
arthropathy, hemophilia, hypertension, vascular remodeling

1 | INTRODUCTION

Hemophilia is an X-linked bleeding disorder that is characterized by Factor VIII or Factor IX deficiency and occurs with a frequency of one in 5000 to one in 30 000 male live births depending on the type and severity of hemophilia[1,2]. Starting in early childhood, PWH suffer from frequent spontaneous joint bleeding that causes hemophilic arthropathy, clinically characterized by joint deformities, synovial hypertrophy, and destruction of cartilage and bone[3]. While the progression of hemophilic arthropathy can be mitigated by clotting factor replacement therapy, it cannot be entirely abrogated[3]. A marked feature of hemophilia is the higher prevalence of hypertension and higher blood pressures than the general population[4-6]. Pronounced differences can already be observed in young adulthood[5]. One of our previous studies, comparing a cohort of nearly 600 PWH with gender-, age-, and race-matched subjects from the general population, showed that higher

Abbreviations: α-SMA, alpha smooth muscle cell action; BMI, body mass index; DBP, diastolic blood pressure; HIV, human immunodeficiency virus; HJHS, Hemophilia Joint Health Score; hsCRP, high-sensitivity C-reactive protein; HTTC, Hemophilia and Thrombosis Treatment Center; ICH, intracranial hemorrhage; MMP, metalloproteases; MSKUS, musculoskeletal ultrasound; PD, power Doppler; PWH, patients with hemophilia; SBP, systolic blood pressure; TNF-β, tumor necrosis factor beta; TSBP, transformed systolic blood pressure; VAS, visual analog scale.

blood pressure measurements were not explained by differences in the usual risk factors. While risk factors such as BMI, smoking, dyslipidemia, diabetes, and renal function[4,5,7] were associated with systolic and diastolic blood pressures, their prevalence was similar or lower in PWH compared to the general population[5]. Likewise, infection with hepatitis C or HIV, which are relatively common in older PWH, did not explain higher blood pressures in PWH[5]. Furthermore, even after treatment with antihypertensive drugs, PWH still had higher blood pressure values than ordinary males treated with such drugs.

Other studies have compared cardiovascular risk between PWH and the general population by composite scoring of risk factors that included hypertension. However, they disagree as to whether cardiovascular risk is higher in PWH[8,9] and do not allow conclusions regarding the role of hypertension and its associations with other risk factors.

Hypertension in the general population is associated with vascular remodeling in large arteries and the microcirculation of various vascular beds such as in the retina, kidney, or brain[10-13]. In particular in the brain, these vascular changes are thought to contribute to the increased risk of intracranial hemorrhage in hypertensive compared to nonhypertensive subjects[14-16]. Poorly controlled hypertension is therefore of heightened concern in hemophilia, where ICH is a leading cause of death in this patient population[17-19].

A unique feature that distinguishes PWH from the general population is joint bleeding that begins at an early age and results in destructive hemophilic arthropathy[3]. Recent findings demonstrated that hemophilic arthropathy is accompanied by vascular remodeling in hypertrophied and altered intraarticular soft tissue[20,21], reminiscent of vascular remodeling of hypertension in other vascular beds. This observation stimulated the hypothesis that vascular remodeling in joint tissues contributes to the hypertension and abnormal blood pressures in hemophilia. To examine this relationship, we prospectively assessed a cohort of 28 adult PWH at the HTTC at the University of California San Diego. Results revealed that the extent of vascular joint remodeling was strongly associated with risk of hypertension and elevated blood pressures. These findings are novel and are consistent with the hypothesis that vascular remodeling and blood pressure dynamics are linked in PWH. We believe that these observations provide new insights into the etiology of the hypertension of hemophilia.

2 | MATERIALS AND METHODS

2.1 | Participants

Patients with severe (<1% intrinsic clotting factor activity) or moderate (1%-5% intrinsic clotting factor activity) hemophilia A or B, aged ≥21 years, who regularly visit the HTTC at UCSD were prospectively enrolled. The study was approved by the UCSD Human Research Protection Program, and written informed consent was obtained from all patients.

2.2 | Joint evaluations

Six joints were examined for each subject: elbows, knees, and ankles. Joint tissue perfusion was studied using high-resolution MSKUS with the GE Logiq S8 model in patients (General Electrics, Fairfield, CT, USA) with gray scale (B-mode) and PD, using transducer frequencies of 8-16 MHz and standardized protocols[22-24]. Pain in each joint was self-assessed by VAS (0 no pain; 10 worst pain), and then the mean was calculated for each subject. Radiographic and clinical joint status was determined by Pettersson scores (best score=0; worst possible score for all 6 joints=78)[25] and HJHS (best score=0; worst possible score for all 6 joints=124)[26]. PD signal was scored semi-quantitatively[27] in three different anatomical locations in each joint and added to a total score (min=0; max=9) as previously described[20]. The physician performing and interpreting the ultrasound examinations was unaware of blood pressure values and any diagnoses of hypertension. Scoring locations were as follows: elbow: humero-radial joint axial, longitudinal and olecranon fossa; knee: medial and lateral recesses and medial meniscal area; ankle: tibio-talar joint axial, longitudinal, and lateral sinus tarsi.

2.3 | Health history and physical measurements

Data were extracted from electronic medical records and from questionnaires administered at the time of joint ultrasound. Hemophilia type and severity (<1% or ≥1% intrinsic clotting factor activity were defined as severe hemophilia or nonsevere hemophilia, respectively) were recorded. Other information included age, ethnicity, presence of infection with hepatitis C or HIV by serology, medication history, and hsCRP. Blood pressure was measured in accordance with the current recommendations of the American Heart Association[28]. Hypertension was defined as prior physician diagnosis of hypertension and use of antihypertensive medication or at least two elevated blood pressure measurements (systolic blood pressure (SBP) ≥140 mm Hg or diastolic blood pressure (DBP) ≥90 mm Hg) in the 12 months preceding joint assessments. Treated hypertension was defined as reported use of antihypertensive medication during the last year of the study period. Mean SBP and DBP were calculated for each patient from blood pressure measurements during the 12 months preceding the joint evaluation (median number of measurements available for analysis: 7; range 1-37).

2.4 | Statistical analysis

In univariate comparisons, frequencies of categorical variables were tested with Fisher's exact test. For continuous variables, we used medians with interquartile ranges. Tests for continuous variables were made with Wilcoxon and Kruskal-Wallis tests as appropriate. We compared continuous variables against SBP and DBP with Spearman rank correlation coefficients.

We used logistic regression to test the hypothesis that vascular remodeling (measured by PD score) contributes to hypertension (the outcome). We used linear regression to test the hypothesis that vascular remodeling (measured by PD score) contributes to higher blood pressure (systolic and diastolic). We tested for confounders because adjusting for a confounder may reduce or enhance the observed association and therefore influence its interpretation[29]. Each confounder

is assumed to be related to the outcome (hypertension or blood pressure) but is not a consequence of the outcome. In addition, each confounder is assumed to be associated with the independent variable of interest but is not a consequence of that variable[30]. The confounders were age, weight, BMI, hsCRP, clotting factor usage (units/y/kg), Pettersson score, HJHS, and pain score.

We added each suspected confounder by itself to the model and noted the change in value of the regression coefficient for PD score. We retained the confounder that caused the greatest change. Note that it is the change in the value of the regression coefficient for PD score that is important, not the *P*-value for the confounder[29].

The values of SBP were not normally distributed, resulting in residuals from the linear regressions that were negatively skewed. They were transformed using a reflecting transformation TSBP=ln(158 - SBP), where TSBP was the new outcome variable for the regression model[31]. The value of 158 was found by iteration until the transformed variable fitted a normal distribution. Note that with this transformation, a negative regression coefficient indicates a positive association.

Finally, for each final confounder model, we ran a test to ensure that collinearity was not a problem among the independent variables[29].

3 | RESULTS

3.1 | Patient characteristics

Twenty-eight patients with an average age of 37 years were enrolled; their characteristics are shown in Table 1.

TABLE 1 Baseline cohort characteristics

Variable	N (%)	Median (IQR)
Number of patients	28	
Age (y)		37 (29-54)
Race		
White	15 (54%)	
Black/African American	4 (14%)	
Hispanic	4 (14%)	
Other	5 (18%)	
BMI (kg/m^2)		27.3 (24.0-29.4)
Weight (kg)		81 (79-97)
hsCRP (mg/mL)		1.0 (0.5-3.0)
Clotting factor usage (units/kg/y)		4559 (1838-7598)
Blood pressure and hypertension		
Systolic BP (mm Hg)		131 (122-136)
Diastolic BP (mm Hg)		79 (72-85)
Hypertensive	15 (54%)	
Not hypertensive	13 (48%)	
Treated for hypertension	10/15 (67%)	
Hemophilia type		
A	23 (82%)	
B	5 (18%)	
Hemophilia severity		
Severe	19 (70%)	
Not severe	8 (30%)	
Number of joints examined		
Per patient	6	
Total	168	
Joint status		
Pettersson score		26 (10-55)
HJHS		14 (8-24)
Pain score		0.5 (0.2-1.0)
PD score		13 (7-20)

Normal Values: hsCRP <5 mg/mL; Maximum Pettersson Score 78; Maximum HJHS 124.

3.2 | Association of hypertension with vascular changes reflected by PD scores

In univariate analysis, hypertensive patients had a higher median PD score compared to nonhypertensive patients (19 vs 10; *P*=.06), were older (48 vs 30 years; *P*=.04), and used less clotting factor concentrate (3704 vs 6950 units/kg/y; *P*=.03) (Table 2A). There were no differences in BMI, hsCRP, Pettersson scores, HJHS (Table 2A), race, hemophilia type or severity, and infection with hepatitis C or HIV (Table 2B) between hypertensive and nonhypertensive patient groups.

Of the variables for joint health in Table 2 (PD score, Pettersson score, HJHS, and pain score), only PD score appeared to be associated with hypertension (Figure 1). We then used logistic regression to examine further the association of hypertension with PD score. The unadjusted odds of hypertension increased by 1.10 (95% CI: 0.99, 1.21, *P*=.07) for each unit increase in PD score (Table 3A).

Pettersson score was the confounder with the greatest effect on the regression coefficient. After accounting for Pettersson score, the adjusted odds ratio increased to 1.27 (95% CI: 1.05, 1.52, *P*=.01) (Table 3A). Thus, the risk of hypertension rose steeply as the PD score increased: a patient with the median PD score of 13 had a probability of being hypertensive that was nine times greater than one with a normal PD score of zero.

3.3 | Association of blood pressures with PD score

In univariate analysis, SBP was positively correlated with PD score (*P*=.06) and age (*P*=.02), while DBP was correlated with neither (Table 4). Both SBP and DBP correlated with weight or BMI if an outlier patient who weighed >120 kg was excluded. Both SBP (*P*<.01) and DBP (*P*=.06) appeared higher among patients who consumed less clotting factor. Patients who reported more pain in their joints had higher SBP (*P*=.05) and DBP (*P*=.01). In addition, SBP was higher among patients with nonsevere hemophilia (*P*=.02) or patients taking antihypertensive medications (*P*<.01), while elevated DBP was seen among HIV-positive patients (*P*=.09) (Table 5).

TABLE 2 Comparison of patients with and without hypertension

(A) Continuous variables			
	Median (IQR)		
Independent Variable	**Not Hypertensive**	**Hypertensive**	***P*-value**
PD Score	10 (6-13)	19 (8-24)	.06
Age (y)	30 (27-39)	48 (29-65)	.04
BMI (kg/m^2)	25.1 (23.7-27.4)	29.3 (27.1-33.7)	.10
Weight (kg)	79.3 (70.7-91.70	87.6 (76.0-100.2)	.25
hsCRP (mg/mL)	0.60 (0.5-2.0)	1.30 (0.8-3.7)	.32
Clotting Factor Usage (units/y/kg)	6950 (4441-8323)	3704 (585-5686)	.03
Pettersson score	24.5 (11.0-43.5)	26.0 (10.0-63.0)	.56
HJHS	10.0 (5.0-23.0)	15.5 (9.0-24.0)	.33
Pain Score	0.3 (0.2-0.7)	0.7 (0.3-1.3)	.19
(B) Categorical variables			
Independent Variable	**Not Hypertensive**	**Hypertensive**	***P*-value**
Race			
Hispanic	3	1	.28
Black/African American	3	1	
White	5	10	
Other	2	3	
Hemophilia type			
A	11	12	1.00
B	2	3	
Hemophilia Severity			
Nonsevere	2	6	.21
Severe	11	8	
Hepatitis C			
Negative	7	6	.71
Positive	6	9	
HIV			
Negative	11	11	.65
Positive	2	4	

HIV, Human Immunodeficiency Virus.
Normal Values: hsCRP <5 mg/mL; Maximum Pettersson Score 69; Maximum HJHS 124; Maximum PD Score 54.

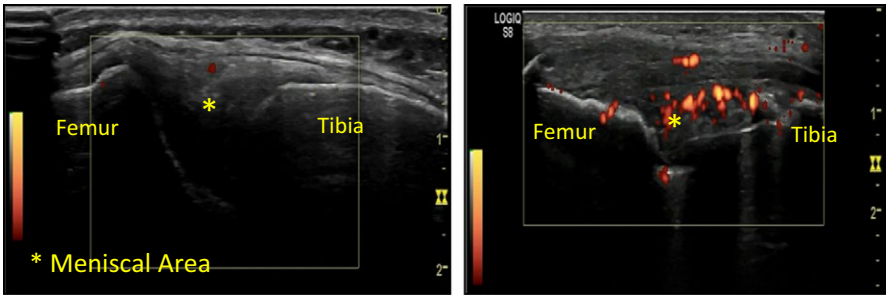

FIGURE 1 Visualization of vascular remodeling in the knee joints of two patients. Two representative examples of power Doppler signals, used to determine the degree of vascular remodeling in the joint in relation to hypertensive status, are depicted. The images were obtained during musculoskeletal ultrasound imaging of the knees in the medial meniscal areas of two different patients in longitudinal axis. The left panel represents a patient with low systolic blood pressure (power Doppler signal absent), whereas the right panel represents a patient with high systolic blood pressure (power Doppler signal pronounced)

TABLE 3 Associations between hypertension or blood pressure and PD score

(A) Hypertension and PD Score				
	Odds Ratio for Hypertension (95% CI)			
	Unadjusted	***P***	**Adjusted**	***P***
PD Score	1.10 (0.99, 1.21)	.07	1.27 (1.05, 1.52)	.01
Pettersson score			0.95 (0.89, 1.01)	.12
(B) Systolic Blood Pressure and PD score				
	Regression Coefficient for transformed SBP (95% CI)			
	Unadjusted	***P***	**Adjusted**	***P***
PD Score	−0.02 (−0.04, −0.00)	.04	−0.03 (−0.06, −0.01)	.01
Pettersson score			0.01 (−0.00, 0.02)	.15
(C) Diastolic Blood Pressure and PD score				
	Regression Coefficient for DBP (95% CI)			
	Unadjusted	***P***	**Adjusted**	***P***
PD Score	0.20 (−0.15, 0.56)	.25	0.47 (−0.07, 1.01)	.08
Pettersson score			−0.11 (−0.31, 0.09)	.28

TABLE 4 Correlation between blood pressure and continuous patient variables

		SBP		**DBP**	
Continuous variable	**n**	r_s	***P*-value**	r_s	***P*-value**
PD score	28	.36	.06	.22	.27
Age (y)	28	.43	.02	.20	.32
Weight (kg)	28	.25	.20	.22	.27
Weight (kg)[a]	27	.39	.04	.36	.07
BMI (kg/m^2)	28	.28	.14	.24	.21
BMI (kg/m^2)[a]	27	.43	.03	.39	.05
hsCRP (mg/mL)	28	.00	1.00	−.16	.41
Clotting factor usage (units/y/kg)	28	−.65	<.01	−.36	.06
Pettersson score	27	.06	.77	.06	.75
HJHS	27	.02	.92	.13	.53
Pain score	27	.38	.05	.50	.01

r_s, Spearman rank correlation coefficient.
[a]Excluded one outlier, patient with a weight>120 kg.

Pettersson score was the confounder with the greatest effect on the regression of transformed SBP on PD score. There was a strong association of PD scores with transformed SBP after adjusting for Pettersson score; regression coefficient =−.03 (95% CI: −0.06, −0.01; *P*=.01) (Table 3B, Figure 2A).

Pettersson score was also the most important confounder for the regression of DBP on PD score. DBP was weakly associated with PD score after adjusting for Pettersson score: regression coefficient=.47 (95% CI: −0.07, 1.01; *P*=.08) (Table 3C; Figure 2B).

4 | DISCUSSION

Evidence accumulated to date has shown that the hypertension of hemophilia is not easily explained by its usual risk factors. This points to a role for hemophilia-specific factors. One specific feature, frequent microhematuria which occurs in approximately one-third of PWH, was recently investigated for its potential to affect renal function in a cohort of 135 PWH, but did not emerge as a risk factor for either renal dysfunction or hypertension[32]. Other hemophilia-specific factors are those related to joint arthropathy which is a progressive major lifelong burden for PWH.

To study the influence of variables defining hemophilic joint disease, we examined four joint-specific characteristics for their associations with hypertension and blood pressures: Pettersson score, HJHS, VAS, and PD score. These provided radiographic, clinical, pain-related, and vascularity-related assessments of joint status, respectively. Of these, only pain and magnitude of PD signals were associated with hypertension and blood pressures. We found that PD signal was almost twice as high in the hypertensive compared to the nonhypertensive patients. Notably, the risk of hypertension and SBP elevation increased steeply with increasing PD score; in this cohort, a patient with the median PD score of 13 had a probability of being hypertensive that was nine times greater than a patient with a normal PD score of zero. On the other hand, DBPs were less affected. These observations are consistent with the hypothesis that vascular remodeling in hemophilic joints contributes to a greater risk of hypertension and elevated blood pressures.

This hypothesis is further supported by the fact that vascular remodeling in the micro- and macrocirculation is a hallmark of hypertension, resulting in vascular stiffness once endothelial changes are

TABLE 5 Association between blood pressure and categorical patient variables

Categorical Variable	n	SBP (mm Hg) Median (IQR)	*P*-value	DBP (mm Hg) Median (IQR)	*P*-value
Race					
Hispanic	4	128 (108, 133)	.32	83 (71, 84)	.60
Black/African American	4	115 (108, 115)		75 (70, 81)	
White	15	132 (126, 139)		81 (73, 87)	
Other	5	127 (108, 136)		75 (69, 79)	
Hemophilia type					
A	23	132 (120, 136)	.74	79 (73, 86)	.63
B	5	126 (123, 130)		78 (70, 81)	
Hemophilia severity					
Nonsevere	8	136 (131, 141)	.02	78 (74, 84)	.89
Severe	19	126 (130, 132)		78 (70, 84)	
Antihypertensive medication					
No	18	123 (108, 132)	<.01	76 (70, 84)	.20
Yes	10	135 (132, 139)		81 (77, 86)	
Hepatitis C					
Negative	13	127 (120, 136)	.66	74 (71, 82)	.16
Positive	15	132 (123, 134)		81 (77, 86)	
HIV					
Negative	22	126 (120, 133)	.61	77 (71, 82)	.09
Positive	6	137 (130, 143)		86 (78, 87)	

Comparisons between race categories were made with the Kruskal-Wallis test, while for the other variables, comparisons were made between categories with the Wilcoxon test.

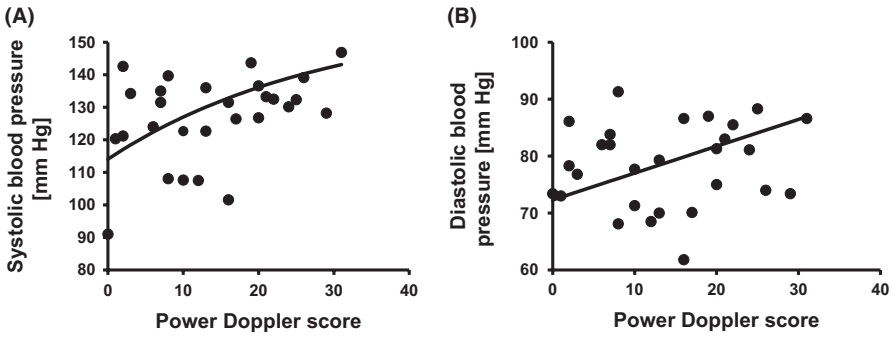

FIGURE 2 Dynamics of blood pressure in relation to vascular remodeling in joints. (A) Systolic blood pressure values and (B) diastolic blood pressure values were plotted against the composite power Doppler signal scores, representing the extent of vascular remodeling in joints. Power Doppler signals were measured during musculoskeletal ultrasound examination of each patient's elbows, knees, and ankles (n=28 patients; power Doppler score 0-54). The regression line was calculated after adjustment for Pettersson score

pronounced, thereby further fueling the hypertension[10,33]. Processes involved are described as eutrophic inward remodeling (rearrangement of the same amount of wall material around a smaller vessel lumen) or hypertrophic remodeling (wall volume increase affecting vascular smooth muscle cells)[33]. It is likely that the hypertrophic mechanism is involved in synovial vascular remodeling in hemophilic joints based on findings of remarkably distorted and thickened vessel walls that stain positive for α-SMA, a marker for vascular smooth muscle cells[20]. Based on this information, we hypothesized that additional vascular remodeling in excess vascular beds, such as in the hemophilic joint, contributes to hypertension in PWH, while also keeping in mind that the reverse may be true.

Increased vascularity, microvascular flow, and abnormal vascular structures have been described as unique to hemophilic joints, manifesting as large, confluent, and pulsatile PD signals that can be quantified during MSKUS examinations[20,34]. The PD signal is a sensitive tool to determine abnormal microvascular flow in joints[35,36], is rarely detected in normal joints or in joints with osteoarthritis[37,38], and is weaker and more spot-like in rheumatoid arthritis than in hemophilic arthropathy[34]. The pronounced abnormal PD signals in hemophilic arthropathy can be considered a direct measure of the extent of vascular remodeling, evidenced histologically by pronounced expression of perivascular alpha α-SMA in intraarticular soft tissues of PWH and hemophilic mice[20]. α-SMA is the most widely used marker

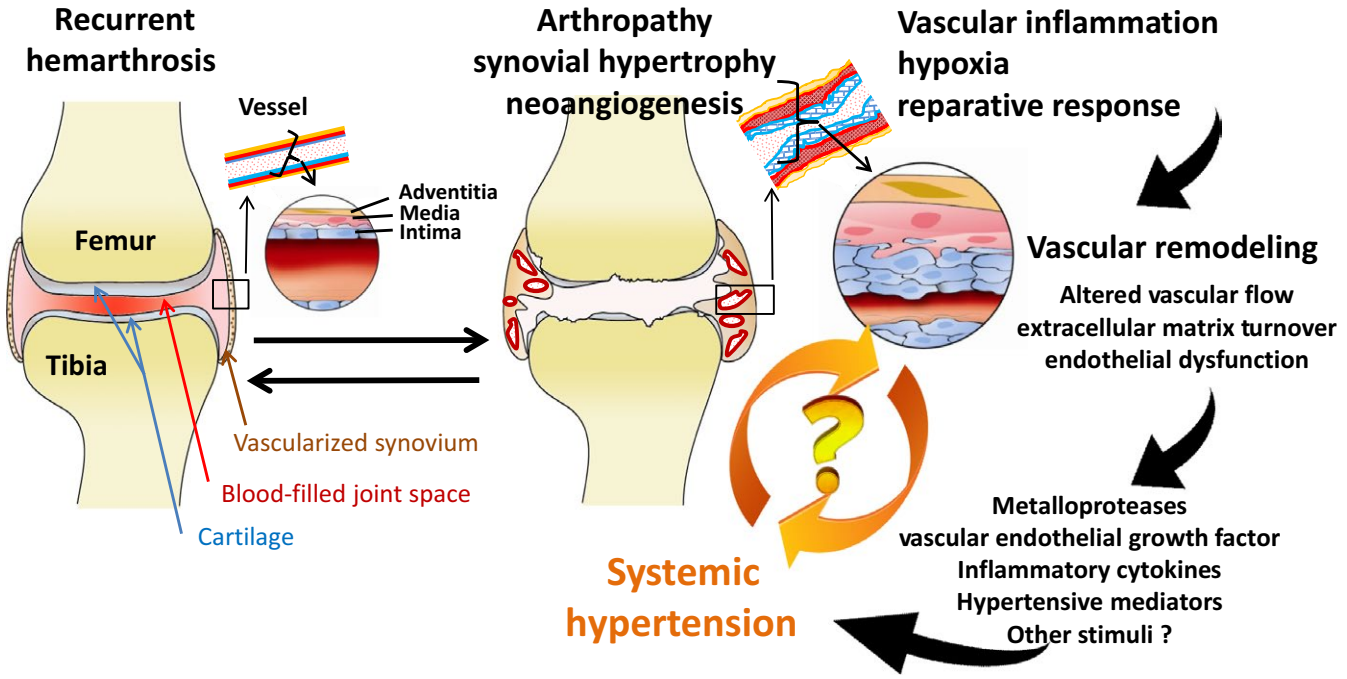

FIGURE 3 Depiction of the interplay of joint bleeding, vascular joint remodeling, and hypertension in patients with hemophilia. This is a provisional scheme with many open questions. A coronal view of the knee joint is depicted. Repetitive joint bleeding results in synovial hypertrophy and neovascularization with vascular remodeling in response to vascular inflammation, local hypoxia, and compensatory tissue repair. These processes may generate local release of metalloproteases, vascular endothelial growth factor, inflammatory, and other mediators that result in systemic hypertension, which in turn may perpetuate vascular remodeling with leaky vessels and rebleeding [Colour figure can be viewed at wileyonlinelibrary.com]

for myofibroblasts, which are mesenchymal-type progenitor cells that facilitate vascular remodeling[39,40] in vascular disorders such as pulmonary hypertension[41].

Another unique feature of PWH is frequent joint bleeding, which, in turn, has previously been associated with vascular remodeling as assessed by the extent of abnormal PD signal[20]. The molecular mechanisms of vascular remodeling, which appear to be associated with joint rebleeding tendencies[11,20], are currently unknown, but may be intertwined with hypertension and blood pressure control. It is plausible that the vicious cycle of perpetuated joint bleeding and vascular remodeling is accompanied by local and/or systemic mediators of angiogenesis and/or inflammation[42-44], which in turn may affect blood pressure control. For example, TNF-β, which is upregulated in joint tissues after hemarthrosis in hemophilic mice[45], increases the activity of MMP-2 and other MMPs that are well known to contribute to maladaptive vascular remodeling in hypertension. These enzymes degrade basement membranes, thereby facilitating migration and proliferation of vascular smooth muscle cells[46]. It has been demonstrated that following joint bleeding, MMPs are overexpressed in joints of hemophilic mice, and basement membrane turnover is accelerated in hemophilic rat joints.[47] Therefore, it is also conceivable that vascular remodeling in the joint is precipitated, aggravated, or perpetuated in response to hypertensive stimuli. This concept is intriguing in light of previous observations, summarized by Schiffrin[10], that invoke the presence of damage-associated molecular patterns and associated immunologic phenomena in the etiology of endothelial dysfunction and hypertension. Bleeding joints, local inflammation, and abnormal synovial milieu may fit this scheme. We emphasize that it remains unclear whether vascular remodeling in the hemophilic joint is a cause or a consequence of the hypertension, but speculate that these conditions fuel a vicious cycle of events that also include bleed perpetuation. It is well documented that chronic hypertension causes altered vessel wall characteristics in microvascular beds such as the kidney, retina, or brain[10-13], triggering hemorrhages and aneurysms[11,48-52]. Similar microvascular changes may occur in hemophilic joints with altered and proliferating soft tissues in response to hemarthrosis. To speculate further, the extent of neovascularization and vascular remodeling may then become a function of abnormal blood pressures and shear stress. In this context, further underlining the presence of vascular abnormalities in hemophilia, it has been previously documented that PWH suffer from pronounced systemic vascular endothelial dysfunction[53]. Endothelial function was ascertained by flow-mediated vasodilation which is a widely used noninvasive test for assessing endothelial health[54]. Toward this end, it will be interesting to study whether endothelial nitric oxide metabolism or angiotensin biology, shown to play a role in other clinical conditions associated with endothelial dysfunction, such as eclampsia, can provide mechanistic insights[55,56].

Figure 3 provides a provisional proposed scheme illustrating how vascular joint remodeling in response to joint bleeding may initiate and perpetuate hypertension, more vascular changes, and joint bleeding.

Consistent with previous observations[57], mean hsCRP was low in our cohort, indicating that systemic inflammation is not a hallmark of

hemophilia, and therefore not driving hypertension and poor vascular health in this patient population.

While these observations are consistent with the hypothesis that vascular remodeling and blood pressure dynamics are linked in PWH, other yet unrecognized hemophilia-specific factors may emerge from future investigations. As neither Pettersson score nor HJHS was associated with SBP or DBP, more simple explanations, such as painful deteriorating joints, do not seem to play a major role.

Our study is limited by its small sample size. Clearly, it has to be considered as a pilot study to introduce the new concept of vascular remodeling in hemophilic joints and its link to hypertension in hemophilia. Larger prospective studies will be required to disentangle the interrelations between vascular remodeling, perpetuated bleeding, hypertension, and blood pressure control. These issues are becoming increasingly important as more PWH survive into old age when they are especially vulnerable to ICH and need better awareness and treatment of hypertension.

5 | PERSPECTIVE

The etiology of the hypertension in hemophilia remains obscure and is not explained by the usual risk factors. Pronounced vascular joint remodeling has been identified recently as unique to hemophilic arthropathy, not present in other arthritic conditions such as rheumatoid arthritis or osteoarthritis. This report links hypertension and vascular remodeling in hemophilia patients, providing new pathophysiological insights that should not only inform medical practice but also spur investigations pertaining to etiology and improved treatment strategies for hemophilia patients.

ACKNOWLEDGMENTS

This work was supported by funding from Biogen ("Prevalence and Etiology of Subclinical Joint Bleeding and Joint Microbleeding in Adults with Hemophilic Arthopathy"), by a Career Development Award from the National Hemophilia Foundation/Novo Nordisk (AvD) and by HRSA service grant H30MC24045.

CONFLICT OF INTEREST

The authors declare that they have no competing interests.

AUTHORS' CONTRIBUTIONS

AvD conceived and designed the study, performed and interpreted joint ultrasounds, interpreted clinical data, and provided oversight. TJC coordinated the clinical study and collected clinical data. THH interpreted radiographs. RFWB analyzed the data. RFWB and AvD wrote the manuscript.

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How to cite this article: Barnes RFW, Cramer TJ, Hughes TH, von Drygalski A. The hypertension of hemophilia is associated with vascular remodeling in the joint. *Microcirculation*. 2017;24:e12387. https://doi.org/10.1111/micc.12387